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ABSTRACT

The Marie Skłodowska-Curie Symposia on Cancer Research and Care (MSCS-CRC) promote collaborations between cancer researchers and care providers in the United States, Canada and Central and Eastern European Countries (CEEC) to accelerate the development of new cancer therapies, new strategies for early detection and prevention, and improve cancer care and the quality of life for patients and their families. The 4th MSCS-CRC (September 25-27, 2024, Buffalo, New York) brought together 147 participants from the US, Canada, Croatia, Czechia, Lithuania, Poland, Romania and Ukraine, and involved representatives of the US Centers for Disease Control and Prevention (CDC), National Cancer Institute (NCI) and their counterparts from Poland, Ukraine Lithuania and other CEECs. They were accompanied by New York State (NYS) and local representatives of the NYS Empire State Development, and of the Translational Research Consortium of Cancer Centers (TRCCC), involving 13 cancer centers from the Northeastern US and Canada, as well as several Pharma and Biotech companies. The 4th Meeting focused on prevention and early detection of smoking- and HPV-related cancers, reducing disparities in cancer detection-, care and outcomes, and increasing the feasibility and reducing costs of high-end treatments, such as cell therapies for patients with advanced cancers. The second focus area were the available sources of funding of regional and international collaborations in these areas. The relevance of the successful model TRCC to promoting the oncology training and research collaborations in the CEE Countries was discussed. The 5th MSCR-CRC meeting will take place September 3-5, 2025, in Warsaw, Poland.

KEY WORDS: Symposium, cancer research, cancer care, international collaborations, regional collaborations

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INTRODUCTION

The Marie Skłodowska-Curie Symposia on Cancer Research and Care (MSCS-CRC), started in 2019 with the overall goal to identify the areas of collaborative opportunities between cancer researchers and care providers in the United States, Canada and Central and Eastern European Countries (CEEC) and eliminate the bariers to such collaborations[8]. MSCS-CRC aims to accelerate the development of new cancer therapies, advance early detection and prevention strategies, increase cancer awareness, and improve cancer care and the quality of life for patients and their families. The latest 4th edition of MSCS-CRC held at the Roswell Park Comprehensive Cancer Center (RPCCC) in Buffalo, NY, brought together 147 participants from the US, Canada, Croatia, Czechia, Lithuania, Poland, Romania, and Ukraine, and included representatives of the National Cancer Institutes of the United States, Poland, Lithuania and Ukraine, members of the academic cancer researh institutions from the above countries and representatives from several Pharma and Biotech companies. Discussions involved representatives of the US Center for Disease Control (CDC), New York State (NYS) Empire State Development, and of the Translational Research Consortium of Cancer Centers (TRCCC), involving 13 cancer centers from North-Eastern US and Canada. The focus of the 4th Meeting was prevention and early detection of smoking- and HPV-related cancers, reducing disparities in cancer detection-, care and outcomes, and increasing the feasibility and reducing costs of high-end treatments, such as cell therapies for patients with advanced cancers. The discussions addressed the needs and arising opportunities in education and training, joint laboratory and clinical research projects in cancer prevention, early detection and treatment, as well as new health policy initiatives, within each of the individual areas of interest in each of the Sessions.

FEDERAL AND NEW YORK STATE SUPPORT FOR INTERNATIONAL PARTNERSHIPS

Mark Parascandola (National Cancer Institute [NCI], USA; Bethesda, MD, USA) discussed the global gaps in the implementation of cancer control and the research needs and opportunities in this area. He highlighted

New York Programs Supporting Biomedical Research and Clinical Trials

- **JLABS@NYC**[1]: Incubator program providing office and lab space, education, and access to industry experts and the startup community.
- **IndieBio New York**[3]: Life science accelerator program for early-stage life science companies providing financial support, lab space, mentoring, and business skills.
- **Biodefense Commercialization Fund**[5]: Grant funding program for startups and academic institutions developing solutions to infectious diseases.

United States Federal Programs Supporting Biomedical Research and Clinical Trials

- **Cancer Prevention and Control Clinical Trials Planning Grant Program**[2]**:** Grant funding mechanism intended to facilitate well planned clinical trials across the cancer prevention and control spectrum aimed at improving prevention/ interception, cancer-related health behaviors, screening, early detection, healthcare delivery, management of treatment-related symptoms, supportive care, and the long-term outcomes of cancer survivors.
- **High-Priority Research in Tobacco Regulatory Science**[4]: Grant funding mechanism to support new high-priority biomedical and behavioral research that will provide scientific data to inform the regulation of tobacco products to protect public health.
- **NCI Clinical and Translational Exploratory/Developmental Studies**[6]: Grant funding mechanism to support preclinical and early phase clinical research, as well as correlative studies, directly related to advancements in cancer treatment, diagnosis, prevention, comparative oncology, symptom management, or reduction of cancer disparities.
- **Bioengineering Research Grants**[7]: Grant funding opportunity to encourage collaborations between life and physical sciences that apply a multidisciplinary bioengineering approach to the solution of a biomedical problem and integrate, optimize, validate, translate or otherwise accelerate the adoption of promising tools, methods, and techniques for a specific research or clinical problem in basic, translational or clinical science and practice.

Fig. 1. Existing Programs and Funding opportunities to Support Biomedical Research and Clinical Trials Available through New York State or United States Federal Mechanisms.

the role of his Center (CGH, NCI, NIH) in supporting innovative research to reduce the global cancer burden, and developing international partnerships and training opportunities in these areas, with the goal of reducing disparities in cancer related outcomes. Malgorzata (Margaret) Wojtowicz (Division of Cancer Prevention (DCP), NCI, NIH,USA), highlighted the Cancer Prevention Clinical Trials Network (CP-CTNet) within her Division, as an opportunity for collaborative cancer prevention clinical research. CP-CTNet is one of the main agent development programs within the Division of Cancer Prevention (DCP), National Cancer Institute (NCI), National Institutes of Health (NIH). It's goal is to conduct federally funded early phase cancer prevention clinical trials assessing the safety, tolerability, and cancer preventive potential of novel agents and interventions. These early-stage clinical studies include phase 0 (micro-dosing), phase I (dose-finding), and phase II (preliminary efficacy) trials to identify safe and effective preventive interventions that can subsequently move into large-scale (phase III) clinical investigations. The network aims are : a) to optimize clinical trial designs, b) to develop surrogate and intermediate endpoint biomarkers, c) to test novel imaging technologies, and d) to develop further insights into mechanisms of cancer prevention by agents and/or strategies. Current Lead Academic Organizations (LAOs) of the CP-CTNet are The University of Texas MD Anderson Cancer Center (Houston, TX), Northwestern University (Chicago, IL) , University of Arizona (Tuscon, AZ), University of Michigan (Ann Arbor, MI), and University of Wisconsin (Madison, WI). The current scientific emphasis of studies conducted within CP-CTNet include (among others): a) targeting the biology of carcinogenesis (immunoprevention, focus on high-risk population, pilot studies integrating high throughput technologies to understand mechanisms of carcinogenesis and drug action), b) strategies to optimize risk/benefit ratio (regional drug delivery e.g. topical drug application forbreast ca., inhaled agents forlung ca.; alternative dosing schedules e.g. intermittent dosing; combinations), c) re-purposing "old" drugs for cancer prevention (focus on drugs affecting multiple chronic diseases e.g. aspirin, NSAIDs, metformin), d) intermediate endpoint biomarkers as surrogates for cancer incidence. Dr. Wojtowicz presented

examples of currently open CP-CTNet studies, discussed the process flow (from submission of a trial concept through study conduct/reporting/closure to making data/specimens available to the research community) and opportunities for new investigators and/or institutions to join CP-CTNet.

Three presentations described the role of the New York State (NYS) Empire State Development Corporation (ESD) in enhancing the Biotech operations in the NYS (Figure 1). *Loretta Beine* (ESD, Long Island, NY, USA) provided and overview of the role of the ESD as the resource for industry attraction and retention. She described the ongoing complementary economic development assistance programs offered by ESD to support and attract all stage, all size life science businesses across New York state[9-13]. *Dylan Williams* (ESD, Albany, NY, USA) discussed the specifics role of ESD in advancing biotechnology, cancer research, and life science innovation. He highlighted the ESD-provided strategic financial assistance to the biotechnology and cancer research entities. Since 2017, ESD's Life Science Initiative has been to create, attract, grow, and retain life science companies by leveraging New York's academic life science assets and promoting venture capital investments in NYS life science companies; creation of accelerated paths to commercialization; and the development of life science entrepreneurial talent. ESD invests in biotechnology accelerators, academic research institutions, start-up commercialization assistance, and entrepreneurial training. *Smitha James* (University at Buffalo [UB], Buffalo, NY, USA) discussed practical examples of the interactions with the ESD within the UB Business and Entrepreneur Partnerships. Supporting both mature companies and innovative startups, UB Business and Entrepreneur Partnerships help biomedical and life sciences companies establish, grow and succeed, providing research support, access to experts, wet labs, office space, shared equipment, funding sources and connections (Figure 1).

ONGOING PARTNERSHIPS WITHIN THE MSCS-CRC AND OPPORTUNITIES FOR EXPANSION

Leszek Kotula (SUNY Upstate Medical University [SUNY-UMU]; Syracuse, NY, USA), discussed his team's experience in international collaborations developing of ABI1-based test for prostate cancer tumor progression and resistance. With his collaborators, including Pawel Wiechno; Elżbieta Sarnowska; Michal Mikula and Iwona Ługowska from the Maria Skłodowska-Curie National Research Institute of Oncology (MSCNRIO), and Kevin Lin from SUNY-UMP, Dr. Kotula evaluates the role of aberrant ABI1 in tumor tissue and liquid biopsy samples as a biomarker for cancer recurrence and predictor of sensitivity to anti-AR treatment. This project is an example of a sucessful joint collaboration between Upstate Medical University and the National Institute of Oncology in Warsaw.

Kathleen Kokolus and *Pawel Kalinski* (RPCCC, Buffalo, NY, USA) described their collaborative preclinical and early-phase clinical research program involving Rosswell Park Comprehensive Cancer Center (NY, USA), University of Pittsburgh (PA, USA), Mt. Sinai Icahn School of Medicine (NY, USA), University of Virginia (VA, USA) and Moffitt Cancer Center (FL, USA) involving live cell-based vaccine (alpha-type-1-polarized dendritic cells; αDC1s), and combinatorial reprograming of tumor mictorenvironments (TME) to sensitize immunotgherpay-resistant solid tumors to PD1 inhibitors.

Their preclinical studies show that a chemokine-modulatory regimen (CKM) combining TLR3-ligands and IFNα synergistically induces transient production of CTL attracting chemokines and suppresses Treg-attractants. CKM also selectively targets (NFκB-high) cancer lesions, but not healthy tissues, allowing its systemic application to abolish heterogeneity of TMEs, promote uniform CTL infiltration and responsiveness to immunotherapies[14-20]. The recently completed trial trial NCT03403634 confirmed the safety and immunologic efficacy of IV infusion of IFNα2b (INTRON-A) and selective TLR3-ligand (rintatolimod/Ampligen) in patients with metastatic triple-negative breast cancer (TNBC)[21]. CKM showed very good tolerability, average 10.3-fold increase in intratumoral CTL markers and preliminary signals of clinical activity (1 objective response, 50% survival of >4 years), when followed by pembrolizumab. Analogous CTL increases were also seen on study NCT04081389 (neoadjuvant CKM/chemotherapy in TNBC)[22] and NCT03403634 (liver-metastatic colon cancer). Ongoing studies NCT04093323 (in PD1-resistant solid tumors), NCT02432378 (in advanced ovarian cancer)[23], test the clinical efficacy of concomitant application of CKM with PD1 blockade and/or DC vaccines. Dr. Kalinski discussed the existing logistic-, legal-, fiscal and regulatory agreements between the participatting cancer centers in the US and biotech partners in the US and Argentina, which allowed the development of the trtials and sharing of patient material and the imported drugs (such as or Bioferon as alternative to the discontinued INRON-A), which can now be used to involve additional partners (including international) in their NCI- and DoD (US Department of Defense)-funded programs, and the newly arisng collaborative needs expanding the results to the areas of acute and chronic infections, such as hepatitis, HIV, HPV and tuberculosis.

Iryna Tanasiichuk (Bogomolets National Medical University; Kyiv, Ukraine) discussed the collaborative development of genetically modified T cells for cancer treatment in Ukraine, where patients' access to such therapies is curently limited. The current bariers involve the high cost of the FDA approved commercial treatments, challenging technology of manufacturing and lack of training needed to produce and use of these cells is the clincal settings. Dr. Tanasiichuk discussed how a collaboration between her institution and *Michael Nishimura* laboratory at Loyola University of Chicago, help to advance the development of the production of genetically modified T cells and the eventual introduction of adoptive cell therapies in Ukraine.

CONDUCTING CLINICAL TRIALS IN POLAND: MECHANISMS OF STATE SUPPORT FOR INTERNATIONAL COLLABORATIONS AND CURRENT COLLABORATIVE NEEDS

Wojciech Fendler (Medical Research Agency [MRA]; Warsaw, Poland)[24] discussed the last 5 years of the MRA experience in supporting the changing clinical trials landscape in Poland and the importance of non-commercial clinical trials as a cornerstone of medical research and the healthcare system (Figure 2). Dr. Fendler discussed how non-commercial trials provide patients with access to cutting-edge medical technologies and novel interventions . He also discussed the importance of ensuring that pateints in all disease areas those with the greatest health burden such as oncology or cardiology, but also the often underfunded rare diseases, have the opportunity to benefit from clinical research. The MRA, established in 2020, has the primary mission of increasing the number of the non-commercial clinical trials in Poland, to broaden the access to new therapeutic options for Polish patients and strengthening medical research. So far, the Agency has supported 248 projects with a total of €735 million, resulting in a sixfold increase in the number of non-commercial clinical trials in Poland. The second area of MRA's efforts is enhancement of the critical clinical trials infrastructure. MRA has provided Polish universities, research institutes and hospitals with PLN 700 million (€178 million) in competitively-funded MRA grants to establish 23 Clinical Trials Support Centers (CTSC) and 19 Regional Digital Medicine Centres. The MRE joined to the European Clinical Research Infrastructure Network (ECRIN) and has been actively guiding the national units towards the standards upheld in other EU countries. The third area of MRA's activities is bolstering the human potential of our healthcare centers, by supporting education and training opportunities in clinical research in the format of postgraduate studies, thematic courses and open seminars. Dr. Fendler highlighted the joint Clinical Scholars Research Program involving Harvard Medical School and MRA launched in 2023 and planned to support 500 participants over the next 5 years.

Iwona Ługowska (MSCNRIO; Warsaw, Poland) presented the insights from her pioneering work building the largest early-phase clinical trials program in Poland, and discussed some of the challenges and opportunities in this area. Early phase oncology trials (Phase I and early Phase II studies) assess the safety, tolerability, pharmacokinetics, and preliminary efficacy of novel anticancer agents. Advancement in the use of biomarker-driven approaches, which identify genetic mutations and molecular profiles specific to tumors, recently enabled more precise match between the individual patients and newly available treatment regimens, including immunotherapy. However, these trials face challenges in Poland and globally, due to the need of recruiting patients with specific genetic profiles. Dr. *Ługowska* discussed the existing ethical considerations and logistic challenges of such trials, whcih require advanced trial designs and adaptive methodologies. She highlighted the need for collaboration between Poland and the USA as being crucial for advancing this dynamic field and improving patient outcomes.

Karolina Nowak (MRA; Warsaw, Poland) outlined the experience at the MRA in promoting collaborations with American partners in oncology clinical trials. Poland's well-developed clinical research sector has been an attractive place for international sponsors. As the sixth highest-populated country in the European Union, with a total population of 37 million, Poland has been a regional leader among the Central and Eastern European countries (CEEC). Dr. Nowak stressed the existence of numerous treatment-naive patient populations available for trial participation. In 2019 alone, over 25,000 Polish patients gained access to novel experimental therapies as trial participants. Based on the Clinical Trial Database run by the NCI, USA25, a total of 3088 clinical trials were started in Poland between April 1, 2019 and May 2024. Oncology represents the dominant area of these trials. The latest data from the Polish National Cancer Registry show that 1.17 million of Poles live with cancer, with the annual incidence of new cancer cases of 440 per 100,000. Since cancer accounts for over 25% of deaths in Poland and 1 in 5 Polish citizens will develop cancer over their lifetimes, MRA recognizes the importance and urgency of innovative cancer research and provides research public grants for non-commercial clinical trials in Poland26. Cancer treatment projects currently remain among the most

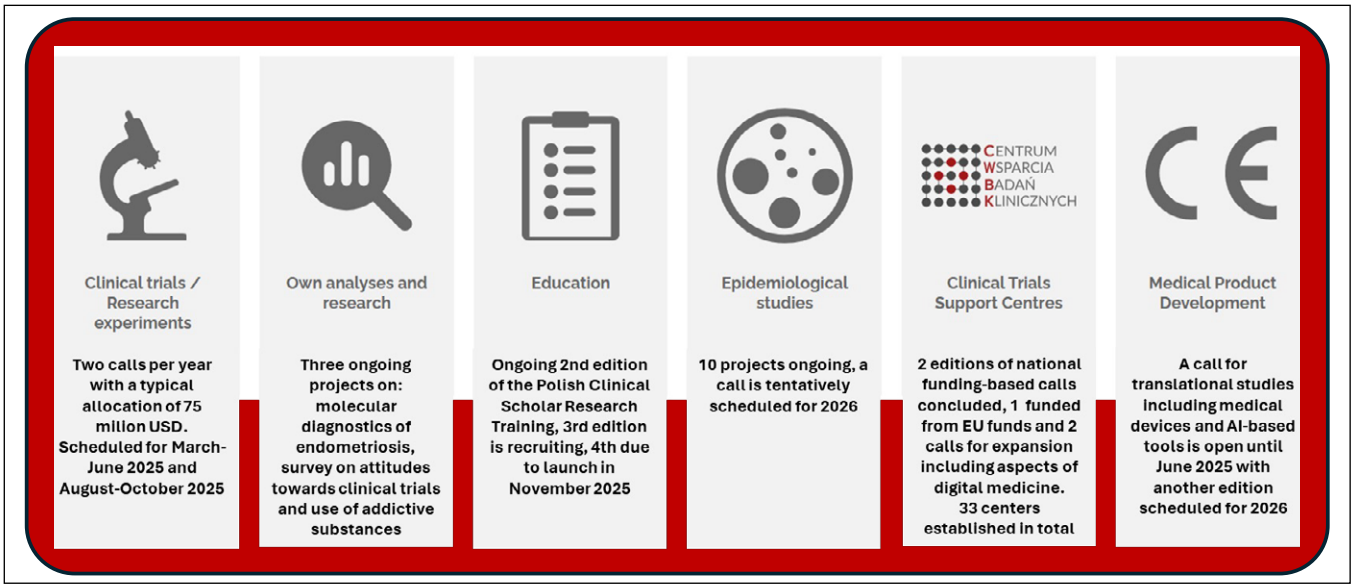

Fig. 2. Funding Opportunities from the Medical Research Agency of Poland in Support of Clinical Trials.

frequent requests from beneficiaries seeking MRA's support. In 2024 the MRA allocated $150 million for a call on cancer research including potential international projects, launching the biggest, targeted medical funding initiative, in the history of Poland. MRA developes new venues of collabotation with the US NCI to address the most pressing science-based and clinical oncology priorities faced by Poland and USA and benefiting patients in both countries. The discussed programs include sharing the knowledge and resources available to both Agencies, and engaging research teams, investigators and clinicians in cross-institutional clinical research, to accelerate the clincial implementation of new strategies into clinical practice, increase the number of non-commercial cancer trials and improve their availability to patients.

ARISING OPPORTUNITIES FOR COLLABORATIONS: TRANSLATIONAL AND CLINICAL RESEARCH

Piotr Rutkowski (MSCNRIO; Warsaw, Poland) presented the example of a phase II trial of Axitinib and Avelumab in patients with unresectable/metastatic gastrointestinal stromal tumor (GIST) who progressed after standard therapy (NCT04258956). A total of 58 patients were enrolled, of which56 were evaluable for safety and efficacy. Partial response was observed in 5 (9%), stable disease in 34 (61%) and progressive disease in 17 patients (30%). In patients with partial response, the median duration of response was 18.5 months (95%CI, 18.3-NA). Median PFS and OS were 4.6 months (95%CI, 2.9-6.4) and 14.2 months (95%CI, 9.2-26.3), respectively. The 12-month PFS and OS rates were 23% (95% CI: 14-37.1) and 59.3% (95% CI: 47.5-74), respectively. This largest trial of a combination of targeted therapy and immunotherapy in pretreated GIST, which showed significant and meaningful efficacy of this novel therapeutic approach. A significant subset of pts achieved long term clinical benefit highlighting the need for a multi-institutional phase III study.

Mikhail Berezin (Washington University School of Medicine; St. Louis, MO, USA) discussed the importance of better understanding of the acute and chronic side effects of cancer treatment. He presented the transcriptional effects of oxaliplatin in mice models and use of bioinformatics to better understand how the interplay of systemic toxicities contributes to specific pathologies, and discussed the arisng opportunities for collaborations to develop new treatments and diagnostic tools to better manage the side effects.

Peter Forsyth and Brian Czerniecki (Moffitt Cancer Center & Research Institute, Tampa, FL, USA) challenged the the notion of an incurable stage of cancer, by presenting the early data from an ongoing trial of a specialized subtype of dendritic cells (cDC1s) for patients with breast cancer who developed leptomeningeal disease (LMD), with a particularly poor prognosis. Their phase I single-arm, dose escalation multicenter study NCT05809752 aims to establish the safety of IT cDC1s, and associations between clinical outcomes and DC-induced changes in cerebro-spinal fluid. cDC1s are administered weekly intrathecallly using Omaya ports over 12 wks, at increasing dose levels ranging from 1 X 10^6 through 5 X 10^7 cDC1s, until disease progression, dose-limiting toxicities or patient withdrawal. As of August 2024, 7 patients were treated [1, 2 & 10 X 10^6 cDC1s] – and no DLTs were found. Preliminary data on

patient status and upcoming opportunities for collaborations were discussed.

Sandro Matosevic (Purdue University, West Lafayette, IN, USA) presented his work on immunotherapy of cancer using natural killer (NK) cells, which have innate ability to recognize and eliminate tumor cells, but become suppressed and dysfunctional in solid cancers. In order to overcome immune resistance of such "cold" tumors, Dr. Matosevic's team employs multi-modal engineering strategies to target multiple suppressive pathways. Targeted pathways include metabolic inhibition via purinergic signaling, antigen escape, and checkpoint-induced immunosuppression driven by TIGIT/CD155 to generate allogeneic, off-the-shelf immunotherapies based on iPSC-derived NK cells, are able to tackle complex mechanisms of treatment resistance in cancer. He discussed the functional gains of such NK cells with reprogrammed TIGIT-CD155 axis and CD73, and pharmacological approaches aimed at improving infiltration of NK cells into tumors via chemokines CXCL10 and CCL5.

Michael Nemeth (RPCCC, Buffalo, NY, USA) discussed new immunotherapeutic opportunities resulting from metabolic reprogramming of the TME. He focused on myeloid-derived suppressor cell (MDSC) as a barrier to effective treatment of metastatic TNBC. During infections, MDSCs constitute a small and transient population which resets the immune system after pathogen elimination. However, in cancer, MDSCs expand their numbers and become persistent, resulting in the suppression of anti-cancer immune responses. Dr. Nemeth's lab developed a new strategy to target the MDSCs by re-purposing a compound called brequinar (BRQ) that is currently being tested in clinical trials of acute myeloid leukemia (or AML). The combination of BRQ and an immune checkpoint inhibitor (ICI) agent, anti-PD-1, suppressed tumor growth in mouse models of TNBC. BRQ is currently being tested in patients with AML, and Dr. Nemeth is seeking new collaborations to translate his latest research in TNBC patients.

Waldemar Priebe (University of Texas MD Anderson Cancer Center [MD Anderson]; Houston, TX, USA) discussed Annamycin (ANN), a novel topoisomerase II poison and analog of doxorubicin (DOX) formulated in liposomes (L-ANN). He presented data on increased penetration and accumulation of ANN in lungs and liver, which was correlated with high antitumor activity against primary and metastatic cancers. He highlighted needs for international collaborative research to advance clinical evaluation of ANN and develop new drugs.

Kęstutis Sužiedėlis (NCI, Lithuania and Vilnius University; Vilnius, Lithuania) presented ongoing projects aiming to develop more efficient cancer radiotherapy in the Laboratory of Molecular Oncology at NCI, Lithuania. His research exploits synthetic lethality to achieve this goal.

OPPORTUNITIES FOR COLABORATIONS TO REDUCE HEALTH DISPARITIES AND ENHANCING PATIENT EXPERIENCE AND QUALITY OF LIFE

Mihaela Balu (University of California; Irvine, CA, USA) discussed latest developments in non-invasive skin cancer imaging using in vivo multiphoton microscopy. Current screening for early detection of melanoma relies on the assessment of macroscopic morphological changes in lesions by a highly experienced board-certified dermatologist. These low-cost screening tools often miss microscopic morphological and functional changes that occur early in melanomagenesis, which are not detectable by these devices or the naked eye. High-resolution screening devices are essential for accurately identifying early evolving lesions and enhancing the melanoma diagnosis beyond the capabilities of expert dermatologists. Multiphoton microscopy (MPM) is capable of generating real-time subsurface images of skin with histologic resolution and sensitivity based on endogenous molecular and chemical contrast. Dr. Balu's group has recently developed the fast large area multiphoton exoscope (FLAME), a unique imaging platform optimized for efficient clinical skin imaging. FLAME rapidly generates macroscopic images (mm to cm-scale) with microscopic resolution (0.5μm) using label-free molecular contrast (fluorescence intensity and lifetime), allowing for the selective detection of melanin, imaging pigment-rich cells such as melanocytes and melanophages with high specificity, while time-resolved NADH fluorescence detection reports on the protein binding activity and metabolic heterogeneity within immune cells present in lesions. The presentation highlighted recent preliminary results of an ongoing clinical study aimed at evaluating the potential of MPM imaging to enhance early melanoma detection by using the newly developed FLAME device. While the current efforts focus on enhancing the accuracy of early melanoma diagnosis, the validated optical biomarkers may also help to better understand melanoma origin, monitor its progression and therapy response and assess other skin conditions.

Jonathan Bramson (McMaster University; Hamilton, ON, Canada) provided update on the development of allogeneic T cell therapies with increased patient accessibility. The existing engineering methods to enhance the ability of cancer patients' white blood cells to attack tumors are highly effective, but also very expensive due

to the need to perform genetic engineering on each patient's own blood cells. To address this problem, Dr. Bramson's group has been developing methods to create universal white blood cell therapies from healthy donors that can be implanted into cancer patients for treatment. Their successful clinical translation may lead to universal white blood cell therapies to overcome the high costs of manufacturing on a patient-by-patient basis and make these therapies available to resource-poor jurisdictions that lack the infrastructure to manufacture personalized cells from the cancer patients themselves.

Brian Czerniecki (Moffitt Cancer Center & Research Institute; Tampa, FL, USA) discussed the emerging alternatives to anti-estrogen therapy for breast cancer prevention in high-risp groups. The currently approved prevention strategies for breast cancer are anti-estrogens, either estrogen blockers (aromatase inhibitors) or estrogen antagonists, such as tamoxifen. They have 33-50% efficacy in reducing the risk of breast cancer, but their side effects reduce their appeal to most women, limiting the prevention role. To develop an alternative immunotherapy approach, Dr. Czeriecki's goup demonstrated that intratumoral delivery of type I polarized dendritic cells (cDC1) pulsed with oncodriver derived Her2 peptides can eliminate the progression of ductal carcinoma in situ (DCIS) to mammary carcinoma, in a mechanism involving CD4 Th cells, gamma delta T cells (γδ T cells) and natural killer T cells (NKT). They have also shown that the prevention or treatment effects can be enhanced by co-administration of DCs pulsed with glycolipid alpha-galactosyl-ceramide (a-gal-cer; an NKT cell activator) and antibody against HER2. These results provide new low-toxicity tools to prevent the development of breast cancer in both pre- and post-menopausal women, resulting in need for multi-center clinical trials.

Kaushal Nanavati (SUNY-UMU; Syracuse, NY, USA) discusses the potential of integrating wellness and integrative medicine into oncology care, expanding the survivorship paradigm. He discussed the role of nutrition and evidence-based guidelines from the American Institute for Cancer Research (AICR), advocating for a diet rich in plant-based foods in supporting overall health and potentially reducing cancer recurrence. Physical exercise, another cornerstone of the presentation, was discussed in the context of the American College of Sports Medicine (ACSM). Stress management is a critical component of integrative care, and the mindfulness-based techniques showed promise in the research from the National Center for Complementary and Integrative Health (NCCIH). Spiritual wellness, often overlooked in traditional oncology care, was also discussed with reference to studies that highlight its strongimpact on mental and emotional health.

Ekaterina (Katia) Noyes (University at Buffalo; Buffalo, NY, USA) disussed the benefits of using new data science methodologies for cancer prognostication and outcomes research. While cancer treatment plans and prognoses have been traditionally predicted by tumor characteristics at diagnosis, Dr. Noyes and her team incorporate the effect of socioeconomic and environmental factors (i.e., literacy, education, employment, environment, access to treatment, obesity and weight loss etc.) on survival, recurrence and probability of developing metastases. They postulated that cancer patients' survival and metastasis risk are affected by their residential area deprivation index (ADI) and access to an NCI-designated cancer center and a a board-certified surgeon, after controlling for patient comorbidities and tumor characteristics.

Ioana-Miruna Stanciu (Carol Davila University of Medicine and Pharmacy and Elias University Emergency Hospital; Bucharest, Romania) discussed the challenges of managing immune-related adverse events (irAEs) in patients treated with immune checkpoint inhibitors (ICIs). She evaluated the incidence of irAEs in ICI-treated patients at the Oncology Clinic of Elias University Emergency Hospital, Bucharest, Romania, from 2018 to 2024. While ICIs represent one of the most significant advances in cancer care, their substantial toxicity profile must be acknowledged. Since no randomized clinical trials have established a standard of care for irAE management, balancing the clinical management of toxicity with maintaining anti-tumor immunity remains challenging. The presentation outlined the incidence and types of irAEs encountered at Elias Hospital—one of the largest oncology clinics in Romania—over the seven-year period. It focused on the clinical management of difficult cases, such as neurological irAEs, which require patient-tailored decisions and, at times, external expertise. The discussion highlighted the need for cross-border communication and collaboration in managing irAEs, particularly for challenging cases. Dr. Stanciu emphasized the importance of creating international expert networks to facilitate real-time communication and guidance for effective patient management.

Telisa Stewart and Elizabeth Luke (SUNY-UMU; Syracuse, NY, USA) presented a community-driven approach to boost human papillomavirus (HPV) vaccination rates in NYS. The HPV vaccine is highly effective, yet barriers to widespread vaccination persist, particularly in rural NYS. The disussed aims of the project were to a) cultivate partnerships to foster collaborative efforts to increase HPV vaccination uptake; b) investigate cultural factors influencing HPV vaccination behavior in Lewis County, NY; and c) implement evidence-based strategies, co-created by community members and

academics, to enhance HPV vaccination uptake. Dr. Stewart emphasized the importance of collaborative efforts between academia and communities to address health disparities and improve cancer prevention efforts. Since many CEEC countries share similar problems, the discussion emphasized the need to disseminate knowledge on vaccine implementation efforts ans strategies to increase the vaccination rates, especially in rual communities.

EDUCATION AND INTERNATIONAL TRAINING

Khurshid Guru (RPCCC; Buffalo, NY, USA) presented the efforts of RPCCC Urology in global education, especially in surgical training. Over last two decades Dr. Guru's team has partnered with teams across the world, traveling to them and hosting them at RPCCC. They have performed live surgeries in over 15 countries, to further new surgical techniques. They have fhosted students, scientists, and faculty during visits to observe ongoing work and learn from each other. Dr. Guru discussed the most effective processes and ways to avoid failures.

Iwona Ługowska (MSCNRIO; Warsaw, Poland) discussed the role of comprehensive medical education in assuring optimal cancer care. With cancer rates rising worldwide, there is an urgent need to prepare the next generation of oncologists to meet the demands of increasingly complex patient care. This necessitates comprehensive multi-disciplinary approach as the centerpiece of training programs and involvement of cross-sector collaborations, experiential learning opportunities, leadership development, effective patient communication and ethical decision-making. Dr. Lugowska stressed the mportace of the integration of these components into oncology curricula, highlighting the benefits of a more holistic educational model to ensure that future oncologists are equipped both with the latest scientific knowledge and with the skills necessary to provide compassionate, patient-centered care.

Mukund Seshadri (RPCCC; Buffalo, NY, USA) highlighted the unique postion of RPCCC as a free-standing Comprehensive Cancer Center with one central mission: to understand, prevent and cure cancer. Consistent with this mission, RPCCC's education and training programs are focused on developing the next generation of cancer research professionals. Dr. Sheshadri presented RPCCC's comprehensive educational and training portfolio that includes immersive cancer research experiences for K-12 students, a long-standing (of more than 65 year old) summer internship program for high school, college and medical students, new nurse residency and nursing scholars program, graduate programs in the Cancer Sciences, postdoctoral training, and oncology-focused residency and fellowship programs.

Edita Sužiedėlienė (Vilnius University; Vilnius, Lithuania) discussed the training and development of early career researchers in Medical and Life Sciences at Vilnius University. Early career researchers (ECRs) are a vital part of academic community of Vilnius University (VU). Established in 1579, VU is the oldest and largest academic institution in Lithuania, conducting research in over 30 research fields. VU participation in the European Universities Alliances network offers shared resources (mentoring and careers outside academia programmes , innovative mobility initiatives) to support ECRs. In recent years, specific focus is given on developing skills to conduct interdisciplinary research and to work in interdisciplinary research teams. Towards this goal, the internal funding scheme for interdisciplinary research projects, which are proposed, led and conducted solely by inter-faculty ECRs teams, have been established at VU. Dr. Sužiedėlienė disussed the institutional experience, challenges and future directions in ECRs training and development.

Wei-Zen Wei (Karmanos Cancer Institute and Wayne State University; Detroit, MI, USA), the current President of the Translational Research Consortium of Cancer Centers (TRCCC)[27], highlighted the role of TRCCC in supporting the development of future leaders in cancer immuno-prevention, interception and therapy. Initiated in 1998, TRCCC is a 501(c)3 organization consisting of 13 Cancer Research Institutions in the Great Lakes area, including Case Comprehensive Cancer Center (Cleveland, OH, USA), Karmanos Cancer Institute (Detroit, MI, USA), McMaster University (Hamilton, ON, Canada), The Ohio State University Comprehensive Cancer Center- The James (Columbus, OH, USA), Penn Medicine's Abramson Cancer Center (Philadelphia, PA, USA), Penn State Cancer Institute (Hersehy, PA, USA), RPCCC (Buffalo, NY, USA), Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (Baltimore, MD, USA), University of Michigan Rogel Cancer Center (Ann Arbor, MI, USA), University of Virginia Comprehensive Cancer Center (Charlottsville, VA, USA), University of Pittsburgh Medical Center Hillman Cancer Center (Pittsburgh, PA, USA), University of Rochester Medicine Wilmot Cancer Institute (Rochester, NY, USA), and West Virginia University Cancer Institute Mary Babb Randolph Cance Center (Morgantown, WV, USA). TRCCC mentors and trainees come together annually to share information, plan collaboration, and review clinical trials to improve the outcome of individuals diagnosed with, or at risk of developing cancer (). Many clinical/scientific leaders emerged from this stimulating and nurturing environment including cancer center directors, departmental

chairs, program leaders, industry founders and more.

The annual meetings of TRCCC is the centerpiece of TRCCC activities. Many ground breaking new findings such as CAR-T cell clinical success were first reported in this event. The responsibility of hosting the annual meeting is rotated among member institutions, helping to introduce different approaches to aspiring scientists. Beyond plenary lectures and faculty discussion forum, every abstract submission is rewarded with the opportunity to give both an oral and a poster presentation. Trainees present their findings in 5 min talks and discuss the details in their posters. In the 2024 meeting, over 350 participants attended 150 presentations. The comprehensive meeting programs are designed to better prepare the trainees for the tasks ahead. Trainees connect with and learn from patient advocates who have experienced cancer and are assisting others inflicted by cancer. Trainees learn the basics in securing financial support for their projects. Representatives from the US NCI provide program and financial information, guiding trainees through the process of grant applications. Different career paths are explained. TRCCC alumni who enter the pharmaceutical or biotech industry, or start their own company share their perspectives. Trainees often give back after becoming faculty or moving to industry by taking on TRCCC service duties.

Member Institutions take advantage of the annual event by holding training program retreats or joint grant and trial discussions on site. Dr. Wei further discussed the role of the stress management in trainees' physical and mental well-being and their family relationships. This goal is facilitated by many attendees bringing their families to the annual event. A wealth of indoor and outdoor activities keep the young happy while mom and/or dad attend the meeting. The intense interactions are boosted by shared meals, coffee break and allotted time for personal activities. The registration fees are kept modest to ensure the event is affordable to all, thanks to support from the participating Cancer Centers and Industry Sponsors. The relevance of the TRCCC model to promoting oncology training and research collaborations in CEE Countries was discussed.

REDUCING CANCER BURDEN IN CEECS: NATIONAL AND INTERNATIONAL EXPERIENCE

Ioana Berindan-Neagoe (Iuliu Haţieganu University of Medicine and Pharmacy; Cluj-Napoca, Romania) discussed her experience in promoting collaborations between Central and Eastern European Countries and the US on the role of noncoding RNA (ncRNA) in cancer. The discovery of ncRNAs opened up new horizons in cancer biology, offering promising avenues for diagnosis, prognosis, and therapy. Cancer-specific ncRNAs circulating in blood represents a particularly hopeful diagnostic approach. Once considered "junk" DNA, ncRNAs have now been recognized for their crucial roles in gene regulation and expression, regulating cellular differentiation, proliferation and apoptosis. Their dysregulation has been linked to the development and progression of many cancers, making them promising biomarkers and therapeutic targets. Dr. Berindan-Neagoe presented a success story of collaborations between cancer researchers, healthcare professionals, and pharmaceutical companies from CEE countries and which have already shown significant progress in noncoding RNA testing and healthcare improvements. The project presents a multidisciplinary, translational research in oncology, involving and combining expertise in oncology, molecular genetics, bioinformatics, biotechnology and technology transfer and commercialization. She highlighted the dependence of effective collaborations on allocation of funds and joint applications for international grants, including a Marie Curie grant to develop and consolidate iinternational research networks.

Andriy Beznosenko (NCI, Ukraine; Kyiv, Ukraine) presented unique experience of Ukraine in navigating cancer care in wartime. Since February 24th, 2022, when the Russian invasion started, cancer care was particularly affected due to the complexity of cancer treatments, long-term and continuous treatments involving combined approaches of surgery, radiation and chemotherapy involving multiple groups of drugs. NCI, Ukraine in Kyiv, the main center of anti-cancer control and treatment in the country, had to adapt to the challenges of the war. The day the full-scale invasion started, there were 450 inpatients, including 40 children, and 96 personnel on the night shift. Rapid evacuation to Poland started for all children via Ukrainian railways. Adult patients were discharged from clinic when it was possible. Cancer care needed to adapt to personel shortages, difficulties reaching the clinic, and mobilization of personnel to Armed Forces or territorial defense. Frequent moves of patients to shelters further complicated the work process but were necessary for their safety. The units of the hospital were temporarily reformed and the clinic started to provide specialized care for the wounded. All the departments, were reopened in the summer of 2022, 90% of the staff had returned. Currently, the key metricks are approaching the pre-war levels. In 2023, the number of patients treated increased compared to the pre-war levels, due to internally displaced patients (29 022 in 2021, 21 169 in 2022 and 38 671 in 2023). Hospital mortality decreased compared to 2022 but, basically, returned to the level of 2021.

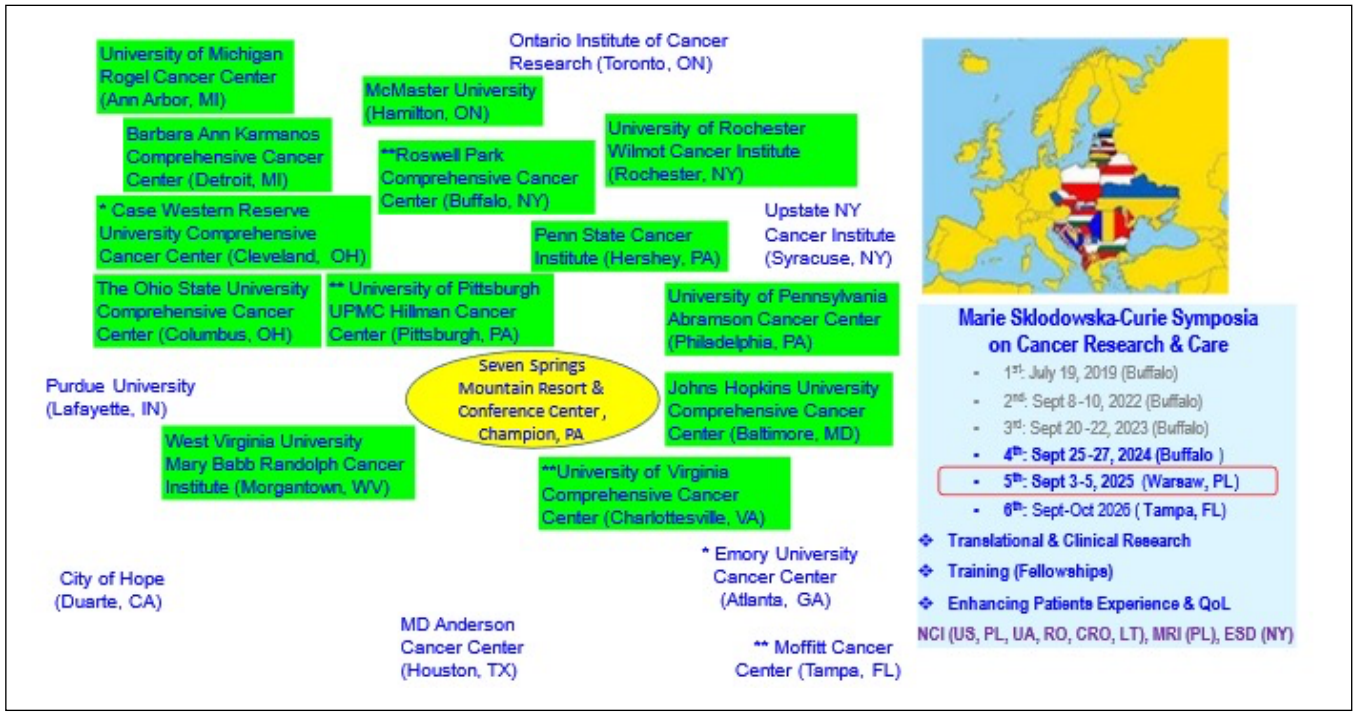

Fig. 3. Translational Research Consortium of Cancer Centers: A Model for Regional Collaborations within CEE? Current academic members of the TRCCC (Green Boxes) and affiliate cancer centers involved in MSCS-CRC.

** Cancer centers currently involved in academic multi-institutional clinical trials of cell therapies within TRCCC.

* Cancer centers with planned in academic clinical trials of cell therapies within TRCCC (existing regulatory, legal, fiscal and logistic arrangements to conduct such collaborative trials).

Philip Castle (NCI, USA; Bethesda, MD, USA) representing the DCP[28], made a convincing case for cancer prevention, stressing the particularly high societal burden of cancer. Betweeen 2020-21 when 6 million people died of COVID-19, approximately 20 million people died of cancer. 30-50% of current cancers and cancer-related deaths are already preventable and new technologies may increase the fraction of preventable cancers even further. The DCP leads, supports, and promotes research and training to reduce risks, burden and consequences of cancer. DCP supports basic and early translational research in the areas of preventive agents, biomarkers for screening and early detection, and symptom management. Through its funding programs[29], DCP supports the discovery, preclinical development and validation of novel primary prevention (prophylaxis), secondary prevention (interception) and mitigation methods. DCP also supports novel approaches and technologies to increase access to current life-saving prevention and control interventions and reduce their risks, in order to increase the uptake.

*Rūta Everatt (*National Cancer Institute, Lithuania; Vilnius, Lithuania) discussed the emerging targets and opportunities for collaboration in the development of more efficient cancer prevention and screening methods, focusing on cancer prevention and screening effectiveness studies carried out at the NCI, Lithuania, and at other research institutions. In 2022, Lithuanian men had the highest incidence in Europe and the third highest mortality rates for all cancers combined[30]. Mortality is particularly high for oesophageal, kidney, gastric, pancreatic, prostate and larynx cancers (1st to 4th highest). Lithuania ranks among the five European countries with the highest mortality in women for kidney, cervical, ovarian and stomach cancers and melanoma. The cancer prevention research at the NCI, Lithuania covers cancer incidence, mortality, survival analyses and the role of risk factors. Preventing cancer by modifying risk factors is the most cost-effective strategy; taking into account high rates of smoking (29.9% in men, 9.7% in women), alcohol consumption (11.9 l pure alcohol/capita) and obesity (55%) in Lithuania. Secondary prevention, i.e. cancer screening and earlier diagnosis, is the second area of efforts. Screening for breast, prostate, cervical and colon cancer has been implemented in Lithuania, but cervical and prostate cancer death rates remain to be the fourth highest in Europe. The evaluation of the effectiveness of screening programmes demonstrated that participation in screening has been effective in reducing cervical cancer deaths (and might have contributed to a moderate decline in prostate cancer mortality in men younger than 65 years of age)[31-36], providing rationale for greater efforts in this area. The NCI of Lithuania is one of the 25 consortium

institutions in the EU4Health funded PRAISE-U project, aimed to improve screening of prostate cancer[37]. The Lithuanian University of Health Sciences is a partner of the EU4Health project TOGAS ("Towards gastric cancer screening implementation in the European Union"). High lung cancer rates and a national screening programme starting in 2025 may offer possibilities to enhance lung cancer screening addressed in the EU4Health project SOLACE. Specific opportunities for collaborations include: a) improving participation in existing cancer screening programmes, by better access to screening (self-sampling, home-based testing, CT screening trucks, etc.); b) optimizing risk-stratified cancer screening and improving the quality of screening programmes; c) cancer screening combined with preventive interventions, e.g. smoking cessation, early detection of co-morbidities; and d) population-based screening studies for aditional cancer types.

Iva Kirac (University Hospital for Tumors; Zagreb, Croatia) discussed the role of the EU Projects in reducing the disparities in cancer care across the EU. Croatia has one of the highest cancer mortalities in the EU and an active participant in several major EU projects, including the Beacon cancer care, Comprehensive Cancer Infrastructure for the European Union (CCI4EU) and Europe on Quality of Life (EUonQoL). The Cancer Care Beacon project is funded by the EU4Health program of the EU with the aim to examine inequalities in diagnosis, treatment and palliative care. The project helps the patients choose the care providers, and helps data dissemination among providers, researchers and policymakers. CCI4EU is a Horizon 2020 project aiming to increase the availability and quality of research in all aspects of cancer care. EUonQoL is a Horizon 2020 project that compiles the existing questionnaires on quality of life and tests them on patients in treatment, survivors, and end-of-life care.

Pawel Koczkodaj (MSCNRIO; Warsaw, Poland) highlighted the ongoping efforts in cancer prevention in Poland, marked by significant policy initiatives and legislative measures. The introduction of the National Oncology Strategy for the years 2020-2030 was a pivotal moment, encompassing a wide array of actions aimed at reducing population exposure to modifiable carcinogenic factors and increasing participation in screening programs. This strategy has been further supported by the European Commission's launch of Europe's Beating Cancer Plan in 2021. Key achievements include the implementation of stringent regulations to limit tobacco consumption, such as bans on smoking in public places, menthol- and opther flavored cigarettes, along with increased excise taxes. Additionally, the introduction of a sugar tax, a nationwide ban on the use of tanning beds by individuals under 18, and the establishment of a free national HPV vaccination program, have significantly contributed to reducing cancer risk factors. The upcoming introduction of health education in schools is expected to further reinforce these preventive measures. Despite these positive developments, Polish population continues to exhibit high levels of exposure to the "big three" modifiable risk factors: tobacco smoke, obesity, and alcohol consumption. According to the OECD report "State of Health in the EU. Poland – Health System Profile 2023," 44% of all deaths in Poland in 2019 were attributable to behavioral risk factors, surpassing the EU average of 39%. Additionally, new health threats such as heated tobacco products and e-cigarettes have emerged. According to the latest Global Youth Tobacco Survey (GYTS 2022) conducted by Cancer Epidemiology and Primary Prevention Department in cooperation with World Health Organization (WHO), 9.7% of boys and 10.4% of girls aged 13-15 are current users of heated tobacco products, while 21.2% of boys and 23.4% of girls use electronic cigarettes. For comparison, in the same age group, traditional cigarettes were used by 11.2% of boys and 12.3% of girls. These statistics highlight the need for sustained and enhanced efforts in public health interventions targeting lifestyle and behavioral changes.

CANCER PREVENTION AND EARLY DETECTION

Philip Castle (NCI, USA; Bethesda, MD, USA) highlighted the opportunities and challenges for global control of cervical cancer. Prophylactic human papillomavirus (HPV) vaccination is highly effective in preventing invasive cervical cancer, especially when given to young women before becoming sexually active. HPV testing has replaced Pap testing as the standard-of-care for cervical cancer screening because of its much greater sensitivity and reliability and it enables the use of self-collected specimens. However, critical gaps remain especially affecting low- and middle-income countries, with a 10-fold greater burden of cervical cancer in the lowest-income countries vs. the highest-income countries. These gaps include: 1) insufficient awarness of condom use as a method of primary prevention of HPV; 2) lack of global procurement strategy to provide affordable vaccination to Global Alliance for Vaccine and Immunization (GAVI)-ineligible lower-income countries; 3) lack of global procurement strategy for in vitro diagnostics; 4) primary and secondary prevention in women living with HIV has not been optimized; 5) lack of sufficiently effective biological therapeutic agent against chronic HPV infection and related abnormalities; 6) limited healthcare infrastructure to provide treatment

of precursors and invasive cervical cancer; and 7) the ability to provide palliative end-of-life care.

Jeffrey E Gershenwald (MD Anderson, Houston, Texas, USA) showcased melanoma as a paradigm for leveraging international collaborations in cancer research and prevention. More than 100,000 individuals in the US and more than 300,000 worldwide are estimated to be diagnosed annually with invasive melanoma[38]. An overaching goal of the MD Anderson Moon Shots Program® melanoma initiative, launched in 2012, is to reduce melanoma incidence and mortality through the development and delivery of personalized treatment options to reduce melanoma mortality and to reduce incidence and ultimately deaths from melanoma through public policy initiatives, education, and early detection. Althougth overexposure to ultraviolet (UV) radiation – from the sun or from indoor tanning devices/solaria – is known to be responsible for >90% of cutaneous melanoma[39], there has been no integrated nationwide US policy to promote UV radiation protection. To date, 22 US states have indoor tanning bed restrictions for minors under 18 years old; there has been a significant reduction in the use of indoor tanning devices by high school students (and adults)[40]. The resulting lessons learned and resources created have fostered collaboration and knowledge exchange with key academic and governmental stakeholders in Poland, including Profs Piotr Rutkowski and Piotr Czauderna, as well as President Duda. This collaboration contributed to the proposal, passage, and implemenation of national legislation that prohibits solaria use for persons <18 years old across Poland nationwide, and in 2020 was recognized by the World Health Organization[41]. Importantly, these efforts fostered subsequent dialog and collaboration with colleagues in Estonia, which recently passed similar legislation that will restrict indoor tanning use by minors under 18 years of age. Additional collaborations in the melanoma arena between the US and Poland include the 8th edition American Joint Committee on Cancer (AJCC) melanoma staging system[42,43], The legacy Cancer Genome Atlas (TCGA) melanoma project[38], and the ongoing US National Cancer Institute's Clinical Proteomic Tumor Analysis Consortium (CPTAC).

Cristian Lungulescu (University of Medicine and Pharmacy Craiova; Craiova, Romania) discussed the unique challenges in incidence and treatment of HPV-related cervical cancer in Romania. While Europe overall has seen a significant decrease in cervical cancer incidence and mortality, Romania continues to register the highest rates in the European Union, followed by Latvia and Bulgaria. The incidence rate in Romania is 32.6 per 100,000 women, and the mortality rate is 16.8 per 100,000 women, which is eight times higher than Finland's rate of 2.2 per 100,000 women. Cervical cancer remains the third most common cancer among women in Romania, with 3,368 new cases in 2022. Many cases are diagnosed at advanced stages, resulting in reduced treatment efficacy. Although the HPV vaccine is effective, the rate of immunization in Romania is still unacceptably low. The national HPV vaccination program was introduced in 2008, targeting girls aged 10 to 11, but faced significant resistance and skepticism. A communication campaign in 2009 yielded modest results, and the program was halted for nearly a decade. It resumed in 2019, targeting girls aged 11-18. As of September 12, 2023, the program has expanded to include free vaccination for boys and girls aged 11 to 19, and 50% vaccine price reduction for women aged 19 to 45. The national cervical cancer screening program, which ran from 2012 to 2017, aimed to screen 6 million women but only reached about 260,000 due to poor promotion, complex procedures, insufficient funding, and limited accessibility, especially in rural areas. The discussion highlighted the need for sharing knowledge between health policy makers, to improve vaccination and boost cancer prevention programs.

Tomasz Zdrojewski (Polish Academy of Sciences and Medical University of Gdańsk; Gdańsk, Poland) contrasted the lessons from prevention of two most common noncommunicable diseases (NCDs): cancer and cardiovascular disease (CVD), which together with chronic respiratory diseases and diabetes are collectively responsible for more than 70% of all deaths worldwide. CVD accounted for the most NCD deaths in 2019 (17.9 million people), followed by cancer (9.3 million), respiratory diseases (4.1 million) and diabetes (1.5 million). Of these deaths, almost 40% are premature (under 70 years of age). Many NCDs can be prevented by reducing the common and modifiable risk factors, e.g. tobacco use, harmful alcohol use, lack of physical activity and unhealthy diet. The potential for NCD prevention is high since an estimated 80% of them are preventable (e.g. elimation of tobacco exposure would prevent nearly 1/4 of cancer deaths and 1/5 of CVD deaths), highlighting the need to identify the most cost-effective interventions. The high-risk individual-level screening projects for lung cancer using low-dose computed tomography (LDCT) carried out in Poland in the last decade (as part of the Pomeranian Lung Cancer Screening Program (PLCSP) are good examples of the beneficial cooperation between oncologists, cardiologists and pulmonologists. The LDCT screening for lung cancer among 50-80 year olds with a 20-pack-year smoking history who currently smoke (or have quit within the past 15 years) was extended to detect hypertension, chronic coronary artery disease, hypercholesterolemia, prediabetes and

diabetes, chronic obstructive pulmonary disease, atrial fibrillation and early stages of heart failure. Such interdisciplinary collaborations significantly increase the medical and economic effects of this program.

SMOKING CESSATION, TOBACCO PRODUCTS AND HEALTH

Indu B. Ahluwalia (Centers for Disease Control and Prevention; Atlanta, GA, USA) represented the Office on Smoking and Health, Global Tobacco Branch [44] at MSCS-CRC-2024. She highlighted the importance of tobacco cessation services. CDC's Office on Smoking and Health (OSH) is the lead federal agency for tobacco control and prevention, working to end tobacco use domestically and globally. The U.S. Department of Health and Human Services Framework to Support and Accelerate Smoking Cessation focuses on reducing tobacco use, increasing knowledge, strengthening and sustaining cessation services, increasing access to and coverage of cessation treatment, advancing and sustaining surveillance and strengthening evaluation, and promoting research. Globally, Article 14 of the WHO Framework Convention on Tobacco Control (WHO FCTC) encourages countries to implement effective "measures to promote cessation of tobacco use and adequate treatment for tobacco dependence." Quitting smoking is beneficial at any age and reduces the risk of premature death, including from many forms of cancer. Dr. Ahluwalia, the branch chief for OSH's Global Tobacco Control, discussed the tobacco use trends globally and domestically, outlining the need for expanded cessation services around the world, especially in communities disproportionately impacted by tobacco products.

Łukasz Balwicki (Medical University of Gdańsk, Gdańsk, Poland) presented the results of the NIKO Study, the collaborative project of the MRA on New Nicotine Products in Poland. Poland has experienced rapid growth of popularity of electronic cigarettes among youth with emerging data showing a growing use of heated tobacco products and e-cigarettes also among adults. Recently, traditional cigarettes sales also started to grow, prompting the interest of the Ministry of Health Agency and MRA to to better understand the growing popularity of emerging nicotine products. The NIKO study involves researchers from Medical University of Gdańsk, Medical University of Łódź, Poznań University of Medical Sciences in collaboration with RPCCC to learn from experience gained during realization of PATH study (Population Assessment of Tobacco and Health), to assist tobacco control decisions in Poland.

Maciej Goniewicz (RPCCC, Buffalo, NY, USA) presented his pioneering decades-long lab- and population science research on the opportunities for cancer risk reducing using alternative tobacco products. Although the best way to avoid the cancer risks associated with smoking is to quit smoking altogether, an alternative strategy to reduce smoking-related mortality and morbidity may be the substitution of less toxic means of delivering nicotine. The concept proceeds from the principle that the combustible tobacco cigarette smoking involves a wide array of carcinogens generated by the combustion of the tobacco. Alternative nicotine delivery systems, like electronic cigarettes (e-cigarettes) and Heated Tobacco Products (HTPs), represent a new stage in which nicotine is delivered in a method that simulates smoking but without involving a tobacco combustion process. Due to relatively short existence of alternative nicotine delivery products, data on the long-term health effects, including cancer risk, of e cigarette and HTPs use are not currently available. Evidence from *in vitro* and *in vivo* laboratory studies, observational human studies, and short-term clinical trials may provide important information on the potential harms of alternative nicotine delivery systems. Current findings provide preliminary evidence that e-cigarettes may be less harmful than conventional tobacco cigarettes. Claims of lowered risk or health benefits of HTPs compared to conventional cigarettes are based almost exclusively on industry-funded research, and evidence from independent studies is needed.

Christine Sheffer (RPCCC, Buffalo NY) presented recent developments and current opportunities for international collaboration and innovation in reducing the prevalence of cigarette smoking. While telephone Quitlines have demonstrated unprecidented reach into the tobacco using population, by all accouts they remain underutilized[45]. Quitline utilization has, in fact, decreased significantly over the past 10 years, and many populations remain underserved. Shifts in communication preferences, digital reach, treatment and training adaptations, and tobacco product use provide new opportunities to develop collaborative, innovative approaches to increase the reach of tobacco and nicotine use treatment services across national boundaries[46]. Dr. Sheffer discussed severalopportunities to collaborate including increasing the number of Tobacco Treatment Specialist training programs[47-49], and developing pre-programmed text-based mobile applications.

REDUCING BARRIERS TO INTERNATIONAL TRAINING

The New Investigator Awards Session included four presentations from international trainees, all having first hand experience with the related opportiunities and bar-

riers to international training and research collaboration. *Brygida Baran* (4Cell Therapies S.A; Warsaw, Poland) discussed new approaches to CAR T cell therapy and lessons from hematologic malignancies (such as multiple myeloma, MM) that can be applicable to solid tumors,. Clinical trials of anti-BCMA CAR T-cell therapy have demonstrated remarkable success, achieving response rates of up to 90% in refractory MM cases. Despite this success, accessibility remains limited in Europe. While two BCMA-targeted products have received FDA (idecabtagene vicleucel) and EMA (ciltacabtagene autoleucel) approvalthe unmet demand persists due to medical and economic factors. 4 Cell Therapies-developed humanized anti-BCMA CAR T-cell therapies for MM and for pancreatic ductal adenocarcinoma (PDAC), targeting the carcinoembryonic antigen-related cell adhesion molecule (CEACAM). *Blanka Borowiec (*Poznań University of Medical Sciences; Poznań, Poland) discussed her experience in translating the experience from the Loyola University in T cell-based gene therapies to cliniocal trials in Poland. Her month-long training at Loyola University in the laboratory of Dr. Michael Nishimura involved the protocols and regulations governing clean room environments and independently performing the entire cell transduction process to generate CAR-T cells. *Szabolcs Bozsányi* (RPCCC; Buffalo, NY, USA) discussed his postdoctoral experience at RPCCC in developing new tools for elimination of UV-induced skin tumors, using non-thermal atmospheric pressure plasma (NTAPP). *Maciej Luba (*MSCNRIO; Warsaw, Poland) discusssed his work on predictive markers for relapse in clear cell renal cell carcinoma (ccRCC) and the relative (and cummulative) values of pan immune-inflammation value (PIV) and the assessment of the tumor infiltrating limphocytes (TILs) in accurate predictions of the tumor progression. The vigorous discussion of the experiences from both continents focused on the challenges in advancing early investigators' careers and the value of international training in moving towards independent faculty positions in Europe.

MSCS-CRC 2025: INNOVATING TOGETHER TO CONQUER CANCER GLOBALLY

The final comments of the MSCS-CRC-2024 were provided by *Iwona Ługowska*; *Michał Mikula,* and *Piotr Rutkowski* from MSCNRIO in Warsaw Poland, who will host the 5th Edition of the Marie Skłodowska-Curie Symposium on Cancer Research and Care on September 3-5, 2025. The focus areas of the 5th Symposium will focus on:

- Artificial Intelligence in Oncology: Leveraging AI for early cancer detection, personalized treatment plans, and improving patient outcomes.
- Global Health Initiatives: Strategies for reducing global cancer disparities and improving access to care in underserved populations.
- Immunotherapy and Precision Medicine: Recent advances and clinical trials aimed at developing targeted cancer therapies.
- Innovative Public Health Policies: Developing and implementing new health policies to support cancer prevention and control.
- Collaborations between Academia and Biotech: Eliminating barriers to effective collaboration in the development and testing of new cancer treatments.

Abstract submission will open in March 2025 and will be accepted until the end of May 2025, with selections announced in June 2025.

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REFERENCES

1. JLABS @ NYC: Johnson & Johnson's New Innovation Hub Opens in New York (2025). https://www.jnj.com/innovation/jlabs-nyc-johnson-johnson-innovation-hub-comes-to-new-york-city. [date accessed: 1/29/2025].
2. PAR-25-104: Cancer Prevention and Control Clinical Trials Planning Grant Program (2025). https://grants.nih.gov/grants/guide/pa-files/PAR-25-104.html. [date accessed: 1/29/2025].
3. - IndieBio – #1 in Early Stage Biotech (2025). https://indiebio.co/program/. [date accessed: 1/29/2025].
4. RFA-OD-001: High-Priority Research in Tobacco Regulatory Science (2025). https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-25-001.html. [date accessed: 1/29/2025].
5. New York State Biodefense Commercialization Fund | Empire State Development (2025). https://esd.ny.gov/biodefensefund. [date accessed: 1/29/2025].
6. PAR-25-139: NCI Clinical and Translational Exploratory/Developmental Studies (2025). https://grants.nih.gov/grants/guide/pa-files/PAR-25-139.html. [date accessed: 1/19/2025].
7. PAR-22-243: Bioengineering Research Grants (2025). https://grants.nih.gov/grants/guide/pa-files/PAR-22-243.html. [date accessed: 1/29/2025

8. Kalinski P, et al. Meeting Highlights: The Third Marie Sklodowska-Curie Symposium on Cancer Research and Care at Roswell Park Comprehensive Cancer Center, Buffalo, Ny, September 20-22, 2023. Wiad Lek. 2023;76:2543-2555.
9. New York Tax-Based Incentives | Empire State Development (2025). https://esd.ny.gov/tax-based-incentives. [date accessed: 1/15/2025].
10. Biotech and Life Sciences | Empire State Development (2025). https://esd.ny.gov/industries/biotech-and-life-sciences. [date accessed: 1/15/2025].
11. Innovation Development Support | Empire State Development (2025). https://esd.ny.gov/innovation-development-support. [date accessed: 1/15/2025].
12. Growth Support in New York | Empire State Development (2025). https://esd.ny.gov/growth-support. [date accessed: 1/15/2025].
13. Operational Support Programs | Empire State Development (2025). https://esd.ny.gov/operational-support. [date accessed: 1/15/2025].
14. Muthuswamy R, et al. NF-kappaB hyperactivation in tumor tissues allows tumor-selective reprogramming of the chemokine microenvironment to enhance the recruitment of cytolytic T effector cells. Cancer Res. 2012;72:3735-3743.
15. Muthuswamy R, Corman JM, Dahl K, Chatta GS, Kalinski P. Functional reprogramming of human prostate cancer to promote local attraction of effector CD8(+) T cells. Prostate. 2016;76:1095-1105.
16. Muthuswamy R, Wang L, Pitteroff J, Gingrich JR, Kalinski P. Combination of IFNalpha and poly-I:C reprograms bladder cancer microenvironment for enhanced CTL attraction. J Immunother Cancer. 2015;3:6.
17. Theodoraki MN, et al. Helicase-Driven Activation of NFkappaB-COX2 Pathway Mediates the Immunosuppressive Component of dsRNA-Driven Inflammation in the Human Tumor Microenvironment. Cancer Res. 2018;78:4292-4302.
18. Wong JL, Obermajer N, Odunsi K, Edwards RP, Kalinski P. Synergistic COX2 Induction by IFNgamma and TNFalpha Self-Limits Type-1 Immunity in the Human Tumor Microenvironment. Cancer Immunol Res. 2016;4:303-311.
19. Kokolus KM, Obermajer N, Kalinski P. Quantitative evaluation of tumor-specific T cells in tumors and lymphoid tissues. Methods Enzymol. 2020;635:149-166.
20. Obermajer N, et al. Promoting the accumulation of tumor-specific T cells in tumor tissues by dendritic cell vaccines and chemokine-modulating agents. Nat Protoc. 2018;13:335-357.
21. Gandhi S, et al. Systemic infusion of TLR3-ligand and IFN-alpha in patients with breast cancer reprograms local tumor microenvironments for selective CTL influx. J Immunother Cancer. 2023,11.
22. Gandhi S, et al. Systemic chemokine-modulatory regimen combined with neoadjuvant chemotherapy in patients with triple-negative breast cancer. J Immunother Cancer. 2024,12.
23. Orr B, et al. Phase I Trial Combining Chemokine-Targeting with Loco-Regional Chemoimmunotherapy for Recurrent, Platinum-Sensitive Ovarian Cancer Shows Induction of CXCR3 Ligands and Markers of Type 1 Immunity. Clin Cancer Res. 2022;28:2038-2049.
24. Medical Research Agency (2025). https://abm.gov.pl/en/. [date accessed: 1/15/2025].
25. Home ClinicalTrials.gov (2025). https://clinicaltrials.gov/. [date accessed: 1/15/2025].
26. ABM (2025). https://konkurs.abm.gov.pl/. date accessed: [1/15/2025].
27. TRCCC | Collaborative Immunotherapy Research (2025). https://www.trccc.org. [date accessed: 1/15/2025].
28. About DCP | Division of Cancer Prevention (2025). https://prevention.cancer.gov/about-dcp. [date accessed: 1/15/2025].
29. Funding Opportunities | Divsion of Cancer Prevention (2025). https://prevention.cancer.gov/funding-and-grants/funding-opportunities. [date accessed: 1/15/2025].
30. Ferlay J EM, Lam F, et al. (2024). Global Cancer Observatory: Cancer Today (version 1.1). Lyon, France: International Agency for Research on Cancer.
31. Gondos A, Krilaviciute A, Smailyte G, Ulys A, Brenner H. Cancer surveillance using registry data: Results and recommendations for the Lithuanian national prostate cancer early detection programme. Eur J Cancer. 2015;51:1630-1637.
32. Patasius A, Smailyte G. All-Cause Mortality Risk in National Prostate Cancer Cohort: An Impact of Population-Based Prostate Cancer Screening. J Clin Med. 2021, 10.
33. Patasius A, Krilaviciute A, Smailyte G. Prostate Cancer Screening with PSA: Ten Years' Experience of Population Based Early Prostate Cancer Detection Programme in Lithuania. J Clin Med. 2020,9.
34. Everatt, R. & Gudaviciene, D. An analysis of time trends in breast and prostate cancer mortality rates in Lithuania, 1986-2020. BMC Public Health. 2022;22:1812.
35. Everatt R, Kuzmickiene I, Intaite B, Anttila A. Effectiveness of the cervical cancer prevention programme: a case-control mortality audit in Lithuania. Eur J Cancer Prev. 2020;29:504-510.
36. Everatt R, Intaite B. Trends in cervical cancer mortality rates in Lithuania, 1987-2016. Cancer Epidemiol. 2018;57:85-89.
37. Beyer K, et al. Health Policy for Prostate Cancer Early Detection in the European Union and the Impact of Opportunistic Screening: PRAISE-U Consortium. J Pers Med. 2024,14.
38. Cancer Genome Atlas N. Genomic Classification of Cutaneous Melanoma. Cell. 2015;161:1681-1696.
39. Islami F, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States, 2019. CA Cancer J Clin2024;74:405-432.

40. Holman DM, Jones SE, Qin J, Richardson L.C. Prevalence of Indoor Tanning Among U.S. High School Students from 2009 to 2017. J Community Health. 2019;44:1086-1089.
41. WHO report on cancer: setting priorities, investing wisely and providing care for all. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
42. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017: 563-585.
43. Gershenwald JE, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67:472-492.
44. Office on Smoking and Health (OSH) | SMoking and Tobacco Use | CDC (2025). https://www.cdc.gov/tobacco/programs/index.html. [date accessed: 1/15/2025].
45. Ahluwalia IB, et al. Tobacco Smoking Cessation and Quitline Use Among Adults Aged >/=15 Years in 31 Countries: Findings From the Global Adult Tobacco Survey. Am J Prev Med. 2021;60:S128-S135.
46. Sheffer CE. Tobacco quitlines: Opportunities for innovation to increase reach and effectiveness. Prev Med. 2022;165:107319.
47. Sheffer CE, et al. Advancing Proficiencies for Health Professionals in the Treatment of Tobacco Use Among Marginalized Communities: Development of a Competency-Based Curriculum and Virtual Workshop. Subst Abus. 2023;44:313-322.
48. Sheffer CE, Webb Hooper M, Ostroff JS. Commentary: Educational and Clinical Training for Addressing Tobacco-Related Cancer Health Disparities. Ethn Dis. 2018;28:187-192.
49. Sheffer CE, et al. The Emerging Global Tobacco Treatment Workforce: Characteristics of Tobacco Treatment Specialists Trained in Council-Accredited Training Programs from 2017 to 2019. Int J Environ Res Public Health. 2021,18.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Study of the relationship between the level of pro-inflammatory cytokines and β2-microglobulin with indicators of changes in the functional status of the kidneys in diabetic nepropathy to determine the degrees of chronic renal failure

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ABSTRACT

Aim: The purpose of this study is to analyze the correlations of pro-inflammatory cytokines and β2-microglobulin with indicators of changes in the functional state of kidneys in patients with diabetic nephropathy, to determine different degrees of chronic renal failure.

Materials and Methods: 80 patients with type 1 and type 2 diabetes, complicated by diabetic nephropathy, at different levels of the functional state of the kidneys were examined.

Results: It has been shown that the level of tumor necrosis factor α (TNFα) in the blood of patients with diabetic nephropathy (DN) is increased already with sufficient kidney function, decreases with chronic renal failure (CRF) of the I degree and reaches maximum values with CRF of the II and III degrees. which indicates the degree of progression of fibroplastic and sclerotic processes in the kidneys with DN. The level of interleukin-1α (IL-1α) in the blood of patients with DN begins to decrease with sufficient kidney function, increases with CRF of the II degree, but remains below the values of the control group and is minimal in patients with CRF of the III degree, which reflects a decrease in the intensity of the acute-phase inflammatory process in the development of CRF.

Conclusions: The development and progression of CRF is accompanied by an increase in the excretion of β2-microglobulin in the urine in parallel with changes in the cytokine profile in the blood.

KEY WORDS: proinflammatory cytokines, chronic renal failure, diabetic nephropathy, ketosteril

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INTRODUCTION

Diabetic nephropathy (DN) remains one of the urgent problems of modern medicine. It develops in 36-48% of patients with diabetes mellitus (DM) type 1 and in 18-26% of patients with diabetes mellitus type 2, has a prolonged natural evolution, which leads to the irreversible development of proteinuria and kidney failure [1,2].

Recent renal registries suggest that 27% to 34% of all cases of terminal chronic renal failure are associated with diabetic nephropathy. In the USA and Europe, every third patient who needs hemodialysis has diabetes [1,3].

The pathogenesis of diabetic nephropathy is the subject of numerous scientific studies around the world. The key chain in the development of this severe complication of diabetes is long-term persistent hyperglycemia, which causes endothelial dysfunction, local hemodynamic disturbances, and the development of glomerular hyperfiltration [4]. Recently, there has been increasing interest in the role of cytokines in the progression of DN, especially the so-called pro-inflammatory cytokines, which activate the metabolism of connective tissue, stimulate the proliferation of fibroblasts, epithelial cells, and the mesangial matrix, and are included as mediators in each link of immunoinflammatory processes [4,5].

Among pro-inflammatory cytokines, the most attention is paid to tumor necrosis factor-α (TNFα) and interleukin-1α (IL-1α), which are secreted by monocytes/macrophages, endotheliocytes and coordinate a complex cascade of local immunoinflammatory reactions that lead to the development of glomerulosclerosis [6,7]. The value of IL-1α and TNFα as diagnostic and prognostic markers of kidney damage at different stages of DN, the possibility of cytokine/anticytokine therapy is studied [8,9]. Also, it remains relevant to determine the excretion of β_2-microglobulin with urine

for the timely diagnosis of tubulointerstitial lesions in patients with DN, an increase in the level of this protein in the plasma may indicate early violations of the filtering function of the kidneys, which is characteristic of this disease [7].

All this indicates the need to deepen scientific research on the importance of pro-inflammatory cytokines in the development and course of DN, the possibility of correcting changes in the cytokine system, which should delay the development of kidney damage in diabetes, and prolong the pre-dialysis period of chronic renal failure [10-12].

AIM

The purpose of this work is to study the relationship between the level of pro-inflammatory cytokines and β_2-microglobulin with indicators of changes in the functional state of the kidneys in patients with diabetic nephropathy, to determine different degrees of chronic renal failure.

MATERIALS AND METHODS

To conduct research, the necessary sample volume was determined to obtain the best result during a random survey, according to the formula:

$$n = \frac{t^2 \cdot \omega \cdot (1 - \omega)}{\Delta_\omega^2},$$

where t is a standardized value at a given level of reliability α = 0.95; ω – the number of patients with confirmed chronic renal failure, %; – marginal sampling error of 5%.

A representative volume of the sample was determined, which was 67-95 people.

In the study, the sample included 80 patients with type 1 and type 2 diabetes, complicated by diabetic nephropathy with varying degrees of kidney function. There are 43 men and 37 women among the patients. At the time of anamnesis collection, the age of the subjects was in the range from 20 to 75 years. Patients with an unspecified diagnosis and with the disease for less than 5 years did not participate in the study. The duration of the disease in patients with type 1 DM was 12.9±3.1 years, and in type 2 DM – 13.2±3.7 years.

The study was conducted over 11 months.

Diabetic nephropathy patients were divided into 4 groups depending on the functional state of the kidneys: 20 patients were diagnosed with sufficient kidney function (group I), 18 patiens had CRF I degree (II group), at 23 patients – CRF II degree (III group) and at 19 patients – CRF III degree (IV group). The basis for the distribution of patients with renal failure according to the degrees of CRF is the classification according to the order of the Ministry of Health of Ukraine №05/462 dated 09/30/2003 "Degrees of chronic renal failure depending on the rate of glomerular filtration and plasma creatinine concentration", and the determination of the stage of diabetic nephropathy was made according to the classification of C.E. Mogensen.

The control group consisted of 10 conditionally healthy persons, 6 men and 4 women, whose average age was 42.7±5.8 years.

The diagnosis was established on the basis of a thorough clinical (interrogation of the patient for complaints, study of the medical and life anamnesis, physical data) and laboratory (daily proteinuria, creatinine and urea content in the blood, glomerular filtration rate, tubular reabsorption) examination of patients with diabetic nephropathy of various degrees functional state of kidneys [2,13].

All patients underwent clinical and laboratory examinations, which included: clinical blood analysis, clinical urine analysis, biochemical blood analysis. The content of pro-inflammatory cytokines (TNFα and IL-1α) in the blood and the excretion of β_2-microglobulin in the urine were studied by enzyme-linked immunosorbent assay (ELISA). Determination of "free" human interleukin-1α in blood serum by the CytElisa – IL-1α method (a sandwich ELISA method that measures "free" forms of the human cytokine interleukin-1α). Determination of "free" human TNFα in blood serum by the CytElisa – TNFα method (a sandwich ELISA method that measures "free" forms of the human cytokine tumor necrosis factor (TNFα)) [14,15].

The study of excretion of β_2-microglobulin with urine was carried out in order to assess the degree of damage to tubulo-interstitial structures in diabetic nephropathy Quantitative determination of β_2-microglobulin in urine by the ELISA method [14,15].

Findings were statistically processed with help of SPSS 19 program product (IBM, USA). Correlation analysis with use of the Spearman coefficient (r) and the Chaddock scale was made for assessing relationships between indices.

RESULTS

The first group of investigated patients with DN with sufficient kidney function (CRF 0 degree) consisted of 20 patients aged 36 to 72 years. The duration of DM in this group averaged 12.3±1.74 years; blood pressure was on average: systolic blood pressure (SBP) – 143±18.3 mm Hg. and diastolic blood pressure (DBP) – 86.5±14.3 mm Hg. The average daily proteinuria was 1.3±0.38 g/

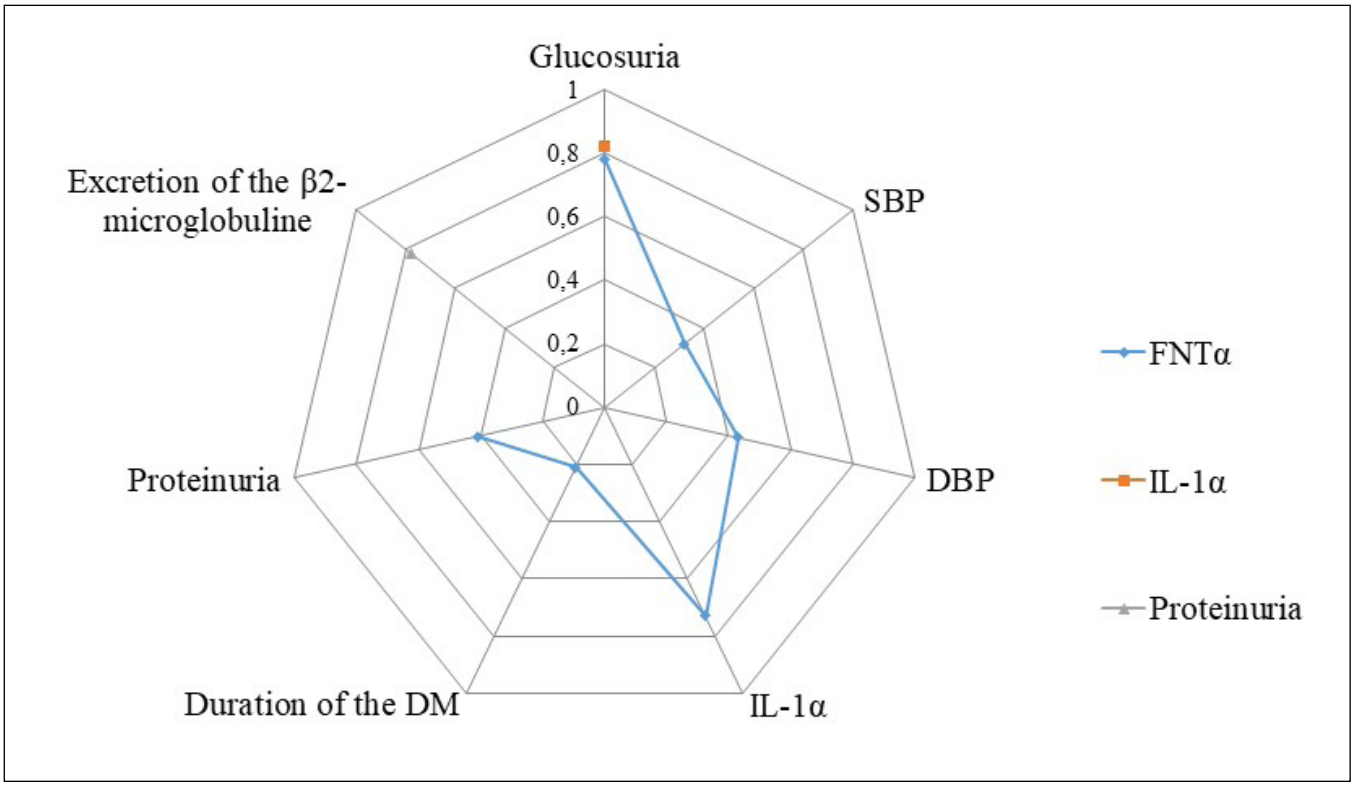

Fig. 1. Significant correlations in the group with sufficient renal function.

day. The content of creatinine in blood serum was on average 89.1±3.76 μmol/l and urea in blood serum was 6.4±0.43 mmol/l. The glomerular filtration rate (GFR) averaged 81.05±6.07 ml/min. and tubular reabsorption (R urine) – 92.5±1.75%.

Excretion of β_2-microglobulin with urine with sufficient kidney function was increased compared to the control group and averaged 0.15±0.04 pg/ml ($p<0.05$).

The content of IL-1α in the blood ranged from 0 to 7.1 pg/ml, on average 5.01±0.38 pg/ml, which is lower compared to the control group ($p<0.05$); the content of TNFα in the blood ranged from 4 to 76 pg/ml, on average 17.38±4.35 pg/ml and was significantly increased compared to the control group ($p<0.05$).

In patients of this group, a direct strong correlation between IL-1α and glucosuria was found ($r=0.82$, $p<0.05$), which confirms the importance of glucose toxicity in the development of immunoinflammatory processes in the kidneys. In addition, there is a direct strong correlation between urinary β_2-microglobulin excretion and daily proteinuria ($r=0.78$, $p<0.05$). This testifies to the fact that proteinuria is one of the most important factors of tubulointerstitial damage, which is established even with sufficient nitrogen excretory function of the kidneys.

A direct strong correlation relationship between TNFα and glucosuria ($r=0.78$, $p<0.05$), a weak correlation relationship between TNFα and SBP ($r=0.32$, $p<0.05$) and moderate – between TNFα and DBP ($r=0.43$, $p<0.05$), direct strong correlation between TNFα and IL-1α ($r=0.73$, $p<0.05$), weak correlation between TNFα and duration of diabetes ($r=0.21$, $p<0.05$) and moderate – between TNFα and proteinuria ($r=0.41$, $p<0.05$). The results of the detected correlations in the first group are presented in Fig. 1.

The decrease in the IL-1α content in the blood of DN patients with sufficient kidney function is explained by the long-term effect of hyperglycemia on immunocytes and endotheliocytes, which leads to the development of a cascade of pathological processes, resulting in the depression of the immune system. One of the main sources of IL-1α is endotheliocytes, which are also affected in diabetes. Endotheliocytes are insulin-independent, in conditions of hyperglycemia, glucose enters them without obstacles and causes a violation of their function. Endothelial dysfunction leads to a decrease in the production of IL-1α and its level in the blood.

It is known that IL-1α reduces the number of receptors for TNFα. A decrease in the content of IL-1α and an increase in the content of TNFα in the blood of patients with DN even with sufficient nitrogen-excreting function of the kidneys is evidence of the development of fibroplastic, sclerosing processes and a decrease in the severity of acute-phase inflammatory reactions even at this stage of the disease.

The second group of studied patients with DN with

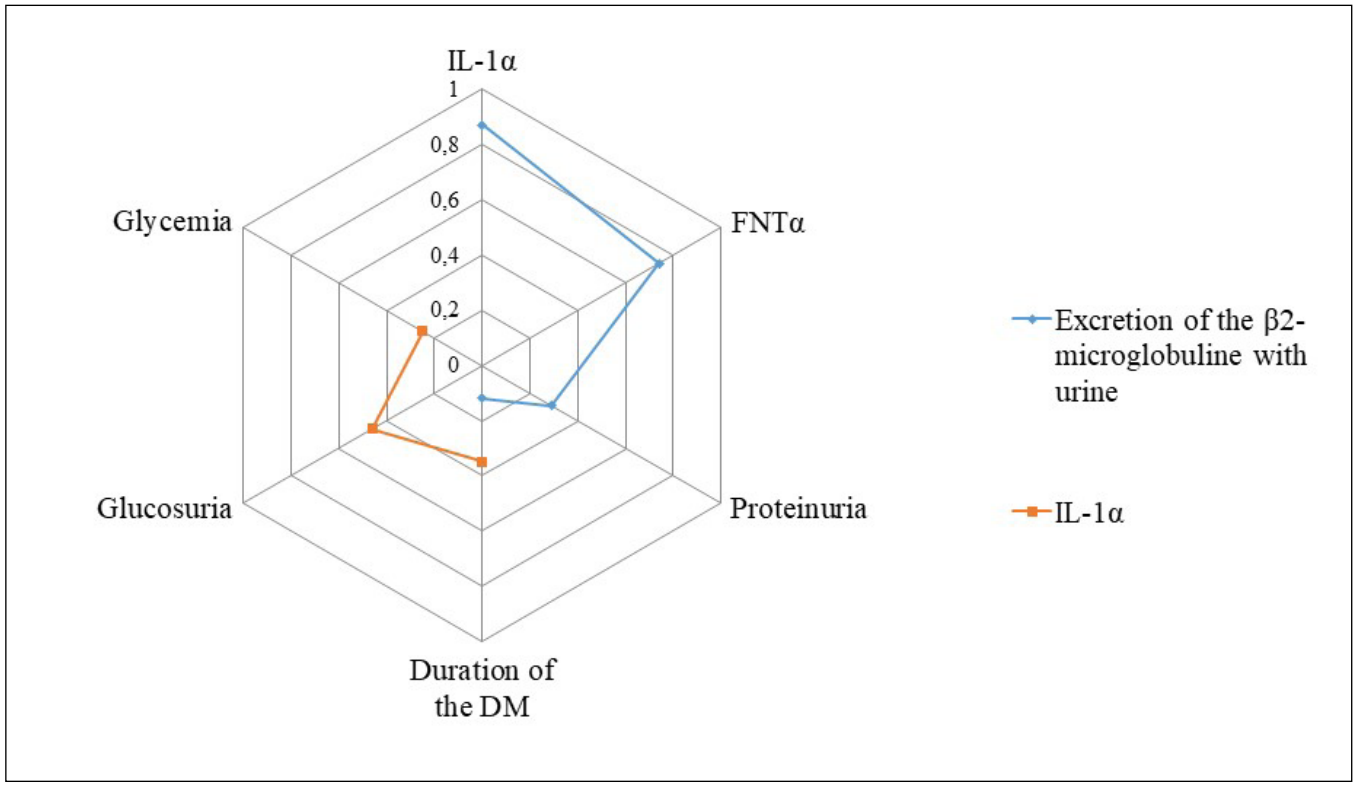

Fig. 2. Significant correlations in the group with CRF of I degree.

CRF I degree consisted of 18 patients aged 26 to 72 years. The duration of diabetes in this group averaged 13.7±2.63 years; blood pressure was on average: SBP – 162±11.4 mm Hg. and DBP – 98±6.6 mm Hg; Daily proteinuria – 2.3±0.52 g/day. The levels of azotemic indicators were: creatinine in blood serum – 163±7.4 μmol/l and urea in blood serum – 11.03±0.69 mmol/l. GFR was 61.6±3.0 ml/min. and R urine – 93±0.18%.

Excretion of β_2-microglobulin with urine in this group was on average 0.43±0.12 pg/ml ($p<0.05$), i.e. it was increased compared to the control group and the indicators of group I ($p<0.05$).

The level of pro-inflammatory cytokines in the patients of the second group was: the content of IL-1α in the blood – on average 3.78±0.47 pg/ml, which is significantly lower compared to the control group ($p<0.05$); the content of TNFα in the blood was on average 9.33±1.65 pg/ml, that is, it significantly exceeded this indicator in the control group ($p<0.05$), but decreased compared to the first group.

Direct strong correlations were revealed between IL-1α and urinary β_2-microglobulin excretion ($r=0.87$, $p<0.05$), between TNFα and urinary β_2-microglobulin excretion ($r=0.74$, $p<0.05$). This may be evidence that the level of pro-inflammatory cytokines in the blood reflects the severity of damage to tubulointerstitial structures and can be used as a marker of immuno-inflammatory processes in the kidneys in DN.

Weak correlations were also found between urinary β_2-microglobulin excretion and proteinuria ($r=0.29$, $p<0.05$), and between urinary β_2-microglobulin excretion and the duration of diabetes ($r=0.12$, $p<0.05$). Direct correlations were also found between the following indicators: moderate – between IL-1α and duration of diabetes ($r=0.35$, $p<0.05$), moderate – between IL-1α and glucosuria ($r=0.46$, $p<0.05$), weak – between IL-1α and glycemia ($r=0.25$, $p<0.05$), which emphasizes the importance of hyperglycemia for the development of immunoinflammatory processes in the kidneys. The results of the detected correlations in the second group are presented in Fig. 2.

In the second group of patients (CKD I degree) a decrease in the content of TNFα in the blood was found in comparison with the patients of the first group, although it remained significantly increased in comparison with the control group. It is possible that this dynamics of the level of TNFα during the development of CKD I degree is a compensatory reaction in accordance with the existence in new conditions (increased creatinine and urea content, blood pressure) and the preservation of protective mechanisms aimed at reducing the rate of kidney sclerosing in diabetic nephropathy.

The third group of investigated patients with DN with CRF II degree consisted of 23 patients aged 21 to 69 years. The duration of diabetes in this group av-

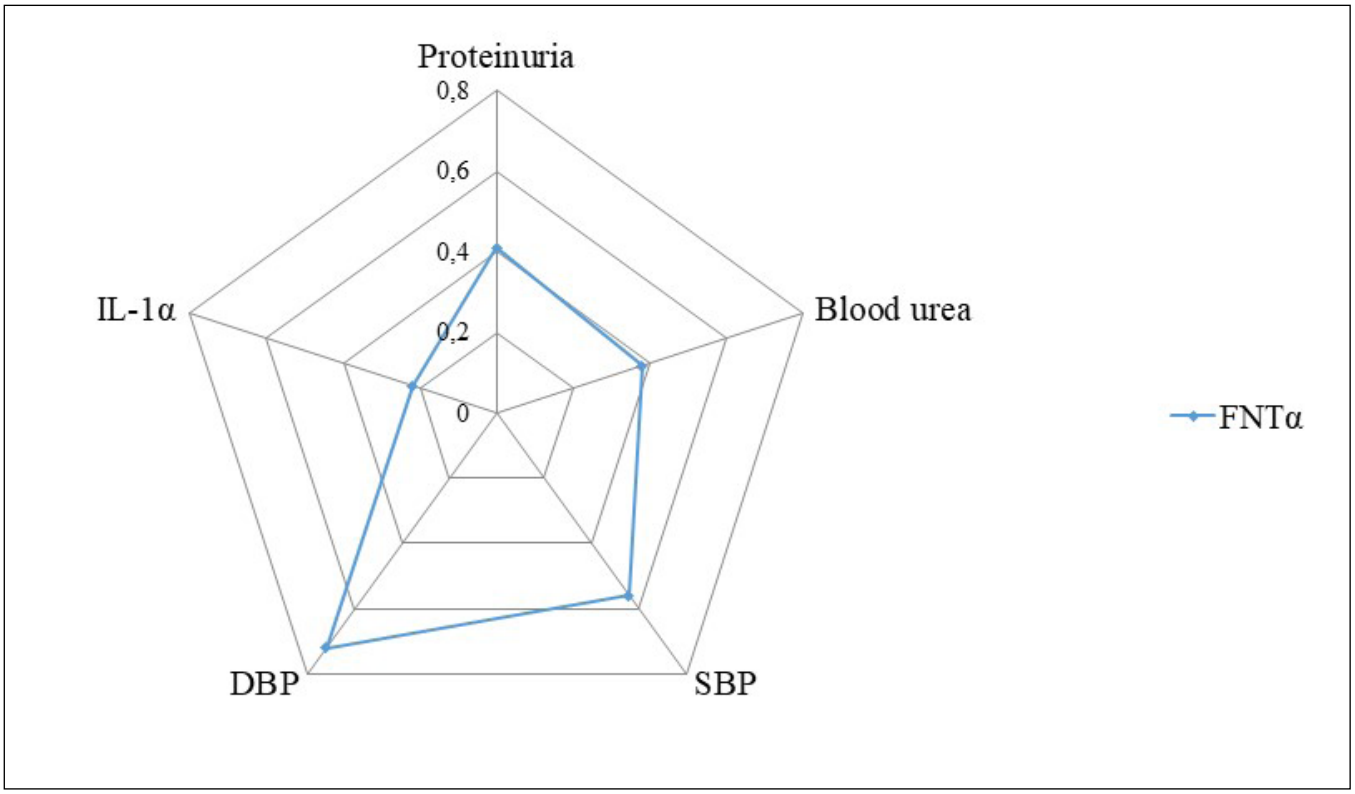

Fig. 3. Significant correlations in the group with CRF of II degree.

eraged 14.1±2.82 years; average blood pressure was: SBP – 168.5±15.6 mm Hg. and DBP – 97±11.2 mm Hg; daily proteinuria – 2.8±0.29 g/day; creatinine content in blood serum – 281.3±16.4 μmol/l, urea in blood serum – 14.3±0.81 mmol/l. GFR was 36.5±3.27 ml/min. and R urine – 93.2±1.23%.

Excretion of β_2-microglobulin with urine is significantly increased in this group: M±m was 1.17±0.07 pg/ml; $p<0.05$ in comparison with the control group, as well as patients of I and II groups.

The content of IL-1α in the blood ranged from 5 to 6.8 pg/ml, on average it was 4.51±0.53 pg/ml, which is significantly lower than the indicator of the control group ($p<0.05$). The increase in the level of IL-1α in the third group, in contrast to the second, reflects an increase in the activity of the immunoinflammatory process in response to the progressive damage of endotheliocytes with increasing intoxication in patients of the III group.

The content of TNFα in the blood of patients of this group increases significantly again and varies from 5 to 116 pg/ml, on average it is 24.65±6.73 pg/ml, which is the highest value among all the studied groups. This allows us to state that the activity of sclerosing processes is maximal in patients with DN with CRF II degree. Such an increase in the level of TNFα is also facilitated by a decrease in the clearance of this cytokine when kidney function deteriorates. Perhaps this also leads to a relative increase in the level of IL-1α in the blood and activation of immunoinflammatory processes in the kidneys.

In this group, a significant increase in correlations between TNFα and other indicators was noted: with proteinuria ($r=0.41$, $p<0.05$), with blood urea ($r=0.38$, $p<0.05$), with SBP ($r=0.56$, $p<0.05$) and with DBP ($r=0.72$, $p<0.05$). The relationship between TNFα and IL-1α at this stage of CRF is significantly weaker ($r=0.22$, $p<0.05$) than in patients of the previous groups. The results of the detected correlations in the third group are presented in Fig. 3.

Based on this, it can be concluded that CRF II degree in patients with DN is the stage of the highest activity of pro-inflammatory cytokines, especially TNFα, which leads to the fatal development of sclerotic changes in the kidneys, the progression of glomerulosclerosis.

The fourth group of investigated patients with DN with CRF III degree consisted of 19 patients aged from 31 to 69 years. The average duration of diabetes in this group was 17.6±2.64 years. Blood pressure was: SBP – 178±20.5 mm Hg. and DBP – 102±6.6 mm Hg. Daily proteinuria was the largest among all groups and averaged 3.2±0.49 g/day. The levels of azotemic parameters were as follows: creatinine in blood serum – 676.2±33.18 μmol/l, urea in blood serum – 22.82±1.36 mmol/l. GFR was 28.6±3.57 ml/min., R urine – 83.14±2.08%. The results of the detected correlations in the fourth group are presented in Fig. 4.

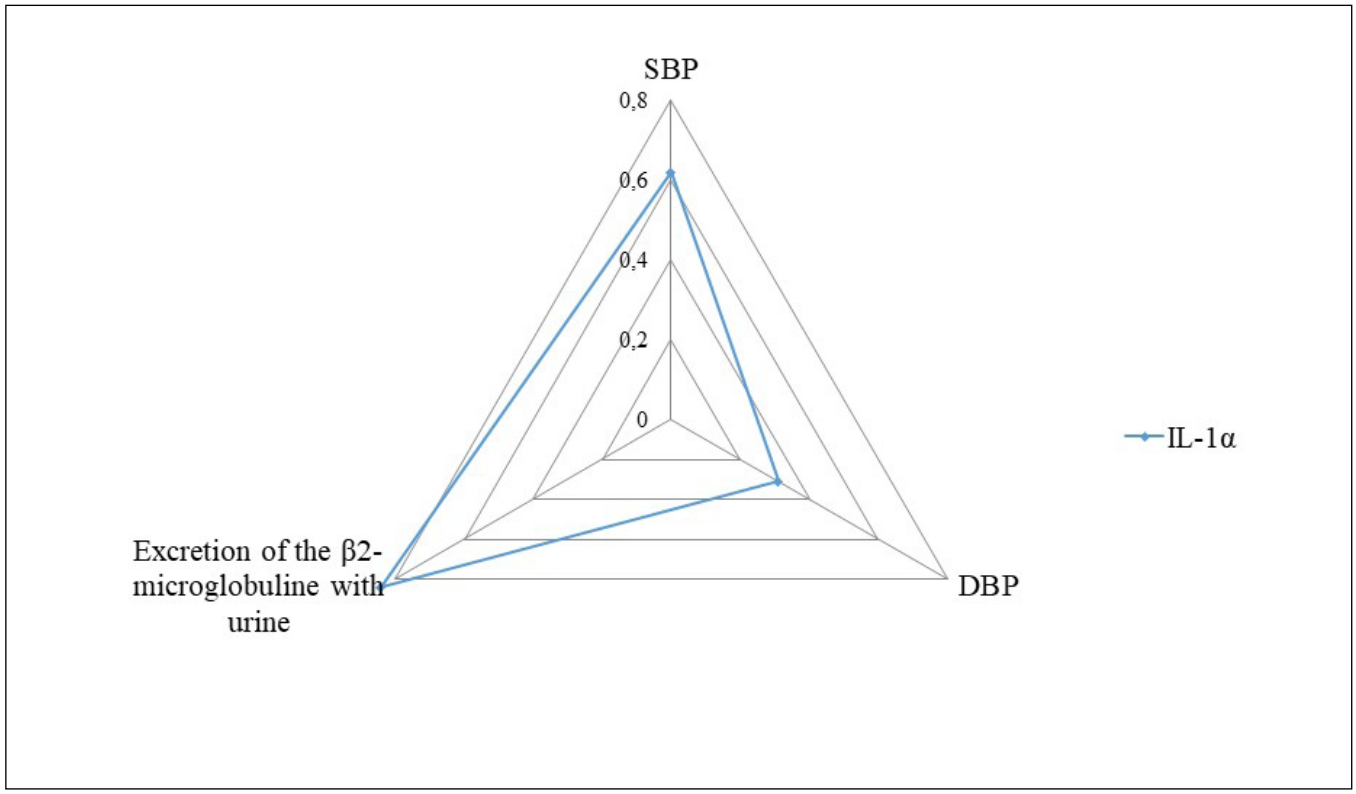

Fig. 4. Significant correlations in the group with CRF of III degree.

With CRF III degree, excretion of β_2-microglobulin with urine reaches the highest values and is on average 3.34±1.63 pg/ml. The content of IL-1α in the blood ranged from 0 to 6.4 pg/ml, with an average of 2.73±0.7 pg/ml and was minimal among all examined groups. In our opinion, this is a sign that the processes of acute inflammation in the kidneys are significantly reduced in CRF III degree and are the least pronounced among all groups of studied patients. The TNFα content in the blood remains at a high level and ranges from 4 to 104 pg/ml, with an average of 20.66±5.25 pg/ml. This indicates the high activity of sclerosing processes in the kidneys, which is the reason for their shrinkage. A certain contribution to maintaining a high level of TNFα is also made by a progressive decrease in the excretory function of the kidneys, as well as an increase in the production of this cytokine by cardiomyocytes.

With CRF III degree, the correlations that were in the previous three groups disappear – between the content of IL-1α in the blood and the duration of diabetes, glucosuria, proteinuria, but direct positive correlations appear between the content of IL-1α in the blood and SBP ($r=0.62$, $p<0.05$), between IL-1α content in the blood and DBP ($r=0.31$, $p<0.05$), as well as between urinary β_2-microglobulin excretion and IL content -1α in blood ($r=0.84$, $p<0.05$). This indicates that patients with DN develop deep damage to the protective mechanisms of cellular immunity as a result of prolonged exposure to hyperglycemia, oxidant stress, hemodynamic damage, and metabolic disorders [13,14].

The results of the study of the content of pro-inflammatory cytokines (TNFα and IL-1α) in the blood and the excretion of β_2-microglobulin in the urine in patients with DN, depending on the degree of CRF, are shown in Fig. 5.

Interleukin-1α is the main mediator of local inflammatory reactions and cellular antigen-specific immune response. The level of this cytokine decreases with the progression of CRF due to endothelial dysfunction, which develops under the destructive influence of hyperglycemia and other factors of disease progression (arterial hypertension, proteinuria, intoxication). This is accompanied by a decrease in the intensity of acute inflammatory reactions in the kidneys.

The level of TNFα increases with the progression of CRF, which leads to the development of sclerosing processes in the kidneys. It is known that this cytokine is produced by macrophages and lymphocytes. Increased expression of TNFα is at the basis of the pathogenesis of autoimmune lesions, induces the expression of tissue procoagulant factors, activation of lysosomal factors, proteases, formation of free radicals and reactive oxygen species.

A decrease in IL-1α content in the blood is accompanied by an increase in the density of fibroblast growth factor receptors on target cells. It is also worth

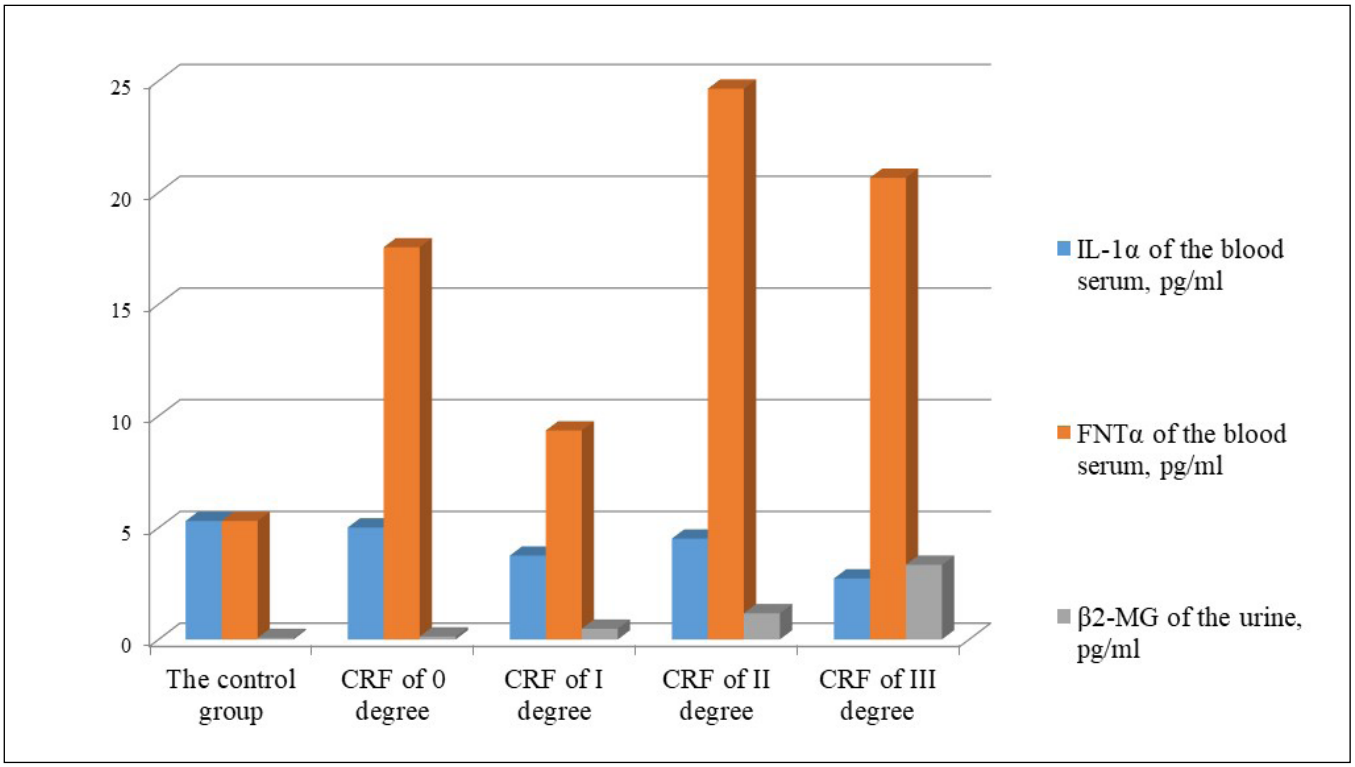

Fig. 5. The content of pro-inflammatory cytokines in the blood and the excretion of β2-microglobulin in the urine in patients with DN at different stages of CRF.

considering the myocardial theory of TNFα synthesis: unequivocal evidence of the production of this cytokine by cardiomyocytes in response to pressure and volume overload has been obtained.

DISCUSSION

Pro-inflammatory cytokines activate the metabolism of connective tissue, stimulate the proliferation of fibroblasts and epithelial cells, regulate the development of an adequate response to the introduction of the pathogen, its localization and removal, and the restoration of the affected tissue structure. The role of pro-inflammatory cytokines in the development and progression of diabetic nephropathy is almost unexplored. The study of pro-inflammatory cytokines in diabetic nephropathy can be useful for deepening the knowledge of the mechanisms of pathogenesis, developing criteria for its progression and prognosis, as well as for developing new approaches to the treatment of this common and dangerous complication of diabetes.

The mechanisms of the damaging effect of hyperglycemia on the structural components of the kidneys are associated with a violation of renal hemodynamics – the development of hyperfiltration, intraglomerular hypertension and hyperperfusion. Under the influence of these factors, the permeability of the basal membrane of the glomerular capillaries increases, the level of protein in the urine, which is the main cause of the spread and sclerosis of the mesangial matrix, dystrophy of the tubular epithelium. [16,17].

The presented studies proved the presence of positive correlations between the content of TNFα in the blood and the level of blood pressure. According to the literature [2,4], the synthesis of TNFα can increase with dyslipidemia, activation of the local renin-angiotensin-aldosterone system (RAAS) and other factors characteristic of chronic renal failure. This cytokine acts as a mediator that controls the proliferation of mesangial cells and the synthesis of the extracellular matrix, thereby potentially contributing to the progression of chronic renal failure and, as a result, contributes to the progression of poisoning and the accumulation of toxins, increasing pressure. in blood vessels, loss of fluid-electrolyte balance, i.e. a violation of the balance of fluid, sodium, potassium and other electrolytes in the body, which can lead to serious complications, a decrease in the number of erythrocytes, which can lead to the development of anemia and a loss of oxygen transfer efficiency, etc. [5, 7].

The presence of correlations between the main factors of the progression of well-controlled diabetes (duration of diabetes, level of proteinuria, blood pressure) and the level of pro-inflammatory cytokines allows us to use the determination of IL-1α and TNFα levels in the blood as potential markers of the progression of diabetic nephropathy. High levels of IL-1α and TNFα in the blood may indicate active inflammatory process-

es, endothelial dysfunction, and damage to kidney cells that contribute to the progression of diabetic nephropathy. This makes them potential markers for the prevention and monitoring of this complication in patients with diabetes. An increase in the level of TNFα and a decrease in the level of IL-1α in the blood can be criteria for an unfavorable prognosis of the course of this disease.

The results of our research indicate that damage to the tubules precedes a violation of the nitrogen-excreting function of the kidneys in DN with chronic renal failure. It is possible that renal interstitial fibrosis is the basis of the progression of kidney damage in diabetic nephropathy.

The mechanisms of action of these cytokines and their interaction with other factors of disease progression require further studies to understand their exact role in the pathogenesis of diabetic nephropathy. Additional research may open new opportunities for treatment and, more importantly, prevention of this serious complication of diabetes.

CONCLUSIONS

Thus, in the work, a study of the relationship between the level of pro-inflammatory cytokines (TNFα and IL-1α) and β_2-microglobulin with indicators of changes in the functional state of the kidneys in patients with diabetic nephropathy, which allows determining different degrees of chronic renal failure. All correlations presented in the work (medium and strong) were significant ($p \leq 0.05$).

It has been proven that changes in the profile of pro-inflammatory cytokines: a decrease in the content of IL-1α and an increase in the content of TNFα in blood serum are markers of the progression of chronic renal failure in patients with diabetic nephropathy. It has been shown that the excretion of β_2-microglobulin with urine increases even with sufficient kidney function, increases in parallel with changes in the cytokine profile during the development and progression of CRF, which indicates early damage to tubulointerstitial structures in patients with DN and confirms the value of urinary β_2-microglobulin excretion as an indicator of progression fibroplastic processes in the tubulointerstitium of the kidneys.

REFERENCES

1. Wong YH, Wong ShH, Wong XT et al. Genetic associated complications of type 2 diabetes mellitus. Panminerva Med. 2021;64(2):274-288. doi: 10.23736/S0031-0808.21.04285-3. DOI
2. Wang Z, Gong Y, Fan F et al. Coronary artery bypass grafting vs. drug-eluting stent implantation in patients with end-stage renal disease requiring dialysis. Renal Failure. 2020;42(1):107-112. doi: 10.1080/0886022X.2019.1710187. DOI
3. Aly RH, Ahmed AE, Hozayen WG. Patterns of Toll-Like Receptor Expressions and Inflammatory Cytokine Levels and Their Implications in the Progress of Insulin Resistance and Diabetic Nephropathy in Type 2 Diabetic Patients. Front Physiol. 2020;23:11:609223. doi: 10.3389/fphys.2020.609223. DOI
4. Badr RE, Salama MI, Abd-Elmaogood AK, Eldeib AEM. Toll-like receptor 2 expression on monocytes and microvascular complications in type 2 diabetic patients. Diabetes Metab. Syndr. 2019;13:1299–1302. doi: 10.1016/j.dsx.2019.01.038. DOI
5. Rysz J, Gluba-Brzózka A, Franczyk B et al. Novel Biomarkers in the Diagnosis of Chronic Kidney Disease and the Prediction of Its Outcome. Int. J. Molecular Sciences. 2017;18:1702. doi: 10.3390/ijms18081702. DOI
6. Ruiz-Ortega M, Rodrigues-Diez R, Lavoz C et al. Special Issue Diabetic Nephropathy: Diagnosis, Prevention and Treatment". J Clinical Medicine. 2020;9:813. doi: 10.3390/jcm9030813" DOI
7. Azim Sharaf UA, Mansour MS, Abdulazim DO. (2017) Recent Advances in Management of Diabetic Nephropathy. Journal of Clinical & Experimental Nephrology; 2:35 DOI: 10.21767/2472-5056.100035.
8. Wang J, Feng Y, Zhang Y et al. TNF-α and IL-1β Promote Renal Podocyte Injury in T2DM Rats by Decreasing Glomerular VEGF/eNOS Expression Levels and Altering Hemodynamic Parameters. J Inflamm Res. 2022;15:6657-6673. doi: 10.2147/JIR.S391473. DOI
9. Maqsood M, Sharif S, Naz Sh et al. Expression of pro-inflammatory cytokines (IL-6 & IL-18) exacerbate the risk of diabetic nephropathy in the Pakistani population Mol Biol. 2023;50(4):3249-3257. doi: 10.1007/s11033-023-08249-z. DOI
10. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. J Physiology, Pathophysiology, Pharmacology. 2019;11(3):45–63.
11. Zheng S, Wang H, Han J et al. Microbiota-derived imidazole propionate inhibits type 2 diabetic skin wound healing by targeting SPNS2-mediated S1P transport. iScience. 2023;26(11):108092. doi: 10.1016/j.isci.2023.108092. DOI
12. Chakraborty R, Parveen R, Varshney P et al. Elevated urinary IL-36α and IL-18 levels are associated with diabetic nephropathy in patients with type 2 diabetes mellitus. Minerva Endocrinol (Torino). 2021;46(2):226-232. doi: 10.23736/S2724-6507.20.03196-X. DOI
13. Mahaboob KS. Diabetic nephropathy: recent advances in pathophysiology and challenges in dietary management. Diabetology & Metabolic Syndrome. 2019;11:137-144. doi: 10.1186/s13098-019-0403-4. DOI
14. Zhang J, Liu J, Qin X. Advances in early biomarkers of diabetic nephropathy. Rev Association Medicine Bras. 2018;64(1):85–92. doi: 10.1590/1806-9282.64.01.85. DOI

15. Magee C, Grieve DJ, Watson CJ, Brazil DP. Diabetic nephropathy: a tangled web to unweave. Cardiovasc Drugs Ther. 2017;31(5–6):579–592. doi: 10.1007/s10557-017-6755-9. DOI
16. Yang B, Zhao XH, Ma G. Role of serum β2-microglobulin, glycosylated hemoglobin, and vascular endothelial growth factor levels in diabetic nephropathy. World J Clin Cases. 2022;10(23):8205-8211. doi: 10.12998/wjcc.v10.i23.8205. DOI
17. Uemura T, Nishimoto M, Eriguchi M et al. Utility of serum β2-microglobulin for prediction of kidney outcome among patients with biopsy-proven diabetic nephropathy. Diabetes Obes Metab. 2024;26(2):583-591. doi: 10.1111/dom.15347. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Identification of oral bacteria in patients with dentulous, partially edentulous and edentulous: A comparative study

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ABSTRACT

Aim: To investigate distribution of oral bacteria among dentulous, partially edentulous, and edentulous patients while examining influence of age and gender on these conditions. It was designed to identify the prevalence of specific bacterial species in the oral cavity and their association with different dental statuses.

Materials and Methods: Samples were taken by rinse the mouth of 66 subjects divided into 3 groups: Dentulous n=49, Edentulous n=43, Partially Edentulous n=58. Ten types of bacteria were analyzed using gram staining and biochemical tests.

Results: Staphylococcus aureus is most prevalent in the edentulous group, accounting for 27.91%, compared to 15.52% in the Partially Edentulous and 10.20% in the dentulous group. This suggests a possible increase in its presence with tooth loss. *Staphylococcus albicans* and *Streptococcus* are more common in the Dentulous and Partially Edentulous groups, with the dentulous group having the highest percentage of *Staphylococcus albus* at 22.45%. Diplococcus pneumoniae shows an increased frequency in the edentulous group 16.28% compared to the other groups, which may indicate a higher risk of pneumonia-related bacteria in patients without teeth. There was a significant association between age and tooth loss. Gender did not show any relationship neither to tooth loss nor to oral cavity bacteria.

Conclusions: Edentulism was most prevalent in individuals aged 50 years and older, emphasizing the role of aging in tooth loss. No significant gender differences were observed, indicating equal impact on males and females. Certain bacteria, like *Staphylococcus aureus* and *Streptococcus*, were more common in edentulous patients.

KEY WORDS: oral bacteria, dentulous, edentulous patients

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INTRODUCTION

Oral microbiome plays a crucial role in maintaining oral health and influencing various systemic conditions. In the context of Iraqi patients, the composition and diversity of the oral microbiome can vary significantly among edentulous, edentulous, and dentulous individuals. Oral pathogenic bacterial species participate in the pathogenesis of both caries and periodontal disease. Oral pathogens engage in negative interactions with the host, passing information, immune response, and even metabolic condition back and forth through systemic organs and the oral cavity. The oral cavity presents a critical point of contact with the external environment for the human body. Because of different microenvironments, microbial compositions among different sites within the oral cavity also differ and are very dynamic due to an intricate input of signals coming from hosts and external ecological factors [1]. Certain oral bacterial species have been linked to specific systemic conditions, for instance, bacterial osteomyelitis, aspiration pneumonia, and endocarditis in infants, preterm low birth weight, and cardiovascular disease in the oral cavity might be considered an ideal incubator because it possesses a temperature of approximately 35 to 36°C and has an abundance of moisture, an excellent supply of various types of foods and difference in oxygen tension [2]. The number of microorganism that can be removed from oral cavity by mouth rinsing various though the day. It has been observed that bacterial counts are highest in the morning on raising. As a result of eating breakfast, brushing the teeth and rinsing the mouth, these numbers decrease. A gradual increase is noted before the mid day meal after the meal a decrease Occurs. A pattern of an increase followed by a decrease is after [3]. The overall balance of the oral flora may be related to the fact that the main food source for the microorganisms is mainly saliva, epithelial cells and inflammatory exudates (gingival crevicular fluid) from the environment. These substances flow continuous-

ly through the oral cavity, removing food particles, bacteria and their waste products, equivalent to a continuous culture device containing a mixed microbial community. Irregular exposure to additional nutrients and inhibitors in human food may even cause bacterial growth to undergo a kind of "synchronization" [4]. The oral microbiome has been consistently found of major importance to oral health. This is best epitomized by Marsh (2010), who discusses the role of dental plaque biofilms in oral health and caries, arguing that dysbiosis would accrue to several oral diseases. This foundational knowledge needs to be further explored in understanding how different patient groups might present unique microbial profiles in edentulous, un-edentulous, and dentulous cases [5]. Hypothetically, it would be expected that edentulous patients would portray a far greater alteration in their oral microbiome as compared to their dentulous counterparts. Mertens et al., (2012) reported long-term results of implant-supported rehabilitation in edentulous patients and noted the problems of microbial colonization and peri-implantitis in this context. The complete lack of teeth led to distinctly varied microbial conditions, requiring targeted therapeutic measures [6]. In contrast to the above study, Jiang et al. (2019) studied the oral microbiome in elderly patients with dental caries as well as health and established a much unique microbiome composition associated with the dental status. The current research supports the theory that the presence of teeth critically influences microbial diversity and composition [7]. The microbiome dynamics in edentulous and dentulous patients also seem to differ. For example, Schulz et al., (2019) took a comparison of the oral microbiome on generalized aggressive periodontitis patients with subject's periodontitis free disclosing considerable variations which could help in understanding of the risk of periodontal disease among dentulous patients [8].

AIM

The study aimed to investigate the distribution of oral bacteria among dentulous, partially edentulous, and edentulous patients while examining the influence of age and gender on these conditions. It sought to identify the prevalence of specific bacterial species in the oral cavity and their association with different dental statuses. Additionally, the study aimed to assess the statistical significance of these relationships to provide insights into the role of oral hygiene, aging, and bacterial colonization in the progression of tooth loss and associated infections, ultimately contributing to improved preventive and therapeutic approaches.

MATERIALS AND METHODS

SAMPLING

A total of 150 salivary samples were collected in this study. The samples were collected from individuals who are attending the medical centers in Abo-Garib. Meanwhile, such samples were equally distributed to both sexes. To each sample, it involved a special form to be filled concerning the name, age, sex, and date of sampling. Materials and Methods: Mouth sample: The subjects were grouped into dentulous n=49, edentulous n=43 and partially edentulous n=58. A 5ml sterile distilled water was poured into the mouth of the subject who had rinsed his/her mouth vigorously and sampled mouth after rinsing in sterile tubes. Components were further individually cultured on BHI broth 15 ml at 37°C for 24h then after incubation was sub-cultured on blood agar and MacConkey agar and later step went for final identification of suspected isolates.

IDENTIFICATION OF BACTERIAL ISOLATES

MICROSCOPICAL EXAMINATION

Samples processed for microscopical examination using Gram stain, a loop full of bacterial isolates was fixed on microscopic slide, then smears were allowed to dry and all fixed smears were stained by Gram stain to examine cell shape, grouping, size and Gram reaction.

BIOCHEMICAL TESTS

CATALASE TEST

A single colony of each bacterial isolate was placed onto a clean glass microscopic slide using a sterile toothpick, a drop of 3% H_2O_2 was added, and the appearance of bubbles indicated a positive result.

OXIDASE TEST

A sterile wooden stick of suspected bacterial isolates was picked up from the slant growth and smeared on filter paper with a drop of freshly prepared oxidase reagent (tetramethyl-para-phenyl-diamine dihydrochloride). Positive: The development of purple colour within 5-10 seconds.

GROWTH ON MANNITOL SALT AGAR MSA

A suspected colonies were inoculated on sterile MSA and incubated for 24-48 hrs, after incubation, changing the color from red to yellow is an indicator of mannitol fermentation.

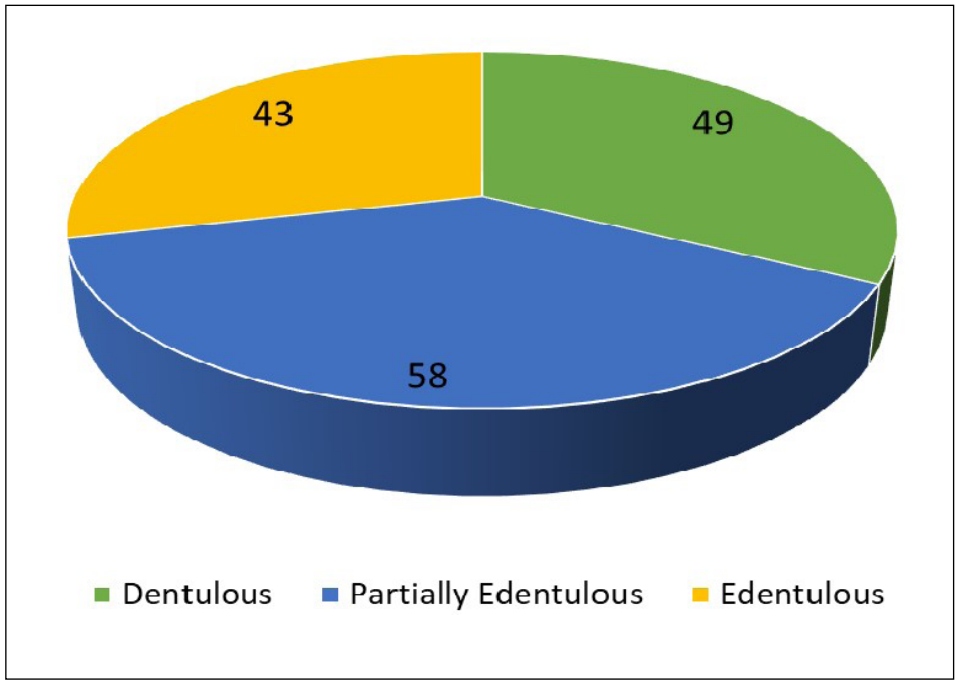

Fig. 1. Distribution of the three groups of patients.

Table 1. Growth of bacteria on blood agar

Types of bacteria	Hemolysis	Catalase	Coagulase	Mannitol
Staph. aureus	B-hemolysis	Positive	Positive	Positive
Staph. albicans	Negative	Positive	Negative	Negative
Staph. saprophyticus	Negative	Negative	Negative	Positive

Table 2. Distribution of age and sex in the three groups of patients

Types of bacteria		Dentulous (n=49)		Pat. Edentulous (n=58)		Edentulous (n=43)		Chi Square	P value
		Freq.	Percent.	Freq.	Percent.	Freq.	Percent.		
Age/ Years	20-29	15	30.61	2	3.45	1	2.33	69.77	0.000 HS
	30-39	14	28.57	3	5.17	3	6.98		
	40-49	13	26.53	23	39.66	2	4.65		
	≥ 50	7	14.29	30	51.72	37	86.05		
Gender	Male	25	51.02	31	53.45	24	55.81	0.21	0.89 NS
	Female	24	48.98	27	46.55	19	44.19		

HS: High Significant at P value <0.01; NS: Non-significant at P value >0.05.

GROWTH ON BLOOD AGAR

Bacterial isolates were inoculated on human blood agar medium prepared and incubated at 37°C for 24-48 hrs., as shown in table 1. The presence of clear zones or green around the colonies represented hemolysis of blood [4].

COAGULASE TEST

A milliliter of the human plasma was placed into two small test tubes, to the first one 0.1 ml of an overnight broth culture of suspected isolate, while nothing tube added, both tubes incubated for 4 hours or overnight. Clot formation indicated coagulase producing isolate as positive result while the second tube used as a control.

DNASE TEST

A loop of suspected isolate from a primary culture was picked up with a sterile bacteriological needle and streaked by the needle-point method on the surface of DNase agar plate. The DNase plate was then incubated at 37°C for 18-24 hours. After incubation, the plate was flooded with 1N Hcl. The appearance of the clear zone around the growth was an indication for DNase production and a positive result.

Table 3. Distribution of detected bacteria in the oral cavity of the three groups of patients

Types of bacteria	Dentulous		Pat. Edentulous		Edentulous		Chi Square	P value
	Freq.	Percent.	Freq.	Percent.	Freq.	Percent.		
Streptococcus	10	20.41	11	18.97	4	9.30	29.39	0.043 S
E. coli	5	10.20	5	8.62	5	11.63		
Klebsiella Spp.	0	0.00	5	8.62	3	6.98		
Proteus	2	4.08	1	1.72	0	0.00		
Pseudomonas	8	16.33	5	8.62	3	6.98		
Staph. aureus	5	10.20	9	15.52	12	27.91		
Staph. albus	11	22.45	8	13.79	2	4.65		
Neisseria Spp.	0	0.00	2	3.45	4	9.30		
Lactobacillus Spp.	0	0.00	5	8.62	3	6.98		
Diplococcus (Pneumonia)	8	16.33	7	12.07	7	16.28		

S: Significant at P value <0.05.

Table 4. Association between detected bacteria and gender in dentulous group

Types of bacteria	Male		Female		Chi Square	P value
	Freq.	Percent.	Freq.	Percent.		
Streptococcus	5	10.20	5	10.20	2.8	0.83 NS
E. coli	4	8.16	1	2.04		
Klebsiella Spp.	0	0.00	0	0.00		
Proteus	1	2.04	1	2.04		
Pseudomonas	4	8.16	4	8.16		
Staph. aureus	2	4.08	3	6.12		
Staph. albus	4	8.16	7	14.29		
Neisseria Spp.	0	0.00	0	0.00		
Lactobacillus Spp.	0	0.00	0	0.00		
Diplococcus (Pneumonia)	4	8.16	4	8.16		

NS: Non-significant at P value >0.05.

UREASE TEST

This was examined by streaking the surface of sterile urea agar slants with the tested bacteria and incubated at 37°C for 24 hrs. Pink color development confirmed the positive test result.

OPTOCHIN TEST

For pneumococci, they are gram positive-diplococci cultured on blood agar and then put optochin disc, only pneumococci give positive reaction (Optochin inhibit the growth of pneumococci).

RESULTS

The pie chart visually illustrates the proportional distribution of the three patient groups: dentulous, partially edentulous, and edentulous. The chart effectively shows that the groups are not equally distributed, with partially edentulous patients appearing to form the largest portion 58%, followed by the dentulous 49% and edentulous groups 43% (Fig.1).

Table 2 presents the distribution of age and sex across three groups of patients categorized as Dentulous, Partially Edentulous, and Edentulous, with a chi-square test applied to determine the significance of differences among these groups. There is a significant association between age and the type of patient group, as indicated by the chi-square value 69.77 and highly significant p-value < 0.001. The chi-square test for gender distribution reveals no significant association between gender and patient group, p = 0.89.

Table 3 illustrates the distribution of detected bacteria in the oral cavity across three groups of patients: Dentulous, Partially Edentulous, and Edentulous, with a chi-square test showing significant variation in bacterial distribution, p = 0.043. Staphylococcus aureus is most prevalent in the edentulous group, accounting for 27.91%, compared to 15.52% in the Partially Edentulous and 10.20% in the dentulous group. This suggests a

Table 5. Association between detected bacteria and sex in partially edentulous group

Types of bacteria	Male		Female		Chi Square	P value
	Freq.	Percent.	Freq.	Percent.		
Streptococcus	5	8.62	6	10.34	5.83	0.75 NS
E. coli	2	3.45	3	5.17		
Klebsiella Spp.	3	5.17	2	3.45		
Proteus	1	1.72	0	0.00		
Pseudomonas	2	3.45	3	5.17		
Staph. aureus	4	6.90	5	8.62		
Staph. albicans	5	8.62	3	5.17		
Neisseria Spp.	1	1.72	1	1.72		
Lactobacillus Spp.	2	3.45	3	5.17		
Diplococcus (Pneumonia)	6	10.34	1	1.72		

NS: Non-significant at P value >0.05.

Table 6. Association between detected bacteria and sex in edentulous group

Types of bacteria	Male		Female		Chi Square	P value
	Freq.	Percent.	Freq.	Percent.		
Streptococcus	5	10.20	6	12.24	3.14	0.92 NS
E. coli	2	4.08	3	6.12		
Klebsiella Spp.	3	6.12	2	4.08		
Proteus	1	2.04	0	0.00		
Pseudomonas	2	4.08	3	6.12		
Staph. aureus	4	8.16	5	10.20		
Staph. albicans	5	10.20	3	6.12		
Neisseria Spp.	1	2.04	1	2.04		
Lactobacillus Spp.	2	4.08	3	6.12		
Diplococcus (Pneumonia)	6	12.24	1	2.04		

NS: Non-significant at P value >0.05.

possible increase in its presence with tooth loss. *Staphylococcus albicans* and *Streptococcus* are more common in the Dentulous and Partially Edentulous groups, with the dentulous group having the highest percentage of *Staphylococcus albus* at 22.45%. *Diplococcus pneumoniae* shows an increased frequency in the edentulous group 16.28% compared to the other groups, which may indicate a higher risk of pneumonia-related bacteria in patients without teeth.

Regarding the distribution of detected bacteria according to sex subgroups of patients, the table 4 presents the distribution of various bacterial isolates among male and female patients (dentulous group), detailing both frequency and percentage. Identical frequencies and percentages for *Streptococcus* and *Pseudomonas* were observed in both genders, at 10.2% and 8.16%, respectively. In contrast, *Staphylococcus albus* showed a significant disparity, being more common in females at 14.29% compared to 8.16% in males. *E. coli* was more prevalent among males, with a frequency of 8.16%, while it was only 2.04% in females. According to the Chi-square test, there are no statistically significant differences between the distributions of males and females (P = 0.83), suggesting that gender does not have a significant impact on bacterial occurrence in this study.

The distribution of bacteria among male and female patients with partial edentulism was the focus of the current study (Table 5). Among males, *Streptococcus* and *Diplococcus* (*Pneumonia*) were found more frequently, at rates of 8.62% and 10.34%, respectively, while in females, the rates were 10.34% and 1.72%. Notably, *Staphylococcus aureus* exhibited a slightly higher occurrence in females (8.62%) compared to males (6.90%). Interestingly, both genders showed equal detection of *Klebsiella spp*., *Pseudomonas*, and *Lactobacillus spp*., whereas *Proteus* was exclusively identified in males. The chi-square analysis indicated no statistically significant association (P = 0.75) between the detection of bacteria and sex, suggesting that there is no gender-based predisposition in the bacterial distribution for this group.

These results are consistent with the overall pattern of bacterial colonization observed in partially edentulous individuals.

The present study examined the link between bacterial presence and sex within the edentulous population (Table 6). The most commonly found bacterium was *Streptococcus*, identified in 10.20% of males and 12.24% of females. In a similar vein, *Staphylococcus aureus* and *Staphylococcus albicans* exhibited marginally higher occurrences in females (10.20% and 6.12%, respectively) compared to males (8.16% and 10.20%). Interestingly, *Diplococcus* (*Pneumonia*) was observed more frequently in males (12.24%) than in females (2.04%), and *Proteus* was exclusively detected in males (2.04%). The Chi-square analysis revealed no statistically significant differences (P = 0.92) between genders, indicating that there is no variation in bacterial colonization based on sex among edentulous individuals. This points to a generally consistent distribution of bacterial species across genders in this demographic.

DISCUSSION

From the birth the oral cavity is exposed to many different microorganisms present in the local and geographic environment. Those microorganism that become oral residents are favored by the nutritional and physiologic conditions are not inhibited by the mechanical and antagonistic mechanisms of the oral cavity. The effect of different oral environments over a long period of time will result in the selection of microorganisms best suited to survive in specific areas of the oral cavity. Microbial association nearly always exists even though different types may occupy separate niches differing perhaps in only one influential environmental factor. Only the aerobic oral microbial flora were studied and isolated 10-types of bacteria according to the media and the facilities from three groups. The numerical increase of the streptococcus genus in the partially edentulous group emphasizes the fact that streptococci constitute a large and complex group of bacteria having widely varying characteristics and that under certain conditions of independent pathogenicity, they may cause a wide specific disease alone [3]. The enterobacteriacae group are usually to be only transiently present in the normal human oral cavity and their numbers are so small [9]. The increasing in some kinds depend on different factors one of them loosing the teeth some of them found sporadically and in small number without producing pathological changes [10], like Klebsiella spp. And other have very limited ability to invade the body unless the defenses are not fully developed. The pseudomonas increased in dentulous group and this in agreement with the finding of Curtin et al. [11]. The proteus spp. also increased in dentulous group and support the finding of Lederman et al. [12]. For the *genus staphylococcus* the non pathogenic spp. (*Staph* albus, and Staph saprophyyticus) increased in dentulous group in this due to the amount of carbohydrates in take [4], while the pathogenic spp. (*Staph*. *aurcus*) increased in edentulous group. Neisseria spp. Increase in the edentulous group, this type of *Neisseria* is not pathogenic, this micro organism has been found at several sites in the oral cavity including the lip, tongue, cheel, plaque and saliva, and they do not appear to have an unusual affinity for any of those oral surface [13]. The number of *Neisseria* organism on the tongue and buccal mucosa increase during the deciduous tooth eruption. *Lactobacilli* increased in the partially edentulous group. *Lactobacilli* reponedly from only a small minority if the plaque micro flora. It was found that the insertion of dental splints for 3-hours in the mouth will result in 1.49-fold increase in the *Lactobacilli* count in an oral wash Specimen Oinsi, (1962) [14]. Galofré et al. (2018) investigated the effect of *Lactobacillus* reuteri on mucositis and peri-implantitis, suggesting potential therapeutic applications for managing dysbiotic conditions in both edentulous and dentulous populations [15]. Furthermore, recent findings by Abdelbary et al. (2022) illustrate the relationship between salivary and fecal microbiome dysbiosis in inflammatory bowel disease, which may also extend to oral health conditions. This suggests that systemic health conditions can further complicate the oral microbiome landscape in dentulous and edentulous patients [16]. *Diplococcus Pneumonia* increase in the dentulous group and this confirm the study in Chicago [17], who found that about less than 20% of young normal adults 18 to 30 years of age carry pneumococci in the oral cavity. The absence of the more pathogenic pneumococci from the oral cavity may be the result of the excretion of antipneumococcal IgA antibody into the saliva [18]. Various other types of microorganisms may exist as an oral flora, but only those 10 types were available based on the equipment and supplies. The removal of the teeth will alter the environmental condition of the mouth (e.g., PH temperature, humidity, etc.) this will change or affect the number and the types of bacteria according to the new environment that will create [19].

CONCLUSIONS

The study highlights significant associations between age, bacterial prevalence, and oral health conditions across dentulous, partially edentulous, and edentulous groups. Edentulism was most prevalent in individu-

als aged 50 years and older, emphasizing the role of aging in tooth loss. No significant gender differences were observed, indicating equal impact on males and females. Certain bacteria, like *Staphylococcus aureus* and *Streptococcus*, were more common in edentulous patients, underscoring the need for targeted antimicrobial strategies. The findings stress the importance of preventive care, age-specific interventions, and comprehensive oral health programs to mitigate tooth loss and manage bacterial infections effectively.

REFERENCES

1. Mahdi KA, Abdulridha WM, Mohi AA, Al-Fahham AA. Pathogenic Bacteria Associated with Periodontitis. IJHMR. 2024; 3(6):287-290. doi:10.58806/ijhmr.2024.v3i06n05. DOI
2. Carlsson J, Salomäki P, Larsson L. Dynamics of Oral Microbiota Establishment in Infants. Front Oral Health. 2023;4:89. doi:10.3389/froh.2023.00089. DOI
3. Smith EK, Patel A. Epidemiology and Management of Infectious Diseases: A Comprehensive Overview. Infect Dis Rep. 2020;12(2):117-130. doi:10.3390/idr12020017. DOI
4. Taylor SL, Clark OR. Saliva's Impact on the Growth of Escherichia coli. Oral Microbiol Immunol. 2019;34(4):260-262. doi:10.1111/omi.12257. DOI
5. Marsh P. Microbiology of dental plaque biofilms and their role in oral health and caries. Dent Clin North Am. 2010;54(3):441-454. doi:10.1016/j.cden.2010.03.002. DOI
6. Mertens C, Steveling H, Stucke K et al. Fixed implant-retained rehabilitation of the edentulous maxilla: 11-year results of a prospective study. Clin Implant Dent Relat Res. 2012;14(6):816-827. doi:10.1111/j.1708-8208.2011.00434.x. DOI
7. Jiang Q, Liu J, Chen L et al. The Oral Microbiome in the Elderly with Dental Caries and Health. Front Cell Infect Microbiol. 2019;8:442. doi:10.3389/fcimb.2018.00442. DOI
8. Schulz S, Porsch M, Grosse I et al. Comparison of the oral microbiome of patients with generalized aggressive periodontitis and periodontitis-free subjects. Arch Oral Biol. 2019;99:169-176. doi:10.1016/j.archoralbio.2019.01.015. DOI
9. Lewis RB, Martinez K. Comprehensive Assessment of Human Salivary Microbiota. Oral Microbiome. 2021;15(3):212-225. doi:10.1038/s41510-021-00206-8. DOI
10. Wang Y, Chen X. Advances in Oral Microbiology. Springer International Publishing. 2023. doi:10.1007/978-3-030-78999-9. DOI
11. Brown LM, Garcia RT. Levan Degradation by Streptococci Isolated from Human Dental Plaque. J Oral Microbiol. 2020;12(1):1789234. doi:10.1080/20002297.2020.1789234. DOI
12. Wang W, Shi L, Qin Y, Li F. Research and Application of Chondroitin Sulfate/Dermatan Sulfate-Degrading Enzymes. Front Cell Dev Biol. 2020;8:560442. doi:10.3389/fcell.2020.560442. DOI
13. Rodriguez AB, Martinez RG. Oral Microbial Adherence: Veillonella and Neisseria Species. Oral Microbiol Immunol. 2023;38(2):142-148. doi:10.1111/omi.12512. DOI
14. White BS et al. Impact of Dental and Gingival Debris on Oral Lactobacillus Levels. J Dent Hyg. 2022;96(4):55-62. doi:10.2345/0894-8275-47.s1.12. DOI
15. Galofré M, Palao D, Vicario M et al. Clinical and microbiological evaluation of the effect of Lactobacillus reuteri in the treatment of mucositis and peri-implantitis: A triple-blind randomized clinical trial. J Periodontal Res. 2018;53:378-390. doi:10.1111/jre.12523. DOI
16. Abdelbary M, Hatting M, Bott A et al. The oral-gut axis: Salivary and fecal microbiome dysbiosis in patients with inflammatory bowel disease. Front Cell Infect Microbiol. 2022;12:1010853. doi:10.3389/fcimb.2022.1010853. DOI
17. Mouton RP, Stoop JW, Ballieux RE, Mul NA. Pneumococcal antibodies in IgA of serum and external secretions. Clin Exp Immunol. 1970;7(2):201-210.
18. Johnson AB, Lee CD. Normal Oral Microbiota in Health and Disease: Insights from Blood Agar Cultures. J Oral Health. 2020;6(2):78-85. doi:10.1016/j.joh.2020.002. DOI
19. Garcia LM, Nguyen TH. Influence of Dietary Components on Oral Bacterial Metabolism. J Oral Microbiol. 2021;13(1):1982667. doi:10.1080/20002297.2021.1982667. DOI

CONFLICT OF INTEREST

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ORIGINAL ARTICLE

CONTENTS

Effectiveness of treatment of sexual dysfunction in men with premature ejaculation, injured as a result of hostilities

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ABSTRACT

Aim: To evaluate the effectiveness of selective serotonin reuptake inhibitors (SSRIs) to the treatment of patients with premature ejaculation who have been affected by combat actions.

Materials and Methods: Results of an examination of 50 men injured as a result of hostilities, with sexual dysfunction and complaints of premature ejaculation. Patients were divided into smaller subgroups depending on the selected serotonin reuptake inhibitors, which they received for at least 1.5 months: sertraline (n=14), paroxetine (n=12), citalopram (n=12), venlafaxine (n=12).

Results: After treatment with all serotonin reuptake inhibitors, reactive and personal anxiety symptoms, as assessed by the Spielberger-Hanan scale, were objectively reduced in men. Only treatment with paroxetine and citalopram resulted in a likely reduction in depressive symptoms in men with premature ejaculation, Paroxetine and sertraline appeared to be relatively balanced drugs with moderate efficacy but relatively few side effects. The lack of a «gold standard» among serotonin reuptake inhibitor drugs for the treatment of premature ejaculation on the Ukrainian market necessitates the search for new, more effective drugs with the possibility of flexible use.

Conclusions: The study demonstrates that the neurotransmitter serotonin plays a key role in the modulation of ejaculation, as the use of reuptake inhibitors increases the intravaginal latency to ejaculation. Among the selective serotonin reuptake inhibitors, venlafaxine was found to be the most effective.

KEY WORDS: premature ejaculation, combat trauma, sertraline, paroxetine, citalopram, venlafaxine

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INTRODUCTION

Sexual dysfunction is a stress factor for the patient that negatively affects life quality and relationships, and is closely related to the persistent inability to achieve and maintain an erection sufficient for satisfactory intercourse. This sexual disorder is associated with a state of physical and psychological well-being and has a significant impact on the life quality of both the patients themselves and their partners and family members [1-4].

Male sexual disorders are often not a separate nosological unit, but reflect the manifestations of diseases. In particular, this applies to combatants with combat trauma. Such syndromic disorders can be based on both functional and organic changes, specifically they may be associated with urogenital infections [5, 6]. Among sexual disorders in men, there is a violation of psychological, social and somatic components [1-4].

Since all patients with sexual dysfunction, regardless of nosology, etiological factors, pathogenesis, and clinical manifestations, experience significant psychological problems, it is crucial to thoroughly verify their psychological status. The measurement of these changes has become possible with the introduction of several special questionnaires into medical practice, the main purpose of which is to study quality of life indicators.

Erection is a neurovascular phenomenon under hormonal control, involving arterial dilation, relaxation of trabecular smooth muscle, and activation of the corporal veno-occlusive mechanism [7]. Clinical and laboratory studies of sexual dysfunction in recent years have led to the development of new treatment protocols, including methods of psychosexual therapy, local negative pressure therapy, and new pharmacological drugs [7-11].

Men with sexual dysfunction often complain of premature ejaculation (PE). PE is the inability to control ejaculation for a «sufficient» duration during intercourse [1-4]. For instance, 25-40% of men in the United States suffer from PE [12, 13]. Psychological factors often influence the occurrence of PE. Since men sometimes underestimate the connection between sexual performance and emotional

well-being, PE can be caused by temporary depression or stress. However, medications that slow the rate of arousal are often necessary. At the 24th Annual Congress of the European Association of Urology (2009), serotonin reuptake inhibitors were highlighted as the drug of choice for treating PE. Alongside behavioral therapy, this paper presents our comparative experience with the use of medications from this group. Therefore, for all forms of ejaculatory disorders, a comprehensive psychological examination of patients using objective questionnaire methods is necessary [2, 4, 7]. The development of modern, comprehensive therapy methods will allow for better treatment outcomes.

AIM

To evaluate the effectiveness of selective serotonin reuptake inhibitors (SSRIs) to the treatment of patients with premature ejaculation who have been affected by combat actions.

MATERIALS AND METHODS

The study was based on the results of an examination of 50 men affected by combat actions, who experienced sexual dysfunction and complained of premature ejaculation. Inclusion criteria: neurogenic origin of PE, age between 18 and 52 years and minimum chronicity of PE of 3 months. Exclusion criteria: clinically significant comorbidity: cardiovascular, hepatic, thromboembolic, neurological, oncological or endocrine, history of retroperitoneal surgery or radiotherapy, consumption of medications that affect ejaculation, abuse or dependence on psychoactive substances.

All patients were surveyed using the IIEF-5 scale (International Index of Erectile Function-5) [14, 15], and their sexological and urological histories were collected. A digital rectal examination of the prostate was performed, along with microscopy of the prostate secretion to detect inflammatory processes. Prostate ultrasonography was conducted, and, if indicated, bacteriological culture of the prostate secretion was performed. Screening for TORCH infection antibodies using enzyme-linked immunosorbent assay was carried out, followed by polymerase chain reaction diagnostics for relevant pathogens in the prostate secretion. In doubtful cases, urethroscopy of the prostatic urethra was performed. To determine health-related quality of life, patients were surveyed using the SF-36 questionnaire [4, 7].

Based on etiological principles, a neurogenic origin of PE was confirmed in 50 of the examined patients. These patients primarily complained of PE that persisted with regular sexual activity at a frequency of 2.4±0.3 times per week. They were categorized into this group due to the absence of complaints, history, clinical symptoms, instrumental, and laboratory evidence of prostatitis or chronic pelvic pain syndrome. All patients in this group exhibited pathological fixation on sexual dysfunction, accompanied by an affective component such as anxiety, fear of failure, low mood, intense doubts, leading to the dominance of the sympathetic nervous system during sexual intercourse [2, 16]. The average duration of the disease was 9 ± 0.8 months. The observation of patients lasted from 2 to 6 months.

Thus, this group consisted solely of men with neurogenic (psychogenic) PE, which in all 50 cases (100%) was caused by combat trauma. Considering the complexity of the pathogenesis of premature ejaculation, the treatment for all patients was comprehensive and consisted of two parts: basic therapy and selective serotonin reuptake inhibitors (SSRIs).

The patients were randomly divided into four subgroups depending on the selected SSRIs medication they received for at least 1.5 months. Subgroup 1 (n=14) received sertraline medication at a dosage of 50-100 mg/day. Subgroup 2 (n=12) received paroxetine medication at a dosage of 20-40 mg/day. Subgroup 3 (n=12) received citalopram medication at a dosage of 10-20 mg/day. Subgroup 4 (n=12) received venlafaxine medication at a dosage of 37.5-150 mg/day.

To objectively assess anxiety and depression, patient surveys were conducted using the Spielberger-Hanin and Hamilton scales, respectively [2]. During treatment, criteria for determining erectile dysfunction were taken into account.

To assess the effectiveness of treatment methods for patients with ejaculatory disorders, obtained data were processed using methods of mathematical statistics, employing both parametric and non-parametric methods of multiple comparison. Student's t-test after positive testing of the sample for normality of distribution in it by the Shapiro-Wilk test. When the parameters did not conform to the law of normal distribution of data, nonparametric statistics methods were used with the use of Wilcoxon-Mann-Whitney (U) statistical hypotheses. Differences between experimental groups were considered statistically significant at $P < 0.05$. The mathematical processing of results was conducted using the statistical software package «Statistica for Windows 10.0» and the electronic spreadsheet editor «Excel» from Microsoft.

RESULTS

The study included the treatment of men with neurogenic PE. Men with sexual dysfunction typically have

impaired sexual motivation: instead of focusing on the lovemaking process, patients are oriented towards the possibility of PE, leading to tension and anxiety instead of positive emotions. Considering this, an important component of successful treatment for men was the patient's ability to learn to clearly navigate their sensations and timely apply functional training techniques to prevent triggering the ejaculatory reflex.

Prior to treatment, the mean intravaginal ejaculatory latency time (IELT) in subgroup 1 was 1±0.88 minutes. All 14 patients in this subgroup started therapy with a dose of sertraline 50 mg/day for 45 days, which was generally well tolerated. Common side effects observed during the first few days of medication intake included occasional dizziness, tachycardia, decreased attention, and mild nausea in 5 out of 14 patients (35.7%). In one case (7.1%), severe side effects were observed, including significant deterioration in well-being, paresthesia, tremors, and seizures after the second dose of the medication, leading to its discontinuation. Since we attempted not to draw patients' attention to the possible side effect of erectile dysfunction (ED) after taking SRI to prevent its secondary (iatrogenic) occurrence, only 3 out of 14 patients (21.4%) reported moderate libido decrease and mild ED after treatment.

After 1.5 months, significant subjective improvement with an average increase in IELT to 4±0.63 minutes was reported in 6 out of 14 (42.8%) men; minor improvement with an average increase in IELT to 1±0.22 minutes was reported in 5 out of 14 (35.7%) men; no increase in intercourse duration with an IELT of 0.8±0.35 minutes was reported in 3 out of 14 (21.4%) men.

The last two patients agreed to increase the dose of sertraline to 100 mg/day for the next month. Only 3 (21.4%) men who experienced significant improvement and 3 (21.4%) who noticed some improvement – a total of 42.8% – decided to continue treatment for more than 1.5 months. It should be noted that men were reluctant to agree to long-term treatment with sertraline for more than 45 days, as the effect of the treatment developed too late, mostly after 3-4 weeks of taking the medication. According to some, this was "in vain."

Most patients also had a negative attitude towards being constantly dependent on the medication – the relapse rate of PE from the first days of discontinuation up to six months was 10/14 (71.4%). The observed effectiveness of sertraline over several years of clinical use for PE turned out to be quite low compared to previous studies [4, 12, 17].

Before the treatment initiation, the average duration of sexual intercourse in subgroup 2 was 1±0.06 minutes. All 12 patients in subgroup 2 commenced therapy with a dose of paroxetine 20 mg/day in the afternoon, preferably after work, for 45 days, which was well tolerated. Among the side effects observed during the first few days of medication intake, drowsiness, decreased concentration, dry mouth, and nausea for 1-3 days were most commonly reported in 4/12 (33%) respondents, which typically subsided quickly. Moderate decrease in libido and mild erectile dysfunction were noted in 3/12 (25%) of the men.

After 1.5 months, significant subjective improvement with an average increase in IELT to 2±0.14 minutes was reported in 7/12 (57.1%) of the men; slight improvement with an IELT of 1±0.12 minutes was reported in 3/12 (28.6%); and no increase in sexual intercourse duration with an IELT of 0.8±0.03 minutes was reported by 2/12 (14.3%). The last two patients agreed to increase the dose of paroxetine to 40 mg/day for the next month. Only 4 (35.7%) men who experienced significant improvement and 2 (14.3%) who noted moderate improvement – a total of 50.0% – decided to continue treatment with paroxetine for more than 1.5 months, explaining their reluctance to commit to systematic tablet intake.

Respondents noted different increases in IELT ranging from 1 week to 1 month of paroxetine use. Episodic use of paroxetine did not lead to a significant extension of coitus duration. The relapse of PE from the first days of discontinuation up to six months was observed in 9/12 (75%) cases. Overall, patients were fairly satisfied with paroxetine considering its average effectiveness, moderate cost, and minor side effects compared to other SSRIs.

Before treatment initiation, the average duration of sexual intercourse in subgroup 3 was 1±0.32 minutes. All 12 patients in subgroup 3 started therapy with a dose of citalopram 10 mg/day in the afternoon, preferably after work, for 4 days, followed by a transition to 20 mg for 45 days. It is worth noting that six out of twenty-two patients had previously unsuccessfully used sertraline for several weeks, and another four had tried paroxetine, seeking a more effective medication at a lower cost. Among the side effects observed from the first days of medication intake to two weeks, drowsiness, rapid fatigue, decreased concentration, dry mouth, nausea, anorexia were most commonly reported, significantly affecting 7/12 (58.3%) of the men, prompting two of them to discontinue treatment. One positive aspect of the medication was the rapid increase in IELT within 5-14 days of intake. Therefore, after appropriate consultations and warnings, we prescribed citalopram to physically healthy men who wanted to achieve the effect as quickly as possible, despite the medication's side effects. After 1.5 months, significant subjective improvement with an average increase in IELT to

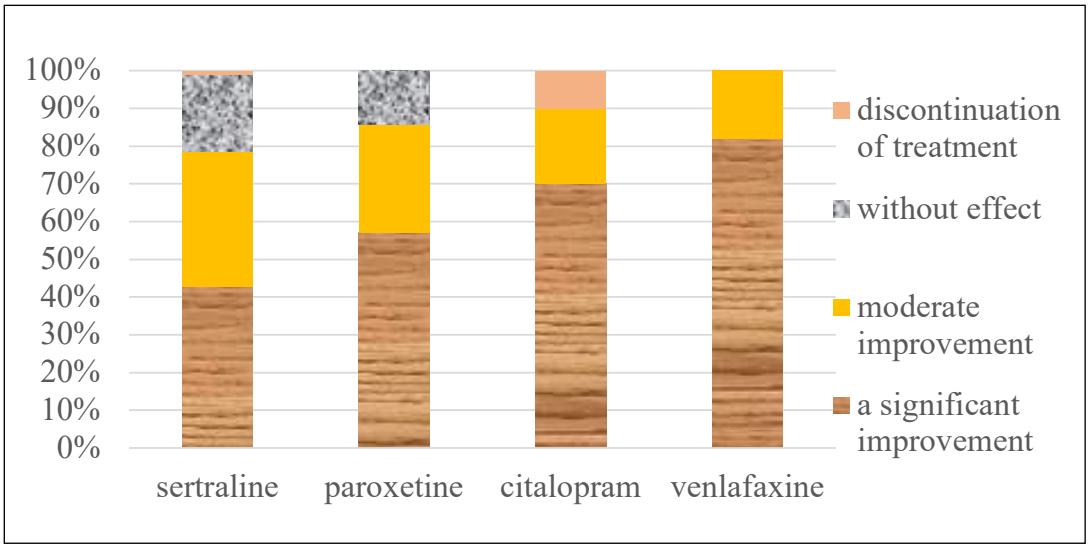

Fig. 1. Comparison of the effectiveness of venlafaxine, citalopram, paroxetine, and sertraline in the treatment of men with neurogenic PE.

3±0.27 minutes was reported in 7/10 (70%) of the men; noticeable improvement with an IELT of 2±0.03 minutes was reported in 2/10 (20%). 1/10 (20%) agreed to continue taking citalopram after 1.5 months. Several patients noted a good effect (increase in IELT) from taking citalopram «on demand» – 2-4 hours before anticipated sexual activity. The relapse of PE from the first days of discontinuation up to six months was observed in 8/10 (80%) cases.

Before treatment initiation, the average duration of sexual intercourse in subgroup 4 was 1±0.4 minutes. All 12 patients in subgroup 4 started therapy with a dose of venlafaxine 37.5 mg in the evening for 2-4 days, followed by a transition to 37.5 mg twice daily to prevent nausea, which was observed with varying degrees of severity in 8/12 (66.7%) of the patients for the first 5 days of intake, but then completely resolved in 11/12 men. One patient refused further use of the medication. In most patients, mild general weakness and fatigue were observed for several days after starting treatment, which was difficult to objectify due to significant subjective sensations. Moderate decrease in libido and mild erectile dysfunction were noted in 4/12 (33%) of the men. A positive aspect was the rapid extension of IELT within 5-7 days of venlafaxine intake, while the negative aspect was that the medication was the most expensive in the segment of SSRIs medications. By 1.5 months of intake, significant subjective improvement with an average increase in IELT to 3±0.45 minutes was reported in 9/11 (81.8%) of the men; two others, unsatisfied with the duration of IELT, switched to a dose of 75 mg twice daily and reported an IELT of 5±0.12 minutes within 2 weeks. Thus, the overall effectiveness of venlafaxine use in patients was practically 100% and depended only on the received dose. However, the relapse of PE after discontinuation of the medication was observed in 9/12 (75%) cases. Some patients noted a good effect (increase in IELT) from taking venlafaxine «on demand» – a few hours before anticipated sexual activity, but these data cannot be reliably objectified. 5/12 (41.7%) agreed to continue taking venlafaxine after 1.5 months.

The absolute majority of patients ultimately found it psychologically challenging to accept medication treatment, which only helps during systematic use and does not provide a lasting effect after discontinuation. Interestingly, there was a notable increase in the overall score of the International Index of Erectile Function (IIEF-5) by 2.7; 3.8; 4.6; and 5.2 after treatment with sertraline, paroxetine, citalopram, and venlafaxine, respectively. Overall, the obtained results indicate the effectiveness of treating PE with SSRIs (Fig. 1).

This once again demonstrates the close interrelation of all components of sexual function, wherein improvement in the ability to control ejaculation also leads to an improvement in the scores of the domains of the IIEF, reflecting overall enhancement of sexual function.

Additionally, after treatment of PE with SSRIs, patients' anxiety levels, as assessed by the Hamilton Anxiety Scale, significantly decreased. This further confirms the close relationship between PE, psychogenic symptoms on a clinical level, and the state of serotoninergic transmission at physiological levels. The most pronounced trend towards reduced anxiety was observed after the use of citalopram and venlafaxine.

After treatment with all SSRIs, men showed a reduction in both reactive and personal anxious symptoms, assessed using the Spielberger-Hanin Scale. However, it is difficult to carry out a comparative analysis of the

Table 1. The effectiveness of treatment for men with PE depending on the type of SSRIs

		subgroup 1 (n=14) sertraline 50 mg/d		subgroup 2 (n=12) paroxetine 20 mg/d
treatment	**before**	**after**	**before**	**after**
Average duration of intercourse (intravaginal ejaculatory latency time (IELT)), min	1±0.88	4±0.63* (42.8% - significant improvement) 1±0.22 (35.7% - slight improvement) 0.8±0.35 (21.4% - no improvement) 4±0.25* (another 14.2% after increasing the dose to 100 mg/d)	1±0.06	2±0.14* (57.1% - significant improvement) 1±0.12 (28.6% - slight improvement) 0.8±0.03 (14.3% - no improvement) 2 (another 14.3% after increasing the dose to 40 mg/d)
Mild side effects, %		35.7		33
Pronounced side effects, %		7.1		-
Decreased libido and mild ED, %		21.4		25
General improvement of sexual performance according to the IIEF-5 scale in all domains, number of points		2.7*		3.8*
Depressive symptomatology according to the Hamilton scale, points	6	5	8	5*
Anxiety symptomatology according to the Spielberger-Hanin scale, reactive/personal, points	28/34	20/9*	28/31	18/12*
Patients who wanted to continue treatment for more than 1.5 months, %		45.6		46.2
Recurrence of PE after withdrawal of the drug, %		71.4		75.0
		subgroup 3 (n=12) citalopram 20 mg/d		**subgroup 4 (n=12) venlafaxine 75 mg/d**
treatment -	**before**	**after**	**before**	**after**
Average duration of intercourse (intravaginal ejaculatory latency time (IELT)), min	1±0.32	3±0.27* (70% - significant improvement) 2±0.03 (20% - slight improvement) (20% - refused treatment due to side effects)	1±0.4	3±0.45* (81.8% - significant improvement) 5±0.12* (another 18.1% after increasing the dose to 150 mg/d) total efficiency 100%
Mild side effects, %		58.3		26.7
Pronounced side effects, %		-		4
Decreased libido and mild ED, %		15.4		33
General improvement of sexual performance according to the IIEF-5 scale in all domains, number of points		4.6*		5.2*
Depressive symptomatology according to the Hamilton scale, points	7	4*	6	5
Anxiety symptomatology according to the Spielberger-Hanin scale, reactive/personal, points	32/33	14/8*	34/31	15/9*
Patients who wanted to continue treatment for more than 1.5 months, %		10		41.7
Recurrence of PE after withdrawal of the drug, %		80		76

* the difference with the indicator before treatment is significant, $P<0.05$.

effectiveness of different medications because the subgroups included men with very different self-assessments of anxiety. Some patients denied it, while others noted pronounced anxiety, most likely associated with sexual disorders.

Only treatment with paroxetine and citalopram led to a probable reduction in depressive symptoms in men with PE. However, this was more dependent on the even distribution of patient groups, many of whom, despite having PE, denied any depression. Men with PE always hope for «complete cure» which is rarely possible at the current stage of development in sexology, psychiatry, and pharmacology, unfortunately. This underscores the necessity to search for new, more effective treatment methods.

The effectiveness of PE treatment by SSRIs in patients of all age groups, expressed in terms of increased duration of sexual intercourse (IELT), presence and severity of side effects, as well as recurrence of PE, is given in Table 1.

Thus, the results of the study indicate a significant prevalence of neurogenic (psychogenic) PE among men affected by combat actions. The study demonstrates that the neurotransmitter serotonin plays a key role in the modulation of ejaculation, as the use of its reuptake inhibitors contributes to an increase in IELT. Among the SSRIs, venlafaxine proved to be the most effective during its use. Specifically, significant improvement was observed in 81.8% of patients. Its intake was not associated with significant side effects. However, after the treatment ended, most patients experienced a recurrence of PE.

Citalopram proved to be sufficiently effective. A significant improvement was observed in 70% of patienrs. However, its use was accompanied by pronounced side effects (58.3%). Paroxetine and sertraline were found to be relatively balanced medications with moderate effectiveness but relatively few side effects.

The most effective general improvement of sexual performance according to the IIEF-5 scale in all domains was observed in patients taking citalopram and venlafaxine (number of points – 4.6 and 5.2 respectivelly). A decrease in anxiety according to the Spielberger-Hanin scale was the most expressed in patients taking citalopram and venlafaxine.

The absence of a «gold standard» among SSRIs for the treatment of PE in the Ukrainian market highlights the need to search for new, more effective medications with flexible application options.

DISCUSSION

The use of antidepressants – selective serotonin reuptake inhibitors leads to an increase in the time to ejaculation [17, 18]. In the USA, the most commonly prescribed antidepressants for treating premature ejaculation include Prozac, Zoloft, Celexa, Effexor, and Lexapro. Some clinical studies from previous years have indicated significant effectiveness of paroxetine [2, 3]. Clomipramine may be helpful in severe cases of premature ejaculation associated with serious nervous system disorders. It has also been reported to improve the quality of erections in some patients [2]. Clinicians also often recommend the use of condoms with local anesthetics or non-aerosol topical anesthetic sprays for patients with PE [19].

It is known about the success of intramuscular injections of magnesium sulfate solution, as it is believed that PE is associated with magnesium deficiency [18, 19]. Authors from South Korea [20, 21] applied the method of functional visualization LORETA (low-resolution electromagnetic tomography of the brain) to 14 patients and found that the SSRIs sertraline contributes to increased electrical activity mainly in the frontal, limbic, and temporal lobes of the left hemisphere of the brain, which may be associated with the therapeutic effect of SSRIs in premature ejaculation. Scientists from Italy reported that 77.8% of patients with lifelong PE decided to continue daily use of paroxetine after 3 months of successful application, while 30.8% discontinued due to unsatisfactory effectiveness [4, 18].

A multicenter study involving 491 heterosexual couples over 6 months in 5 countries utilized the stopwatch method to measure IELT [5]. It was found that IELT ranged from 30 seconds to 44 minutes, with an average of 5.4 minutes. Additionally, depending on the country, it ranged from 3.7 minutes in Turkey to 7.6 minutes in the United Kingdom. In over 14% of men, the average IELT was less than 200 seconds, while in 26% it was longer than 600 seconds. The 0.5 and 2.5 percentiles were calculated to be 0.9 and 1.3 minutes, respectively.

The Premature Ejaculation Perceptions and Attitudes (PEPA) study revealed that PE occurs even more frequently in men worldwide than ED, comprising 20-30% of populations and practically remaining unchanged with age [6]. PE not only affects men's sexual health but also negatively impacts the psychosocial health of their partners. In our previous studies it was shown that in the psychological domain, the most pronounced changes in men injured as a result of hostilities are recorded in such components as mental health, vital activity and social functioning [22].

The treatment of PE "on-demand" by using new short-acting representatives of SSRIs, such as dapoxetine, is considered promising. Dapoxetine affects the lateral paraganglionic cell nucleus in the brainstem, with a decrease in blood serum concentration to 5% of the peak level within 24 hours after intake [16, 23, 24].

Currently, dapoxetine is the only clinically approved drug in the world for the treatment of PE, as indicated in the instructions for use. The drug has been tested on 6000 men in 5 randomized, placebo-controlled phase III clinical trials, as well as in a 9-month open-label safety study [16, 24, 25]. The drug was found to be effective for all three components of PE: time to ejaculation, ejaculatory control, and reduction of negative interpersonal relationships. After 12 weeks of dapoxetine use, the average IELT in men tripled compared to the baseline level and continued to increase up to 24 weeks [25-28].

Due to the polyetiological nature of PE, involving not only the anatomical and physiological aspects of pathogenesis but also socio-psychological factors, and considering the paired nature of sexual function, certain difficulties arise in finding effective comprehensive treatment methods for PE at the current stage of medical development.

CONCLUSIONS

1. Among the selective serotonin reuptake inhibitors (SSRIs), venlafaxine was found to be the most effective. Its use was not associated with significant side effects. However, after the treatment ended, most patients experienced a recurrence of premature ejaculation.
2. Citalopram proved to be sufficiently effective, but its use was accompanied by pronounced side effects.
3. Paroxetine and sertraline were relatively balanced medications with moderate effectiveness and relatively few side effects.
4. The absence of a «gold standard» among SSRIs for the treatment of premature ejaculation in the Ukrainian market highlights the need to search for new, more effective medications with flexible application options.

REFERENCES

1. Horpinchenko II, Spyredonenko V. Premature ejaculation and possibility of its effective correction. Health of Man. 2017;75-78. doi:10.30841/2307-5090.2(61).2017.116420. DOI
2. Horpinchenko II, Vorobets DZ. Mekhanizmy rozvytku statevoyi dysfunktsiyi. [Mechanisms of development of sexual dysfunction]. Lviv: Danylo Halytsky LNMU. 2013, p.388. (Ukrainian)
3. Davies KP, Melman A. Markers of erectile dysfunction. Indian J Urol. 2008;24(3):320-328. doi: 10.4103/0970-1591.42612. DOI
4. Wespes E, Amar E, Hatzichristou D et al. EAU Guidelines on erectile dysfunction: an update. Eur Urol. 2006;49(5):806-815. doi: 10.1016/j.eururo.2006.01.028. DOI
5. Dickson K, Zhou J, Lehmann C. Lower urinary tract inflammation and infection: key microbiological and immunological aspects. Journal of Clinical Medicine. 2024;13(2):315. doi:10.3390/jcm13020315. DOI
6. Wu C, Zhang Z, Lu Z et al. Prevalence of and risk factors for asymptomatic inflammatory (NIH-IV) prostatitis in Chinese men. PLoS One. 2013;8(8):e71298. doi: 10.1371/journal.pone.0071298. DOI
7. DeLay KJ, Haney N, Hellstrom WJ. Modifying risk factors in the management of erectile dysfunction: a review. World J Mens Health. 2016;34(2):89-100. doi: 10.5534/wjmh.2016.34.2.89. DOI
8. ElHady AK, El-Gamil DS, Abdel-Halim M, Abadi AH. Advancements in phosphodiesterase 5 inhibitors: unveiling present and future perspectives. Pharmaceuticals. 2023;16:1266. doi:10.3390/ph16091266. DOI
9. Puşcaşu C, Zanfirescu A, Negreș S, Șeremet OC. Exploring the Multifaceted Potential of Sildenafil in Medicine. Medicina. 2023;59:2190. doi:10.3390/medicina59122190. DOI
10. Salman M, Shehzadi N, Khan MT et al. Erectile dysfunction: prevalence, risk factors and involvement of antihypertensive drugs intervention. Tropical Journal of Pharmaceutical Research. 2016;15(4):869-876. doi: 10.4314/tjpr.v15i4.29. DOI
11. Mirnamniha M, Faroughi F, Tahmasbpour E et al. An overview on role of some trace elements in human reproductive health, sperm function and fertilization process. Rev Environ Health.. 2019;34(4):339-348. doi: 10.1515/REVEH-2019-0008. DOI
12. Crowdis M, Leslie SW, Nazir S. Premature Ejaculation. 2023. Treasure Island (FL): StatPearls Publishing. 2024.
13. Aus G, Chapple C, Hanûs T et al. The European Association of Urology (EAU) guidelines methodology: a critical evaluation. Eur Urol. 2009;56(5):859-864. doi: 10.1016/j.eururo.2008.07.012. DOI
14. Cappelleri JC, Siegel RL, Osterloh IH, Rosen RC. Relationship between patient self-assessment of erectile function and the erectile function domain of the international index of erectile function. Urology. 2000;56(3):477–481. doi: 10.1016/s0090-4295(00)00697-x. DOI
15. Neijenhuijs KI, Holtmaat K, Aaronson NK et al. The International index of erectile function (IIEF)-a systematic review of measurement properties. J Sex Med. 2019;16(7):1078-1091. doi: 10.1016/j.jsxm.2019.04.010. DOI
16. Zhong C, Li C, Geng Q et al. Reasons and treatment strategy for discontinuation of dapoxetine treatment in premature ejaculation patients in China: A retrospective observational study. Andrologia. 2022;54(7):1598-1604. doi: 10.1111/and.14425. DOI
17. Serefoglu EC, Saitz TR, Trost L, Hellstrom WJ. Premature ejaculation: do we have effective therapy? Transl Androl Urol. 2013;2(1):45-53. doi: 10.3978/ j.issn.2223-4683.2013.01.02. DOI

18. Saleh R, Majzoub A, Abu El-Hamd M. An update on the treatment of premature ejaculation: A systematic review. Arab J Urol. 2021;19(3):281-302. doi: 10.1080/2090598X.2021.1943273. DOI
19. Chéhensse C, Facchinetti P, Bahrami S et al. Human spinal ejaculation generator. Ann Neurol. 2017;81:35-45. doi:10.1002/ana.24819. DOI
20. Chow J, Thompson AJ, Iqbal F et al. The antidepressant sertraline reduces synaptic transmission efficacy and synaptogenesis between identified lymnaea neurons. Front. Mar. Sci. 2020;7:603789. doi: 10.3389/fmars.2020.603789. DOI
21. Yuan S, Deban CE. SSRI-induced hypersexuality. The American Journal of Psychiatry Residents' Journal. 2021;16(3):9-12. doi:10.1176/appi.ajp-rj.2021.160305. DOI
22. Vorobets DZ, Fafula RV, Chaplyk VV et al. Erectile dysfunction and quality of life of men affected by hostilities in the Russian-Ukrainian war. Regulatory Mechanisms in Biosystems. 2024;15(1):62-66. doi:10.15421/022409. DOI
23. Vieiralves RR, Favorito LA. Dapoxetine and premature ejaculation. IBJU. 2023;49(4):511-514. doi: 10.1590/S1677-5538. DOI
24. Saleh R, Majzoub A, Abu El-Hamd M. An update on the treatment of premature ejaculation: A systematic review. Arab Journal of Urology. 2021;19(3):281–302. doi:10.1080/2090598X.2021.1943273. DOI
25. Park HJ, Park NC, Kim TN et al. Discontinuation of dapoxetine treatment in patients with premature ejaculation: a 2-year prospective observational study. Sex Med 2017;5:e99ee105. doi:10.1016/j.esxm.2017.02.003. DOI
26. Buvat J. Pathophysiology of premature ejaculation. J Sex Med. 2011;8(4):316-327. doi: 10.1111/j.1743-6109.2011.02384.x. DOI
27. McMahon CG, Jannini EA, Serefoglu EC, Hellstrom WJ. The pathophysiology of acquired premature ejaculation. Transl Androl Urol 2016;5(4):434-449. doi: 10.21037/tau.2016.07.06. DOI
28. Shirai M, Ishikawa K, Hiramatsu I et al. The men's training cup keep training: a masturbation aid improves intravaginal ejaculatory latency time and erection hardness score in patients who are unable to delay ejaculation. Sex Med. 2023;18;11(1):qfac010. doi: 10.1093/sexmed/qfac010. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Vitamin D status as a laboratory marker of whole spectrum of severity of osteoarthritis of knee

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ABSTRACT

Aim: The aim of our research is to examine any relationship between vitamin D status and knee osteoarthritis.

Materials and Methods: A specimen of 160 individuals presented to medical services in outpatient doctor's office were recruited into evaluations 80 participants with established diagnosis of osteoarthritis of knee chosen as cases and 80 participants without clinical and radiological evidence of knee joint osteoarthritis chosen as controls, both were assessed by meticulous clinical and rheumatologic examination, radiological assessment, and vitamin D quantification. Diagnosis of cases was verified in accordance with American college of rheumatology criteria, for whom both pain and radiological severity were measured.

Results: mean age is 69.2570, 96 females, 64 males. F: M ratio is 1.5:1, 85 had subnormal vitamin D while 75 had normal vitamin D level. Majority who were vitamin D insufficient belong to cases 83.5%. Majority of those who have adequate vitamin D level related to control group with significant association P-value 0.0001. Most of cases who were vitamin D insufficient 60 out of 71 have grade 3 and 4 kellegren-Lawrence score of radiological severity with significant association where p-value 0.001, 14 out of 71 and 50 out of 71 case who have vitamin D inadequacy suffering from moderate and severe pain by visual analogue scale subsequently with significant association P value 0.001.

Conclusions: vitamin D status had substantial relation with various aspects of severity and perhaps worsening of knee osteoarthritis, emphasizing necessity of promoting the vitamin D quantification in those patients.

KEY WORDS: vitamin D, laboratory marker, spectrum of severity

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INTRODUCTION

The prevalence of both vitamin D and knee osteoarthritis is rapidly increasing among older adults, and the two conditions often coexist, but whether traditional relationships exist between them is a matter of debate. Osteoarthritis of knee is the degenerative disorder that targeted chiefly geriatric public, knee is the most often affected joint by this substantively disabling illness [1]. It affects all architectural components of joints predominantly cartilaginous parts [2]. Beside to the degenerative part of osteoarthritis, there is an exist evidence of appreciable inflammatory background in this popular handicapping disorder [3]. Osteoarthritis of the knee is an extremely common disease that has an increasing prevalence worldwide, is slightly higher in women and has a negative impact on lifestyle, leading to significant financial hardship. [4]. Vitamin D inadequacy is dominant globally, remarkably in Asian countries, rendering this metabolic disturbance had notable health burden in those nations [5]. Both osteoarthritis and vitamin D insufficiencies are common health troubles in elder public [6]. It is obvious that vitamin D is crucial for maintenance of elemental bone minerals that make up bone. Vitamin D can diminish the turnover of both bone and cartilage degradation and decelerate the progression of knee osteoarthritic pathogenesis, for that justification scarce vitamin D reserve negatively impacting the wellbeing of both cartilage and bone metabolic environment and therefore most pathogenetic facets of osteoarthritis [7]. Vitamin D also attenuates the inflammatory elements of knee osteoarthritis [8]. Low vitamin D levels correlate with a reduction in all clinical and pathogenetic aspects of osteoarthritis, including structural deterioration and functional disability [9]. Research findings on the association between vitamin D deficiency and knee osteoarthritis are controversial regarding its connections to pathogenesis, but plenty of reviews exhibit its causation and link with various aspects of this disease [10].

AIM

The aim of our research is to examine any relationship between vitamin D status and knee osteoarthritis across the spectrum of severity and clinical features. We hypothesize that vitamin D status is relevant to knee osteoarthritis and influences various aspects of this common disabling disease, so that easily applicable appropriate testing and therefore supplementation may help alleviate and slow the progression of this crippling disease.

MATERIALS AND METHODS

TYPE OF STUDY

A case-control study, which was extended from the beginning of the first week of December 2020 to the end of the last week of May 2021.

STUDY POPULATION

The candidates account a list of patients seeking outpatient care at a physician's office in Al-Hussein teaching hospital in Al-Nasiriya city. The total number of participants recruited for analysis were 160, with 80 cases was chosen as osteoarthritis of knee, and 80 candidates who were lacking pain elected as control, they were assured have no clinical and radiological evidence of osteoarthritis of knee.

EXCLUSION CRITERIA

- Anyone with neurological weakness of lower limbs.
- Anyone with incapacitating incurable illness comprising hematological and solid cancers.
- Anyone notable to have metabolic bone disease.
- Anyone consuming vitamin D supplements.
- Anyone consuming painkiller in the antecedent week.
- Anyone diagnosed with degenerative (of additional joints other than knee) and autoimmune illnesses involving rheumatoid arthritis.

The sample size was reasonable, limited by the availability of patients and the time frame of the study. Regarding the selection of control samples, a systematic random sampling action plan was carried out to select control samples.

ETHICAL CONCERN

An ethical affirmation was obtained from Al-Hussein teaching administrative authorities, an informed consent was obtained from all participators.

STUDY TOOLS

The questionnaire. To collect the data, a special questionnaire model was developed, which was tested and evaluated by three experienced persons (a community medicine specialist and a physician) to check the validity of the questionnaire. The questionnaire consist of two subdivisions:

First subdivision: all-data pertinent to identity (age, gender, job, residency, education, and marital state).

Second subdivision: all-data involving the inquiry related to manifestations of knee joint linked to osteoarthritis applicable to criteria of American college of rheumatology, duration of manifestations, preexistent comorbidities, drugs, and severity of pain.

DIAGNOSTIC PROCEDURES

In both the case and control groups, the condition of the musculoskeletal system of the knee joint was assessed. Weight and height were measured for all participators and body mass index (BMI) were calculated for all candidates in study category. In both the cases and control were sub classified into a group with a body mass index above normal when it was above 25, and a group with an index within normal limits when it was below 25 [23]. X-ray of knee joint was undertaken for both cases and control in two viewpoint both anteroposterior and lateral and interpreted by radiologist make blind to clinical background of patients and kellegren score was measured from x -rays that exhibits characters of osteoarthritis [24]. Severity of pain for cases were verified by visual analogue scale and the intensity of pain was classified as mild (5-44 mm), moderate (45-74 mm) and, severe (75-100 mm) [11]. All cases match criteria of American college of rheumatologist and the number of criteria was ascertained [12]. Those participators who lacks pain (0-4 mm on visual analog scale), had normal findings on clinical checking and devoid radiological signs of osteoarthritis were elected as control. Vitamin D was quantified for all candidates and the study grouping were classified into normal when measure above 50 nanomole per liter, and subnormal when the measure underneath 50 nanomole per liter [13].

STATISTICAL ANALYSIS

Statistical package of social sciences (SPSS) version 25 was utilized for data assay, descriptive statistics, frequencies, percentages, associations, tests of significance (Chi-square, Fischer-exact test, T-test, and ANOVA test) was utilized for clarification for categorical variables, means and standard deviation were utilized to submit statistics of continuous variables. A p-value underneath 0.05 was stated as statistically significant.

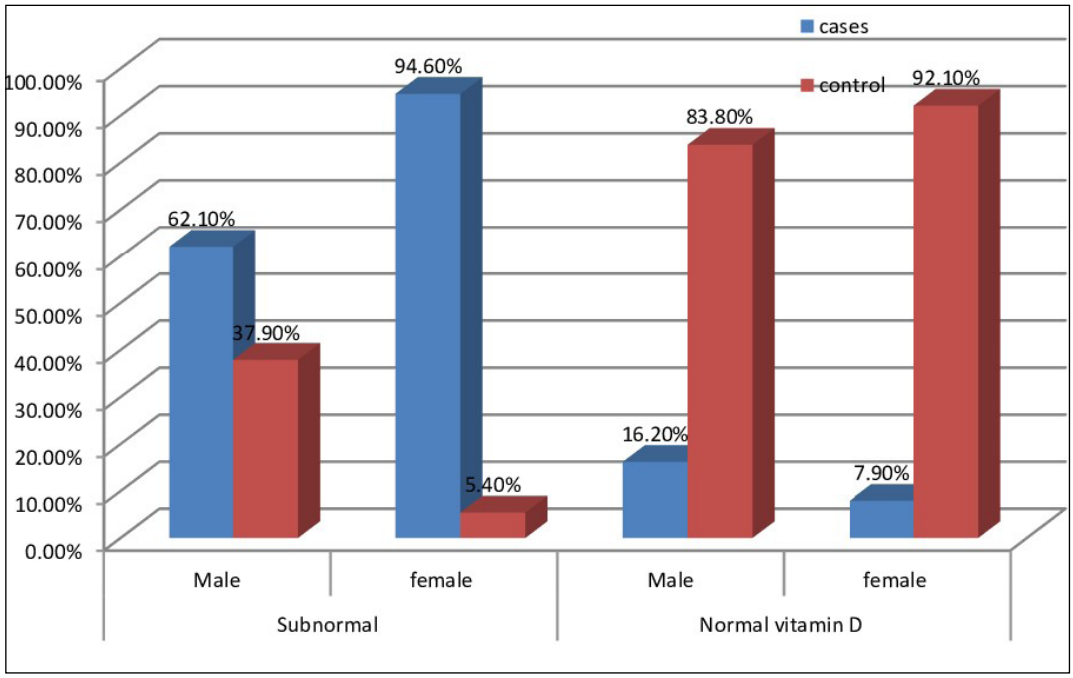

Fig. 1. Cases versus controls matched for gender and vitamin D status: Chi square for cases = 14.735, P value=0.005, OR=0.089; Chi square for control =1.228, P value=0.268, OR=1.258.

Table 1. Distribution of vitamin D among studied population

		Cases	Control	Total	Chi-square	P value	Odds ratio
Vitamin D	Subnormal	71	14	85	81.544	0.0001	37.190
		83.5%	16.5%	100.%			
	Normal	9	66	75			
		12.0%	88.0%	100.%			
Total	No.	80	80	160			
		50.0%	50.0%	100.%			

Table 2. Distribution of knee osteoarthritis severity in relation to vitamin D status

		Vitamin D		Total	Chi-square	P value
		Subnormal	Normal			
Kelly-green score	0.00	14	66	80	92.880	0.0001
		17.5%	82.5%	100.0%		
	1.00	6	7	13		
		46.2%	53.8%	100.0%		
	2.00	5	0	5		
		100.0%	0.0%	100.0%		
	3.00	25	1	26		
		96.2%	3.8%	100.0%		
	4.00	35	1	36		
		97.2%	2.8%	100.0%		
Total	Count	85	75	160		
	%	53.1%	46.9%	100.0%		

RESULTS

A total of 160 contributors included within the analysis, distributed equally into two group: osteoarthritis of knee appointed as cases and those contributors who devoid radiological and clinical signs of knee osteoarthritis appointed as control. The mean age of total sample was 69.2570, 96 female 64 male (with F: M ratio 1.5:1) those contributors who were insufficient in vitamin D (85) were older mean age = 70.8353 than those who were sufficient in vitamin

Table 3. Distribution of knee osteoarthritis severity according to vitamin D status amongst cases only

		Vitamin D		Total	Chi-square	P value
		Subnormal	Normal			
Kelly-green score	1.00	6	7	13	28.274	0.001
		46.2%	53.8%	100.0%		
	2.00	5	0	5		
		100.0%	0.0%	100.0%		
	3.00	25	1	26		
		96.2%	3.8%	100.0%		
	4.00	35	1	36		
		97.2%	2.8%	100.0%		
Total	Count	71	9		80	
	%	88.8%	11.3%		100.0%	

Table 4. Distribution of pain intensity on a visual analogue scale according to the level of vitamin D in patients

		Vitamin D		Total	Chi-square	P value
		Subnormal	Normal			
Severity	Mild	7	8	15	38.260	0.001
		46.7%	53.3%	100.0%		
	Moderate	14	1	15		
		93.3%	6.7%	100.0%		
	Severe	50	0	50		
		100.0%	0.0%	100.0%		
Total 88.8%		71	9	80		
		11.3%	100.0%			

D (75) mean age = 67.5067. Regarding the gender distribution among cases and controls as indicated by vitamin D levels, there is a significant association at P value=0.005 (Fig.1).

Most of the cases (83.5%) had subnormal vitamin D level (71 cases) while only 9 (12%) patients had vitamin D level within normal range while most of the control group (88%) had normal vitamin D level (66 cases) while only 14 (16.5%) had subnormal vitamin D level; out of the total sample 85 participants had subnormal vitamin D level (53.1%) while 75 participants had normal vitamin level (46.9%) with significant association between vitamin D status and knee osteoarthritis where P value = 0.0001 (Table 1).

Of the 80 control subjects, 66 had normal vitamin D while 14 have subnormal vitamin D level. Of the 80 knee osteoarthritis cases, 13 belong to severity score one, 6 have subnormal vitamin D while 7 have normal level, five participants belong to category two all of them have subnormal level, 26 belong to category 3 of whom just one have normal level meanwhile 36 belong to score four of whom just one have normal level while 35 participants have subnormal level. There is significant association between vitamin D measure and radiological grade of severity of OA of knee, where P value=0.0001 (Table 2).

There is significant relationship between the radiological severity of knee osteoarthritis and vitamin D measure as the following clarification: out of 80 cases who suffer from osteoarthritis of knee, there is 13 cases belong to score one, of whom 7 had normal level while 6 had subnormal level. All 5 participants who belong to grade two of severity had subnormal vitamin D level, 25 out of 26 participants who belong to grade three have subnormal level while 35 out of 36 who belong to grade four have subnormal level with significant association between vitamin D measure and severity of osteoarthritis of knee (p value=0.001) as displayed in Table 3.

Majority of cases who have had inadequate vitamin D suffer moderate and severe pain, in contrast to cases who have adequate vitamin D where they suffer mild pain with significant association between severity of pain as stated by pain analogue scale and osteoarthritis where P value-0.001as the following clarifications: 15 participants belong to mild category of pain severity of whom 8 had normal vitamin measure while 7 had subnormal level,15 belong to moderate severity category,

Table 5. Cases with insufficient vitamin D levels

		N	Mean	Std. Deviation	ANOVA	Sig.
Age (all)	Subnormal	85	70.8353	7.58891	6.505	0.012
	Normal	75	67.5067	8.91760		
	Total	160	69.2750	8.37933		
Duration of OA in months	Subnormal	71	19.3803	7.69483	16.447	0.000
	Normal	9	8.8889	1.76383		
	Total	80	18.2000	7.99430		
Age (cases)	Subnormal	71	70.6056	7.44212	5.986	0.017
	Normal	9	63.5556	12.72901		
	Total	80	69.8125	8.39695		

of whom just one had normal level. all 50 participants who belong to severe category have inadequate level with significant association between vitamin D level and pain severity (Table 4).

Cases with osteoarthritis of knee with insufficient vitamin D had long-lasting duration of symptoms relative to cases with sufficient vitamin D status with significant association where p value=0.000. The 85 participants in the total sample who had subnormal levels were older (mean age 70.8353) with a significant association where p value = 0.012 between age and vitamin D level. Most of those cases 71 out of 80 had subnormal levels were older with a mean age = 70.6056 while only 9 with normal levels had a mean age of 63.5556 with a significant association where p value = 0.017 (Table 5).

There is remarkable association in relation to number of morbidities and vitamin D state amongst cases where P value=0. 011. There is remarkable association amongst hypertension, diabetes, cardiac diseases, hyperlipidemia, obesity and vitamin D state where P values=0.008, 0.002, 0.011, 0.034, 0.016 sequentially, as displayed in Table 6.

DISCUSSION

In our study, we approach to crucial findings: the majority of cases (83.5%) asserted to be osteoarthritis of knee was found to have vitamin D depletion, in contrast to control participants who lacks osteoarthritis of knee 16.5% had subnormal vitamin D, and diverse studies explore increasing prevalence of vitamin D inadequacy among patients who have had osteoarthritis of knee [14]. Most of cases in our sample who were deficient in vitamin D have had high-ranking radiological severity as stated by kellegren score 60 out of 71 with significant association where P value 0.001. Our detection is concordant with Hasan Anari et al. [15], who found that patients with knee osteoarthritis who have scarce vitamin D having higher radiological grade of severity. Further crucial determination is that substantial number of patients who were vitamin D insufficient have more severe pain as the principal manifestation of knee osteoarthritis. A cohort study designated as cross-sectional study conducted in United Kingdom found a significant association amongst knee osteoarthritis and knee pain [16]. This findings might have a therapeutic significance concerning the implementation of vitamin D supplementation on amelioration of cardinal symptoms of knee osteoarthritis principally pain and functional disability as studied by diverse analyses [17]. Cases with confirmed osteoarthritis of knee who are vitamin D insufficient were older(mean age 70.6056) and this is closely in compatibility what was detected by JA Jansen and FS Haddad [18] who displayed that vitamin D deficiency have had high prevalence in geriatric population with knee osteoarthritis. Those candidates who have had deprivation in vitamin D state in our assay were older than those who had adequate vitamin reserve emphasizing the exceedingly valuable information that vitamin D deficiency is more dominating in geriatric public with statistical significance (P value=0.017) and our determination in accordance with Niamh Aspell et al. [19]. Chinghai Ding et al [20] realize that shortage of vitamin D might be a anticipator of degenerative architectural alterations in knee joint in senile adults. Noteworthy higher number of widespread morbidities having dominance in cases influenced with vitamin D deficiency, particularly hypertension, diabetes, cardiac disease, hyperlipidemia, and obesity were strongly interconnected with vitamin D deficiency (P values 0.008, 0.002, 0.011, 0.034, 0.016) respectively. A variety of analyzed reviews illuminate powerful interrelation of vitamin D deficiency with a heterogeneous co-morbid disorders [21,22]. Our analysis had particular limitations, initially greater size is required to explore more potent association of vitamin D status causally with a heterogeneous facets of clinic pathological

Table 6. Differences in vitamin D conditions among cases and control in accordance with some determinants

Determinants		Cases			X^2, P, odds R	Control			X^2, P, odds R
		Subnor.	Nor.	Total		Subnor.	Nor.	Total	
Morbidity	.00	1	1	2	18.738, 0.011	0	14	14	69.226 0.001
		50.0%	50.0%	100.0%		0.0%	100.0%	100.0%	
	1.00	2	2	4		0	28	28	
		50.0%	50.0%	100.0%		0.0%	100.0%	100.0%	
	2.00	6	3	9		0	17	17	
		66.7%	33.3%	100.0%		0.0%	100.0%	100.0%	
	3.00	10	2	12		2	7	9	
		83.3%	16.7%	100.0%		22.2%	77.8%	100.0%	
	4.00	19	1	20		10	0	10	
		95.0%	5.0%	100.0%		100.0%	0.0%	100.0%	
	5.00	33	0	33		2	0	2	
		100.0%	0.0%	100.0%		100.0%	0.0%	100.0%	
hypertension	No	15	6	21	8.557 0.008 0.143	4	45	49	7.563 0.007 0.187
		71.4%	28.6%	100.0%		8.2%	91.8%	100.0%	
	Yes	56	3	59		10	21	31	
		94.9%	5.1%	100.0%		32.3%	67.7%	100.0%	
Diabetes mellitus	0	14	6	20	9.390 0.002 0.123	0	51	51	29.843 0,001 1.933
		70.0%	30.0%	100.0%		0.0%	100.0%	100.0%	
	1	57	3	60		14	15	29	
		95.0%	5.0%	100.0%		48.3%	51.7%	100.0%	
Heart disease	0	18	6	24	6.324 0.011 0.170	2	52	54	21.905 0.001 0.045
		75.0%	25.0%	100.0%		3.7%	96.3%	100.0%	
	1	53	3	56		12	14	26	
		94.6%	5.4%	100.0%		46.2%	53.8%	100.0%	
Hyperlipidemia	No	16	5	21	4.499 0.034 0.233	1	59	60	41.753 0.001 2.813
		76.2%	23.8%	100.0%		1.7%	98.3%	100.0%	
	Yes	55	4	59		13	7	20	
		93.2%	6.8%	100.0%		65.0%	35.0%	100.0%	
Obesity	1.00	7	4	11	8.056 0.016 0.137	8	40	48	0.058 0.277 0.867
		63.6%	36.4%	100.0%		16.7%	83.3%	100.0%	
	2	64	5	69		6	26	32	
		92.8%	7.2%	100.0%		18.8%	81.3%	100.0%	
Total		71	9	80		14	66	80	
percentage		88.8%	11.3%	100.0%		17.5%	82.5%	100.0%	

range of osteoarthritis of knee, hormonal checking including parathyroid hormone was not achieved because of restricted capacity and accessibility in our hospital to shed light on the influence of vitamin D insufficiency on bone and cartilage turnover with resultant causal impacts. Further research and studies of bigger size are necessary in the future incorporating the probable beneficial impact of vitamin D on alleviating all aspects of knee osteoarthritis [23, 24].

CONCLUSIONS

Vitamin D status had substantial relation with various aspects of severity and perhaps progression in osteoarthritis of knee. The insufficiency of vitamin D in cases of osteoarthritis of knee is prevalent specifically in comorbid elder patients with long duration of illnesses, inadequate level of vitamin D. It is substantially linked to increasing severity both radiologically and clinically as evidenced by increased pain severity.

REFERENCES

1. Aiyong C, Huizi L, Dawei W et al. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. E Clinical Medicine. 2020;29-30:100587. doi: 10.1016/j.eclinm. DOI
2. Laura AS, Paul IM, Deborah W et al. Structural Associations of Symptomatic Knee Osteoarthritis. Arthritis Rheumatol. 2014;66(11):3018-3027. doi:10.1002/art.38778. DOI
3. Yoke Yue Chow, Kok-Yong Chin. The role of Inflammation in the Pathogenesis of Osteoarthritis. Mediators Inflamm. 2020:2020:8293921. doi: 10.1155/2020/8293921. DOI
4. David S, Pavlos M, Bert V et al. Epidemiology of Knee Osteoarthritis in General Practice: a registration based styd. BMJ Open. 2020;10:e031734. doi:1136/bmjopen-2019-031734. DOI
5. Jiang Z, Pu R, Li N et al. High prevalence of vitamin D deficiency in Asia: A systemic review and met analysis. Crit Rev Food Sci Nutr. 2021. doi:10.1080/10408398.2021. DOI
6. Ana MV, Joanne S. Osteoarthritis And Aging. EMJ. 2018;3(1):116-123.
7. Rachel JG, Matthew FD, Devendra KA et al. Vitamin D and its Effects on Articular Cartilage and Osteoarthritis. Orthop J Sports Med. 2017;5(6):2325967117711367. doi: 10.1177/2325967117711376. DOI
8. Wang X, Hunter D, Xu J et al. Metabolic triggered inflammation in osteoarthritis. Osteoarthritis Cartilage. 2015;23(1):22-30. doi:10.1016/j.joca.2014.10.002. DOI
9. Thomas M, Sittisak H. Role of Vitamin D in Osteoarthritis: Molecular, Cellular, and Clinical Perspectives. Int J Endocrinol. 2015;2015:383918. doi:10.11555/2015/383918. DOI
10. Clara YP. Vitamin D in the Prevention and Treatment of Osteoarthritis: From Clinical Interventions to Cellular Evidence. Nutrients. 2019;11(2):243. doi:10.3390/nu 11020243. DOI
11. Hawker GA, Mian S, Kendzerska T et al. Measures of adult pain: Visual Analog Scale for Pain(VAS pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (SF-36 BPS), and Measures of Intermittent and Constant Osteoarthritis Pain(ICOAP). Arthritis Care Res (Hoboken). 2011;63(11):S240-52. doi:10.1002/acr.20543. DOI
12. Mushfiqur MR, Jacek AK, Charlie HG et al. Validation of Administrative Osteoarthritis Diagnosis Using a Clinical and Radiological Population-Based Cohort. International Journal of Rheumatology. 2016;6475318. doi:10.1155/2016/6475318. DOI
13. Mathias S, Michael FH. Vitamin D and neurocognitive function. Clin Interv Aging. 2014;9:559-568. doi:10.2147/CIA.S51785. DOI
14. Haroon M, Bond U, Quillinan N et al. The prevalence of Vitamin D deficiency in consecutive new patients seen over a 6-month period in general rheumatology clinics. Clin Rheumatol. 2011;30(6):789-94. doi: 10.1007/s10067-010-1659-0. DOI
15. Anari H, Enteshari-Moghaddam A, Abdolzadeh Y et al. Association between serum Vitamin D deficiency and Knee Osteoarthritis. Mediterr J Rheumatol. 2020;30(4):216-219. doi:10.31138/mjr.30.4.216. DOI
16. Muraki S, Dennison E, Jameson K et al. Association of Vitamin D status with Knee pain and radiographic Knee osteoarthritis. Osteoarthritis Cartilage. 2011;19(11):13016. doi:10.1016/j.joca.2011.07.017. DOI
17. Gao XR, Chen YS, Deng W. The effect of vitamin D supplementation on knee osteoarthritis: A meta-analysis of randomized controlled trials. Int J Surg. 2017;46:14-20. doi:10.1016/j.ijsu.2017.08.010. DOI
18. Jansen AJ, Haddad FS. High prevalence of vitamin D deficiency in elderly patients with advanced osteoarthritis scheduled for total knee replacement associated with poorer preoperative functional state. Ann R Coll Surg Engl. 2013;95(8):569-572. doi: 10.1308/003588413X13781990150374. DOI
19. Aspell N, Laird E, Healy M et al. The Prevalence and Determinants of Vitamin D Status in Community-Dwelling Older Adults: Results from English Longitudinal Study of Ageing (ELSA). Nutrients. 2019;11(6):1253. doi: 10.3390/nu11061253. DOI
20. Ding C, Cicuttini F, Parameswaran V et al. Serum levels of Vitamin D, Sunlight exposure, and Knee cartilage loss in older adults: The Tasmanian older adult cohort study. Arthritis Rheum. 2009;60(5):1381-9. doi:10.1002/art.24486. DOI
21. Al Zarooni AAR, Al Marzouqi FI, Al Darmaki SH et al. Prevalence of vitamin D deficiency and associated comorbidities among Abu Dhabi Emirates population. BMC Res Notes. 2019;12(1):503. doi: 10.1186/s13104-019-4536-1. DOI
22. Kostoglou-Athanassiou I, Athanassiou P, Lyraki A et al. Vitamin D deficiency and Comorbidity. Ther Adv Endocrinol Metab. 2012;3(6):181-7. doi: 10.1177/2042018812471070. DOI
23. Raud B, Gay C, Guiguet-Auclair C, et al. Level of obesity is directly associated with the clinical and functional consequences of knee osteoarthritis. Sci Res. 2020;10:3601. doi: 10.1038/s41598-020-60587-1. DOI
24. Olsson S, Akbarian E, Lind A et al. Automating classification of osteoarthritis according to Kellgren-Lawrence in the knee using deep learning in an unfiltered adult population. BMC Musculoskelet Disord. 2021;22:844. doi:10.1186/s12891-021-04722-7. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Coping behavior of students as a means of overcoming stressful situations under martial law

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ABSTRACT

Aim: The aim is to study the peculiarities of students' coping behavior in stressful situations under martial law.

Materials and Methods: During the 2023-2024 academic year, the research was conducted based among 3rd-year students (n = 82) aged 20-22 years, including women (n = 42) and men (n = 40). Research methods: bibliosemantic, diagnostic, system analysis and generalization, statistical. The diagnostic work involved using the following methods: "Coping Inventory for Stressful Situations" and "Strategic Approach to Coping Scale."

Results: It has been found that the problem of students being in a stressful situation of war is directly related to their coping behavior. It has been found that female students' indicators of emotion-oriented coping strategies are more pronounced than those of male students (p 0.05) high level of expression of the following models of behavior to overcome stressful phenomena: search for social support (women – 57.1 %; men – 55.0 %), social contact (women – 54.8 %; men – 52.5 %), precautionary actions (women – 52.4 %; men – 50.0 %).

Conclusions: The effectiveness of any coping strategy depends on the current situation in students' lives and their existing personal resources. In stressful situations, students' coping behavior is effective, and the following coping strategies are rational: emotion-oriented, search for social support, and problem-oriented. This confirms students' productive personal standpoint, allowing them to adapt to any stressful situation under martial law.

KEY WORDS: coping behavior, students, stress, stressful situations, psychophysical well-being, war

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INTRODUCTION

The annexation of Ukrainian territory, armed conflict, and war are the most significant negative factors that currently affect the emotional state of young people and cause serious consequences for their psychophysical well-being, including stress, anxiety, depression, post-traumatic stress disorder, and other conditions [1]. Young people need conscientious supervision to detect symptoms of PTSD promptly and to provide effective psychological assistance [2].

Experts [3, 4] note that stress is the most characteristic mental condition that occurs as a result of extreme life factors, including those provoked by war. This is a nonspecific body reaction that responds to environmental stimuli and prepares the body for active physical action—attack or flight. It is also worth noting that virtually every change in any person's life is a stressor, as it requires some effort to cope with a new situation.

According to scientists [5], regardless of the origin of the stressor (biological or social), it causes nonspecific reactions and is determined by individual personality traits. These reactions can lead to physiological and structural disorders in people (especially young people) if the load is excessive or social conditions do not allow adequate physical activity. Thus, they believe both large and small social and individual difficulties can create stressful situations. Such situations can develop dynamically and significantly impact an individual's psychophysical well-being if they participate in or witness armed conflict and hostilities [6].

The problem of stress in crises is directly related to coping behavior [7]. Coping behavior is a cognitive and behavioral effort a person uses to cope with specific internal or external factors that strain or exceed a person's resources [8]. Hence, it can be argued that such behavior includes the attempts of a particular subject to evade,

mitigate, get used to, or master the consequences of a stressful situation.

Today, the issue of coping behavior is considered in various fields of psychology, for example, within the framework of personality psychology and clinical psychology [9]. Also, cross-cultural and social psychology representatives consider psychological coping when studying the factors that precede and help choose specific coping strategies and analyze the consequences of stress overcoming at the level of individual adaptation [10].

The specificity of current social and political changes leads to other problems that young people have not previously encountered in their lives, and this necessitates the need for them to address new challenges of psychological coping with stressful situations. Therefore, the social situation of development not only actualizes the adaptive potential of each individual but also sets the task of its continuous growth and renewal in uncertain, "difficult," constantly changing situations. According to scientists [11, 12], crises can significantly exceed the adaptive capabilities of any person, resources, and skills they usually use. We are talking about some extraordinary, objectively stressful situations, which currently include the full-scale war against Ukraine unleashed by the Russian Federation.

AIM

The aim is to study the peculiarities of students' coping behavior in stressful situations under martial law.

MATERIALS AND METHODS

PARTICIPANTS

To study the peculiarities of students' coping behavior in stressful situations under martial law, during the academic year 2023-2024, we conducted diagnostic work among 3rd-year students (n = 82) aged 20-22 years, including women (n = 42) and men (n = 40) at the National Academy of Internal Affairs (Kyiv, Ukraine).

To achieve the research aim, a set of interrelated methods was used: bibliosemantic, diagnostic, method of system analysis and generalization, and statistical. The bibliosemantic method was used to conduct an analytical review of scientific sources on the outlined issues. The diagnostic method involved conducting research work with students as representatives of modern youth. For this purpose, valid methods were used: "Coping Inventory for Stressful Situations (CISS)" and "Strategic Approach to Coping Scale (SACS)" [13, 14].

The "Coping Inventory for Stressful Situations (CISS)" includes a list of reactions to stressful situations to identify a person's prevailing coping strategies. Subjects were asked to rate 48 reactions from 1 to 5 on a scale. When processing the results, the scores given by the respondents were summarized, taking into account the key for interpreting the research method. It helped to identify the following coping strategies: problem-oriented strategy, emotion-oriented strategy, avoidance strategy, distraction strategy, and social distraction strategy (or search for social support).

The "Strategic Approach to Coping Scale (SACS)" revealed nine models of coping behavior in stressful situations: assertive actions, social contact, social support seeking, precautionary actions, impulsive actions, avoidance, manipulative (indirect) actions, antisocial actions, and aggressive actions. The respondents had to evaluate how they usually act in stressful situations and answer 54 statement questions by choosing one of the proposed options on a five-point scale. After receiving the respondents' answers, the sum of points for each line was calculated according to the "key."

PROCEDURE

The research was conducted in three stages. The first stage provided an analytical review of the literature on the peculiarities of people's coping behavior in crises and determined diagnostic and methodological tools for conducting an empirical study. In the second stage, the diagnostic work was carried out with the help of the selected tools. Electronic forms with the tasks of the methods were created to conduct the experiment, which contained brief instructions for completing the tasks. The respondents were not provided with keys to interpret the results. The third stage involved processing, systematization, generalization of indicators, and logical and semantic interpretation of the data. The research was organized, and the results were processed by the Department of Legal Psychology of the National Academy of Internal Affairs (NAIA, Kyiv, Ukraine).

STATISTICAL ANALYSIS

The statistical method was used to process the experimental data obtained. The reliability of the difference between the indicators presented in percentages was determined using Pearson's Chi-square (χ^2) criterion. The significance of the difference was set at $p < 0.05$. All statistical analyses were performed using SPSS version 10.0 software adapted for medical and biological research.

ETHICS

The research was carried out in accordance with the requirements of the Regulations on academic integrity at the National Academy of Internal Affairs. This document

Table 1. Coping strategies of students in stressful wartime situations (n = 82), including women (n = 42), men (n = 40); number of people / %

Coping behavior strategies	Frequency of occurrence	Students		Significance of the difference	
		W (n=42)	M (n=40)	χ^2	p
Problem-oriented	frequently	19 / 45.2	20 / 50.0	0.46	>0.05
	sometimes	16 / 38.1	14 / 35.0		
	never	7 / 16.7	6 / 15.0		
Emotion-oriented	frequently	27 / 64.3	23 / 57.5	2.77	<0.05
	sometimes	11 / 26.2	10 / 25.0		
	never	4 / 9.5	7 / 17.5		
Avoidance	frequently	17 / 40.5	13 / 32.5	2.57	<0.05
	sometimes	18 / 42.9	17 / 42.5		
	never	7 / 16.6	10 / 25.0		
Distraction	frequently	14 / 33.3	14 / 35.0	0.42	>0.05
	sometimes	18 / 42.9	18 / 45.0		
	never	10 / 23.8	8 / 20.0		
Social distraction (search for social support)	frequently	23 / 54.8	21 / 52.5	0.54	>0.05
	sometimes	16 / 38.1	15 / 37.5		
	never	3 / 7.1	4 / 10.0		

Legend: W – women, M – men.

Table 2. Indicators of students' behavioral patterns in overcoming stress under martial law (n = 82), including women (n = 42), men (n = 40); in %

Coping strategies	Behavioral patterns (actions)	The level of expression of behavioral patterns in students						Significance of the difference	
		Low		Average		High		χ^2	p
		W	M	W	M	W	M		
Active	Assertive actions	9.5	10.0	52.4	55.0	38.1	35.0	0.21	>0.05
Prosocial	Entering into social contact	9.5	12.5	35.7	35.0	54.8	52.5	0.46	>0.05
	Search for social support	7.2	12.5	35.7	32.5	57.1	55.0	1.61	>0.05
Passive direct	Precautionary actions	4.7	7.5	42.9	42.5	52.4	50.0	0.70	>0.05
	Impulsive actions	23.8	22.5	52.4	52.5	23.8	25.0	0.06	>0.05
Passive indirect	Avoidance	57.1	60.0	23.8	22.5	19.1	17.5	0.17	>0.05
	Manipulative actions	47.6	52.5	28.6	27.5	23.8	20.0	0.59	>0.05
Antisocial	Antisocial actions	64.3	62.5	21.4	22.5	14.3	15.0	0.07	>0.05
	Aggressive actions	66,7	65,0	19,0	20,0	14,3	15,0	0.06	>0.05

Legend: W – women, M – men.

was approved by the Academic Council of the National Academy of Internal Affairs (protocol No. 5 of 27.03.2018) and put into effect by order of the rector of the Academy (Order No. 422 of 30.03.2018). Prior consent to participate in the study was obtained from all respondents.

RESULTS

In the course of the research, we obtained relevant results and outlined specific trends in the behavior of modern youth. In particular, the coping behavior of young people in stressful war situations is as follows (Table 1).

Evaluation of the results of the "Coping Inventory for Stressful Situations (CISS)" showed that emotion-oriented coping (emotion-oriented strategy) prevails among most students (women: frequently – 64.3 %, sometimes – 26.2 %; men: frequently – 57.5 %, sometimes – 25.0 %). This is quite a natural phenomenon, as the stressful situation associated with experiencing acts

of armed aggression by Russia and a full-scale war on the territory of Ukraine provokes high emotional stress in young people. The impact of such potent stressors can cause people to immerse themselves in their feelings, experience substantial emotional distress, and even cause emotional disorders. It has been found that female students' indicators of emotion-oriented coping strategies are more pronounced than those of men, and the difference is significant ($p < 0.05$).

The state of increased stress often forces a person to seek restoration of habitual mental activity in the immediate social environment (relatives, friends, colleagues, etc.), so it is not surprising that the second place is occupied by the strategy of searching for social support (social distraction) (women: frequently – 54.8 %, sometimes – 38.1 %; men: frequently – 52.5 %, sometimes – 37.5 %). At the same time, no significant difference was found between the indicators of students of different gender groups ($p > 0.05$).

At the same time, coping behavior focused on solving various kinds of problems (problem-oriented strategy) is more often demonstrated by male students (frequently – 50.0 %, sometimes – 35.0 %), compared to female students (frequently – 45.2 %, sometimes – 38.1 %). Such indicators show, first of all, that a significant number of young people strive for rational behavior in stressful situations under martial law. However, there was no significant difference between the scores for this coping strategy in both groups of respondents ($p > 0.05$). The relative prevalence of this strategy among men indicates that they are more resilient in perceiving urgent problems provoked by the war compared to women, who may show some confusion in perceiving complex obstacles and crises. This can also explain the fact that the "avoidance" coping strategy is significantly more often manifested by female students ($p < 0.05$), with a rate of 40.5 %, compared to male students (frequently 32.5 %).

As for the strategy of "distraction," it also takes place in the behavior of students in stressful situations, but it is used less often than the above (women: frequently – 33.3 %, sometimes – 42.9 %; men: frequently – 35.0 %, sometimes – 45.0 %). There is no significant difference in these indicators ($p > 0.05$).

The use of the "Strategic Approach to Coping Scale (SACS)" method allowed us to identify the degree of preference of students for a particular pattern of behavior in stressful situations under war (Table 2).

Thus, in particular, students showed a high level of expression of the following behaviors to overcome stressful phenomena under martial law: search for social support (women – 57.1 %; men – 55.0 %), entering into social contact (women – 54.8 %; men – 52.5 %), precautionary actions (women – 52.4 %; men – 50.0 %). At the average level of severity, the following behaviors received the most responses: assertive actions (defending one's position: women – 52.4 %; men – 55.0 %), impulsive actions (women – 52.4 %; men – 52.5 %), and again precautionary actions (women – 42.9 %; men – 42.5 %). The following behaviors were observed at a low level of expression: aggressive actions (women – 66.7 %; men – 65.0 %), antisocial actions (women – 64.3 %; men – 62.5 %), and avoidance (women – 57.1 %; men – 60.0 %). As we can see, female students' scores on these behavioral patterns are mostly more pronounced. Still, there is no significant difference between the levels of behavioral patterns in the respondents of both groups ($p > 0.05$).

Thus, the results confirm the focus of wartime students on the external environment, particularly the desire to seek support and assistance from the immediate environment that inspires trust (relatives, friends, colleagues). They also indicate a high level of personal coping resources and skills for actively solving life problems. Also noteworthy are the significant scores on the assertiveness scale, which may indicate students' intentions to express and defend their point of view and their determination in their stated opinions and standpoints. A low level of aggressiveness, tendency to antisocial actions, and avoidance also demonstrate a favorable tendency to control one's behavior to prevent negative consequences and, hence, to overcome stressful situations. In addition, this may indicate a high degree of effectiveness of the respondents' coping behavior and their mature personal standpoint since this is how the ability to adapt to various stressful situations provoked by war and hostilities is manifested.

DISCUSSION

The war has a significant impact on the psycho-emotional state of people living in the conflict zone and exposed to constant stressful situations. The wartime period is accompanied by numerous psychological problems in ordinary people, which manifest themselves in the form of increased anxiety, tension, stress disorders, and other negative emotional states [1]. These problems can affect people's quality of life, psychological state, and psychophysical well-being in general. Studying the possibilities of overcoming stressful phenomena provoked by war and hostilities is particularly important in this context. This issue is exacerbated by the fact that young people who need proper and timely psychological support because they are at the stage of their personal and life formation (development) are affected by the adverse effects of war and stress [2].

Strong external or internal stimuli (stressors) disrupt the balance of the psychophysical well-being of any individual. The body tries to adapt to the stimulus by arousal. This nonspecific arousal is a stressful state. If the stimulus is not eliminated, stress increases, develops, and causes various specific changes in the body. People try to protect themselves and prevent or suppress stress. However, the body's capabilities are not unlimited and quickly depleted under the influence of a high-stress level, including those caused by war [6, 11]. For this purpose, various methods and practices are becoming relevant, allowing the activation of defense mechanisms that can actively counteract stressful situations. According to scientists [7], the problem of stress in crises is directly related to the coping behavior used by a person to cope with specific internal or external factors that strain or exceed their resources.

Researchers distinguish between active and passive coping behaviors. Active coping behavior is considered as specific actions of an individual to eliminate or reduce the strength of the stressor's impact, to break the connection between stress and the physical or social environment. Passive coping consists of internal ways of coping with stress to reduce emotional stress before the stressful situation changes [15].

Usually, the structure of the coping process in young people is as follows: perception of stress, cognitive assessment, development of coping strategies, and evaluation of the result of actions [16]. All of these components (stages) are aimed at forming the psychological protection that a person needs as a result of exposure to psycho-traumatic situations. Therefore, such behavior can counteract (change) a stressful situation.

Some researchers have concluded that expressing emotions is a reasonably effective way to overcome a stressful situation [17, 18]. The only exception to this is the open manifestation of aggression due to its antisocial orientation. The students we interviewed undoubtedly pay attention to their emotions, but they can somewhat control them. This is manifested in a low level of aggressiveness, as well as avoidance of antisocial behavior (e.g., alcohol and drug abuse, vandalism, committing offenses, etc.).

At the same time, according to the results of psychosomatic research [19], a constant feeling of anxiety and systematic mental tension lead to a violation of a person's psychological well-being. At the same time, emotional interpretation of the situation and self-blame provoke psychological and psychosomatic changes. On the other hand, searching for social support and solving current problems significantly reduces the level of anxiety, irritability, and depression. The results of our research among students confirm this.

According to some authors [10, 13, 20] who have studied the effectiveness of various forms of coping, the least effective for overcoming stress is avoidance, reducing one's capabilities, self-blame, etc. According to the results of our survey of students, such a form of coping behavior as avoidance is present in the mechanism of protection of young people from stressful phenomena. Still, it has a low level of manifestation. Instead, more effective forms of student coping behavior fundamentally influence the crisis to change it (problem-oriented strategy), or at least its constructive interpretation. In general, scientists have mixed opinions about the effectiveness of using coping behaviors for psychological stress management. Some believe certain protective behaviors are maladaptive, as they disrupt a person's adequacy and orientation. At the same time, quite a few researchers suggest that the imaginary reduction of stress in the case of defensive coping allows the individual to focus and mobilize their efforts to overcome crises, including those provoked by war [7, 8, 14, 16, 21-23]. The criteria for the effectiveness of psychological coping are a reduction in neuroticism and vulnerability to stress, the duration of positive effects, and the mental well-being of young people. Psychological defense strategies will be productive in cases where the stressful situation is under the control of the individual.

CONCLUSIONS

It has been found that coping behavior is a rational tool that helps people control stressful situations under martial law. The effectiveness of any coping strategy depends on the current situation in the life of a young person and their existing personal resources. Stress can become a trigger and lead to functional and psychosomatic diseases in young people.

It has been determined that in stressful situations, students' coping behavior is effective, and the following coping strategies are efficacious: emotion-oriented, search for social support, and problem-oriented. It has been found that female students' indicators of emotion-oriented coping strategies are more pronounced than those of male students, and the difference is significant ($p < 0.05$). Male students often demonstrate coping behavior focused on solving various problems (problem-oriented strategy). It has been found that students have a significantly ($p > 0.05$) high level of expression of the following models of behavior to overcome stressful phenomena in war conditions: search for social support (women – 57.1 %; men – 55.0 %), social contact (women – 54.8 %; men – 52.5 %), precautionary actions (women – 52.4 %;

men – 50.0 %). At the same time, the insufficient development of constructive forms of coping behavior causes the pathogenic effect of stressful situations on students.

A high level of manifestation of personal coping resources and skills of active problem-solving has been revealed. The productive personal standpoint of students and proper self-control from aggressive and antisocial actions ensure the ability to adapt to any stressful situation in wartime.

PROSPECTS FOR FURTHER RESEARCH

It is planned to investigate the peculiarities of coping behavior of representatives of older age groups, taking into account the stressful situations under martial law.

REFERENCES

1. Zasiekina L, Duchyminska T, Bifulco A, Bignardi G. War trauma impacts in Ukrainian combat and civilian populations: Moral injury and associated mental health symptoms. Mil Psychol. 2024;36(5):555-566. doi:10.1080/08995605.2023.2235256. DOI
2. Cameron N. Child growth and armed conflict. Ann Hum Biol. 2023;50(1):301-307. doi:10.1080/03014460.2023.2224059. DOI
3. Zielinska M, Tkachenko Y, Ducki M. The war in Ukraine: A voice from Poland. Anaesth Crit Care Pain Med. 2022;41(3):101062. doi:10.1016/j.accpm.2022.101062. DOI
4. Bendavid E, Boerma T, Akseer N et al. The effects of armed conflict on the health of women and children. Lancet. 2021;397(10273):522-532. doi:10.1016/S0140-6736(21)00131-8. DOI
5. Harb GC, Schultz JH. The nature of posttraumatic nightmares and school functioning in war-affected youth. PLoS One. 2020;15(11):e0242414. doi: 10.1371/journal.pone.0242414. DOI
6. Shaheen M, Schindler L, Saar-Ashkenazy R et al. Victims of war-Psychoendocrine evidence for the impact of traumatic stress on psychological well-being of adolescents growing up during the Israeli-Palestinian conflict. Psychophysiology. 2020;57(1):e13271. doi:10.1111/psyp.13271. DOI
7. Wei Y, Shi Y, Zhou Q et al. Effect of Chinese young children's epidemic cognition on their coping behavior: Mediating role of emotion. BMC Psychol. 2023;11(1):65. doi:10.1186/s40359-023-01106-5. DOI
8. Taylor SE, Stanton AL. Coping resources, coping processes, and mental health. Annu Rev Clin Psychol. 2007;3:377-401. doi:10.1146/annurev.clinpsy.3.022806.091520. DOI
9. Woo SE, Hofmans J, Wille B, Tay L. Person-centered modeling: Techniques for studying associations between people rather than variables. Annu Rev Organ Psychol Organ Behav. 2024;11:453-480. doi:10.1146/annurev-orgpsych-110721-045646. DOI
10. Jong A, Riddleston L, Mathur M et al. Young people's recommended coping strategies to manage social isolation: Lessons from the COVID-19 pandemic lockdown in the UK. Curr Res Behav Sci. 2023;5:100133. doi:10.1016/j.crbeha.2023.100133. DOI
11. McLoughlin E, Arnold R, Moore LJ. The tendency to appraise stressful situations as more of a threat is associated with poorer health and well-being. Stress Health. 2024;40(3):e3358. doi:10.1002/smi.3358. DOI
12. Okhrimenko IM, Fedyk AO, Zhygalkina NV et al. Changes in somatic and mental health indicators of instructor-officers under stress Wiad Lek. 2024;77(2):293-298. doi:10.36740/WLek202402116. DOI
13. Choi Y, Moon E, Park JM et al. Psychometric properties of the Coping Inventory for Stressful Situations in Korean adults. Psychiatry Investig. 2017;14(4):427-433. doi:10.4306/pi.2017.14.4.427. DOI
14. Pedrero Pérez EJ, Santed Germán MA, Pérez García AM. Adaptación española de la Escala Multiaxial de Afrontamiento Estratégico (SACS) de Hobfoll [Spanish adaptation of Hobfoll's Strategic Approach to Coping Scale (SACS)]. Psicothema. 2012;24(3):455-460. (Spanish)
15. Cordes MF, Ahmed AE, Singer DE. Psychological distress in active-duty U.S. service members who utilized mental health services: Data from a 2018 DoD survey. Journal of Affective Disorders. 2024. doi:10.1016/j.jad.2024.11.051. DOI
16. Graves BS, Hall ME, Dias-Karch C et al. Gender differences in perceived stress and coping among college students. PLoS ONE. 2021;16(8):e0255634. doi:10.1371/journal.pone.0255634. DOI
17. Montero-Marin J, Prado-Abril J, Piva Demarzo MM et al. Coping with stress and types of burnout: Explanatory power of different coping strategies. PLoS ONE. 2014;9(2):e89090. doi:10.1371/journal.pone.0089090. DOI
18. Okhrimenko IM, Barko VV, Vavryk LV et al. The impact of professional stress on the mental health of law enforcement officers. Wiad Lek. 2023;76(6):1428-1435. doi:10.36740/WLek202306115. DOI
19. Batrinos ML. Testosterone and aggressive behavior in man. Int J Endocrinol Metab. 2012;10(3):563-568. doi:10.5812/ijem.3661. DOI
20. Yevdokimova O, Okhrimenko I. Coping strategies for overcoming stress in atypical situations. BRAIN. Broad Research in Artificial Intelligence and Neuroscience. 2020;11(2):56-63. doi:10.18662/brain/11.2Sup1/94. DOI
21. Zhang Y, Luo X, Che X, Duan W. Protective Effect of Self-Compassion to Emotional Response among Students with Chronic Academic Stress. Front Psychol. 2016;7:1802. doi:10.3389/fpsyg.2016.01802. DOI

22. Garbarino J. The war-zone mentality – mental health effects of gun violence in U.S. children and adolescents. N Engl J Med. 2022;387(13):1149-1151. doi:10.1056/NEJMp2209422. DOI
23. Taghavi K, Isaacs D, McLeod L et al. The ethics of war-time data in paediatric trauma: Attitudes, angles and impacts. BMJ Glob Health. 2023;7(8):e013071. doi:10.1136/bmjgh-2023-013071. DOI

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ORIGINAL ARTICLE

CONTENTS

Evaluation of serum levels of calprotectin, lactoferrin and zinc in patients with type II diabetes mellitus

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ABSTRACT

Aim: The current study aimed to evaluate the role of serum calprotectin, lactoferrin and serum zinc in patients with type II diabetes mellitus.

Materials and Methods: Sixty subjects have been investigated in this study, (40) patients with T2DM and 20 apparently healthy participants (control group) during the period between October 2021 to January 2022. Zinc was measured using a calorimetric method, while calprotectin and lactoferrin were measured by ELISA.

Results: The findings also revealed that levels of serum calprotectin and lactoferrin have significantly increased in in patients with T2DM as compared to healthy subjects. The result also showed that serum zin is decreased in patients groups. The correlation matrix exhibited that there was a strong positive correlation between calprotectin and lactoferrin, a significant negative correlation between zinc and calprotectin.

Conclusions: It was concluded that high serum calprotectin and lactoferrin indicated a strong inflammatory status in T2DM patients. Zinc is likely to be negative affected by the high inflammatory response indicated by that high serum calprotectin.

KEY WORDS: calprotectin, lactoferrin, zinc, T2DM, inflammation

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INTRODUCTION

Diabetes mellitus still remainsone of the most worldwide concerning health problems in the current time, with high prevalence and spread in developing states, it is expected that at the time of 2030, the incidence of DM in developing countries tend to increase by 170%, while developed countries may show only 42% increase in DM incidence [1]. Diabetes mellitus is considered as a chronic hormonal disorder, it develops when insulin cannot be secreted sufficiently by β-cells in the pancreas, or/and if the cells cannot effectively utilize insulin [2]. Calprotectin has been classified as an internal activator of the membrane receptors spanning and expressing on immune cells like dendritic cells and macrophages. Therefore, calprotectin is suggested to perform as an endogenous differentiational biomarker for phagocytic cells and as an exterior protein complex, like that's called as a damage-associated molecular pattern (DAMP) [3]. Increased concentrations of serum calprotectin have been observed to be a predicter for vascular changes in patients with type 2 diabetic (T2DM). There was a positive significant correlation has been reported between HbA1c in patients with T2DM and calprotectin levels. This finding suggested that blood glucose levels or glucose metabolites may have effect on calprotectin metabolism of in diabetics [3]. Lactoferrin (Lf) has been known to be found in high levels in human and mammalian milk, in addition to be present in small quantities in exocrine fluids (i.e., salivary secretions, semen, tears, gastrointestinal secretions, vaginal secretions) and inside body cells (i.e., white blood cells, enterocytes, adipocytes, and neutrophils). Lactoferrin is an iron-binding glyco-protein that has antibacterial activity; it also enhances immunological defense mechanisms against invading microorganisms [4]. Thus, it was found that lactoferrin reduces oxidative stress, inflammatory response and apoptotic processes, which are the main mechanisms involved in the development of various cardiac metabolic disorders [5, 6]. Zinc is considered as an essential element for synthesizing insulin into hexamic structure that is stable structurally and functionally. Zinc is also associated to

Table 1. Demographic characteristics of patients and control groups

Indicators		Patients No. = 40		Control No. = 20		Chi Square	P value (Sig.)
		Freq.	Percent	Freq.	Percent		
Age/Years	20-24	13	32.5	7	35.0	0.05	0.97(NS)
	25-29	10	25.0	5	25.0		
	30-34	17	42.5	8	40.0		
Gender	Male	23	57.5	8	40.0	1.64	0.20(NS)
	Female	17	42.5	12	60.0		

NS: Non-significant at P value >0.05.

Table 2. Differences in calprotectin and lactoferrin between patients and healthy groups

Indicators	Patients No. = 40		Control No. = 20		Independent t-test	P value (Sig.)
	Mean	SD	Mean	SD		
Calprotectin (µg/dl)	70.41	40.69	36.28	7.73	5.12	0.000 (HS)
Lactoferrin (µg/dl)	8.77	4.55	6.41	1.29	2.33	0.02 (S)

SD: Standard Deviation; HS: High Significant at P value <0.01; S: Significant at P value <0.05.

Table 3. Pearson correlation coefficient (r) between calprotectin, lactoferrin and zinc in patients with T2DM

Markers	Serum Zinc	Calprotectin
Calprotectin	- 0.509**	
Lactoferrin	- 0.101	0.668**

** High Significant at P 0<0.01

the synthesizing, storing and secreting insulin. In addition, zinc has a protective effect on pancreatic tissue from oxidative stress as a cofactor for the enzyme of superoxide dismutase [7]. In hypozincemic status, the synthesis, storage, and action of insulin can be altered. It has been observed that decreased levels of zinc in T2DM resulted from excretion of zinc through urine or may be because of zinc loss from body cells when glucose is transported into muscles [8].

AIM

The goal of the current study was to evaluate the role of serum calprotectin; lactoferrin and serum zinc in patients with type II diabetes mellitus.

MATERIALS AND METHODS

Sixty subjects have been investigated in this study, 40 patients with T2DM and 20 apparently healthy participants (control group). The study was conducted at the Endocrine Center in Al-Sadr Medical City in Al-Najaf province, in Iraq, during the period between September 2021 and January 2022. Blood sampling (10 ml) had been done after 12 hours of fasting. After separation of serum, and the concentration of zinc was measured by a calorimetric method and spectrophotometry. Calprotectin and lactoferrin were measured by ELISA kits.

Statistical analysis was conducted by SPSS program (version 25) which included descriptive statistics (percentage and frequency) and inferential statistics (t-test and Chi-square test). Pearson Correlation Coefficient (r) was utilized to assess correlation between quantitative variables.

RESULTS

The demographic indicators of both patients and control groups reveal no notable discrepancies in terms of age or gender distribution. The age categories (20-24, 25-29, and 30-34 years) are evenly represented in both groups, with a chi-square test indicating a P-value of 0.97, which is deemed non-significant. Additionally, there is no significant difference in gender distribution; males make up 57.5% and 40% of the patient and control groups, respectively, while females represent 42.5% and 60%, accompanied by a P-value of 0.20 (Table 1). Serum levels of calprotectin and lactoferrin have been evaluated in patients and control groups. The results exhibited a significant increase P<0.05 in calprotectin (µg/dl) in patients compared to healthy group (Table 2 and Fig.1). The same table revealed that there was significant increase P<0.05 in lactoferrin (µg/dl) in patients compared to control group (Fig.2). Regarding serum zinc, a comparison of serum zinc levels between control groups and patients was presented, revealing

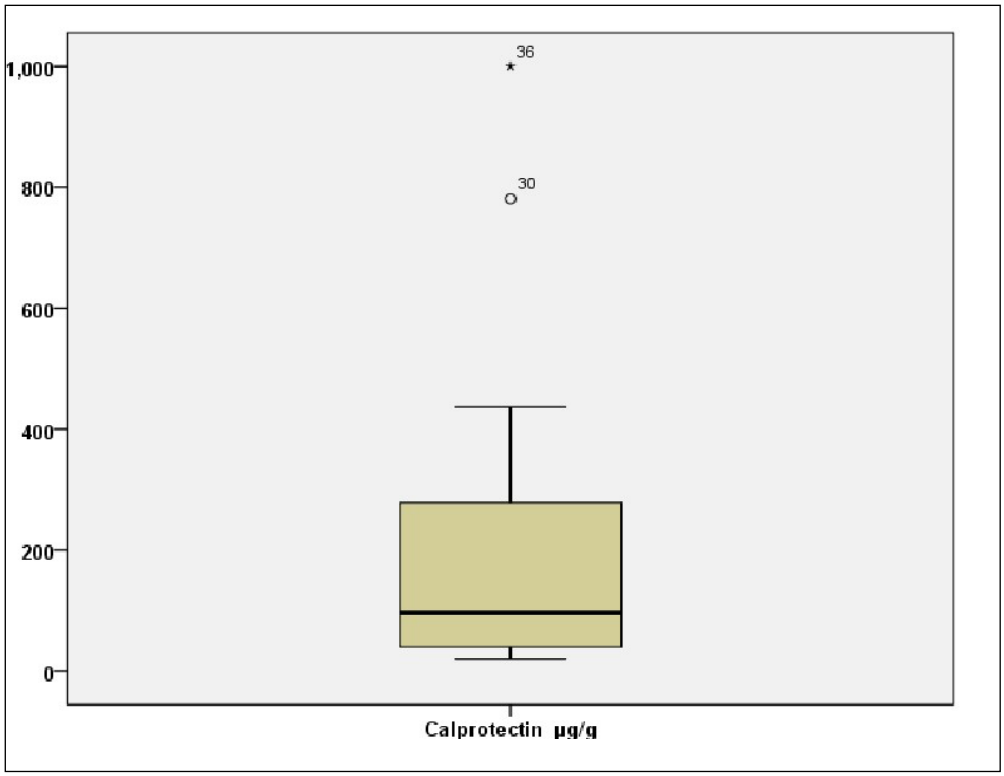

Fig. 1. Distribution of calprotectin in patients with T2DM.

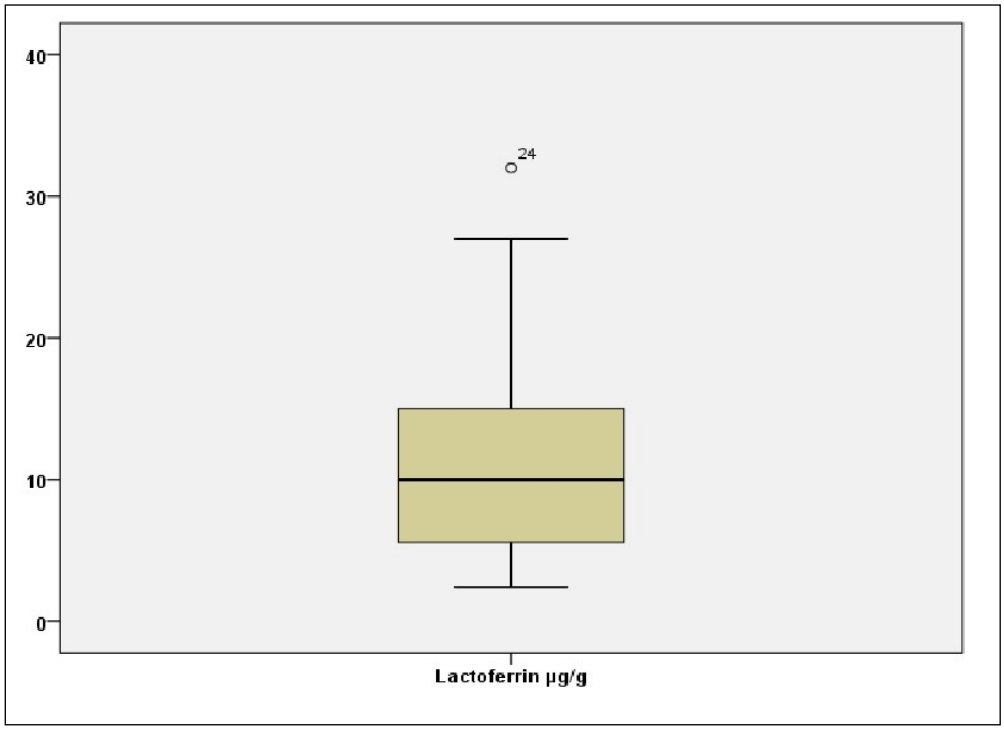

Fig. 2. Distribution of lactoferrin in patients with T2DM.

a significant difference (P-value < 0.001). In the patient group, the average serum zinc level is 61.95 µg/dl, which is considerably lower than the control group's mean of 82.4 µg/dl. The error bars demonstrate the variability within each group, indicating a more restricted range for patients in contrast to the controls (Fig.3, Fig.4).

The correlation test has been achieved by Pearson correlation coefficient (r) after assessing the normality of data (table 3). There was a negative high significant correlation P<0.01 between serum zinc and calprotectin r = -0.509; the findings also pointed out that there is a positive significant correlation P<0.01 between serum Lactoferrin and calprotectin r=0.668.

DISCUSSION

Calprotectin consists of two proteins subunits bounded by calcium atom (S100A8 & S100A9), from which the

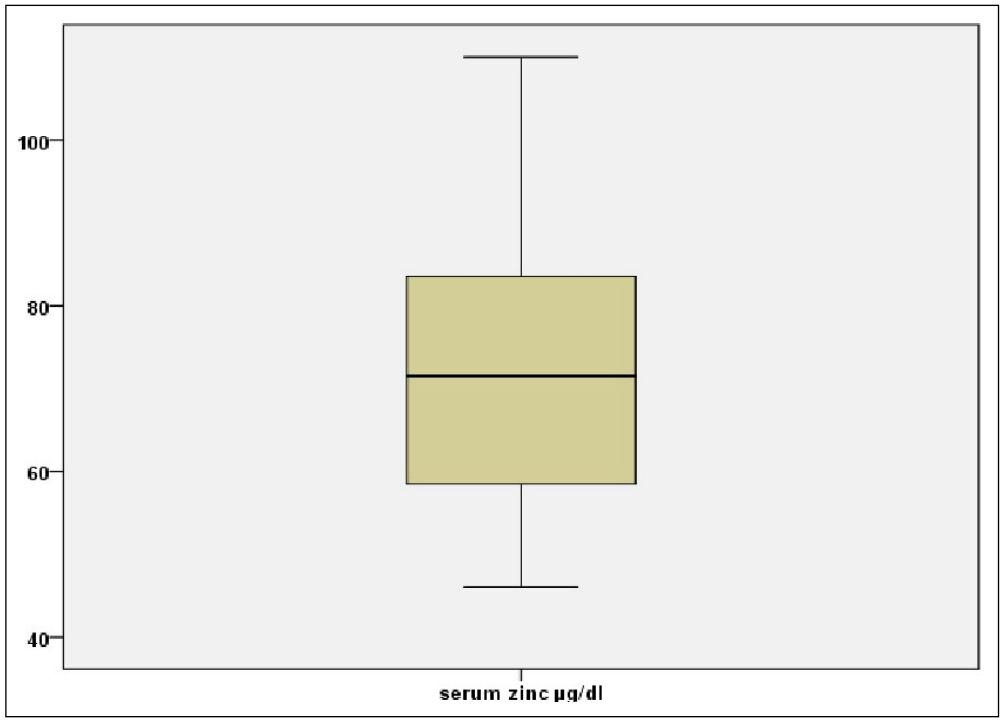

Fig. 3. Distribution of zinc levels in patients with T2DM.

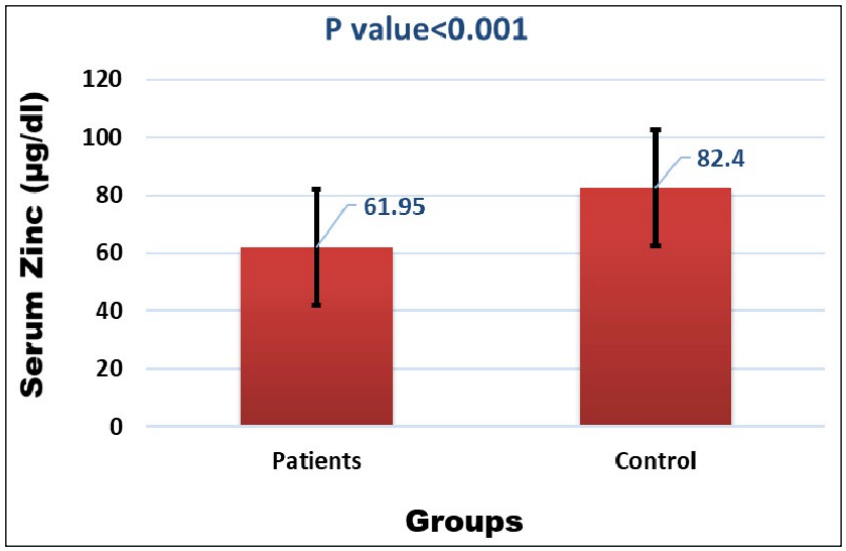

Fig. 4. Differences in zinc between patients and control groups.

name of calprotectin is derived. Calprotectin is classified a strong proinflammatory marker that was observed to increase in chronic inflammation like irritable bowel syndrome (IBS), atherosclerotic lesions, different types of arthritis, and immunological rejection [4]. The present study has found that calprotectin in increased in diabetic patients, this result is supported by previously published studies conducted by Pedersen et al. [9] and Zhang et al. [10]; they found that serum calprotectin exhibited a significant increase in type II diabetic patients. Calprotectin is reported to be secreted by neutrophilic and monocytic cells, which are increased during inflammatory responses. Diabetic patients are basically considered to be under chronic inflammation conditions. Ortega et al. and Mortensen et al., found that plasma concentrations of calprotectin were correlated with inflammation independently of obesity status in T2DM patients [11, 12]. Pedersen et al. [9] observed that T2DM patients tended to have increased levels of serum calprotectin, which were related to myocardial ischemia. Calprotectin was found to be effectively released from macrophages in response to their phagocytic activity and was found to be correlated with inflammatory response more than two decades. It was also found that glucose or/and metabolic end of glycation may have effects on calprotectin metabolism especially high levels in diabetic patients [4]. Regarding Lactoferrin, the findings of the present study agreed with Mohamed & Schaalan [5], they found that lactoferrin was significantly increased in patients with diabetes compared to control group.

Lactoferrin is a transferrin-family iron-binding glycoprotein with a wide range of immunological and biological functions, including antibacterial, immunomodulatory, and anticancer capabilities. Despite being a member of the transferrin family, most of these functions are not expected to be linked to its capacity to bind iron [13]. It has been reported that high lactoferrin levels 931±387 ng/mL are found in moderately obese patients with T2DA more than those of severely obese, nondiabetic subjects. Serum lactoferrin concentrations are greatly associated with insulin resistance (IR) despite lipid profile levels. lactoferrin was reported to be higher in older T2D patients, indicating that unsuccessful therapy may be related to lactoferrin high levels, as well as, high levels of baseline lactoferrin provide a strong prediction among patients with newly diagnosed diabetes for the long-term risk of deadly ischemic heart disease [14]. Some previous studies had suggested ant-diabetic effects for lactoferrin; Mohamed, & Schaalan first suggested that the anti-inflammatory, hypolipidemic and hypoglycemic effects of IF were controlled through the TLR-4, NF-B, SIRT-1 axis, a necessary pathway for signaling that activates anti-inflammatory transcription regulatory factors, in addition to suppression of TNF- and IL-1, in a obese children cohort of T2DM. In a colitis experiment, proinflammatory cytokines have been inhibited by lactoferrin which reveals that lactoferrin, secreted at the inflammation site by secondary granules of active neutrophils, may permit an inhibitory feedback pathway to avoid increased neutrophil aggregates and stimulation [5]. Vengen et al. [14] reported that an increased lactoferrin levels at baseline in newly diagnosed diabetic patients may reflect a more active proinflammatory state and, as a result, a higher risk of cardiovascular disease. Lactoferrin could also be used as a predictive factor for neutrophil count, which is linked to inflammation levels. The neutrophil count is a well-studied predictor of coronary disorders. Lactoferrin is a protein found in neutrophil granules that aid in the progression of an inflammatory response. The present study has shown that there is a significant decrease ($P<0.05$) in serum zinc level in diabetic patients in comparison to healthy group as illustrated in table 3. These results come in agreement with Farooq et al. [15], they found that patients with T2DM have Zn deficiency compared to normal subjects. However, Rusu et al. [16] revealed that the plasma levels of zinc in patients with diabetes were either normal or higher than that of healthy individuals; they attributed that to the occurrence of vascular complications as a trigger for higher serum zinc level in patients with diabetes. Zinc plays a significant task in how muscle and adipose cells use glucose. It serves as a cofactor which activates enzymes inside the cells that took part in glucose, lipid and protein metabolism. Diabetes impacts zinc homeostasis in a variety of ways, though the declines in total body zinc are most likely due to hyperglycemia rather than any main diabetes-related lesion [8]. It was proposed that low Zn levels seen in the diabetic community resulted from the reduced gastrointestinal absorption and high rate of urinary excretion [15]. Previous studies revealed that high blood glucose may have impact on the active transport of Zn secretion into the renal tubular resulting in more zinc to be excreted in urine. In addition, Zn tends to elevate insulin sensitivity by enhancing the insulin molecules binding ability to their receptors [8]. It was also reported that decreased levels of zinc in patients with diabetes are due to loss of zinc molecules as they enhance glucose translocation into muscles [7]. Recently, it was found that mean HbA1C concentration in newly diagnosed T2DM patients exhibited an inverse association with serum zinc levels with Pearson correlation coefficient about $r=-0.804$ indication a strong negative correlation between these two biomarkers [15]. Another study conducted by Seo and his co-workers and found that serum Zn concentration in men was inversely correlated with high fasting blood glucose and shown to have a positive correlation with high TGs, while a negative correlation was seen between serum Zn and HDL cholesterol levels [17]. There is a still a controversial opinion about which primarily effect on the other, diabetes and hyperglycemia on metabolism of zinc or the changes in homeostasis of zinc effect on glucose metabolism. Saha-Roy and his team suggested that low concentrations of zinc can interfere with the function of pancreas and plays a significant role in the pathogenesis of diabetes mellitus [7].

CONCLUSIONS

The current research reveals substantial changes in serum concentrations of calprotectin, lactoferrin, and zinc in patients when compared to healthy controls. Notably, patients showed significantly increased levels of calprotectin ($P<0.05$) and lactoferrin ($P<0.05$), indicating their possible use as biomarkers for the condition being studied. In contrast, serum zinc levels were markedly lower in patients (mean 61.95 µg/dl) than in controls (mean 82.4 µg/dl), with a highly significant difference ($P<0.001$). Furthermore, a Pearson correlation analysis indicated a strong negative correlation ($r=-0.509$, $P<0.01$) between serum zinc and calprotectin, alongside a positive correlation ($r=0.668$, $P<0.01$) between serum lactoferrin and calprotectin. These results highlight complex interactions among these biomarkers, emphasizing their potential diagnostic and prognostic significance in the condition under examination.

REFERENCES

1. Manigrasso MB, Juranek J, Ramasamy R, Schmidt AM. Unlocking the biology of RAGE in diabetic microvascular complications. Trends Endocrinol Metab. 2014;25(1):15-22. doi:10.1016/j.tem.2013.08.002. DOI
2. Yigazu DM, Desse TA. Glycemic control and associated factors among type 2 diabetic patients at Shanan Gibe Hospital, Southwest Ethiopia. BMC Res Notes. 2017;10(1):597. doi:10.1186/s13104-017-2924-y. DOI
3. Calcaterra V, De Amici M, Leonard MM, et al. Serum Calprotectin Level in Children: Marker of Obesity and its Metabolic Complications. Ann Nutr Metab. 2018;73(3):177-183. doi:10.1159/000492579. DOI
4. Abd El-Hafez FF, Nsr-Allah AAM, Mohamed AKA et al. Novel Biomarker Serum Calprotectin for Early Diagnosis of Diabetic Peripheral Neuropathy in Type 2 Diabetes Patients. Egypt. J. Hosp. Med. 2021;82(2):379-385. doi:10.21608/EJHM.2021.144904. DOI
5. Mohamed WA, Schaalan MF. Antidiabetic efficacy of lactoferrin in type 2 diabetic pediatrics; controlling impact on PPAR-γ, SIRT-1, and TLR4 downstream signaling pathway. Diabetol Metab Syndr. 2018;10:89. doi: 10.1186/s13098-018-0390-x. DOI
6. Mayeur S, Veilleux A, Pouliot Y et al. Plasma Lactoferrin Levels Positively Correlate with Insulin Resistance despite an Inverse Association with Total Adiposity in Lean and Severely Obese Patients. PLoS One. 2016;11(11):e0166138. doi:10.1371/journal.pone.0166138. DOI
7. Saha-Roy S, Swati B, Choudhury Kanika M et al. Status of serum magnesium, zinc and copper in patients suffering from type-2 diabetes mellitus. J Drug Deliv Ther. 2014;4:70–2. doi:10.22270/jddt.v4i1.754. DOI
8. Saharia GK, Goswami RK. Evaluation of serum zinc status and glycated hemoglobin of type 2 diabetes mellitus patients in a tertiary care hospital of Assam. J Lab Physicians. 2013;5(1):30-33. doi:10.4103/0974-2727.115923. DOI
9. Pedersen L, Nybo M, Poulsen MK et al. Plasma calprotectin and its association with cardiovascular disease manifestations, obesity and the metabolic syndrome in type 2 diabetes mellitus patients. BMC Cardiovasc Disord. 2014;14:196. doi: 10.1186/1471-2261-14-196. DOI
10. Zhang W, Kong Y, Wang L et al. Prognostic value of serum calprotectin level in elderly diabetic patients with acute coronary syndrome undergoing percutaneous coronary intervention: A Cohort study. Medicine (Baltimore). 2020;99(33):e20805. doi:10.1097/MD.0000000000020805. DOI
11. Ortega FJ, Sabater M, Moreno-Navarrete JM et al. Serum and urinary concentrations of calprotectin as markers of insulin resistance and type 2 diabetes. Eur J Endocrinol. 2012;167(4):569-578. doi:10.1530/EJE-12-0374. DOI
12. Mortensen OH, Nielsen AR, Erikstrup C et al. Calprotectin--a novel marker of obesity. PLoS One. 2009;4(10):e7419. doi: 10.1371/journal.pone.0007419. DOI
13. Eizirik DL, Colli ML, Ortis F. The role of inflammation in insulitis and beta-cell loss in type 1 diabetes. Nat Rev Endocrinol. 2009;5(4):219-226. doi:10.1038/nrendo.2009.21. DOI
14. Vengen IT, Dale AC, Wiseth R et al. Lactoferrin is a novel predictor of fatal ischemic heart disease in diabetes mellitus type 2: long-term follow-up of the HUNT 1 study. Atherosclerosis. 2010;212(2):614-620. doi:10.1016/j.atherosclerosis.2010.06.008. DOI
15. Farooq DM, Alamri AF, Alwhahabi BK et al. The status of zinc in type 2 diabetic patients and its association with glycemic control. J Family Community Med. 2020;27(1):29-36. doi:10.4103/jfcm.JFCM_113_19. DOI
16. Rusu ML, Marutoiu C, Rusu LD et al. Testing of magnesium, zinc and copper blood levels in diabetes mellitus patients. Acta Universitatis Cibiniensis Seria F Chemia. 2005;8:61–6.
17. Seo JA, Song SW, Han K et al. The associations between serum zinc levels and metabolic syndrome in the Korean population: findings from the 2010 Korean National Health and Nutrition Examination Survey. PLoS One. 2014;9(8):e105990. doi:10.1371/journal.pone.0105990. DOI

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This case-control study was approved by the medical ethics committee in the Faculty of Medicine/Kufa University (Reference №: MEC-16 on June 21, 2020).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Profile of antibiotic resistance of the main infectious contaminants on the wound surface of wounded men in the Russian-Ukrainian war

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ABSTRACT

Aim: To study the spectrum of antibiotic resistance of causative agents of wound infection in wounded men at the stage of specialized medical care.

Materials and Methods: Retrospective analysis of the results of culture of wound secretions on chromogenic media. The research involved 113 samples of biomaterial from 85 wounded. Sensitivity of antibiotics was studied by the Kirby-Bauer method.

Results: Analysis of the microflora of the wound surface made it possible to determine the dominance of gram-negative bacteria, they were isolated in 80% of cases. The microbial spectrum of gram-negative bacteria is represented by *Pseudomonas aeruginosa* – 31 isolates, *Acinetobacter baumannii* – 29 isolates, *Enterobacter aerogenes* – 21 isolates, *Proteus vulgaris* – 13 isolates, *Escherichia coli* – 7 isolates, *Enterobacter cloacae* – 5 isolates, *Klebsiella pneumoniae* – 7 isolates and gram-positive bacteria *Staphylococcus aureus* – 5 isolates, *Enterococcus fecalis* – 32 isolates. Among all tested isolates of gram-negative non-fermenting bacteria and enterobacteria, the highest sensitivity was observed to colomycin and polymyxin B, from 60 to 80%. When analyzing of antibiotic sensitivity of *Klebsiella pneumoniae and Acinetobacter baumannii,* it was found that these pathogens retain 80-100% of their actual antibiotic sensitivity to polymyxins.

Conclusions: Gram-negative strains isolated from wound infection are sensitive to antibiotics: 70% to polymyxins (colistin), 30% to aminoglycosides (amikacin), 24-16% to cephalosporins (cefoperazone-sulbactam/cefoperazone-avibactam).

KEY WORDS: combat trauma, microbiome, antibiotic resistance

Wiad Lek. 2025;78(2):295-302. doi: 10.36740/WLek/197142 DOI

INTRODUCTION

Wounds resulting from combat operations with the use of modern weapons require the speed of decision-making related to the provision of medical care, as they are characterized by a specific course of the wound process and the addition of secondary purulent complications. Purulent-septic processes occur as a result of 75% of gunshot and shrapnel wounds. They require long-term intensive therapy, multi-stage exhausting treatment aimed at combating the consequences of injury, and are always accompanied by severe complications [1, 2]. The development of the inflammatory process as a trigger of an immune response directed simultaneously against the infectious agent and triggers several mechanisms of the pathological action on cells of human body. It was shown a significant influence of opportunistic and pathogenic microorganisms as part of associations or monoinfection on the morphofunctional state of spermatozoa [3].

The main role in the pathogenesis of the development of infectious complications in the early and late period of wounds is played by infectious agents, the dominance of which can change depending on the state of the immune system and the transportation of the wounded to different institutions for the purpose of receiving qualified medical care. This creates conditions for the uncontrolled transfer and spread of polyresistant strains of microorganisms inside and outside the hospitals.

Scientists also note a worldwide trend of dominance of certain types of microorganisms that contaminate combat wounds. According to the order of the Ministry of Health of Ukraine No. 403 from February 27, 2023 "On the approval of the Procedure for conducting enhanced epidemiological surveillance of antimicrobial resistance of microorganisms that cause purulent-inflammatory infections of wounds in the wounded as a result of hostilities" [4], it is important to carry out a bacteriological examination of samples of biological materials patients, isolation and identification of microorganisms, determination and assessment of the

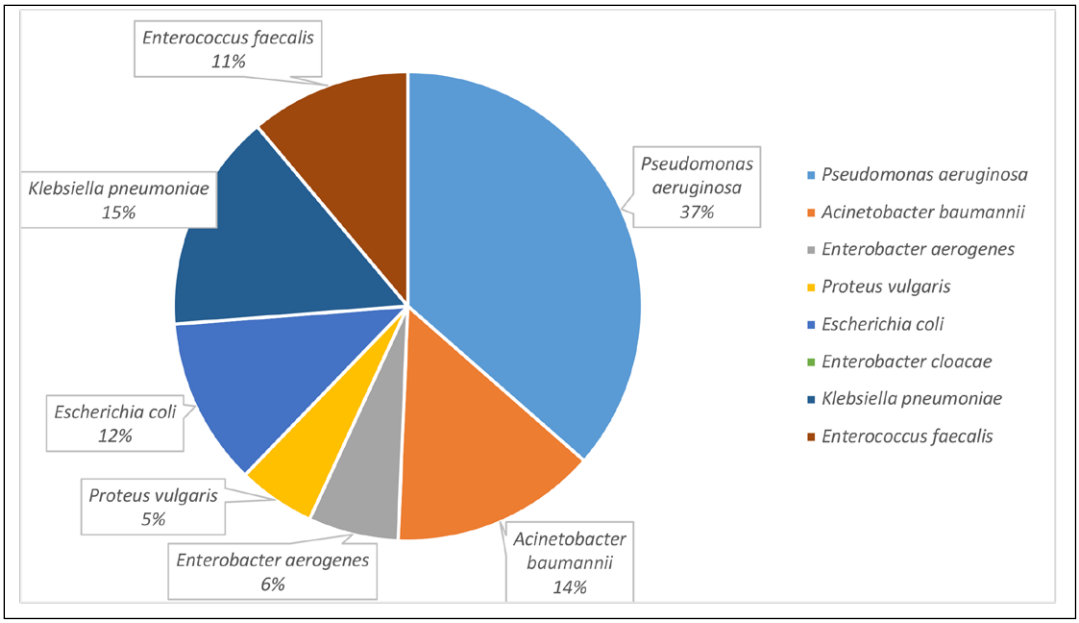

Fig. 1. Results of the study of the bacterial profile of combat injuries.

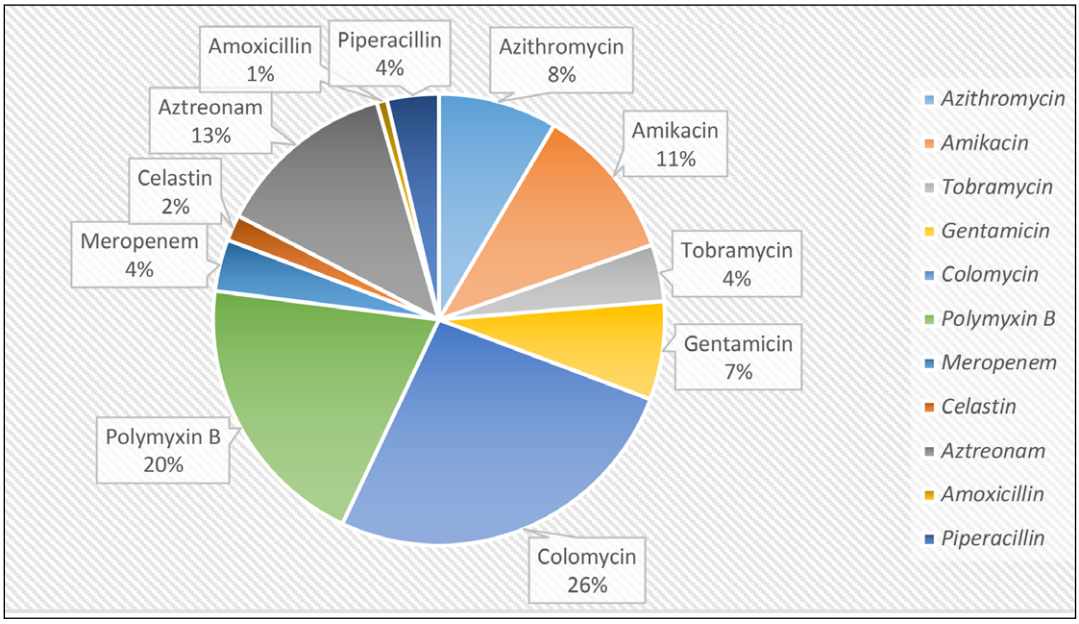

Fig. 2. Antibiotic sensitivity of gram-negative bacteria.

sensitivity of microorganisms to antimicrobial drugs, since the problem is characteristic of both the global and local levels. In everyday clinical practice, this means that infections caused by problematic polyresistant strains of microorganisms do not respond to traditional (protocol) treatment schemes. The wide distribution of methicillin-resistant staphylococci and enterobacteria producing beta-lactamases of a wide spectrum of action leads to the need to use new, more expensive antibacterial drugs. Irrational antibiotic therapy and, as a result, increased resistance of microorganisms prolong the duration of stay of the wounded in the hospital, lead to serious complications, and in some cases lead to the formation of scars. If purulent-septic complications are caused by polyresistant microorganisms, this increases the risk of mortality, and is also accompanied by a delay in the response to adequate antimicrobial therapy.

AIM

The aim is to study the spectrum of antibiotic resistance of causative agents of wound infection in wounded men at the stage of specialized medical care.

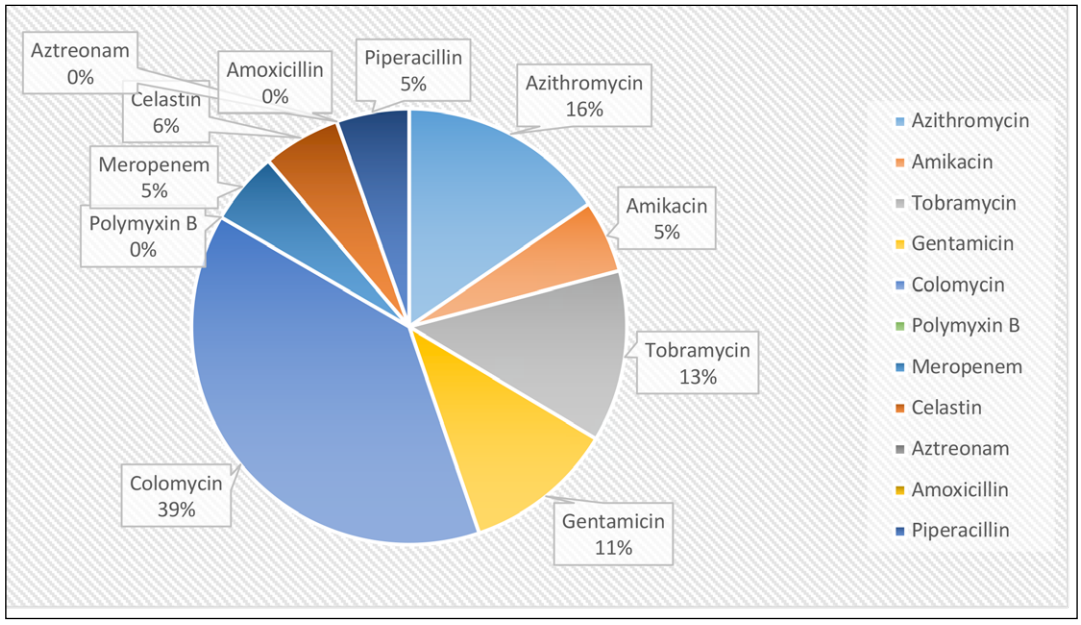

Fig. 3. Antibiotic sensitivity of *Klebsiella pneumoniae* (share of resistant strains, %).

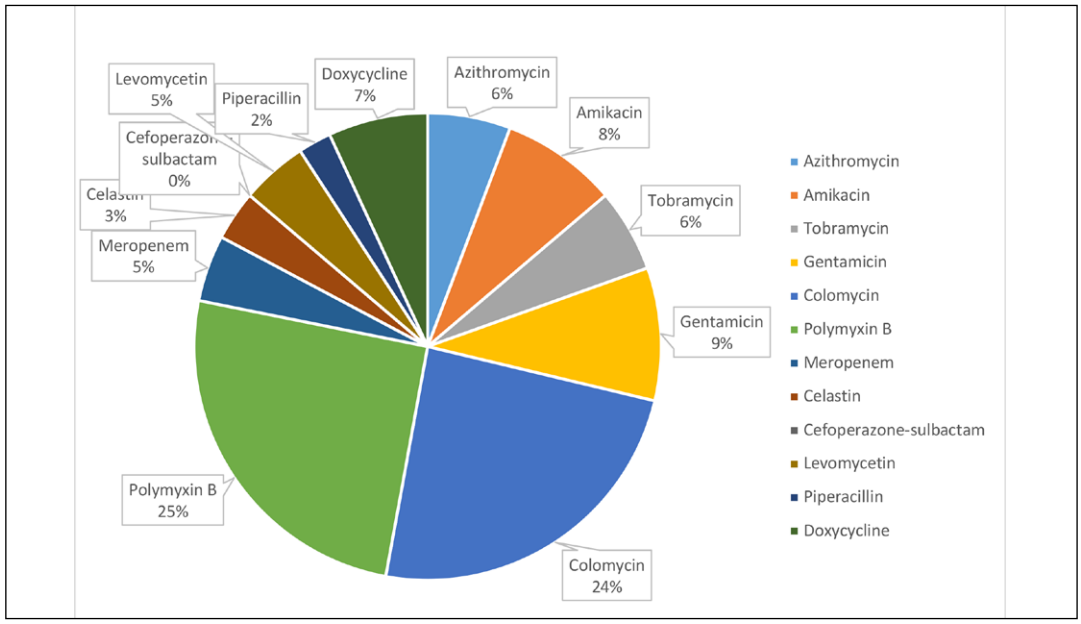

Fig. 4. Antibiotic sensitivity of *Acinetobacter baumannii*.

MATERIALS AND METHODS

Retrospective analysis of the results of culture of wound secretions on chromogenic media. The research involved 113 samples of biomaterial from 85 wounded. Sensitivity of antibiotics was studied by the Kirby-Bauer method.

RESULTS

The paper presents the results of microbiological analysis of the spectrum of pathogens isolated from combat wounds. Collection of material for bacteriological examination in the hospital was carried out in patients with landmine-explosive injuries, gunshot bullet injuries, shrapnel injuries, or injuries complicated by sepsis and multiple organ failure. It should be emphasized that, according to statistics, 90% of the material is taken against the background of previous antibiotic therapy. This often obscures the true picture of the microbiological landscape.

As a result of the conducted microbiological studies, 113 isolates of microorganisms were isolated. Analysis of the microflora made it possible to determine the dominance of gram-negative bacteria, they were isolated in 80% of cases. The microbial spectrum of gram-negative bacteria is represented by *Pseudomonas aeruginosa* – 31 isolates,

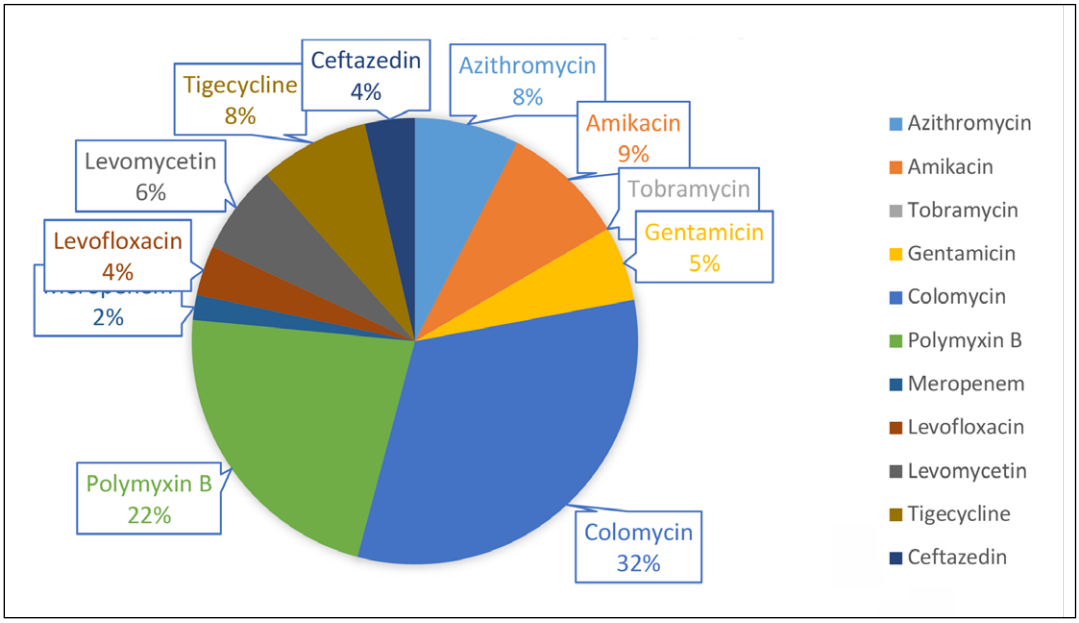

Fig. 5. Antibiotic sensitivity of *Enterobacter aerogenes*.

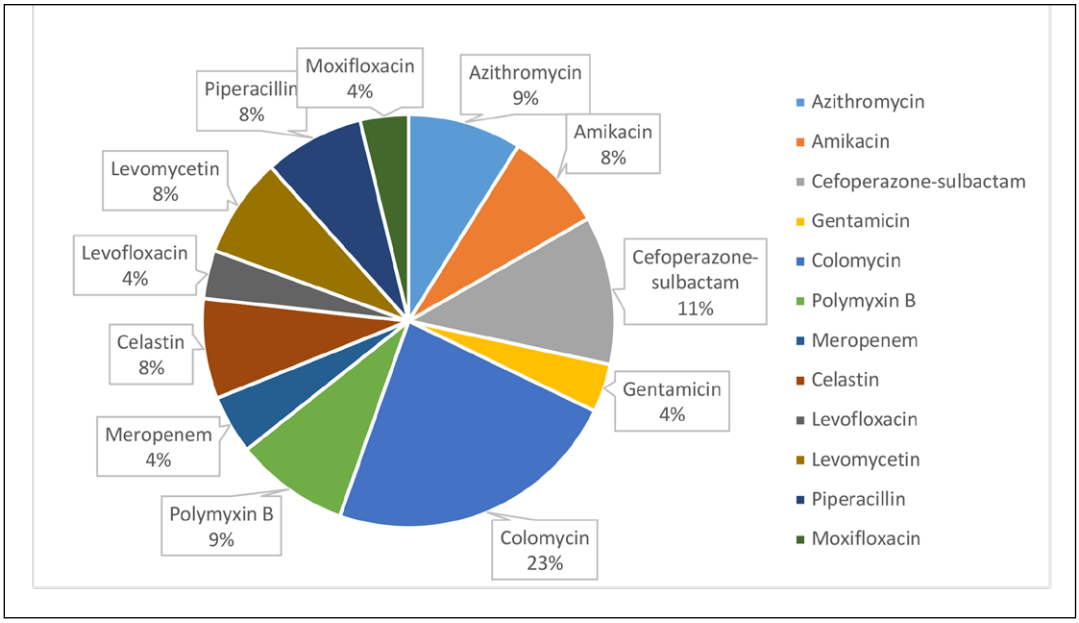

Fig. 6. Antibiotic sensitivity of *Escherichia coli*.

Acinetobacter baumannii – 29 isolates, *Enterobacter aerogenes* – 21 isolates, *Proteus vulgaris* – 13 isolates, *Escherichia coli* – 7 isolates, *Enterobacter cloacae* – 5 isolates, *Klebsiella pneumoniae* – 7 isolates and gram-positive *Staphylococcus bacteria aureus* – 5 isolates, *Enterococcus faecalis* – 32 isolates. (Fig. 1).

The analysis of the results of our research proved a high degree of resistance of the selected gram-negative microorganisms to most antibiotics, including carbapenems. Given that gram-negative bacteria are the dominant microbiome of combat wounds and in the development of infectious complications of gunshot wounds, their sensitivity to the most commonly used antibiotics was investigated and analyzed (Fig. 2). Thus, among all tested isolates of gram-negative non-fermenting bacteria and enterobacteria, the highest sensitivity was observed to colomycin and polymyxin B – from 60 to 80%. Also, these strains were resistant to fosfomycin, clindamycin, and rifampicin. Azithromycin, amikacin, tobramycin and gentamicin can be called the drugs of choice in the treatment of isolated gram-negative bacteria, since the average sensitivity to these drugs was from 20 to 50%.

When analyzing the antibiotic sensitivity of *Klebsiella pneumoniae*, *Acinetobacter baumannii*, it was found that these pathogens retain 80-100% of their actual

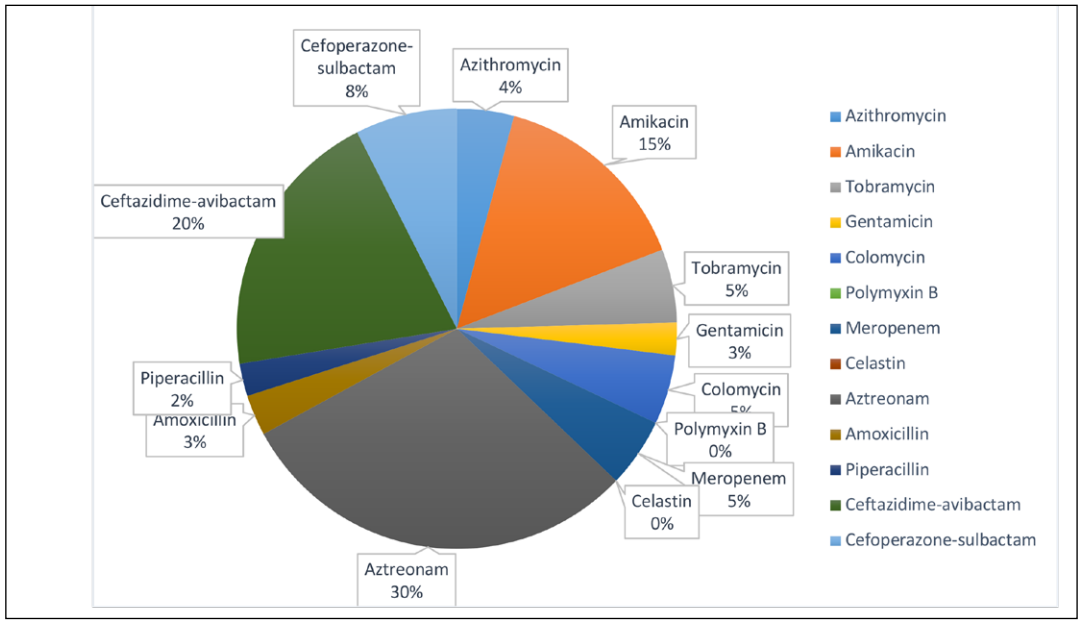

Fig. 7. Antibiotic sensitivity of *Proteus vulgaris*.

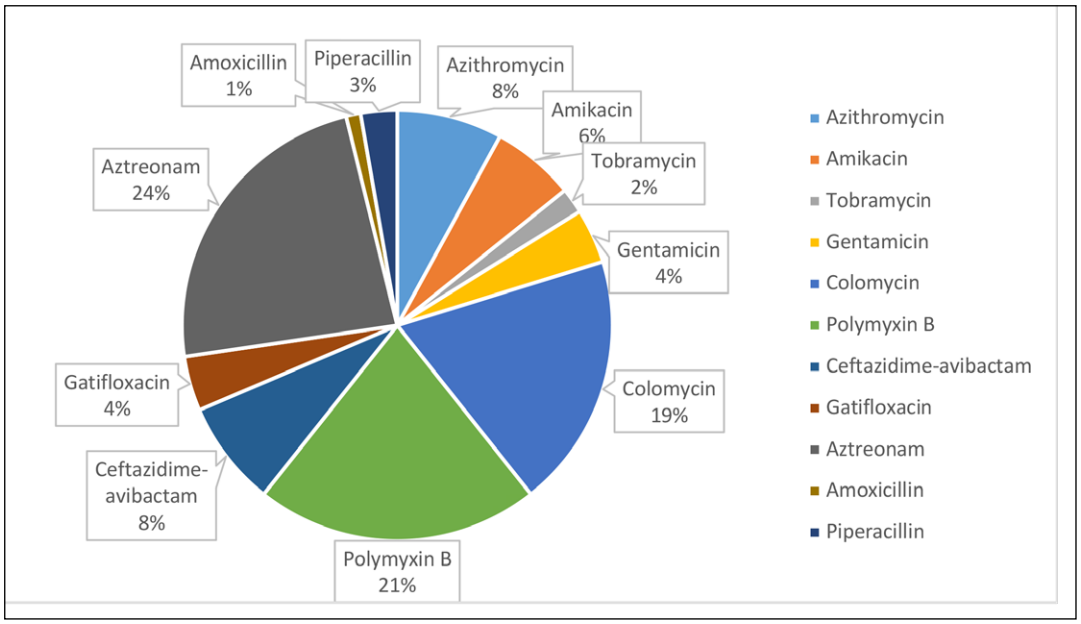

Fig. 8. Antibiotic sensitivity of *Pseudomonas aeruginosa*.

antibiotic sensitivity to polymyxins (Fig. 3, Fig. 4). Gentamicin and amikacin equally maintain moderate sensitivity at the level of 30% and are the drugs of choice for both pathogens. An interesting surprise was the moderate sensitivity of these pathogens to ceftriaxone at the level of 7-14%, although sensitivity to meropenem and celastin was also observed within the same limits.

It was found that all *Klebsiella* strains were resistant to this antibiotic as well. Resistance of *Acinetobacter baumannii* to piperacillin/tazobactam was at the level of 7%, and in *Klebsiella pneumoniae* – 14%.

The analysis of the antibioticogram showed a high sensitivity to polymyxins at the level of 65-90% (Fig. 5). And 100% resistance to cephalosporins, aztreonam, meropenem and piperacillin. The drugs of choice were azithromycin at the level of 21% and amikacin –25%.

When analyzing the antibiotic resistance of *Escherichia coli* (Fig. 6) isolated from patients with combat injuries, it was found that the bacteria have a high degree of resistance to almost all tested antibiotics, except for azithromycin and amikacin, the average sensitivity to which was from 20 to 30%.

The level of resistance to cephalosporins of the 3rd and 4th generation is 100%, since *Escherichia coli* is a

producer of beta-lactamases of a wide spectrum of action and in the treatment only drugs that inhibit the most important beta-lactamases are required, therefore, in the analysis with cefoperazone-sulbactam with it turned out that the causative agent is indeed sensitive, as indicated by 43% of antibiotic sensitivity. Since, compared to other β-lactam antibiotics, cefoperazone-sulbactam is able to penetrate faster through the outer membrane of gram-negative bacteria and, in addition, to exert a pronounced postantibiotic effect on them, which lasts 7–10 hours.

Which is quite effective for combat injuries of the abdominal cavity when it is necessary to transport the patient over long distances. It should be noted that low sensitivity to aminoglycoside drugs is a natural retribution for their unjustified and widespread use and should serve as a signal to review their use in everyday clinical practice.

When studying the antibiotic sensitivity of 13 strains of *Proteus vulgaris*, there was a double feeling, on the one hand, it is generally accepted that the pathogen is very resistant to antibiotics due to the plasmids present in the bacterium, which makes it extremely difficult to treat. On the other hand, incorrect antibiotic therapy for *Proteus vulgaris*, before the patient entered our department, could lead to its dominance in the biofilms of the urogenital tract and, as a result, to the formation of struvite stones. Especially in patients with long-term use of catheters.

However, as practice has shown, *Proteus vulgaris* was moderately sensitive to the test antibiotics, but a high sensitivity to amikacin – 50%, aztreonam – 100%, cefoperazone – sulfbactam – 25%, and ceftazidime – aviabactam – 70% was observed (Fig. 7). However, unfortunately, 90% of resistance to fluoroquinolones and cephalosporins.

Analyzing the antibiotic sensitivity of *Pseudomonas aeruginosa*, its 100% resistance to doxycycline, clindamycin, ofloxacin, and levofloxacin was established. The same pattern is observed among cephalosporin preparations, but the sensitivity to ceftazidime-avibactam was at the level of 29%. However, positive points were also noted, in particular, when setting antibiotic sensitivity to polymyxins – 78% (Fig. 8).

DISCUSSION

It should be noted that in recent years, the specific weight of *Klebsiella* bacteria in the microbial spectrum of gunshot wound contaminants has increased, and this is a global issue because they produce various carbapenemases [5], which increases their resistance to certain types of antibiotics. To date, about 500 types of broad-spectrum beta-lactamases (BLRS) have been described, and this list is constantly being updated. As a rule, the genes that encode the synthesis of beta-lactamases are located on plasmids, which facilitates easy transfer between bacteria and, subsequently, the rapid spread of resistant pathogens.

Of particular concern among clinicians is the trend of increasing resistance of pathogens such as *Klebsiella pneumoniae* and *Acinetobacter baumannii*, which cause complications among patients with combat injuries and are also associated with concomitant pathology in soldiers. According to the analyzed data of bacteriological studies of combat injuries in the territory of Ukraine in the period 2014-2017, the share of these microorganisms isolated was 9.4% and was represented by the species *Klebsiella pneumoniae* and *Klebsiella oxytoca*, so during the full-scale war, pathogens were isolated in the wound contents of 1/3 of the examined [6, 7]. According to the EUCAST recommendations, when resistance to meropenem is detected, the establishment of sensitivity to piperacillin/tazobactam is a mandatory step.

Klebsiella aerogenes, formerly known as *Enterobacter aerogenes*, is a catalase-positive bacterium that causes opportunistic infections. Infections caused by this pathogen are generally susceptible to antibiotics, although complicated by induced resistance mechanisms, particularly beta-lactamase. Often, strains of *Enterobacter aerogenes* quickly become resistant to standard antibiotics during treatment, which requires special supervision, especially if it concerns gastrointestinal tract injuries and urogenital tract diseases.

Escherichia coli is singled out as a leading pathogen among diseases, injuries and complications, especially if it is related to the organs of the abdominal cavity. Over the past 20 years, the frequent treatment of infections caused by *Escherichia coli* has been determined by the widespread and completely unfounded use of 3rd generation cephalosporins, in particular cefotoxime, ceftriaxone, and cefoperazone in clinical practice.

There are many factors that can cause a delay and/or inability to heal a chronic wound, namely: the patient's age, obesity, oxygen saturation of the wound, long-term use of non-steroidal anti-inflammatory drugs. However, infiltration by biofilms, including *Salmonella enterica*, *S. bongori*, *Staphylococcus epidermidis*, *S. aureus*, *Pseudomonas aeruginosa*, is probably the biggest factor [8].

When treating wounds, it is important to consider not only antimicrobial efficacy, but also how they may affect the complex cellular and extracellular mechanisms involved in wound healing. Because modern combat trauma is characterized by the massiveness of affected tissues, a high degree of contamination, and simultaneous damage to various organs and systems [9-12].

CONCLUSIONS

1. Analysis of the microbiological structure of secretions from an abdominal wound cavities and areas of the pelvis showed that the inflammatory process is initiated mainly by Gram-negative bacteria, to a lesser extent by Gram-positive bacteria. Isolated strains have a significant resistance to antibacterial drugs (49%), which indicates the need for constant periodic monitoring of antimicrobial therapy.
2. Gram-negative strains isolated from wound infection are sensitive to antibiotics, only 70% to polymexins (colistins), 30% to aminoglycosides (amikacin), 24-16% – cephalosporins (cefoperazone-sulbactam / cefoperazone-avibactam).
3. The use of antibiotics in the treatment of combat wounds is a prerequisite for effective treatment of servicemen, shortening of periods of incapacity for work and quick return to the ranks.

REFERENCES

1. Khomenko IP, Gerasimenko OS, Yenin RV et al. Peculiarities of surgical treatment of gunshot wounds to the abdomen. The Ukrainian Journal of Clinical Surgery. 2018;9:71-74. doi:10.26779/2522-1396.2018.09.71. DOI
2. Khomenko IP, Tsema EA, Tertyshnyi SV, Shklyarevich PO. Dynamika mikrobnoho obsimeninnya vohnepal'noyi rany pry kompleksniy khirurhichniy obrobtsi. [Dynamics of microbial contamination of a gunshot wound during complex surgical treatment]. Khirurhiya Ukrayiny. 2018;1:7-13. (Ukrainian)
3. Melnyk OV, Vorobets MZ, Fafula RV et al. Urogenital infection as a factor of development of male infertility. Microbiological journal. 2023;85(2):93-112. doi:10.15407/microbiolj85.02.093. DOI
4. Fomina NS, Fomin OO, Kovalchuk VP et al. The microflora of a modern combat wound and its sensitivity to antibiotics – what's new? Part II. Ukraine Med Journal. 2023;5(157):1-4. doi: 10.32471/umj.1680-3051.157.247288. DOI
5. Kryshevskyi YuP, Horoshko V. Antibiotic resistance and sensitivity of microorganisms isolated in patients with abdominal injuries. Emergency medicine. 2020;16:56-64. doi: 10.22141/2224-0586.16.5.2020.212225. DOI
6. Fomina N, Sukmanska H, Kordon Yu, Trofimenko J. Improving the methods of local treatment in case of aphthous lesions on the oral mucosa. Vinnytsia National Medical University Bulletin. 2020;24(1):106–109. doi: 10.31393/reports-vnmedical-2020-24(1)-28. DOI
7. Trutyak IR, Fil AYu, Medzin VI, Trutyak RI. Surgical treatment of the consequences of modern combat trauma. Trauma. 2017;18(4):58-62. doi: 10.22141/1608-1706.4.18.2017.109345. DOI
8. Alves PJ, Barreto RT, Barrois BM et al. Update on the role of antiseptics in the management of chronic wounds with critical colonisation and/or biofilm. Int Wound J. 2021;18(3):342-358. doi: 10.1111/iwj.13537. DOI
9. Hrytsai MP, Poliachenko YuV, Tsokalo VM et al. Treatment tactics in case of infectious complications in patients with combat injuries of the musculoskeletal system (according to the clinic's own experience). Erra orthopaedica. 2023;1(116):46-57. doi:10.37647/2786-7595-2023-116-1-46-57. DOI
10. Burmeister DM, Johnson TR, Lai Z et al. The gut microbiome distinguishes mortality in trauma patients upon admission to the emergency department. J Trauma Acute Care Surg. 2020;88(5):579-587. doi: 10.1097/TA.0000000000002612. DOI
11. Khomenko IP, Korol SO, Khalik SV et al. Clinical and Epidemiological analysis of the structure of combat surgical injury during Antiterrorist operation. Joint Forces Operation. Ukrainian Journal of Military Medicine. 2021;2(2): 5-13. doi:10.46847/ujmm.2021.2(2)-005. DOI
12. Kok CR, Bram Z, Thissen JB et al. The military gear microbiome: risk factors surrounding the warfighter. Appl Environ Microbiol. 2024;90(1):e0117623. doi: 10.1128/aem.01176-23. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

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ORIGINAL ARTICLE

CONTENTS

The role of maternal ABO blood group and malondialdehyde as diagnostic marker in the development of gestational diabetes mellitus

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ABSTRACT

Aim: The aim of research is to assess whether various blood groups can be associated with the occurrence of gestational diabetes mellitus and if malondialdehyde can be used for the diagnosis of GDM.

Materials and Methods: A case control study started from September 2022 to June 2023 enrolled 200 pregnant women aged between 15-45 years, cases included 100 patients selectively collected with a confirmed diagnosis of gestational diabetes mellitus, and 100 were healthy normal in Kerbala obstetrics and gynecology hospital, both patient and controls group categorized according to blood group type.

Results: Pregnant women with gestational diabetes mellitus are mostly of blood group AB in comparison with pregnant women without Gestational diabetes mellitus, and both A and B were significantly higher among control pregnant women, additionally, two groups' blood group O levels were almost identical. Malondialdehyde mean was significantly higher in pregnant women with Gestational diabetes mellitus with p-values 0.001. Statistically significant differences could not be detected in the mean levels of MDA across the various blood groups (p= 0.505).

Conclusions: This research reveals that mother's ABO blood group has a role in the development of GDM and the blood group AB is more likely to develop GDM, blood group A & B are less likely to develop GDM and may be regarded as a protective factor. MDA can be used for the diagnosis of GDM but further studies are required to support this finding.

KEY WORDS: Gestational diabetes mellitus, pregnancy condition, spontaneous hyperglycemia

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a common pregnancy condition characterized by the occurrence of spontaneous hyperglycemia throughout pregnancy [1]. Throughout a normal pregnancy, the pregnant body experiences a sequence of physiological alterations to meet the needs for the developing child. An essential adapting metabolic pathway entails insulin sensitivity [2]. As pregnancy advances, several substances that stimulate insulin resistance such as estrogen, progesterone, leptin, cortisol, placental lactogen, and placental growth hormone are included [3]. Although it can happen in many settings, β-cell malfunction and persistent insulin resistance describe the vast majority of GDM cases (~80%). Insulin-resistance is already present throughout pregnancy, and it becomes much worse at this time. Consequently, women who are impacted tend to have a higher level of insulin-resistance compared to healthy pregnant women. As a result, they have a bigger decrease in glucose utilization and an increase in glucose synthesis and concentrations of free fatty acids (FFA). β-cells are believed to degrade as a result of more insulin being produced because of higher energy expenditure and insulin resistance, which gradually depletes the cells [4, 5]. The ABO blood type system is considered the most significant in humans. Typically, the blood type of a person does not undergo any changes from the moment of embryo creation. Multiple studies have shown a correlation between the ABO blood type and many health conditions such as infection, cancer, cardiovascular illness, and nervous system disorders [6]. Prior research has also investigated the correlation between ABO blood group and difficulties during gestation [7, 8]. The association between ABO blood type and negative pregnancy outcomes such as preeclampsia, venous thromboembolism, postpartum hemorrhage, and gestational diabetes mellitus is a subject of debate. Insulin-resistance and the onset of type-II

DM are heavily correlated with the ABO antigens, which in turn affect a wide variety of biomarkers. Included in this set of biomarkers are interleukin-6, E-selectin, P-selectin, tumor necrosis factor-α, and soluble intercellular adhesion molecule-1 [9]. The majority of researches examining the correlation between ABO blood type and gestational diabetes mellitus provide inconclusive results, while there have been reports indicating that those with AB blood type may have a lower chance of developing gestational diabetes mellitus [10]. Several researches have shown that individuals with AB blood type have a higher susceptibility to gestational diabetes mellitus [11]. Currently, the available data about the relation between ABO-blood type and GDM is insufficient and contradictory. Oxidative stress refers to the ongoing condition of oxidative damage in a cell, tissue, or organ, resulting from reactive oxygen species (ROS). The majority of reactive oxygen species originates from endogenous sources, namely as by-products of normal and essential activities, such as the production of energy by mitochondria. The level of oxidative stress was shown to be higher in pregnant affected with GDM compared to those with a normal pregnancy [12]. Oxidative stress has been linked to the development of several disorders, including GDM [13]. It delineates a disparity between cellular pro- and anti-oxidants. Damage to cells may occur when oxidative stress upsets the delicate balance of DNA, lipids, and proteins. Both free radical and nonradical forms of oxygen are referred to as reactive oxygen species. These forms include the superoxide anion (O_2–), hydroxyl radical (•OH), and hydrogen peroxide (H_2O_2) [14]. An excessive amount of glucose in the body is linked to oxidative stress. Pregnant with GDM were shown to create an excessive amount of free radicals and have poor systems for removing these harmful molecules [15]. Reactive oxygen species hinder the process of insulin-stimulated glucose absorption by disrupting the functioning of both GLUT4 and IRS-1 also, slows down muscle and liver glycogen production. When reactive oxygen species break down phospholipids in pathological conditions like diabetes mellitus, malondialdehyde (MDA) is the byproduct. MDA is the primary and widely researched molecule resulting from lipid peroxidation, recognized for its mutagenic and hazardous properties, moreover, MDA may be generated enzymatically as an incidental byproduct during the production of thromboxane A2 [16]. Lipid peroxidation produces malondialdehyde (MDA), which has been used as a biomarker to measure oxidative stress in various biological samples (e.g., blood, urine, and exhaled breath condensate, or EBC) in people with various diseases (e.g., cancer, heart disease, lung disease, neurodegenerative disease, etc.) Moreover, the identification of these final substances in inflammatory illnesses indicates that lipid peroxidation has a substantial impact on this particular form of illness [17].

AIM

The aim of our research is to assess whether various blood groups can be associated with the occurrence of gestational diabetes mellitus and if malondialdehyde can be used for the diagnosis of GDM.

MATERIALS AND METHODS

The present study is a case control study started from September 2022 to June 2023 enrolled 200 pregnant women aged between 15-45 years, cases included 100 patients selectively collected with a confirmed diagnosis of gestational diabetes mellitus, and 100 were healthy normal in Kerbala obstetrics and gynecology hospital. The patients were categorized into four categories according to the blood group type, blood group O (51) patient, AB (25) patient, A (13) patient and Blood group B (11) patient. The control group included 100 healthy pregnant women also collected from the obstetrics and gynecology hospital in Kerbala governorate. The control group were divided into four groups depending on the blood group type. Blood group O (41) women, AB (8) women, A (25) women and Blood group B (26) women. The study was conducted under the endorsement of the scientific and ethical committees in the Faculty of Medicine, University of Kufa, Iraq.

INCLUDED PATIENTS

All pregnant women at the second and the third trimester who have a confirmed diagnosis of gestational diabetes mellitus.

EXCLUDED PATIENTS

Pregnant women who have diabetes (both type I and II), pregnant women in the first trimester with diabetes, pregnant women in a baby with congenital anomalies, obese pregnant women, pregnant women who smoke.

COLLECTED SAMPLES

After skin sterilization five milliliters of blood were aspirated from anti- cubital vein split into two halves, the first two milliliters of blood used for the detection of the blood group type, allowing the reminder blood three milliliters to clot for 10-20 min., at room temperature, in gel tubes to obtain serums by centrifuging at (2000-

Table 1. Body mass index and age difference in patients and controls

Variable	Studied group				P -values
	Pregnant with GDM		Control pregnant		
	Mean ±SD	Ranges	Mean ±SD	Ranges	
Age (years)	33 ±7.4	18-45	32.6 ±7.7	18-45	0.655
BMI (kg/m^2)	23.5± 2	19.5-28.2	23.8 ±2.1	19.5-28.2	0.397
Student T test, significant ≤0.05					

Table 2. Blood groups distribution in patients and controls

Variable		Studied group		P value
		Pregnant with GDM	Control pregnant	
Blood group	A	13(33.3%)	26(66.7%)	<0.00*
	AB	25(75.8%)	8(24.2%)	
	B	11(31.4%)	24(68.6%)	
	O	51(54.8%)	42(45.2%)	
Total		100	100	200
*Chi-Square test, significant ≤0.05				

Table 3. Level of malondialdehyde in patients and controls.

Variable	Studied group				P value
	Pregnant with GDM		Control pregnant		
	Mean ± SD	Range	Mean ± SD	Range	
MDA	186.6 ± 103.4	78.3-716.6	73.4 ± 21.7	30.6-112	<0.001*
*Student T test, significant ≤0.05					

3000) r.p.m., for 20 minutes, after that the obtained serum stored at -15 C to perform the biochemical tests for malondialdehyde (MDA).

BODY MASS INDEX CALCULATION

Women's weight before pregnancy and height are used to calculate their BMI. The BMI formula is (body weight divided by the body height in square meters) and expressed in (kg/m^2) [18].

$BMI = weight/ (height)^2$

DETERMINATION OF BLOOD GROUP TYPE BY ANTI A, ANTI B, ANTI AB MONOCLONAL REAGENTS

The hemagglutination principle is utilized by the manual technique, which can be done on a plate or in a tube. When exposed to the antibody-containing reagent, test red blood cells that carry the antigen agglutinate.

MEASUREMENT OF MALONDIALDEHYDE (MDA) BY ENZYMES LINKED IMMUNOSORBENTS ASSAY (ELISA-KITS)

We used the Competitive-ELISA approach with ELISA-kit. These kits come with micro-plates that have already coated with MDA, throughout the procedure, the detection biotinylated Ab, which is specific to MDA. By spectrophotometric measurement of the changes in color is taken at a wave-length of 450±2 nm. After that, we compare the samples' optical densities (ODs) to the standard curve to find the MDA concentrations in the samples.

STATISTICAL ANALYSIS

Data is analyzed using SPSS version 26, which is a statistical tool for the social sciences. Presenting descriptive statistics in the form of frequency tables, the representation of continuous variables includes portraying them as the mean value offset by the standard deviation. As an alternative, categorical variables were described by numbers and percentages. We utilized the chi-square test to identify associations between two categories of data, the Student T used to identify associations between categories of data and continuous variables. Statistical analysis by Receiver operative characteristic curve (ROC) used to evaluate the performance of MDA in detecting GDM. Statistical significance was determined by a P-value of 0.05 or less.

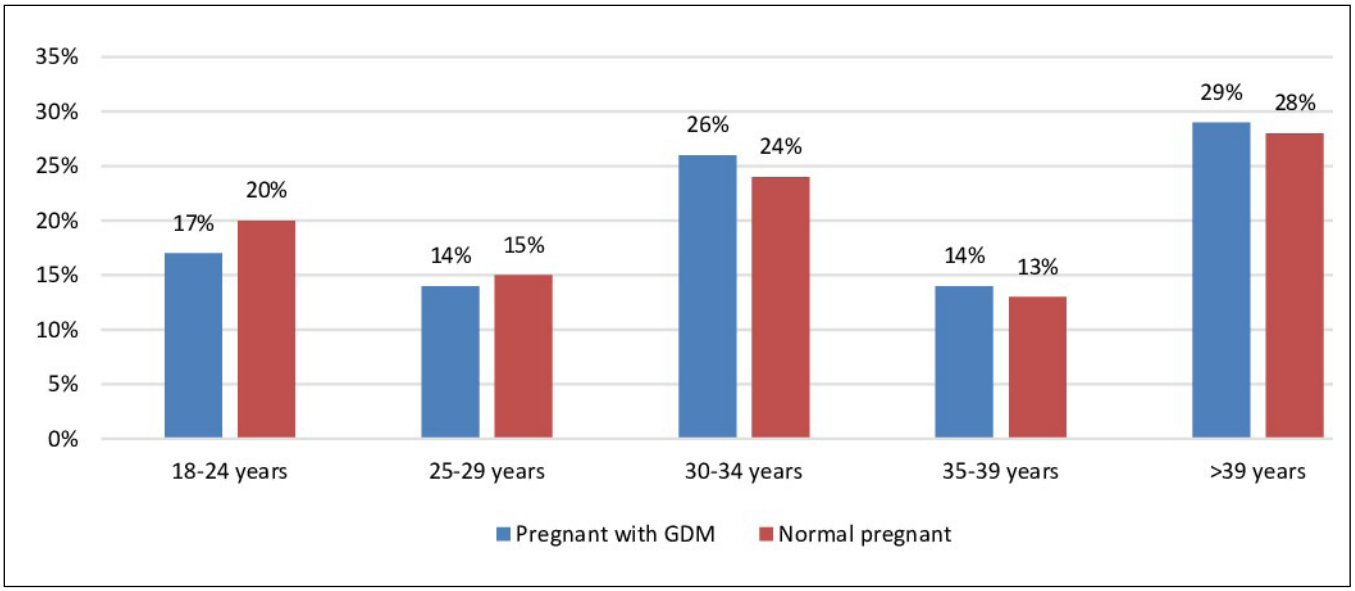

Fig. 1. Age distribution between two studied groups.

RESULTS

THE DIFFERENCE IN AGE AND BODY MASS INDEX IN PATIENTS AND CONTROLS

When comparing the two groups, we found that they were very comparable in age and BMI (p higher than 0.05) (Table 1, Fig.1).

BLOOD GROUPS DISTRIBUTION IN PATIENTS AND CONTROLS

Pregnant women with gestational diabetes mellitus (GDM) are mostly of blood group AB in comparison with pregnant women without GDM, and both A and B were significantly higher among control pregnant women (Table 2). Additionally, the two groups' blood group O levels were almost identical.

LEVEL OF MALONDIALDEHYDE IN THE TWO GROUPS

The studied MDA marker mean was significantly higher in pregnant women with GDM with p-values 0.001 (Table 3, Table 4, Fig.2).

EVALUATION OF MALONDIALDEHYDE'S DIAGNOSTIC UTILITY USING ROC CURVE

The ROC curve for MDA was shown in fig. 3, obtained from the values of OGTT and MDA tests with an area under the curve 0.972 and p value <0.001., with cut of value of 78.7 had sensitivity of 99% and specificity of 41%.

DISCUSSION

During pregnancy if appropriate steps not performed to control the early stage of GDM, the health of mothers and infants would suffer greatly. The most significant human blood grouping system is ABO. Numerous studies have shown that the blood group type is linked to a wide range of illnesses. The relationship between GDM and ABO-blood group is debatable at the moment [19].

BODY MASS INDEX AND AGE DIFFERENCE BETWEEN PATIENTS AND CONTROLS

This study reveals there is no valuable (p>0.05) differences in the mean age and BMI in the two groups. Since obesity is a cause for gestational diabetes mellitus, we intentionally excluded obese pregnant women from the research to focus on the ABO blood type impact, thus this suggests that the two groups were comparable in age and body mass index. Comparable findings were observed in a French cohort, where pregnant women with and without GDM were found to be of similar ages [20]. But according to case-control research carried out in Thailand, age was a crucial factor linked to the development of GDM, with those over 30 having a considerably higher risk of the disease than those under 30 [21]. Likewise, a Turkish cohort study also showed that pregnant women with and without GDM differed significantly in age [22]. Therefore, it is still unclear whether age is a predictor of GDM, and further research that accounts for confounding variables is needed to confirm this link. Known risk factors for gestational diabetes mellitus include advanced maternal age,

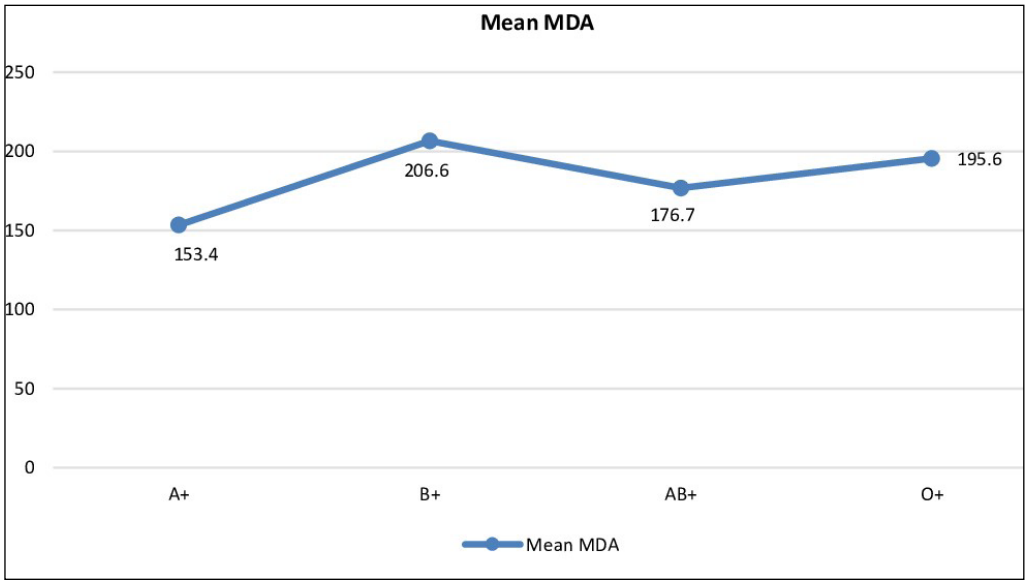

Fig. 2. Mean level of MDA among different blood groups category.

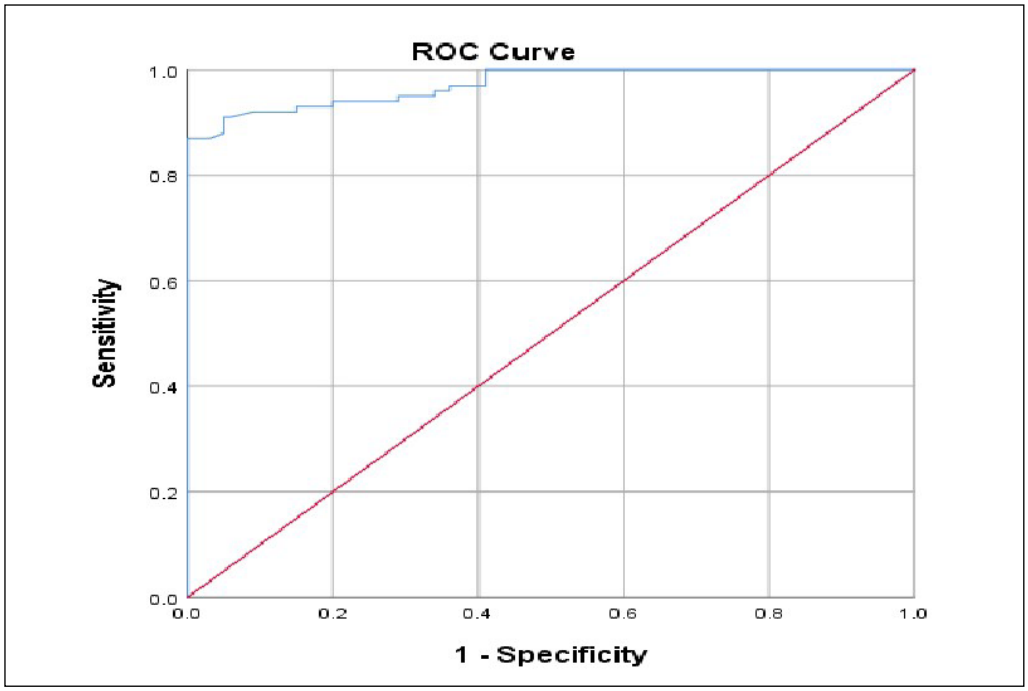

Fig. 3. ROC curve for MDA.

high BMI, excessive (GWG), ethnic race, polycystic ovarian syndrome (PCOS), low stature, high parity, previous large-for-gestational (LGA) deliveries, and a family history of diabetes (DM) [23]. Mother's age is a well-considered risk factor for GDM, since prior research has consistently indicated that older pregnant women have a higher likelihood of developing GDM [24]. However, there is disagreement over what constitutes a reasonable cut-off point. Americans Diabetes Association (ADA) state that age greater than 25 years considered as a risk factor, according to retrospective research of Japanese women (138,530), the incidence of GDM increase by age, in women over forty exhibiting a relative risk of 15.1% [25].

DISTRIBUTION OF BLOOD GROUPS IN PATIENTS AND CONTROLS

The pregnant with gestational diabetes had a significantly greater percentage of blood groups AB (p value ≤ 0.05) than the pregnant women in the healthy control group. These findings suggested that the ABO blood type could be linked to some unfavorable pregnancy outcomes. Patients with AB-blood group were found to have higher risk of gestational diabetes by Karagoz [26]. Another study by Shimodaira suggested that AB-blood group elevate the risk for gestational DM [11]. Additionally, blood group O was found to be roughly the same in both groups, despite the fact that the percentage of

blood types A and B was much greater in the control pregnant women. These findings may indicate that people with blood groups A and B are less likely to acquire GDM. Like our study [26] investigation revealed that participants who have blood group B had a much-decreased chance of acquiring DM; as a result, blood group B may be thought of as a protective factor for the incidence of DM. It should be noted that the blood groups were normally distributed in Karbala Blood Bank for 2023 as follows (O^+ 26.75 percent, O^- 5.11 percent, AB^+ 8.33 percent, AB^- 1.18 percent, A^+ 26.81 percent, A^- 3.62 percent, B^+ 24.83 percent, B^- 3.37 percent).

THE LEVEL OF MALONDIALDEHYDE IN PATIENTS AND CONTROLS

In line with a study by Chen X. and Scholl T. [6], which found that gestational diabetes subjects had significantly higher MDA levels than those of uncomplicated pregnancies. We found in our study that the mean MDA was much more in GDM pregnant women than in healthy pregnant women. Higher levels of malondialdehyde show that GDM is linked to more oxidative stress than healthy pregnancy, in a study [27] the elevated MDA levels in the GDM participants point to the possibility of oxidative stress [27]. MDA levels, a marker of oxidative stress, have increased in the participants' investigations by Pandey M et al. [28]. According to a study of Adeniji A and Oparinde D [29] patients with GDM had significantly higher MDA levels than those with uncomplicated pregnancies. According to the current study, there is more oxidative stress in GDM, which may increase the production of free radicals. Non-enzymatic protein glycation is one of the suggested mechanisms for oxygen free radical creation at higher glucose concentrations during pregnancy, and it may cause the production of oxygen free radicals. Enhanced oxidative stress and mitochondrial electron transport chain flow and oxidative activities of the fetus. A major byproduct of lipid peroxidation is hydroperoxides which have been demonstrated to modify prostaglandin production, which may be the cause of the emergence of embryopathy associated with diabetes [30]. Another study of Grissa O et al. [31] provides more evidence that the reactive oxygen species produced during GDM combine with free lipid to produce lipid peroxidation products, which in turn induce harmful stress to cells by producing MDA. Similarly, lipid peroxidation and oxidative stress have been shown to significantly increase in some GDM studies [32, 33].

DIAGNOSTIC ACCURACY OF MALONDIALDEHYDE BY RECEIVER OPERATING CHARACTERISTIC CURVE

An earlier work of Lappas M et al. [13] emphasized the crucial role oxidative stress plays in the development of GDM. An imbalance between the antioxidant and oxidizing systems is implicated in the development of gestational DM and its accompanying effects this is according to mounting evidence. It has been noted that pregnant GDM patients have decreased antioxidative enzymes and an increase in circulating oxidative stress brought on by hyperglycemia. Both the mother and the fetus may suffer negative consequences from increased oxidative stress [34]. Under pathological circumstances, such as diabetes mellitus, reactive oxygen species induced phospholipid breakdown produces malondialdehyde, the byproduct of lipid peroxidation. It may be readily quantified in plasma and is frequently used to show oxidative stress and lipid peroxidation [35]. The ROC curve is a graph that may be used to analytically evaluate how well a binary diagnostic classification system is doing. One further way to evaluate a test's diagnostic efficacy is to compare its findings to those of other tests using the ROC curve. Understanding the concept of sensitivity and specificity, which are used to assess a diagnostic test's performance, is a prerequisite to comprehend the ROC curve. The percent of people who test +ve for a target disease that genuinely have it is known as sensitivity, while the percent of people who test -ve for the disease is known as specificity [36]. ROC-curve that has the greatest AUC was thought to perform the best diagnostics-performance when comparing the results of two or more diagnostic tests [37]. Figure 3 displays the ROC curve analysis for MDA in our study, with a p value of less than 0.001 and an AUC of 0.972, with threshold level of 78.7, exhibited 99% sensitivity, with 41% specificity. Since there is no information available regarding the MDA ROC curve for GDM diagnosis, our work may be considered one of the first in this area. The big AUC value suggests a high accuracy of the MDA test, meaning it can be used to predict GDM in women in the future.

CONCLUSIONS

This research reveals that mother's ABO blood group have a role in the development of GDM Blood group AB is more likely to develop GDM while blood group A & B are less likely to develop GDM and may be regarded as a protective factor. The other finding is that MDA can be used for the diagnosis of GDM but further studies are required to support this finding.

REFERENCES

1. Arslanian S, Bacha F, Grey M et al. Evaluation and management of youth-onset type 2 diabetes: a position statement by the American Diabetes Association. Diabetes Care. 2018;41:2648–2668. doi: 10.2337/dci18-0052. DOI
2. Gortazar L, Flores-Le Roux JA, Benaiges D et al. Trends in prevalence of gestational diabetes and perinatal outcomes in Catalonia, Spain, 2006 to 2015: The Diagestcat Study. Diabetes Metab. Res. Rev. 2019;35:e3151. doi: 10.1002/dmrr.3151. DOI
3. Haneda M, Noda M, Origasa H et al. Japanese Clinical Practice Guideline for Diabetes 2016. J. Diabetes Investig. 2018;9:657–697. doi: 10.1111/jdi.12810. DOI
4. Tanner HL, Nitert DM, Callaway LK et al. Ketones in pregnancy: Why is it considered necessary to avoid them and what is the evidence behind their perceived risk? Diabetes Care. 2021;44(1):280-289. doi: 10.2337/dc20-2008. DOI
5. Plows JF, Stanley JL, Baker PN et al. The pathophysiology of gestational diabetes mellitus. International journal of molecular sciences. 2018;19(11):3342. doi: 10.3390/ijms19113342. DOI
6. Chen X, Scholl TO. Oxidative stress: changes in pregnancy and with gestational diabetes mellitus. Current Diabetes Reports. 2005;5:282-288. doi: 10.1007/s11892-005-0024-1. DOI
7. Franchini M, Mengoli C, Lippi G. Relationship between ABO blood group and pregnancy complications: a systematic literature analysis. Blood Transfus. 2016;14:441-448. doi: 10.2450/2016.0313-15. DOI
8. Abegaz SB. Human ABO Blood Groups and Their Associations with Different Diseases. Biomed Res Int. 2021;2021:6629060. doi: 10.1155/2021/6629060. DOI
9. Alam S, Hasan MK, Neaz S et al. Diabetes Mellitus: insights from epidemiology, biochemistry, risk factors, diagnosis, complications and comprehensive management. Diabetology. 2022;2:36-50. doi:10.3390/diabetology2020004. DOI
10. Zhang C, Li Y, Wang L et al. Blood group AB is protective factor for gestational diabetes mellitus: a prospective population-based study in Tianjin, China. Diabetes Metab Res Rev. 2015;31(6):627-637. doi:10.1002/dmrr.2650. DOI
11. Shimodaira M, Yamasaki T, Nakayama T. The association of maternal ABO blood group with gestational diabetes mellitus in Japanese pregnant women. Diabetes Metab Syndr. 2016;10(2):S102-S105. doi:10.1016/j.dsx.2016.03.003. DOI
12. Phoswa WN, Khaliq OP. The Role of Oxidative Stress in Hypertensive Disorders of Pregnancy (Preeclampsia, Gestational Hypertension) and Metabolic Disorder of Pregnancy (Gestational Diabetes Mellitus). Oxid Med Cell Longev. 2021;2021:5581570. doi:10.1155/2021/5581570. DOI
13. Lappas M, Hiden U, Desoye G et al. The role of oxidative stress in the pathophysiology of gestational diabetes mellitus. Antioxid Redox Signal. 2011;15(12):3061-3100. doi:10.1089/ars.2010.3765. DOI
14. Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: A review. Eur J Med Chem. 2015;97:55-74. doi:10.1016/j.ejmech.2015.04.040. DOI
15. Zhu C, Yang H, Geng Q et al. Association of oxidative stress biomarkers with gestational diabetes mellitus in pregnant women: a case-control study. PLoS One. 2015;10(4):e0126490. doi:10.1371/journal.pone.0126490. DOI
16. Cristani M, Speciale A, Saija A et al. Circulating Advanced Oxidation Protein Products as Oxidative Stress Biomarkers and Progression Mediators in Pathological Conditions Related to Inflammation and Immune Dysregulation. Curr Med Chem. 2016;23(34):3862-3882. doi:10.2174/0929867323666160902154748. DOI
17. Busch CJ, Binder CJ. Malondialdehyde epitopes as mediators of sterile inflammation. Biochim Biophys Acta Mol Cell Biol Lipids. 2017;1862(4):398-406. doi:10.1016/j.bbalip.2016.06.016. DOI
18. Serbesa ML, Iffa MT, Geleto M. Factors associated with malnutrition among pregnant women and lactating mothers in Miesso Health Center, Ethiopia. Eur J Midwifery. 2019;3:13. doi:10.18332/ejm/110131. DOI
19. Kennelly MA, McAuliffe FM. Prediction and prevention of Gestational Diabetes: an update of recent literature. Eur J Obstet Gynecol Reprod Biol. 2016;202:92-98. doi:10.1016/j.ejogrb.2016.03.032. DOI
20. Lemaitre M, Passet M, Ghesquière L et al. Is the Development of Gestational Diabetes Associated With the ABO Blood Group/Rhesus Phenotype? Front Endocrinol (Lausanne). 2022;13:916903. doi:10.3389/fendo.2022.916903. DOI
21. Sapanont K, Sunsaneevithayakul P, Boriboonhirunsarn D. Relationship between ABO blood group and gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2021;34(8):1255-1259. doi:10.1080/14767058.2019.1633299. DOI
22. Kırlangıç MM, Şahin ME. Assessment of the roles of ABO blood types and Rh factors in gestational diabetes mellitus. Perinatal J. 2022;30:38–42. doi: 10.2399/prn.22.0301007. DOI
23. Leng J, Shao P, Zhang C et al. Prevalence of gestational diabetes mellitus and its risk factors in Chinese pregnant women: A prospective population-based study in Tianjin, China. PLoS One. 2015;10(3):e0121029. doi: 10.1371/journal.pone.0121029. DOI
24. Lee KW, Ching SM, Ramachandran V et al. Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018;18(1):494. doi:10.1186/s12884-018-2131-4. DOI
25. Morikawa M, Yamada T, Yamada T et al. Prevalence of hyperglycemia during pregnancy according to maternal age and pre-pregnancy body mass index in Japan, 2007-2009. Int J Gynaecol Obstet. 2012;118(3):198-201. doi:10.1016/j.ijgo.2012.04.019. DOI

26. Hatice K, Erden A, Ozer O et al. The role of blood groups in the development of diabetes mellitus after gestational diabetes mellitus. Ther Clin Risk Manag. 2015:11:1613-7. doi: 10.2147/TCRM.S92294. DOI
27. Jaya B, Devi RM, Saikumar P, Karthikeyan E. A comparative study of oxidative stress among gestational diabetics and normal pregnancy. National Journal of Physiology, Pharmacy and Pharmacology. 2019;9(1):86-89. doi: 10.5455/njppp.2019.1135029112018. DOI
28. Pandey MK, Mittra P, Maheshwari P. Oxidative stress in epilepsy with comorbid psychiatric illness. Natl J Physiol Pharm Pharmacol. 2013;3:92-96. doi: 10.5455/njppp.2013.3.92-96. DOI
29. Adeniji AO, Oparinde DP. The profiles of lipid peroxidation and anti-oxidant activities in gestational diabetes mellitus and normal pregnancies in Nigerian population. Open J Obstet Gynecol. 2013;3:472-476. doi: 10.4236/ojog.2013.36087. DOI
30. Wu Y, Reece EA, Zhong J et al. Type 2 diabetes mellitus induces congenital heart defects in murine embryos by increasing oxidative stress, endoplasmic reticulum stress, and apoptosis. Am J Obstet Gynecol. 2016;215(3):366.e1-366.e10. doi:10.1016/j.ajog.2016.03.036. DOI
31. Grissa O, Atègbo JM, Yessoufou A et al. Antioxidant status and circulating lipids are altered in human gestational diabetes and macrosomia. Transl Res. 2007;150(3):164-171. doi:10.1016/j.trsl.2007.03.007. DOI
32. Suhail M, Patil S, Khan S, Siddiqui S. Antioxidant Vitamins and Lipoperoxidation in Non-pregnant, Pregnant, and Gestational Diabetic Women: Erythrocytes Osmotic Fragility Profiles. J Clin Med Res. 2010;2(6):266-273. doi:10.4021/jocmr454w. DOI
33. López-Tinoco C, Roca M, García-Valero A et al. Oxidative stress and antioxidant status in patients with late-onset gestational diabetes mellitus. Acta Diabetol. 2013;50(2):201-208. doi:10.1007/s00592-011-0264-2. DOI
34. Karacay O, Sepici-Dincel A, Karcaaltincaba D et al. A quantitative evaluation of total antioxidant status and oxidative stress markers in preeclampsia and gestational diabetic patients in 24-36 weeks of gestation. Diabetes Res Clin Pract. 2010;89(3):231-238. doi:10.1016/j.diabres.2010.04.015. DOI
35. Sultan S, Alzahrani N, Al-Sakkaf K. The postpartum effect of maternal diabetes on the circulating levels of sirtuins and superoxide dismutase. FEBS Open Bio. 2018;8(2):256-263. doi:10.1002/2211-5463.12370. DOI
36. Jung SM, Lee E, Park SJ. Validity of bispectral index monitoring during deep sedation in children with spastic cerebral palsy undergoing injection of botulinum toxin. Korean J Anesthesiol. 2019;72(6):592-598. doi:10.4097/kja.19129. DOI
37. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. Caspian J Intern Med. 2013;4(2):627-635.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Modified radical mastectomy under local anesthesia using Tumescent Technique experience of Teaching Hospitals in Iraq

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ABSTRACT

Aim: To evaluate the advantages, disadvantages, safety, and restrictions of local anaesthetic against general anesthesia for mastectomy.

Materials and Methods: In this prospective clinical trial, which was carried out at Al-Sader teaching hospital from October 2020 to September 2023, 25 patients (LA group) with a mean age of 64.0±6.3 years (range 55-76 years) underwent a unilateral total mastectomy for breast cancer under local anesthesia using tumescent technique (by manual infiltration technique), and an additional 25 patients (GA group) as a control group with a mean age of 64.9±6.9 years (range 55-75 years) underwent a unilateral mastectomy.

Results: With use of light sedation for 6 patients, anesthetic is sufficient for all 25 patients. The amount of blood loss intraoperatively measured by number of gauze used during the procedure, approximately 3 gauze, 20 cc of blood for each gauze was significantly lower in LA group than GA group, 2.7±0.4, 5.4±0.4 gauze respectively P<0.001. More than 8 hours after surgery, patients are pain-free. No postoperative complications like necrosis of skin flap, wound infection, or hematoma, when compared to GA group, surgery took substantially longer in LA group 48.9±14.3 minutes than in GA group 38.2±2.9 minutes; P<0.001. The day after the surgery, the patient was discharged.

Conclusions: The use of tumescent anesthesia (which is safe and effective) is an attractive alternative method for general anesthesia in properly selected candidates (class IV according to American society of anesthesia).

KEY WORDS: Mastectomy, local anesthesia, tumescent technique

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INTRODUCTION

In Western nations, breast cancer is the most common cause of death for middle-aged and older women. This alarming statistic highlights the importance of early detection and effective treatment options available to combat this disease [1]. The use of tumescent local anesthesia [by infiltration of large volumes of local anesthetic and isotonic saline (25 ml of 1% lidocaine and 1 ml of 1:1000 epinephrine in 1 L of isotonic saline)] can be an alluring alternative method to general anesthesia in elderly women with breast cancer and medical comorbidities that made them at risk for general anesthesia like chronic obstructive pulmonary diseases [2].In both industrialized and developing nations, breast cancer is the most common reason for mortality for women in their middle years. Up to a quarter of a million new cases were diagnosed globally in 2010 [3]. It is the cause of 29% of all newly identified malignancies in females and accounts for 14% of all cancer-related fatalities in females [4].

ETIOLOGICAL FACTORS

Geographical: In the Western world, breast cancer affects more women than any other type of cancer. It is becoming more common in developing nations and annually kills hundreds of thousands of women globally [5]. **Gender:** Men make up less than 0.5% of breast cancer patients, yet their diagnosis often comes at a later stage, underscoring the importance of education and vigilance among all genders regarding the signs and symptoms of this disease [6]. **Age:** Breast cancer is extremely rare in those under the age of 20. After that, it becomes more

common, affecting 20% of women by the time they are 90 years old [7]. **Genetic:** Women with a family history of breast cancer tend to experience it more frequently. Around 5% of all breast cancers are linked to a specific mutation, yet this has significant effects on tumor counseling and prevention in these women [7]. **Diet:** Due to the high prevalence of breast cancer among women in developed nations, dietary variables may contribute to its genesis. Research suggests that diets high in saturated fats and low in fruits and vegetables may increase risk, while a balanced diet rich in antioxidants could offer protective benefits [8]. **Endocrine:** Breastfeeding appears to be particularly beneficial against breast cancer since it affects nulliparous women more than multiparous women. Additionally, it seems protective to have your first kid young, especially if it coincides with a late menarche and an early menopause. Furthermore, hormonal factors such as prolonged exposure to estrogen without the balancing effects of progesterone can elevate risk, highlighting the importance of understanding individual reproductive histories in cancer prevention strategies [9]. **Previous radiation:** This was thought to be interesting historically. However, it is a serious issue for women who have undergone mantle radiation therapy, which involves receiving high doses of radiation to the breast, as part of the treatment for Hodgkin's lymphoma. The risk increases if radiation was administered while the breast was developing and manifests approximately ten years after treatment [10]. The most frequent type of anesthesia used in cutaneous surgery is localized anesthesia. Some patients, such as those with congestive heart failure and chronic obstructive pulmonary disease, have comorbid conditions that put them at risk for general anesthesia [11]. One of the earliest risk classification schemes was developed by the American Society of Anesthesiologists; it is divided into five strata [12].

I. A healthy, normal patient.

II. People who have a minor systemic illness.

III. Those who suffer from a serious systemic illness that restricts daily activity but is not life-threatening.

IV. People who suffer from incapacitating conditions that constantly endanger their lives.

V. It is unlikely that a morbidly ill patient will survive for 24 hours, with procedure or not.

A technique for localized anesthesia called tumescent anesthesia involves injecting large amounts of isotonic saline and local anesthetic into the skin. This method has the following benefits:

(1) Simplicity;

(2) Postoperative analgesia;

(3) Minimal incidence of bleeding; and

(4) Ability to anesthetize a sizable portion of the body [13].

AIM

In order to analyze the risks, advantages, safety, and limitations of mastectomy under local anaesthetic with general anesthesia, this study will execute a mastectomy utilizing the tumescent technique under local anaesthetic.

MATERIALS AND METHODS

With approval from the scientific council of the board center and patient agreement for surgery, video recording, and taking images while preserving patient's dignity, the study was a prospective clinical experiment carried out from October 2020 to September 2023 at Al-Sader teaching hospital. Fifty patients in total, divided into two groups, under local anesthesia, 25 patients (LA group) with a mean age of 64 years (range 55-76 years) underwent mastectomy for breast cancer, and additionally 25 patients with a mean age of 64.9 years (range 55-75 years) and unilateral breast carcinoma underwent mastectomy under general anesthesia as the control group (GA group). All patients were diagnosed using the triple assessment method (history and physical examination, radiological examination, and histopathological examination, including fine needle aspiration and/or trucut biopsy), before being staged according to TNM staging. In our study, all patients fell into the [T3, N0, N1 and M0] in both groups. The tumescent technique uses (25 ml of 1% lidocaine and 1 ml of 1:1000 epinephrines to 1 L of Ringers lactate) by manual infiltration technique. Every patient is followed up with routine visits to the private clinic and the breast clinic.

PROCEDURE

A mark is made on the skin ellipse before the procedure. Excellent access to the axillary region is provided by a low horizontal ellipse that rests in the skin folds with slight obliquity, keeping the medial end of the incision low and below the area of apparent cleavage. The breast is injected using a syringe (50 cc), infusion set, three-way valve, small caliber multirole blunt spinal needle, and the tumescent solution is manually infused along the lateral sternal line (T1-T6) and along the midaxillary line (T2-T7).Following solution infusion, the breast turns pale and tight. Using unipolar cautery and blunt dissection, the skin is excised as intended, and the incisions are then deepened through the subcutaneous fat. The optimal dissection plane lies between the subcutaneous fatty tissue and the mammary tissue, but with the help of hydrostatic dissection, which is made easier by tumescent solution; it is a very simple plane to follow. Too small skin flaps put the skin at risk of ischemia, whereas too thick skin flaps leave a significant amount of remaining breast tissue in place. The plane

Table 1. Age distribution of the studied group

LA		Group		P
		GA		
Age(years)	Mean ± SD	64.0 ± 6.3	64.9 ± 6.9	0.67
	Range	55 – 76	55 – 75	

Table 2. Distribution of chronic diseases among the studied groups

Disease	LA		GA		P-value
	No.	%	No.	%	
HT	21	84.0	6	24.0	< 0.001
DM	16	64.0	7	28.0	0.011
HF	9	36.0	0	0.0	0.001
IHD	17	68.0	8	32.0	0.011
Valvular heart disease	4	16.0	0	0.0	0.037
Respiratory diseases	8	32.0	1	4.0	0.010

Table 3. Comparison of mean bleeding amount and operation time between the LA and GA groups

Variable	LA	GA	P
Bleeding amount	2.7 ± 0.4	5.4 ± 0.4	< 0.001
Operation time	48.9 ± 14.3	38.2 ± 2.9	0.001

descends onto the deep fascia with the upper flap raised first, followed by the lower flap. The bleeding vessels are then cauterized with unipolar cautery (occasionally do ligation of larger vessels) after the breast has been separated from the chest wall by the pectoralis fascia from the top down. The axilla is treated either through dissection (19 patients) or sampling (6 patients), which is the most painful and sensitive place in the process. These pains are alleviated by using propofol or midazolam as a moderate sedative. Traditionally, subcuticular suturing over vacuum drainage is used to close skin flaps.

RESULTS

Twenty five patients (the mean age of LA group was 64.0±6.3, range 55-76 years) as in Table 1 with breast cancer undergone a unilateral total mastectomy by local anesthesia. All individuals encompassed within this study exhibit a significant prevalence of chronic medical comorbidities, which are meticulously detailed in the accompanying Table 2.The anesthesia is adequate in all 25 patients with the use of mild sedation in 6 patients. The amount of blood loss intraoperatively measured by number of gauze used during the procedure, approximately 3 gauze, 20 cc of blood for each gauze was significantly lower in LA group than GA group, 2.7±0.4, 5.4±0.4 gauze respectively P<0.001 as in Table 3. There are no postoperative complications such as wound infection, hematoma or skin flap necrosis. The operation time was significantly longer in LA group 48.9±14.3 minutes than in GA group 38.2±2.9 minutes P-value=0.001 as in Fig. 1. The patient was discharged in the first day after the surgery.

DISCUSSION

Tumescent anesthesia usually used in plastic and dermatological surgeries, elderly female patient with breast cancer has comorbid conditions that might increase their operative risks if they underwent general anesthesia, so in the current study we try to use tumescent anesthesia as an alternative way for mastectomy and it is the first study in Iraq that concern the mastectomy under local anesthesia. The anesthetic infiltration effect and pain control in all 25 patients are excellent combined with mild sedation (6 patients) by using propofol or midazolam. Regarding intraoperative events the patients are fully conscious during the procedure and experience mild pain when doing axillary dissection that is overcome by mild sedation. The time of procedure is prolonged due to infiltration of tumescent solution. The bleeding during the procedure is little in comparison to procedures under general anesthesia due to the effect of adrenalin which causes vasoconstriction. The dissection is very easy due to the aid of hydrostatic dissection which is performed by tumescent solution. No patient develops lidocaine allergy or toxicity mainly due to the loss of most infiltrative solutions during the dissection and the excised breast tissue. Regarding the postoperative complications: no patient develops wound infection, hematoma or skin flap

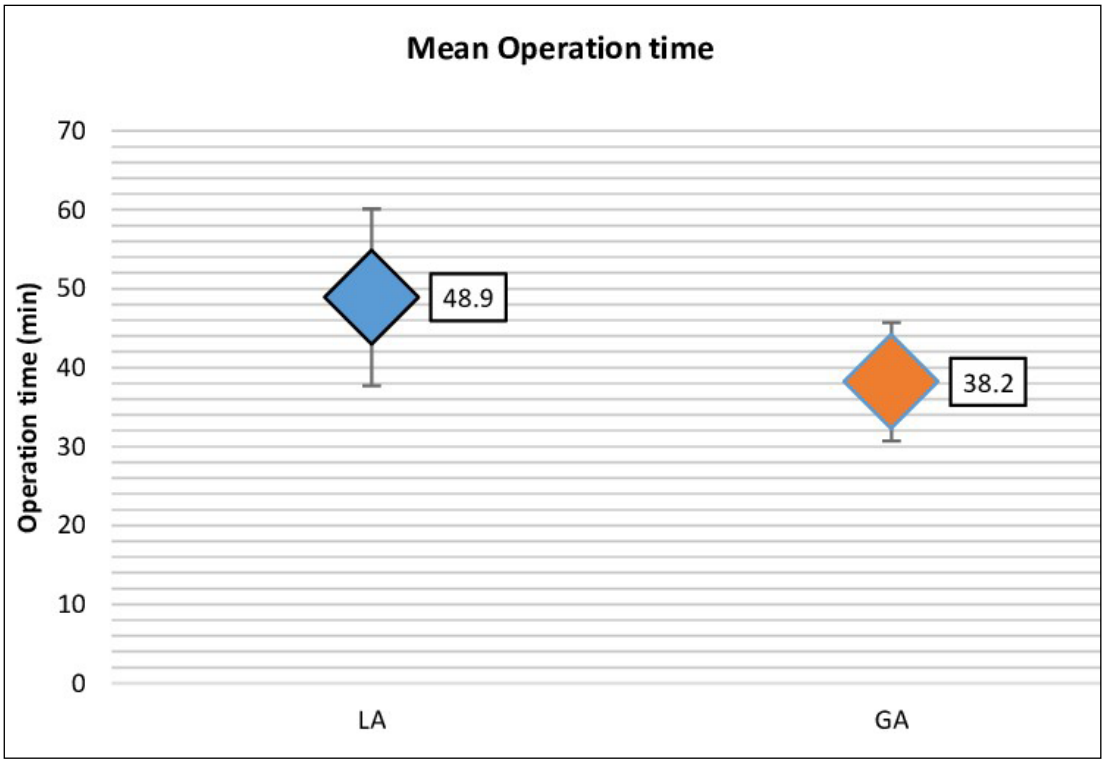

Fig. 1. Comparison of operation time of the studied group.

necrosis with tumescent technique, one patient develop hematoma postoperatively in GA group. Regarding the pain, all patients with tumescent technique are pain free for at least 8 hours without the use of analgesia compared with the use of analgesia for all patients in GA group. Numerous publications have described modified radical mastectomy surgeries carried out under local anesthesia utilizing various techniques using scalpel, scissor, and electrocautery. Four patients aged 61 to 91 who were ASA class IV received a total mastectomy for breast cancer utilizing the tumescent procedure, according to Grant W. Carlson's [14] description, there was no postoperative morbidity in the form of hematoma, skin flap necrosis, or wound infection. The patients were discharged from the hospital 1- 4 days after surgery, which is longer than in our study. The average operating time was 35 minutes, whereas in our study, the mean operating time for the LA group was 48.9 minutes. The operating time varied from 24 to 46 minutes according to Joseph et al., [15] a straightforward mastectomy was performed under local anesthetic and sedation on seven patients with ASA grades III or IV, their ages ranged from 80 to 94 years old (with a mean of 88 years), blood loss was minimal (mean = 95.7cm^3), compared to our study which is lower 54 cm3, as was operating time (mean = 62 min), while the operating time is 48.9 min in our study. Most patients were returned to their homes in day 2, compare to our study which is in day one after surgery. There were no complications related to the procedure as our study. Shoher et al. [16] described 53 patients with multicentric disease, of the 53 cases, there have been no cases of flap necrosis or 'button-holing' of the skin flap, which is certainly a possibility with electrocautery compare to our study. There have been no cases of systemic complications from the tumescent solution. No patient developed bleeding requiring transfusion, nor did any patient develop a hematoma postoperatively. One patient developed a small, superficial stitch abscess 2 weeks post-operatively. A knotted suture was removed and the patient recovered without further complication, as compared to our study also there is no systemic complication, wound infection, hematoma or skin flap necrosis.

CONCLUSIONS

It is concluded that use of tumescent anesthesia (which is safe and effective) is an attractive alternative method for general anesthesia in properly selected candidate (class IV according to American society of anesthesia).

RECOMMENDATIONS

1. Using tumescent anesthesia for mastectomy in patients has breast cancer with ASA IV who was unfit for general anesthesia.
2. Improvement technique by using infusion pumps to decrease time and effort of the procedure.
3. Further study with a larger sample size of patients to assess the possible side effect of the tumescent anesthesia and to assess the ability and benefit of application of tumescent technique for patients with ASA I & II.

REFERENCES

1. Sekar R, Vardhan MV. Approach to Predict Early Stage of Breast Cancer using Machine Learning. International Conference Intelligent Computing and Control Systems. 2023. doi:10.1109/ICICCS56967.2023.10142851. DOI
2. Paul TK, Chowdhury A, Khan Lodi RA et al. Surgical Management of Breast Cancer under Local Anaesthesia: A Surgeon's Perspective. Delta Medical College Journal. 2017. doi:10.3329/DMCJ.V5I2.33343. DOI
3. Williams NS, Christopher JK, Ronan PB, O'Connell B. loves short practice of surgery, 26th Ed (chapter 51). Taylor & Francis Group. 2013, pp.798-819.
4. Kelly K, Hunt, John FR. Robertson, and Kirby I. Bland, Schwartz's Principles of Surgery, 10th Ed (chapter 17). McGraw-Hill Education. 2015, pp.497-564.
5. Dalda Y, Dalda Ö, Baskiran DY, Gönültaş F. Curative breast cancer surgery with local anesthesia. Journal of Experimental and Clinical Medicine. 2023. doi:10.52142/omujecm.40.1.36. DOI
6. Karvandian K, Zebardast J, Zolfaghari Borra N. Risk Assessment and Anesthesia Classification in Breast Cancer Surgery. 2018. doi:10.32768/ABC.201854168-172. DOI
7. Mehboob R. Breast Cancer- Awareness and Early Detection. Pakistan Biomedical Journal. 2022. doi:10.54393/pbmj.v5i10.814. DOI
8. Iacoviello L, Bonaccio M, de Gaetano G, Donati MB. Epidemiology of breast cancer, a paradigm of the "common soil hypothesis. Seminars in Cancer Biology. 2021. doi:10.1016/J.SEMCANCER.2020.02.010. DOI
9. Badwe RA, Parmar V, Nair NS et al. Effect of Peritumoral Infiltration of Local Anesthetic Before Surgery on Survival in Early Breast Cancer. Journal of Clinical Oncology. 2023. doi:10.1200/JCO.22.01966. DOI
10. Irshad K, Ahmed HH, Jamaluddin MF. Mastectomy under Local Anesthesia in Locally Advanced Breast Cancer in an Unfit Patient. Bangladesh Journal of Medical Science. 2022. doi:10.3329/bjms.v21i3.59593. DOI
11. Brewer JD, Roenigk RK. Tumescent anesthesia as an aid for wide local excision in dermatologic surgery. Surg Cosmet Dermatol. 2010;2(2):140-3.
12. Hunt KK, Green MC, Buchholz TA. Sabiston textbook of surgery. 19th Ed (chapter 36). 2012, pp.824-884.
13. Bussolin L, Busoni P, Giorgi L et al. Tumescent Local Anesthesia for the Surgical Treatment of Burns and Postburn Sequelae in Pediatric Patients. Anesthesiology. 2003;99(6):1371–5. doi: 10.1097/00000542-200312000-00020. DOI
14. Carlson GW. Total Mastectomy under Local Anesthesia: The Tumescent Technique. Breast J. 2005;11(2):100-2. doi: 10.1111/j.1075-122X.2005.21536.x. DOI
15. Joseph AY, Bloch R, Yee S. Simple anesthesia for simple mastectomies. Breast Cancer Res Treat. 2003;77(2):189-91. doi: 10.1023/a:1021386722363. DOI
16. Shoher A, Hekier R, Lucci A Jr. Mastectomy performed with scissors following tumescent solution injection. J Surg Oncol. 2003;83(3):191-93. doi: 10.1002/jso.10265. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Educational program to asses and promote knowledge of Al-Zahraa hospital nurses about trichomoniasis disease, Al-Najaf city

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ABSTRACT

Aim: This study included implementing an educational program to evaluate and promote nurses' knowledge of trichomoniasis disease which caused by *Trichomonas vaginalis* parasite**.**

Materials and Methods: 100 randomly samples of nurses working in different units in Al-Zahraa Hospital – Najaf City, Iraq. This semi-experimental study was performed. The study was conducted from December 2023 until April 2024. It included a sample of different ages, gender and experience, working in different units in the hospital, married and unmarried, as well as those living in urban and rural areas.

Results: The results show the total rating of sample knowledge concerning Trichomoniasis in primary test was a moderate with a mean (0.57) and the mean of next test was a good (0.84), also the results observed a highly significant difference ($P < 0.01$) between pre-test and post-test assessments. In addition, according to their Socio-Demographic Characteristics, the study showed no significant difference in the knowledge scores in the next test.

Conclusion: This study concluded that there was an improvement in knowledge after the program for all nurses.

KEY WORDS: educational program, experimental study, trichomoniasis, nurses, knowledge, promote , assess, sexual transmitted disease

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INTRODUCTION

Bacteria, viruses, fungi, protozoan parasites cause "Sexually transmitted diseases". The portals of entry for these pathogens involved the reproductive organs, skin, mouth, urinary tract, anus, and rectal region [1]. Normally, trichomoniasis is correlated to Sexually transmitted disease, in addition, it is a common indicator of high-risk of behavior for sex [2, 3]. *Trichomonas vaginalis* has been increasingly recognized over the past decade, underlining the importance of this pathogen as a public health problem [4, 5]. Men and women of different ages are prone to infection with trichomoniasis, the disease connected with the hygienic practice, the use of rubber sheath worn (condom), and a sex hormone concentration in women. It is a clearly related to sterility, abortion and the low-weight of birth. As the disease is sexually transmitted, thus several partners are a main risk factor of infectious and its disseminate [6]. Metronidazole and tinidazole are the only drugs approved for treating trichomoniasis among infected subjects [7]. The overall public should be more knowledgeable about diseases that affect sexual and reproductive health in women so, they can take preventing and protective measures such as the use of acting contraceptives, avoiding the misuse of antibiotics, using condoms and improved healthier habits. In the cases of sexually transmitted infections, checking and treating both partners is also necessary [3]. Sexually transmitted infections have numerous consequences and understanding disease processes by nurses make them responsible for providing "health education" to all people, irrespective their gender, age or sexual tendency on how to avoid sexually transmitted infections. Nurses have a crucial role in the protection from sexually transmitted disease through providing exact information regarding these diseases, their barring, treatment and prospective complications, sobering researches revealed to compel nurses to be part of the resolution [1].

AIM

The aim of our study was to assess nurses' knowledge of the parasite, which is a sexually transmitted disease of public health relevance, and its long-term impact.

Table 1. Frequency of demographic and occupational characteristics for study contributors (n=100)

Socio-Demographic Characteristics	Rating and Intervals	frequency	%
Age	21-29	56	56
	30-28	26	26
	39-47	14	14
	48-56	3	3
	57-66	1	1
Gender	Males	32	32
	Females	68	68
Residence	Urban	75	75
	Rural	25	25
Occupational Title	Technical nurse	37	37
	Nurse	63	63
Years of Experience	1-12	71	71
	13-24	22	22
	25-36	7	7
Marital status	Single	36	36
	Married	64	64
Working Unit	Emergency Department	30	30
	Critical Care Unit	11	11
	Operating Room	20	20
	Others	39	39
Qualification	Technical Nursing	24	24
	Institute	18	18
	Diploma Nursing School	16	16
	Bachelor Nursing	38	38
	Master Degree	4	4
Total		100	100%

MATERIALS AND METHODS

The semi-experimental study was conducted on 100 random samples of nurses working in different units in Al-Zahraa Hospital – Najaf City, after obtaining their agreement to answer the Socio-demographic item and training. The researchers get an acceptance from maternity and newborn department in the Nursing College, Kufa University, Health Directorate of Al-Najaf province, Al-Zahraa teaching hospital. The study began from December 2023 until April 2024. The study included implementing an educational program to evaluate and promote nurses' knowledge ofthe trichomoniasis disease which causes by *Trichomonas vaginalis* parasite. The nurses were divided into small groups. They were met in a private hall. A pre-test was conducted, followed by a workshopwas to provide them with information. Then a brochure was distributed that included everything related to the Trichomonas Vaginalis parasite, and after a specified and agreed-upon period, the post-test was conducted. The test included questions about the pathogenic cause of trichomoniasis, its method of transmission, its symptoms and effect on men and women, complications, risk factors, treatment and prevention.

THE STUDY INCLUDED FOUR PARTS

Part 1: Socio- demographic information about the nurses (age, gender, residence, occupational title, years of experience, marital status, working unit, and qualification). This information was collected at the beginning of the study by interviewing them.

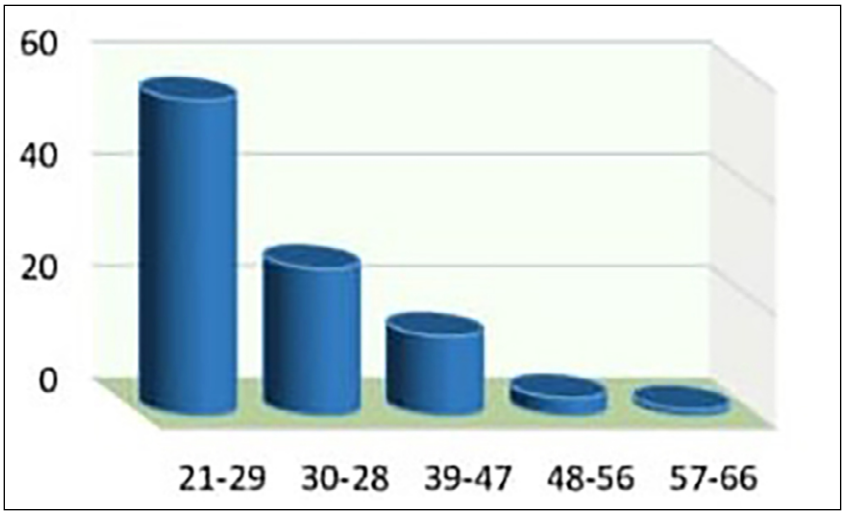

Fig. 1. Distribution of respondents by age groups (years) (n=100).

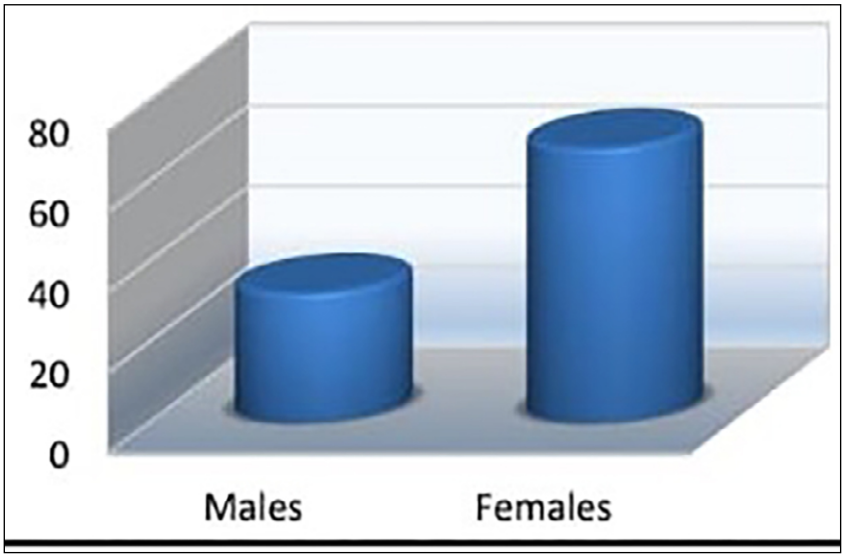

Fig. 2. Distribution of respondents by their gender (n=100).

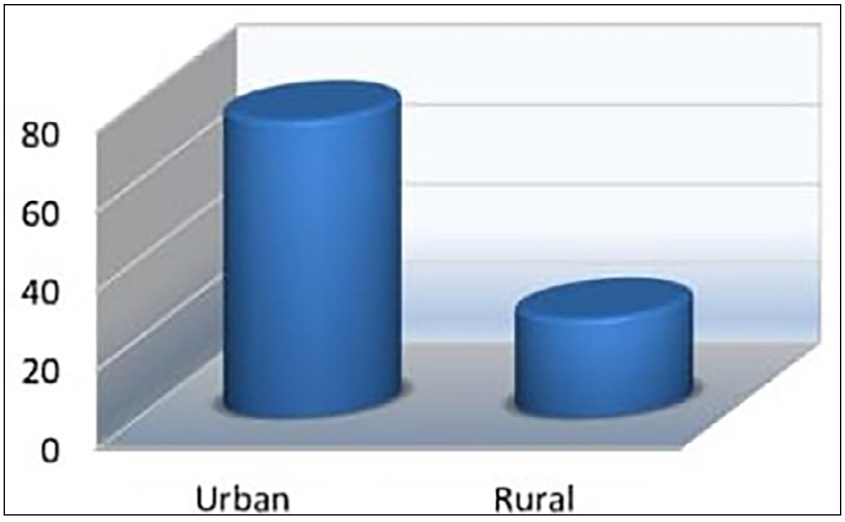

Fig. 3. Distribution of respondents according to their residence (n=100).

Part 2: Included questions to test them and evaluate their knowledge of the disease before implementing the program

Part 3: Training: It included conducting a workshop and distributing the brochure, which aims to enhance their knowledge

Part 4: It included re-taking the test to evaluate the extent of the acquired knowledge, the role of theeducational program in that, and achieving the specific goal of the study. The test includes 30 questions that contain general questions about Trichomonas Vaginalis; the first

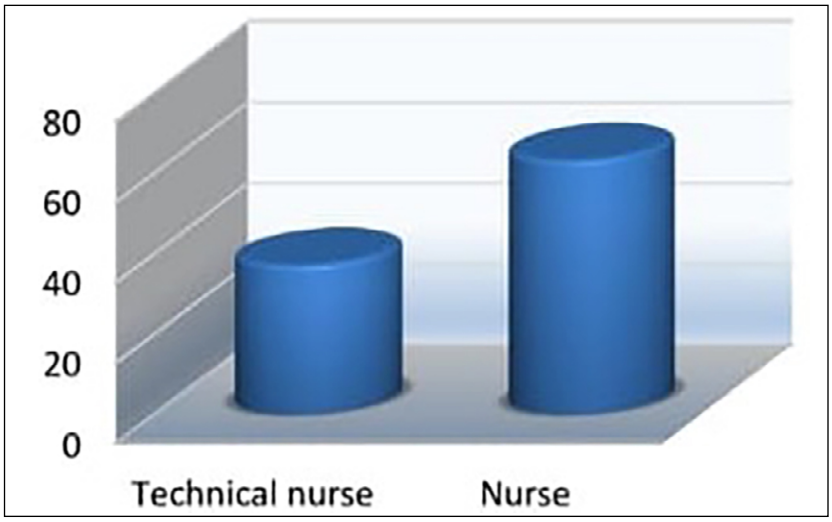

Fig. 4. Distribution of respondents according to their occupation (n=100).

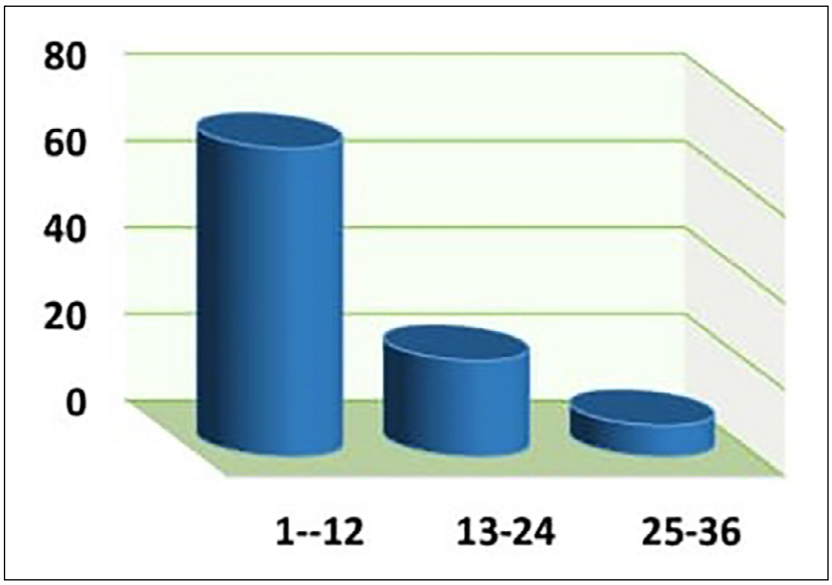

Fig. 5. Distribution of respondents according to their experience (n=100).

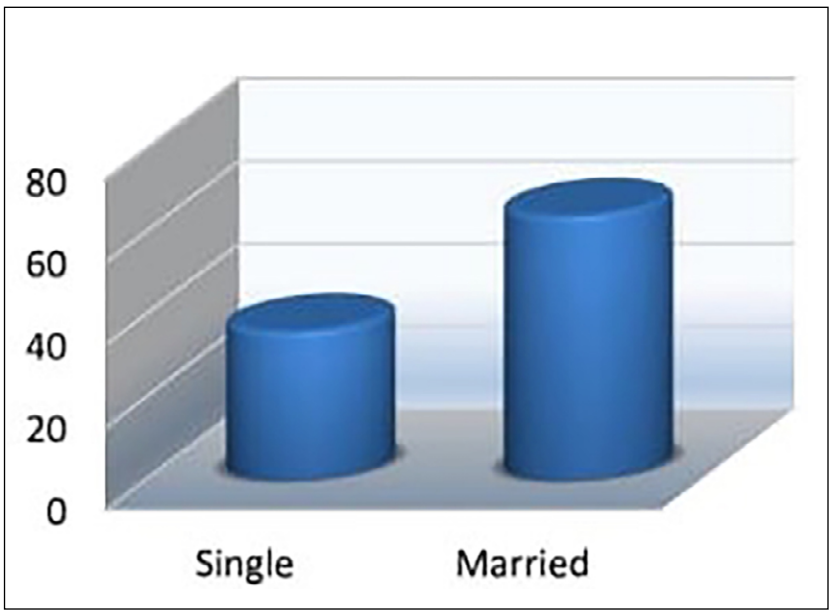

Fig. 6. Distribution of respondents according to their marriage (n=100).

15 questions are short questions, for each there are four answers, including one correct answer. But the other 15 questions,the answer is true or false depending on the type of question. Validity of the study instrument is conducted through a panel of experts who have years of experience in nursing field.

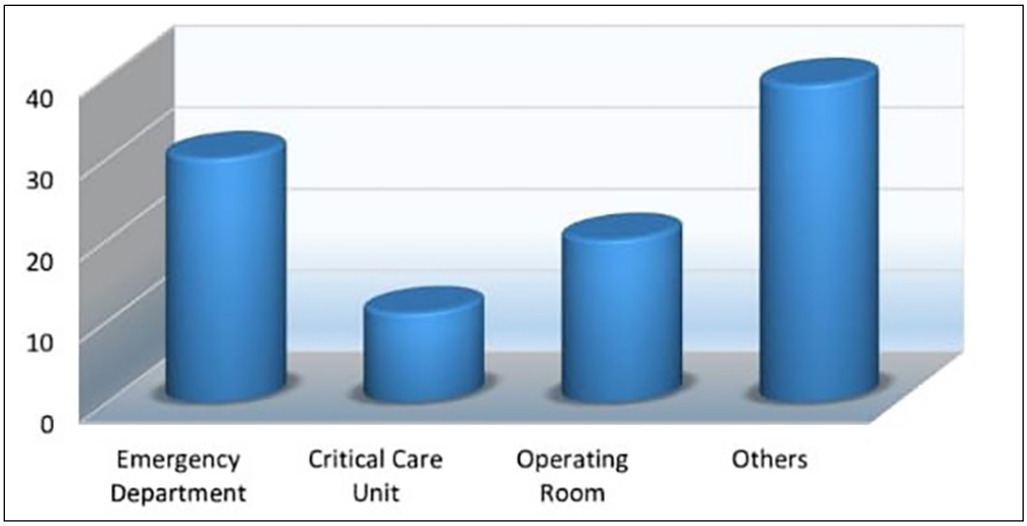

Fig. 7. Distribution of respondents according to their working unit (n=100).

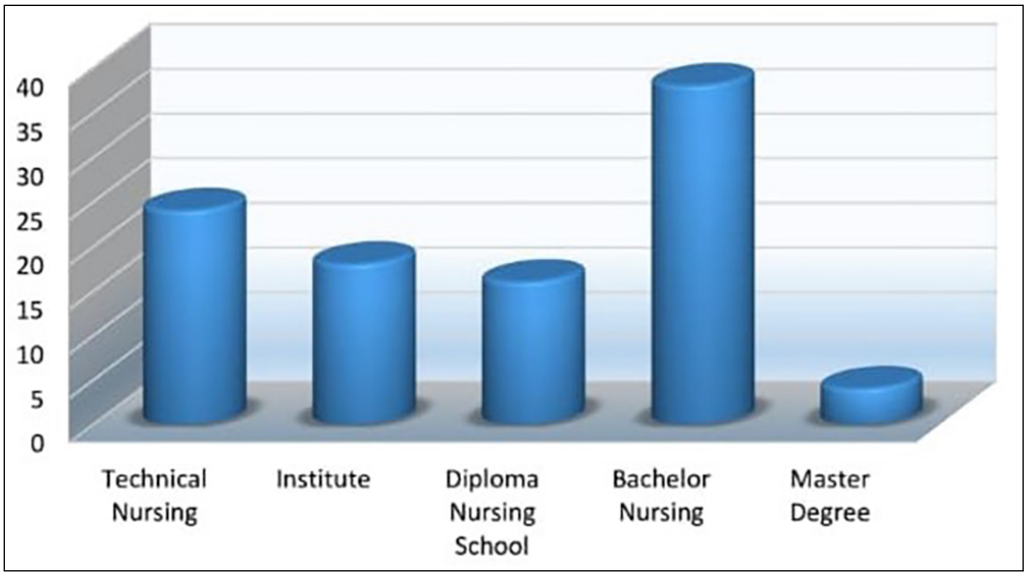

Fig. 8. Distribution of respondents according to their qualification (n=100).

STATISTICAL ANALYSIS

All the data in the current study were entered into the SPSS program (version 20). The minimum values, the maximum values, the means, and the standard deviation were calculated. Chi-square (non-parametric test) was used for qualitative data. One-way ANOVA, independent t test, and Paired t test, were used for quantitative data according to the fulfillment of the conditions required for each test. P-value ≤0.05 was considered statistically significant.

RESULTS

Overall of 100 samples of nurses were included. Systematically the study was an offered the results of the data analysis in tables and these were correlated with the aim of the study which was to evaluate the effectiveness of education program to enhancing nurses' knowledge about trichomoniasis as follows: Table 1: Summarize the frequency distribution of the nurse contributors by their demographic data and Occupational Characteristics.

This table explained that most of the contributors (56 %) were in the ages group 21-29 years old, while the fewest contributors in the ages 57-66 years old where 1%, (Fig.1). As well as, the table shows that the majority of contributors (68%) were female, and major part (75%) resided in urban areas, while the smallest percentages (32% and 25%) were males and residents of rural areas, respectively (Fig.2 and Fig.3). On the other hand, regarding occupational titles, 63% of the participants were nurses, and 37% were technical nurses (Fig.4).

The results regarding length of service in nursing show that the largest proportion (71%) of the sample had between 1 and 12 years of service (Fig.5). For marital status – 64% of the groups were married (Fig.6). Also, the majority worked in the emergency department and working in others units, 30% and 39% respectively, in addition, concerning qualification, those with bachelor's nursing was (38%) where represented more than others groups (Fig.7 and Fig.8).

Table 2. Assessment of the sample's knowledge regarding Trichomoniasis in the primary and next test

Items		Knowledge Regarding Trichomoniasis for the Study sample (n=100)							
		Pre-Test				Post-Test			
		F.	%	MS	SD	F.	%	MS	SD
Q1: Sexually transmitted diseases mean	Incorrect	32	32	.68	.47	11	11	.89	.31
	Correct	68	68			89	89		
Q2: Types of STDs are:	Incorrect	38	38	.62	.49	20	20	.80	.40
	Correct	62	62			80	80		
Q3: What is the causative agent of trichomoniasis?	Incorrect	51	51	.49	.50	23	23	.77	.42
	Correct	49	49			77	77		
Q4: What is the name of the parasite that causes trichomoniasis	Incorrect	40	40	.60	.49	7	7	.93	.26
	Correct	60	60			93	93		
Q5: What is the mode of transmission for trichomoniasis	Incorrect	37	37	.63	.49	4	4	.96	.20
	Correct	63	63			96	96		
Q6: Which statement about Trichomoniasis is TRUE?	Incorrect	51	51	.49	.50	15	15	.85	.36
	Correct	49	49			85	85		
Q7: What are the common symptoms of trichomoniasis in women?	Incorrect	47	47	.53	.50	16	16	.84	.37
	Correct	53	53			84	84		
Q8: Most men with this infection have which of the followingsymptoms	Incorrect	57	57	.43	.50	14	14	.86	.35
	Correct	43	43			86	86		
Q9: How long can someone be infected with trichomoniasis without showing symptoms?	Incorrect	67	67	.33	.47	39	39	.61	.49
	Correct	33	33			61	61		
Q10: Urine and vaginal test used to diagnose	Incorrect	40	40	.60	.49	17	17	.83	.38
	Correct	60	60			83	83		
Q11: Complication of trichomoniasis	Incorrect	47	47	.53	.50	9	9	.91	.29
	Correct	53	53			91	91		
Q12: Risk factor of trichomoniasis	Incorrect	49	49	.51	.50	16	16	.84	.37
	Correct	51	51			84	84		
Q13: How is trichomoniasis treated?	Incorrect	56	56	.44	.50	21	21	.79	.41
	Correct	44	44			79	79		
Q14: Treatment for *Trichomonas Vaginalis* includes:	Incorrect	73	73	.27	.45	42	42	.58	.50
	Correct	27	27			58	58		
Q15: You should abstain completely from while you take metronidazole and at least for 3 days after finishing thetreatment course	Incorrect	46	46	.54	.50	8	8	.92	.27
	Correct	54	54			92	92		
Q16: Most STDs affect both men and women, but in many casesthe health problems they cause can be more severe for women	Incorrect	41	41	.59	.49	12	12	.88	.33
	Correct	59	59			88	88		
Q17: Syphilis is one type of sexually transmitted disease	Incorrect	45	45	.55	.50	11	11	.89	.31
	Correct	55	55			89	89		
Q18: Can trichomoniasis be prevented?	Incorrect	65	65	.35	.48	24	24	.76	.43
	Correct	35	35			76	76		
Q19: Does trichomoniasis increase the risk of other STIs?	Incorrect	26	26	.74	.44	9	9	.91	.29
	Correct	74	74			91	91		

Table 2. Cont.

Q20: Can trichomoniasis cause complications during pregnancy?	Incorrect	24	24	.76	.43	3	3	.97	.17
	Correct	76	76			97	97		
Q21: Can trichomoniasis be cured?	Incorrect	31	31	.69	.46	10	10	.90	.30
	Correct	69	69			90	90		
Q22: Metronidazole cannot cause certain side effects	Incorrect	61	61	.39	.49	26	26	.74	.44
	Correct	39	39			74	74		
Q23: Trichomoniasis may also cause a woman to deliver a premature	Incorrect	25	25	.75	.44	10	10	.90	.30
	Correct	75	75			90	90		
Q24: There is a vaccine for trichomoniasis	Incorrect	53	53	.47	.50	26	26	.74	.44
	Correct	47	47			74	74		
Q25: Trichomoniasis can cause infertility for men and women	Incorrect	35	35	.65	.48	12	12	.88	.33
	Correct	65	65			88	88		
Q26: Trichomoniasis can infect the bladder	Incorrect	52	52	.48	.50	25	25	.75	.44
	Correct	48	48			75	75		
Q27: Trichomoniasis can diagnose by culture analysis	Incorrect	26	26	.74	.44	9	9	.91	.29
	Correct	74	74			91	91		
Q28: Men suffer from pain during urination	Incorrect	22	22	.78	.42	9	9	.91	.29
	Correct	78	78			91	91		
Q29: The life cycle of trichomoniasis has trophozoite and thecyst	Incorrect	36	36	.64	.48	20	20	.80	.40
	Correct	64	64			80	80		
Q30: Heart palpitations, Nausea and vomiting, Chest pain,Sweating, Agitation, Anxiety, Difficulty breathing this side effect occurs if the patient drinks alcohol during treatment.	Incorrect	47	47	.53	.50	11	11	.89	.31
	Correct	53	53			89	89		

%: percentage, F: frequency, MS: Mean of score: poor (mean of scores 0-0.33), moderate (mean of scores 0.34-0.67), good (mean of scores 0.68 and more), SD: standard deviation, Assess: assessment.

Table 2 demonstrated the average percentages and assessment of contributors' answers to the items related to knowledge about trichomoniasis. In the pre-test, this table showed that the correct answers to questions number 9, 14, 18 and 22 had lower percent were 33%, 27%, 35% and 39% respectively compared with remaining questions. In the post-test, the table revealed that the correct answers to questions number 9, 14, 18 and 22 increased with mean score 61%, 58%, 76% and 74% respectively. Also the table observed that before the Program, the correct answers to questions number 19, 20, 23, 27, and 28 had higher percentage of 74%, 76%, 75%, 74% and 78% respectively, and in the next test, these percentages increased to 91%, 97%, 90%, 91% and 91% mean score respectively, additionally, there was variation in nurses' responses to the remaining questions between primary and next test. Also, the finding revealed lower percentage of correct answers for questions 9 and 14 in the posttest with mean score of 61% and 58% respectively, and the majority of mean score of correct answers in the posttest of question 5 was 96%. However, the table showed there was an elevation in the percentage of correct answers for all questions in the posttest compared to the pre-test.

Concerning nurses' knowledge of trichomoniasis in the primary test, the study recorded that the frequency of poor knowledge was 3%, moderate knowledge was 76% and good knowledge was 21%, furthermore, the table in the next test demonstrated the frequency of poor knowledge was 0%, moderate knowledge was 6 % and good knowledge was 94%**,** as shown in table 3.

In the table 4 the result showed the total assessment in the primary test was a moderate (0.57), while the next test was a good (0.84). As well as, the results revealed variances in nurses' knowledge assessment, showing highly significant difference between primary and next test assessments ($P < 0.01$).

In addition, the statistical test for the relationship between age and the samples' knowledge was 1.668. Regarding gender, residence, occupational title, and years of experience, were 1.355, 0.715, 1.472 and 0,649 respectively. Also, the results showed the statistical test for marital status, working unit and qualification were 0.660, 1.713 and 1.094 respectively. The results

Table 3. Overall assessment of the samples' Knowledge Regarding Trichomoniasis in the primary and next test

Overall Items	Knowledge Regarding Trichomoniasis for the Study sample (n=100)									
	Pre-Test					Post-Test				
	F.	%	MS	SD	Assess.	F.	%	MS	SD	Assess
Knowledge Regarding Trichomoniasis	Poor	3	3	.57	.14	Moderate	0	0	.84	.09	Good
	Moderate	76	76				6	6			
	Good	21	21				94	94			

%: percentage, F: frequency, MS: Mean of score: poor (mean of scores 0-0.33), moderate (mean of scores 0.34-0.67), good (mean of scores 0.68 and more), SD: standard deviation, Assess: assessment.

Table 4. Mean variance (Paired T-Test) of nurses' knowledge at periods of measurements (pretest and posttest)

Overall Items	Periods of Measurements	M.S.	SD	t-value	d.f.	p-value
Knowledge Regarding Trichomoniasis	Pre-test	.57	.14	20.334	99	0.0001^{HS}
	Post-test	.84	.09			

M.S. Mean of Score, SD. Standard deviation, d.f degree of freedom, P = probability value. NS. Non-Significant at (P > 0.05), HS. High Significant at (P< 0.01).

demonstrated no significant difference in the nurse's Knowledge according to their Demographic Characteristics, as the p-values were more than 0.05, (Table 5).

DISCUSSION

Globally, sexually transmitted infections continue a significant public health subject, mainly between the younger populations. Despite being avoidable and treatable, sexually transmitted infections remain prevalent. In many developing and undeveloped countries, absence of admission to treatment is a main factor. Another main factor is the absence of knowledge and awareness [8]. Developing periodic educational programs and evaluations regarding *Trichomonas vaginalis* on a regular basis would enhance competency to provide high quality nursing care [9]. The random sample in this study included male and female participants of different ages and qualifications, with experience ranging from 1 to 36 years and working in different units in Al-Zahraa Hospital – Al Najaf city (Figures 1-8). In present study, the effect of educational program on the nurses' knowledge about trichomoniasis was researched, the results show the total of study sample knowledge level regarding Trichomoniasis in the Pretest was a moderate (0.57), and in the post it was good (0.84), (Table 3), with highly important difference (P <0.01) between primary and next test level. At pretest findings in our study revealed that samples' knowledge is moderate knowledge in symptoms and complication, in contrast, at posttest reported good knowledge (Table 2). This significant rise in educational level of symptom and complication after training was in line with other studies and gave the same results as Börekçi et al.[10] that was conducted the pretest and post to determine the influence of the education level of students basing peer on knowledge about Sexually transmitted disease in of Mersin University in Turkey, and study of Sallam et al. [9] who conducted in a Military Hospital, Egypt, to asses and enhance the nurses' knowledge about trichomoniasis with pre-posttest. Also, current study showed moderate knowledge in the risk factor, treatment and prevented approach at pretest while with the implementation of the educational program, nurses' knowledge increased to better knowledge, (Table 2). This result in agreement with results/ avaible in literature [9, 10]. The moderate level of nurses' knowledge in this study before training may be due to the lack of interest or the tendency of this group to develop their knowledge of these diseases because of their connection to the issue of sex and what results from malpractices. The results in our semi experimental study differ from other descriptive studies conducted on different groups of societies to measure their knowledge about the sexual transmitted disease. This variance might be due to differences in education, then awareness about a sexually transmitted disease [11], concluded in a study conducted to evaluate nurse's Knowledge and Practice concerning sexually transmitted diseases in Sirajganj, Bangladesh, that the assessment of nurses' knowledge was high, and 84.6% of respondents have awareness, but only 15% did not have knowledge about signs and symptoms. Performing of health professionals is well, according to their responsibilities, but their knowledge about sexually transmitted disease was limited duo to not have sufficient information. Therefore, improvement of superiority of their services needs more training [12]. Also, Fred M. [13] mentioned in study conducted among graved women admitted to antenatal centers of General Hospital Luweero / Uganda, that the high level of knowledge established of midwives and nursing assistants, with the majority effective was 16-25 age group. The outcomes regarding sexually trans-

Table 5. Relationship among demographic characteristics of the sample and knowledge at the post-test

Socio-Demographic Characteristics	Rating and Intervals	Mean	SD	Statistical Test	P-Value
Age	21-29	.83	.09	1.668#	0.164NS
	30-28	.86	.08		
	39-47	.86	.08		
	48-56	.79	.05		
	57-66	.93	.		
Gender	Males	.82	.10	1.355^	0.179 NS
	Females	.85	.08		
Residence	Urban	.84	.09	0.715^	0.476NS
	Rural	.83	.07		
Occupational Title	Technical nurse	.82	.10	1.472^	0.144NS
	Nurse	.85	.08		
Years of Experience	1-12	.84	.09	0.649#	0.525NS
	13-24	.86	.08		
	25-36	.83	.07		
Marital status	Single	.85	.09	0.660^	0.511NS
	Married	.84	.09		
Working Unit	Emergency Department	.82	.09	1.713#	0.169NS
	Critical Care Unit	.88	.06		
	Operating Room	.85	.09		
	Others	.84	.09		
Qualification	Technical Nursing	.86	.08	1.094#	0.364NS
	Institute	.84	.08		
	Diploma Nursing School	.86	.09		
	Bachelor Nursing	.82	.10		
	Master Degree	.85	.04		

NS: nonsignificant.

mitted infections presented by Lagadinou et al. [14] highlighted emphasize the crucial need for best designed, ongoing programs of sexual education to raise students' awareness around sexually transmitted infections and their avoiding, the researchers revealed that most of the contributors have an aware of the major sexually transmitted infections and their mode of transmission in study designed to evaluate the knowledge and attitudes of nursing and medical students in study performed at the University of Patras, western Greece. Osanyin et al. [15] mentioned that most of the participants had awareness and had a positive attitude about protection of sexually transmitted infections, but the knowledge and practices remained not enough , so, the study recommended enhanced education to increase the knowledge and practices related to sexually transmitted infections between young single individual, the study was performed in Surulere, Lagos State, Nigeria between young single persons. Vakilian K [16] observed that "the university students' knowledge" is far from the wanted level. Also Mansor et al. [17] determined in their study that the knowledge of sexually transmitted infections in higher education institutions among students was unacceptable, to strengthen existing sexual education programs might be transporting more information about other sexually transmitted infections rather than concentrating on HIV only, upcoming program should concentrate on students who have a skill certificate or diploma and others, then those remaining off-campus. Keizur et al. [18] mentioned knowledge concerning sexually transmitted infections between undergraduate women students was limited, educational programs and through the health center of university might

raise testing rates. The findings of Amakali et al. [19] study revealed poor knowledge of sexually transmitted disease and negative attitudes towards the management of patients with sexually transmitted disease among the study respondents in the study performed to determine the knowledge among undergraduate diploma nursing students regarding sexually transmitted diseases sexually transmitted disease at the University of Namibia. The conclusion of Sunil et al. [20] study indicate that most students of the high school have low knowledge of sexually transmitted infections, so it is important to introduce educational programs about sex to increase awareness of student around sexually transmitted infections and protective methods. There was a non- significant difference in the knowledge of male and female sample, no association in the knowledge according to ages and qualifications, and no difference in the knowledge with the experience years and married and single participant, also the nurses who work in different units have the same knowledge at posttest in our study (Table 5), this means that the program has an obvious impact on the all study sample. In this result, our study agreed and disagreed with other studies conducted in different countries as study conducted in the Medical Sciences/ Markazi University, Iran, to asses of healthcare staff' knowledge, attitude, and practice linked to sexually transmitted infections revealed that there was the same knowledge in study sample (physicians midwives, and health professionals) according to gender, ages, the experience years and marital status but the knowledge score different between occupational sample [12], and Alshemeili et al. [21] study conducted in the United Arab Emirates who found that male and female were not related to the level of knowledge and showed age and marital status were significantly related to the level of sample knowledge, exactly, contributors who were slightly older, also literature date mentioned that men and women no difference associated with knowledge [16]. Specific gaps of knowledge exist for HIV and non-HIV sexually transmitted infections, which should be addressed through educating sex, concentrating on high-risk groups exactly, passive attitudes and deafen behavior should be addressed through raising focused sexually transmitted infections knowledge [22]. In study conducted in Nigeria by Adekunle et al. [23] revealed that the 172 female contributors more than 80% not know of trichomoniasis before the study, and did not hear the route of transmission or how to avoid it. The importance of the current study lies in the fact that the spread of sexually transmitted diseases is continuously and increasing, especially *Trichomonas vaginalis* parasite such recorded by many studies as Al-Abbas [24] when they researched the prevalence rats of *Chlamydia trachomatis* and *Trichomonas vaginalis* in female who visited Al-Zahraa Hospital, Al- Najaf city, Kadhum N [25] study reported high rate of disease with *Trichomonas vaginalis* in non-pregnant female group attending Basrah Teaching Hospital, Basrah Maternity and Children teaching Hospital and Al-Faihaa Hospital, showed a high rate of infection with *Trichomonas vaginalis* among partners in Al-Hamza province, Iraq, and recorded the highest rate with *Trichomonas vaginalis* among women who attended the hospitals and medical clinics from different regions of Karbala province [6, 26]. In addition *Trichomonas vaginalis*, can remain asymptomatic for long periods, which may result in severe complications. In women with pelvic inflammatory illness, trichomoniasis was strongly correlated with and predicted [27]. The occurrence of *Trichomonas vaginalis* and, its associated risk factors among the asymptomatic population is very high [28]. Based on the findings of the Merdaw et al. [29] study, the genetic diversity in the *Trichomonas vaginalis* in Iraqi isolates can associate with clinical manifestations (infertility and cervical abnormalities). Therefore, increasing knowledge for nurses' groups that come into contact with society is important for transferring and communicating information to the largest possible number of people, hospital visitors, studies have revealed that communicating information through peers is more effective. The education based on the peer education is effective, particularly among youths, who are normally under the effect by their peers in many habits counting in relations of "positive and negative health behaviors" [10].

CONCLUSIONS

Our study included an educational program that may be the first in Al-Najaf City to evaluate and promote the knowledge of a group of nurses about the risk factors, symptoms and complications of the disease, how to prevent and treat it, and methods of transmission of trichomoniasis. This study concluded that the knowledge level improved from moderate to good after the program for all nurses in different age, gender, married, single, different working unit and years of experience, in the total assessment, the knowledge of nurses about trichomoniasis in the Pretest, was a moderate mean score (0.57) and the posttest was a good (0.84) mean score, with no significant difference in the nurse's Knowledge according to their Demographic Characteristics.

LIMITATIONS

One of the limitations of this study is that the sample size did not include the entire province and did not include all sexually transmitted diseases. Therefore, we recommend conducting similar studies of all disease transmitted by sexual method that include other groups and the nursing group that are much relevant and influential in society.

REFERENCES

1. Patterson C, Fields L, Moxham L. Breaking the chain of transmission: Nurses' role in preventing STI's. Australian Nursing and Midwifery Journal. 2017;25(3):43-43.
2. Schwebke JR, Burgess D. Trichomoniasis. Clinical Microbiology Review. 2004;17(4): 794-803. doi: 10.1128/cmr.17.4.794-803.2004. DOI
3. Agabi YA, Kilson MD, Uneze SB et aal. Candida albicans and Trichomonas Vaginalis: High prevalence and risk factors in women attending a Gynecology clinic in Jos, Nigeria. Microbes and Infectious Diseases. 2023;4(3):1065-1071. doi: 10.21608/MID.2022.162426.1381. DOI
4. Poole DN, McClelland RS. Global epidemiology of Trichomonas vaginalis. Sexually transmitted infections. 2013;89(6):418-422. doi: 10.1136/sextrans-2013-051075. DOI
5. Eyong EEJ, Landred K, Njimated NON, Katamssadan TH. Prevalence and risk factors of trichomoniasis in patients attending two medical centers in urban and rural areas in the North West Region, Cameroon. Int J Bio Chem Scien. 2023;17(3):848-863. doi: 10.4314/ijbcs.v17i3.8. DOI
6. Al-Ardi MH. Seroprevalence and risk factors of Trichomonas vaginalis among couples in Al-Hamza City-Iraq. Al-Kufa University Journal for Biology. 2021;13(1):33-39. doi: 10.36320/ajb/v13.i1.8140. DOI
7. Mabaso N, Abbai N. Distribution of genotypes in relation to metronidazole susceptibility patterns in Trichomonas vaginalis isolated from South African pregnant women. Parasitology Research. 2021;120:2233–2241. doi: 10.1007/s00436-021-07177-w. DOI
8. Lim AG, Chong VH, Salleh SM, Poh SH. Awareness, knowledge level, and misconceptions about sexually transmitted infections among secondary school students in Brunei Darussalam. The Southeast Asian Journal of Tropical Medicine and Public Health. 2017;48(2):386-395.
9. Sallam TA, Hussein HES, Megahed LAE et al. Educational program to enhance nurses' knowledge and prevention regarding Trichomonas vaginalis in A Military hospital. Journal of the Egyptian Society of Parasitology. 2022;52(3)^459-469. doi: 10.21608/JESP.2022.278078. DOI
10. Börekçi G, Uysal DA, Özel A, Aksu D. Using peer-based education to increase the knowledge level of vocational high students about sexually transmitted diseases. Istanbul Medical Journal. 2020;21(4). doi: 10.4274/imj.galenos.2020.60343. DOI
11. Begum R, Hossain MM, Khatun MR et al. Nurses' knowledge and practice regarding sexually transmitted diseases at 250 bedded bangamata sheikh fazilatunnessa mujib general hospital, Sirajganj, Bangladesh. Saudi Journal of Nursing and Health Care. 2023. doi: 10.36348/sjnhc.2023.v06i11.005. DOI
12. Navidi I, Hadavand F, Ahmadlo A. Comparison of knowledge, attitude, and practice of healthcare staff toward sexually transmitted infections in Markazi province, Iran. HIV & AIDS Review. International Journal of HIV-Related Problems. 2022;21(2):155-163. doi: 10.5114/hivar.2022.115540. DOI
13. Fred M. Assessment of Trichomoniasis Prevalence and healthcare provider knowledge among pregnant women: A Study at Luweero general hospital, Uganda. Idosr. Journal of Science and Technology. 2024; 10(1):51-56. doi: 10.59298/IDOSR/JST/24/101.235156. DOI
14. Lagadinou M, Spiliopoulou K, Paraskevas T et al. Knowledge and attitudes of medical and nursing students in a Greek university regarding sexually transmitted diseases. Int J Environ Res Public Health. 2024;21(3):251. doi: 10.3390/ijerph21030251. DOI
15. Osanyin GE, Ogunyemi DO, Oluwole EO, Oyekanmi OD. Knowledge, attitude and preventive practices of sexually transmitted infections among unmarried youths in an urban community in Lagos State, Nigeria. African Journal of Primary Health Care and Family Medicine. 2020;12(1):1-7. doi: 10.4102/phcfm. v12i1.2221. DOI
16. Vakilian K. Investigating the knowledge of sexually transmitted diseases in university students of Iran. The Open Public Health Journal. 2021;14(1):277-281. doi:10.2174/1874944502114010277. DOI
17. Mansor N, Ahmad N, Rahman HA. Determinants of knowledge on sexually transmitted infections among students in public higher education institutions in Melaka state, Malaysia. PLoS ONE. 2020;15(10):e0240842 doi: 10.1371/journal.pone.0240842. DOI
18. Keizur EM, Bristow CC, Baik Y, Klausner JD. Knowledge and testing preferences for Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis infections among female undergraduate students. Journal of American College Health. 2020;68(7):754-761. doi: 10.1080/07448481.2019.1616742. DOI
19. Amakali K, Amungulu J, Emvula O. Undergraduate nursing students' knowledge and attitudes, regarding the management of sexual transmitted diseases. Indiana Journal of Humanities and Social Sciences. 2024;5(2):24-29. doi: 10.5281/zenodo.10729219. DOI
20. Sunil G, Prathap P, Asokan N, Sajna MV. Assessment of knowledge regarding sexually transmitted infections among high school students in an educational sub-district in Southern India- A cross-sectional study. Indian Journal of Dermatology, Venereology and Leprology. 2023;90(3):419. doi: 10.25259/IJDVL_978_2021. DOI
21. Alshemeili A, Alhammadi A, Alhammadi A et al. Sexually transmitted diseases knowledge assessment and associated factors among university students in the United Arab Emirates: a cross-sectional study. Frontiers in Public Health. 2023;11:1284288. doi: 10.3389/fpubh.2023.1284288. DOI

22. Al-Gburi G, Al-Shakarchi A, Al-Dabagh JD, Lami F. Assessing knowledge, attitudes, and practices toward sexually transmitted infections among Baghdad undergraduate students for research-guided sexual health education. Front Public Health. 2023;11:1017300. doi: 10.3389/fpubh.2023.1017300. DOI
23. Adekunle ON, Mogaji HO, Adeleke MT et al. Prevalence of trichomoniasis and associated risk factors among female attendees of primary health care centers in Ijebu-North, Southwest Nigeria. Journal of Innovative Research in Life Sciences. 2022;3(2):7-7.
24. Al-Abbas WDS, Radhi OA. Incidence of Chlamydia trachomatis and Trichomonas vaginalis genital infections among non-pregnant women in Al-Najaf Province. Kufa Journal for nursing sciences. 2019;9(1):1-8. doi: 10.36321/kjns.vi20191.2251. DOI
25. Kadhum NJ. Epidemiological study on Trichomonas vaginalis among the women who Attended the hospitals of Basra province. Journal of Basrah Researches (Sciences). 2020;46(2):64-73.
26. Alhusseini ZA, Alquraishi MA. Epidemiological study and detection of Trichomonas vaginalis parasite in holy Karbala governorate. Tokyo Medical Journal. 2021;44(6):3297-305.
27. Abdul Jabbar ZR, Al-Warid HS. Some clinical features of trichomoniasis associated with pelvic organs tenderness in sample of Iraqi women. The Egyptian Journal of Hospital Medicine. 2022;89(1):4526-4534. doi: 10.21608/EJHM.2022.258680. DOI
28. Ajani TA, Elikwu CJ, Fayemiwo SA et al. Trichomonas vaginalis infection among asymptomatic undergraduate students in a private university in Ogun State, Nigeria. Ann Ib Postgrad Med. 2022;20(2):135-142.
29. Merdaw MAZ, Kadhim HS, Alriyahee AF et al. Genetic variation of Trichomonas vaginalis isolates from Iraqi Women: Association with fertility and cervical abnormalities. Journal of University of Babylon for Pure and Applied Sciences. 2019. doi:10.13140/RG.2.2.16210.50885. DOI

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Features of complex medicamental therapy in patients with silent myocardial ischemia of high risk after myocardial infarction

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ABSTRACT

Aim: To determine the peculiarities of the course of silent myocardial ischemia (SMI) in patients with post-infarction cardiosclerosis depending on the risk factors (RFs); to reveal the interdependence between the presence of pathological turbulence of the heart rhythm and the peculiarities of the course of SMI in patients with post-infarction cardiosclerosis and the effectiveness of treatment applying S-amlodipine and enalapril in complex therapy.

Materials and Methods: There were observed 154 patients with SMI with a history of myocardial infarction, having received anti-anginal therapy. The diagnosis of SMI was made according to Holter ECG monitoring data. Among the additional indices of the severity of the patient's condition, the maximum value of the ST segment deviation amplitude was evaluated.

Results: It was determined that in patients with SMI with post-infarction cardiosclerosis, there is a positive correlation between the presence of RFs and Holter ECG monitoring indices, in particular, the average daily values of the number of ischemic episodes, the total daily duration of ST segment depression and the average duration of one ischemic episode. Enalapril and S-amlodipine are the effective means of pharmacotherapy in the SMI.

Conclusions: The silent myocardial ischemia, which is associated with the presence of such Rfs as arterial hypertension, diabetes melitus, dyslipidemia or their combination, is characterized by a severe course of the disease, which is manifested by a worsening of the clinical condition, a decrease in tolerance to physical exertion, significant changes in hemodynamics.

KEY WORDS: heart rate turbulance, heart rate variability, anti-ischemic therapy, post-infarction cardiosclerosis

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INTRODUCTION

SMI – is a special form of coronary artery disease (CAD), which is characterized by atherosclerotic damage to the coronary arteries and the occurrence of myocardial ischemia, in which the intensity of efferent nociceptive stimulation does not reach a level sufficient to cause pain [1]. In the SMI pathogenesis, at the same time, a lower degree of severity of ischemic and atherosclerotic changes is noted, compared to stable angina pectoris. The presence of SMI for a long time is the cause of local or diffuse damage to the heart muscle, disturbances in the kinetics of the left ventricle, and leads to the progression of heart failure. This is the reason why patients with SMI should be included into the group with a complicated course of CAD [2].

One of the most prognostically unfavourable complications of CAD, including its silent form, is sudden cardiac death (SCD) [3]. The fight against the emergence of life-threatening arrhythmias and SCD is one of the most important tasks of the modern health care system of Ukraine and the world in general. The importance of this problem is due to high mortality, especially among young and working-aged people [4]. Current selection criteria for primary prevention of SCD in patients with SMI are insufficiently effective. In many cases, SCD is the first, but at the same time, it is the fatal manifestation of the disease [5]. Therefore, the main direction of modern research in medicine is to identify the silent form of myocardial ischemia, followed by the search for early risk markers and ways to effectively prevent SCD [6].

Research over the past three decades suggests a probable relationship between autonomic regulation and mortality from cardiovascular diseases (CVD), including SCD. There is experimental evidence [7] of a correlation between the frequency of occurrence of fatal arrhythmias and destabilization of the balance of the sympathetic and parasympathetic parts of the autonomic nervous system (ANS) [8]. This led to the discovery of quantitative markers of autonomic regulation – heart rate variability (HRV), the analysis of which is one of the main quantitative methods of assessing the mechanisms of neurohumoral regulation of the heart,

which allows establishing the relationship between the sympathetic and parasympathetic divisions of the ANS in temporal and spectral dimensions and quantitatively characterize the activity of different departments of the ANS. An imbalance of the ANS, which leads to a decrease in HRV, causes an increased risk of severe cardiovascular complications and death [9].

The lack of clear criteria for the detection of SMI, assessment of the risk of life-threatening arrhythmias and SCD provoked by modified (smoking, dyslipidemia, arterial hypertension (AH), etc.) and unmodified risk factors (RFs) of CVD, differentiated approaches to the application of basic methods of early diagnosis and treatment, do not allow in many cases achieve the desired clinical effect during the treatment of patients with cardiovascular pathology. Thus, in-depth elucidation of the factors, mechanisms of their occurrence, formation and progression, and complications of SMI constitute an actual and important scientific problem for practical medicine [10,11].

One of the most relevant aspects of the study of CAD is the issue of effective and adequate anti-anginal therapy [12]. The choice of therapeutic tactics for each patient with CAD should be based on the clinical-pathogenetic peculiarities of the course of the disease, the presence of concomitant pathology, and the individual effectiveness of the therapeutic regimen. At the same time, CAD should be considered as a multifactorial disease, in the development and course of which the patient's lifestyle and environmental factors play a significant role. A number of scientific works prove the importance of these modified factors for assessing the prognosis of the course of CAD and determining the risk of its complications [13, 14].

AIM

To study and determine the peculiarities of the course of SMI in patients with post-infarction cardiosclerosis depending on the RFs. To reveal the interdependence between the presence of pathological turbulence of the heart rhythm and the peculiarities of the course of SMI in patients with post-infarction cardiosclerosis and their prognostic value for assessing the severity of the disease course and the effectiveness of treatment applying S-amlodipine and enalapril in complex therapy.

MATERIALS AND METHODS

The study was conducted on the basis of Regional Clinical Cardiology Center.

The members of the Ethics Commission at the Ivano-Frankivsk National Medical University decided that this study would not contradict the main provisions of the GCP, Convention Council of Europe on human rights and biomedicine, the Helsinki Declaration of the World Medical Association on ethical principles for the conduct of scientific medical research with the participation of man and the Law of Ukraine «On Medicines». All patients signed an informed consent to participate in a clinical trial.

There were observed 154 patients with SMI with a history of myocardial infarction (MI), having received anti-anginal therapy. Among the examined patients there were 112 men – it was 72.7%, and 42 women – it was 27.3%. The average age of the patients was (53.5±2.82) years: men – (51.2±1.2), women – (56.9±1.5) years old. The most numerous was the age group of patients aged 30-44 and 50-59 years, respectively – 37.0% and 42.9% of the examined. During the clinical-functional examination of the above-mentioned patients, 30 healthy persons were also examined in order to form a control group. The homogeneity of the patients included into the study, was established by age and gender.

For a detailed study of the clinical-functional and laboratory peculiarities of SMI at different stages of its course and the influence of the medicines selected on the course of the disease, all the examined were divided into the following groups: I) – patients with SMI receiving basic therapy: metoprolol succinate 25 mg/day, clopidogrel 75 mg/day and atorvastatin at a dose of 20 mg/day (n=39) – BT; II) – patients with SMI, who in addition to the BT were prescribed enalapril at a dose of 2.5-10 mg per day (n=37) – BT+ E; III) – patients with SMI, who against the background of BT were prescribed S-amlodipine 2.5-5 mg per day (n=40)– BT+sA; IV) – patients with SMI receiving combined treatment with medicines of BT together with enalapril 2.5-10 mg/day and S-amlodipine at a dose of 2.5-5 mg/day (n=38) – BT+E+sA.

The diagnostic criteria were: episodes of SMI verified with the help of Holter ECG monitoring and a test with dosed physical load. The diagnosis of SMI was made according to Holter ECG monitoring data, using the rule of "three units": deviation of the ST segment with an amplitude of 1 mm or more, lasting at least 0.08 s from point j, for 1 min or more, with an interval between episodes of at least 1 min.

Among the additional indices of the severity of the patient's condition, the maximum value of the ST segment deviation amplitude was evaluated. In addition, the occurrence of accompanying rhythm disturbances during myocardial ischemia was noted, which is important not only for the diagnosis of SMI, but also makes it possible to differentiate arrhythmogenic ST segment shift. The total number of supraventricular and ventricular extrasystoles

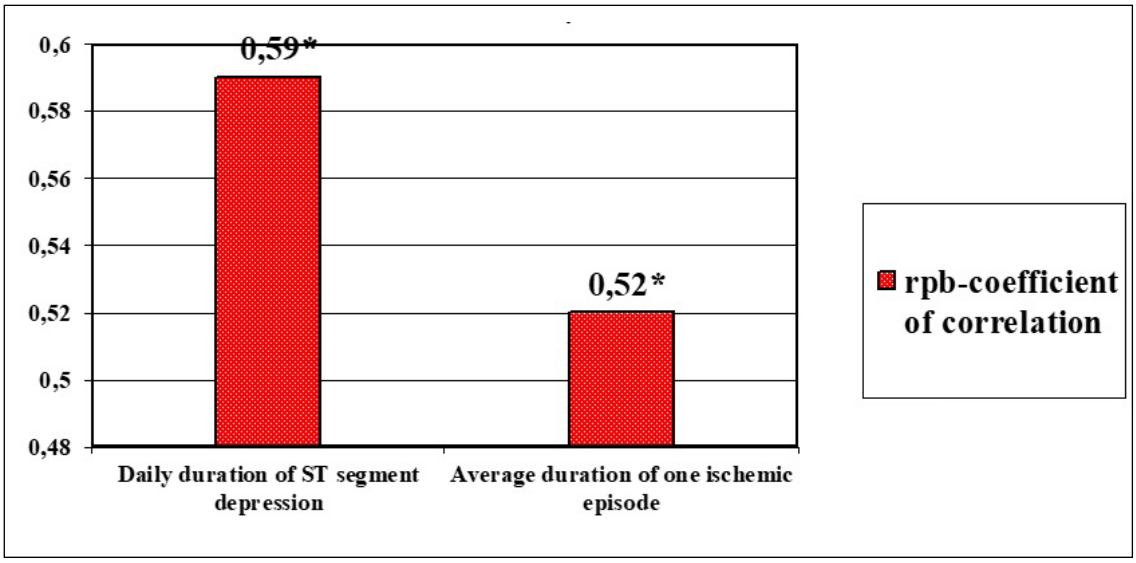

Fig. 1. A point-biserial correlation analysis between the presence of RFs and indices of Holter ECG monitoring in patients with SMI. Note. The probability of a difference in average values is *p<0.05.

(VE) was calculated, and the class of VE according to V. Lown was determined. The analysis of heart rate turbulence (HRT) parameters was carried out according to the criteria offered by G. Schmidt and co-authors [12] with the determination of indices of the "start" of HRT and the "slope" of HRT.

Determination of HRTO (%) and HRTS (ms/RR) was performed as follows. The HRTO index – is the ratio between the sum of the values of the first two RR sinus intervals occuring after extrasystole and the two RR sinus intervals preceding extrasystole to the sum of the two RR sinus intervals before extrasystole:

HRTO (%) = $((RR_1 + RR_2) - (RR_{-3} + RR_{-2}))/(RR_{-3} + RR_{-2})$;

where RR_1, RR_2 – are the intervals that come after the compensatory pause; RR_{-3}, RR_{-2} – are the intervals that precede the VE.

To determine HRTS (ms/RR), the slope of the change in RR intervals was calculated using straight regression lines for every 5 RR intervals out of 20 occurring after a compensatory pause. The HRTS value was taken as the maximum regression slope. Values of HRTO < 0% and HRTS > 2.5 ms/RR were considered normal, and HRTO > 0% and HRTS < 2.5 ms/RR – pathological ones.

Daily monitoring of heart rate variability (HRV) was carried out using the system of daily monitoring and analysis of HRV. Among daily HRV indices, statistical (SDNN-i, SDNN, rMSSD, pNN50), total power of heart rate fluctuations (TP) and spectral indices (LF, HF) were studied, and the LF/HF ratio was calculated. Indices were calculated automatically for every 5 minutes of recording. Five-minute intervals, which included non-stationary processes, artifacts and frequent extrasystoles, were excluded from the calculation in direct recording analysis.

For temporal analysis of HRV, the following indices were calculated: SDNN – standard deviation (SD) of values of normal NN intervals during 24 hours; SDANN – standard deviation of the average values of NN intervals for every 5 minutes of continuous ECG recording; and iSDNN – index – average of standard deviations of N-N intervals for every 5 minutes; rMSSD – standard deviation of the difference of N-N consecutive intervals; pNN50 – the percentage of consecutive N-N intervals, the difference between them exceeds 50 ms.

Spectral analysis made it possible to detect periodic changes in the frequency of the sinus rhythm using special mathematical methods, while the sequence of sinus contractions is transformed into a sequence of frequencies (in Hz), each of which corresponds to the amplitude of the oscillations. Thus, high frequencies (High Frequency – HF) – 0.15-0.40 Hz are the markers of the activity of the parasympathetic part of the ANS; low frequencies (Low Frequency-LF) – 0.04-0.15 Hz – sympathetic department. The ratio of sympathetic and parasympathetic effects on HRV was characterized by the LF/HF ratio (norm 1.5-2.0).

Spectral analysis of HRV was performed based on the study of the following indices: HF – high-frequency component of the spectrum (0.15-0.40 Hz), index of the activity of the parasympathetic part of the ANS; LF – a low-frequency component of the spectrum (0.04-0.15 Hz), which reflects slow heart rate fluctuations, closely related to the heart's response to vegetative influences; LF/HF – the coefficient of sympatho-parasympathetic balance, reflecting the balance of activity of the sympathetic and parasympathetic divisions of the ANS; VLF – the power of very low-frequency waves (0.0033-0.04 Hz), reflecting the activity of the humoral mechanisms of slow-acting heart rhythm regulation; TP – the total power of the spectrum, is an analogue of the SDNN index.

All the data of the work were processed using the package of applied and statistical programs STATISTICA 10. For all indices, the value of the average arithmetic sample (M), its dispersion and the average error (m) were calculated. To identify the probability of differences in research results, the Student's

Table 1. The influence of the studied schemes of anti-ischemic therapy on the dynamics of heart rate variability analysis indices according to Holter ECG monitoring in patients with SMI

Indices	Norm n=30	Basic therapy (I group), n=39		Basic therapy + enalapril (II group), n=40		Basic therapy + S-amlodipine (III group), n=37		Basic therapy + enalapril + S-amlodipine (IV group), n=38	
		before treatment	after treatment, p	before treatment	after treatment, p	before treatment	after treatment, p	before treatment	after treatment, p
SDNN, ms	155,6± 7,95	107,4± 5,61 p<0,001	123,32± 5,24* Δ+14,8	103,7± 5,34 p<0,001	125,7± 7,1* Δ+21,2	111,6± 5,5 p<0,001	139,7± 5,68** Δ+25,2	105,2± 6,02 p<0,001	147,1± 8,16*** Δ+39,8
RMSSD, ms	38,2± 2,25	21,4 ±1,18 p<0,001	25,3 ±1,16* Δ+18,2	23,5 ±1,21 p<0,001	29,3 ±1,64** Δ+24,7	22,9 ±1,09 p<0,001	34,7 ±1,51*** Δ+51,5	20,8± 1,27 p<0,001	36,5 ±1,38 *** Δ+75,5
pNN50, %	20,3± 0,93	23,6 ±1,37 p<0,05	18,3± 1,58 *	24,1± 1,75 p<0,05	18,2± 1,39 *	22,9± 1,57 p<0,05	16,9 ±0,64 **	23,5± 1,93 p<0,05	17,1± 0,82 **
TP, ms^2	4120,6± 194,34	2289,15± 147 p<0,001	2730,09± 161* Δ+19,3	2179,27± 183 p<0,001	3174,3± 132*** Δ+45,65	2301,64± 113 p<0,001	3300,01± 155*** Δ+43,4	2259,35± 101 p<0,001	3645,85± 179 *** Δ+61,4
ln ULF	10,8± 0,49	11,92± 0,67	11,6± 0,53 p_1>0,05	11,98± 0,78	11,57± 0,42 p_1>0,05	11,91± 0,71	11,26± 0,68 p_1>0,05	11,89± 0,92	11,04± 0,59 p_1>0,05
ln VLF	8,04± 0,33	8,34± 0,51	8,1± 0,38 p_1>0,05	8,39± 0,47	8,1± 0,29 p_1>0,05	8,34± 0,45	7,85± 0,31 p_1>0,05	8,32± 0,69	7,73± 0,4 p_1>0,05
LF, ms^2 Δ %	1103,9± 67	1820,14± 112 p<0,001	1512,56± 89 p_1<0,05	1901,92± 125 p<0,001	1470,23± 81 **	1813,35± 94 p<0,001	1205,28 ± 69 ***	1793,03± 138 p<0,001	1050,48± 61 ***
HF, ms^2, Δ %	631,7± 28	674,1± 53	657,4± 46 p_1>0,05	678,9± 39	653,4± 32 p_1>0,05	636,4± 48	602,5± 29 p_1>0,05	649,6± 36	617,6± 31 p_1>0,05
LF/HF	1,75±0,1	2,7±0,16	2,3±0,1 *Δ-14,8	2,8± 0,15	2,25± 0,14 *Δ-19,6	2,83± 0,19	2,0± 0,07 ***Δ-29,3	2,74±0,17	1,7±0,09 ***Δ-37,95

Note. P – the probability of changes in relation to norm indices, the probability of a difference compared to the indices before treatment: *- p<0,05, **- p<0,01, *** – p<0,001.

coefficient (t) was determined, after which the probability of sample differences (p) and the confidence interval of the average were determined according to Student's distribution tables. Values with p<0.05 were considered probable. To determine the relationship between parametric indices, the correlation coefficient was determined.

RESULTS

In our study, the frequency of occurrence of the SMI was analyzed, taking into account the presence of RFs. It was found that in patients with dyslipidemia, AH, diabetes mellitus (DM) and the presence of two or more RFs, the formation of asymptomatic variants of MI was observed more often compared to patients without RFs. At the same time, it should be noted that the frequency of ventricular tachycardia (VT), syncopal conditions did not depend on the presence of RFs. The results obtained can be explained by the different degree of sensitivity of individuals to efferent nociceptive stimulation, which is partly determined by the individual characteristics of the patient and his/her lifestyle. The interrelationship of the RFs of CAD and the probability of the formation of asymptomatic MI indicate a significant influence of external factors on susceptibility to myocardial ischemia. An important aspect of the study was the investigation of lifestyle peculiarities of patients that increase the risk of dyslipidemia or carbohydrate metabolism disorders. It has been determined that DM is more often observed in people with hypodynamia and excess body weight.

A clinical-instrumental analysis was performed in patients with SMI with post-infarction cardiosclerosis. The evaluation of the data obtained of the ECG-study in 12 standard leads showed that in patients with SMI, in comparison with the subjects studied in the control group, rhythm disorder according to the type of supraventricular and VE, as well as sinus tachycardia, were more often detected. The peculiarities of the course of the SMI in patients with post-infarction cardiosclerosis, depending on the RFs, were analyzed. When performing an ECG in people with dyslipidemia, compared to patients without RFs, focal cicatricial changes were detected more often (76.5% vs. 9.1%; p<0.001), in studied with type II DM, VE (48.3% vs. 9.1%; p<0.05), and in patients with 2 or more RFs had LV hypertrophy (73.8% vs. 9.1%; p<0.001) and focal cardiosclerosis (88.1% vs. 18 .2%; p<0.001).

The results of the standard ECG study provided the necessity for the performance of a Holter ECG monitoring. When analyzing Holter ECG monitoring indices, it was

determined that patients with SMI with RFs such as AH, DM and dyslipidemia have higher average daily values of the number of ischemic episodes per day, total daily duration of ST segment depression, total ST depression amplitude, average duration of one ischemic episode in comparison with individuals without RFs ($p<0.05$). When analyzing the dynamics of the indices of the average value of maximum ST segment depression, the average depth of ST segment depression, the average heart rate during ST segment depression, the heart rate at the maximum depth of ST shift, no significant differences were found in various groups of studied patients ($p>0.05$). The frequency of SMI episodes is proportionally related to the RFs number of the complicated course of CAD.

A point-biserial correlation analysis was performed between the presence of RFs and the duration of myocardial ischemia in patients with SMI.

As one can see from fig.1, a direct correlation of average strength was established between the daily duration of the ST segment and the presence of FRs. The point-biserial correlation coefficient (rpb) was +0.59 ($p<0.05$). When analyzing the correlation interrelationship between the average duration of one ischemic episode and the presence of FRs, a statistically significant correlation of the average strength was found. The point-biserial correlation coefficient was equal to +0.52 ($p<0.05$).

The obtained results proved that such RFs as AH, type II DM, dyslipidemia can negatively affect the condition of myocardial perfusion and provoke ischemia of the heart muscle in patients with SMI. This is manifested by more intense manifestations of ischemic changes detected during Holter ECG monitoring.

Analysis of the prevalence of VT and other ventricular rhythm disturbances did not reveal significant differences between the study groups ($p>0.05$). A significantly higher frequency of VE was noted in patients with concomitant type II DM, AH, lipid metabolism disorders, and the presence of two or more RFs, compared to patients without RFs ($p<0.05$). When analyzing the dynamics of indices of the average value of heart rate, P-Q and Q-T intervals, no differences in these indices were found in different groups of the studied patients ($p>0.05$). The results of the echocardiographic study proved that the course of SMI in patients with dyslipidemia, DM and AH is accompanied by more pronounced hypertrophy of the LV and lower indices of its systolic function in comparison with patients with the absence of RFs. It was determined that when at least one RF was identified, higher indices of the volumes and sizes of the LV into systole and diastole were observed ($p<0.01$), as well as a decrease in LV ejection fraction ($p<0.05$).

It is noteworthy that higher values of LV myocardial mass were recorded in patients with concomitant AH; they are characterized by a more intensive development of LV hypertensive remodeling processes compared to patients of other studied groups. The results obtained in this group may be due to a higher blood pressure and a higher value of the aortic stiffness index. It was found that for patients with SMI in the presence of concomitant hypertension, DM, two or more RFs, the average diastolic value of the thickness of the back wall of the LV and the interventricular septum was significantly higher ($p<0.001$) compared to the group of patients with no RFs.

Evaluating the effectiveness of the used treatment regimens for six months, the advantages of the combined use of S-amlodipine and enalapril against the background of BT were proven.

The study analyzed the dynamic indices of complaints in the examined patients under the influence of anti-anginal therapy. It was noted that in all studied groups during the treatment, a positive dynamics of decreasing the frequency of manifestation of subjective clinical signs of the disease course was observed. A significant reduction in heart rate and the feeling of interruptions in the work of the heart during physical exertion and at rest was already observed after 3 months of medicinal treatment. Changes in tolerance to physical exertion in patients with SMI after treatment were studied. It was noted that the complex use of BT medicines in combination with S-amlodipine and enalapril in patients with SMI was accompanied by the most pronounced increase in tolerance to physical exertion compared to other groups.

The results of Holter ECG monitoring proved that the investigated treatment regimens were effective in reducing ischemia indices. The total duration of ischemia, the number of ischemic episodes, and the mean and maximum depth of ST segment depression decreased in all four groups. A statistically significant decrease in the frequency of episodes of myocardial ischemia during the day under the influence of BT and enalapril, as well as when using BT in combination with S-amlodipine, was noted.

It was determined that the most intense anti-anginal effect was observed in the combined treatment with enalapril and S-amlodipine. The index of the average daily number of ischemic episodes before the start of the study in the group I decreased at 30.7% after the end of the treatment course ($p<0.001$). The average number of episodes of myocardial ischemia during the day in the group II decreased at 37.94% and amounted to (3.19 ± 0.15) after therapy ($p<0.001$). It was proved that the addition of S-amlodipine to the basic therapy in patients of the group

III was accompanied by a more pronounced anti-anginal effect, reducing the average daily number of ischemic episodes at 49.2% ($p<0.001$). It should be noted that anti-anginal treatment of the group IV patients using a combination of BT, enalapril and S-amlodipine led to the most statistically significant change in this index in the studied patients, namely at 59.5% ($p<0.001$).

The dynamics of HRT in patients with SMI during their treatment was evaluated using the offered medicinal regimens. In the group of patients with pathological values of turbulence onset (TO), there was no trend towards pathological values of turbulence slope (TS), only 5 (3.2%) patients of all studied groups were registered both pathological parameters of HRT before the start of anti-anginal treatment.

Normalization of HRT indices was established as a result of the use of BT and when using a combination of BT with S-amlodipine and enalapril. The analysis of the dynamics of HRT indices showed that under the influence of the studied treatment regimens, the degree of detection of the pathological value of HRT decreased in all groups of patients ($p<0.05$). In particular, in the BT group, the frequency of registration of the pathological value of the onset of turbulence after therapy was 10.3%, against 23.1%, in patients receiving BT with enalapril – 8.1%, against 18.9% ($p<0.05$), in patients treated with BT in combination with S-amlodipine – 5.0%, against 20.0% ($p<0.05$), and in patients of the group of combined therapy – 2.6%, against 23.7% ($p<0.05$). Therefore, the most effective for the normalization of HRT was the therapy based on the combination of BT with S-amlodipine and enalapril. The higher effectiveness of anti-anginal therapy with S-amlodipine and enalapril when added to BT for the elimination of pathological HRT has been proven.

HRV is an important index for evaluating the therapeutic effectiveness of the studied medicines. Analysis of HRV makes it possible to evaluate the effect of pharmacotherapy on the activity of the ANS, and is also important for predicting the course of the disease. Patients with SMI were characterized by a significant decrease in daily HRV compared to practically healthy individuals. The dynamics of HRV parameters is shown in table 1.

They were observed a statistically significant decrease in the time indices of the total HRV: SDNNi, SDNN, rMSSD, pNN50 ($p<0.05$). A decrease in total HRV may be associated not only with an increase in sympathetic activity, but also with a decrease in all autonomic influences on the heart, which is confirmed by a decrease in the total power spectrum (TP). A decrease in high-frequency oscillations of the heart rhythm (RMSSD, pNN50) in patients of the study group indicates a decrease in parasympathetic influence.

It is known that a significant decrease in HRV increases the risk of developing acute cardiovascular disease. Analyzing the indices of the total HRV, it was found that almost all time indices characterizing the total HRV in patients with SMI compared to patients without ischemia, were reduced, however, significant differences between the groups were found only in relation to the index of total power (2263.15 ± 126.05) ms^2 and (4120.6 ± 194.34) ms^2 ($p<0.05$).

The rate of SDNN in patients with SMI was low before the start of anti-anginal therapy and probably increased in all groups of patients after 6 months of treatment ($p<0.05$). Characterizing the parameters of the spectral analysis of HRV, it was established that the LF level, which reflects the low-frequency component of HRV and characterizes the sympathetic tone, was significantly higher in patients with SMI than in the control group ($p<0.05$). The LF/HF index (sympathovagal index) in patients with SMI was significantly ($p<0.05$) higher compared to the group of healthy individuals, which characterizes a shift in the sympathetic-parasympathetic balance towards the predominance of the sympathetic division of the ANS. The absolute values of the HF index did not change significantly under the influence of anti-anginal treatment in all groups ($p>0.05$).

Thus, the investigated schemes of anti-anginal treatment had a positive effect on HRV, which was confirmed by the dynamics of indices of time and frequency analyzes of Holter ECG monitoring. In the course of treatment with S-amlodipine and when combining this medicine with enalapril against the background of BT, sympathetic-parasympathetic dynamic balance was restored.

DISCUSSION

Our study proved the importance of the influence of modified RFs on the characteristics of the clinical picture and on certain pathogenetic aspects in patients with CAD.

In the absence of clinically-manifest symptoms, SMI, nevertheless, is characterized by a complex of clinical-pathogenetic signs inherent in other forms of CAD. The study of SMI, the study of the peculiarities of its course allows to some extent deny the erroneous statement about the easier development of this disease in comparison with ischemic pathology, which is characterized by the pronounced anginal symptoms.

These research data allow us to consider SMI as a disease leading to a decrease in the electrical stability of the myocardium, the development of LV hypertrophy, and an increase in the thickness of its walls. The described processes are accompanied by the pronounced phenomena of myocardial ischemia. Thus, in the ab-

sence of clinically-manifest symptoms, SMI is nevertheless characterized by a complex of clinical-pathogenetic signs inherent in other forms of CAD [5]. The study of SMI and of the peculiarities of its course allows to some extent deny the false statement about the easier development of this disease in comparison with ischemic pathology, which is characterized by pronounced anginal symptoms. The evaluation of the results of the Holter ECG monitoring showed that the presence of such RFs as AH, violation of carbohydrate and lipid metabolism in patients with SMI with a history of MI, is associated with a probable decrease in the electrical stability of cardiomyocytes and is capable ofinducing rhythm disturbances according to the type of supraventricular and VE. Thus, in the absence of clinically-manifest symptoms, SMI is nevertheless characterized by a complex of clinical-pathogenetic signs inherent in other forms of CAD. The study of SMI and of the peculiarities of its course allows to some extent deny the false statement about the easier development of this disease in comparison with ischemic pathology, which is characterized by pronounced anginal symptoms.

A more pronounced intensive anti-ischemic effect was determined when using against the background of BT, combined adequate therapy with enalapril and amlodipine in comparison with the performed BT in a separate combination with each of these medicines [10]. The high anti-ischemic efficiency of the studied medicines makes their use justified in the therapeutic algorithm of management of patients with SMI. In the course of this work, the effectiveness of the studied schemes of antianginal therapy for the normalization of HRT and HRV indices was proven. The results of the study could be a fundamental step towards the development of a clinical protocol for the SMI treatment.

CONCLUSIONS

The SMI, which is associated with the presence of such RFs as AH, DM, dyslipidemia or their combination, is characterized by a severe course of the disease, which is manifested by a worsening of the clinical condition, a decrease in tolerance to physical exertion, significant changes in hemodynamics and autonomic regulation, more intense manifestations of myocardial ischemia, pronounced remodeling of the LV ($p<0.05$), compared to individuals without RFs ($p<0.05$).

It was determined that in patients with SMI with post-infarction cardiosclerosis, there is a positive correlation of medium strength between the presence of RFs and Holter ECG monitoring indices, in particular, the average daily values of the number of ischemic episodes, the total daily duration of ST segment depression and the average duration of one ischemic episode.

In patients with SMI with post-infarction cardiosclerosis and LV systolic dysfunction, chronic HF, in the presence of heart rhythm disorders, additional information obtained with the help of Holter ECG monitoring can be of significant importance in choosing the strategy and tactics of patient management.

Enalapril and S-amlodipine are the effective means of pharmacotherapy in the SMI. The combined use of these drugs with BT in the studied patients allows the reduction of daily myocardial ischemia at 55.1% ($p<0.001$), to normalize indices of HRT and HRV. Therefore, the study of symptoms, as well as possible causes and circumstances contributing to the occurrence of SMI in patients with post-infarction cardiosclerosis, is still an urgent task, the solution of which would allow us to identify such patients, and modern anti-ischemic therapy would help to improve the prognosis.

REFERENCES

1. Kumar A, Avishay DM, Jones CR et al. Sudden cardiac death: epidemiology, pathogenesis and management. Rev Cardiovasc Med. 2021;22(1):147- 158. doi: 10.31083/j.rcm.2021.01.207. DOI
2. Marijon E, Garcia R, Narayanan K et al. Fighting against sudden cardiac death: need for a paradigm shift–Adding near-term prevention and pre-emptive action to long-term prevention. Eur Heart J. 2022;43:1467-1464. doi:10.1093/eurheartj/ehab903. DOI
3. Severino P, D'Amato A, Netti L et al. Diabetes mellitus and ischemic heart disease: the role of ion channels. Int J Mol Sci. 2018;19(3):802. doi:10.3390/ijms19030802. DOI
4. Kovalchuk V, Svechnikova O, Bulavin L. Multifractal Analysis of Cardiac Series and Predictors of Sudden Cardiac Death. Ukr J Phys. 2021;66(10):879. doi:10.15407/ujpe66.10.879. DOI
5. Valensi P, Meune C. Congestive heart failure caused by silent ischemia and silent myocardial infarction. Herz. 2019;44:210-217. doi: 10.1007/s00059-019-4798-3. DOI
6. Dongmo Fokoua-Maxime Ch, Lontchi-Yimagou E, Erwan Cheuffa-Karel T et al. Prevalence of asymptomatic or "silent" myocardial ischemia in diabetic patients: Protocol for a systematic review and meta-analysis. PLoS ONE. 2021;16(6):e0252511. doi:10.1371/journal.pone.0252511. DOI
7. Indolfi C, Polimeni A, Mongiardo A et al. Old unsolved problems: when and how to treat silent ischaemia. Eur Heart J Suppl. 2020;22(L): L82-L85. doi:10.1093/eurheartj/suaa141. DOI

8. Ivanov VP, Mezhievska IA, Maslovskyi VYu. Characteristics of anatomic injury of coronary arteries in patients with acute myocardial infarction without ST elevation depending on plasma level of gene 2 growth stimulating factor and risk of adverse events. Acta Med Leopoliensia. 2020;26(1):20-25. doi:10.25040/aml2020.01.020. DOI
9. Prasad DS, Kabir Z, Devi KR et al. Prevalence and risk factors for silent myocardial ischemia (PRISM): A clinico-observational study in patients of type 2 diabetes. Indian Heart J. 2019;71:400-405. doi: 10.1016/j.ihj.2019.12.002. DOI
10. Dongmo Fokoua-Maxime C, Lontchi-Yimagou E, Erwan Cheuffa-Karel T et al. Prevalence of asymptomatic or "silent" myocardial ischemia in diabetic patients: Protocol for a systematic review and meta-analysis. PLoS One. 2024;19(11):e0314301. doi: 10.1371/journal.pone.0314301. DOI
11. Polimeni CIA, Mongiardo A, De Rosa S, Spaccarotella C. Old unsolved problems: when and how to treat silent ischaemia. Eur Heart J. 2020;22:L82–L85. doi:10.1093/eurheartj/suaa141. DOI
12. Prasad DS, Kabir Z, Devi KR et al. Prevalence and Risk factors for Silent Myocardial ischemia (PRISM): A clinico observational study in patients of type 2 diabetes. Indian Heart J. 2019;71:400–405. doi: 10.1016/j.ihj.2019.12.002. DOI
13. Bullock-Palmer RP, Shaw LJ, Gulati M. Emerging misunderstood presentations of cardiovascular disease in young women. Clin Cardiol. 2019;42:476-483. doi: 10.1002/clc.23165. DOI
14. Sullivan S, Hammadah M, Al Mheid I et al. Sex Differences in Hemodynamic and Microvascular Mechanisms of Myocardial Ischemia Induced by Mental Stress. Arterioscler Thromb Vasc Biol. 2018;38:473-80. 11. doi: 10.1161/ATVBAHA.117.309535. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Connection and assessment of the psychological status of orthodontic patients with various types of malocclusion

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ABSTRACT

Aim: Assessment of relationship between the psychological status of orthodontic patients and the type of malocclusion using the Eysenck Personality Questionnaire.

Materials and Methods: Interviews were conducted using the Eysenck test. After the survey, the results of the questionnaire were analyzed according to the openness scale and 206 people aged 12 to 38 years were included in the further study. All patients were divided into groups according to the classification of malocclusion according to Angle – I, II and III class.

Results: During the verification of the first hypothesis regarding the relationship between patients with malocclusion and the level of neuroticism, a relationship was established in patients with II class ($\chi 2=8.87$, $p=0.064$). When establishing a relationship between patients with different classes of malocclusion and personality traits, no correlations were found ($\chi 2=1.72$, $p=0.787$). According to the results of the Pearson's Chi-square analysis, a relationship was established between patients with different classes of malocclusion and types of temperament ($\chi 2=32.0$ $p=0.004$).

Conclusions: According to the results of our research, patients with pathology of III class according to Angle most often have the temperament type of sanguine and melancholic with introverted personality traits, with II class – melancholic and choleric, with I class according to Angle – sanguine and choleric, who are characterized by extraversion traits.

According to the psychosocial status, patients with pathology of I and II class correspond to a high level of neuroticism, with III class – to an average level of neuroticism.

KEY WORDS: psychological impact, facial aesthetics, malocclusion, orthodontic treatment, temperament type

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INTRODUCTION

Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity. If a person loses at least one link from this chain, which are interconnected and complement each other, he cannot be considered completely healthy [1].

A malocclusion negatively affects the psychological state of adults and adolescents, their social interaction, quality of life and self-esteem, which is directly proportionally reflected in the social adaptation of the patient, his behavior and self-perception [2]. Some patients may complain of discomfort and even pain, especially in the area of the temporomandibular joint [3]. But not only the function of the maxillofacial system suffers, but the aesthetics of the face, which has a direct impact on the patient's mental health and social stereotypes can have a serious impact on the psychosocial status [4].

Nowadays, the demand for orthodontic treatment is constantly growing, especially among adults, who make up more than half of all orthodontic patients, for whom improving their appearance and social recognition is an important motive for undergoing orthodontic treatment [5, 6]. Early studies have shown that many adult patients with malocclusion have problems with social psychological adjustment, which interferes with the normal relationship between the doctor and the patient, despite the successful results of orthodontic treatment. An orthodontist, who cured a patient with malocclusion as a physical disability, can significantly improve his psychological condition [7].

The use of psychological tests in dentistry and orthodontics helps to identify emotional aspects, phobias, anxiety or discomfort that the patient may feel during orthodontic procedures. In cases of hearing-impaired patients, psychological tests are the only objective method of psychodiagnosis, which may allow developing an individual approach to each patient, providing more comfortable and effective orthodontic care [8].

The connection between personal traits and the psychological state of patients and the results of dental treatment has been recognized, which is important to know before the start of long-term orthodontic treatment, in which the patient himself takes an active part [9].

Patients with malocclusion have higher rates of neuroticism, psychological symptoms such as paranoid ideas, anxiety, self-deprecation, introversion, and shyness [10].

AIM

The aim of this study was to assess the relationship between the psychological status of orthodontic patients and the type of malocclusion using the Eysenck Personality Questionnaire.

MATERIALS AND METHODS

This study was conducted at the Department of Postgraduate Education of Orthodontists at the Poltava State Medical University in the period from March to May 2023 and was approved by the Bioethics Problem Commission № 221 dated 12.21.2023. Written informed consent was obtained from all participating patients before the start of the study.

SELECTION OF THE RESEARCH METHOD

Interviews were conducted according to the Eysenck test [11]. The method makes it possible to evaluate the symptom complex of extraversion, introversion and neuroticism. The questionnaire contains 57 questions to which the participants answered «yes» or «no» depending on the real situation, 24 of which assess extroversion-introversion, the other 24 questions characterize stability-instability, and the last 9 are included in the scale of openness and probability of results.

This test helps to identify personal characteristics and possible psychological difficulties that can affect the behavior, interaction and perception of the patient before treatment and to find an approach to the patient with bite pathology depending on its form.

Processing of the questionnaire was carried out with the help of a key, starting with the openness scale. If the examinee has 5 or more points, the results of his surveys are not taken into account, and the reasons for the dishonest answers are searched. Then we define extroversion and introversion by the number of points (more than 12 and less than 12, respectively). The lower the score, the more introverted person, the higher the score, the more sociable person. The same scores are applied to the scale of neuroticism: if 12 points or more – neuroticism, less – emotional stability.

INCLUSION CRITERIA

Patients with malocclusion and permanent bite.

EXCLUSION CRITERIA

Congenital facial defects previously treated orthodontically or individuals in whom aesthetic defects were eliminated by prosthetic or restorative methods,.

Before the further study 206 patients who applied to the Department of Postgraduate Education of Orthodontists with malocclusion, aged from 12 to 38 years.

After the survey, the results of the questionnaire were analyzed according to the openness scale, which objectively assesses the reliability of passing the test. Patients who provided inaccurate information were also excluded.

Regarding orthodontic pathology, all patients were divided into groups according to the classification of malocclusion according to E. Angle- I, II and III class. This classification is internationally accepted and characterizes malocclusion in the sagittal plane. The first class is characterized by a neutral relationship on the first molars and an anomaly of the teeth in the frontal area. The second class corresponds to the distal ratio on the first molars of the upper and lower jaw, the third class corresponds to their mesial ratio.

STATISTICAL ANALYSIS

Statistical data processing was carried out in open statistical software for the desktop Jamovi free license v. 2.3.28.0 [12, 13].

In order to establish the relationship between the classes of malocclusion and the type of temperament, the level of neuroticism and personality traits (extraversion and introversion), an analysis of the mutual distribution of frequencies by Pearson's $\chi 2$ was conducted.

The null hypothesis was that there is no relationship between the psychological status of patients and the type of malocclusion. The alternative hypothesis is that there is a relationship.

RESULTS

During the verification of the first hypothesis regarding the relationship between patients with malocclusion and the level of neuroticism, a relationship was

Table 1. Analysis of the mutual distribution of frequencies between patients with malocclusion and level of neuroticism

Class according to Angle	Number of patients	Level of neuroticism (N, %)		
		High	Medium	Low
I	90	36 (42.8%)	38 (42.2%)	16 (17.8%)
II	80	38 (47.5 %)	24 (30.0%)	18 (22.5%)
III	36	9 (25.0 %)	21 (58.3%)	6 (16.7%)
		χ2= 8.8 p=0.064		

Table 2. Analysis of the established relationship between the level of neuroticism of patients with malocclusion by gender and age

Allocation criteria	Characteristics by gender and age	The value of χ^2	p
Sex	Female	6.48	0.166
	Male	35.36	<0.001*
Age(years)	12-18	9.63	0.047*
	19-25	7.79	0.100
	More than 26	14.33	0.006*
χ2=35.36, p<0.001; χ2=9.63, p=0.047; χ2=14.33, p=0.006			

Table 3. Analysis of the mutual distribution of frequencies between patients with malocclusion and personality traits

Class according to Angle	Number of patients	Personality trait		
		Extrovert	Medium	Introvert
I	90	46 (51%)	7 (7.8%)	37(41.1%)
II	80	43 (53.8 %)	7 (8.8%)	30(37.5%)
III	36	15 (41.7 %)	3 (8.3%)	18 (50%)
		χ2=1.72, p=0.787		

established in patients with II class (χ2=8.87, p=0.064) Table 1.

In general, for patients with I class (group 1) the inherent average degree of neuroticism of the personality type is 38 (42.2%), while for the II class malocclusion (group 2) the high level of neuroticism is 38 (47.5%). The average level of neuroticism of 21 (58.3%) is most often characteristic to III class. When dividing patients by gender, a relationship was established between the level of neuroticism and persons of the male category, χ2=35.36, p<0.001) Table 2.

When dividing patients by age, a relationship was established by the level of neuroticism in the age groups of 12-18 years (χ2=9.63, p=0.047) and older than 26 years (χ2=14.33, p=0.006). table 2.

The second hypothesis was characterized by the existence of a relationship between patients with different classes of malocclusion and personality traits (extraversion and introversion). During its inspection, it was found that there is no connection (χ2=1.72, p=0.787) table 3. Therefore, the analysis of the relationship between personality traits and age and gender was not conducted.

In general, when dividing patients with I and II class according to Angle, the most extroverts were found – 46 (51.1 %) and 43 (53.7 %), respectively. At the III class according to Angle, the most introverts were found – 18 (50%).

The third hypothesis was to determine the relationship between patients with different classes of malocclusion and temperament types. In the group of patients with I class pathology according to Angle, there are most sanguine 22 (24.4%) and choleric 23 (25.5%), slightly less phlegmatic and melancholic. There are 20 cholerics (25%) and 16 sanguine (20%) in group 2. And there are 15 (41.6%) sanguine and 9 (25.0%) melancholics in group 3.

Regarding the combination of temperament types, they correspond to the following gradation: the same number of melanocholeric and cholerosanguinic, and a slightly smaller group of melanophlegmatic and phlegmatosanguinic.

Based on the results of the Pearson Chi-square analysis, a relationship was established between patients with different classes of malocclusion and types of temperament (χ2=32.0 p=0.004) Table 4.

When dividing patients by gender, a connection was established between the type of temperament and the female persons (χ2=24.2, p= 0.044) Table 5.

When dividing the patients by age, a connection was established by the type of temperament in the age group of 12-18 years (χ2=40.9, p<0.001) Table 5.

Table 4. Analysis of the mutual distribution of frequencies between patients with malocclusion and type of temperament

Type of temperament	Class according to Angle (N, %)			
	I class	II class	III class	Total
sanguine	22 (24.4%)	16 (20.0%)	15 (41.7%)	53 (25.7%)
melancholic	17 (18.9%)	9 (11.3%)	9 (25.0%)	35 (17.0%)
melanophlegmatic	3 (3.3%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
melanocholeric	4 (4.4%)	19 (23.8%)	3 (8.3%)	26 (12.6%)
choleric	23 (25.6%)	20 (25.0%)	3 (8.3%)	46 (22.3%)
phlegmatic person	16 (17.8%)	12 (15.0%)	6(16.7%)	34(16.5%)
cholerasanguinic	2 (2.2%)	3 (3.8%)	0 (0.0%)	5 (2.4%)
phlegmatosanguinic	3 (3.3%)	1 (1.3%)	0 (0.0%)	4 (1.9%)
Total	90 (100.0%)	80 (100.0%)	36 (100.0%)	206 (100.0%)
$\chi 2=32.0$ p=0.004				

Table 5. Analysis of the established relationship between patients with malocclusion and type of temperament and gender and age

		The value of x^2	p
Sex	Female	24.2	0.044*
	Male	NaN	NaN
Age(years)	12-18	40.9	<0.001*
	19-25	NaN	NaN
	More than 26	NaN	NaN
$\chi 2=24.2$,p=0.044; $\chi 2=40.9$, p<0.001			

DISCUSSION

An important part of diagnosing orthodontic patients and planning orthodontic treatment is their psychological assessment. The main motivating factors for patients starting orthodontic treatment are the desire to straighten their teeth and improve their smile. Orthodontists are looking for any clues that will help them treat patients successfully, which is why research on specific personality traits that can be used as predictors of patient satisfaction is an important factor. In this study, we aimed to gain some understanding of the personality traits of orthodontic patients that would be relevant in the treatment planning of adult patients with malocclusion, because understanding the motivation and psychological profile of adult orthodontic patients can help orthodontists improve their communication.

An individual's personality is formed by a unique combination of the main four types of temperaments: choleric, sanguine, melancholic, and phlegmatic [14].

Each temperament can be described by the following characteristics. A choleric person is determined, explosive, intense, passionate, has low sensitivity, high reactivity and activity, impatient, has great perseverance, but may have difficulties in switching attention. Sanguines are communicative, enthusiastic, dynamic, with increased reactivity, lively, excitedly respond to everything that attracts their attention, have lively facial expressions and expressive movements, have a high threshold of sensitivity, able to quickly concentrate, disciplined, easily get along with new people, quickly get used to new requirements and circumstances, effortlessly not only switches from one job to another, but also retrains, mastering new skills. Melancholics are organized, perfectionists, are timid, restrained, overly vulnerable, painfully sensual, insecure, the slightest difficulties make them give up, lack energy, are not persistent, get tired easily and have little capacity for work, they are characterized by distraction and a slowed pace of all mental processes. Phlegmatics, on the other hand, are quiet, mystical, winged, restrained, slow, energetic and capable of working, patient, resilient, self-possessed, have difficulty getting along with new people, and respond weakly to external stimuli [15]. Extraversion, introversion mainly determines what a person's reactions and activities depend on – from external impressions that arise at the moment (extrovert), or from images, representations and thoughts related to the past and future (introvert).

At the same time, there is an opinion that both character and facial features are the result of a person's temperament [16].

According to the results of our study on the personal and phychological aspects of the characteristics of orthodontic patients, an almost equal level of distribution of patients with an extroverted personality type was established in patients with I and II classes and a high level of neuroticism,

which is generally consistent with the results of other studies [17]. This suggests that adult orthodontic patients have high levels of anxiety, tension and depression.

At the same time, patients with III class are dominated by introverts. Such patients are withdrawn, may have difficulty adapting to their environment, and have higher levels of anxiety and depression.

According to the data of McKiernan et al. it is known that the perception of malocclusion in patients with neurotic features is significantly different from the perception of a «normal» group of adult patients, due to which such patients can create problems for clinicians regarding expectations both during and at the end of orthodontic treatment [10]. It is possible that these traits are related to differences in the perception of attractiveness and expectations of society.

Research by Phillips et al. shows that adults with malocclusion have a significantly stronger correlation with their neurotic personality [18]. Such individuals can easily become nervous, anxious, irritable and depressed; this can cause them to respond to their environment with poor emotional control and experience negative feelings during certain stressful situations.

In conclusion, we would like to note that more and more orthodontic research is moving away from the traditional biomedical model to a biopsychosocial perspective and assessment of the quality of life related to oral health. The importance of taking into account the inherent psychosocial parameters of orthodontic patients is increasingly being recognized [19].

CONCLUSIONS

The success in the treatment of any pathology is influenced by the psycho-emotional status of the patient and the degree of concern about his pathology.

According to the results of our research, patients with pathology of III class according to Angle most often have the temperament type of sanguine and melancholic with introverted personality traits, with II class – melancholic and choleric, with I class according to Angle – sanguine and choleric, who are characterized by extraversion traits.

According to the psychosocial status, patients with pathology of I and II class correspond to a high level of neuroticism, with III class – to an average level of neuroticism.

An orthodontist must be competent in psychology, because thanks to a correctly established psychological status and type of temperament, he can establish feedback with patient, which increases the probability of quality treatment and obtaining the desired result not only in the understanding of the «norm» from the point of view of medicine, but also in understanding and self-perception of the patient himself.

Psychological tests can detect both quantitative and qualitative changes, adding another dimension through which better treatment planning and implementation can be achieved through a more complete understanding of patients' problems and expectations.

REFERENCES

1. Yeromenko E. Boyovyy khortynh u kompleksi naukovo-pedahohichnykh zasobiv vykhovannya fizychnoyi kul'tury ta osnov zdorov'ya studentiv. [Combat horting in the complex of scientific and pedagogical means of education of physical culture and fundamentals of health of students]. Akademichni zapysky. 2020;1(189):120–8. doi. 10.36550/2415-7988-2020-1-189-120-128. (Ukrainian)
2. Meazzini MC, Tortora C, Cohen N et al. Comparison of the psychosocial impact on patients affected by cranio facial anomalies between traditional orthodontic brackets and aligners. Int J Adolesc Med Health. 2020;34(5):357-365. doi: 10.1515/ijamh-2020-0117. DOI
3. Stasiuk AA, Vyzhenko YY, Makarova AN et al. The evaluation of heads of temporomandibular joint (TMJ) position in patients with malocclusion. The New Armenian Medical Journal. 2020;14(1):48-53.
4. Linden JH. Body image: A handbook of theory, research, and clinical practice. New York: Guilford Press.. (2002). xxii + 530 Pages. American Journal of Clinical Hypnosis. 2004;46(4):55–234. doi: 10.1080/00029157.2004.10403620. DOI
5. Abreu LG. Orthodontics in Children and Impact of Malocclusion on Adolescents' Quality of Life. Pediatr Clin North Am. 2018;65(5):995-1006. doi: 10.1016/j.pcl.2018.05.008. DOI
6. Ben Gassem AA, Aldweesh AH, Alsagob EI et al. Psychosocial Impact of Malocclusion and Self-Perceived Orthodontic Treatment Need among Young Adult Dental Patients. Eur J Dent. 2023;17(3):713-719. doi: 10.1055/s-0042-1753452. DOI
7. Azuma S, Kohzuki M, Saeki S et al. Beneficial effects of orthodontic treatment on quality of life in patients with malocclusion. Tohoku J Exp Med. 2008;214:39. doi: 10.1620/tjem.214.39. DOI
8. Kuroyedova VD, Sokolohorska-Nykina YK. The problem of orthodontic treatment of patients with hearing difficulty (literature review). Wiad Lek. 2018;71(5):1071-1075.
9. Rai A, Kumari M, Kumar T et al. Analytical study of the psychosocial impact of malocclusion and maxillofacial deformity in patients undergoing orthodontic treatment. J Med Life. 2021;14(1):21-31. doi: 10.25122/jml-2020-0022. DOI
10. McKiernan EX, McKiernan F, Jones ML. Psychological profiles and motives of adults seeking orthodontic treatment. Int J Adult Orthodon Orthognath Surg. 1992;7(3):187-198.

11. Eysenck HJ. Personality and experimental psychology: The unification of psychology and the possibility of a paradigm. Journal of Personality and Social Psychology. 1997;73:1224-1237. doi: 10.1037/0022-3514.73.6.1224. DOI
12. The jamovi project (2022). jamovi. (Version 2.3) [Computer Software]. Retrieved from https://www.jamovi.org. [Accessed 30 October 2024]
13. R Core Team. R: A Language and environment for statistical computing. (Version 4.1) [Computer software]. 2021. https://cran.r-project.org. (R packages retrieved from MRAN snapshot 2022-01-01). [Accessed 30 October 2024]
14. Fariba KA, Gupta V, Kass E. Personality Disorder. 2023. In: StatPearls. Treasure Island (FL): StatPearls Publishing.
15. Goodacre CJ, Naylor WP. Evolution of the Temperament Theory and Mental Attitude in Complete Denture Prosthodontics: From Hippocrates to M.M. House. J Prosthodont. 2020;29(7):594-598. doi: 10.1111/jopr.13215. DOI
16. Wilkinson C. Facial reconstruction-anatomical art or artistic anatomy? J Anat. 2010;216(2):235-50. doi: 10.1111/j.1469-7580.2009.01182.x. DOI
17. Zhang GN, Liu Y, Li WY et al. [Correlation between social psychology and personality characteristics and treatment options for adult patients with skeletal malocclusion]. Hua Xi Kou Qiang Yi Xue Za Zhi. 2020;38(3):308-313. doi: 10.7518/hxkq.2020.03.014. (China) DOI
18. Phillips C, Bennett ME, Broder HL. Dentofacial disharmony: psychological status of patients seeking treatment consultation. Angle Orthod. 1998;68:547-556. doi: 10.1043/0003-3219(1998)068<0547:DDPSOP>2.3.CO;2. DOI
19. Rai A, Kumari M, Kumar T et al. Analytical study of the psychosocial impact of malocclusion and maxillofacial deformity in patients undergoing orthodontic treatment. J Med Life. 2021;14(1):21-31. doi: 10.25122/jml-2020-0022. DOI

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Vancomycin powder as a preventive measure for wound infection in total hip arthroplasty: a prospective cohort study

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ABSTRACT

Aim: To compare the results of use of vancomycin powder in the prevention of wound infection in operations of hip replacement that is total to a control group.
Materials and Methods: 40 patients undergoing total hips arthroplasty during period (January 2021 to January 2022). Patients were allocated in a random way into two categories so that one group received vancomycin powder and served a study group; the other group received no such intervention and served as a control group. Patients underwent steps: after completion of surgery, regular closure in layers was done; drain was inserted into sub-muscular layers while vancomycin powder (1 gm) was put in subcutaneous layer before skin closure; drain was closed for two hours and then reopened.
Results: Superficial infection was seen in 1 (5.0%) and 2 (10.0%), in vancomycin category & group of control and variation was insignificant statistically (p=1.0). Deep infection was seen in 0 (0.0%) and 3 (15.0%), in vancomycin category and group of control, and variation was insignificant statistically (p=0.231). Wound complication was seen in 2 (10.0%) and 0 (0.0%), in vancomycin group and group of control, respectively and variation was insignificant statistically (p=0.487). Return to operating room was seen in 1 (5.0%) and 1 (5.0%), in vancomycin category and category of control, respectively and variation was insignificant statistically (p=1.0). Peri-prosthetic fracture was not reported.
Conclusions: Utilization of powder of vancomycin is safe and efficient way in preventing deep wound infection accompanying total hip arthroplasty but small sample size herein suggested need for further future studies to validate our results.

KEY WORDS: vancomycin powder, prevention of wound infection, total hip arthroplasty

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INTRODUCTION

When pathogenic organisms develop in a wound and cause both local symptoms and signs finally a systemic inflammatory reaction, causing surgical site infection [1]. A greater number of patient- or surgery-specific risk factors are associated with higher infection rates [2, 3]. Diabetes mellitus, rheumatoid arthritis, obesity, and smoking were risk factors for patients. Complications in association with total hip replacement which are till now very substantial include infection. During last thirty years, alternative management options have been introduced to enhance clearance of infection while keeping on joint function during therapy and enhance results of reimplantation. The best course of treatment is typically thought to involve removing the implant, performing a complete debridement, and then administering systemic and local antibiotic therapy using impregnated spacers. The disease's heterogeneity is one of the challenges in treating infected THA. Numerous bacteria types that are sensitive to different antibiotics, present a challenge for surgeons and medical professionals. Then, while juggling the patient's comorbidities, the reconstruction must be planned in the context of an aberrant soft tissue and bone state. The gold standard that is suggested appears to be challenging to apply to the total patients, and there is a dearth of excellent literature discussing alternatives [4]. In general, individuals who have contraindication for revision surgery are treated with suppressive antibiotics. This is typically brought on by severe or numerous medical comorbidities and people with short life spans. Recent research on the exclusive use of antibiotic therapy is few. Trebse et al. [5] conducted a prospective follow-up of twenty-four individuals with culture-confirmed infection. The only kind of treatment for seven of these individuals was combined antibiotic medication. Despite the fact that there were no recurrences over the three-year period of follow-up, this sample size is too little to get firm results. In patients with early type I and type III infections, surgical debridement combined with therapy using antibiotic and retention of implant may be taken into consideration. According to reports, the eradication rate ranges from 26 to 71% [6].

Table 1. Demographic characteristics and duration of follow up.

Characteristic	Vancomycin group, n = 20	Control group, n = 20	p
Age (years)			
Mean ±SD	59.05±10.02	60.35±8.15	0.655^{NS} (I)
Range	45 -78	44 -79	
Gender			
Male, n (%)	9 (45.0 %)	10 (50.0 %)	0.752^{NS} (C)
Female, n (%)	11 (55.0 %)	10 (50.0 %)	
BMI (kg/m²)			
Mean ±SD	26.85±5.11	27.05±4.81	0.899^{NS} (I)
Range	18 -36	18 -35	
Duration of follow up (months)			
Mean ±SD	9.00±3.36	9.85±2.37	0.361^{NS} (I)
Range	5 -15	6 -14	

n: number of cases, SD: standard deviation, BMI: body mass index, I: independent t-test, C: chi-square test, NS: not significant.

Table 2. Chronic medical illnesses and smoking

Characteristic	Vancomycin group, *n* = 20	Control group, *n* = 20	*p*
DM, *n* (%)	3 (15.0 %)	4 (20.0 %)	1.000^{NS} (Y)
HT, *n* (%)	8 (40.0 %)	9 (45.0 %)	0.749^{NS} (C)
IHD, *n* (%)	3 (15.0 %)	4 (20.0 %)	1.000^{NS} (Y)
COPD, *n* (%)	3 (15.0 %)	4 (20.0 %)	1.000^{NS} (Y)
Smoking, *n* (%)	11 (55.0 %)	12 (60.0 %)	0.749^{NS} (C)

n: number of cases, DM: diabetes mellitus, HT: hypertension, IHD: ischemic heart disease, COPD: chronic obstructive pulmonary disease, Y: Yates correction, C: chi-square test, NS: not significant.

Consider using an open strategy that includes thorough debridement and lavage. A profound periprosthetic joint infection (PJI) is one of the more severe surgical consequences. PJI risk is often estimated to be 1%. However, there is a lot of variation in this number in the research that is currently available, with numbers ranging from 0.57% to 2.23% [7]. An evaluation that is retrospective including 265 subjects who underwent hip arthroplasty that is total was carried out by Dial et al. [8]. They followed 137 of them in a group of vancomycin powder as they received it at moment of closure of the wound, but the initial 128 individuals in the group of control did not. They arrive at conflicting conclusions and suggested additional, larger sample size investigations. In Iraq, the information about the role of vancomycin powder in the protection against infection of wound in operations of hip replacement that is total is scares; therefore, the aim of the current study was to compare the results of use of vancomycin powder in the prevention of wound infection in operations of total hip replacement to a control group.

AIM

The aim of this research is to compare the results of use of vancomycin powder in the prevention of wound infection in operations of hip replacement that is total to a control group.

MATERIALS AND METHODS

The current comparative interventional investigation was done in the orthopedic unit in the surgical department belonging to Adiwaniyah teaching Hospital, Adiwaniyah Province, Iraq. The study enrolled 40 patients undergoing total hips arthroplasty during the period extending from January 2021 to January 2022. Patients with rheumatoid arthritis or any condition with immune suppression were excluded from the study. Patients were allocated in a random manner into two categories so that one of them were given vancomycin powder and served a study group; whereas, the other group received no such intervention and served as a control group. In the study group, patients underwent the following steps: after completion of the surgery, regular closure in layers was done; drain was inserted into the sub-muscular layers while vancomycin powder 1 gm was put in the subcutaneous layer before skin closure; the drain was closed for two hours and then reopened. Patients were followed up for a period ranging from 5 to 15 months. The following variables were

Table 3. Indications of total hip replacement

Characteristic	Vancomycin group, n = 20	Control group, n = 20	p
Osteoarthritis, n (%)	17 (85.0 %)	16 (80.0 %)	1.000 ^{NS} (Y)
Avascular necrosis, n (%)	3 (15.0 %)	4 (20.0 %)	1.000 ^{NS} (Y)

n: number of cases, Y: Yates correction, NS: not significant

Table 4. Outcome and complications

Characteristic	Vancomycin group *n* = 20	Control group *n* = 20	*p*
Superficial infection, *n* (%)	1 (5.0 %)	2 (10.0 %)	1.000 ^{NS} Y
Deep infection, *n* (%)	0 (0.0 %)	3 (15.0 %)	0.231 ^{NS} F
Wound complication, *n* (%)	2 (10.0 %)	0 (0.0 %)	0.487 ^{NS} F
Return to operating room, *n* (%)	1 (5.0 %)	1 (5.0 %)	1.000 ^{NS} Y
Peri-prosthetic fracture, *n* (%)	0 (0.0 %)	0 (0.0 %)	---

n: number of cases; Y: Yates correction; F: Fischer exact test; NS: not significant

taken into consideration: age, gender, body mass index (BMI), chronic medical illness, indications of operation and outcome and complications. Outcome measures included: superficial infection, deep infection, wound complication, return to operation room and peri-prosthetic fracture.

STATISTICAL ANALYSIS

Data were analyzed based on statistical package for social sciences (SPSS, version 16). The variable demonstration was done using percentage, counts, average, range and standard deviation. Independent samples t-test was applied to contrast means of two groups. Chi-square, Yeats correction and Fischer exact tests were used to compare proportions between groups when statistical assumptions were established. The level of significance in the study was at $p \leq 0.05$.

RESULTS

Demographic characteristics and duration of follow up are shown in table 1. Averages of age, body mass index and duration of follow up showed no statistical variation between vancomycin category and control group (p>0.05). No significant difference was also noticed in the frequency distribution of patients according to gender between vancomycin group and control group (p=0.752).

The rates of chronic medical illnesses and smoking are shown in table 2. There was no significant difference in the rates of diabetes mellitus, chronic obstructive pulmonary disease, essential hypertension, smoking and heart disease (p>0.05).

Indications of total hip replacement are shown in table 3. Osteoarthritis was the main indication as it accounted for 17 (85.0%) and 16 (80.0%) in vancomycin group and control group, respectively and it was followed by avascular necrosis which was accounted for 3 (15.0%) and 4 (20.0%), respectively. There was no significant variation in the rate of indications between vancomycin group and control group (p=1.0).

Outcome and complications are shown in table 4. Superficial infection was seen in 1 (5.0%) and 2 (10.0%), in vancomycin group and control group, respectively and variation was statistically insignificant (p=1.0). Deep infection was seen in 0 (0.0%) and 3 (15.0%), in vancomycin category and category of control, respectively and variation was statistically insignificant (p=0.231). Wound complication was seen in 2 (10.0%) and 0 (0.0%), in vancomycin category and group of control, respectively and variation was statistically insignificant (p=0.487). Return to operating room was seen in 1 (5.0%) and 1 (5.0%), in vancomycin category and group of control, respectively and variation was statistically insignificant (p=1.0), peri-prosthetic fracture was not reported.

DISCUSSION

Surgical site infection is an important concern to all surgeons because of significant morbidity linked to that particular complication [9-11]. Contaminations at the operative site have a substantial participation in mortality and morbidity in postoperative care. Numerous microbiological, patient-related, and procedure-related variables might increase the risk of surgical site infection. Optimizing patient variables and the use of a range of evidence-based pharmacologic and non-pharmacologic interventions are key components in the prevention of postoperative infection. Antimicrobial prophylaxis, which has been demonstrated to be successful at lowering the risk of surgical site infection, is at the forefront of these precautions [9]. Following

the use of spinal instrumentation, deep surgical site infections have been demonstrated to be reduced by vancomycin powder, according to extensive research in the spine literature [12, 13, 23, 24]. A recent study showing a decreased occurrence of PJI after revision TKA or THA utilizing vancomycin was published [14, 21, 22, 25]. Vancomycin's usefulness and safety during THA, however, are not well known. One of the problems specific to endoprosthetics is that the inclusion of vancomycin results in a higher rate of wear of the implanted body. This subject was tackled by a mechanical in-vitro study, but the results did not show higher rates of third body polyethylene wear after cyclic administration with the vancomycin that was added intra-articularly [15-17]. In this investigation we found that vancomycin powder was able to prevent deep infection rate and reduce superficial wound infection, but because of small samples size, the difference did not reach statistical significance. However, we found that sterile wound complications were more frequently encountered in study group when compared to control group; despite that, the difference was statistically not significant. In the study of Dial et al., [8] there was significant reduction in rate of deep wound infection following application of vancomycin powder; however, they noticed that formation of sterile seroma that require management surgically was more frequent in subjects given vancomycin powder [18-20].

CONCLUSIONS

In conclusion, the administration of powder of vancomycin is safe and efficient way in preventing deep wound infection accompanying total hip arthroplasty but the small sample size in this study suggested the need for further future studies to validate our results.

REFERENCES

1. Johnson R, Jameson SS, Sanders RD et al. Reducing surgical site infection in arthroplasty of the lower limb: A multi-disciplinary approach. Bone Joint Res. 2013;2(3):58-65, doi:10.1302/2046-3758.23.2000146. DOI
2. Gurkan I, Wenz JF. Perioperative infection control: an update for patient safety in orthopedic surgery. Orthopedics. 2006;29:329-339. doi: 10.3928/01477447-20060401-13. DOI
3. Moucha CS, Clyburn T, Evans RP, Prokuski L. Modifiable risk factors for surgical site infection. J Bone Joint Surg. 2011;60:398-404.
4. Senthi S, Munro JT, Pitto RP. Infection in total hip replacement: meta-analysis. Int Orthop. 2011;35(2):253-260. doi:10.1007/s00264-010-1144-z. DOI
5. Toms AD, Davidson D, Masri BA, Duncan CP. The management of peri-prosthetic infection in total joint replacement. J Bone Joint Surg Br. 2006;88:149-155. doi: 10.1302/0301-620X.88B2.17058. DOI
6. Trebse R, Pisot V, Trampuz A. Treatment of infected retained implants. J Bone Joint Surg Br. 2005;87(2):249-256. doi: 10.1302/0301-620X.87B2.15618. DOI
7. Phillips JE, Crane TP, Noy M et al. The incidence of deep prosthetic infections in a specialist orthopaedic hospital: A 15-year prospective survey. J Bone Joint Surg Br. 2006;88:943-8. doi: 10.1302/0301-620X.88B7.17150. DOI
8. Dial BL, Lampley AJ, Green CLm Hallows R. Intrawound Vancomycin Powder in Primary Total Hip Arthroplasty Increases Rate of Sterile Wound Complications. Hip Pelvis. 2018;30(1):37-44, doi:10.5371/hp.2018.30.1.37. DOI
9. Young PY, Khadaroo RG. Surgical site infections. Surg Clin North Am. 2014;94(6):1245-1264. doi: 10.1016/j.suc.2014.08.008. DOI
10. Reichman DE, Greenberg JA. Reducing surgical site infections: a review. Rev Obstet Gynecol. 2009;2(4):212-221.
11. Shakir A, Abate D, Tebeje F, Weledegebreal F. Magnitude of Surgical Site Infections, Bacterial Etiologies, Associated Factors and Antimicrobial Susceptibility Patterns of Isolates Among Post-Operative Patients in Harari Region Public Hospitals, Harar, Eastern Ethiopia. Infect Drug Resist. 2021;14:5015-5016. doi:10.2147/IDR.S329721. DOI
12. Kang DG, Holekamp TF, Wagner SC, Lehman RA. Intrasite vancomycin powder for the prevention of surgical site infection in spine surgery: a systematic literature review. Spine J. 2015;15:762–770. doi: 10.1016/j.spinee.2015.01.030. DOI
13. Otte JE, Politi JR, Chambers B, Smith CA. Intrawound vancomycin powder reduces early prosthetic joint infections in revision hip and knee arthroplasty. Surg Technol Int. 2017;30:284-289.
14. Bakhsheshian J, Dahdaleh NS, Lam SK et al. The use of vancomycin powder in modern spine surgery: systematic review and meta-analysis of the clinical evidence. World Neurosurg. 2015;83:816-823. doi: 10.1016/j.wneu.2014.12.033. DOI
15. Qadir R, Ochsner JL, Chimento GF et al. Establishing a role for vancomycin powder application for prosthetic joint infection prevention-results of a wear simulation study. J Arthroplasty. 2014;29:1449–1456, doi: 10.1016/j.arth.2014.02.012. DOI
16. Lazar H, Suwalski P, Lorusso R et al. Topical Vancomycin for Sternal Wound Infection Prophylaxis: Reinventing the Wheel All Over Again. Ann Thorac Surg. 2023;116(2):440-441. doi: 10.1016/j.athoracsur.2022.11.033. DOI
17. Premkumar A, Kolin DA, Farley KX et al. Projected Economic Burden of Periprosthetic Joint Infection of the Hip and Knee in the United States. J Arthroplasty. 2021;36:1484–1489.e3. doi: 10.1016/j.arth.2020.12.005. DOI

18. Garofalo R, Fontanarosa A, De Giorgi S et al. Vancomycin powder embedded in collagen sponge decreases the rate of prosthetic shoulder infection. J Shoulder Elbow Surg. 2023;32(8):1638–1644. doi: 10.1016/j.jse.2023.02.129. DOI
19. Harper KD, Park KJ, Brozovich AA et al. Otto Aufranc Award: Intraosseous Vancomycin in Total Hip Arthroplasty – Superior Tissue Concentrations and Improved Efficiency. J Arthroplasty. 2023;38:S11–S15. doi: 10.1016/j.arth.2023.04.028. DOI
20. Wong MT, Sridharan SS, Davison EM et al. Can Topical Vancomycin Prevent Periprosthetic Joint Infection in Hip and Knee Arthroplasty? A Systematic Review. Clin Orthop Relat Res. 2021;479(8):1655–1664. doi: 10.1097/CORR.0000000000001777. DOI
21. Peng Z, Lin X, Kuang X et al. The application of topical vancomycin powder for the prevention of surgical site infections in primary total hip and knee arthroplasty: A meta-analysis. Orthop Traumatol Surg Res. 2021;107(4):102741. doi: 10.1016/j.otsr.2020.09.006. DOI
22. Xu H, Yang J, Xie J et al. Efficacy and safety of intrawound vancomycin in primary hip and knee arthroplasty. Bone Joint Res. 2020;9:778–788. doi: 10.1302/2046-3758.911.BJR-2020-0190.R2. DOI
23. Liao S, Yang Z, Li X et al. Effects of different doses of vancomycin powder in total knee and hip arthroplasty on the periprosthetic joint infection rate: a systematic review and meta-analysis. J Orthop Surg Res. 2022;17(1):546. doi: 10.1186/s13018-022-03445-2. DOI
24. Martin VT, Zhang Y, Wang Z et al. A systematic review and meta-analysis comparing intrawound vancomycin powder and povidone iodine lavage in the prevention of periprosthetic joint infection of hip and knee arthroplasties. J Orthop Sci. 2024;29(1):165-176. doi: 10.1016/j.jos.2022.11.013. DOI
25. Cohen EM, Marcaccio S, Goodman AD et al. Efficacy and Cost-effectiveness of Topical Vancomycin Powder in Primary Cementless Total Hip Arthroplasty. Orthopedics. 2019;42:e430–e436. doi: 10.3928/01477447-20190321-05. DOI

CONFLICT OF INTEREST

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ORIGINAL ARTICLE

CONTENTS

Morphological condition of the skin following a 4-week opioid exposure in an experimental study

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ABSTRACT

Aim: The study aimed to determine the peculiarities of the micro- and ultrastructural organization of the skin under conditions of a four-week administration of an opioid to experimental animals.

Materials and Methods: The study material included skin samples of white rats with injected vascular beds, histological preparations, and ultrathin skin sections. The research methods involved injection techniques, histological analysis, electron microscopy, morphometric measurements, and statistical analysis.

Results: The results of the study revealed that after four weeks of nalbuphine administration to experimental animals, blood stasis was observed in the lumen of the capillaries and venules, along with perivascular edema and perivascular infiltrates consisting of neutrophils, lymphocytes, macrophages, and tissue basophils. The electron density of the nuclei and cytoplasm of the granular layer keratinocytes was reduced, keratinocytes in the stratum spinosum acquired a rounded shape, with some nuclei appearing shrunken and hyperchromatic, and their cytoplasm exhibiting vacuolization. In the reticular layer, thickened bundles of collagen fibers were observed, with localized swelling and fragmentation of the collagen fibers. Excessive formation of scales was noticed in the stratum corneum. The papillary layer of the dermis contained numerous mast cells and lymphocytes near blood vessels. The shape of sebaceous and sweat gland cells was altered, with swollen cytoplasm, and lymphohistiocytic infiltration was observed around them. A decrease ($p<0.05$) in the density of capillary loops in the subpapillary vascular plexus of the skin in the gluteal region of white rats after four weeks of nalbuphine administration, along with an increase ($p>0.5$) in the trophic activity index of the skin, confirms profound destructive changes in the vascular architecture of the skin.

Conclusions: Four weeks of nalbuphine administration induces irreversible pathological processes in all skin components.

KEY WORDS: skin, nalbuphine, opioids, experiment, morphology

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INTRODUCTION

In modern medical practice, opioids are widely used to manage pain in the postoperative period and to alleviate suffering of patients with oncological diseases [1-5]. However, the safety of opioid use and the impact on the structural organization of organs remains a controversial issue. Scientific literature includes research papers emphasizing the positive effectiveness of opioids, particularly nalbuphine [6]. Nevertheless, most studies highlight the negative impact of opioids on the body [7-10]. Moreover, it is essential to consider not only the medical but also the social problem. The number of individuals with opioid addiction, whose lives are persistently tied to opioid consumption, continues to grow [11-13]. Studies focusing on the effects of opioids on the immune system are of particular interest. Research findings indicate suppression of immune responses under opioid use [14], while some authors describe the development of an inflammatory reaction in response to opioid exposure [15]. Opioids have also been shown to cause destructive changes in skeletal tissue [16]. Only comprehensive experimental studies can elucidate the mechanisms of opioid action at the organ, tissue, and cellular levels [17]. A significant number of experimental and clinical studies are dedicated to examining the skin layers under various factors in both experimental and clinical settings [18, 19], as the skin is a complex organ that directly interacts with the external environment, performing barrier and protective functions, as well as helping maintain the internal equilibrium of the body. The skin is the largest human organ, continuously affected by exogenous and endogenous factors. Thus, the morphofunctional organization of the skin during prolonged opioid use is currently of a particular interest.

AIM

To determine the microstructural and ultrastructural features of skin organization under conditions of opioid administration to experimental animals for four weeks.

MATERIALS AND METHODS

The study was conducted on 25 sexually mature male white rats, aged 3 months, with an initial body weight of 160–180 g.

All animals were kept in the vivarium of Danylo Halytsky Lviv National Medical University. The experiments were conducted in compliance with the humane treatment requirements for laboratory animals as regulated by the Law of Ukraine "On the Protection of Animals from Cruelty" (No. 3447-IV, dated 21.02.2006) and the treaty of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (Strasbourg, 18.03.1986).

The research material included skin samples from white rats with injected vascular networks, histological preparations, and ultramicroscopic sections of the skin.

The modeling of prolonged opioid exposure in white rats was performed through daily intramuscular administration (once per day) of the narcotic analgesic nalbuphine into the right gluteal region. The administration followed this schedule: week 1: 8 mg/kg, week 2: 15 mg/kg, week 3: 20 mg/kg, week 4: 25 mg/kg. The impact of the opioid was studied in four weeks from the start of the experiment. The control group consisted of 10 rats that received a 0.9% sodium chloride solution.

Euthanasia was performed by overdose of intraperitoneal anesthesia with thiopental sodium (at a dose of 25 mg/kg of an animal's body weight).

For the injection of the vascular network in a rat's skin, an injectable gelatin microgel-based composite ink was used. A volume of 10–15 ml of the mixture was sufficient to fill the arterial network. After clearing the preparations in glycerin, the vascular segments of the skin were photographed under transmitted light using an MBI-1 microscope at magnifications of ×80 (objective 10, eyepiece 8) and ×160 (objective 20, eyepiece 8). The images were captured with an Olympus FE 210 digital camera.

For morphometric analysis of the vascular architecture of the rat's skin, measurements of the diameter of arterioles, capillaries, and venules were taken. The density of the exchange vessel walls (specifically capillaries) was determined by counting the number of vessels per unit of area (with the area of the microscope field of view chosen as the unit of measurement). Additionally, the trophic activity index of the tissue, or the diffusion radius, was assessed.

For histological examination, skin samples from the white rat's gluteal region were placed in Bouin's solution. The material was embedded in paraffin, and 5-7 μm thick sections were cut using a MC-2 sliding microtome. The histological sections were stained with hematoxylin and eosin, and benzopurpurin (diamino red) according to standard protocols. The preparations were studied under a light microscope (MBI-1) at magnifications of ×120 (objective 8, eyepiece 15), ×160 (objective 8, eyepiece 20), and ×600 (objective 40, eyepiece 15). Micropreparations were photographed using the "AverMedia" computer system.

Electron microscopy of the white rat's skin was performed using the UEMB-100K electron microscope at an accelerating voltage of 75 kV and magnifications of ×4000 to ×8000.

Statistical analysis of the research results was conducted on a computer using the "InStat" statistical software package for medical, biological, and epidemiological data processing.

RESULTS

After four weeks of nalbuphine administration to white rats, the lumen of the arterioles becomes uneven, with areas of both constriction and dilation. The venules expand, deform, and acquire irregular shapes, with some exhibiting aneurysmal bulges. Isolated aneurysmal sacculations in microvessels were observed. These changes result in alterations in the spatial configuration of the subpapillary and dermal vascular networks, as well as the subcutaneous venous plexus in the gluteal region of the white rat's skin following four weeks of nalbuphine administration.

The subpapillary vascular plexus of the white rat's skin at this stage of the experiment is characterized by the following morphometric parameters: the diameter of the intrapapillary capillary loop is 6.26±0.12 μm, the tissue trophic activity index of the skin is 22.47±2.44 μm, the diameter of the venules in the subpapillary vascular plexus is 59.65±0.83 μm, the diameter of the arterioles in the dermal vascular plexus increases to 55.18±4.18 μm, the diameter of the venules in the dermal vascular plexus increases to 142.31±2.46 μm, the diameter of the venules in the subcutaneous venous plexus increases to 158.57±1.98 μm.

After four weeks of the experiment, intensive keratinization processes take place, as evidenced by the thickening of the stratum corneum of the epidermis (Fig. 1).

In the stratum corneum, excessive formation of scales is observed. However, at this stage of the experiment, a reduction in folds and thinning of the epidermis are occasionally noted. The secretory sections and excretory ducts of the sweat glands are dilated. The papillary layer of the dermis is infiltrated with polymorphonuclear leukocytes. Edema of the reticular layer and hypodermis is observed, with loosening of collagen fibers in the reticular layer (Fig. 2).

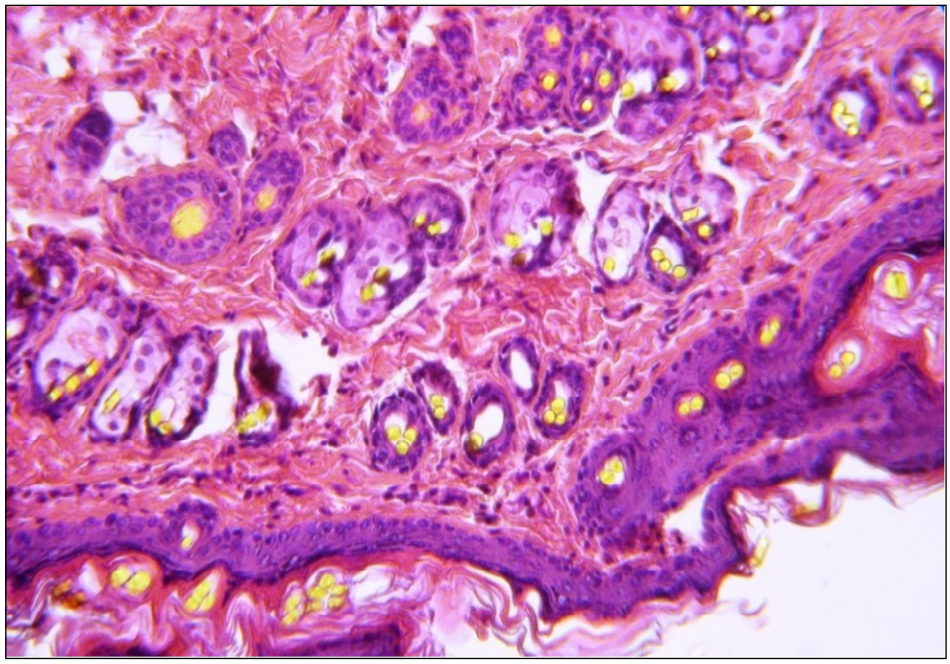

Fig. 1. Skin of the gluteal region of a white rat after 4 weeks of nalbuphine administration. Microphotograph. Staining with hematoxylin and eosin. Magnification: objective 8x, eyepiece 15x.

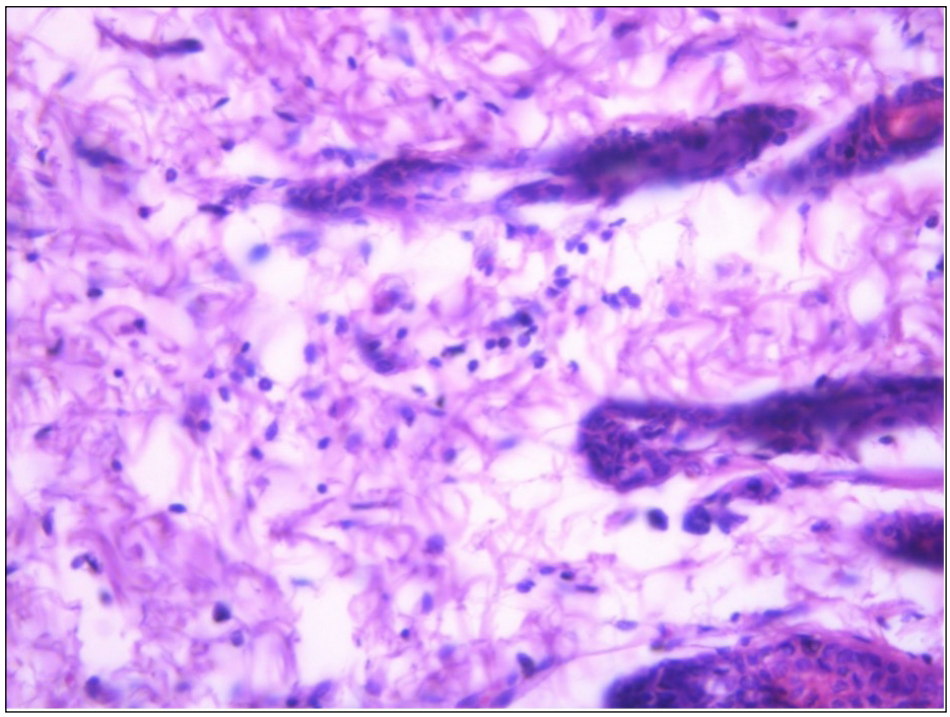

Fig. 2. Skin of the gluteal region of a white rat after 4 weeks of nalbuphine administration. Early atrophic changes in hair follicles and moderately pronounced round-cell infiltration in the hypodermis are observed. Microphotograph. Staining with hematoxylin and eosin. Magnification: objective 20x, eyepiece 15x.

After four weeks of nalbuphine administration to rats, changes in the vascular system of the skin were also observed. The lumens of the dermal blood vessels were dilated and filled with blood cells. The walls of some arterioles were thinned, endothelial swelling was noted. However, the walls of other arterioles were thickened, and the endothelial cells were unevenly distributed along the inner surface of the vessels. "Varicose" dilation of hypodermal venules and perivascular polymorphonuclear infiltrates were also observed.

After four weeks of the experiment, keratinocytes in the stratum corneum form continuous layers, merging with one another. In some areas, vacuole-like structures were detected between the cells. Dystrophic changes in the granular layer cells were predominantly manifested as nuclear pyknosis and cytoplasmic vacuolization (Fig. 3). Cells in the basal layer exhibited altered shapes and sizes, with condensed chromatin in some keratinocyte nuclei, absent nucleoli, invaginated nuclear envelopes, and vacuoles in the cytoplasm. Mast cell cytoplasm also displayed vacuolization, with hyperplastic and hypertrophic mitochondria showing widened spaces between cristae, the matrix is clarified.

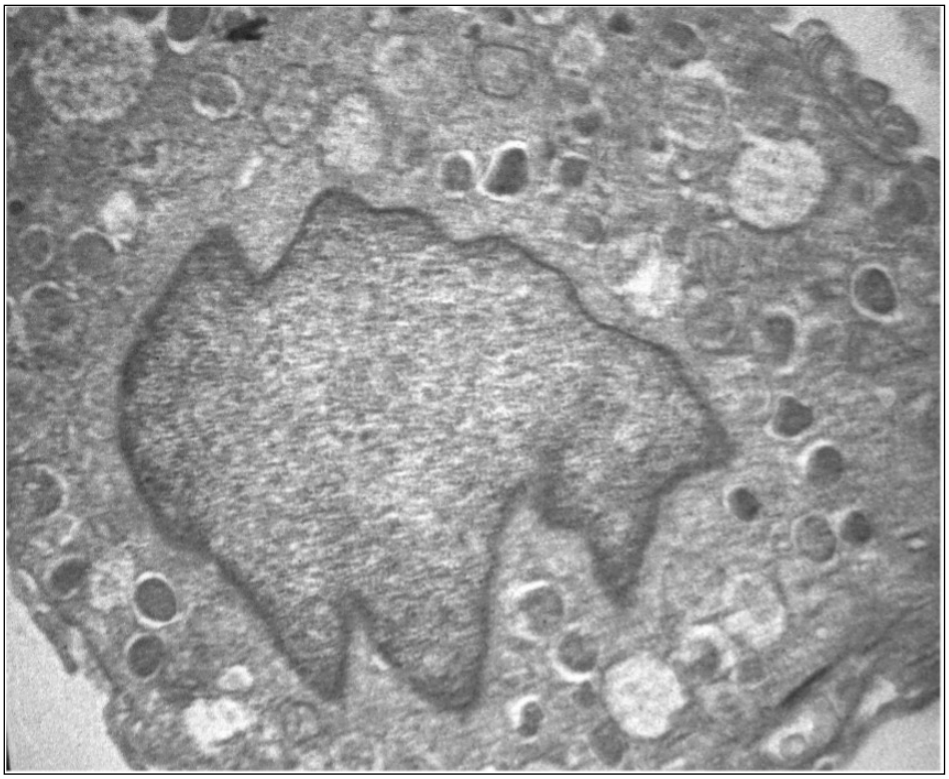

Fig. 3. Ultrastructure of the granular layer of the skin in the gluteal region of a white rat after 4 weeks of opioid administration. Electron micrograph. Magnification: x8000.

In the papillary layer of the dermis, a decrease in the number of connective tissue cells was observed, along with clearing and widening of the intercellular spaces, indicative of edema. Fibroblasts exhibited low electron density in their cytoplasm and nuclei. Peripheral areas of fibroblast cytoplasm showed vacuolization, with loosened membranes of the endoplasmic reticulum tubules, Golgi complex, and mitochondria. Disorganized ribosomes and polysomes were sporadically detected. Venules were congested with blood. The cells of the terminal secretory sections of sebaceous glands were hypertrophied, with enlarged nuclei, invaginated nuclear envelopes, hyperplastic mitochondria, and destroyed mitochondrial cristae.

Thus, profound changes in the epidermis and structural components of the dermis were observed after four weeks of nalbuphine exposure.

DISCUSSION

The results of our study confirmed the primary role of vascular reactions in response to opioid exposure [20]. Several studies in the specialized literature have been dedicated to investigating the mechanisms underlying reduced resistance of skin capillaries under various pathological conditions. The indicator of skin capillary permeability was the number of petechiae that appeared following the examination. Three degrees of skin vascular reactions were distinguished: first degree – on a slightly hyperemic skin, small and medium-sized hemorrhages were evenly scattered across the entire field; second degree – a hyperemic field with numerous small, medium, and large hemorrhages; third degree – confluent hemorrhages of various sizes scattered across the entire test field in unlimited numbers. The second and third degrees were considered a pathological permeability of the skin vessels [21, 22]. Our study confirms that the development of macro- and microangiopathies — such as skin hyperemia, the presence of small, medium, and large hemorrhages, arteriolar and capillary dilation, arteriolar tortuosity, thickening of arteriolar walls, thrombi in venules, enlargement of pericapillary zones, endothelial swelling, proliferation, loosening, and desquamation into the vascular lumen — under prolonged (four-week) nalbuphine administration can be considered the triggering mechanism for all subsequent profound changes in the structural organization of the skin. Changes in the skin at the cellular level identified in our study, combined with comparisons to scientific literature on the effects of nalbuphine on cells of other organs [23, 24], allow us to outline the patterns of cellular reorganization resulting from nalbuphine exposure. These patterns include changes in cell shape, disruption of cytoplasmic electron density, organelle destruction (particularly of mitochondria), apoptosis, karyopyknosis, nucleolar deformation or lysis, and invaginations of the nuclear and cytoplasmic membranes.

CONCLUSIONS

1. After four weeks of nalbuphine administration, a noticeable impact on the morphological condition

of the skin was observed. The arterioles and capillaries of the skin were dilated, with arterioles becoming tortuous. The diameter of the arterioles in the subpapillary arterial plexus increased to 28.62±1.07 μm (control: 22.24±0.73 μm), while the diameter of the intrapapillary capillary loop increased to 6.20±0.11 μm (control: 5.91±0.26 μm). A reduction ($p<0.05$) in the density of capillary loops in the subpapillary vascular plexus of the gluteal skin and an increase ($p>0.5$) in the trophic activity index confirm profound destructive changes in the vascular architecture of the skin. The loops of the vascular plexuses lost their regular delicate pattern, with microaneurysms in the arterioles and saccular dilations of the venules being identified.

2. In the skin micropreparations of experimental animals after four weeks of nalbuphine administration, phenomena of blood stasis in the lumens of capillaries and venules were observed, along with endothelial swelling, perivascular edema, and perivascular infiltrates consisting of neutrophils, lymphocytes, macrophages, and tissue basophils. The epidermal folds were slightly smoothed, while the cells of the stratum corneum appeared flat and elongated, occasionally losing their distinct contours and partially or completely merging with each other.
3. The electron density of the nuclei and cytoplasm of keratinocytes in the stratum granulosum was reduced. Keratinocytes in the stratum spinosum acquired a rounded shape (in contrast to the polygonal shape observed in the control). The nuclei of some keratinocytes were shrunken and hyperchromatic, with cytoplasmic vacuolization noted. In the reticular layer, thickened bundles of collagen fibers were observed, along with localized edema and loosening of collagen fibers. Excessive formation of scales was detected in the stratum corneum. The papillary layer of the dermis showed numerous mast cells and lymphocytes near blood vessels. The shape of cells in sebaceous and sweat glands was altered, with swollen cytoplasm, and lymphohistiocytic infiltration was observed around them.

REFERENCES

1. Slat S, Yaganti A, Thomas J, Helminski D. Opioid Policy and Chronic Pain Treatment Access Experiences: A Multi-Stakeholder Qualitative Analysis and Conceptual Model. J Pain Res. 2021;14:1161–1169. doi: 10.2147/JPR.S282228. DOI
2. Liu X, Hu J, Hu X, Li R. Preemptive Intravenous Nalbuphine for the Treatment of Post-Operative Visceral Pain: A Multicenter, Double-Blind, Placebo-Controlled, Randomized Clinical Trial. Pain therapy. 2021. doi: 10.1007/s40122-021-00275-8. DOI
3. Larsen D, Maani ChV. Nalbuphine. In: StatPearls. Treasure Island (FL) : StatPearls Publishing. 2021. https://pubmed.ncbi.nlm.nih.gov/30484997/ [Accessed 15 April 2024]
4. Béliveau A, Castilloux A-M, Tannenbaum C, Vincent Ph. Predictors of long-term use of prescription opioids in the community-dwelling population of adults without a cancer diagnosis: a retrospective cohort study. CMAJ OPEN. 2021;9(1):E96–E106. doi: 10.9778/cmajo.20200076. DOI
5. Beck TC, Hapstack MA, Dix TA. Therapeutic Potential of Kappa Opioid Agonists. Pharmaceuticals (Basel). 2019;12(2):95. doi: 10.3390/ph12020095.237. DOI
6. Davis MP, Fernandez C, Regel S et al. Does nalbuphine have a niche in managing pain? J. Opioid Manag. 2018;14(2):143–151. doi: 10.5055/jom.2018.0441. DOI
7. Seth P, Rudd RA, Noonan RK, Haegerich TM. Quantifying the Epidemic of Prescription Opioid Overdose Deaths. Am J Public Health. 2018;108(4):500–2. doi: 10.2105/AJPH.2017.304265. DOI
8. Taqi MM, Faisal M, Zaman H. OPRM1 A118G Polymorphisms and Its Role in Opioid Addiction: Implication on Severity and Treatment Approaches. Pharmgenomics Pers Med. 2019;12:361–368. doi: 10.2147/PGPM.S198654. DOI
9. Shekarchizadeh H, Khami MR, Mohebbi SZ et al. Oral health status and its determinants among opiate dependents: a cross-sectional study. BMC Oral Health. 2019;19(1):5. doi:10.1186/s12903-018-0691-3. DOI
10. Ciurylo W, Noh E. Opioid-associated amnestic syndrome. Cureus J. Med. Sci. 2021;13:16714. doi: 10.7759/cureus.16714. DOI
11. Kreek MJ, Reed B, Butelman ER. Current status of opioid addiction treatment and related preclinical research. Sci Adv. 2019;5(10):9140. doi: 10.1126/sciadv.aax9140. DOI
12. Hurtado I, Garcia-Sempere A, Peiro S, Sanfelix-Gimeno G. Increasing Trends in Opioid Use From 2010 to 2018 in the Region of Valencia, Spain: A Real-World, Population-Based Study. Front Pharmacol. 2020:11:612556. doi: 10.3389/fphar.2020.612556. DOI
13. Bedene A, van Dorp ELA, Faquih T, Cannegieter SC. Causes and consequences of the opioid epidemic in the Netherlands: a population-based cohort study. Scie Rep. 2020;10(1):15309. doi: 10.1038/s41598-020-72084-6. DOI
14. Plein LM, Rittner HL. Opioids and the immune system – friend or foe. Br J Pharm. 2018;175(14):2717–2725. doi: 10.1111/bph.13750. DOI
15. Alasmari F, Alasmari MS, Assiri MA et al. Liver metabolomics and inflammatory profiles in mouse model of fentanyl overdose treated with Beta-lactams. Metabolites. 2023;13:965. doi: 10.3390/metabo13080965. DOI

16. Vandenbosch M, Pajk S, Van den Bogaert W et al. Post-mortem analysis of opioids and metabolites in skeletal tissue. J. Anal. Toxicol. 2022;46:783–790. doi: 10.1093/jat/bkab095. DOI
17. Kirla KT, Erhart C, Groh KJ et al. Zebrafish early life stages as alternative model to study 'designer drugs': Concordance with mammals in response to opioids. Toxicol. Appl. Pharmacol. 2021;419:115483. doi: 10.1016/j.taap.2021.115483. DOI
18. Li J, Zeng X, Yang X, Ding H. Lycopene ameliorates skin aging by regulating the insulin resistance pathway and activating SIRT1. Food Funct. 2022;13(21):11307–11320. doi: 10.1039/d2fo01111e. DOI
19. Korolev AI, Fedorovich AA, Gorshkov AY et al. Structural and functional state of various parts of skin microcirculation at an early stage of hypertension in working-age men. Microvasc. Res. 2023;145:104440. doi: 10.1016/j.mvr.2022.104440. DOI
20. Feng T, Zeng S, Ding J et al. Comparative analysis of the effects of opioids in angiogenesis. BMC Anaesthesiol. 2021;21:257. doi: 10.1186/s12871-021-01475-7. DOI
21. Vereshchaka VV. Pathophysiological mechanisms of redusing resistance of skin capillaries in microcirculation impairments. Fiziol Zh (1994). 2000;46(6):116–118.
22. Vereshchaka V. Vplyv hipertonichnoyi khvoroby na rozvytok morfolohichnykh zmin shkiry: histokhimichne doslidzhennya. [The influence of hypertension on the development of morphological changes in skin: histochemical investigation]. Biolohiya. 2014;2(67):9–13. (Ukrainian)
23. Ivasivka KhP, Paltov YV, Kryvko YY. Vplyv molekuly opioyidnoho anal'hetyka na strukturu orhanu v mezhakh spektru diyi. [Influence of the opioid analgesic molecule on organ structure within the spectrum of action]. Svit nauky. 2019;2(9(49)):15–19. (Ukrainian)
24. Fik VB, Paltov YeV, Kryvko YuYa. Osoblyvosti ul'trastrukturnoyi orhanizatsiyi tkanyn parodontu pislya dvanadtsyaty tyzhniv opiodnoho vplyvu. [Ultrastructural organization features of periodontal tissues after twelve weeks of opiod influence]. Svit medytsyny ta biolohiyi. 2020;3(73):234–237. (Ukrainain)

CONFLICT OF INTEREST

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ORIGINAL ARTICLE

CONTENTS

The regional burden of acute pancreatitis in Ukraine: current trends in incidence, etiology, morbidity, gender distribution and mortality

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ABSTRACT

Aim: The aim of the study was to analyze trends in incidence, etiology, gender distribution, morbidity and mortality for acute pancreatitis and to determine whether they correspond to the world trends and to identify changes in trends under the influence of the circumstances of recent years, in particular the COVID-19 pandemic and the full-scale war unleashed by Russia on the territory of Ukraine.

Materials and Methods: The retrospective study of the prospectively maintained data base of the incidence rate dynamics, mortality, age and gender distribution of AP at the regional level in the period from 2011 to 2022 was done. The data were obtained from the statistics services of the regional healthcare department and two clinical hospitals, Vinnytsia, Ukraine.

Results: Over the past 12 years, 18715 patients with AP have been treated at the regional level. Annually, 1559±259 people require inpatient treatment for this pathology, with an average annual length of hospital stay of 10850±856 days. The incidence rate of AP in 2022 consisted 134,4 cases/100000 population. During the studied period, the population of the region decreased by 8,02%. On the other hand, there is an increase in cases of AP, namely, in 2022, the number of patients with acute pancreatitis reached 177,83% from the level of 2011. There was also an increase in overall mortality from AP from 1,7% to 2,2%.

Conclusions: During the 12-year period under study, against the background of a decrease in the average population at the regional level, there was a tendency for the incidence and mortality of AP to increase.

KEY WORDS: acute pancreatitis, etiology, incidence rate, age distribution, gender distribution

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INTRODUCTION

Acute pancreatitis (AP) remains an urgent problem of modern medicine. Total mortality in acute pancreatitis ranging from 3,9% to 9,7% [1,2]. Mortality in sever acute pancreatitis is significantly higher and reaches up to 30% in patients with infected necrosis [3,4]. Despite the global trend towards a constant increase in the incidence of acute pancreatitis in the world, there are differences between the incidence rates of this pathology both between continents and within the continent [5-8].

Understanding the geographical features of the burden and trends in different countries of the world will help to develop effective preventive methods. There is an increasing number of studies showing the impact of socio-economic, ethnic, and cultural differences on various factors in the development of pancreatitis [9-11].

A 2022 meta-analysis, which included the results of 34 studies, demonstrated a steady increase in the incidence of acute pancreatitis over the past 56 years in most countries of the Western world [12]. For the countries of North America, the incidence rate of acute pancreatitis is high and is 34 cases of acute pancreatitis per 100000 population per year, for Europe the overall incidence rate is 29 cases of acute pancreatitis per 100000 population, which varies in different countries [13], and according to the 2016 meta-analysis in Europe, this indicator was 33,7 cases of acute pancreatitis per 100000 population [14]. In the 10-year literature we analyzed, we did not find clear data on the incidence of acute pancreatitis among population of Ukraine.

However, in our opinion, the influence on many factors, including epidemiological factors related of the COVID-19 pandemic, long-term restrictions on the moment of associated with lockdown, the full-scale war caused by the Russian Federation in Ukraine, internal migration of population, related with this are significant influencing factors on the

general incidence rates of many diseases, including acute pancreatitis.

AIM

The aim of the study was to analyze trends in incidence, etiology, gender distribution, morbidity and mortality for acute pancreatitis and to determine whether they correspond to the world trends and to identify changes in trends under the influence of the circumstances of recent years, in particular the COVID-19 pandemic and the full-scale war unleashed by Russia on the territory of Ukraine.

MATERIALS AND METHODS

At the first stage of our research the retrospective study of morbidity, mortality, gender distribution, etiology of acute pancreatitis for 12 years at the Vinnytsia region, Ukraine, was carried out on the basis of the data from the statistics department of the regional health care department of the Vinnytsia region.

At the second stage of our study, an analysis of data on incidence, etiology, gender distribution, and mortality in acute pancreatitis was conducted based on a prospectively maintained database. This database includes medical records of hospitalized patients who received treatment from 2017 to 2022 in two medical institutions of the city. These institutions belong to secondary and tertiary healthcare centers, providing medical care to the majority of the city's patients. In total 677 patients were treated for acute pancreatitis in the period from 2017 to 2022 on the basis of the Vinnytsia city clinical emergency hospital and Vinnytsia regional Pirogov memorial clinical hospital and were prospectively included in the study. All patients in hospitalization gave their consent to the processing of personal data and data obtained during their examination and treatment. The diagnosis of acute pancreatitis was formulated in accordance with the recommendations of Atlanta 2012, the diagnosis of acute postoperative pancreatitis was formulated in accordance with the criteria of the International research group on pancreatic surgery (ISGPS) 2022 [15].

The patients data were entered in tabular form divided into several groups: demographic (age, gender, place of residence), etiological (the reason for the development of AP was indicated), anamnestic (how much time it took from the moment of the first symptoms to hospitalization in a hospital), the main vital indicators during hospitalization (pulse rate, blood pressure, saturation, heart rate, body temperature, diuresis), laboratory indicators, which were determined on the day of hospitalization, as well as on the 3rd, 5th, 7th, 9th, and 11th days of hospital stay, imaging methods (esophagogastroduodenoscopy, ultrasound examination of the abdominal organs and chest, radiological examination of the abdominal organs and chest, computer tomography of the abdominal organs and chest), clinical indicators (severity of the disease, the presence of complications of AP, the presence of concomitant pathology, the treatment performed). Among the laboratory indicators, routine indicators were determined: hemoglobin, blood sugar, leukocyte level and leukocyte formula, hematocrit, erythrocyte sedimentation rate, total protein level, total bilirubin level, serum/urine amylase, urine diastase, amylase/diastase of drainage fluid, electrolytes (sodium, potassium, calcium, chlorine), alanine aminotransferase, aspartate aminotransferase, urea, creatinine, platelet level, prothrombin index, plasma fibrinogen/fibrin.

Determination of the etiological factor of AP was carried out on the basis of a carefully collected anamnesis. When drinking alcohol on the eve of the disease, the genesis of the disease was interpreted as alcoholic. The biliary etiology of AP does not have a specific biochemical marker, so it was interpreted with the visualization of calculi in the gallbladder and/or ducts, the presence of biliary colic attacks in the anamnesis, dysfunction of the sphincter of Oddi. In the modern generally accepted classification of AP according to the recommendations of Atlanta 2012, there is no alimentary genesis of AP. This may be due to the fact that nutritional factors closely interact with other etiological factors, such as alcohol or metabolic disorders, which makes it difficult to classify them separately. However, we consider that this etiological form of AP is important, so we signled it separately. Therefore, the consumption of a large amount of fatty, fried, spicy food on the eve of the disease was interpreted as an alimentary factor. If in the anamnesis the patients noted the simultaneous consumption of alcohol and fatty/fried food, in such a case the etiological factor was interpreted as alimentary-alcoholic. Postoperative pancreatitis was treated according to the classification system proposed in 2022 by the international study group on pancreatic surgery (ISGPS). In patients with polytrauma, the development of AP was interpreted as post-traumatic. A rare cause of AP was the taking of certain medications by patients. The presence of a stress factor in the absence of all other causative factors was interpreted as the psychoemotional genesis of AP. In the absence of visible causative factors in the anamnesis, the etiological factor was interpreted as of unknown etiology.

All patients underwent a comprehensive clinical and laboratory examination, esophagogastroduodenoscopy, X-ray examination of the chest and abdominal organs, and computerized tomography of the abdominal and chest cavities, if necessary. Among the imaging methods during hospitalization, all patients underwent ultrasound examination of the abdominal organs, which was also performed during the inpatient treatment of patients in dynamics. If necessary, an ultrasound examination of the chest cavity was performed. Computed tomography of the abdominal organs and retroperitoneal space, enhanced by intravenous contrast, was performed in all patients with severe pancreatitis, as well as in doubtful cases during diagnosis, when infection of fluid accumulations is suspected.

The main criteria for including patients in the group were:

1. The patient's age ≥ 18 years on the day of signing the informed consent;
2. Women of reproductive age, in whom pregnancy is excluded;
3. Patients must have a diagnosis of acute pancreatitis of one of the following etiologies: alcoholic, alimentary, biliary, postoperative (including ERCP-induced), post-traumatic, drugs-induced, of unknown etiology;
4. Patients must have at least two of the following three symptoms of pancreatic inflammation (according to the criteria for the diagnosis of acute pancreatitis, according to the Atlanta guidelines, 2012): abdominal pain corresponding to the disease, biochemical signs of pancreatitis (serum amylase and/or lipase more than three times the upper limit of normal), characteristic imaging data of the abdominal cavity [15].
5. Patients with postoperative pancreatitis should have an increase in the level of serum amylase in the first 0-2 days of the postoperative period, corresponding clinically significant signs of acute pancreatitis and radiological changes corresponding to acute inflammation of the pancreas or its remnant (according to the criteria of the International research group on pancreatic surgery (ISGPS), 2022) [16].
6. Written, voluntary, signed informed consent must be obtained from the subject or a legally authorized representative in accordance with local regulations for the processing of information and data obtained in the process of examination and treatment. The subject or legally authorized representative must be able to read and understand the informed consent form.

Exclusion criteria:

1. The age of patients at the time of hospitalization is less than 18 years;
2. Women who are pregnant;
3. The diagnosis of acute pancreatitis indicated in the medical record does not meet the criteria for diagnosis Atlanta, 2012;
4. A serious disorder of the immune system, for example: known absolute neutropenia (absolute number of neutrophils < 500 cells/μL), a known infection caused by the human immunodeficiency virus (HIV), chemotherapy or radiation in the past 3 months;
5. A positive test for COVID-19 at the time of hospitalization or during the hospital stay.

Patient data were entered into the prospectively supported database in Excel. Patients of the study cohort were divided into groups according to the following criteria: sex distribution (men and women), etiology of the disease (nutritional, alcohol, biliary factor, postoperative pancreatitis, post-traumatic, drug, stress factor or unknown etiology), severity of the disease according to the Atlanta 2012 classification (mild course, moderately severe, severe), morphological form of the disease (edematous, aseptic necrotic, infected necrotic), presence of complications (with and without complications), treatment outcomes (survived or died).

Statistical analysis of the results was performed using SPSS version 24.0 software. Data visualization was performed using the R software package version 4.3.3. The normality of the data distribution was assessed using the Shapiro-Wilk test (W-test). For normally distributed data (p-value from the W-test > 0,05), the mean (M) ± standard deviation (σ) was used. Such data includes patient age, length of stay, and other quantitative variables. A significant part of the data, including the prevalence of etiologic factors, complication rates, mortality rates, and some others, was presented as percentages for the convenience of comparing categorical variables and visualizing their distribution between patient groups.

If the data were normally distributed, a parametric t-test for independent samples was used. This test allowed us to assess the presence of statistically significant differences between the mean values in two independent groups (e.g., patient age). Categorical variables (e.g., etiologic factors, disease severity, presence or absence of complications) were analyzed using Pearson's χ^2 test to determine whether there were statistically significant differences in the distribution of variables between groups.

The analysis of dynamic series was conducted to assess changes in the incidence of acute pancreatitis

during the study period. To do this, the following indicators were calculated: absolute increase/decrease – to assess changes in the number of cases, increase/decrease rates – to assess the relative change in morbidity compared to the previous period, and the fixed-base index – to compare changes over years with a fixed base (2011) to determine morbidity trends in the region.

Results with a p-value of less than 0,05 were considered statistically significant.

RESULTS

Over the past 12 years, 18715 patients have received inpatient treatment for AP in the Vinnytsia region. Annually 1559±259 people require inpatient treatment due to this pathology with the average annual hospital stay 10850±856 days. The incidence rate of AP in 2022 consisted 134,4 cases/100000 population.

The dynamics of the population and the number of patients with acute pancreatitis at the regional level in the period from 2011 to 2022 are shown in graph. There is a significant increase in the incidence of acute pancreatitis during this period against the background of a decrease in the population (Fig. 1).

Changes in the absolute number of the population, cases of acute pancreatitis and growth/decrease rates during 2011-2022 are shown in Table 1. During the study period, there was a steady decline in the population. On average, the population decreased by 12-14 thousand people annually, with an acceleration of the decline in the following years. In the first years, such as 2012 and 2013, the population decline rate was the lowest – about -0,43% and -0,44%, respectively. The largest decline occurred in 2022, when the population decreased by 19,6 thousand people and the highest rate of population decline was observed – -1,28%. It is also worth noting that since 2017, the population decline has become more noticeable, from 11,8 thousand in 2017 to almost 20,0 thousand in 2022.

As for the change in the absolute number of cases of acute pancreatitis, the number of patients with acute pancreatitis increased from 1141 in 2011 to 2029 in 2022 (Table 1). During the entire study period, there were only three years when the number of cases of acute pancreatitis decreased, in particular in 2016 (-32 patients), 2017 (-14 patients), and the largest drop occurred in 2018, when the number of patients decreased by 199 people. In 2020-2022, the number of patients with acute pancreatitis increased sharply, with the largest increase (+254 patients) in 2021. Regarding the growth rate of the number of patients with AP, the highest growth rates were observed in 2014 (+16,21%) and 2021 (+16,30%), indicating a significant increase in the number of patients with AP in these years. The largest decrease in the number of patients with AP occurred in 2018 (-11,81%), indicating a sharp decrease in the number of patients (Table 1).

The analysis of the table 2 with dynamic indices (2011 = 100%) shows a steady decline in the population every year. In 2022, the population amounted to 91,98% of the 2011 level, which indicates a significant reduction in its size. Throughout the entire observation period, there was a stable downward trend in population size.

In contrast to the population, the number of patients with acute pancreatitis has increased significantly over the entire observation period (Table 2). The dynamics index shows that in 2022 the number of patients reached 177,83% of the 2011 level. Moreover, until 2018, the number of patients had slight fluctuations, with some declines. However, since 2020, there has been a sharp increase, especially in 2021 and 2022.

Regarding the dynamics of the number of surgical interventions for acute pancreatitis in patients at the regional level, the overall trend is unstable, with fluctuations in the proportion of operated patients during this period. In particular, in 2011-2013, there was an increase in the proportion of operated patients to about 4% of all patients with AP. From 2014 to 2015, there was a significant decrease in the proportion of operated patients with AP to about 2%, after which this figure gradually increased again in 2016-2019. In 2020, there was a significant peak when the proportion of operated patients reached about 5%. Since 2021, the proportion of operated patients with AP has been decreasing, and in 2022 the lowest point of the graph is observed, which is less than 3% (Fig. 2).

Analysis of the database of 677 patients who were treated for acute pancreatitis in two hospitals during 2017-2022 found that among the study cohort of patients there were 411 (60,7%) men and 266 (39,3%) women. The average age of the patients was 49,99±13,38 years. Men with acute pancreatitis were significantly younger than women: the average age of men was 47,34±14,32 years, women – 54,15±16,31 years ($p<0,05$). Only 9,9% (67) of patients were hospitalized early from the onset of the disease – up to 6 hours. The vast majority of patients – 90,1% (610) were hospitalized 6 hours after the onset of the disease (Table 3).

The length of the hospital stay depended on the severity of the disease, the presence of complications, concomitant pathology and varied from several days to several months, which can explain the wide confidence interval of this indicator – 10,77 ± 6,65 days.

The classification of acute pancreatitis into mild, moderate and severe forms of the course by severity

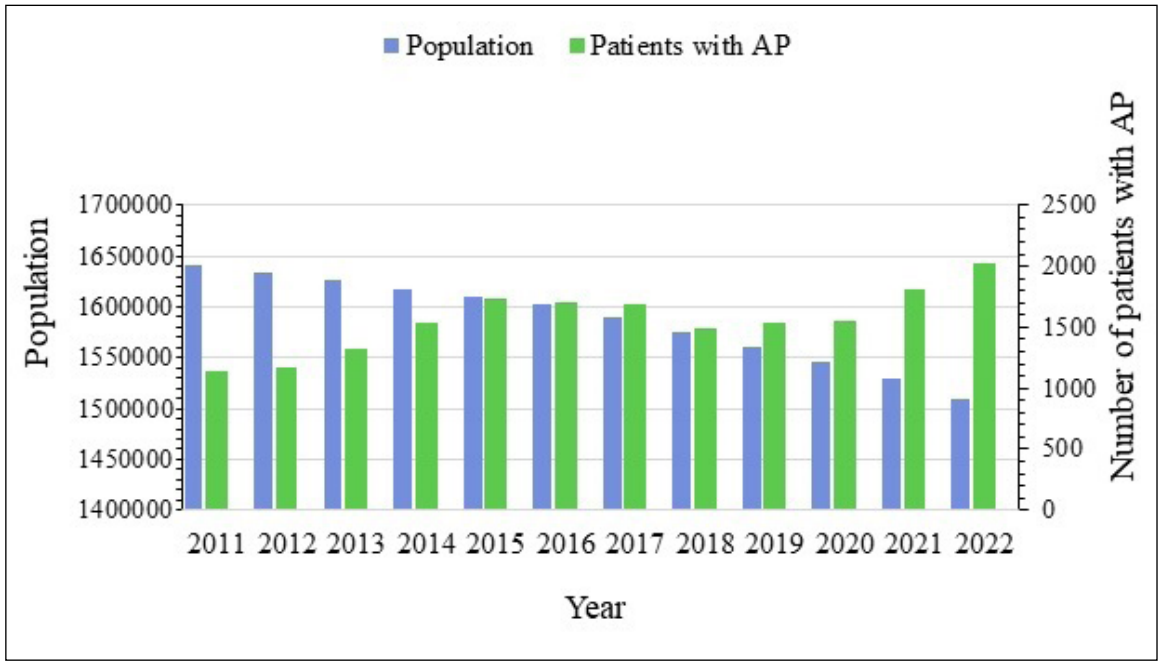

Fig. 1. Dynamics of the population and number of patients with acute pancreatitis at the regional level in 2011-2022.

Table 1. Dynamics of the number of population and patients with acute pancreatitis in 2011-2022 in absolute terms and their growth/decrease rates at the regional level

Years	Population (thsd)	Absolute increase / decrease (thsd)	Growth rate (%)	Patients with acute pancreatitis (persons)	Absolute increase / decrease (persons)	Growth rate (%)
2011	1641,2	-	-	1141	-	-
2012	1634,2	-7,0	-0,43%	1168	+27	+2,37%
2013	1627,0	-7,2	-0,44%	1326	+158	+13,53%
2014	1618,0	-9,0	-0,55%	1541	+215	+16,21%
2015	1610,6	-7,4	-0,46%	1732	+191	+12,40%
2016	1602,2	-8,4	-0,52%	1700	-32	-1,85%
2017	1590,4	-11,8	-0,74%	1686	-14	-0,82%
2018	1575,8	-14,6	-0,92%	1487	-199	-11,81%
2019	1560,4	-15,4	-0,98%	1535	+48	+3,23%
2020	1545,4	-15,0	-0,96%	1558	+23	+1,50%
2021	1529,1	-16,3	-1,05%	1812	+254	+16,30%
2022	1509,5	-19,6	-1,28%	2029	+217	+11,98%

was performed according to the criteria of the Atlanta 2012 classification. More than half of all patients had a mild form of acute pancreatitis – 52,6% (356) of cases, which included only the edematous morphological type of the disease. In 28,4% (192) of patients, acute pancreatitis had a moderate severity of the course and was represented in the vast majority by an edematous morphological form – 69,8% (134) of cases, in 29,2% (56) of cases – by an aseptic necrotic form, and in 1,0%(2) – infected necrotic form. A severe form of acute pancreatitis developed in 129 (19,0%) patients and was represented by an edematous form of the disease in 9,3% (12) cases, an aseptic necrotic form in 57,4% (74) cases, and an infected necrotic form in 33,3% (43) of cases.

According to the development of different morphological forms in different age ranges, the distribution is as follows: the edematous form of acute pancreatitis affected all age categories of patients from 18 to 88 years. The more severe the course of acute pancreatitis, the in later age it developed in patients. In particular, with the aseptic necrotic form, the age of the patients varied from over 20 years old to 88 years old. For the infected necrotic form, the age range of patients started after 30 years and up to 84 years (Fig. 3).

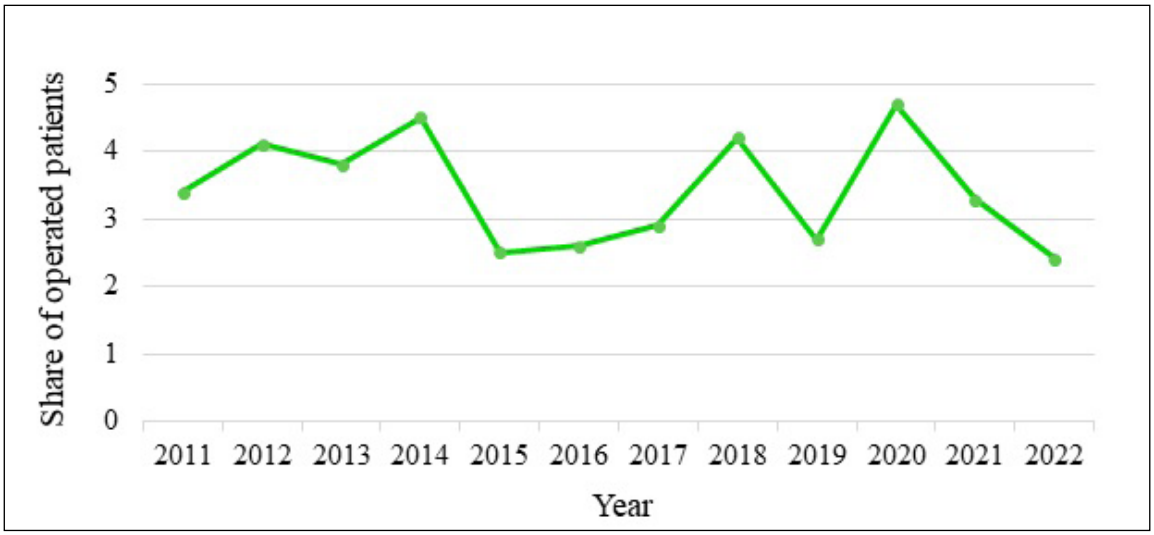

Fig. 2. Dynamics of the share of operated patients with acute pancreatitis at the regional level in 2011-2022

Table 2. Dynamics of the number of population and patients with acute pancreatitis with a fixed base (2011) at the regional level

Years	Population (thsd)	Dynamic index with fixed base (2011 = 100%)	Patients with acute pancreatitis (persons)	Dynamic index with fixed base (2011 = 100%)
2011	1641,2	100,00%	1141	100,00%
2012	1634,2	99,57%	1168	102,37%
2013	1627,0	99,13%	1326	116,21%
2014	1618,0	98,59%	1541	135,06%
2015	1610,6	98,14%	1732	151,80%
2016	1602,2	97,62%	1700	148,99%
2017	1590,4	96,90%	1686	147,77%
2018	1575,8	96,02%	1487	130,32%
2019	1560,4	95,08%	1535	134,53%
2020	1545,4	94,16%	1558	136,55%
2021	1529,1	93,17%	1812	158,81%
2022	1509,5	91,98%	2029	177,83%

The genesis of acute pancreatitis differed significantly in the groups by gender and severity of the course. Thus, in women, the dominant factors of acute pancreatitis, regardless of the severity group, were alimentary and biliary, which together accounted for 61,3% (163). In the group of women with a mild course of acute pancreatitis, ERCP-induced pancreatitis occurred more often than in men – 13 cases and 4 cases, respectively ($p<0,05$). In men, the biliary factor was represented to a lesser extent than in women in all three severity groups. On the other hand, the dominant factors of acute pancreatitis in men in all three severity groups were food and alcohol – 61,8% (254) (Fig. 4).

Among all 677 patients with acute pancreatitis, there were 59 (8,7%) deaths, of which 31 (52,5%) were men, 28(47,5%) were women. The age distribution of fatal cases is characterized by a wide range – fatal cases from acute pancreatitis occurred in patients of both sexes from 20 to 80 years of age. The vast majority of fatal cases occurred in patients with alimentary and alcoholic genesis of the disease – 62,7%(37). The alcoholic acute pancreatitis occurred most frequently in patients from 30 to 60 year age groups in both lethal and survival cohorts. The age range of surviving patients in most cases was also between 30 and 60 years old, that is, working age, which emphasizes the socio-economic burden that this disease has on society (Fig. 5).

The reason of acute pancreatitis, such as post-traumatic, postoperative and ERCP-pancreatitis deserves special attention. There was gender variability too: in men, post-traumatic pancreatitis significantly prevailed, while in women, postoperative genesis and ERCP-induced factor prevailed. In particular, men have post-traumatic pancreatitis in 0,9%(4), postoperative

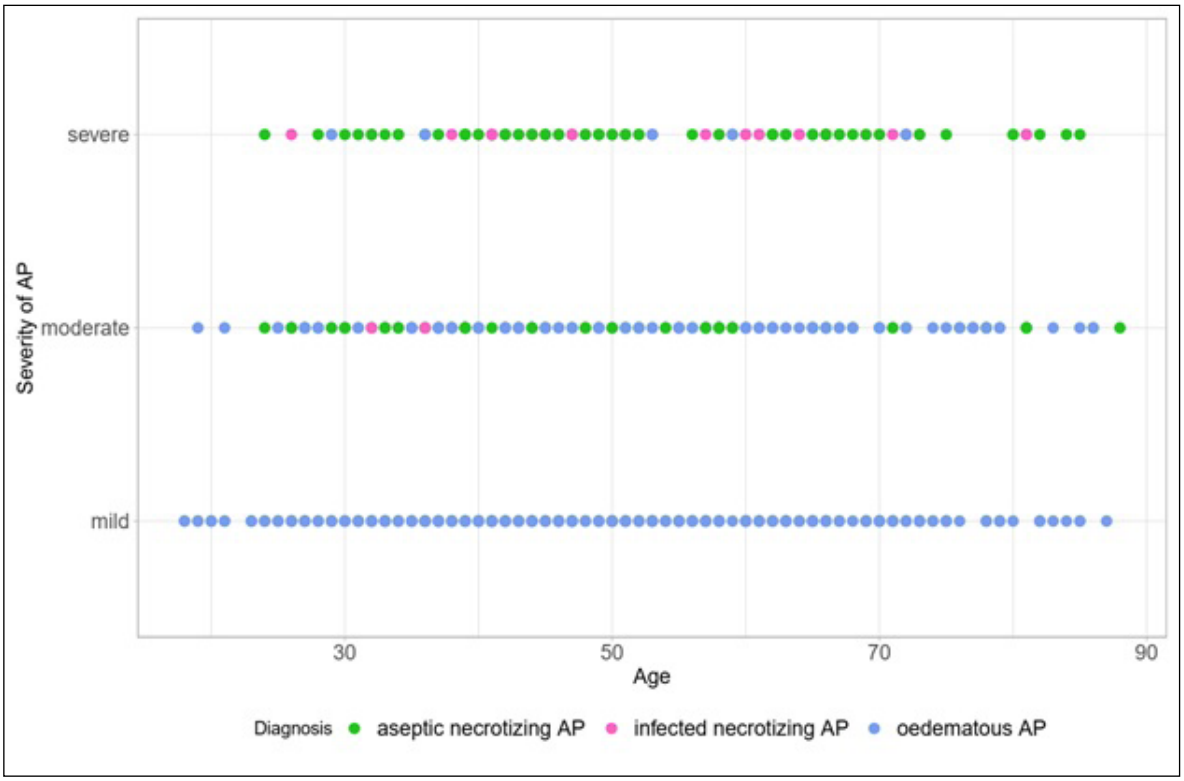

Fig.3. Distribution of patients of the study cohort with acute pancreatitis depending on age, severity of acute pancreatitis and morphological form of the disease.

pancreatitis – in 3,9%(16), ERCP – in 1,7%(7). There was no post-traumatic pancreatitis in women, instead, postoperative pancreatitis developed in 4,3%(11) of cases, and ERCP-induced pancreatitis – in 4,3%(11).

By gender and age, the distribution among patients of study cohort with acute pancreatitis in the general group was as follows: in the group of surviving patients, men dominated – 380 (61,5%), whose average age was 47,02±14,45 years. There were less women than men – 238 (38,5%), but their average age was higher than men and amounted to 53,02±16,55 years ($p<0,05$). In the group of patients who died, more than half of the cases were also men – 31 (52,5%), their average age was lower than the average age of women who died – 49,76±13,24 years and 61,46±12,6 years, respectively ($p<0,05$). So, in the group of men over the age of 50, a decrease in both morbidity and mortality from acute pancreatitis was noted, whereas in women over 50, an increase in both indicators was noted (Fig. 6).

The vast majority of fatal cases occurred in patients with the necrotic form of the disease – 56(94,9%), but there were also 3(5,1%) fatal cases in patients with the edematous form of the disease. The cause of death in the early stage was the development of enzyme endotoxemia and multiple organ failure. Aseptic necrotic form was the cause of death in more than half of all deceased patients with acute pancreatitis – 38 (64,4%) cases, infected necrotic form was the cause of death due to septic complications in 18(30,5%) cases (Fig. 7).

249 (36,8%) of all patients with acute pancreatitis developed complications, both early and late. In 72,3%(180/249) of them it was a combination of several complications simultaneously. According to the number of complications, pleurisy was the most common – 80 cases, fluid accumulation – 59 cases, peritonitis – 37 cases. Among purulent complications of acute pancreatitis, phlegmon of the retroperitoneal space developed in 25 cases, parapancreatic abscess – in 14 cases. Pancreatic pseudocyst developed in 31 cases. The development of pancreatogenic diabetes mellitus, as a result of the destruction of pancreatocytes and the impossibility of their endocrine function, occurred in 14 patients. Due to a severe general condition, 89(13,1%) patients with acute pancreatitis required hospitalization in the intensive care unit and resuscitation (Table 3).

DISCUSSION

CHANGES IN THE POPULATION AND THE INCIDENCE OF ACUTE PANCREATITIS AT THE REGIONAL LEVEL IN 2011-2022

This study analyzed the population and its incidence of acute pancreatitis at the regional level during 2011-2022. According to our estimates, a 12-year temporal

Table 3. Baseline characteristics upon admission of patients of the study cohort with acute pancreatitis (n=677)

Output data	
Age, years, M ± SD	49,99 ± 13,38
Gender, male/female	411\266
Duration of inpatient treatment, days, M ± SD	10,77 ± 6,65
Time from the moment of the first symptoms to the hospitalization of the patient	
• Until 6 Hours	67(9,9%)
• 6-24 hours	212(31,3%)
• 24-48 hours	184(27,2%)
• > 48 hours	214(31,6%)
Etiology	
• Alimentary	254(37,5%)
• Alcoholic	71(10,5%)
• Alcoholic-alimentary	24(3,5%)
• Biliary	126(18,6%)
• Drugs-induced	9(1,3%)
• Postoperative	27(3,9%)
• Posttraumatic	4(0,6%)
• ERCP-induced	25(3,7%)
• Provoked by psycho-emotional stress	3(0,4%)
• Of unknown etiology	134(19,8%)
The result of treatment	
Patients who survived	618(91,3%)
Patients who died	59(8,7%)
Morphological type of acute pancreatitis (Revised Atlanta classification, 2012)	
Oedematous interstitial acute pancreatitis	502(74,2%)
Necrotizing acute pancreatitis	175(25,8%)
• Aseptic necrotic	130 (0,74)
• Infected necrotic	45 (0,26)
Severity (Revised Atlanta classification, 2012)	
Mild	356(52,6%)
Moderate	192(28,4%)
Sever	129(19,0%)
The presence of concomitant pathology, the number of patients	586(86,6%)
Complication of acute pancreatitis	
There are no complications	428(63,2%)
Complication	249(36,8%)
• Fluid accumulations	59
• Pleurisy	80
• Peritonitis	37
• Postoperative pancreatic fistula	2
• Phlegmon of the retroperitoneal space	25
• Pancreatic pseudocyst	31
• Parapancreatic abscess	14
• Pancreatogenic diabetes mellitus	14
• Other complications	154
Hospitalization to the department	
Surgery	582(86,0%)
Intensive care and resuscitation	89(13,1%)
Another department	6(0,9%)

M±SD, where M is the mean, SD is the standard deviation.

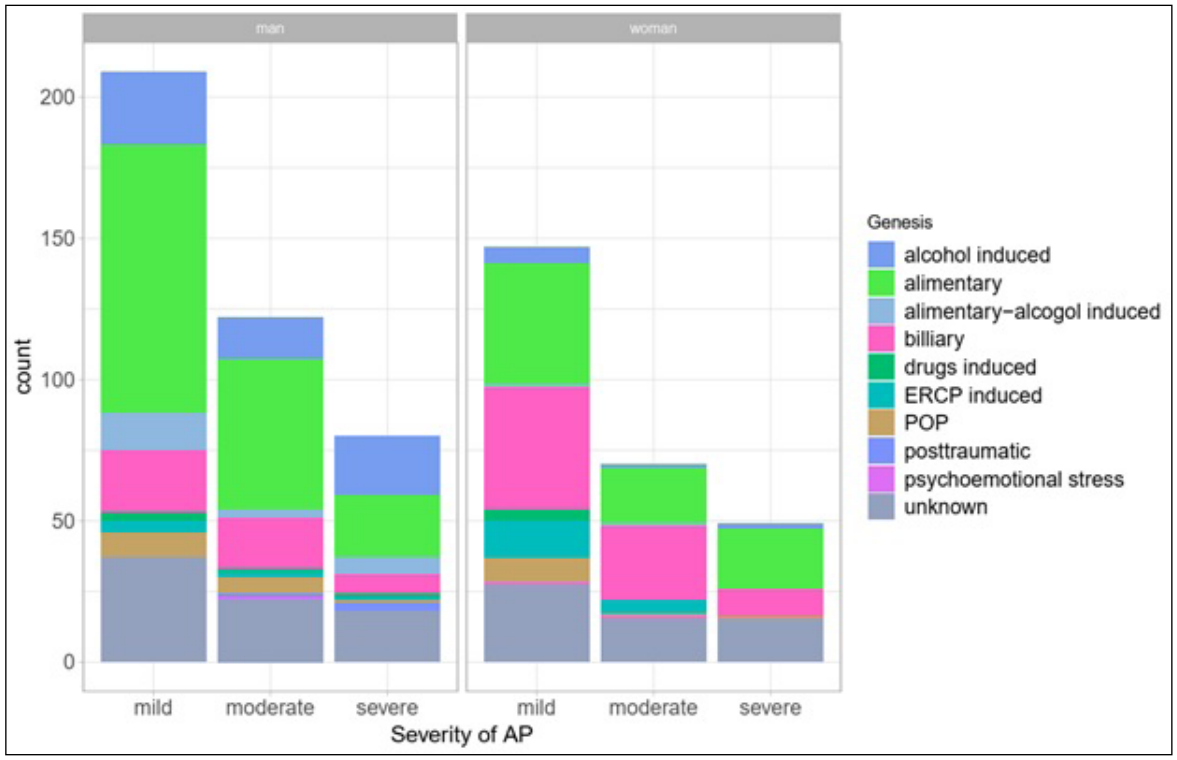

Fig. 4. Distribution of patients of the study cohort with acute pancreatitis by gender, genesis and severity of acute pancreatitis.

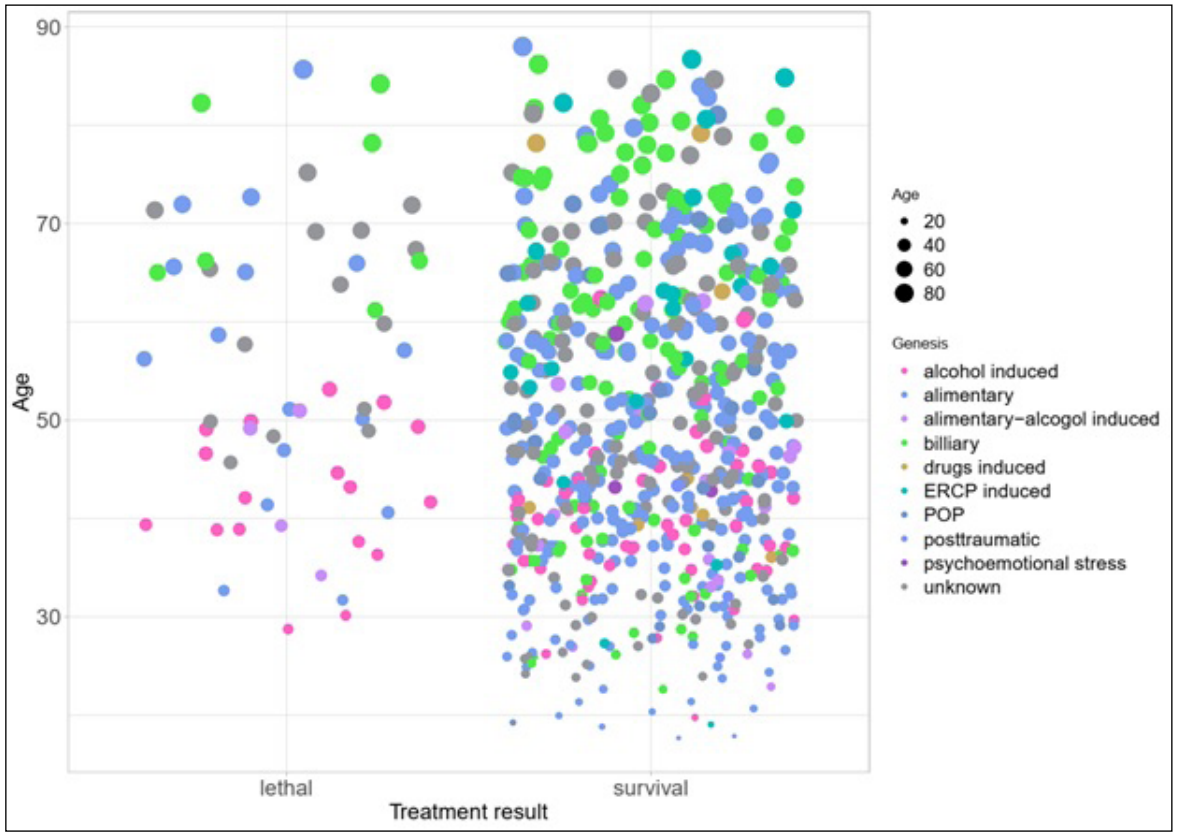

Fig. 5. Distribution of the patients of the study cohort with acute pancreatitis according to treatment results, genesis of acute pancreatitis and age.

analysis of the population dynamics and the number of patients with acute pancreatitis at the regional level revealed a statistically significant increase in the number of cases of acute pancreatitis against the background of a declining population. In particular, during the study period, the population of the region decreased by 8,02%. It should be noted that every year the population decline became more and more significant, reflecting

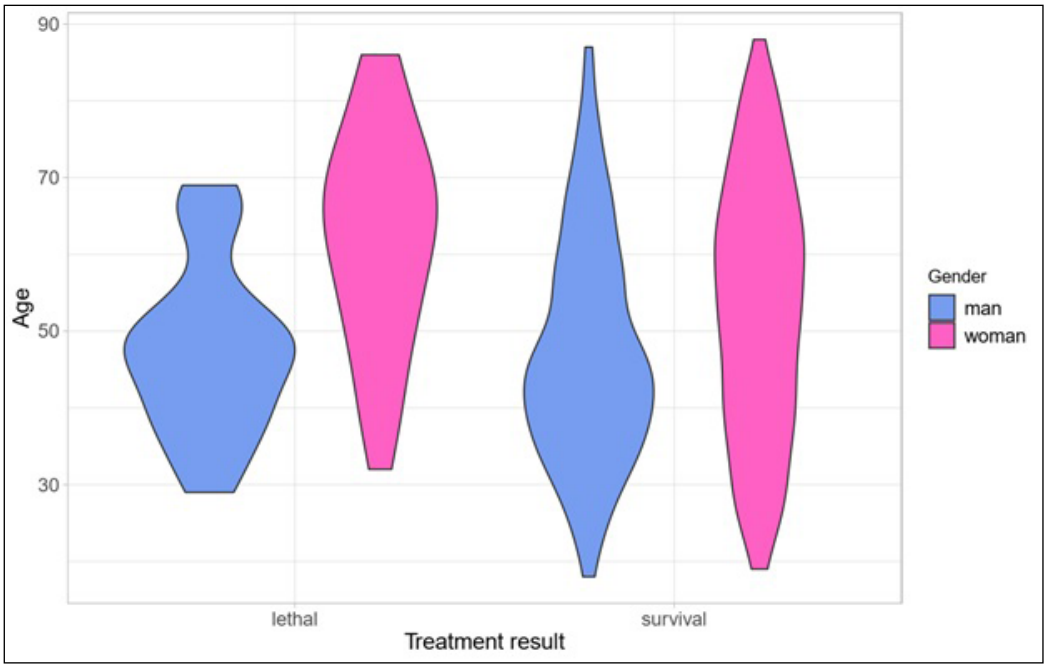

Fig. 6. Distribution of patients of the study cohort with acute pancreatitis depending on age, gender and results of treatment.

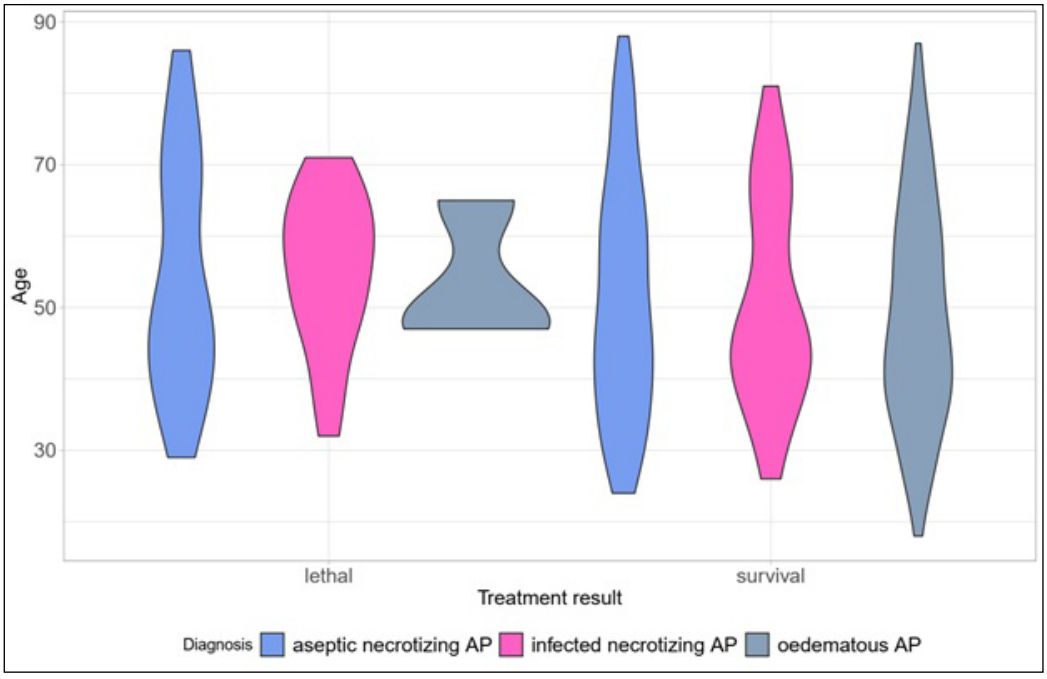

Fig.7. Distribution of patients of the study cohort with acute pancreatitis depending on age, treatment results and morphological form of acute pancreatitis.

the national trend of depopulation. For example, at the time of independence, Ukraine had 51,5 million inhabitants, and in 2019 – 37 million [17]. As for the population dynamics of European countries, according to the official website of the European Union, over the past two decades, from 2003 to 2023, the total population of the EU increased from 431,2 million to 448,8 million, i.e. by 4% [18].

It is worth noting that against the backdrop of population growth in the EU countries over the past decade, there has been a slowdown in natural population growth. Also, the picture in Western Europe, which had a relatively stable level of growth, mainly due to migrants, and Eastern Europe, which includes Ukraine, is different [18]. During the 20-year period from January 1, 2003 to January 1, 2023, the total population of the EU increased from 431,2 million to 448,8 million, a growth of 4%. Thus, in our opinion, the decline in the population of the region under study may be not only a consequence of demographic problems, such as aging, high mortality after the COVID-19 pandemic and low birth rates, but also a consequence of migration processes that have increased significantly since the outbreak of the war in Ukraine unleashed by Russia.

As for the dynamics of the incidence of acute pancreatitis, during the study period there was an increase in cases of acute pancreatitis. In particular, the index of dynamics shows that in 2022 the number of patients with acute pancreatitis reached 177,83% of the level of 2011, which amounted to 134,4 cases/100000 people. Thus, a clear contrast in the dynamics has been revealed – on the one hand, the population of the study region is decreasing, on the other hand, the number of cases of acute pancreatitis is increasing. The increase in the frequency of this pathology at the regional level was in line with global trends. The literature analyzed by us reports an increase in the incidence of acute pancreatitis in recent decades worldwide, regardless of continent [8,9,12,19]. For example, in Germany, according to a systematic analysis of 516618 hospitalized cases between 2008 and 2017, there was an increase in the annual incidence of AP from 48858 (2008) to 52611 (2017), mainly due to an increase in the incidence of biliary AP [20]. In England, according to the results of the population-based observational study of acute pancreatitis, the incidence of AP in 2000 was 20,5 cases/100000 population, and data from 2019 show that this rate has approximately doubled in this region [21]. We did not find clear data on the incidence of acute pancreatitis in Ukraine per 100 thousand people in the available literature. The incidence of AP in 17 other European countries ranges from 4,6 to 100 per 100000 [22]. Thus, the incidence of AP in the region we studied, which in 2022 amounted to 134,4 cases/100000 people, is significantly higher than the incidence of AP in other European countries.

In addition to morbidity, there has also been an increase in overall mortality from 1,7% to 2,2% over the past 12 years due to this pathology among the population we studied at the regional level. At the same time, in other European countries, there is a decrease in the overall mortality rate from AP. For example, in Germany, according to a systematic analysis of standardized data of patients with AP during the study period from 2008 to 2017, the average hospital mortality was 2,85% and has improved significantly over time, which, according to the authors, is due to the improvement of interdisciplinary treatment concepts [20]. An observational study conducted between 2008 and 2015 based on data from one of the largest hospital databases available in the United States also found a decrease in overall mortality rates from 2,9% to 2,0% during study period [23].

In our opinion, this fact can be explained only by multifactorial factors. In recent years, in Ukraine, there has been a change in the eating habits of the population and the abandonment of home cooking in favor of fast food. The emergence of clear unified criteria for the diagnosis of acute pancreatitis in accordance with the Atlanta 2012 recommendations reduced the number of overdiagnosis and misdiagnosis of acute pancreatitis in upper abdominal pain of other etiology and made it possible to accurately collect statistically reliable data. The rapid development of laboratory diagnostic and imaging methods, the possibility of 24-hour x-ray examinations at the emergency department level in emergency clinics, the high availability of these methods for patients contributed to high and accurate diagnosis of acute pancreatitis in the last decade [24]. The increase in the level of stress among the population, associated with a full-scale war in Ukraine, is a factor in the increase in morbidity, including acute pancreatitis.

GENDER, AGE, ETIOLOGICAL AND SOME CLINICAL CHARACTERISTICS OF PATIENTS WITH AP OF THE STUDIED COHORT

The gender distribution of patients with acute pancreatitis in our study cohort showed that the number of men exceeded the number of women with acute pancreatitis by 1,5 times. Our data are in line with the global data, which also indicate the prevalence of men over women among patients with AP – 68,9% vs. 31,1% [19]. Regarding age characteristics, in our study cohort of patients with AP, the average age of men was lower than the average age of women – 47,34±14,32 vs. 54,15±16,31 years, respectively ($p<0,05$). This may indicate a difference in the influence of risk factors between the sexes or that acute pancreatitis in men often manifests itself at a younger age. Further research may help to better understand these gender and age differences in the development of AP.

In the top three most common causes of the development of this pathology in the study cohort of patients, without taking into account the gender distribution, the nutritional factor was in the first place – 37,5% (254), in the second place was biliary factor – 18,6% (126), in the third place was alcohol factor – 10,5% (71). There were differences in the dominant causes of AP in men and women. In particular, in men, the dominant causes of AP were nutritional and alcohol factors, which together accounted for 61,8% (254), in contrast to women, in whom the dominant causative factors were nutritional and biliary factors, which together accounted for 61,3% (163). The predominance of the alcohol factor in men coincides with the general global trend, according to which in 45,7% of men the cause of death was an alcohol factor [19]. It logically follows that health care

measures aimed at reducing alcohol consumption among the population can effectively reduce the incidence and mortality of acute pancreatitis, especially among male patients.

The severity of acute pancreatitis has a wide variability from mild forms, which need conservative treatment to sever forms with life-threatening complications and mortality. Studies by other authors demonstrated a wide variability in the overall mortality of AP from 2,22% in the mild form to 45,63% in the severe form [24]. In our study in the vast majority of patients, acute pancreatitis had a mild course – 52,6%(356) of cases, the morphological type of acute pancreatitis in the vast majority was edematous interstitial – 74,2%(502). The overall mortality rate for acute pancreatitis in the studied group was 8,7%(59), had a wide range of variability with different severity, and corresponded to similar indicators in other studies that demonstrated overall mortality rate from 5,5% till 7,14% [19,26]. Thus, our results confirm the general global trends in the incidence of complications and mortality in various forms of acute pancreatitis.

During 2011-2022, there was an unstable dynamics of the proportion of patients with acute pancreatitis undergoing surgery. Periodic fluctuations in the number of surgical interventions may be due to various factors, such as changes in approaches to the treatment of acute pancreatitis, availability of new therapies or improved diagnostics that allow avoiding surgery. The high peak in 2020 may be due to certain circumstances, such as the COVID-19 pandemic, which may have affected medical practices or forced more aggressive treatments due to late hospitalization of patients. However, the overall trend indicates a decrease in the number of surgeries by the end of the survey period, which is fully consistent with current trends of refraining from open surgical interventions in favor of wait-and-see tactics in acute pancreatitis [27].

CONCLUSIONS

This study revealed a significant increase in the incidence of acute pancreatitis in Vinnytsia region during 2011-2022, reaching 134,4 cases/100 thousand people in 2022, which is 177,83% of the 2011 level and is in line with global trends towards an increase in the number of cases of acute pancreatitis. At the same time, the population of the region decreased by 8,02% between 2011 and 2022, which is part of the all-Ukrainian demographic crisis caused by both natural decline and active migration, in particular as a result of the COVID-19 pandemic and the full-scale war. The main etiologic factors for the development of the disease were nutritional (37,5%), biliary (18,6%) and alcohol (10,5%) factors. Men suffered from acute pancreatitis more often than women, and the average age of men was lower (47,34 ± 14,32 years) compared to the average age of women (54,15 ± 16,31 years). The mortality rate from acute pancreatitis in Vinnytsia region increased from 1,7% to 2,2% in 2011-2022, while the global trend is downward. This indicates a discrepancy in local and global trends in mortality from acute pancreatitis. In terms of treatment tactics, the general trend shows a decrease in the number of operations for AP by the end of the observation period, which is in line with the latest global recommendations. The results emphasize the importance of further research and development of preventive programs to reduce morbidity and mortality from acute pancreatitis in Ukraine.

REFERENCES

1. Miller J, Wu Y, Safa R et al. Derivation and validation of the ED-SAS score for very early prediction of mortality and morbidity with acute pancreatitis: a retrospective observational study. BMC Emergency medicine. 2021;21(1). doi: 10.1186/s12873-021-00410-w. DOI
2. Kikuta K, Masamune A, Shimosegawa T. Impaired glucose tolerance in acute pancreatitis. World journal of gastroenterology. 2015;21(24):7367-7374. doi: 10.3748/wjg.v21.i24.7367. DOI
3. Vasudevan S, Goswami P, Sonika U et al. Comparison of various scoring systems and biochemical markers in predicting the outcome in acute pancreatitis. Pancreas. 2018;47(1):65–71. doi: 10.1097/MPA.0000000000000957. DOI
4. Büchler M, Gloor B, Müller C et al. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. Ann Surg. 2000;232(5):619-26. doi: 10.1097/00000658-200011000-00001. DOI
5. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas. 2006;33(4):323-30. doi: 10.1097/01.mpa.0000236733.31617.52. DOI
6. Roberts SE, Morrison-Rees S, John A et al. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017;17(2):155-165. doi: 10.1016/j.pan.2017.01.005. DOI
7. Oskarsson V, Hosseini S, Discacciati A et al. Rising incidence of acute pancreatitis in Sweden: National estimates and trends between 1990 and 2013. United European Gastroenterol J. 2020;8(4):472-480. doi: 10.1177/2050640620913737. DOI

8. Knudsen JS, Heide-Jørgensen U, Mortensen FV et al. Acute pancreatitis: 31-Year trends in incidence and mortality – A Danish population-based cohort study. Pancreatology. 2020;20(7):1332-1339. doi: 10.1016/j.pan.2020.09.011. DOI
9. Li CL, Jiang M, Pan CQ et al. The global, regional, and national burden of acute pancreatitis in 204 countries and territories, 1990-2019. BMC Gastroenterol. 2021;21(1):332. doi: 10.1186/s12876-021-01906-2. DOI
10. Párniczky A, Kui B, Szentesi A et al. Prospective, multicentre, nationwide clinical data from 600 cases of acute pancreatitis. PLoS One. 2016;11(10):e0165309. doi: 10.1371/journal.pone.0165309. DOI
11. Zerem E, Kurtcehajic A, Kunosić S et al. Current trends in acute pancreatitis: Diagnostic and therapeutic challenges. World J Gastroenterol. 2023;29(18):2747-2763. doi: 10.3748/wjg.v29.i18.2747. DOI
12. Iannuzzi J, King J, Leong J et al. Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis. Gastroenterology. 2022;162(1):122-134. doi: 10.1053/j.gastro.2021.09.043. DOI
13. Petrov M, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol. 2019;16(3):175-184. doi: 10.1038/s41575-018-0087-5. DOI
14. Xiao AY, Tan ML, Wu LM et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. Lancet Gastroenterol Hepatol. 2016;1(1):45-55. doi: 10.1016/S2468-1253(16)30004-8. DOI
15. Banks P, Bollen T, Dervenis C et al. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11. doi: 10.1136/gutjnl-2012-302779. DOI
16. Marchegiani G, Barreto S, Bannone E et al. Postpancreatectomy acute pancreatitis (PPAP): definition and grading from the international study group for pancreatic surgery (ISGPS). Ann Surg. 2022;275(4):663-672. doi: 10.1097/SLA.0000000000005226. DOI
17. Rogoża J. Ukraine in the face of a demographic catastrophe. OSW Commentary. Center for easten studies. 2023;524:1-7. https://www.osw.waw.pl/en/publikacje/osw-commentary/2023-07-11/ukraine-face-a-demographic-catastrophe [Accessed 28 April 2024]
18. Eurostat. Interactive publications: Demography of Europe – 2024 edition. European Commission. 2024. https://ec.europa.eu/eurostat/web/interactive-publications/demography-2024 [Accessed 28 April 2024]
19. Ghiță AI, Pahomeanu MR, Negreanu L. Epidemiological trends in acute pancreatitis: A retrospective cohort in a tertiary center over a seven year period. World J Methodol. 2023;13(3):118-126. doi: 10.5662/wjm.v13.i3.118. DOI
20. Loosen SH, Essing T, Jördens M et al. Current epidemiological trends and in-hospital mortality of acute pancreatitis in Germany: a systematic analysis of standardized hospital discharge data between 2008 and 2017. Z Gastroenterol. 2022;60(3):310-319. doi: 10.1055/a-1682-7621. DOI
21. PanWessex Study Group, Wessex Surgical Trainee Research Collaborative, Mirnezami A et al. Population-based observational study of acute pancreatitis in southern England. Ann R Coll Surg Engl. 2019;101(7):487-494. doi: 10.1308/rcsann.2019.0055. DOI
22. Roberts SE, Morrison-Rees S, John A et al. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017;17(2):155-165. doi: 10.1016/j.pan.2017.01.005. DOI
23. Ingraham NE, King S, Proper J et al. Morbidity and Mortality Trends of Pancreatitis: An Observational Study. Surg Infect (Larchmt). 2021;22(10):1021-1030. doi: 10.1089/sur.2020.473. DOI
24. Boxhoorn L, Voermans RP, Bouwense SA et al. Acute pancreatitis. Lancet. 2020;396(10252):726-734. doi: 10.1016/S0140-6736(20)31310-6. DOI
25. Popa C, Badiu D, Rusu O et al. Mortality prognostic factors in acute pancreatitis. J Med Life. 2016;9(4):413-418.
26. Nawacki Ł, Głuszek S. Hospital mortality rate and predictors in acute pancreatitis in Poland: A single-center experience. Asian J Surg. 2024;47(1):208-215. doi: 10.1016/j.asjsur.2023.07.063. DOI
27. Leppäniemi A, Tolonen M, Tarasconi A et al. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg. 2019;14:27. doi: 10.1186/s13017-019-0247-0. DOI

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

The association between chronic diseases and lifestyle: A comparative study between two groups

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ABSTRACT

Aim: To identify lifestyle factors associated with chronic diseases and explore the biological mechanisms linking these behaviors to disease development.
Materials and Methods: A quasi-experimental design was used to compare a study group receiving the program to a control group. Data was collected through questionnaires and analyzed statistically.
Results: Participants in the study group showed significant improvements in healthy lifestyle behaviors compared to the control group. The study found that the program significantly improved health behaviors ($p < 0.01$, $r > 0.6$), highlighting the importance of targeted interventions for chronic disease prevention.
Conclusions: The study highlights the effectiveness of lifestyle interventions in promoting healthier behaviors among chronic disease patients. Future research can explore the impact of socioeconomic factors on health behaviors to develop targeted interventions.

KEY WORDS: Chronic Diseases, Healthy lifestyle, health promotion model

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INTRODUCTION

Chronic diseases are a significant global health challenge with a strong correlation to lifestyle factors. Despite medical advancements, prevalence remains high, necessitating further research to identify specific risk factors and inform prevention strategies [1-4]. This research explores the link between chronic diseases and lifestyle choices, drawing on theories like Planned Behavior and Social Change to understand individual and societal influences on health behaviors [5, 6]. While the Theory of Planned Behavior focuses on individual factors, the Theory of Social Change examines societal influences on behavior [7-10]. The Health Promotion Model emphasizes the influence of individual characteristics, environmental factors, and behavior-specific cognitions on health-promoting behaviors, aligning with the study's focus on lifestyle choices and chronic disease management [11-12]. The Health Promotion Model provides a framework to assess how factors like health awareness, knowledge, and socio-demographic characteristics influence lifestyle behaviors of chronic disease patients, suggesting that improving health literacy can lead to better health outcomes [13-16]. A literature review shows a strong link between lifestyle choices and chronic disease prevalence, with healthy behaviors reducing disease risk. Educational interventions targeting lifestyle modifications have proven effective in improving health outcomes [3,17-20]. Unhealthy lifestyles, including poor diet and sedentary behavior, significantly contribute to the development and progression of chronic diseases like diabetes, hypertension, and cardiovascular disease [24-25]. Comparative studies show disparities in health outcomes linked to lifestyle behaviors, with educational interventions improving health-related quality of life for chronic disease patients [26-27]. Understanding socio-demographic factors influencing lifestyle choices can help tailor interventions to promote healthier behaviors and mitigate the impact of chronic diseases across populations [28]. Unhealthy lifestyle choices, significantly increase the risk of developing chronic diseases like diabetes, hypertension, and cardiovascular disorders [29]. Comparing different population groups, this study aims to explore the correlation between lifestyle factors and chronic diseases, highlighting the impact of lifestyle interventions on health outcomes [30-31]. Comparative studies reveal disparities in lifestyle practices between populations, with higher education levels linked to better health literacy and healthier choices. Interventions targeting lifestyle modifications can enhance disease management and quality of life [32]. Understanding the intricate relationship between lifestyle and chronic diseases is vital for developing effective health promotion strategies to mitigate the burden of these conditions [33-34].

AIM

This study aims to compare lifestyle factors between two distinct groups, identify lifestyle-related risk factors for

chronic diseases, and understand the biological mechanisms linking lifestyle and chronic disease development.

MATERIALS AND METHODS

RESEARCH DESIGN

This study employs a quasi-experimental design to evaluate the impact of an instructional program on promoting healthy lifestyle changes among chronic disease patients. The study involves two groups: a study group that receives the intervention and a control group that does not.

STUDY SAMPLE

A sample size of 222 participants was determined through G- power analysis to ensure adequate statistical power. The study included 111 individuals in the study group and 111 individuals in the control group. Participants were selected using non-probability purposive sampling [35].

DATA COLLECTION

Data was collected at three time points: pretest, posttest 1, and posttest 2. The Health Promotion Lifestyle Profile II (HPLP II) was used to assess participants' engagement in health-promoting behaviors across six domains, including: health responsibility, physical activity, nutrition, spiritual growth, interpersonal relations, and stress management [36].

PROGRAM DESIGN

A researcher-developed five-session instructional program was implemented and evaluated using a pretest-posttest1 and posttest 2 design. An instructional program designed for this study was an educational program focusing on promoting healthy lifestyle behaviors among patients with chronic diseases. The program consisted of a series of sessions covering topics such as health responsibility, physical activity, nutrition, spiritual growth, interpersonal relationships, and stress management as health promotion model. The program was implemented on two groups: the study group, which received the instructional program, and the control group, which received no instructional program. Data was collected through pre- and post-program questionnaires to assess the program's effectiveness in improving lifestyle behaviors. These factors were influenced by an instructional program aimed at promoting healthy behaviors, as the results showed a significant improvement in these factors among the study group after the implementation of the instructional program. This methodology aims to rigorously evaluate the impact of the instructional program on the health behaviors of patients with chronic diseases, providing valuable insights into effective health promotion strategies

DATA ANALYSIS

Data analysis will involve descriptive and inferential statistics, such as paired sample t-tests and correlation coefficients, to determine the effectiveness of the program.

ETHICAL CONSIDERATIONS

The study obtained ethical approval from the Research Ethics Committee and the Diwaniyah Health Department in No. 227, June 2, 2024. Informed consent was obtained from all participants.

TIMELINE

The study will be conducted from August 1, 2024, to November 1, 2024.

RESULTS

The results of the study are presented in a clear and organized manner using tables and figures to facilitate understanding. Below are the key findings of the research regarding the effectiveness of the instructional program on the healthy lifestyle of patients with chronic diseases. Building upon the findings of the doctoral dissertation.

Table 1 summarizes the age, sex, educational level, and other demographic variables of participants in both groups, showcasing significant differences in age and education level.

This table 2 shows the distribution of Body Mass Index (BMI) categories across pretest, posttest 1, and posttest 2 for both study and control groups, indicating significant improvements in the study group.

In table 3, compares smoking behavior changes among participants before and after the intervention, showing an increase in attempts to quit smoking in the study group.

Table 4 that presents levels of physical activity in the study and control groups, indicating an increase in moderate activity levels in the study group after the instructional program.

Table 5 that summarizes Health Promotion Lifestyle Profile II scores for the study group, reflecting significant improvements in healthy lifestyle dimensions from pretest to posttest 2.

Table 6 displays Health Promotion Lifestyle Profile II scores for the control group, showing minimal changes in lifestyle behaviors across testing periods.

Table 7 that compares the effectiveness of the instructional program on healthy lifestyle for patients with chronic diseases between the study and control groups, highlighting significant improvements in the study group.

Table 1. Socio-demographic characteristics of study and control groups

Socio-demographical characteristics		Study group (n=111)			Control group (n=111)			Type-test (sig)*
		F	%	M± SD	F	%	M ± SD	
Age	30-39	8	7.2	3.459±1.204	9	8.1	3.621±1.160	CFT=0.00
	40-49	15	13.5		8	7.2		
	50-59	32	28.8		25	22.5		
	60-69	30	27.0		43	38.7		
	70-79	25	22.5		26	23.4		
	Total	111	100.0		111	100.0		
Sex	Male	69	62.2	1.378±0.487	83	74.8	1.252±0.436	CFT= 0.812
	Female	42	37.8		28	25.2		
	Total	111	100.0		111	100.0		
Edu. Level	Reads and writes	11	9.9	3.783±1.816	11	9.9	4.135±1.885	MT= 0.21
	Primary	20	18.0		14	12.6		
	Medium	22	19.8		18	16.2		
	Preparatory	19	17.1		16	14.4		
	Institute	17	15.3		23	20.7		
	College	17	15.3		22	19.8		
	Higher Diploma	1	0.9		3	2.7		
	Master	3	2.7		2	1.8		
	PhD	1	0.9		2	1.8		
	Total	111	100.0		111	100.0		
Marital status	Single	5	4.5	2.225±0.759	4	3.6	2.387±0.906	CFT= 0.002
	Married	90	81.1		83	74.8		
	Divorced	5	4.5		6	5.4		
	Widow	8	7.2		13	11.7		
	Separated	3	2.7		5	4.5		
	Total	111	100.0		111	100.0		
Occupation	Employee	51	45.9	2.072±1.255	54	48.6	2.270±1.420	CFT=0.00
	Earner/Freelancer	17	15.3		20	18.0		
	Retired	16	14.4		16	14.4		
	Unemployed	16	14.4		17	15.3		
	Housewife	11	9.9		4	3.6		
	Total	111	100.0		111	100.0		
Work per week	Fulltime >=35 hr.	17	15.3	2.945±1.043	22	19.8	2.702±1.058	MT= 0.9
	Part time 15-34 hr.	12	10.8		17	15.3		
	Part time<15 hr.	42	37.8		44	39.6		
	Not Working	40	36.0		28	25.2		
	Total	111	100.0		111	100.0		
Place of residence	Urban	92	82.9	1.171±0.378	84	75.7	1.243±0.430	CFT= 0.350
	Rural	19	17.1		27	24.3		
	Total	111	100.0		111	100.0		
Monthly family income	Less than 300,000	21	18.9	2.594±1.123	35	31.5	2.387±1.214	MT= 0.00
	300,000-600,000	33	29.7		22	19.8		
	601,000-900,000	31	27.9		38	34.2		
	901,000-1,200,000	23	20.7		9	8.1		
	1,201,000-1,500,000	2	1.8		6	5.4		
	1,501,000 or more	1	0.9		1	0.9		
	Total	111	100.0		111	100.0		

N: Sample size, F: Frequency, %: Percentage, M+SD: median +standard deviations * – statistically significant method as 2 nominal variables that use fisher test (CFT) and 2 ordinal variables that use median test (MT). Statistically significant is 0.01 that confidence level at 0.99 in 2 tailed.

Table 2. Frequency of the BMI for the study and control groups

Groups	Classification BMI	Pretest		Posttest 1		Posttest 2	
		M±SD	F (%)	M±SD	F (%)	M±SD	F (%)
Study N (111)	Underweight (18.5)	4.0±1.2	2 (1.8%)	4.0±1.1	0	4.0±1.2	0
	Normal weight (18.5-24.9)		3 (2.7%)		3 (2.7%)		14 (12.6%)
	Pre-obesity (25.0-29.9)		41 (36.9%)		46 (41.4%)		47 (42.3%)
	Obesity Class I (30.0-34.9)		26 (23.4%)		25 (22.5%)		21 (18.9%)
	Obesity Class II (35.0-39.9)		20 (18.0%)		19 (17.1%)		15 (13.5%)
	Obesity Class III (Above 40.0)		19 (17.1%)		18 (16.2%)		14 (12.6)
Control N (111)	Underweight (18.5)	4.1±1.2	2 (1.8%)	4.2±1.2	2 (1.8%)	4.3±1.2	2 (1.8%)
	Normal weight (18.5-24.9)		2 (1.8%)		2 (1.8%)		2 (1.8%)
	Pre-obesity (25.0-29.9)		39 (35.1%)		36 (324%)		32 (28.8%)
	Obesity Class I (30.0-34.9)		25 (22.5%)		23 (20.7%)		20 (18.0)
	Obesity Class II (35.0-39.9)		22 (19.8)		25 (22.5%)		28 (25.2%)
	Obesity Class III (Above 40.0)		21 (18.9%)		23 (20.7%)		27 (24.3%)

N: Sample size, F: Frequency, %=Percentage, M+SD= median +Standard deviations.

Table 3. Smoking behavior change

Groups	Smoking status	Pretest		Posttest 1		Posttest 2		sig*
		F	%	f	%	F	%	
Study Group	Never smoked	43	38.7	43	38.7	43	37.8	0.00
	Currently smokes	54	48.6	46	41.4	36	32.4	
	Quit smoking	14	13.5	22	20.7	32	29.7	
	Total	111	100.0	111	100.0	111	100.0	
Control Group	Never smoked	45	40.5	45	40.5	44	39.6	0.02
	Currently smokes	55	49.5	55	49.5	57	51.4	
	Quit smoking	11	9.9	11	9.9	10	9.0	
	Total	111	100.0	111	100.0	111	100.0	

N: Sample size, F: Frequency, %: Percentage, * – statistically significant: non parametric T-test- Mann-Whitney U, statistically significant is 0.01 that confidence level 0.99 in 2 tailed.

DISCUSSION

Table 1 presents demographic data including age, gender, education, marital status, occupation, work hours, residence, and monthly income for both the study (n=111) and control (n=111) groups. Notably, most participants were 60-69 years old (27% in the study, 38.7% in the control), and a large percentage of the control group were male (74.8%). The study compared two groups, finding significant differences in demographics like age, education, marital status, and income. Table 2 presents the changes in BMI categories for both groups across three time points (pretest, posttest 1, and posttest 2). The study group showed significant improvements, particularly in reducing the number of participants classified as overweight and obese from pretest to posttest. The educational intervention significantly reduced obesity rates in the study group. Additionally, table 3 compares smoking habits among participants before and after the program. It indicates an increase in the number of participants attempting to quit smoking in the study group, highlighting the effectiveness of the instructional program. Table 4 displays the change in physical activity levels between the study and control groups. Notably, the study group's moderate activity levels increased significantly, whereas the control group maintained lower levels of physical activity throughout the study. Overall, table 5 shows the scores reflecting significant improvements in the study group across various dimensions of healthy lifestyle behaviors from pretest to posttest1 posttest 2, moving from "weak" to "good" levels, particularly in health responsibility (total score improved significantly). Table 6 reflects minimal changes in the control group's lifestyle scores, remaining at "weak" levels throughout the study. It emphasizes the lack of significant improvement compared to the study group. Table 7 presents statistical comparisons between study and control groups regarding the effectiveness of the instructional program on healthy lifestyles. The statistical significance of improvements in the study group is highlighted, with p-values less than 0.01, indicat-

Table 4. Changes in physical activity levels in the study and control groups at Pretest, Posttest 1, and Posttest 2 following the intervention.

	Scale		Pretest		Posttest 1		Posttest 2		M±SD	Level
	Qs	C	F	%	F	%	F	%		
Study group	Q1	1	6	5.4	21	18.9	22	19.8	2.780±1.898	Moderate Activity
		2	7	6.3	18	16.2	19	17.1		
		3	6	5.4	21	18.9	24	21.6		
		4	36	32.4	28	25.2	25	22.5		
		5	56	50.5	23	20.7	21	18.9		
	Total		111	100.0	111	100.0	111	100.0		
	Q2	1	41	36.9	42	37.8	44	39.6		
		2	5	4.5	18	16.2	20	18.0		
		3	6	5.4	23	20.7	21	18.9		
		4	59	53.2	28	25.2	26	23.4		
	Total		111	100.0	111	100.0	111	100.0		
	Q3	1	16	14.4	31	27.9	33	29.7		
		2	13	11.7	28	25.2	32	28.8		
		3	82	73.9	52	46.8	46	41.4		
	Total		111	100.0	111	100.0	111	100.0		
Control group	Q1	1	6	5.4	11	9.9	1	0.9	1.732±1.520	Weak activity
		2	5	4.5	12	10.8	12	10.8		
		3	17	15.3	25	22.5	31	27.9		
		4	43	38.7	37	33.3	38	34.2		
		5	40	36.0	26	23.4	29	26.1		
	Total		111	100.0	111	100.0	111	100.0		
	Q2	1	45	40.5	33	29.7	28	25.2		
		2	5	4.5	20	18.0	19	17.1		
		3	27	24.3	26	23.4	25	22.5		
		4	34	30.6	32	28.8	39	35.1		
	Total		111	100.0	111	100.0	111	100.0		
	Q3	1	7	6.3	17	15.3	10	9.0		
		2	12	10.8	17	15.3	19	17.1		
		3	92	82.9	77	69.4	82	73.9		
	Total		111	100.0	111	100.0	111	100.0		

Qs: Questions, C: Choice answers, F: Frequency, %: Percentage, M+SD: median +standard deviations.

ing strong evidence of the program's effectiveness. These findings highlight the effectiveness of the instructional program in promoting healthy behaviors among chronic disease patients. This study aligns with previous research, highlighting the effectiveness of educational interventions in promoting healthy lifestyles and the significant impact of demographic factors, particularly age, on health behaviors and chronic disease prevalence [37]. This study aligns with *Graf et al.* (2024) in recognizing gender differences in chronic disease prevalence, though no significant gender disparity was observed between the study and control groups [38]. Individuals with higher education levels have been associated with better health literacy and adherence to lifestyle modifications, as highlighted by Van den et al. [39]. The current study observed a significant difference in educational levels between the groups, suggesting that education may influence intervention effectiveness. Additionally, a higher proportion of married individuals in the study group, aligning with previous research by Balaj et al. (2024) on the positive impact of social support on health outcomes, may have contributed to their increased motivation and support for healthier lifestyles [40]. Socioeconomic factors, particularly income, significantly influence chronic disease prevalence and lifestyle choices. Individuals with higher incomes are more likely to engage in health-promoting activities. The current study found a correlation

Table 5. Health Promotion Lifestyle Profile II Scores for Study Group

HPLP II scores for study group									
Type test	Domains	Measure of Scale5-Likert					Total M Score		*Levels
		Never	Rarely	Sometime	Often	Always	M	SD	
		M	M	M	M	M			
Pretest	HR	3.2	4.6	1.6	0.6	0.3	2.06	0.41	Weak
	PA	3.3	4.75	1.9	0.7	0.4	2.21	0.43	Weak
	N	3.6	4.11	1.3	0.6	0.34	1.99	0.42	Weak
	SG	3.45	4.11	1.56	0.6	0.33	2.01	0.45	Weak
	IR	3.1	5.1	1.1	0.4	0.3	2.0	0.39	Weak
	SM	2.9	3.7	2.4	0.67	0.33	2.0	0.42	Weak
	Total	3.25	4.39	1.64	0.59	0.33	2.04	0.42	Weak
Post test 1	HR	1.1	1.9	3.8	5.71	5.34	3.57	0.42	Good
	PA	1.2	2.4	4.8	5.3	5.9	3.92	0.46	Good
	N	1.5	3.65	2.6	5.9	4.6	3.65	0.5	Good
	SG	1.5	1.7	5.6	5.8	4.8	3.88	0.5	Good
	IR	1.1	1.3	4.6	5.9	5.1	3.6	0.48	Good
	SM	1.57	1.7	4.5	6.4	5.88	4.01	0.51	Good
	Total	1.32	2.1	4.31	5.83	5.27	3.77	0.47	Good
Posttest 2	HR	1.8	2.8	4.8	5.9	5.7	4.2	0.54	Good
	PA	1.34	2.11	2.4	5.3	5.9	3.41	0.43	Good
	N	1.9	2.7	2.4	6.6	5.8	3.88	0.41	Good
	SG	1.6	1.9	3.75	6.9	5.8	3.99	0.46	Good
	IR	1.4	1.7	4.75	6.9	5.8	4.11	0.53	Good
	SM	1.6	2.4	2.8	6.8	5.9	3.9	0.52	Good
	Total	1.6	2.26	3.48	6.4	5.81	3.91	0.48	Good

*Interval of mean score; Very weak 1.00-1.49, Weak 1.50-2.49, Moderate 2.50-3.49, Good 3.50-4.49 and Excellent 4.50-5.00, HR=Health responsibility, PA=Physical activity=Nutrition, SG=Spiritual growth, IR=Interpersonal relations, SM=Stress management.

between income levels and health outcomes, suggesting that lower-income individuals may have limited access to resources for a healthy lifestyle [41]. The study's findings align with previous research emphasizing the importance of structured health education programs in managing chronic diseases and improving lifestyle choices [3, 4, 14]. The connection between BMI, chronic diseases, and lifestyle interventions is further reinforced by these studies [42-43]. The study also supports previous research on the role of health education in reducing smoking rates and increasing physical activity [44]. These findings collectively highlight the positive impact of instructional programs on health behaviors and outcomes in chronic disease patients [45-47]. These findings collectively highlight the positive impact of instructional programs on health behaviors and outcomes in chronic disease patients [48-50]. Overall, the study's findings underscore the critical importance of tailored health interventions in managing chronic diseases. The discussion in this study indicates that structured instructional programs enhance healthy lifestyle behaviors among patients with chronic diseases, necessitating their implementation in clinical settings. However, the study faces limitations related to a specific sample and a quasi-experimental design, which affects the generalizability of the results and limits conclusions about causal relationships. Additionally, the short follow-up period restricts understanding of the sustainability of behavioral changes and their impacts.

CONCLUSIONS

The program significantly improved participants' lifestyle behaviors, as measured by the HPLP II. This was evident in increased physical activity and decreased BMI. The control group, lacking the intervention, showed no significant changes. Higher education levels correlated with better health outcomes. The findings emphasize the importance of health education in promoting healthier lifestyles among chronic disease patients. Future research can explore the impact of socioeconomic factors on health behaviors to develop targeted interventions.

Table 6. Health Promotion Lifestyle Profile II Scores for control Group

HPLP II scores for control group									
Type test	Domains	Measure of Scale5-Likert					Total M Score		*Levels
		Never	Rarely	Sometime	Often	Always	M	SD	
		M	M	M	M	M			
Pretest	HR	2.9	2.5	1.4	1.8	0.4	1.8	0.34	Weak
	PA	3.3	4.7	1.7	1.3	0.5	2.3	0.38	Weak
	N	3	4.5	0.7	0.5	0.3	1.8	0.31	Weak
	SG	3.4	4.46	1.9	0.1	0.24	2.02	0.37	Weak
	IR	3.7	4.88	1.83	0.32	0.57	2.26	0.57	Weak
	SM	2.8	3.9	1.9	0.5	0.4	1.9	0.31	Weak
	Total	3.18	4.15	1.57	0.75	0.40	2.01	0.38	Weak
Post test 1	HR	4.1	3.33	1.1	0.7	0.27	1.9	0.47	Weak
	PA	2.4	3.1	2.1	0.5	0.4	1.7	0.4	Weak
	N	2.6	3.82	1.55	0.2	0.33	2.06	0.42	Weak
	SG	3.4	4.3	1.4	0.9	0.3	2.06	0.42	Weak
	IR	2.6	3.7	1.9	0.5	0.2	1.78	0.38	Weak
	SM	3.2	4.2	1.73	0.2	0.17	1.9	0.5	Weak
	Total	3.0	3.74	1.63	0.5	0.27	1.9	0.43	Weak
Posttest 2	HR	2.8	4.9	0.8	0.3	0.2	1.8	0.33	Weak
	PA	4.1	2.1	1.5	0.6	0.7	1.8	0.97	Weak
	N	3.4	2.59	1.96	0.78	0.27	1.9	0.3	Weak
	SG	2.2	4.5	1.9	0.6	0.3	1.9	0.3	Weak
	IR	3.2	4.3	1.5	0.33	0.22	1.91	0.28	Weak
	SM	3.1	3.3	1.6	0.3	0.2	1.7	0.56	Weak
	Total	3.13	3.61	1.54	0.48	0.31	1.83	0.45	Weak

* Interval of mean score; Very weak 1.00-1.49, Weak 1.50-2.49, Moderate 2.50-3.49, Good 3.50-4.49 and Excellent 4.50-5.00, HR=Health responsibility, PA=Physical activity=Nutrition, SG=Spiritual growth, IR=Interpersonal relations, SM=Stress management.

REFERENCES

1. Maizlish PL, Ybarra VC. The Burden of Chronic Disease, Injury, and Environmental Exposure. 2nd ed. USA: California: California Department of Public Health, Center for Healthy Communities. 2020. https://www.cdph.ca.gov/Programs/CCDPHP/DCDIC/CDCB/CDPH%20Document%20Library/BurdenReport04-04-13_ADA.pdf [Accessed 24 April 2024]
2. Abbas A, Younis N. Efficacy of Pender's Health Promotion-based Model on Intervention for Enhancing University of Mosul Hypertensive Employees' Eating Behaviors: A Randomized Controlled Trial. Bionatura. 2022; 7. doi: 10.21931/RB/2022.07.03.46. DOI
3. WHO. Healthier behaviors: incorporating behavioral and cultural insights. 2020. https://www.who.int/europe/initiatives/healthier behaviours-
4. incorporating-behavioural-and-cultural-insights [Accessed 24 April 2024]
5. Alhamad HA, Hassan HB. Effectiveness of Instructional Program on Patients' Nutritional Habits for Patients with Peptic Ulcer. Iraqi National Journal of Nursing Specialties. 2023; 36(1):35-48. doi: 10.58897/injns.v36i1.637. DOI
6. Gentile A, Alesi M. Parents' intention to vaccinate their children according to the Theory of Planned Behavior: A scoping review. Life Span Disabil. 2024;27:21-42. doi: 10.57643/lsadj.2024.27.1_02 DOI
7. Alligood MR. Nursing Theorists and their work. 10th ed. India: ELSEVIER; 2022.
8. Douglas ME, Blumenthal H, Guarnaccia CA. Theory of planned behavior and college student 24-hour dietary recalls. J Am Coll Health.2024;72(1):47-54. doi: 10.1080/07448481.2021.2015357 DOI
9. Cockerham WC, Health Lifestyle Theory in a Changing Society: The Rise of Infectious Diseases and Digitalization. J Health Soc Beh.2023; 64(3), 437-451. doi: 10.1177/00221465231155609 DOI
10. Ahmed MM, Naji A, Younis NM. Efficacy of an educational program based on health belief model to enhance weight control behaviors among employees at the University of Mosul: a randomized controlled trial. Revis Bionatura 2023;8(3):28 . doi:10.21931/RB/2023.08.03.28 DOI

11. Al Omari Q, Alshammari M, Al Jabri W, Al Yahyaei A, Aljohani KA, Sanad HM, Aljezawi M. Demographic factors, knowledge, attitude and perception and their association with nursing students' intention to use artificial intelligence (AI): a multicentre survey across 10 Arab countries. BMC Med Edu. 2024; 24(1):1456. doi:10.1186/s12909-024-06452-5 DOI
12. Hussein AA, Ahmed MM, Younis NM, Ibrahim RM. Apply Pender's Health Promotion Towards Hypertension of Employees in Mosul City/ Iraq. J Curr Med Res Opin. 2024;7(05):2529-2535. doi: 10.52845/CMRO/2024/7-5-19. DOI
13. Jalali A, Ziapour A, Ezzati ., Kazemi S, Kazeminia M. The impact of training based on the Pender Health Promotion Model on self-efficacy: A systematic review and meta-analysis. Am J Health Prom.2024; 38(7), 918-929. doi: 10.1177/08901171231224101. DOI
14. Wahid HSA, Hussein EA. Effectiveness of Preventive Health Behaviors- Oriented Education Program on Pregnant Adolescents' Knowledge in Al-Diwanyiah City: Follow-up Study. Ann RSCB. 2021;25(6):14774-14780.
15. Abd F, Faraj R. Effectiveness of the Health Action Process Approach on Promoting the Health Behaviors of Male High School Students in Al-Rusafa District. Iraqi Nat J Nurs Spec. 2022;35(1). doi: 10.58897/injns.v35i1.620 . DOI
16. Ganmi AH, Perry L, Gholizadeh L, Alotaibi. Behaviour change interventions to improve medication adherence in patients with cardiac disease: Protocol for a mixed methods study including a pilot randomised controlled tria. Collegian 2018;25(4):385-394. doi:10.1016/j.colegn.2017.10.003 DOI
17. ALI H, Qassim WJ. Assessment of Old Age Behaviors Toward Cardiovascular Health Promotion. Iraqi Nat J Nurs Spec. 2023;36(1):26-34. doi:10.58897/injns.v36i1.709. DOI
18. Prather H, Fogarty AE, Cheng AL, Wahl G, Hong B, Hunt D. Feasibility of an intensive interprofessional lifestyle medicine program for patients with musculoskeletal conditions in the setting of lifestyle-related chronic disease. PM R. 2023;15(1):41-50. doi: 10.1002/pmrj.12728 . DOI
19. Al-Mayahi AM, Al-Jubouri M B, Jaafar SA. Healthy lifestyle behaviors and risk of cardiovascular diseases among nursing faculty during COVID-19 Pandemic. Revista Brasileira de Enfermagem. 2023;76:e20220372. Retrieved from https://www.scielo.br/j/reben/a/KsywcYBV9RsqzZHHzzhqyhf/?format=html&lang=en
20. Athbi HA, Hassan HB. Health beliefs of patients with coronary heart disease toward secondary prevention: the health beliefs model as a theoretical framework. Indian J Publ Health Res Develop.2019;1(1):821-826. doi:10.5958/0976-5506.2019.00161.X DOI
21. Hussain E, Mohammed Z. Parents' Attitudes toward Immunization and its Relation with Pediatric Immunization Compliance at Primary Health Care Centers in Karbala City, Iraq. 2021; 34(1), 50-58. doi:10.58897/injns.v34i1.460 DOI
22. WHO. Noncommunicable diseases: Risk factors. 2023. https://www.who.int/europe/initiatives/healthier behaviours-
23. incorporating-behavioural-and-cultural-insights [Accessed 24 April 2024
24. Khleel H, Mohammed W. Evaluation of Pregnancy-related Health Behaviors' Change during Pregnancy for Pregnant Women Attending Abo Ghareeb Primary Health Care Sector. Iraqi Nat J Nurs Spec.2021;34(1):59-68. doi:10.58897/injns.v34i1.461 DOI
25. Mousa AM, Mansour K. Effectiveness of an Instructional Program Concerning Healthy Lifestyle on Patients' Attitudes after Percutaneous Coronary Intervention at Cardiac Centers in Baghdad City. Iraqi Nat J Nurs Spec. 2020;33(1):1-11. Retrieved from chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.iraqoaj.net/iasj/download/3a3b4ee0036dd0c9.
26. Najee AF, Shaker H. Effectiveness of an Instructional Program on Knowledge of Type 2 Diabetic Patient Toward Ocular Self-Care at Diabetic and Endocrine Center in Al-Nasiriya City. Indian J Foren Med Toxicol. 2019;13(4):936-939. Doi: https://doi.org/10.5958/0973-9130.2019.00417.1 .
27. CDC. Chronic Disease Prevention and Health Promotion. 2023. https://www.cdc.gov/nccdphp/index.html [Accessed 24 April 2024]
28. Muhealdeen-Alkasab HE, Aziz AR. Effectiveness of Instruction Program on Adolescent Girls' Dietary Habits Diagnosed with Iron Deficiency Anemia. Iraqi Nat J Nurs Spec. 2023;36(1):137-148. doi:10.58897/injns.v36i1.682 DOI
29. Shinjar FJ, Bakey SJ, Khudur KM. Effectiveness of an education program on hemodialysis patients, knowledge towards dietary regimen at Al-Hussein Teaching Hospital in Al-Nasiriyha City. Iraqi Nat J Nurs Spec. 2018;9(10):622. doi:10.5958/0976-5506.2018.01202.0. DOI
30. Akca N, Saygili M, Ture A. The relationship between the perception of chronic disease care and health-related quality of life in adults with chronic kidney disease. Chronic Illness. 2022; 18(4): 874-888. doi: 10.1177/17423953211039792 . DOI
31. Khemka S, Reddy A, Garcia R, Jacops M, Red. Role of diet and exercise in aging, Alzheimer's disease, and other chronic diseases. Ag Res Rev. 2023; 91: 102091. doi: 10.1016/j.arr.2023.102091 . DOI
32. Ng R, Sutradhar R, Yao Z, Wodchis W, Ros. Smoking, drinking, diet and physical activity—modifiable lifestyle risk factors and their associations with age to first chronic disease. Int J Epidemiol. 2020;49(1). doi: 10.1093/ije/dyz078 . DOI
33. Zhu, Zhang, Luo, Liu, Lai, Hu, et al. Effect of the number of unhealthy lifestyles in middle-aged and elderly people on hypertension and the first occurrence of ischemic stroke after the disease. Front. Cardiovasc Med J. 2023; 10. doi: 10.3389/fcvm.2023.1152423 . DOI
34. Arena, Pronk NP, Laddu, Faghy A, Bond, Lavie J. COVID-19, Unhealthy lifestyle behaviors and chronic disease in the United States: Mapping the social injustice overlay. Prog Cardiovasc Dis. 2023; 76, 112. doi: 10.1016/j.pcad.2023.02.010. DOI
35. Cavallo M, Morgana G, Dozzani I, Gatti A, Vandoni M, Pippi R, et al. Unraveling Barriers to a Healthy Lifestyle: Understanding. Nutrients. 2023;15(15):3473. doi: 10.3390/nu15153473 . DOI
36. WHO. Noncommunicable diseases. 2023 a. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases [Access: 24 April 2024]

37. Fual FG. Power Analysis Calculators. American Statistical Association. 2023, pp.27-32
38. Zambrano Bermeo RN, Estrada Gonzalez C, Herrera Guerra EDP, Aviles Gonzalez CI. Reliability and Validity of the Health-Promoting Lifestyle Profile II Spanish Version in University Students. Healthcare 2024;2(13):1330. doi: 10.3390/healthcare12131330 . DOI
39. Tabrizi JS, Doshmangir L, Khoshmaram N, Shakibazadeh E, Abdolahi HM, Khabiri, R. (2024). Key factors affecting health promoting behaviors among adolescents: a scoping review. BMC Health Serv Res.2024;24(1):58. doi: 10.1186/s12913-023-10510-x . DOI
40. Graf et al. The Importance of Gender-Sensitive Health Care in the Context of Pain, Emergency and Vaccination: A Narrative Review. Int J Environ Res Public Health. 2024;21:13. doi: 110.3390/ijerph21010013. DOI
41. Van den et al. Sex and Gender Differences in Psychosocial Risk Profiles Among Patients with Coronary Heart Disease — the THORESCI-Gender Study. Int J Behav Med. 2024;31:130-144. doi: 110.1007/s12529-023-10170-5 DOI
42. Balaj el al. Effects of education on adult mortality: a global systematic review and meta-analysis. The Lancet Public Health. 2024; 9(3): E155-e165. doi: 10.1016/ S2468-2667(23)00306-7. DOI
43. Nguyen THT, Bui TT, Lee J, Choi KS, Cho H, Oh J. K. Socioeconomic inequality in health-related quality of life among Korean adults with chronic disease: an analysis of the Korean Community Health Survey. Epidemiol Health 2024;46:e2024018. doi: 10.4178/epih.e2024018. DOI
44. Heriseanu A, Karin E, Walker J. The impact of obesity and overweight on response to internet-delivered cognitive behavioral therapy for adults with chronic health conditions. Int J Obes. 2023; 47: 487-495. doi: 10.1038/s41366-023-01285-6 . DOI
45. Kren J, Hacje L. The Burden of Chronic Disease. Mayo Clinic Proceedings: Innovations. Quality & Outcomes: Lifestyle medicine.2024; 8(1). doi: doi: 10.1016/j.mayocpiqo.2023.08.005. DOI
46. Ghasemian A, Sargeran K, Shamshiri. Effects of educational interventions based on the theory of planned behavior on oral cancer-related knowledge and tobacco smoking in adults: a cluster randomized controlled trial. BMC. 2024; 24(25). doi; 10.1186/s12885-024-11845-2.
47. Kardan M, Jung A, Iqbal M, Keshtkar, Gei. Efficacy of digital interventions on physical activity promotion in individuals with noncommunicable diseases: an overview of systematic reviews. BMC Digital Health. 2024; 2(1): 40. doi: 10.1186/s44247-024-00097-6 DOI
48. Mejia PC, Feliciano E, Feliciano A, et al. The effectiveness of health education and lifestyle program in improving the blood pressure in hypertensive patients. Int J Adv Appl Sci. 2019;6(11):21-29.doi: 10.21833/ijaas.2019.11.004 .
49. Uemura K, Yamada M, Okamoto H. The Effectiveness of an Active Learning Program in Promoting a Healthy Lifestyle among Older Adults with Low Health Literacy: A Randomized Controlled Trial. Gerontology. 2021;67:25–35. doi: 10.1159/000511357 . DOI
50. Habibzadeh H, Shariati A, Mohammadi F, Babayi S. The effect of educational intervention based on Pender's health promotion model on quality of life and health promotion in patients with heart failure: an experimental study. BMC Cardiovasc Disord. 2022; 1-13. doi: 10.1186/s12872-021-02294-x . DOI
51. Jayedi A, Soltani S, Abdolshahi A, Shap-Bidar S. Healthy and unhealthy dietary patterns and the risk of chronic disease: an umbrella review of meta-analyses of prospective cohort studies. Brit J Nutr. 2020; 124(11):1133-1144. doi:10.1017/S0007114520002330 . DOI
52. Sheer AJ, Lo M. Counseling Patients with Obesity. Treasure Island (FL): StatPearls Publishing. 2024.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Comparative study of energy-based technologies in thyroidectomy: Harmonic focus, ligasure tiny jaw, and conventional techniques at a single institution

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ABSTRACT

Aim: This study aims to evaluate the exact and harmonic focus of ligature with the traditional suture ligation approach with respect to surgical problems, hospital stay, drainage volume, and time spent in the operating room during open thyroidectomy.

Materials and Methods: Between February 2018 and March 2020, 180 patients suffering from thyroid disease underwent an open total thyroidectomy at Al-Sader Medical City's general surgery department. These patients were divided into three groups at random: 60 patients were assigned to Group 1 (Ligasure precise) (LS), 60 patients to Group 2 (harmonic FOUCS) (HF), and 60 patients to Group 3 conventional (CAT).

Results: Regarding age, sex, or histological diagnosis, the three groups did not differ statistically significantly. The mean operative time for the Ligasure (LS) group was 34 minutes, while the Harmonic focus (HF) group was 38 minutes, which was less than that of the Conventional technique (CAT) group. The CAT group had a significantly larger mean drainage volume than the other 2 groups ($P<0.001$). The three groups' postoperative hypocalcaemia levels did not differ statistically significantly. ($p=$ n.s.). The HF group had a shorter mean hospital stay than the LS group, while the CAT group had the longest hospital stay ($P<0.05$).

Conclusions: LigaSure Precise and Harmonic FOUCS are energy-based technologies that are equally safe and efficient when used for vascular dissection.

KEY WORDS: thyroidectomy, Ligasure, harmonic, conventional cautery, ligation vessels

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INTRODUCTION

At this time, the French Academy of Medicine prohibited thyroid surgery. Similar sentiments prevailed on the other side of the English Channel when Liston angrily said that it was "impossible to remove the thyroid gland from a living organism in a sound state without running the risk of the patient dying from bleeding." It is definitely not a procedure to be considered. [1] Even farther away, on the other side of the Atlantic, Gross criticized thyroid surgery, calling it "horrid butchery" and saying that "no honest and sensible surgeon would ever engage in it." [2] At the moment, a number of methods are used to accomplish surgical hemostasis, such as suturing and ligation (using threads, clips, and staplers), coagulation (both monopolar and bipolar electrocoagulation), ultrasonic coagulation (Ultracision, Harmonic Scalpel®; Ethicon EndoSurgery, Cincinnati, OH), and electro-migration sealing (LigaSure® Vessel Sealing System; Valleylab, Boulder, CO).Electrosurgical instruments utilise heat energy to denature proteins, but the resulting lateral thermal dispersion can potentially damage critical structures in the surgical area. In recent years, researchers have been exploring innovative devices that minimize thermal spread to reduce operation times and decrease the likelihood of intraoperative complications. The Harmonic Scalpel FOCUS Shears System from Ethicon and the LigaSure Precise from Covidien are two prominent energy-based ligation technologies utilized in thyroid surgeries. In 2000, both the FDA in the United States and the European Medical Device Directive approved ultrasonic coagulating-dissection systems and electrothermal bipolar vascular sealing as effective methods for sealing the vasculature and tissue of the thyroid gland. [3-6] The vessel ligation technologies of these two devices are based on different principles. The Harmonic FOCUS Shears (HF) operate using mechanical vibrations, while the LigaSure Precise (LP) functions as a closed-loop bipolar device. Recent innovations in shear designs, such as the Precise® and Focus®, have been developed

Table 1. Criterion for inclusion and exclusion

Inclusion standards
Before participating in the study, the patient will complete an informed consent form.
People with multinodular goiters or thyroid cancer who are scheduled for a total thyroidectomy
Exclusion standards
Malignant aggressive cancer patients require dissection of lymph node block
individuals suffering from coagulation issues
Goiters in the cervical region prior to neck surgery
coexisting parathyroid disorders
history of neck radiation

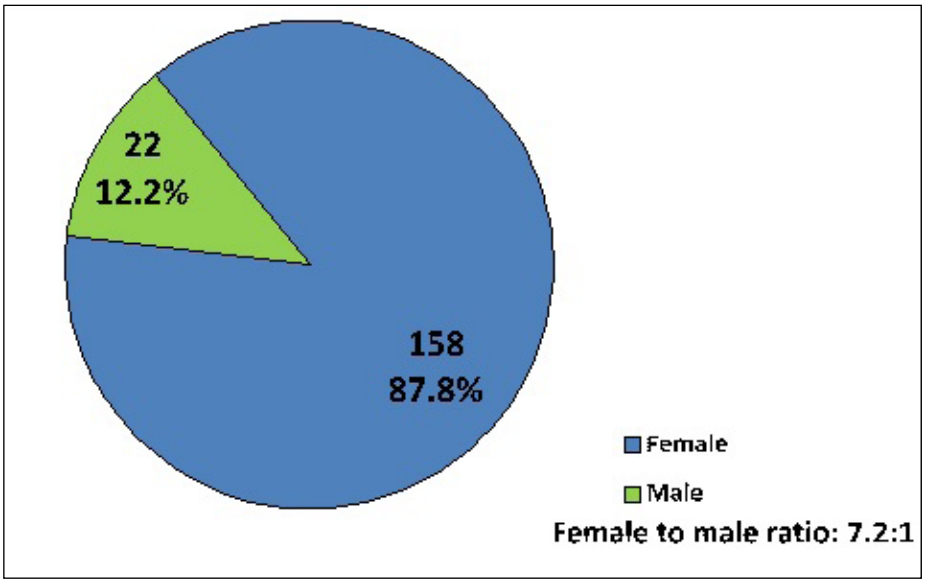

Fig. 1. Gender distribution of total 180 patients of the study with female to male ratio of 7.2 to 1 ($p<0.001$)

to enhance surgical efficiency. The safety of surgery and the impact of perioperative blood loss reduction cannot be overstated, even with a slight increase in cost [7]. This ultimately led to a lower rate of perioperative problems and a clearer understanding of the anatomy of the parathyroid gland and recurrent laryngeal nerve. [8]

AIM

This study compares LigaSure Precise and Harmonic Focus with conventional suture ligation techniques regarding operative time, hospital stay duration, drainage volume, and complications from surgery while removing the whole gland.

MATERIALS AND METHODS

Between 2019 and March 2023, open total thyroidectomies were performed on 180 consecutive patients with benign or malignant thyroid diseases at Al-Sadder Medical City's General Surgery Department and Al Furat General Hospital in Najaf. These procedures were performed by a single surgical team renowned for their expertise in thyroid surgery. The patients were divided into three groups at random: the Ligasure (LS)group, which consisted of 60 patients who underwent the majority of the procedure using LigaSure precise ; the harmonic focused (HF) group, which consisted of 60 patients who underwent the majority of the procedure using Harmonic FOCUS; and the Conventional technique group, which consisted of 60 patients who underwent the procedure using tools like the traditional clamp and tying method, absorbable ligature, bipolar diathermy, and clips (Table 1). We employed the FOCUS LigaSure precise LS (Vessel Sealing System; Valleylab, Boulder, CO, USA) and Ultracision Harmonic Scalpel (Ethicon Endo-Surgery) Level 3_5, which is the setting most frequently utilized during thyroid surgery, is selected for the generator. There are two sites on the hand-piece: a maximal site for denser tissue and a minimal site for delicate tissue. All 180 patients were blinded to the surgical procedure used and signed informed consent forms before being included in the study. Under general anesthesia and with endotracheal intubation, each patient underwent a total thyroidectomy. Every patient was positioned in a supine position with their necks

Table 2. Comparison of mean operative time among the studied groups

Statistics	Operative time (minutes)		
	Ligasure	Harmonic	Conventional
Mean	75	71	109
SD*	12	11	16
Range	50 – 90	60 – 90	90 - 150
P. values			
P1: Ligasure vs. Harmonic = 0.144 (NS)			
P1: Ligasure vs. Conventional < 0.001 (S)			
P1: Harmonic vs. Conventional < 0.001 (S)			
*SD: standard deviation of the mean			

Table 3. Comparison of mean Hospital stay among the studied groups

Statistics	Hospital stay (hours)		
	Ligasure	Harmonic	Conventional
Mean	29	20	35
SD*	16	4	13
Range	18 – 73	16 – 36	18 - 72
P1: Ligasure vs. Harmonic : < 0.001 (S)			
P1: Ligasure vs. Conventional = 0.0017(S)			
P1: Harmonic vs. Conventional < 0.001 (S)			
*SD: standard deviation of the mean			

outstretched, and a soft cushion was usually used to support and wrap their shoulders. A 4–6 cm incision was made across the thyroid isthmus, depending on the size of the thyroid. Due to the possibility of retraction and the difficulty in controlling hemostasis in the event of bleeding, the superior thyroid arteries were first split using LigaSure and then ligated with 0 silk suture for further safety. LigaSure was used to create subplatysmal flaps in the LS group, and the strap muscles were divided midline and laterally reflected. The duration of the procedure, the amount of fluid in the suction balloon (drainage volume) in the first 24 hours after the procedure, the length of hospital stay, and the frequency of issues (such RLN injury and hypocalcaemia rate) were all included in the study's findings. Suction drainage was used to calculate the actual difference in loss of blood between the groups and to assess the overall amount of blood lost after the procedure; 24 hours following the treatment, the drains were withdrawn. The RLN statuses were evaluated both before and immediately following surgery using direct laryngoscopy.

RESULTS

The 180 patients' average age who were enrolled in this study was 38.3 ± 10.1 years, with a range of 20 to 70 years. In addition, there were 46 patients there were 22 patients over 50, 45 patients between 41 and 50, 67 patients between 31 and 40, and 21 patients between 21 and 30. The female-to-male ratio was 7.2 to one, and the females were significantly dominating (P value <0.001) (Fig. 1). The average operating time for the LigaSure, harmonic, and conventional groups was 75, 71, and 109 minutes, respectively; however, the mean operating time for the conventional group was significantly longer than that of the other two groups (P <0.001), but not significantly different from that of the LigaSure and harmonic groups (P >0.05) (Table 2). The Ligasure group had an average drainage volume of 48 ± 13 (range: 20–70 ml), the harmonic group had an average drainage volume of 38 ± 14 (range: 10–70 ml), and the conventional group had an average drainage volume of 130 ± 39 (range: 75–200 ml). The mean drainage volume was substantially bigger in LigaSure than in the harmonic group (P = 0.022), but it was much smaller in the traditional group than in the other two groups (P<0.001), according to the ANOVA test and repeated pairwise comparisons. As it shown in (Table 3), It was found that the harmonic group had the shortest hospital stay, with an average of 20 ± 4 hours, followed by the LigaSure group (29 ± 16) and the conventional group (35 ± 13 hours). The differences were statistically significant in all comparisons (P <0.05). Regretfully, one case (1.7%) in the Harmonic group and one case (1.7%) in the LigaSure group experienced temporary RLN damage; both cases recovered after two months

DISCUSSION

The use of energy-based tools in thyroid surgery has led to the development of an experienced phrase that includes understanding the tool's mechanism of action, safety distance, activation, and lag durations as essential components for carrying out a safe procedure and avoiding damage to surrounding structures. [9]. Harmonic FOCUS treatment lowers the rate of symptomatic hypocalcemia, according to Anandaravi et al. [10], but it has no discernible effect on the incidence of recurrent laryngeal nerve palsy. Ferri et al. [11] found the same results in their similar trial, while Ciftici et al. [12] found no difference in postoperative complications between LigaSure precise, Harmonic FOCUS, and conventional technique, despite the fact that these studies noted a decrease in postoperative hypocalcaemia linked to these devices. While Cosenza et al. [13] revealed that, in comparison to the conventional group, the ligasure and harmonic groups operating times were noticeably shorter, Ciftici et al. [12] discovered that the working time was shorter in the harmonic group than the conventional group, with the ligasure group falling in between the two other groups. Our results revealed that the mean duration of surgery in the conventional group (CAT group) was significantly longer than the other two groups (LS group and HF group) ($P < 0.001$), even though the mean duration of surgery in the HF group was shorter than the LS group ($P > 0.05$). The Harmonic Focus's lower working time is most likely a result of its special ultrasound technology, which enables simultaneous cutting and coagulation. Despite reducing the overall duration of surgery compared to traditional methods, these technologies do not demonstrate an improvement in the ratio of complications [14,15]. Numerous studies have produced contradictory findings, and prior research has not offered definitive data comparing the expenses of various novel procedures. [16,17]. The reason for this shift is that hospitals and health centers employ different target parameters to measure costs. This is particularly true in specialized centers where operating rooms are packed and longer workdays are a significant influence technologies require additional positive indicators to justify their use [18].

CONCLUSIONS

We support both the safety and effectiveness of the LigaSure Small Jaw and Harmonic Focus vessel sealing systems for routine thyroid surgery.

The real advantage of these devices in thyroid surgery is the related time savings, and less drainage volume making the application of these techniques a matter of balance between efficiency and price.

REFERENCES

1. Hannan SA. The magnificent seven: a history of modern thyroid surgery. Int J Surg. 2006;4:187-91. doi: 10.1016/j.ijsu.2006.03.002. DOI
2. Pant H, Snyderman CH. Hemostasis in Otolaryngology-Head and Neck Surgery. Otolaryngol Clin North Am. 2016;49(3):xix-xx. doi: 10.1016/j.otc.2016.03.013. DOI
3. Zarebczan B, Mohanty D, Chen H. A comparison of the LigaSure and Harmonic Scalpel in thyroid surgery: a single institution review. Ann Surg Oncol. 2011;18(1):214-8. doi: 10.1245/s10434-010-1334-3. DOI
4. Ruggiero R, Gubitosi A, Conzo G et al. Sutureless thyroidectomy. Int J Surg. 2014;12(1):S189-93. doi: 10.1016/j.ijsu.2014.05.011. DOI
5. Hammad AY, Deniwar A, Al-Qurayshi Z, et al. A prospective study comparing the efficacy and surgical outcomes of Harmonic Focus Scalpel versus LigaSure Small Jaw in thyroid and parathyroid surgery. Surg Innov. 2016;23(5):486-9. doi: 10.1177/1553350616639143. DOI
6. Ethicon Endo-Surgery, Inc. Summary of safety and effectiveness report on the UltraCision Harmonic Scalpel. 1999. http://www.accessdata.fda.gov/cdrh_docs/pdf/K993054.pdf [Accessed 26 October 2024]
7. The Council of the European Communities. Council directive 93/42/EEC concerning medical devices. http://eur-Lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:EN:PDF [Accessed 26 October 2024]
8. Ethicon Endo-Surgery, Inc. Traditional 510(k) summary of the Harmonic FOCUS Shears, aka, Ultrasonic surgical instrument. http://www.accessdata.fda.gov/cdrh_docs/pdf10/K100597.pdf [Accessed 26 October 2024]
9. Dionigi G, Wu CW, Kim HY et al. Safety of energy based devices for hemostasis in thyroid surgery. Gland Surg. 2016;5(5):490-494. doi: 10.21037/gs.2016.09.01. DOI
10. Anandaravi BN, Aslam MA, Nair PP. Prospective randomized study using Focus Harmonic Scalpel versus conventional hemostasis for vessel ligation in open thyroid surgery. Int Surg J. 2017;4:1431-7. doi:10.18203/2349-2902.isj20171156. DOI
11. Ferri E, Armato E, Spinato G, Spinato R. Focus Harmonic Scalpel compared to conventional haemostasis in open total thyroidectomy: a prospective randomized trial. Int J Otolaryngol. 2011:2011:357195. doi: 10.1155/2011/357195. DOI
12. Ciftici F. Differences in thyroidectomy outcomes based on surgical method: A comparison of LigaSure Precise, Harmonic Focus and traditional methods. Int Surg. 2016;101(3-4):121-6. doi:10.9738/INTSURG-D-15-00176.1. DOI
13. Cosenza G, Morano C, Cilurso F et al. LigaSure small jaw vs. Harmonic Focus and clamp-tie technique in total thyroidectomy for benign disease: A prospective randomized trial. Clin Surg. 2018;3:2038.

14. Manouras A, Lagoudianakis EE, Antonakis PT et al. Electrothermal bipolar vessel sealing system is a safe and time-saving alternative to classic suture ligation in total thyroidectomy. Head Neck. 2005;27(11):959-62. doi: 10.1002/hed.20271. DOI
15. Manouras A, Markogiannakis H, Koutras AS et al. Thyroid surgery: Comparison between the electrothermal bipolar vessel sealing system, Harmonic Scalpel, and classic suture ligation. Am J Surg. 2008;195(1):48-52. doi: 10.1016/j.amjsurg.2007.01.037. DOI
16. Sebag F, Fortanier C, Ippolito G et al. Harmonic Scalpel in multinodular goiter surgery: impact on surgery and cost analysis. J Laparoendosc Adv Surg Tech A. 2009;19(2):171-4. doi: 10.1089/lap.2008.0043. DOI
17. Leonard DS, Timon C. Prospective trial of the ultrasonic dissector in thyroid surgery. Head Neck. 2008;30(7):904-8. doi: 10.1002/hed.20805. DOI
18. Oussoultzoglou E, Panaro F, Rosso E et al. Use of BiClamp decreased the severity of hypocalcemia after total thyroidectomy compared with LigaSure: a prospective study. World J Surg. 2008;32(9):1968-73. doi: 10.1007/s00268-008-9671-0. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Associated gene polymorphism (*ABCG2*) and drug-resistant in patients with epilepsy

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ABSTRACT

Aim: To evaluate useful variations in ABCG2 gene in relation to reaction of epileptic tablets in people with partial epilepsy. Additionally, explore opportunity of blended outcomes of variations in more than one transporter genes.

Materials and Methods: The study included sixty-five sufferers and forty healthful people; there were no top notch versions in phrases of age, gender, antiseizure medication therapy, or precise kinds of prescription drugs used. Polymorphism testing involved DNA extraction from the sample. Data pertaining to studies that examined correlation between ABCG2 polymorphisms were sought out. A total of 105 individuals, 65 of whom were patients and 40 of whom were healthy controls, were enrolled from October 2023 to April 2024 in this case-control research that took place in a hospital setting.

Results: Common age of sufferers turned into 22.51 ± 5.89 years, while manage organization had a median age of 19.24 ± 3.77 years. Distribution of sufferers and control individuals had a comparable frequency, with no brilliant disparities in terms of gender, antiseizure drug therapy, or antiseizure remedy kind. The heterozygous genotype CT became observed to be greater commonplace in patients compared to the manage group. The correlation among the ABCG2 C>T poly allele polymorphism and the risk of epilepsy was quite widespread.

Conclusions: Overall, the study found that the ABCG2 C>T (rs2231137) polymorphism is associated with an increased risk of epilepsy. Specifically, the patient group was more likely to have the heterozygous genotype CT, with the allele C, compared to the control group.

KEY WORDS: ABCG2 gene, reaction of epileptic tablets, antiseizure medication therapy

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INTRODUCTION

ATP-binding cassette transporters play a function in the way medicines are processed and how the frame responds to them in unique conditions. There had been several recognized versions in ATP-binding cassette transporter genes that are related to adjustments within the way prescription drugs are transported. A worldwide incidence rate of 41 to 187 per 100,000 persons is associated with epilepsy, a common neurological disorder in children [1-2]. The incidence is higher in developing nations, particularly in rural areas [2]. Twenty percent of patients still experience severe drug-resistant seizures, even though several antiseizure medications (ASM) have been developed in the past few years [3]. The inability to gain seizure control or independence after adequate trials of two properly chosen antiseizure medication (ASM) regimens, either alone or in combination, is a hallmark of drug-resistant epilepsy (DRE) [4-5]. The pathophysiology of epilepsy, the pharmacokinetics of the ASM, the interaction between the ASM and its target(s), and genetic variables are the primary determinants of the response to antiseizure medicine (ASM) [6-7]. To understand the biological process behind DRE, two related theories have been put forward, the "target" and the "transporter" hypotheses [8-9]. Genetic variations have the potential to affect the pharmacokinetics and pharmacodynamics of ASMs at every step of their process, from gastrointestinal absorption to drug distribution to the brain, pharmacological activity at brain sites, disposal, and metabolism [10]. The efficacy of the therapy can be altered by these variables, which can affect transporters and target proteins [10]. An essential physiological role of the Blood-Brain Barrier (BBB) is to protect and stabilize the central nervous system (CNS) [11]. Members of the superfamily of ATP binding cassette (ABC) transporters allow chemicals to pass through the blood-brain barrier (BBB) [12]. A crucial member of the ABC superfamily of transporters, the ABCG2 protein is encoded by the ABCG2 gene located on chromosome 4q22. One possible explanation for

the difficulty in administering pharmacological therapy for seizures is that the brain acts as a barrier, blocking the entrance of ASMs and other pharmacological substances [13]. Although the transporter theory does not completely explain its origin, it is considered that the activation of efflux transporters in the blood-brain barrier (BBB) contributes to the establishment of antimicrobial drug resistance [14]. A large number of antiseizure medicines (ASMs) work by influencing sodium channels. Consequently, the SCN1A gene has been suggested as a possible locus to investigate SNPs' role in drug-resistant epilepsy (DRE) [16-17]. Another possible element that might be involved in drug recognition exams (DRE) is drug metabolism. The CYP3A subfamily, and more especially CYP3A4 and CYP3A5, is responsible for the majority of ASM metabolism [18-21]. There is more genetic diversity in the CYP3A5 gene than in the CYP3A4 gene, which causes variations in expression and catalytic activity from person to person. Antiseizure medication (ASM) response may thus be affected by CYP3A5 genetic variants [22]. Recent studies have highlighted the critical role of ATP-binding cassette (ABC) transporters in drug pharmacokinetics and pharmacodynamics. These membrane proteins significantly influence the absorption, distribution, and elimination of various pharmaceuticals. The [23] demonstrated that ABC transporters, particularly P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance-associated proteins (MRPs), actively efflux drugs from cells, potentially limiting their therapeutic efficacy. This research has led to the development of novel strategies to overcome transporter-mediated drug resistance and improve drug delivery to target tissues. For instance, Chen et al. (2024), [24] reported the successful use of nanoparticle-based drug delivery systems to bypass ABC transporter-mediated efflux, enhancing the efficacy of anticancer drugs in multidrug-resistant tumor cells. The impact of ABC transporters on drug response has gained significant attention in the field of personalized medicine. Genetic polymorphisms in ABC transporter genes have been associated with variations in drug response and toxicity among individuals. The [25] reported on a large-scale implementation of ABC transporter genotyping in a major healthcare system, demonstrating improved treatment outcomes and reduced adverse effects through personalized drug selection and dosing strategies.

AIM

To evaluate useful variations in ABCG2 gene in relation to reaction of epileptic tablets in people with partial epilepsy. Additionally, explore opportunity of blended outcomes of variations in more than one transporter genes.

MATERIALS AND METHODS

SAMPLES COLLECTION

Participants with epilepsy were surveyed in order to get samples. Polymorphism testing involved DNA extraction from the sample. Data pertaining to studies that examined the correlation between ABCG2 polymorphisms were sought out. A total of 105 individuals, 65 of whom were patients and 40 of whom were healthy controls, were enrolled from October 2023 to April 2024 in this case-control research that took place in a hospital setting.

DNA EXTRACTION AND GENOTYPING

Before genomic DNA extraction, blood samples were taken from participants and kept at 4 degrees Celsius in Ethylene-diamine-tetra-acetic acid (EDTA) tubes. Using the traditional salting-out method, genomic DNA was isolated from whole blood. The most significant SNPs in the candidate genes were selected, including ABCG2 chr4:88139962 C>T (rs2231137). In this study, we genotyped SNPs using the Primer1 ARMS-PCR primer generation programme and the NCBI-SNP database, scientific Researcher Co. Ltd. Iraq provided the primers, as shown in Table 1.

STATISTICAL ANALYSIS

In a study of Egyptian epileptic patients, the chi-square test was used to evaluate the Hardy-Weinberg equilibrium of three ABCG2 gene SNPs coupled with drug resistance. We conducted the Chi-square test to see if there was a statistically significant relationship between the 95% CI and the observed odds ratio (OR). An estimate was considered significant if its P value was less than or equal to 0.05, after the data were examined using bilateral probability.

RESULTS

A total of sixty-five patients and forty healthy controls were included in the present investigation. Table 2 shows the demographic information of the control group and the patients. In contrast to the control group, which had an average age of 19.24 ± 3.77 years, the patients' average age was 22.51 ± 5.89 years. The average ages of the patients and the control group did not differ significantly (P = 0.277). Again, when looking

Table 1. Primer sequences used for high-resolution melting method

SNPs	Sequencing	
ABCG2 C>T (rs2231137)	F	AAACCTGTGAGGTTCACTGTAGG
	R	CTGCAGAAAGATAAAAACTCTCCAG

Table 2. Demographic characteristics of patients and control subjects

Characteristic	Patients n = 65	Control n =40	P value
Age (years)			
Mean ±SD	22.51 ± 5.89	19.24 ± 3.77	0.277 † NS
Range	18-22	19-22	
18-19 *n* (%)	19 (29.23%)	15 (37.5%)	0.598 ¥ NS
20-21 *n* (%)	24 (36.92%)	11 (27.5%)	
>22 *n* (%)	22 (33.84%)	15 (37.5%)	
Gender			
Male, *n* (%)	33 (50.76%)	19 (47.5%)	0.299 ¥ NS
Female, *n* (%)	32 (49.23%)	21 (52.5%)	
Epilepticus history status			
Positive	41 (63.07%)	0 (0.00%)	0.001 ¥ S
Negative	14 (21.87%)	0 (0.00%)	
Number of antiseizure medication therapy			
1 antiseizure medication	26 (40.0%)	0 (0.00%)	0.0621 ¥ NS
2 antiseizure medications	11 (16.92%)	0 (0.00%)	
>2 antiseizure medications	28 (43.07%)	0 (0.00%)	
Type of antiseizure medications			
Non-enzyme inducing	31 (47.69%)	0 (0.00%)	0.524 ¥ NS
Enzyme inducing and combination	34 (52.30%)	0 (0.00%)	
ASMs used in patients (%)			
Carbamazepine	25 (38.46%)	0 (0.00%)	0.741 ¥ NS
Valproic acid	24 (36.92%)	0 (0.00%)	
Oxcarbazepine	16 (24.61%)	0 (0.00%)	

n: number of cases; SD: standard deviation; †: independent samples t-test; ¥: Chi-square test; NS: not significant at $P > 0.05$; HS: highly significant at $P \leq 0.05$.

at the frequency distribution by age, we could not find any significant difference between the control group and the patients (P = 0.598). While the control group included 21 females (52.5%) and 19 males (47.5%), the patients' group included 33 men (50.76%) and 32 females (49.23%). Patients and controls did not differ significantly (P = 0.299) in terms of gender distribution. Furthermore, when considering the amount of medication used to treat seizures, The patient group included 28 people (or 43.17% of the total) who were using more than 2 antiseizure medications, 11 people (16.92%) who were taking 2 drugs, and 26 people (40.0%) who were using 1 drug. The gender distribution of the patients and control individuals did not differ significantly (P = 0.0621). This class of antiepileptic medications of the patients surveyed, 31 (or 47.69%) were found to not induce enzymes, whereas 34 (or 52.30%) were found to induce enzymes or both. The gender distribution of the control individuals and patients did not differ significantly (P = 0.524). Just how many patients were given ASMs? Eleven people (34.61%) in the patient group took carbamazepine, twenty-four people (39.21%) took valproic acid, and sixteen people (24.61%) took oxycarbazepine. The gender distribution of the control individuals and patients did not differ significantly (P = 0.741). The data presented above show that the sick group and the control group are statistically equivalent.

GENOTYPIC ANALYSIS FOR STUDIED GENES IN PATIENTS AND CONTROL GROUPS

Table 3 displays the correlation between the ABCG2 C>T (rs2231137) POLY gene variant and the probability of

Table 3. Genotypes frequency in patients and control group

C>T (rs2231137)						
Genotype	**Patients n=65**	**Control n=40**	**P1**	**P2**	**OR**	**95% CI**
CC	28	15	0.019 ¥ S	0.625 ¥ S	1.0667	0.4634- 2.4554
CT	33	20		0.553 ¥ NS	2.0625	0.4949- 8.5954
TT	4	5		Reference	Reference	Reference

P1: overall comparison; P2: Individual genotype comparison versus reference; n: number of cases; ¥: Chi-square test; OR: odds ratio; CI: confidence interval; EF: etiologic fraction; NS: non-significant.

Table 4. POLY allele frequency in patients and control group

rs1354742084 A>C					
Genotype	**Patients n=130**	**Control n=80**	**P**	**OR**	**95%CI**
C	89	50	0.035 ¥ HS	1.3024	0.7259 - 2.3369
T	41	30		0.7678	0.4279 - 1.3776

n: number of alleles; ¥: Chi-square test; OR: odds ratio; CI: confidence interval; EF: etiologic fraction; PF: preventive fraction; HS: highly significant at $P \leq 0.01$.

acquiring epilepsy. The frequency of the heterozygous genotype CT was 33 occurrences in the patients group and 20 occurrences in the control group. The statistical significance of this difference was determined to be P=0.019. The odds ratio for patients with epilepsy who had genotype CT was 1.0667 (95% CI: 0.4634-2.4554), indicating that it was a risk factor.

Table 4 shows the association between the ABCG2 C>T (rs2231137) polyallele polymorphism and the risk of epilepsy. Allele C occurred more frequently in the sick group (89 instances) than in the control group (50 instances). A statistical analysis revealed a significant difference (P = 0.035).

DISCUSSION

This case-control research aimed to determine whether there was a correlation between three genes thought to have a role in the development of drug-resistant epilepsy (DRE) and certain single nucleotide polymorphisms (SNPs). As the number of T alleles in the ABCG2 gene increases, we found that the single nucleotide polymorphism (SNP) rs2231137 is associated with a higher risk of drug resistance epilepsy (DRE). For the first time in this particular cohort, the finding and the high link provide evidence that the ABCG2 gene may be involved in the development of drug-resistant epilepsy (DRE). Research using prospective methodologies and bigger sample sizes may be stimulated by these findings. The results show that among Egyptians, the ABCG2 (rs2231137) polymorphism is significantly associated with epilepsy and Pharmaco-resistant epilepsy. Previous studies have failed to discover a connection between the ABCG2 rs2231137 SNP and drug-resistant epilepsy (DRE) [26], which contradicts our findings. Research by Shen et al. sought to determine how the ABCG2 rs2231137 polymorphism affected Lamotrigine's efficacy in treating seizures in Chinese individuals. There was shown to be no statistically significant relationship between the two variables [27]. Additionally, for epilepsy patients, the existence of genetic variants in the ABCG2 transporter (rs2231137) does not significantly affect the prediction of treatment response, as [28] showed. In this groundbreaking study, we use a systematic review of the literature to show that the ABCG2 rs2231137 SNP is associated with an elevated risk of DRE in children. A number of studies have shown that genetic polymorphisms cause an overexpression of ABC transporter proteins like ABCG2 [29], but no one has yet provided a clear explanation for this phenomenon. Excessive synthesis of ABC transporters, particularly ABCG2, at the blood-brain barrier (BBB), is a pathophysiological mechanism of drug-resistant epilepsy (DRE). Inhibiting the entrance of several antiseizure drugs (ASMs) including gabapentin, lamotrigine, levetiracetam, and phenobarbital, ABCG2 is expressed at greater levels in endothelial cells, astrocytes, and neurons of the blood-brain barrier (BBB). Pharmacokinetic parameters such as distribution, action, and excretion are significantly affected by cytochrome P450 genes, which are involved in the metabolism of most antiseizure drugs. Therefore, these genes can affect how well these drugs work to suppress seizures generally [30]. Several cytochrome P450 proteins, including as the CYP3A5 enzyme, are involved in the metabolism of ASMs. A mutant allele known as CYP3A5*3 (rs776746) causes the enzyme CYP3A5 to not function as a catalytic agent [31]. Multiple criteria indicate that CYP3A5*3 is not associated with pharmacoresistance. Other cytochrome P450 proteins metabolize ASMs in addition to CYP3A5. They can make up for each other's diminished activity since CYP3A4 and CYP3A5 are structurally and substrate selectivity-wise quite similar. A single nucleotide poly-

morphism (SNP) in the gene may have less of an impact due to this compensatory [32]. There is polymorphism in both the CYP3A5 and CYP3A4 enzymes, although only the latter shows inducible effects [33]. The effect of inductions on enzymes that metabolize drugs is thought to be larger than that of polymorphisms. Our population of drug-resistant patients may be taking many drugs, each of which may include a chemical that increases CYP3A activity and, by extension, the influence of CYP3A5 variants on treatment efficacy. This is similar to the findings of other studies [34-35]. Because drug-resistant epilepsy (DRE) has such far-reaching consequences in neurological, psychological, educational, social, and occupational domains, investigating its causes is essential for the creation of alternative seizure medicines (ASM) and treatment approaches [36]. The study's findings can help clinicians apply precision medicine principles to tackle these specific problems, such as unregulated emergencies and high quantities of ineffective antimicrobial drugs (ASM), which lead to significant neuropsychiatric consequences like depression and anxiety disorders, social harm, reduced quality of life, increased occurrence of other medical conditions like intellectual disability and attention and learning difficulties, and an elevated risk of death [37]. Depending on the patient's reaction to medications, this helps choose the best course of therapy and can also shed light on how to personalize treatment for certain genotypes. However, before drawing any conclusions, it is critical to identify and resolve the study's shortcomings. Odds ratio (OR) confidence intervals are wider and the marginal p-value is 0.05 because of the study's small sample size. This means that bigger sample sizes and prospective study methodologies are required to confirm the results. We also did not look for a connection between the potential SNPs and ASM concentrations, mainly because clinical settings seldom monitor ASM concentrations. Children from Iran were the subjects of our case-control research, which took place in a single referral hospital. Hence, to make the results more generalizable, further research in groups with different genetic patterns is needed. Our research has shown that there is evidence linking a specific genetic variation in the ABCG2 gene-more specifically, an increase in the frequency of the T allele-to an increased risk of drug-resistant epilepsy in children. The implications of this finding for understanding the role of ABCG2 gene variation in drug-resistant epilepsy in children are substantial. To find more SNPs associated with drug-resistant epilepsy (DRE) on a genome-scale, genome-wide association studies are required.

CONCLUSIONS

The study found that the ABCG2 C>T (rs2231137) polymorphism is associated with an increased risk of epilepsy. Specifically, the patient group was more likely to have the heterozygous genotype CT, with the allele C, compared to the control group.

ABBREVIATION

ABC: ATP-Binding Cassette (ABC)
ASM: Antiseizure Medications
DRE: Drug-Resistant Epilepsy
CNS: Central Nervous System
BCRP: Breast Cancer Resistance Protein
MRPs: Multidrug Resistance-Associated Proteins
BBB: Blood-Brain Barrier

REFERENCES

1. Wirrell EC. Predicting pharmacoresistance in pediatric epilepsy. Epilepsia 2013;54(2):19–22. doi: 10.1111/epi.12179. DOI
2. Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. Epileptic Disord 2015;17(2):117–23. doi: 10.1684/epd.2015.0736. DOI
3. Pohlmann-Eden B, Weaver DF. The puzzle(s) of pharmacoresistant epilepsy. Epilepsia 2013;54(2):1–4. doi: 10.1111/epi.12191. DOI
4. Kwan P, Arzimanoglou A, Berg AT et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51(6):1069–77. doi: 10.1111/j.1528-1167.2009.02397.x. DOI
5. Tellez-Zenteno JF, Hernandez-Ronquillo L, Buckley S et al. A validation of the new definition of drug-resistant epilepsy by the International League against Epilepsy. Epilepsia 2014;55(6):829–34. doi: 10.1111/epi.12633. DOI
6. Weber YG, Nies AT, Schwab M, Lerche H. Genetic biomarkers in epilepsy. Neurotherapeutics 2014;11(2):324–33. doi: 10.1007/s13311-014-0262-5. DOI
7. Balestrini S, Sisodiya SM. Pharmacogenomics in epilepsy. Neurosci Lett. 2018;667:27–39. doi: 10.1016/j.neulet.2017.01.014. DOI
8. Kasperaviciute D, Sisodiya SM. Epilepsy pharmacogenetics. Pharmacogenomics. 2009;10(5):817–36. doi: 10.2217/pgs.09.34. DOI
9. Rogawski MA, Johnson MR. Intrinsic severity as a determinant of antiepileptic drug refractoriness. Epilepsy Curr. 2008;8(5):127–30. doi: 10.1111/j.1535-7511.2008.00272.x. DOI
10. Loscher W, Klotz U, Zimprich F, Schmidt D. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia 2009;50(1):1–23. doi: 10.1111/j.1528-1167.2008.01716.x. DOI

11. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7(1):a020412. doi: 10.1101/cshperspect.a020412. DOI
12. Leandro K, Bicker J, Alves G et al. ABC transporters in drugresistant epilepsy: mechanisms of upregulation and therapeutic approaches. Pharmacol Res. 2019;144:357–76. doi: 10.1016/j.phrs.2019.04.031. DOI
13. Vasiliou V, Vasiliou K, Nebert DW. Human ATP-binding cassette (ABC) transporter family. Hum Genomics. 2009;3(3):281–90. doi: 10.1186/1479-7364-3-3-281. DOI
14. Tang F, Hartz AMS, Bauer B. Drug-Resistant Epilepsy: Multiple Hypotheses. Few Answers. Front Neurol. 2017;8:301. doi: 10.3389/fneur.2017.00301. DOI
15. Escayg A, Goldin AL. Sodium channels SCN1A and epilepsy: mutations and mechanisms. Epilepsia. 2010;51(9):1650–8. doi: 10.1111/j.1528-1167.2010.02640.x. DOI
16. Manna I, Gambardella A, Bianchi A et al. A functional polymorphism in the SCN1A gene does not influence antiepileptic drug responsiveness in Italian patients with focal epilepsy. Epilepsia. 2011;52(5):e40–4. doi: 10.1111/j.1528-1167.2011.03097.x. DOI
17. Abo El Fotoh WM, Abd El Naby SA, Habib MS et al. The potential implication of SCN1A and CYP3A5 genetic variants on antiepileptic drug resistance among Egyptian epileptic children. Seizure. 2016;41:75–80. doi: 10.1016/j.seizure.2016.07.005. DOI
18. Ghosh C, Marchi N, Desai NK et al. Cellular localization and functional significance of CYP3A4 in the human epileptic brain. Epilepsia. 2011;52(3):562–71. doi: 10.1111/j.1528-1167.2010.02956.x. DOI
19. Klotz U. The role of pharmacogenetics in the metabolism of antiepileptic drugs: pharmacokinetic and therapeutic implications. Clin Pharmacokinet. 2007;46(4):271–9. doi: 10.2165/00003088-200746040-00001. DOI
20. Loscher W, Delanty N. MDR1/ABCB1 polymorphisms and multidrug resistance in epilepsy: in and out of fashion. Pharmacogenomics. 2009;10(5):711–3. doi: 10.2217/pgs.09.47. DOI
21. Panomvana D, Traiyawong T, Towanabut S. Effect of CYP3A5 genotypes on the pharmacokinetics of carbamazepine when used as monotherapy or coadministered with phenytoin, phenobarbital or valproic acid in Thai patients. J Pharm Sci. 2013;16(4):502–10. doi: 10.18433/j3q888. DOI
22. Emich-Widera E, Likus W, Kazek B et al. CYP3A5*3 and C3435T MDR1 polymorphisms in prognostication of drug-resistant epilepsy in children and adolescents. Biomed Res Int. 2013;2013:526837. doi: 10.1155/2013/526837. DOI
23. Robey RW, Pluchino KM, Hall MD et al. Revisiting the role of ABC transporters in multidrug-resistant cancer. Nat Rev Cancer. 2018;18(7):452-464. doi: 10.1038/s41568-018-0005-8. DOI
24. Chen Y, Zhang C, Huang Y et al. Intranasal drug delivery: the interaction between nanoparticles and the nose-to-brain pathway. Adv Drug Deliv Rev. 2024:207:115196. doi: 10.1016/j.addr.2024.115196. DOI
25. Xu K, Duan S, Wang W et al. Nose-to-brain delivery of nanotherapeutics: Transport mechanisms and applications. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2024;16(2):e1956. doi: 10.1002/wnan.1956. DOI
26. Kim DW, Lee SK, Chu K et al. Lack of association between ABCB1, ABCG2, and ABCC2 genetic polymorphisms and multidrug resistance in partial epilepsy. Epilepsy Res. 2009;84(1):86–90. doi: 10.1016/j.eplepsyres.2008.12.001. DOI
27. Kwan P, Wong V, Ng PW et al. Gene-wide tagging study of the association between ABCC2, ABCC5 and ABCG2 genetic polymorphisms and multidrug resistance in epilepsy. Pharmacogenomics. 2011;12(3):319–25. doi: 10.2217/pgs.10.183. DOI
28. Shen CH, Zhang YX, Lu RY et al. Specific OCT1 and ABCG2 polymorphisms are associated with Lamotrigine concentrations in Chinese patients with epilepsy. Epilepsy Res. 2016;127:186–90. doi: 10.1016/j.eplepsyres.2016.09.004. DOI
29. Chen J, Su QB, Tao YQ et al. ABCC2 rs2273697 is associated with valproic acid concentrations in patients with epilepsy on valproic acid monotherapy. Pharmazie. 2018;73(5):279–82. doi: 10.1691/ph.2018.7344. DOI
30. Chen J, Su Q, Qin J et al. Correlation of MCT1 and ABCC2 gene polymorphisms with valproic acid resistance in patients with epilepsy on valproic acid monotherapy. Drug Metab Pharmacokinet. 2019;34(3):165–71. doi: 10.1016/j.dmpk.2018.01.006. DOI
31. Chen P, Yan Q, Xu H et al. The effects of ABCC2 G1249A polymorphism on the risk of resistance to antiepileptic drugs: a meta-analysis of the literature. Genet Test Mol Biomarkers. 2014;18(2):106–11. doi: 10.1089/gtmb.2013.0362. DOI
32. Wang Y, Tang L, Pan J et al. The recessive model of MRP2 G1249A polymorphism decreases the risk of drug-resistant in Asian Epilepsy: a systematic review and meta-analysis. Epilepsy Res. 2015;112:56–63. doi: 10.1016/j.eplepsyres.2015.02.007. DOI
33. Guengerich FP. Cytochrome p450 and chemical toxicology. Chem Res Toxicol. 2008;21(1):70–83. doi: 10.1021/tx700079z. DOI
34. Lee SJ, Bell DA, Coulter SJ et al. Recombinant CYP3A4*17 is defective in metabolizing the hypertensive drug nifedipine, and the CYP3A4*17 allele may occur on the same chromosome as CYP3A5*3, representing a new putative defective CYP3A haplotype. J Pharmacol Exp Ther. 2005;313(1):302–9. doi: 10.1124/jpet.104.078758. DOI
35. Berno G, Zaccarelli M, Gori C et al. Analysis of single-nucleotide polymorphisms (SNPs) in human CYP3A4 and CYP3A5 genes: potential implications for the metabolism of HIV drugs. BMC Med Genet. 2014:15:76. doi: 10.1186/1471-2350-15-76. DOI
36. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138(1):103–41. doi: 10.1016/j.pharmthera.2012.12.007. DOI
37. Laxer KD, Trinka E, Hirsch LJ et al. The consequences of refractory epilepsy and its treatment. Epilepsy Behav. 2014:37:59-70. doi: 10.1016/j.yebeh.2014.05.031. DOI

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

In Ovo evaluation effects of normal saline on cardiovascular system development

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ABSTRACT

Aim: To estimate the effect of normal saline on early development stage of embryo during pregnancy after LD50 dose determination and to record of heart electrocardiogram ECG for chick embryo and make histopathological sections for the heart to find if it suitable for pregnant women.

Materials and Methods: Novel data- acquisition record for embryo ECG, vision findings as well as histopathological study for 42h of development can support the exact harm and sudden death causes for embryo during first months of pregnancy.

Results: LD50 results show significant variation ($p<0.05$) between dose 2µl and other lethal doses and ECG show same variation according to recording in amplitude, QRS, and heart rate on the other hand the histopathological slides show clear teratology signs of veins malformation specially in dose 6, 8, and 10 µl and heart muscle rupture with sign of edema and pathological apoptosis.

Conclusions: Due to harmful effect of normal saline on chick embryo development especially heart and veins which lead to sudden death, they must not use for pregnant women during first 4 months or before pregnancy.

KEY WORDS: *In Ovo* evaluation, embryo cardiovascular system, saline

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INTRODUCTION

Experiments have employed the chick experimental model as a xenograft host for decades. Developmental biology's last uncharted territory is the study of early human development, which can now be done with the chick system [1, 2]. Comparative gene expression profiling between humans and chickens has been done, and the results show that cDC subsets are homologous [3]. Human and chicken dendritic cells link innate and adaptive immune responses, yet these diverse cell types are known to differ significantly. For example, the bursal secretory DCs in the bursa of Fabricius contain a particular subgroup of DCs found in birds but not mammals [4]. The chorioallantoic membrane of the chicken embryo has resurfaced for various uses. Compared to classical models, this one is more advantageous due to its cost-effectiveness, time efficiency, and ease of use. Because the chicken embryo eventually develops an embryonic immune system that is functionally similar to the human immune system, this review illustrates how the chicken embryo can be utilized as a model for immunological-based studies [5]. The chorioallantoic membrane assay for LD50 in chick embryos might provide a quick and low-cost substitute for rodents. It also has minimal bureaucratic barriers and is simple to execute. In addition, this model makes it possible to use a wide range of analytical techniques in Nano toxicological studies, from other side, chick embryo model was the pathogenic and immunization evaluation for a lot of drugs [6, 7]. Numerous studies have shown that the formation of coronary arteries starts when PE mesothelial cells migrate from the liver primordium to the surface of the heart, where they differentiate into a range of cell lineages that constitute different parts of the heart [8]. Thus, the technique that can simultaneously characterize non-invasively the cardiac and body movements (heartbeats) in terms of both strength and frequency could be applied to improve the development of precision poultry production systems and monitor embryos in physiological studies by using ballistocardiography methodology to investigate the non-invasive behavioral pattern of the cardiac and body movements of embryos during the incubation period that relies on an eggshell that has electric charges on it, or a single capacitor plate [9, 10]. A few embryos experienced cardiac failure and passed away in a matter of hours; intriguingly, these embryos have a cardiac failure pattern resembling that of end-stage heart failure in humans [11]. The primary mechanism of electrophysiology and ionic currents in the fertilized egg (embryonic

chicken) is similar to those of mammalian hearts. On the other hand, little is understood about the heart repolarization mechanism during development [12]. By developing ischemic data, the chick embryo model can further our understanding of pathophysiology and help us explore the fundamental mechanisms or possible therapeutic approaches in ischemia-associated disorders. This will increase our ability to treat ischemic stroke in humans [13].

AIM

The aim is to estimate the effect of normal saline on early development stage of embryo during pregnancy after LD50 dose determination and to record of heart electrocardiogram ECG for chick embryo and make histopathological sections for the heart to find if it suitable for pregnant women.

MATERIALS AND METHODS

STUDY DESIGN

Two separate experiments were conducted in two parts: first, for the LD50 study as shown in Fig. 1, and second, the same groups were selected for the cardiovascular toxicology study with control and saline as shown in Fig. 2.

Fertile eggs (*Gallus domesticus*) were selected for this project by incubate 75 eggs after air sac injection with normal saline (locally produced i/v 0.9% normal saline solution) to determine the LD50 dose (by use Hamilton syringe), and all embryo were monitored by non-invasion electrocardiography (ECG), vision test for blood vessels and heartbeat.

The same strain was selected for second experiment (about 105 fertilized eggs) with selected dose and after 42h ECG monitoring, vision test and make histopathological slides to diagnosis of the lesions.

The following measurements, instruments and methods were used:

• Incubation: using a Cimuka PD30 SH incubator with well-calibrated heater and humidity for both experiments;

• ECG: using a IWX214 working physiological system with three electrodes for non-invasive testing 0.3-35 Hz, millivolts;

• Vision testing: after recording the ECG, the same eggs are examined to diagnose changes in blood vessels and heartbeats and compare with the ECG results.

HISTOPATHOLOGICAL STUDY

Embryos from the same tested eggs were dissected using a microtome (3 microns) after formalin fixation and drying to create a block. Whole body eosin/hematoxylin staining was prepared, and cardiac tissue and cell analysis was performed.

RESULTS

In examining the ECG of chick embryo we focused particularly on the relationship between amplitude, QRS segment, between QRS, and heart rate [14], (Fig.3). As indicated in Table 1, a Kruskil-Wallis nonparametric one-way ANOVA test was performed to see if the LD50 differed significantly ($p<0.05$).

Table 1 illustrates how the increased mortality associated with the higher doses, 8µl and 10µl, reduced the doses utilized in the lethal dose in subsequent studies. In addition, not fertile eggs add to the results for accuracy [15].

Table 2 obviously show the ECG reading parameters with significant differences (*P* value <0.05) between control and doses 2µl ,4µl ,6µl respectively for all selective embryo except in two doses 8 µl and 10 µl due to death in early stage (before 42h). On the other hand, clear significant differences between all parameters in amplitude, QRS segment, between QRS, and heart rate.

The mean rank by group interaction (Fig. 4) revealed significant differences (P value < 0.05) between control and 4 µL dose (mean range 23 and 53) in magnitude, with the same p value (< 0.05) between 2 µL, 4 µL and 6 µL doses (mean range 38, 53 and 8, respectively).On the other hand, the QRS segment values show a significant difference between ($p<0.05$) between all doses and control (average rate 28.83, 32.17, 8 and 53) with one exception between control and dose 2µl. Similar rhythm can be clarified for both parameters: between QRS segments and heart rate with significant differences ($p<0.05$) between control and both doses 2µl and 6µl, also p value (<0.05) between 4µl and 6µl doses.

After recording the ECG, a visual inspection of control and chicken embryos injected after 42 hours was carried out. However, the embryo injected with 2 µl showed some malformations compared to the control, while at doses of 4 µl, 6 µl, 8 µl and 10 µl, signs of teratology could be clearly diagnosed (Fig. 5), with a small ligation-like shape in the right vitelline artery. Image (Fig.5B) illustrates the precise method to stop blood flow to the specified area of the chicken embryo vascular bed, thereby blocking blood flow in the surrounding vascular bed. While, in image (Fig.5C) showed the ischemic area of the vascular bed with complete growth retardation. On the other hand, image (Fig.5D) clarified bleeding in the area vascular and surround with clotting was seen at the edge of area pellucid and area vascular. Curvature in the neural tube was seen in some embryos. Image

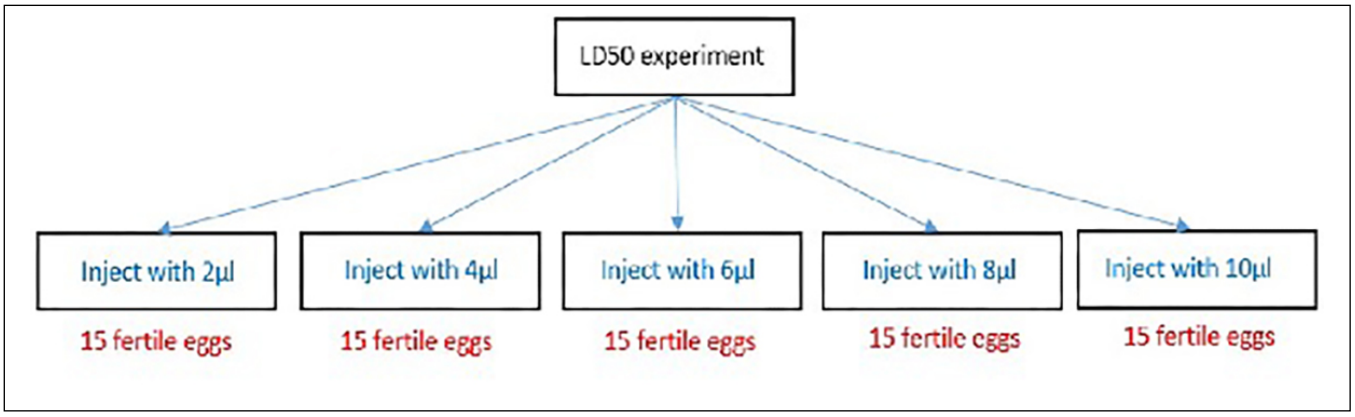

Fig. 1. LD50 study design.

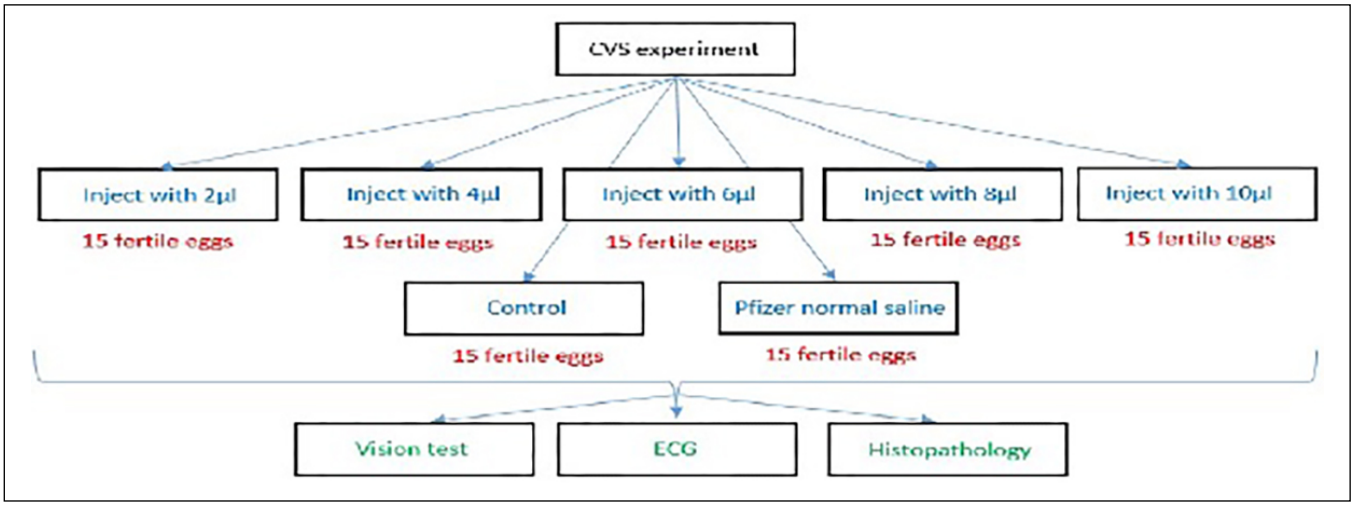

Fig. 2. CVS toxicology study design.

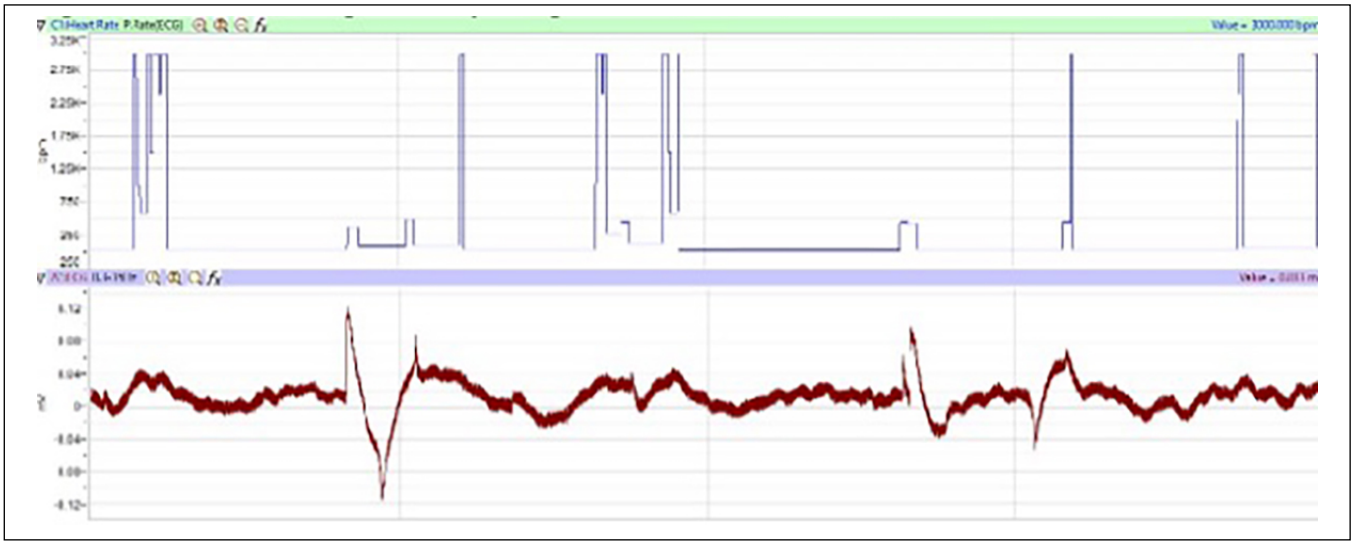

Fig. 3. Chart's surface displays online-calculated heart rate (HR) in BPM below and recordings of ECG signals above in µV.

(Fig.5E) of a completely dead embryo. The control group's hearts were seen to be developing typically. On the other hand, the regular saline-injected group had poorly grown hearts, as seen by the shorter transverse cardiac diameter (Fig. 6A). A histopathological analysis identified certain variations in the morphology of cardiomyocytes and ventricular structures. The embryos in the injected group showed a disordered arrangement of trabecular muscles in the left and right ventricles (Fig. 6B), along with some modifications in the tubular development of the heart. Cardiomyopathy in ventral aorta with primitive cardiac tube enlargement with partial ischemic sign as it shown in figure 7B. These findings suggested that normal saline impeded early embryos'

Table 1. Lethal dose (LD50) for saline solution on chicken embryo

Dose	Numbers	Dead	Live	Not fertile
Control	15	0	15	0
Normal saline	15	2	13	0
2 µl	15	5	5	5
4 µl	15	10	1	5
6 µl	15	10	5	0
8 µl	15	15	0	0
10 µl	15	15	0	0

Table 2. One-way ANOVA test for ECG recordings on chicken embryos

Dose	Parameters							
	Amplitude		QRS segment		Between QRS		Heart rate	
	Mean	SDs	Mean	SDs	Mean	SDs	Mean	SDs
Control	0.042	0.003	0.008	0.033	16.73	0.047	139.2	5.185
2 µl	0.145	0.001	1.888	0.023	5.069	0.017	218.2	1.334
4 µl	0.232	0.019	2.323	0.017	7.143	0.018	179.4	1.454
6 µl	0.017	0.001	1.424	0.015	1.042	0.012	299.6	2.063

*The mean difference is significant at the 0.05 level.

ability to build their hearts typically, which may be a crucial factor in embryonic demise.

DISCUSSIONS

An attempt is made to determine each test group's LD50 based on the data on embryo mortality (Table 1). Since mortality below and above 50% was occurred in various strains on different days, the LD50 values shown in Table 3 are derived on different dosages and days, it's obviously show the increasing of mortality rate start from normal saline group until completely lethal calculation for dose 10µl group compare with control group [16]. The estimated doses at LD50 for the inoculation of chicken embryos with the normal saline was 2µl, 4µl, 6µl, 8µl and 10µl respectively. This result is the first to report the appropriate dose inoculate these chicken embryos lines [17]. It should be taken into account that the embryo mortality on the dose. Therefore, determining the proper infectious dose is crucial; it should not be too high to prevent significant embryonic mortality [18]. Almost the whole incubation period was spent with the chicken embryos moving, but their pattern, pace, and type of movement varied during that time. The data in Fig. 3 show that two distinct forms of embryonic activity were observed during the incubation period: body and heart movements. Since the embryos were still small and immature during the early stages of incubation, body motions had little effect on the signal, which had a frequency between 0.3 and 0.8 Hz and 19–50 beats per minute [19]. The heart activity of chicken embryos causes micro-movements throughout the egg, which alters the lengths between the plates and, consequently, the potential difference between the receiving signal and the shell. At 42 hours after incubation, the first cardiac work single signals were recorded. The signal amplitude climbed non-steadily from 0.042 to 0.232 mV/s, and then abruptly dropped to 0.017 mV/s as the heart rate increased from 139 to 299 beats per minute. They were seen in the early hours before the high-dose group's embryonic fatalities [20]. The QRS segment during embryonic development in fertilized chicken eggs observed a gradual increase in QRS from 0.008 to 2.323mV/s; these results may be related to the expression during embryonic development of the genes encoding the cardiac potassium channels affected in repolarization [21]. On the other hand, visual test shows venous constriction, and after 48 hours of incubation, bleeding and clotting segments obtained from shell-free culture were obtained by transplantation of embryos at the early stage of cardiac loop formation using time-lapse analysis of chicken embryos with normal (left) and defective (right) vasculogenesis. Image series shown starts with embryos show a normal development of the extraembryonic vasculature except for groups 4µl and more after incubation. Nevertheless, the embryo on the right, which received a dose of 4 µl, died from end-stage heart failure with decompensated cardiac function for the group that received a 6 µl dose. A few hours later, the embryo showed signs of cardiac

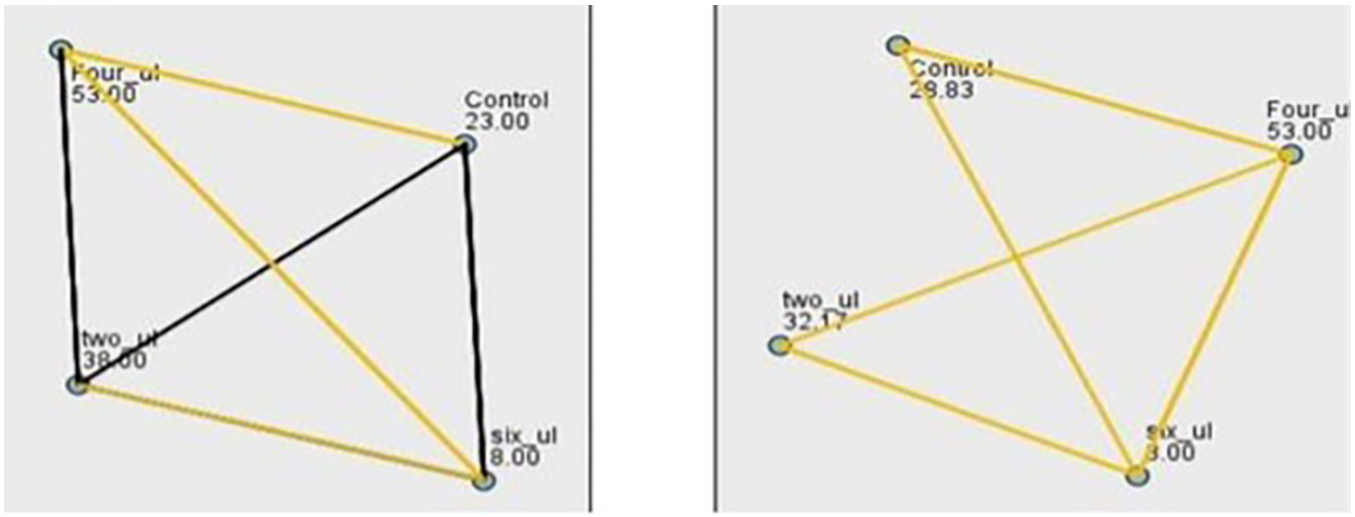

Fig. 4. Pairwise comparison between doses for both amplitude and QRS in chicken embryo.

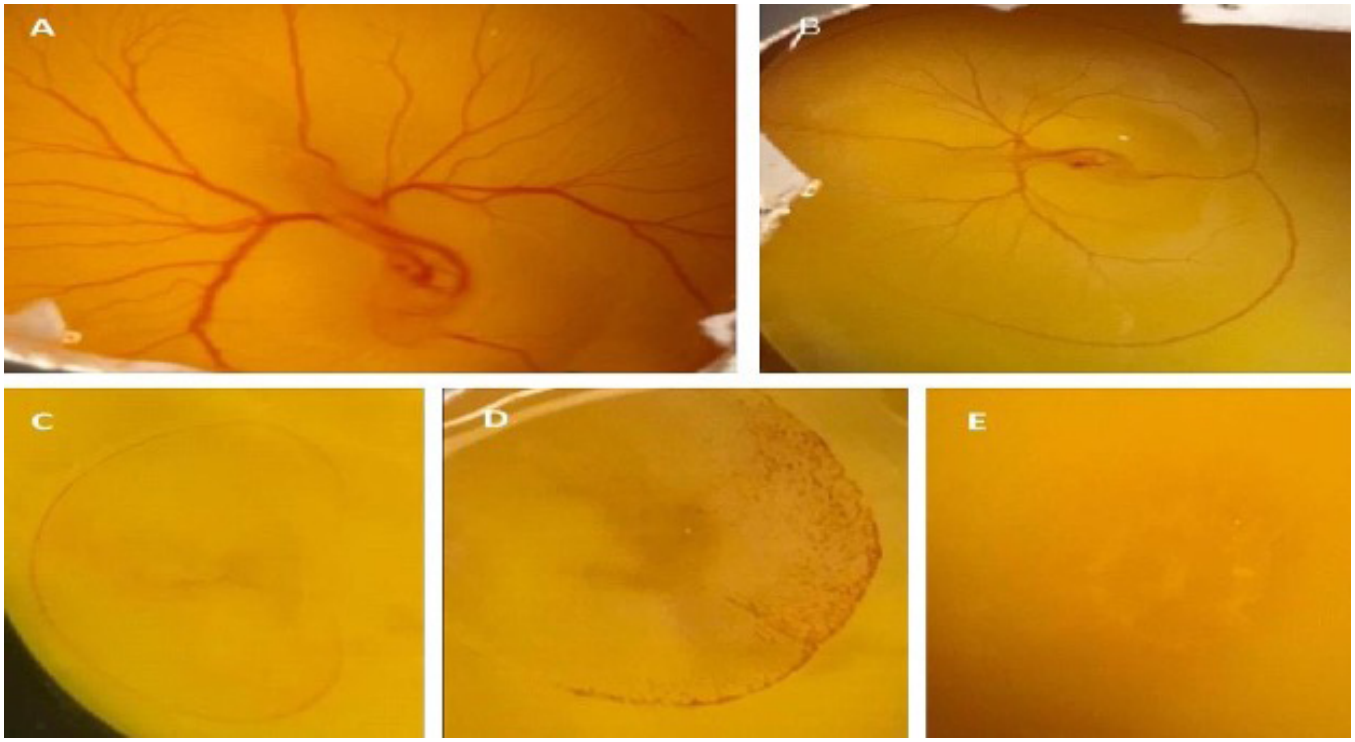

Fig. 5. Morphology (visual test) of chicken embryo at 42h: (A) Control embryo (2.0X); (B) Dose 2µl; (C) dose 4µl; (D) dose 6µl; (E) dose 8µl of normal saline solution.

failure, including peripheral vascular stasis and congested organs due to central pooling. According to the Histopathological investigation, the experimental groups (4µl and 6µl) experienced lesions in their heart tissue due to the doses utilized, which could potentially account for the high dose-related death rate of chicken embryos. The chicks probably died in the early hours, which resulted in histopathological lesions in the heart muscle chicken embryos. However, the other chicken embryos survived since the effect of normal saline was insufficient to cause death. Because the disturbed hemodynamics during the development of the heart valve and ventricle are so important, the results show an immediate decrease in the levels of the left atria ventricle (AV) canal, which leads to a further reduction in wall shell stress levels (WSS) in the left AV canal and relatively increased WSS levels in the right AV canal. According to Syamantak et al., a novel ex vivo ischemia model might be derived from the chick embryo partial ischemia paradigm. As a result,

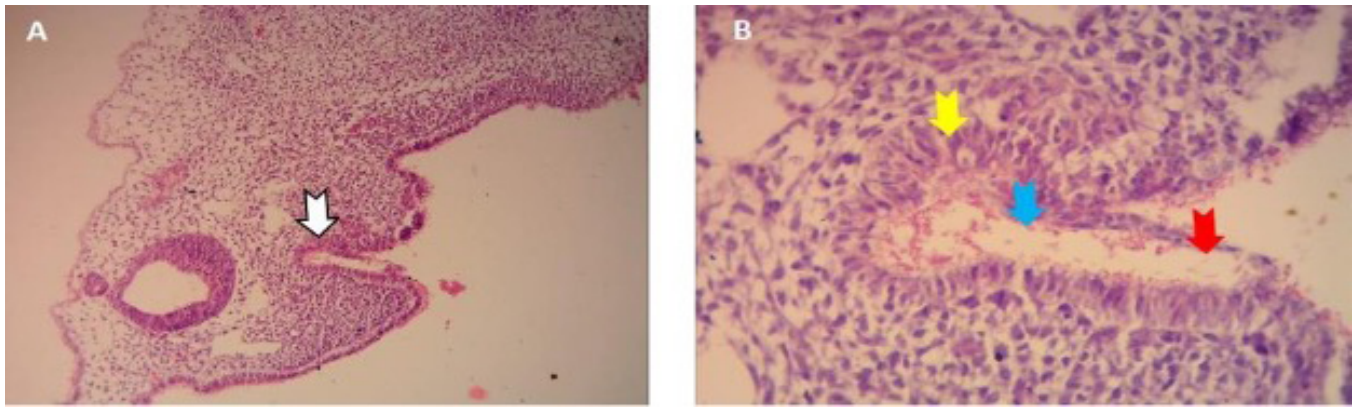

Fig. 6. Microtomes of control group of chicken embryos stained with eosin/hematoxylin: (A) control group 42h with normal tubular heart development (E&H); (B) ventral aorta (yellow), Primitive cardiac tube (Red), Vitelline vein development (E&H) (Blue).

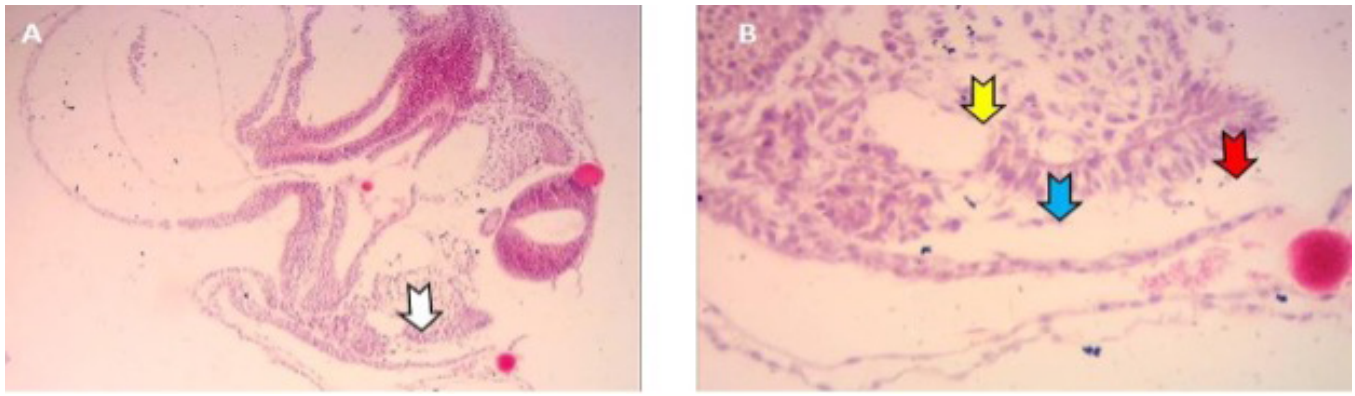

Fig. 7. Microtomes of 2 µl group of chicken embryos stained with eosin/hematoxylin: (A) dose 2, group 42h with moderate changes in tubular heart development (E&H) (Red), (B) ventral aorta cardiomyopathy (yellow), primitive cardiac enlargement (Blue), vitelline vein partial ischemia sign (E&H) 600x (Blue).

the current model can be utilized with established in vivo ischemia models to assess the effectiveness of anti-ischemic medications and gain a mechanistic understanding of the onset of ischemia.

CONCLUSIONS

Normal saline, especially 0.9% NaCl, contains more minerals than the solution itself. Some of these are related to the water source used to manufacture it, such as chlorine in tap water, or may be due to uncontrolled storage conditions that result in some toxic substances being released from the container itself. Therefore, for intravenous prophylaxis, the solution should be used with caution, especially during pregnancy due to its life-threatening effects on embryos in the early months of pregnancy, resulting in sudden embryonic death due to heart problems.

REFERENCES

1. Li W, Huang L, Lin W et al. Engraftable neural crest stem cells derived from cynomolgus monkey embryonic stem cells. Biomaterials. 2015:39:75-84. doi: 10.1016/j.biomaterials.2014.10.056. DOI
2. Martyn I, Kanno TY, Brivanlou AH. Chick Models and Human-Chick Organizer Grafts. Methods Mol Biol. 2019;2005:77-89. doi: 10.1007/978-1-4939-9524-0_6. DOI
3. Vu Manh T-P, Bertho N, Hosmalin A et al. Investigating evolutionary conservation of dendritic cell subset identity and functions. Front. Immunol. 2015. doi:10.3389/fimmu.2015.00260. DOI
4. Rehman ZU, Umar S, Meng C et al. Dendritic cell harmonised immunity to poultry pathogens; a review. World's Poultry Science Journal. 2017;73(3):581-590. doi:10.1017/S0043933917000496. DOI
5. Garcia P, Wang Y, Viallet J, Jilkova ZM. The chicken embryo model: A novel and relevant model for immune-based studies. Frontiers in immunology. 2021;12:791081. doi:10.3389/fimmu.2021.791081. DOI

6. Buhr CR, Eckrich J, Kluenker M et al. Determination of the LD50 with the chick embryo chorioallantoic membrane (CAM) assay as a promising alternative in nanotoxicological evaluation. Nanotoxicology. 2021;15(5): 690-705. doi: 10.1080/17435390.2021.1916635. DOI
7. Wakenell PS, Sharma JM, Slocombe RF. Embryo vaccination of chickens with infectious bronchitis virus histologic and ultrastructural lesion response and immunologic response to vaccination. Avian diseases. 1995;39(4):752-65.
8. Tomanek RJ. Formation of the coronary vasculature during development. Angiogenesis. 2005;8(3):273-84. doi: 10.1007/s10456-005-9014-9. DOI
9. Kemps B, Bamelis F, De Ketelaere B et al. Assessment of embryonic growth in chicken eggs by means of visible transmission spectroscopy. Spectroscopy. 2009:42033154. doi:10.1002/btpr.321. DOI
10. Pawlak K, Niedziolka J. Non-invasive measurement of chick embryo cardiac work. Czech J. Anim. Sci. 2004;49(1):8–15. doi: 10.17221/4265-CJAS. DOI
11. Tutarel O, Norozi K, Hornung O et al. Images in cardiovascular medicine. Cardiac failure in the chick embryo resembles heart failure in humans. Circulation. 2005;112(24):e352-3. doi: 10.1161/CIRCULATIONAHA.105.536029. DOI
12. Lee GS, Filipovic N, Lin M et al. Intravascular pillars and pruning in the extra embryonic vessels of chick embryos. Dev Dyn. 2011;240(6):1335-43. doi: 10.1002/dvdy.22618. DOI
13. Klocke R, Tian W, Kuhlmann MT, Nikol S. Surgical animal models of heart failure related to coronary heart disease. Cardiovasc Res. 2007;74(1):29-38. doi: 10.1016/j.cardiores.2006.11.026. DOI
14. Suzuki Y, Musashi H, Tazawa H. Noninvasive heart rate monitoring system for avian embryos based on the ballistocardiogram. Med Biol Eng Comput. 1989;27(4):399-404. doi: 10.1007/BF02441432. DOI
15. Rudolph B. Variations Investigations to Enterococcus faecalis as possible factor for etiology of amyloid arthropathy of brown layers. PhD thesis. 2004.
16. Tazawa H, Akiyama R, Moriya K. Development of cardiac rhythms in birds. Comp Biochem Physiol A Mol Integr Physiol. 2002;132(4) 675-89. doi: 10.1016/s1095-6433(02)00125-3. DOI
17. Matsushima T, Miura M, Patzke N et al. Fetal blockade of nicotinic acetylcholine transmission causes autism-like impairment of biological motion preference in the neonatal chick. Cereb Cortex Commun. 2022;3(4):tgac041. doi: 10.1093/texcom/tgac041. DOI
18. Phuphanin A, Sampanporn L, Sutapun B. Smartphone-Based Device for Non-Invasive Heart-Rate Measurement of Chicken Embryos. Sensors (Basel). 2019;19(22):4843. doi: 10.3390/s19224843. DOI
19. Kain KH, Miller JW, Jones-Paris CR et al. The chick embryo as an expanding experimental model for cancer and cardiovascular research. Dev Dyn. 2014;243(2):216-28. doi: 10.1002/dvdy.24093. DOI
20. Lee GS, Filipovic N, Lin M et al. Intravascular pillars and pruning in the extraembryonic vessels of chick embryos. Dev Dyn. 2011;240(6):1335-43. doi: 10.1002/dvdy.22618. DOI
21. Wiesmann N, Brieger J, Eckrich J. Toxicological Analysis by Assessment of Vascularization and Cell Viability Using the Chicken's Chorioallantoic Membrane (CAM Assay). Methods Mol Biol. 2023;2644:403-421. doi: 10.1007/978-1-0716-3052-5_26. DOI

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We reiterate our thanks to them and to the Dean of the College for providing a scientific atmosphere that contributes to creativity and innovation
This work done according to describe euthanasia procedures for chick embryos in various stages of development as well as to ensure euthanasia procedures and it will be our pleasure to introduce all documents and images to support above. The College of Pharmacy's Ethical Committee permitted the study to proceed in some health locations.

CONFLICT OF INTEREST
The Authors declare no conflict of interest

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ORIGINAL ARTICLE

CONTENTS

Point prevalence study of antibiotics use in Ramadi hospitals

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ABSTRACT

Aim: To describe antibiotic use in Al-Ramadi hospitals using the Biomérieux VITEK2 compact system.

Materials and Methods: A lot of different hospitals in Al- Ramadi were visited, checking Patients' illness profile. Information about antibiotics prescription pattern in Al- Ramadi hospitals had been collected from urinary tract infected patients using the Biomérieux VITEK2 compact system.

Results: Out of 67 specimens obtained from Urinary tract infection, fifty-two isolates were *E. coli*, eight isolates were *Klebsiella pneumoniae*, four were *Burkholderia cepacian*, and two were *Raoultella spp* and only one isolate *Acetobacter aceti*. The data analysis revealed that females had a higher prevalence of infection than males, with 41(68.30%) and 26(38.80%), respectively.

Conclusions: Resistance rates have shown variations over the years, they have typically remained elevated for antibiotics commonly employed in the empirical management of urinary tract infections. For successful treatment, it will be crucial to adjust therapy based on culture results and to consider resistance rates during empirical treatment.

KEY WORDS: antibiotic resistance, *E. coli, Klebsiella Pneumoniae*, urine cultures

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ABBREVIATIONS

AMs: Antimicrobial medicines
AMR: Antimicrobial resistance
HAIs: Hospital-Acquired Infections
WHO: World Health Organization
PPS: Point Prevalence Study
HRT: Hormone Replacement Therapy

INTRODUCTION

Antimicrobial medicines (AMs) are the pharmacological standard of care for infectious diseases. Any use of antimicrobials, especially antimicrobials (antibiotics), contributes to antimicrobial resistance (AMR), but misuse and overuse exacerbate resistance [1]. Antimicrobial-resistant infections can lead to severe illness and longer hospital stays, resulting in higher healthcare costs, medical errors, and mortality [2]. A systematic review found that antibiotic use was significantly higher in hospitals outside of Europe compared with those in Europe [3]. In hospitals, antibiotic therapy often has inadequate drug selection with respect to type of microorganism, route of administration, or duration of treatment [4]. As a result, most hospitalized patients either face potentially serious side effects or develop infections with resistant or difficult-to-treat pathogens (e.g., *Clostridium difficile*) without therapeutic response [5]. Hospitals can enhance their selection against antibiotic-resistant organisms through the frequent use of broad-spectrum antibiotics (e.g., cephalosporins, carbapenems), they also focus on common pathogens of hospital-acquired infections (HAIs), such as the group of (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter spp*.), leading to a vicious cycle of increased broad-spectrum antibiotic use [6]. The World Health Organization (WHO) Global Action Plan on Antimicrobial Resistance aims to strengthen surveillance and optimize antimicrobial prescribing [7]. These measures are being scaled up through interventions such as antimicrobial stewardship programmers (ASPs) in hospitals to improve clinical outcomes, ensure cost-effectiveness of antimicrobial therapy, and reduce the consequences of unintended use [8], however, the effort, coordination, and resources required to actively monitor hospital antimicrobial prescribing practices are high. Continuous collection of antibiotic prescribing data is not easy

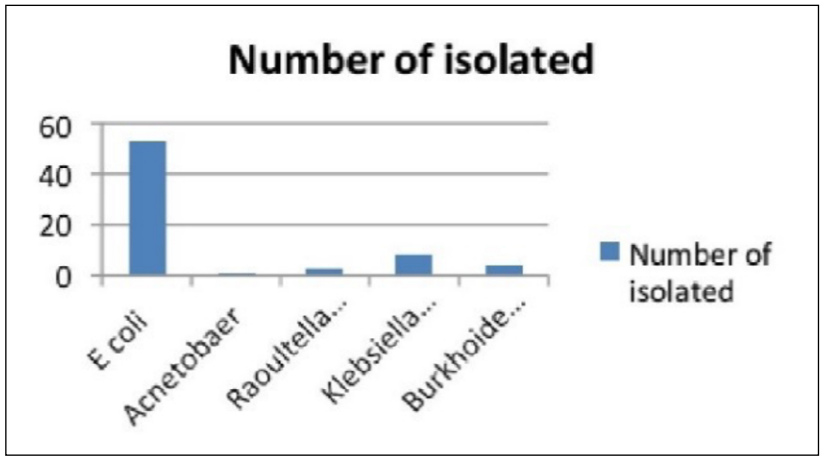

Fig 1. Distribution of bacteria from Urinary Tract infections (UTIs) patients

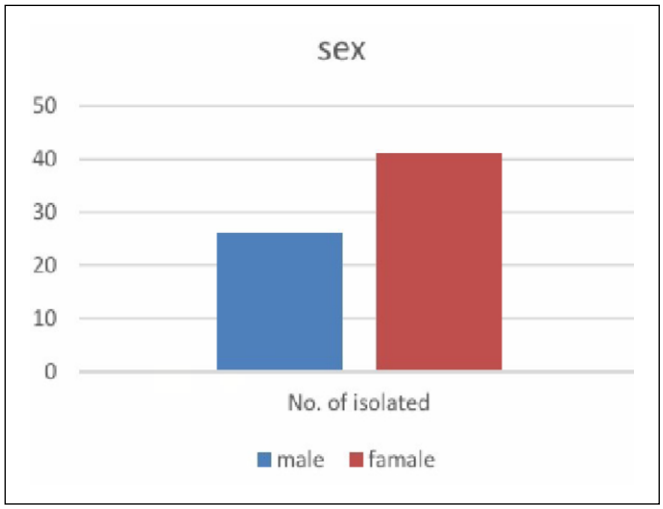

Fig. 2. Distribution of bacteria from Urinary tract infections (UTIs) patients. The data is presented in percentages based on gender criteria.

due to the high workload and resource requirements [9]. A feasible alternative is to collect data at specific time points. This can be done using a point prevalence study (PPS) approach, such studies can:

- Measure antibiotic consumption over time and assess changes in prescribing trends,
- Set quality improvement targets in different hospital departments,
- Evaluate the effectiveness of interventions implemented on response indicators identified in previous studies [10].

Point Prevalence Study evidence supports improving responsible use of antibiotics. Surveillance of hospital-acquired infections (HAIs) demonstrates the need for improved infection prevention and control, which forms the basis for combating antimicrobial resistance in healthcare settings. Point prevalence studies (PPS) are a useful approach to examine antibiotic prescribing patterns and identify targets for optimizing antibiotic use [11], therefore, the Global PPS Initiative and the WHO (WPPS) have proposed standardized methods for conducting PPS in hospitals [12].

AIM

The aim of this study is to describe antibiotic use in Al-Ramadi hospitals using the Biomérieux VITEK2 compact system.

MATERIALS AND METHODS

ISOLATION AND DETECTION OF BACTERIA

According to conventional procedures [13-14], all specimens were diagnosed microscopically (using Gram stain), morphologically, and biochemically. Commercial kits (VITEK2 gram negative and positive colorimetric identification kit) were used to perform several biochemical assays (BioMerieux, France).

ANTIBIOTICS SUSCEPTIBILITY

Antibiotics susceptibility tests by using the Biomérieux VITEK2 compact system (BioMerieux, France) against the following antibiotics: Cefotaxime, colistin, ceftazidim, cefipim, imepenem, meropenem, amikacin, tobramycin, gentamycin, trimethoprim / sulfamethaxazole, and ciprofloxacin.

STATISTICAL ANALYSIS

Data were analyzed using SPSS version 16 and Microsoft Office Word and Excel 2007. Nominal data were expressed as number and percent. Independent sample T-test was used for comparison of mean.

RESULTS

Out of 67 specimens obtained from different infection, 52 isolates were *E. coli*, 8 isolates were *Klebsiella pneumoniae*, 4 were *Burkholderia cepacian*, 2 were *Raoultella spp* and only one isolate *Acetobacter aceti* (Fig. 1). The data

Table 1. Distribution of infection according to the age

Age	No. of isolate	[%] of isolate
55-64	28	41.80%
45-54	14	20.90%
35-44	7	10.44%
25-34	5	7.46%
15-24	4	5.97%
5-14	4	5.97%
1-4	3	4.40%
<1	2	2.98%

analysis revealed that females had a higher prevalence of *infection* than males, with 41(68.30%) and 26(38.80 %), respectively Figure 2.

ANTIBIOTIC RESISTANCE PATTERN OF GRAM-NEGATIVE BACTERIA

As shown in Figure 3, the pattern of resistance was *Burkholderia* spp. resistant to cefotaxime, ciprofloxacin and colistin. E. coli was resistant to cefotaxime with moderate resistant to ciprofloxacin, K. pneumoniae were highly resistant to cefotaxime and colistin with moderate resistant to ciprofloxacin and gentamicin. *Acetobacte*r spp and *Raoutella* spp show highly resistant to cefotaxime, ciprofloxacin, colistin and gentamicin. In general, Gram-negative bacteria were more resistant to cefotaxime, with several species resistant to multiple antibiotic classes

Klebsiella pneumoniae, Burkholderia cepacian, Raoultella spp and *Acetobacter aceti* highly resistance to most of antimicrobial agents mainly cefotaxime, ciprofloxacin, colistin while *E. coli* show moderate resistance to ciprofloxacin and sensitive to gentamycin and colistin. The percentage of resistant isolates to each antibiotic is shown in Figure 3.

Age is a significant risk factor for UTI in both MDR and non-MDR patients. In the MDR group, the highest incidence of UTI was found in people aged 55-64 years as shown in Table 1 that represent the highest incidence of UTIs among MDR patients was observed in those 55-64 years old. In general, women had a higher incidence of UTIs in both MDR and non-MDR patients compared to men. Additionally, the primary bacteria responsible for infections in both MDR and non-MDR patients were Gram-negative *E. Coli*.

DISCUSSION

Through our research conducted between 18, Nov. 2024 to 10 Dec. 2024 in Ramadi hospitals, we detected antibiotic-resistant bacteria mainly *E. coli* and *Klebsiella pneumoniae*. We found significant resistance of bacteria to antibiotics, indicating the misuse of antibiotics and improper prescription by physicians and healthcare professionals in acute cases. These findings suggest a serious responsibility in handling antibiotics in hospitals in terms of frequent prescription, cases where these drugs are not prescribed according to guidelines, and pharmacists dispensing these antibiotics illegally without a prescription, leading to the widespread spread of bacterial resistance through transmission or misuse [15], therefore, we propose that the Iraqi Ministry of Health install legal signage and monitor improper prescriptions by physicians and pharmacists, holding violators accountable. This resistance is projected to be fatal to millions of people by 2050, with an estimated 10 million deaths due to antibiotic resistance. *E. coli, K. pneumoniae,* and *Acinetobacter* spp., all Gram-negative bacteria, were prevalent in UTI patients in our study [16]. Among these, *E. coli* was the most common. After comparing our results with the study "Prevalence and pattern of antibiotic use and resistance among Iraqi patients: a cross-sectional study" published in the African Health Sciences which examined a number of bacteria in 850 patients, we found similar infection rates for the same types of bacteria we detected: *Escherichia coli*: 123(14.5%), *Klebsiella Pneumonia*: 11(1.29%), Gentamycin: 103(12.11%), Ciprofloxacin: 345(40.58%), Cefotaxime: 209(24.58%) [17]. Our research has revealed a significant increase in antibiotic resistance among bacteria, a trend that poses a serious threat to public health. A comparison of our findings with previous studies shows a concerning disparity, with resistance rates in Ramadi hospitals being notably higher for Cefotaxime at 75% compared to the 24.58% reported in compared study and for Ciprofloxacin we see that our research note 50% comparing with compered study 40.58% it higher, but for Gentamycin we note 0% resistance but in compared study we see it 12.11% and that mean there is no resistance of gentamycin in Ramadi hospital and it good for patient who used it to treating from E-coli [16]. As our study showed, gender plays a crucial role in the risk of UTI. *Escherichia coli* and *Klebsiella pneumoniae* were the most common bacteria found in both male and female patients. Notably, *E. coli* was more frequent in females 45% than in males 30%. This observation is consistent with previous studies [18] suggesting that anatomical differences, especially the proximity of the anus to the female urethra, may facilitate bacterial migration and colonization [19]. Hormonal changes, such as the decline in estrogen after menopause, can also increase the risk of UTI, which is why hormone replacement therapy (HRT)

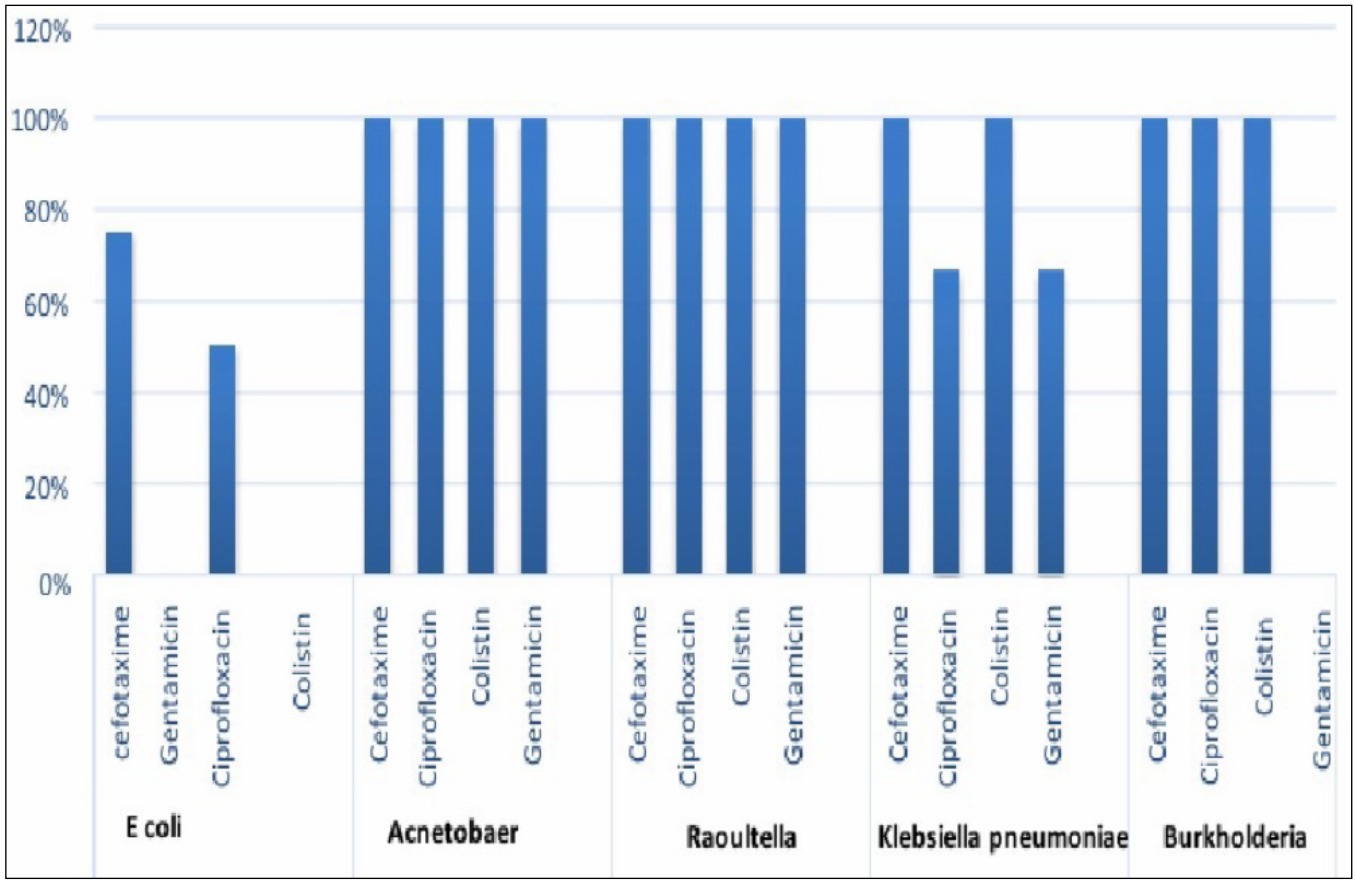

Fig. 3. Antibiotic resistance pattern of Gram-negative bacteria.

is a valuable preventive measure in postmenopausal women [20]. Hormone replacement therapy (HRT) can affect urinary tract infections (UTIs), especially in postmenopausal women. Decreased estrogen levels after menopause can affect urinary tract health and may increase the frequency of UTIs. HRT, particularly estrogen therapy, can relieve menopausal symptoms and improve urinary tract health, potentially reducing the incidence of UTIs. However, the link between HRT and UTIs is complex and varies from person to person. Some studies have shown a benefit, while others have shown no significant effect or a possible increased risk of UTIs. Multiple factors, including urine patterns, hygiene habits, and underlying health conditions, contribute to the risk of UTIs [21]. Good hygiene and hydration are other effective strategies to minimize the risk of infection [18]. Our study found that Gram-negative bacteria, including *E. coli*, are multidrug resistant, and the resistance these bacteria exhibit is mainly due to β-lactam resistance. The thick peptidoglycan coating of *E. coli* and the production of biofilms help it adhere to the walls of the urinary system and develop antibiotic resistance [22]. The presence of β-lactamases in *E. coli* provides protection against antibiotics [23]. In addition, excessive use of antibiotics can cause side effects such as diarrhea and allergic reactions, making treatment ineffective [24]. Age is a significant risk factor for UTI in both MDR and non-MDR patients. In the MDR group, the highest incidence of UTI was found in people aged 55-64 years. Elderly people are more susceptible to comorbidities due to known risk factors for UTI such as diabetes and hypertension. In addition, gender and bacterial etiology play an important role in the risk level of UTI, with women facing a higher risk due to anatomical differences, and Gram-negative bacteria being the leading cause of UTI in both MDR and non-MDR cases [24]. Our research aligns with findings from Özlem Aytaç, who discovered that *K. pneumoniae* exhibited the highest resistance to cefixime at 53.3%, while its lowest resistance was noted against imipenem at 12.1%. The samples collected from outpatients showed the least resistance, whereas the ward patients exhibited the greatest resistance rates, particularly to cefixime at 81% and ciprofloxacin at 72.1%. Additionally, higher resistance levels were observed in intensive care patients for ertapenem at 48.9%, meropenem at 50.2%, and piperacillin-tazobactam (PRP) at 57.3%.

Our study identified MDR in Gram-negative bacteria, including E. coli, which exhibited 100 % resistance, primarily due to beta-lactam resistance, The thick

peptidoglycan coating of E. coli, along with biofilm production, contributes to its ability to adhere to urinary system walls and develop antibiotic resistance [21]. The presence of beta-lactamase enzymes in E. coli provides defense against antibiotics, in addition, overuse antibiotics have side effects such as diarrhea, allergic reaction and become ineffective in treating [23].

CONCLUSIONS

The current study showed high rates of resistance among clinical isolates of urine origin. In particular, resistance to cefotaxime, ciprofloxacin, and colistin was high (100%) across all crop species. That represent the highest incidence of UTIs among MDR patients was observed in those 55-64 years old. In general, women had a higher incidence of UTIs in both MDR and non-MDR patients compared to men with 41(68.30%) and 26(38.80 %), respectively .The gradual replacement of drugs once considered first-line treatment with broad-spectrum drugs such as cephalosporins, fluoroquinolones, and aminoglycosides remains an ongoing challenge in Iraq, an issue that has led to poor antimicrobial stewardship, especially in resource-poor primary health care settings. Scarce and excessive antimicrobial drugs are less affected by established antimicrobial stewardship programs. Our findings reveal another worrying issue associated with these broad-spectrum antibiotics, which were previously considered a last resort. Among urinary pathogens, resistance to cephalosporins, fluoroquinolones, and aminoglycosides was high (100%). Thus, despite being considered last-resort agents, these agents might become increasingly ineffective in the treatment of resistant infections under current prescription practices.

This study highlights the significance of using antibiotics rationally, the need for vigilant monitoring of local epidemiological data, and the importance of implementing necessary precautions. Additionally, it is essential to remember that reevaluating each treatment based on the antimicrobial susceptibility profile is vital for enhancing treatment success and reducing resistance rates, especially given the elevated resistance rates associated with antibiotics commonly employed in the empirical management of UTIs.

ETHICAL APPROVAL

This study has been approved by Al Maarif University, College of Pharmacy Research Ethics Committee (approval date 9/12/2024, number 388).

REFERENCES

1. Holmes AH, Moore LSP, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016;387(10014):176-187. doi:10.1016/S0140-6736(15)00473-0 DOI
2. Founou RC, Founou LL, Essack SY. Clinical and economic impact of antibiotic resistance in developing countries: a systematic review and meta-analysis. PLoS One. 2017;12(12):1-18. doi:10.1371/journal. pone.0189621 DOI
3. Saleem Z, Hassali MA, Godman Betal. Point prevalence survey sofantimicrobial use: a systematic review and the implications. Expert Rev Anti Infect Ther. 2020;18:897 910. doi:10.1080/14787210.2020. 1767593 DOI
4. Fridkin S, Baggs J, Fagan R, et al. Vital signs: improving antibiotic use among hospitalized patients. MMWR Morb Mortal Wkly Rep. 2014;63(9):194-200.
5. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of adverse events with antibiotic use in hospitalized patients. JAMA Intern Med. 2017; 177(9): 1308 1315. doi:10.1001/jamainternmed.20 17.1938 DOI
6. Paterson DL. Collateral damage from cephalosporin or quinolone antibiotic therapy. Clin Infect Dis. 2004; 38(Suppl4):341-345. doi:10.1086/382690 DOI
7. World Health Organization. Global action plan on antimicrobial resistance; 2015. https://www.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1 [Access: December 2024]
8. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2:Art. No.:CD003543. doi:10.1002/ 14651858.CD003543.pub4 DOI
9. World Health Organization. WHO methodology for point prevalence survey on antibioticusein hospitals, version 1.1. 2018. https://apps.who.int/iris/handle/10665/280063 [Access: December 2024]
10. Antimicrobial Resistance Collaborators. Global Burden of Bacterial Antimicrobial Resistance in 2019: a systematic analysis. Lancet 2022;399(10325):629-655. doi:10.1016/S0140-6736(21)02724-0 DOI
11. Ansari F, Erntell M, Goossens H, Davey P. The European surveil- lance of antimicrobial consumption (ESAC) point-prevalence survey of antibacterial use in 20 European hospitals in 2006. Clin Infect Dis. 2009; 49(10):1496-1504. doi:10.1086/644617 DOI
12. Versporten A, Zarb P, Caniaux I, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health. 2018;6(6):e619–e629. doi:10.1016/S2214-109X(18)30186-4 DOI

13. Collee JG, Marmion BP, Fraser AG, et al. Mackie and McCartney practical medical microbiology. 14th ed. London: Churchill Livingstone, 1996; p. 14.
14. Jensen MLV, Siersma V, Søes LM, Nicolaisdottir D, Bjerrum L, Prior PJH. Antibiotic use increases risk of Urinary Tract infections caused by resistant Escherichia coli among elderly in primary care: a case-control study Antibiotics. 2022;11(10):1382
15. Salman MS. Antibiotic Resistance of Bacteria Isolated in Urinary Tract Infections. J Contemp Med Sci. 2024; 10(2 March-April): 163–166
16. Gu J, Chen X, Yang Z, Bai Y, Zhang X. Gender differences in the microbial spectrum and antibiotic sensitivity of uropathogens isolated from patients with urinary stones. J Clin Lab Anal. 2022; 36(1):e24155. doi: 10.1002/jcla.24155. DOI
17. Hashim HT, Hashim AT, Ali HT, et al. Prevalence and pattern of antibiotic use and resistance among Iraqi patients: a cross-sectional study. African Health Sciences. 2024:24(3):47-57
18. Deltourbe L, Mariano LL, Hreha TN, Hunstad DA, Ingersoll MA. The impact of biological sex on diseases of the urinary tract. Mucosal Immunol. 2022;15(5):857-866. doi: 10.1038/s41385-022-00549-0. DOI
19. Taga S, Suga H, Kimura T, Arima H. Hormone replacement therapy using human iPS cell-derived pituitary organoids. Drug Delivery System. 2020;35(4): 285-292. doi:10.2745/dds.35.285 DOI
20. Ordonez J, Christie AL, Zimmern BE. Role of flexible cystoscopy in the management of postmenopausal women with recurrent urinary tract infections. Urology 2022;169:65-69. doi: 10.1016/j.urology.2022.07.040 DOI
21. Eberly A, Floyd K, Beebout C, et al. Biofilm formation by uropathogenic Escherichia coli is favored under oxygen conditions that mimic the bladder environment Int J Mol Sci. 2017;18(10):2077. doi: 10.3390/ijms18102077. DOI
22. Zeng X, Lin J. Beta-lactamase induction and cell wall metabolism in gram-negative bacteria. Front Microbiol. 2013;4:128. doi: 10.3389/fmicb.2013.00128. DOI
23. Wise J. Antimicrobial resistance: MPs call on UK government to maximize potential of bacteriophages. BMJ. 2024 Jan 3:384:q1. doi: 10.1136/bmj.q12. DOI
24. Aytaç Ö. Antibiotic resistance rates of Klebsiella pneumoniae strains isolated from urine cultures. Northwestern Med J. 2024; 4(2):64-69. doi: 10.54307/NWMJ.2024.108 DOI

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REVIEW ARTICLE

CONTENTS

Calcium pyrophosphate dihydrate deposition disease (chondrocalcinosis): a review

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ABSTRACT

Calcium pyrophosphate dihydrate deposition disease (CPPD) is a metabolic arthropathy characterized by gross calcium pyrophosphate crystals deposition within articular cartilage, in the periarticular and articular tissues. The disease is also called by other names such as pseudogout or chondrocalcinosis. Deposition of calcium pyrophosphate dihydrate crystals provokes an inflammation within the synovial membrane followed by degenerative changes in cartilage and bone. The underlying mechanism for increased intraarticular accumulation of calcium crystals is not known. CPPD is fairly common condition affecting mostly older people. It manifests in three clinical forms: asymptomatic (the most common), acute and chronic. Diagnosis is made on the basis of X-ray or ultrasound examination, but definitive confirmation requires demonstration of calcium pyrophosphate dihydrate crystals in the synovial fluid. Treatment of acute CPPD is similar to treatment of gout attack and consists in physical measures and medication with NSAIDs, colchicine or sometimes steroids. This review summarizes recent findings about the etiopathogenesis, diagnosis and management of CPPD.

KEY WORDS: calcium pyrophosphate dihydrate deposition disease; CPPD; chondrocalcinosis; crystal-induced arthritis

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INTRODUCTION

Calcium pyrophosphate dihydrate deposition disease (CPPD) is a metabolic arthropathy characterized by gross calcium pyrophosphate crystals deposition within articular cartilage, both hyaline and fibrocartilage in the periarticular and articular tissues. The disease is also called by other names such as pseudogout or chondrocalcinosis [1-3]. It is the third most common inflammatory arthritis. Deposition of calcium pyrophosphate dihydrate crystals provokes an inflammation within the synovial membrane followed by degenerative changes in cartilage, bone and tendon sheath. Symptoms and signs, as well the course of CPPD resembles gout, hence its former name – pseudogout. Although the diseases have similar symptomatology, the cause of their occurrence is different. The CPPD prevalence in the general population is around 5-15% and increases with age, so that about 30% of population older than 80 years is affected by this condition [1, 4, 5]. The knee joint is the most commonly involved, followed by shoulder and wrist. Clinical course of CPPD is usually mild and about 70% patients is asymptomatic, while in 25% of cases the disease manifests in acute episodes, in a gout-like form. About 5% of patients with CPPD deposition develops a chronic rheumatoid arthritis-like condition [1-6].

REVIEW AND DISCUSSION

ETIOPATHOGENESIS

The underlying mechanism for increased intra-articular accumulation of calcium crystals is not known.

Basic calcium phosphate (BCP) crystals have been shown to provoke inflammatory and cartilage-damaging responses, similar to sodium urate crystals in gout. Calcium crystals are able to induce an inflammatory response resulting in the production of interleukin IL-1β after nuclear factor-Kb (NF-Kb) activation and through the NLRP3 inflammasome. Inflammatory response induced by monosodium urate, calcium pyrophosphate dihydrate and basic calcium phosphate crystals affects three distinct leukocyte populations: polymorphonuclear cells, monocytes and lymphocytes. Of these three, calcium pyrophosphate dihydrate crystals were found to be the most potent stimulators of inflammatory cytokines [2, 5]. The possible mechanisms leading to development of CPPD are shown in Table 1. **Older people** who have a genetic predisposition are more at risk for developing the condition [1, 2, 6]. An association between CPPD and osteoarthritis has been shown in some studies [3, 7]. Recent epidemiological studies have suggested that CPPD has been associated with an

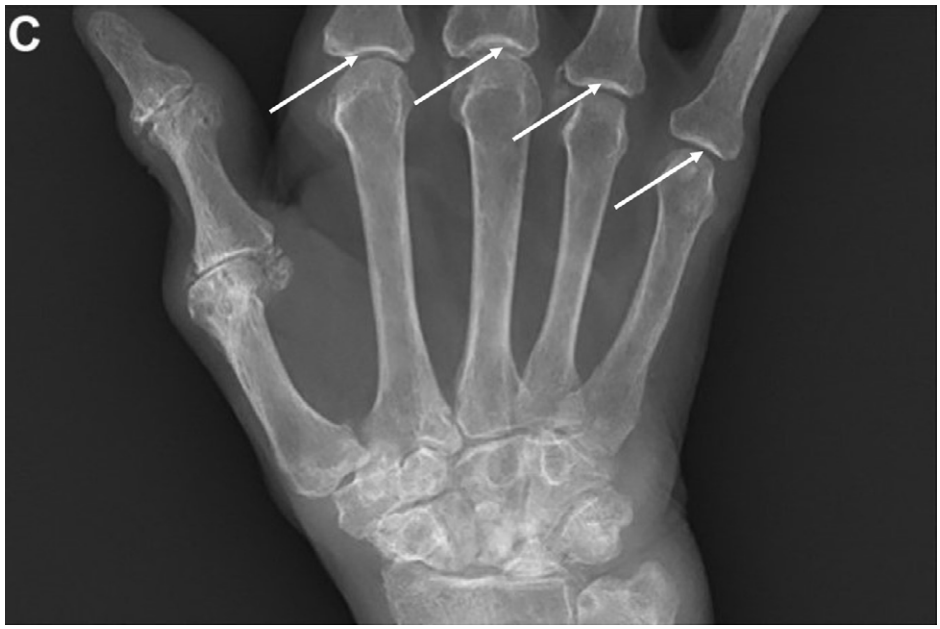

Fig. 1. X-ray of the hand demonstrating CPPD involving the metacarpo-phalangeal joints II-V (white arrows). Note also degenerative changes in the wrist and all joints of the thumb.

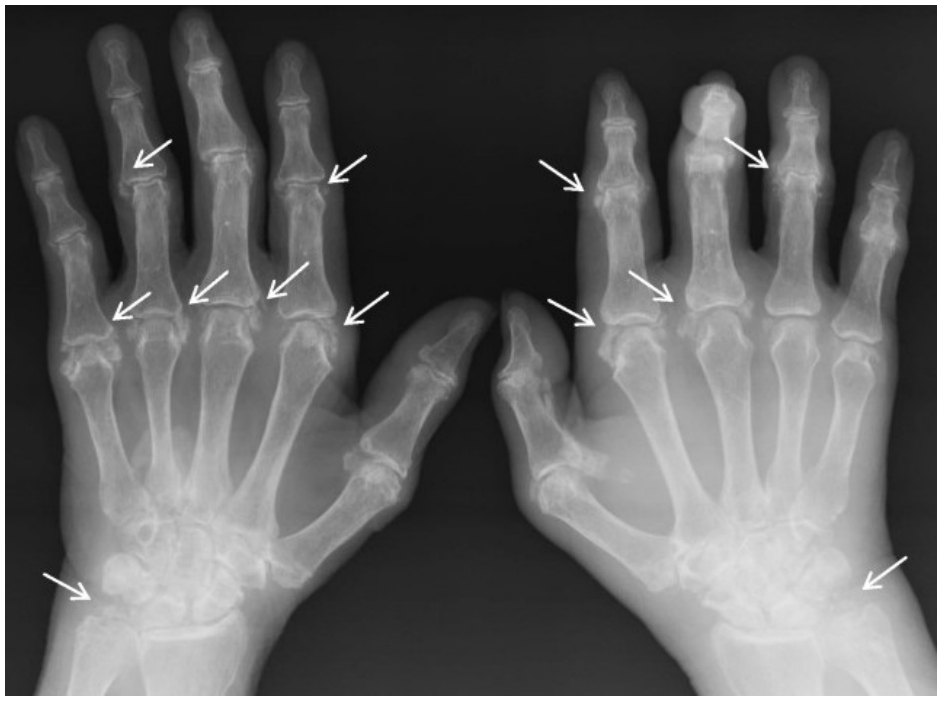

Fig. 2. X-ray of the hand demonstrating CPPD involving the multiple hand joints and ulno-carpal joint (white arrows).

elevated risk for nonfatal cardiovascular disease events, however this association is still in clinical trials [2, 5].

CLINICAL PRESENTATION AND COURSE

The disease manifests in three clinical forms, including:

- Asymptomatic CPPD (the most common, signs present only in images),
- Acute CPPD (self-limited synovitis, formerly known as pseudogout),
- Chronic CPPD

These forms differ from each other in some aspects which will be discussed in this section [1-7]:

a. The asymptomatic form is the most common, constituting about 70% of all cases. In asymptomatic disease, radiological features may be found in X-rays performed for other reasons, but they have not translation into clinical symptoms;
b. The acute form is the second common, constituting about 25% of all cases. It presents typically as an acute arthritis involving one joint, and less frequently 2-3 joints at the same time. Large joints such as knees, ankles, shoulders and wrists are more frequently involved than small joints, but the disease may affect any other joint. Presentation as migratory, polyarticular or bilateral arthritis is much

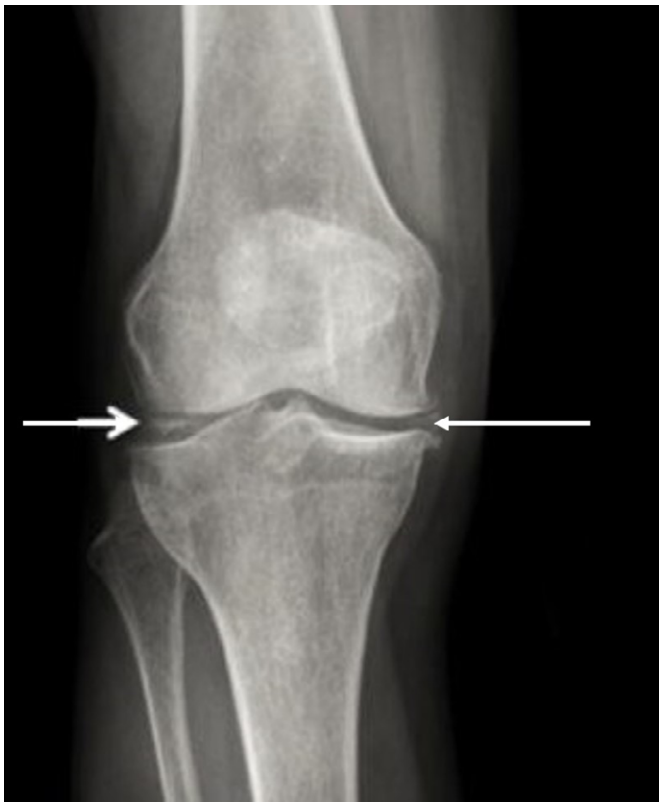

Fig. 3. X-ray of the knee demonstrating CPPD involving the menisci (white arrows).

less common. The disease typically affects older patients, over 65 years of age. The acute CPPD is characterized by rapid onset, and typical symptoms and signs include:

- Pain (local, confined to the affected joint/joints),
- Local increase of temperature,
- Swelling around the affected join(s),
- Redness over the affected joint(s),
- Reduction of movements in the affected joints.

The rapid onset in a form of attack resembles attack of a gout and can be confused with this condition. The course of an acute CPPD is usually self-limiting and symptoms and signs typically resolve slowly within one or two weeks. Attacks may be triggered by some conditions such as trauma, infection or concomitant systemic disease. Between acute episodes, most of patients remains asymptomatic. Attacks can affect the same joint or a different one in each episode. In case of involving a large joint such as hip, knee or shoulder, the patient can present systemic symptoms such as fever, chills and feeling unwell (malaise). This symptomatology may suggest septic arthritis, and if the patient has risk factors such as diabetes, history of trauma or systemic infection, septic arthritis should be considered in differential diagnosis. As it has been already mentioned, this condition can produce symptoms resembling gout, and therefore, despite differences in clinical patterns between the diseases, the definite diagnosis relies upon the microscopic examination of the synovial fluid and demonstration of the specific crystal deposits. As aspiration of the synovial fluid from small joints is not always available, other diagnostic modalities include X-ray and ultrasound examination (this will be discussed later in the article);

c. Chronic CPPD is the rarest form, constituting about 5% of all cases. It may present as bilateral, symmetrical, and deforming inflammatory arthritis. It lasts months or years, and destruction occurs over time resulting in degenerative changes of the affected joints which resembles osteoarthritis. Wrists and metacarpophalangeal (MCP) joints are commonly affected, although the disease can involve also extensor tendon sheaths. Development of wrist tenosynovitis can increase pressure in the carpal tunnel and produce symptoms of median nerve compression and may require synovectomy [8]. Similar changes around the elbow joint can produce symptoms and signs of ulnar nerve compression. When located in the wrist it can cause carpal instability (i.e. scapholunate) [9]. Radiographic findings are characterized by subchondral sclerosis, epiphyseal geodes, osteophytes, but with no marginal erosions [1-8].

Less frequently the joints of the spine may be involved in CPPD, particularly in the cervical and lumbar spine, leading to limited mobility and lower back pain (in lumbar spine involvement) [1, 2].

DIAGNOSIS

Diagnosis of the CPPD is not easy in asymptomatic patients, as it can be only recognized in an accidentally taken the X-ray. Moreover, radiologic changes are not specific and if not strongly expressed, can be easily missed (a proportion of patients with CPPD has negative X-rays). The definitive diagnosis of the condition can be made by examining of the synovial fluid. Other imaging modalities include ultrasonography, X-ray, computed tomography (CT) and magnetic resonance (MRI). Effectiveness and availability of these imaging modalities will be discussed below:

a. Examination of the synovial fluid

As it has been mentioned, the definitive diagnosis of the CPPD is made by the visualization of rhomboid-shaped crystals in the synovial fluid taken form the affected joint. This obviously requires performing aspiration of the joint, what may be demanding in small joints of the hand (it is easier in big joints such as knee or shoulder). The identification of calcium pyrophosphate dihydrate crystals in synovial fluid by light microscopy, compensated polarized light microscopy, or phase contrast microscopy is the reference standard for

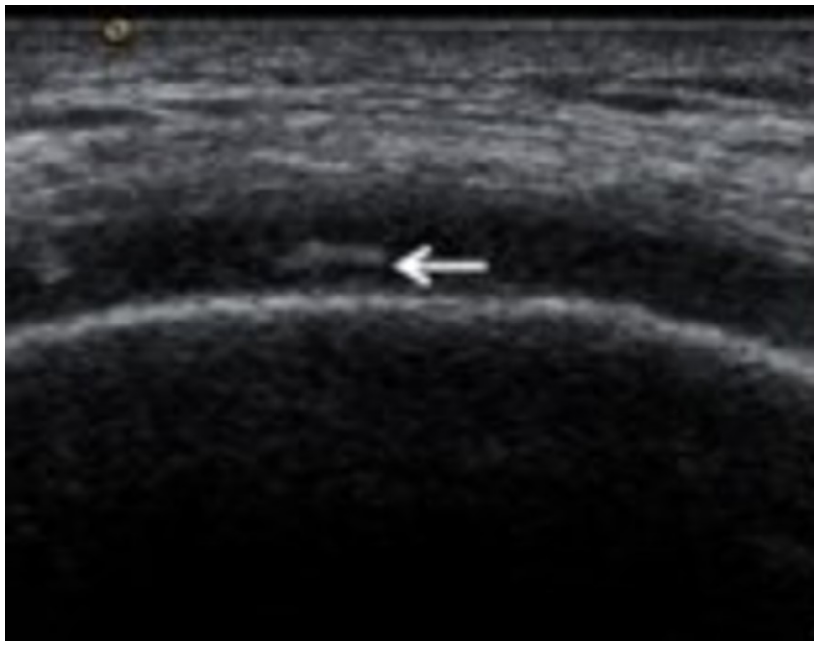

Fig. 4. US of the MCP joint affected with CPPD. Note thin, hyperechoic band within hyaline cartilage, parallel to the surface of the cartilage.

Table 1. Etiopathogenesis of calcium pyrophosphate dihydrate deposition disease (CPPD)

Pathogenetic mechanism
Calcium pyrophosphate dihydrate crystals deposition in the pericellular matrix of cartilage is considered a primary first step of the disease
Concomitant disease effect. CPPD be a manifestation of metabolic or endocrine disorders leading to abnormal Ca and P metabolism, such as hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia, hemochromatosis, gout and osteoarthritis.
Micro-trauma effect. Calcium pyrophosphate dihydrate crystals deposition may be provoked by micro-injuries that deteriorate collagen and other cartilage proteins.
Genetic predispositions. Polymorphisms in the ANKH gene which encodes a transmembrane inorganic pyrophosphate shuttle protein.
Other causes can be a lack of magnesium, excess calcium or iron

Table 2. Treatment of calcium pyrophosphate dihydrate deposition disease (CPPD)

Acute CPPD
Physical measures: cool packs, temporary rest of the affected joint (limb).
Non-steroid anti-inflammatory drugs (NSAIDs)
Colchicine (orally)
Systemic steroids
Intraarticular steroid injection.
Chronic CPPD
Generally the same as in acute form.
In refractory cases: Methotrexate or Hydroxychloroquine
Novel treatments: Anakinra and histone deacetylase inhibitors (HDACis).

CPPD diagnosis. Calcium pyrophosphate dihydrate crystals have characteristically a parallel-epipedic form, and are usually located intracellular, with absent or weak positive birefringence. In some cases more sophisticated methods are necessary such as, chemical analysis of the synovial fluid or atomic force microscopy [1, 2, 5];

b. X-ray examination

Calcium pyrophosphate dihydrate crystals may be seen on X-rays in the fibrocartilage of the joints (Fig. 1-3). Typical localization include the meniscus of the knee (Fig. 3), triangular fibrocartilage of the wrists, labra of the acetabulum, symphysis pubis and annulus fibrosus of the intervertebral discs. Synovial calcification is almost always seen in knee, metacarpophalangeal (Fig. 1), metatarsophalangeal joints, radiocarpal and distal radioulnar joints of the wrists (Fig. 2) [1, 2, 5, 10, 11]. Tendon calcifications are frequently seen in the quadriceps, triceps, and the Achilles tendon Obviously,

only a proportion of patients with symptomatic CPPD is radiologically positive. Abhishek et al., demonstrated that almost 40% of individuals with CPPC do not present with calcific radiographic findings on knees, despite being the most common site of CPPD involvement. The authors found that only 80% of patients with CPPC could be identified on the basis of radiographs of knees, pelvis, wrists or hands [7];

c. Ultrasound examination

Ultrasound evaluation has been studied extensively in the last 10 years, and has been proposed as a primary diagnostic method for CPPD by the European League against Rheumatism [1, 4, 6, 10]. This is because synovial fluid aspiration or synovial biopsy in small joints is difficult to perform. In these cases use of widely available ultrasonography to diagnose CPPD is very be useful. Ultrasonography can demonstrate calcium pyrophosphate dihydrate crystals in peripheral joints, appearing typically as thin hyperechoic bands within hyaline cartilage, parallel to the surface of the cartilage and hyperechoic sparkling spots in fibrocartilage (Fig. 4) [4, 10, 12]. Calcifications within the cartilage usually have not a posterior shadow because linear calcium pyrophosphate dihydrate crystals have not sufficient compactness to stop the ultrasound beam progression. The range of possible expression ranged from isolated hyperechoic spots to extended deposits, which might involve a great portion of the hyaline cartilage [4, 10, 12]. The sensitivity of US in diagnosing CPPD is estimated at 80% and specificity is even higher, reaching 93%-100% [2, 4, 10, 12]. Due to wide availability, US is now a first line imaging technique in diagnosing CPPD;

d. Computed tomography (CT)

CT is less frequently used in diagnosing CPPD and its use is limited to suspected disease in the spine, which is often asymptomatic. Calcium pyrophosphate dihydrate crystals may accumulate in the transverse ligaments of the atlas or alar ligaments, what results in formation of so called "crowned dens syndrome" [2, 5]. The syndrome relies on calcifications of odontoid articular structures. In the "crowned dens syndrome", CT is the first line imaging that allows identification of the different radiographic features of the disease:

- Simple band of calcification or double band of thin calcifications in the transverse ligament,
- Irregular calcifications crowning the dens apex,
- Bone erosions of the dens itself;

e. Magnetic resonance imaging (MRI)

Likewise CT, magnetic resonance imaging is rarely used in diagnosis CPPD and its usefulness is confined to the disease involving the spine. Calcium pyrophosphate dihydrate crystals uptake in ligamentous structures of the spine such as ligamentum flavum and posterior longitudinal ligament, can results in myelopathy, cord compression and spinal stenosis. Thus, MRI may be useful in diagnosing these rare complications of CPPD involving the spine [2, 5];

f. Practical tips for extended diagnostics of suspected chondrocalcinosis

Chronic chondrocalcinosis is rarely confused with rheumatoid arthritis, more often with degenerative and inflammatory changes of the joints (osteoarthritis). In such cases, extended diagnostics may not be needed, because the treatment of both diseases is basically similar. This may only be necessary if the treatment used fails. Similarly, differentiation of the acute phase of chondrocalcinosis and a gout attack is relatively easy, due to the elevated concentration of uric acid in gout. Only in doubtful cases, e.g. normal or borderline uric acid levels, or in cases of treatment failure, such diagnostics may be necessary.

DIFFERENTIAL DIAGNOSIS

The acute phase of the disease is usually differentiated from gout attack or septic arthritis. It is relatively easy to distinguish the CPPD from gout, as the patient usually presents with history of gout (diagnosed earlier). Additionally, uremic acid concentration in serum is elevated in an acute gout episode. Septic arthritis presents with more severe symptoms and, if involves big joints, is associated with systemic reaction (fever, chills, elevated inflammatory parameters – leucocyte rate, CRP). Movement of the affected joint is very painful and range of motion is limited. Ultrasonographic and radiological findings can help in making the confident diagnosis [1, 2, 5].

The chronic phase, CPPD is usually differentiated from osteoarthritis (OA) and rheumatoid arthritis (RA). Differentiating CPPD form OA can be challenging based upon clinical signs and symptoms, however, US and X-ray studies may help in making a proper diagnosis. Both of these diseases can occur simultaneously and overlap each other, so that their unambiguous distinguishing may be possible only after synovial fluid examination. Osteoarthritis combined with CPPD generally affects knees, has an atypical distribution (radiocarpal joint, glenohumeral joint, hindfoot/midfoot involvement) and may be associated with more severe signs and symptoms. In contrast, rheumatoid arthritis history and clinical presentation is usually enough different form CPPD, that confusion between these two diseases is rare.

TREATMENT

At present, there are no widely accepted, disease-modifying therapies which reduce the articular

deposition of calcium pyrophosphate dihydrate crystals. Therefore, at present the goal of treatment in CPPD is reducing the inflammatory response, the frequency and severity of clinical symptoms caused by the disease [1, 2, 5]. Patients with asymptomatic CPPD do not require any treatment. Treatment of symptomatic patients requires both non-pharmacological and pharmacological measures, according to clinical presentation and risks factors. Proper treatment should include prompt resolution of the acute episode, prevention of chronic joint damage and management of concomitant diseases. Unfortunately, most treatment approaches are based upon clinical experience, but not on scientific evidence based on results of prospective, controlled studies. The list of treatment modalities is shown in Table 2.

TREATMENT OF ACUTE CPPD

The majority of CPPD patients who require intervention are those with acute form of the disease.

In such a situation, the treatment is similar to treatment of gout attack, and includes cool packs, temporary rest of the affected joint (limb), non-steroid anti-inflammatory drugs (NSAIDs), low dose oral colchicine, and sometimes systemic steroids. Joint aspiration with intraarticular long-acting steroid injection might be necessary if primary treatment fails in relieving the symptoms [1, 2, 5]. NSAIDs and colchicine are relatively effective, but limited by toxicity and adverse effects which may be dangerous in older patients. A short course of oral or parenteral steroids is recommended in patients who failed to improve after NSAIDs or colchicine treatment, or who have contraindications to use these drugs [2, 5].

Colchicine is relatively old drug, but it has been still used in acute gout attacks. The mechanism of action is through stabilizing activity on the cytoskeleton and cell membranes, but it also inhibits the neutrophil's motility and activity, leading to an anti-inflammatory effect. Colchicine is effective in acute CPPD and in preventing recurring attacks. *Likewise in* acute gout, colchicine is most effective if treatment is started within 12-24 hours after onset of symptoms. The earlier the treatment is started, the more rapid and complete resolution occurs. Small doses of colchicine (3x0,5 mg daily, per os) are recommended at the beginning of therapy, because it reduces adverse effects of the drug on gastrointestinal tract such as diarrhoea and abdominal cramping. In most patients, the effect of this therapy is rapid and strong, and symptoms usually begin to subside in 12-24 hours [2, 5]. Intravenous administration of colchicine is not recommended, because it is associated with risk of severe pancytopenia and death. The duration of therapy for the acute episode may range from one to several weeks, depending on how early colchicine has been introduced [2, 5]. For the prophylaxis of recurrent acute CPPD, low-dose oral NSAIDs, or low-dose (0,5 mg daily) oral colchicine is recommended.

TREATMENT OF CHRONIC CPPD

Patients with chronic CPPD require a continuous treatment with low-dose NSAIDs or colchicine and sometimes with low-dose oral steroids. This therapy is usually effective, however it may be confused by acute episode of the condition. In patients who fail to improve, in whom such treatments are contraindicated or not well-tolerated, alternative therapeutic modalities can be used such as methotrexate and hydroxychloroquine [2]. Methotrexate could be considered as an for patients with severe CPPD who failed to respond to standard therapy. The drug works not only as an immunosuppressant but also as a potent anti-inflammatory agent. Hydroxychloroquine has shown some beneficial effect in chronic CPPD arthritis with no significant adverse effects [2, 4, 5].

NOVEL TREATMENTS: ANAKINRA AND HISTONE DEACETYLASE INHIBITORS (HDACIS)

Anakinra is a biologic immunosuppressant that is an antagonist of human interleukin-1 (IL-1) type I receptors. Anakinra blocks the biological activity of IL-1α and IL-1β and is approved for the treatment of rheumatoid arthritis, COVID-19 infection, periodic fever syndromes and Still's disease. Effectiveness of anakinra was compared to prednisone in the treatment of acute CPPD in a randomized controlled study. Results of this study demonstrated similar effectiveness between anakinra and prednisone, but anakinra showed faster onset of action than prednisone [13].

Histone deacetylase inhibitors (HDACis) have been shown to downregulate calcium pyrophosphate dihydrate crystal formation in human articular chondrocytes. Extracellular pyrophosphate, calcium and extracellular matrix are essential components of CPP crystal formation [5, 14]. A high concentration of extracellular pyrophosphate in synovial fluid is positively correlated with the formation of CPP crystals. Histone deacetylase inhibitors (HDACis) were able to decrease extracellular pyrophosphate and CPP formation by regulating ankylosis human (*ANKH*), ectonucleotide pyrophosphatase 1 (*ENPP1*), and tissue nonspecific alkaline phosphatase (*TNAP*) genes expressions in human

chondrocytes. The underlying molecular mechanisms of HDACis – mediated regulation of *ANKH, ENPP1*, and *TNAP* expression is probably associated with the histone acetylation status of the promoters of these three genes [5, 14]. Histone deacetylase inhibitors may have the potential to be developed into drugs to prevent calcium pyrophosphate dihydrate crystals formation or treat CPPD related diseases in the future.

CONCLUSIONS

Calcium pyrophosphate dihydrate disease (chondrocalcinosis, pseudogout) is a fairly common condition affecting mostly older people. Diagnosis is made on the basis of X-ray or ultrasound examination, but definitive confirmation requires demonstration of CPP crystals in the synovial fluid. Most of patients is asymptomatic, but when symptomatic, the disease presents in acute or chronic form. Treatment of acute CPPD is similar to treatment of gout attack and consists in physical measures and medication with NSAIDs, colchicine or steroids. Calcium crystal deposition diseases are increasing in incidence due to aging of the population. They are associated with a high burden of disability. Despite this, they remain under-studied with lack of evidence based treatment guidelines.

In conclusion, this review demonstrates several new findings with regard to CPPD, such as development of more precise classification criteria and improvements in the accuracy of diagnostics, particularly examination of the synovial fluid taken from the affected joint. New findings include identification of factors associated with acute flare of disease and an association with increased cardiovascular risk. New treatment modalities, i.e. with histone deacetylase inhibitors still remain controversial, however advances in understanding the underlying molecular mechanisms of disease suggest potential targets for future drug development.

REFERENCES

1. Zhang W, Doherty M, Bardin T, et al. European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. Ann Rheum Dis. 2011;70:563-70.
2. Rosales-Alexander JL, Balsalobre Aznar J, Magro-Checa C. Calcium pyrophosphate crystal deposition disease: diagnosis and treatment. Open Access Rheumatol. 2014;6:39-47.
3. Sanmarti R, Kanterewicz E, Pladevall M, Pañella D, Tarradellas JB, Gomez JM. Analysis of the association between chondrocalcinosis and osteoarthritis: a community based study. Ann Rheum Dis. 1996;55(1):30-3.
4. Vele P, Simon SP, Damian L, Felea I, Muntean L, Filipescu I, Rednic S. Clinical and ultrasound findings in patients with calcium pyrophosphate dihydrate deposition disease. Med Ultrason. 2018;20(2):159-63.
5. Flood R, Stack J, McCarthy G. An update on the diagnosis and management of calcium crystal disease. Curr Rheumatol Rep. 2023;25(8):145-51.
6. Lim CH, Ng BH, Teh HL. Calcium pyrophosphate dihydrate deposition disease: a forgotten common arthritis in the elderly. BMJ Case Rep. 2019;12(11):e232828.
7. Abhishek A, Doherty S, Maciewicz R, Muir K, Zhang W, Doherty M. Evidence of a systemic predisposition to chondrocalcinosis and association between chondrocalcinosis and osteoarthritis at distant joints: a cross-sectional study. Arthritis Care Res. (Hoboken) 2013;65(7):1052-8.
8. Borisch N. Arthroscopic synovectomy of the wrist in chondrocalcinosis. Handchir Mikrochir Plast Chir. 2016;48(5):266-72.
9. Kahloune M, Libouton X, Omoumi P, Larbi A. Osteoarthritis and scapholunate instability in chondrocalcinosis. Diagn Interv Imaging. 2015;96(1):115-9.
10. Cipolletta E, Filippou G, Scirè CA, et al. The diagnostic value of conventional radiography and musculoskeletal ultrasonography in calcium pyrophosphate deposition disease: a systematic literature review and meta-analysis. Osteoarthritis Cartilage 2021;29(5):619-32.
11. Rigsbee CA, Sizemore TC, Lohr KM. Severe calcium pyrophosphate dihydrate deposition disease of the metacarpophalangeal joints. BMJ Case Rep. 2018;2018:bcr2018226132.
12. Gamon E, Combe B, Barnetche T, Mouterde G. Diagnostic value of ultrasound in calcium pyrophosphate deposition disease: a systematic review and meta-analysis. RMD Open 2015;1:e000118.
13. Dumusc A, Pazar Maldonado B, Benaim C, Zufferey P, Aubry-Rozier B, So A. Anakinra compared to prednisone in the treatment of acute CPPD crystal arthritis: a randomized controlled double-blinded pilot study. Joint Bone Spine 2021;88(2): 2020-1.
14. Chang CC, Lee KL, Chan TS, Chung CC, Liang YC. Histone deacetylase inhibitors downregulate calcium pyrophosphate crystal formation in human articular chondrocytes. Int J Mol Sci. 2022; 23(5): 2604.

CONFLICT OF INTEREST

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REVIEW ARTICLE

CONTENTS

The impact of systemic osteoporosis on the bone structure of the alveolar processes

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ABSTRACT

Aim: Review and analysis of contemporary professional literature on the impact of systemic osteoporosis on the bone structure of the alveolar processes, with a particular focus on the pathogenetic mechanisms of disorders of bone remodelling processes.

Materials and Methods: The bibliosemantic method was used to clarify the state of the problem, to study the analysis of the results of previous scientific research based on the sources of literature and electronic resources.

Conclusions: Thus, the literature shows that the resorptive processes associated with osteoporosis not only alter the bones of the supporting and peripheral skeleton, but also alter the structure of the bone tissue of the jaw. The introduction of a pathogenesis-based approach to treatment will allow significant progress to be made in the dental care of patients with primary osteoporosis. Given the high prevalence of osteoporosis in patients of various profiles, the role of the dentist in the diagnosis and correction of this pathology is becoming increasingly important. It is of particular importance to direct attention to older patients, given the increased risk of developing postmenopausal and senile osteoporosis.

KEY WORDS: osteoporosis, bone tissue, alveolar processes, remodelling processes, mineral density

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INTRODUCTION

Osteoporosis (OP) is a systemic skeletal disease characterised by a decrease in bone mass and impaired bone quality (microarchitecture), which leads to bone fragility and manifests itself in fractures following minor trauma [1]. The most common manifestations of OP are vertebral compression fractures, fractures of the distal forearm, proximal femur, and proximal humerus. In recent years, OP has not only become a significant public health concern, but also one of the most common causes of disability and mortality among patients. The International Osteoporosis Foundation (IOF) has published a report on the prevalence of osteoporosis in the European Union. In the report, 'Improving the Assessment of Fracture Risk', it was noted that after the age of 50, this disease is diagnosed in every third woman and every fifth man. Of these, 24% of women and 33% of men die within the first year after a hip fracture [2].

Given the high prevalence of osteoporosis in patients of various profiles, the role of the dentist in the diagnosis and correction of this pathology is becoming increasingly important. It is of particular importance to direct attention to older patients, given the increased risk of developing postmenopausal and senile osteoporosis [3]. Furthermore, in men with androgen deficiency, bone mineral density loss is more pronounced than in women with hypogonadism [4].

A number of studies have demonstrated a strong correlation between estrogen deficiency and the onset of periodontitis and osteoporosis [5, 6]. In recent years, an increasing number of researchers have proposed that postmenopausal osteoporosis contributes to the development and progression of periodontitis [7]. It has been demonstrated that periodontal bacteria contribute to the loss of alveolar bone tissue in periodontitis by increasing the activity of osteoclasts and/or by releasing toxins and pro-inflammatory cytokines [8]. Nevertheless, the precise mechanisms remain uncertain.

Bone tissue, like all other tissues, responds to a general or local pathological process and has a great adaptive response to variations in functional load [9]. As a consequence of alterations in the orientation and thickness of bone plates, the structure of bone tissue in general and in the jaw system in particular is remodelled. The eruption of milk and permanent teeth, tooth loss, and the use of prosthetics result in alterations to the load on specific areas of the alveolar processes, which in turn lead to the restructuring (remodelling) of the bone structure of the jaws [10].

AIM

A review and analysis of contemporary professional literature on the impact of systemic osteoporosis on the bone structure of the alveolar processes, with a particular focus on the pathogenetic mechanisms of disorders of bone remodelling processes.

MATERIALS AND METHODS

The bibliosemantic method was used to clarify the state of the problem, to study the analysis of the results of previous scientific research based on the sources of literature and electronic resources.

REVIEW AND DISCUSSION

The bone tissue of the jaws is not much different in structure and chemical composition from other bones of the skeleton [11]. However, the alveolar bone is unique in that the processes of internal restructuring are more active than in other bones of the skeleton. The height of the alveolar ridge is maintained by a physiological balance between bone formation and resorption. This is regulated not only by systemic factors but also by local factors [12, 13].

In accordance with the change in functional load on the dentition, remodelling modifies the structural anatomy of bone tissue so that the trabeculae and structures under load are strengthened to the maximum extent possible. Conversely, in the absence of load, bone tissue resorbs (Wolf's law). Systemic and local regulatory mechanisms frequently conflict with one another. Studies have demonstrated that even in instances of calcium deficiency, masticatory load can regulate bone mass [14].

In recent years, there has been a great deal of interest in elucidating the relationship between metabolic bone diseases and alterations in the jawbone tissue. It appears that systemic processes occurring within the body inevitably impact the condition of the dentition. Nevertheless, the relationship between osteoporosis and oral health remains a matter of contention [15].

The precise role of osteoporosis in the reduction of jaw bone mass, the pathogenesis of periodontal disease, tooth loss, and other changes remains unclear. According to [16], there may be three possible relationships: 1) systemic osteoporosis may act as a risk factor for periodontitis; 2) systemic osteoporosis may act as a risk factor for jaw osteopenia, regardless of the presence of periodontitis; 3) periodontitis may act as a primary (exclusive) risk factor for jaw osteopenia. Despite the numerous scientific studies conducted over the past two decades, certain issues remain controversial and insufficiently studied. For instance, [17] discovered a correlation between systemic osteoporosis, diminished jaw bone mass, and tooth loss. Furthermore, there is evidence that treatments aimed at increasing bone mineral density, such as hormone replacement therapy or bisphosphonate administration, help to preserve teeth and slow down alveolar bone loss.

A number of authors have conducted analyses of the relationship between systemic osteoporosis and alveolar bone volume, as well as the effect of estrogen on the condition of alveolar bone and teeth [18, 19]. The authors observed a positive correlation between systemic bone loss and the degree of alveolar bone resorption. The administration of estrogen has a similar effect on the jawbone as it does on other parts of the skeleton.

In a study conducted by M. Tezal and J. Wactawski-Wendè (2010), a correlation was established between the mineral density of bone tissue, different parts of the skeleton and the height of the alveolar ridge in the interproximal parts. The study involved 70 women aged 51 to 78 years. A reduction in skeletal bone mass was found to be correlated with a reduction in the height of interdental bone septa and gingival recession. The findings permit the authors to conclude that postmenopausal osteoporosis represents a risk factor for periodontal disease [20].

Balshi TJ and Wolfinger GJ (2007) conducted a comprehensive literature review to investigate the interrelationship between osteoporosis and periodontitis. A number of studies have indicated that osteoporosis results in both a loss of bone mass in the supporting skeleton and a decrease in jawbone density. Although the aetiologies of these diseases are distinct, some studies have demonstrated that the treatment of osteoporosis can improve the condition of periodontal tissues [21].

J. Wactawski-Wende et al. posit that the loss of alveolar height and the number of lost teeth in postmenopausal women is contingent upon the severity of osteopenia [22]. As stated by E.A. Krall (2011) and M.S. Reddy (2012), a reduction in bone mineral density in patients with osteoporosis, both in men and women, represents a risk factor for the development of periodontitis. Conversely, drugs used to treat osteoporosis have a favourable effect on the state of the oral cavity [23, 24].

In a study published in 2018, J.S. Mattson and colleagues investigated the relationship between systemic osteoporosis and periodontal status. Their findings indicated that the correlation between mandibular bone loss and tooth loss is observed in only a subset of patients. Furthermore, it is acknowledged that a multitude of potential factors contribute to the development of osteoporosis and periodontal disease, rendering it challenging to establish a direct correlation between the reduction in bone mineral density observed in osteoporosis, tooth loss, alveolar bone loss, and periodontitis. This highlights the necessity for further research in this area [25].

M. Jeffcoat et al. (2015) presented a synthesis of the findings from 15 clinical trials with the objective of elucidating the relationship between jaw bone loss and systemic osteoporosis. Indeed, 13 of the 15 studies demonstrated a positive correlation between systemic and local bone loss, specifically in the bones of the facial skeleton. The author considers that the interpretation of the literature is complicated by the variety of methods used to assess the severity of osteopenia, alveolar bone mass, and periodontitis [26].

The objective of Dervis E. (2019) was to analyse the described research methods, which were dedicated to the following areas: The following research methods were employed in the study:1) assessment of bone mineral density (BMD); 2) assessment of osteoporosis-induced changes in the oral cavity; 3) identification of the relationship between mandibular BMD and skeletal BMD; 4) identification of changes in the jaws and periodontal tissues in osteoporosis; 5) diagnosis of changes in oral tissues in conditions of estrogen deficiency; 6) study of the effect of hormone replacement therapy, calcium and vitamin D preparations on the state of the oral cavity. A meta-analysis of 97 studies conducted globally revealed that systemic osteoporosis is associated with a heightened risk of reduced jawbone density. However, this association has not been definitively established [27].

In a study published in 2016, M.A. Amorim and colleagues found no correlation between systemic osteoporosis and densitometric parameters of mandibular bone quality. A study by W. Becker et al. (2020) demonstrated that a simple visual assessment of bone quality at the implant site may be a more informative predictor of implant osseointegration than mineral density values obtained from peripheral skeletal bone examination [28].

Yu B & Wang CY (2022) postulates that osteoporosis and periodontal disease share several common risk factors, including advanced age, tobacco consumption, and deficiencies in calcium and vitamin D within the body. The author concurs with the assertion that osteoporosis, irrespective of periodontitis, results in a reduction in alveolar bone height. Furthermore, it is posited that pharmacological intervention for osteoporosis serves to maintain alveolar bone volume [29].

A number of studies have been conducted in recent years with the objective of assessing mandibular bone structure in the context of osteoporosis. For instance, investigated the correlation between skeletal bone mineral density, mandibular alveolar bone mass, structure, and thickness. The authors posit that a reduction in the trabecular pattern of the alveolar bone on intraoral radiographs represents a significant clinical indicator of skeletal BMD. This is superior to densitometric parameters of the alveolar bone in predicting the value of bone mineral density. A dense trabecular pattern is indicative of high BMD, whereas a sparse pattern is indicative of low bone mass [30].

The correlation between skeletal bone mineral density and alveolar bone mass was relatively weak, likely due to the significant influence of local functional factors on jaw bone. Subsequent studies have demonstrated that, although alveolar bone mass and thickness are primarily influenced by masticatory load, in women with postmenopausal osteoporosis, measurement of alveolar bone thickness in the premolar region can be employed to estimate the probable level of bone mineral density. The reduction in alveolar bone size with age and in women with postmenopausal osteoporosis is likely to be due to periosteal resorption, which is associated with skeletal bone loss. The authors posit that alveolar bone thickness can be utilized as one of several parameters to predict skeletal bone density [31].

S. Sidiropoulou-Chatzigiannis et al. (2017) highlight that osteoporosis results in a reduction in alveolar bone density and loss of jaw bone mass due to a disruption in the coordination of bone resorption and remodelling. Both bone resorption and bone formation are accelerated, and excessive bone resorption typically results in bone loss [32].

The bone tissue of the jaw, as an integral part of the skeletal system, responds to exogenous and endogenous factors affecting the human body. D. Knezovic Zlataric et al. (2007) analysed the systemic and local factors associated with alveolar bone loss. The study showed that osteoporosis, kidney disease and hormonal disorders were closely correlated with bone loss among systemic factors, and chronic periodontitis, early tooth loss and inadequate prosthetics among local factors [33, 34, 35].

The bone tissue of the alveolar ridge, as well as the skeleton, has been shown to be highly sensitive to hormonal disturbances in the body. Studies by dentists and osteologists have identified the role of hypoestrogenism in postmenopausal women in the development of systemic osteoporosis and pathological processes in the periodontium. Data from F. Sanfilippo, A.E. Bianchi (2013) confirm that ageing and oestrogen deficiency have a negative impact on tooth stability and residual alveolar ridge resorption. However, the authors emphasise that the change in the morphological structure of the edentulous maxilla is mainly due to mechanical factors as a result of changes in its function [36, 37].

Choël L. et al. (2016) assessed bone mineral density before implant placement. According to the authors, the cortical and trabecular bone of the mandible is more sensitive to systemic effects in women, whereas it is more sensitive to local effects in men. This is consistent with studies that have shown an association between osteoporosis and jaw bone loss [38, 39].

CONCLUSIONS

Thus, the literature shows that the resorptive processes associated with osteoporosis not only alter the bones of the supporting and peripheral skeleton, but also alter the structure of the bone tissue of the jaw. The introduction of a pathogenesis-based approach to treatment will allow significant progress to be made in the dental care of patients with primary osteoporosis.

REFERENCES

1. Ensrud KE, Crandall CJ. Osteoporosis. Ann Intern Med. 2024;177(1):ITC1-ITC16. doi:10.7326/AITC202401160. DOI
2. Willers C, Norton N, Harvey NC et al. Osteoporosis in Europe: a compendium of country-specific reports. Arch Osteoporos. 2022;17(1):23. doi:10.1007/s11657-021-00969-8. DOI
3. Walker MD, Shane E. Postmenopausal Osteoporosis. N Engl J Med. 2023;389(21):1979-1991. doi:10.1056/NEJMcp2307353. DOI
4. Vilaca T, Eastell R, Schini M. Osteoporosis in men. Lancet Diabetes Endocrinol. 2022;10(4):273-283. doi:10.1016/S2213-8587(22)00012-2. DOI
5. Bandrivsky Y, Bambuliak A, Bandrivska O et. al. Pharmacological correction of the activity of bone remodelling markers in the oral fluid of patients with generalised periodontitis depending on blood type. Pharmacia. 2024;71:1–6. doi:10.3897/pharmacia.71.e114268. DOI
6. Zhu L, Zhou C, Chen S et al. Osteoporosis and Alveolar Bone Health in Periodontitis Niche: A Predisposing Factors-Centered Review. Cells. 2022;11(21):3380. doi:10.3390/cells11213380. DOI
7. Zamani S, Kiany F, Khojastepour L et al. Evaluation of the association between osteoporosis and periodontitis in postmenopausal women: A clinical and radiographic study. Dent Res J (Isfahan). 2022;19:41.
8. Bandrivsky Y, Bandrivska O, Goncharuk-Khomyn M et al. Morphometric features of periodontal phenotype and anthropometric parameters of the maxillary central incisor in patients with generalized periodontitis and various blood types. Journal of International Dental and Medical Research. 2024;17(1):168–175.
9. Bandrivsky Y, Bandrivska O, Gnid R, Minko L, Shevchuk M. Indicators of markers of bone metabolism in patients with generalized periodontitis depending on blood group. Arch Balk Med Union. 2019;54(1):72-77. doi:10.31688/ABMU.2019.54.1.10. DOI
10. Herbert AM, Dean MN, Summers AP, Wilga CD. Biomechanics of the jaws of spotted ratfish. J Exp Biol. 2022;225(16):jeb243748. doi:10.1242/jeb.243748. DOI
11. Tsyhykalo OV, Kuzniak NB, Dmytrenko RR et al. Peculiarities of the human maxilla morphogenesis. Wiad Lek. 2022;75(10):2339-2346. doi:10.36740/WLek202210105. DOI
12. Hildebolt CF. Osteoporosis and oral bone loss. Dentomaxillofac Radiol. 1997;26(1):3-15. doi:10.1038/sj.dmfr.4600226. DOI
13. Payne JB, Stoner JA, Nummikoski PV et al. Subantimicrobial dose doxycycline effects on alveolar bone loss in post-menopausal women. J Clin Periodontol. 2007;34(9):776-787. doi:10.1111/j.1600-051X.2007.01115.x. DOI
14. Nasu M, Amano Y, Kurita A, Yosue T. Osseointegration in implant-embedded mandible in rats fed calcium-deficient diet: a radiological study. Oral Dis. 1998;4(2):84-89. doi:10.1111/j.1601-0825.1998.tb00262.x. DOI
15. Hong SW, Lee J, Kang JH. Associations between oral health status and risk of fractures in elder adults. Sci Rep. 2023;13(1):1361. doi:10.1038/s41598-023-28650-9. DOI
16. Ohishi T, Matsuyama Y. Minodronate for the treatment of osteoporosis. Ther Clin Risk Manag. 2018;14:729-739. doi:10.2147/TCRM.S149236. DOI
17. Li Y, Ling J, Jiang Q. Inflammasomes in Alveolar Bone Loss. Front Immunol. 2021;12:691013. doi:10.3389/fimmu.2021.691013. DOI
18. Belluci MM, de Molon RS, Rossa C Jr et al. Severe magnesium deficiency compromises systemic bone mineral density and aggravates inflammatory bone resorption. J Nutr Biochem. 2020;77:108301. doi:10.1016/j.jnutbio.2019.108301. DOI
19. Cheng CH, Chen LR, Chen KH. Osteoporosis Due to Hormone Imbalance: An Overview of the Effects of Estrogen Deficiency and Glucocorticoid Overuse on Bone Turnover. Int J Mol Sci. 2022;23(3):1376. doi:10.3390/ijms23031376. DOI
20. Tezal M, Wactawski-Wende J, Grossi SG et al. The relationship between bone mineral density and periodontitis in postmenopausal women. J Periodontol. 2010;71(9):1492-1498. doi:10.1902/jop.2000.71.9.1492. DOI
21. Balshi TJ, Balshi SF, Wolfinger GJ. The evolution of advanced prosthodontic care: a 30-year patient report. J Prosthodont. 2007;16(1):43-49. doi:10.1111/j.1532-849X.2006.00153.x. DOI
22. Wactawski-Wende J, Grossi SG, Trevisan M et al. The role of osteopenia in oral bone loss and periodontal disease. J Periodontol. 1996;67(10):1076-1084. doi:10.1902/jop.1996.67.10s.1076. DOI
23. Krall EA. Osteoporosis and the risk of tooth loss. Clin Calcium. 2011;16(2):287-290.
24. Reddy MS, Geurs NC, Gunsolley JC. Periodontal host modulation with antiproteinase, anti-inflammatory, and bone-sparing agents. A systematic review. Ann Periodontol. 2012;8(1):12-37. doi:10.1902/annals.2003.8.1.12. DOI
25. Mattson JS, Cerutis DR, Parrish LC. Osteoporosis: a review and its dental implications. Compend Contin Educ Dent. 2018;23(11):1001-1014.
26. Jeffcoat M. The association between osteoporosis and oral bone loss. J Periodontol. 2015;76(11):2125-2132. doi:10.1902/jop.2005.76.11-S.2125. DOI

27. Dervis E. Oral implications of osteoporosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2019;100(3):349-356. doi:10.1016/j.tripleo.2005.04.010. DOI
28. Amorim MA, Takayama L, Jorgetti V, Pereira RM. Comparative study of axial and femoral bone mineral density and parameters of mandibular bone quality in patients receiving dental implants. Osteoporos Int. 2016;17(10):1494-1500. doi:10.1007/s00198-006-0131-0. DOI
29. Yu B, Wang CY. Osteoporosis and periodontal diseases – An update on their association and mechanistic links. Periodontol 2000. 2022;89(1):99-113. doi:10.1111/prd.12422. DOI
30. Koth VS, Salum FG, de Figueiredo MAZ, Cherubini K. Repercussions of osteoporosis on the maxillofacial complex: a critical overview. J Bone Miner Metab. 2021;39(2):117-125. doi:10.1007/s00774-020-01156-4. DOI
31. Penoni DC, Fidalgo TK, Torres SR et al. Bone Density and Clinical Periodontal Attachment in Postmenopausal Women: A Systematic Review and Meta-Analysis. J Dent Res. 2017;96(3):261-269. doi:10.1177/0022034516682017. DOI
32. Sidiropoulou-Chatzigiannis S, Kourtidou M, Tsalikis L. The effect of osteoporosis on periodontal status, alveolar bone and orthodontic tooth movement. A literature review. J Int Acad Periodontol. 2007;9(3):77-84.
33. Knezović Zlatarić D, Pandurić J, Korsić M, Dodig D. Dijagnosticke metode za rano otkrivanje osteoporoze u stomatologiji [Assessment tools in early detection of osteoporosis in dentistry]. Arh Hig Rada Toksikol. 2007;58(1):33-39. doi:10.2478/v10004-007-0006-6. (Croatian) DOI
34. Demkovych A. Endogenous intoxication in development of experimental periodontitis of bacterial-immune genesis. Folia Medica. 2023;65(1):149-154. doi:10.3897/folmed.65.e71970. DOI
35. Lysokon Y, Bandrivsky YL, Luchynskyi MA. Analysis of the results of treatment of destructive forms of apical periodontitis with osteotropic drugs in a short term. Wiad Lek. 2022;75(1):228-231.
36. Sanfilippo F, Bianchi AE. Osteoporosis: the effect on maxillary bone resorption and therapeutic possibilities by means of implant prostheses--a literature review and clinical considerations. Int J Periodontics Restorative Dent. 2013;23(5):447-457.
37. Shcherba V, Demkovych AE, Vorobets AB, Yanchii IR. Submicroscopic changes of periodontal components under experimental lipopolysaccharide periodontitis combined with hypothyroidism. Fiziolohichnyi zhurnal. 2023;69(4):85-91. doi:10.15407/fz69.04.085. DOI
38. Choël L, Last D, Duboeuf F et al. Trabecular alveolar bone microarchitecture in the human mandible using high resolution magnetic resonance imaging. Dentomaxillofacial Radiology. 2004;33(3):177–182. doi:10.1259/dmfr/42933309. DOI
39. Demkovych A, Rubas L, Luchynskyi V et al. Changes of ultrastructural organization in periodontal complex components in experimental periodontitis and its correction with quercetin. Pharmacia. 2022;69:563-569. doi:10.3897/folmed.65.e7197010.3897/pharmacia.69.e82128. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Uterine Leiomyoma in women of reproductive age: A systematic review

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ABSTRACT

Aim: The objective of this literature review was to determine the current aspects of the clinic, diagnosis and treatment of uterine leiomyoma in women of reproductive age.

Materials and Methods: Pubmed, Google Scholar, Web of Science, and Scopus databases were used to search for materials on current aspects of the clinic, diagnosis, and treatment of uterine leiomyoma in women of reproductive age.

Conclusions: Women who have a pregnancy in the background of leiomyomas of the uterus, constitute a high-risk group for the occurrence of obstetric and perinatal complications, therefore, in the most dangerous periods of pregnancy, hospitalization in a specialized obstetrical hospital is recommended. It is advisable to exclude the tactics of passive surveillance of women of childbearing age with leiomyoma of the uterus. Women of childbearing age with leiomyoma of the uterus are recommended to carry out organ-preserving operations in the volume of leiomyomectomy in order to preserve the reproductive function of the woman.

KEY WORDS: leiomyocyte, cytokines, growth factors, hormone-dependent canals

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INTRODUCTION

Leiomyoma of the uterus is a hormone-dependent benign tumor that develops from the smooth muscle tissue of myometrium and connective tissue, which is one of the most common tumors of female genital organs.

In the structure of gynecological morbidity, leiomyoma ranks second afte inflammatory processes of the uterus and its appendages [1]. The literature provides data on which every 5th woman in the world is ill with leiomyoma of the uterus [2]. It has been established that 20-50% of women of reproductive age suffer from this pathology, although the true morbidity is much higher, since only half of the patients have symptoms associated with leiomyoma [3]. It was believed that leiomyoma was a disease of premenopausal age, because the maximum percentage of the incidence was due to this period of life of a woman.

However, more recently, the facts of "rejuvenation" of uterine leiomyomas are becoming more common, more frequent cases of the disease occur in 18-22-year-old women [4].

Moreover, in most cases, not only one, but several tumor nodes of different sizes appear in the wall of the uterus. If one node appears, then wait for both the second and third ones.

Therefore, doctors call leiomyom a multiple tumor. So, as the main cause of the disease – a hormonal shift, leiomyomas almost never bother young girls and women in menopause [5]. It is suggested that 80% of all women between the ages of 30 and 40 have a high risk of leiomyoma in the uterus . Unfortunately, in 20-30% of cases, the latter is an etiological factor in infertility and another 15-30% causes miscarriage of pregnancy [6]. It is also worth noting the fact that 70-80% of all gynecological interventions occur in this particular disease [7]. After the onset of menopause, leiomyoma of the uterus is regressed [8].

AIM

The objective of this literature review was to determine the current aspects of the clinic, diagnosis and treatment of uterine leiomyoma in women of reproductive age.

MATERIAS AND METHODS

Pubmed, Google Scholar, Web of Science, and Scopus databases were used to search for materials on current aspects of the clinic, diagnosis, and treatment of uterine leiomyoma in women of reproductive age.

REVIEW AND DISCUSSION

This disease was included in the International Classification of Illnesses X, called leiomyoma, and not the "myoma" of the uterus, although the latter term is more common in clinical medicine as the generalized name of benign tumors of myometrium, and the term "leiomyoma" was considered to be a histological term for a long time (for tumors , where the stromal fibroblastic component is completely absent, unlike the "myoma" where it is present, but to a lesser extent, and "fibromyom", where the latter is substantially expressed). The achievements of the world's medical genetics over the last two decades have proven that uterine leiomyoma is a benign tumor of the uterus that develops from myometrium smooth muscle, regardless of the presence or absence of the fibroblastic component in the tumor site and the level of hormone dependence.

Mashal et al. [14] proved that each node of the uterine leiomyomy is a monoclonal tumor originating from one mutant smooth muscle cell of myometrium (mutant leiomyocyte): one mutant - one node, many mutant myocytes - diffuse leiomyoma of the uterus, multiple nodes. The role of genetic factors on chromosomal and gene levels in the etiology of uterine leiomyomas is beyond doubt, although not fully understood. The significance of chromosomal aberrations, namely, translocation ofregions of the 12th and 14th chromosomes, has been determined reliably: these sites change places [t (9)], deletions in the 7th chromosome [del (7) (q22q32), and also mutations of certain genes (NMGIC and NMGIY) responsible for encoding proteins that regulate DNA transcription.

SOME MECHANISMS OF MORPHOGENESIS OF UTERINE LEIOMYOMAS AT THE MOLECULAR CELLULAR LEVEL

The main mechanisms of pathological cell proliferation, hyperplasia and neoplasia in the organs of the female reproductive system are schematically depicted in Fig.1.

As shown in Fig.1, at present, at least three main mechanisms of activation of signaling pathways stimulating leiomyocyte to pathological growth and division [8] have been clarified.

One of them involves cytokines that regulate proliferation, cell growth and apoptosis (interferon alpha, some interleukins, tumor necrosis factor, etc.) [9, 13]. The nuclear transcription activation factor (NF-kB) coming from the cytokines is a terminal cytoplasmic signal conductor. Penetrated into the nucleus of the cell, it includes the genes needed for active cell division (see Fig. 1).

The second way of stimulation of proliferation is closely related to growth factors that are involved in the processes of cell division of oncogenes and the factors that stimulate the formation of vessels necessary for tumor growth. The most potent cell division stimulants are: epidermal growth factor, insulin-like growth factor (type 1), epithelial and fibroblast growth factors. The most potent stimulant for neoangiogenesis is endothelial growth factor. The third way of stimulating myocytes to pathological growth and division is through the hormone-dependent channels. Sex steroid hormones, namely: excessive estrogenic effects combined with insufficient progesterone - play one of the key positions. There are 3 main fractions of estrogen: estron (E1), estradiol (E2) and estriol (E3). In the first two - pronounced proliferative activity, in the third - is completely absent. It should be noted that E2 is evaluated as the main regulator of the cell cycle. Progesterone (P) is not related to the activation of cell division stimulation pathways, which is associated with proliferative activity (in this case, it acts as an antagonist of estradiol and estrone), but it has a direct and indirect effect on the hyperplasia of target cells of steroid hormones, including leiomyocytes. Its effects are realized after binding to the receptors of two types: the antiproliferative effect is realized through the alpha receptors (P - antipode E2 and E1), and through receptors beta -hyperplastic effect (see Fig. 1).

Consequently, estradiol and estrone can be converted into 2 forms of metabolites: 2-OH-estrone and 16-alpha-ON-estrone as a result of catalysis by various forms of the cytochrome P-450 enzyme and cause ambiguous effects on the proliferative activity of cells:

2-OH-estron normal cell division regulator and does not stimulate excessive (proliferative) activity, while 16-alpha-ON-estrone, on the contrary, is an inducer of over active cell growth and cell division and an estrogen agonist.

All three levels of activation of signaling pathways to the cell, which subsequently lead to pathological proliferation and tumor transformation, are interrelated. This means that the biological effects of hormones, growth factors and cytokines are interrelated. Thus, interferons are antagonists for the action of E2 and E1 on cells. Therefore, in the case of a local (in a pathological center) reduction of the factors regulating the antiproliferative activity of tissues, the influence of factors that stimulate

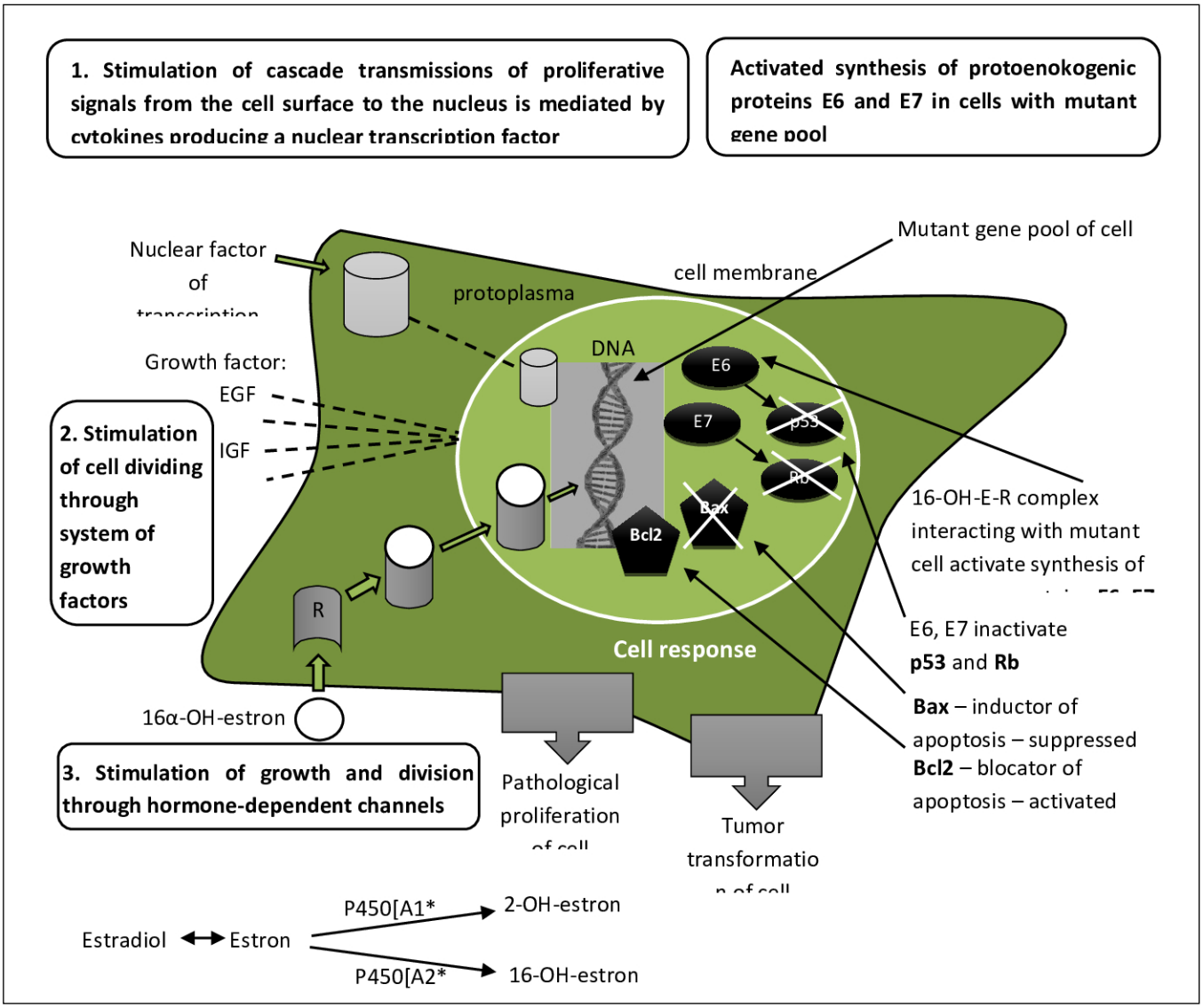

Fig. 1. The main mechanisms of pathological cell proliferation, hyperplasia and neoplasia in the organs of the female reproductive system.

proliferative activity - E2, E1, interleukin-8, epidermal growth factor, will necessarily be increased, which indicates the local growth of the proliferative potential. It is in the focus of the localization of the myoma that changes that determine the pathways of the disease - either in the direction of its progression, or in the direction of stabilization and regression. In this regard, the dynamics and intensity of the production of various cytokines, especially in the area of the myomatous nodes, as well as the microenvironment cells, may be of great importance [10].

MORPHOGENESIS AND MORPHOSTRUCTURE OF LEIOMYOMAS AT THE TISSUE LEVEL

Morphogenesis and further growth of the myomatous node undergo three stages of development:

1. Formation of active growth zone in myometrium near the microvessels in the form of accumulation of immature myocytes of different levels of differentiation, still unorganized in the beam. In contrast to the normal growth zone, in the active - much more intense metabolism and vascular-tissue perfusion.

2. Growth of a tumor without signs of differentiation (the node is identified only by microscopy).

3. Growth of the tumor with its differentiation and ripening (the node can already be determined macroscopically).

According to cytogenetic studies, all leiomyoma cells of the uterus are the descendants of a single maternal myogenic precursor cell. Recently, the possibility of formation of myoma nodules at the embryonic stage is confirmed by induction of mutagenic effects in the lessdifferentiated cells located in the zones of growth in myometrium (the "precursors of uterine leiomyo-

mas"). These focal points do not prolong themselves and activate only after menarche under the influence of sexual tropical and steroid hormones, growth factors and various altering factors of the endo- and exogenous environments of the body [11]. The factors that trigger this process are not fully understood, and they are numerous [12].

The original transformed mutant cell passes its properties only to its descendants. That is why multiple leiomyomas in one uterus are not clonally related [10].

According to the classical works of Uelzeko-Stroganova KP on morphology of the female reproductive system in the 30th years of the last millennium, the formation of precursors of myomatous nodes occurs at the embryonic stage. These data are confirmed in moder scientific research. The most recent confirmation is the theory of Fujii S., according to which smooth muscle cells of mesodermal origin are formed at the embryonic stage: from the 14th to the 30th week of fetal pregnancy [15]. That is why these undifferentiated cells can be exposed to many factors from the mother's body (trophic hormones, sex steroids, growth factors, etc.) and the environment (xenobiotics), epigenetic factors. These precursor cells (already with apparent mutations) are stored in myometrium and begin to grow under the influence of trigger factors, and predominantly after 28 menarche. The growth of these cells lasts for many years against the background of the marked activity of the ovaries under the influence of estrogens, progesterone and other hormones [11]. The development of uterine leiomyomas occurs in areas of growth, located mainly around the thin-walled vessel (active growth zones) [12].

Thus, leiomyoma of the uterus is a tumor of monoclonal origin. Primitive cells of myoma are transformed into myoblasts and fibroblasts. Active areas of growth are characterized by high levels of exchange and high vascular-tissue permeability. Leiomatous node repeats in its development parenchymal-stromal features of the layer of myometrium, from which it develops. Clinically, this is manifested by the fact that numerous leiomatous nodes in one uterus develop independently of each other. Their different growth rates are due to cell division, which is not clonally linked [10].

Most scientists [11,12,14] believe that leiomyoma of the uterus meets the criteria for a true tumor. The latter is confirmed by its monoclonal developmental nature, large size, autonomous growth of the tumor under the influence of growth factors and cytokines, activation of the process of angiogenesis, genetic instability. As a result of mutations, the accuracy of the reproduction of the genetic apparatus decreases, the mechanism of DNA repair is violated, the regulation of the cell cycle in the deformed cells changes, which leads to tumor progression.

There are two theories of the occurrence of precursors of uterine leiomyomas:

the first one is ontogenetic second - secondary somatic mutation in the normal cell myometrium under the influence of various factors [12].

The literature data of recent years (Khadartsev A. A. et al., 2013) reveal the value of stem cells (SC) in the onset and growth of uterine leiomyomas.

Researchers believe that the cause of adenomyosis, uterine leiomyomas is the tissue of the endometrium, which was formed even in the embryonic development period. Stem cells of the bone marrow can penetrate myometrium, resulting in diffuse changes and pathology development. The reason is the tissue cells of the endometrium, which remained in the myometrium during the period of intrauterine development. Such cells may be stem cells (SC).

Many years ago it was established that SC is located just in the basal layer of the endometrium. It is proved that there is an imbalance between the index of proliferation in different layers of the endometrium [9]. SC is a cell of mesenchymal origin that produces a growth factor.

According to most scientists, uterine leiomyoma occurs due to numerous somatic mutations in normal cells of myometrium, which leads to a gradual decrease in regulation and their growth. The tumor grows from the precursor cell in which the initial mutation occurred, and is a consequence of a violation of tissue homeostasis, supported by the balance between cell proliferation and the process of apoptosis.

The ontogenetic development of smooth muscle cells of ectodermal origin (digestive system, excretory system) runs faster than smooth muscle cells of mesodermal origin, to which the sexual system belongs. Undifferentiated cells, which are further differentiated into uterine smooth muscle cells, have a longer unstable period, during which they are exposed to various maternal factors (sex hormones, growth factors, viruses, toxins, etc.), resulting in their structure defects.

Such defective cells are referred to as precursor cells for the leiomatous node. The activity of cells begins with the presence of trigger factors. Regardless of when the precursor cell is formed, mutations in it promote the stimulation of proliferative processes.

Yakovleva IA, Kukute BG. (1979) have shown that in most myomatous nodes (about 75% of all cases) stroma predominates over parenchyma, and the mitotic activity of myocytes is practically equal to 0 (no mitoses are present), while in other nodes (about 25%) myogenic elements are more numerous. The second group of leiomyome clinically manifests itself in rapid growth, multiple nodes [10].

Hyperplasia of the connective tissue (fibroplastic) component of myometrium is secondary and can be expressed in the nodes of the uterine leiomyomas to a greater or lesser extent, depending on the nature and intensity of the harmful effects of the factors of the exogenous and endogenous environments of the organism on the genetic fund of its cells.

CLASSIFICATION OF UTERINE LEIOMYOMAS ACCORDING TO CLINICAL AND MORPHOLOGICAL TYPE AND ACTIVITY OF PROLIFERATIVE PROCESSES

1. Simple myoma, develops as benign muscular hyperplasia - slow growth, proliferative processes are not expressive.
2. Proliferating myoma is a vertebral tumor with high mitotic activity.
3. Pre-sarcoma - characterized by the presence of multiple atypical elements, heterogeneity of cell nuclei with large hyperchromic nuclei**.**

The tumor node repeats the morphological structure of one of the three layers of myometrium from which it originally developed. That is why, according to the histological evaluation of the tissues of the site, the composition of the parenchyma and stroma is different [11].

The morphostructure of the uterine fibroids is not constant. Depending on the number of muscle cells, the degree of their proliferation, differentiation and the presence of signs of atypia, there are three forms of uterine leiomyomas: simple, proliferative and pre-sarcomatous. According to clinical and morphological studies, leiomyoma of the uterus of a simple type is benign, inactive, slowly growing and contains mainly connective tissue elements [12]. This form of the tumor is characterized by a phenotypic transformation of myocytes, a decrease in blood flow in myometrium and myomatous nodes. The proliferative form of uterine leiomyomas is benign, active, multiple, rapidly growing by a tumor with a high proliferative potential and is often accompanied by proliferative processes in the endometrium, cervix, benign and malignant ovarian, mammary glands [9].

The precursor to proliferative distinguishes the presence of multicentric centers of proliferation with signs of atypia (heterogeneity of nuclei and cells, rarely occurring multicore cells with enlarged hyperchromic neclei of round or oval form). Cells with figures of mitosis often occur in it, including and atypical ones - this is an obvious path to the malignancy of the

uterine leiomyomas. In a simple leiomyoma of the uterus, there is virtually no mitosis, in

proliferative - mitotic activity is elevated. The latter form and, moreover, pre-sarcomatous are diagnosed much more often in women with a rapid growth of tumors, whereas for simple leiomyoma of the uterus more characteristic of slow and moderate growth rates.

A simple uterine leiomyoma is macroscopically represented by nodes of dense fibrous white fibers with clear boundaries. The sizes of knots can be different: from 1 to 4 cm in diameter. Placed nodes are mostly sub-serous and intramuscular. A simple leiomyoma is composed of smooth muscle bundles that are chaotic. The macroscopic node of the uterine leiomyomas has small dimensions, dense consistency, clear boundaries, pseudocapsule. With a pseudocapsule cut, the knot can easily be removed to its base, where the vessels are located.

By correlation of parenchyma and stroma in simple leiomyoma of the uterus, connective tissue elements predominate. Myocytes in these zones of myometrium show increased synthetic activity due to extracellular matrix production. Leiomyoma of a simple type is characterized by active processes of ripening, differentiation of tumor myocytes with their subsequent aging. Synthetic functions prevail, namely the production of elements of the extracellular matrix over proliferative activity. The stroma is presented of connective tissue with a large amount of collagen fibers. Vessels are sinusoid type [8].

Leiomyoma proliferative type is characterized by large sizes (up to 9 10 cm in diameter) of numerous nodes. Localization of nodules is predominantly submucosal, intramural.

Myocytes of these tumors are characterized by rapid proliferation (hyperplasia, hypertrophy). The consistency of the nodes of the fibroids is more softer than the simple ones. Cells of proliferation of tumor myocytes are localized in the perivascular spaces around the vessels. Proliferative myocytes are represented by large complex muscle cells with "juicy" hyperchromic nuclei. Stroma in proliferative zones contains predominantly connective tissue.

The tissues of myometrium outside the zones of nodes are represented by hypertrophied muscle fibers with a large number of cells of "active growth zones" [9].

THE MAIN MECHANISMS OF PATHOGENESIS OF LEIOMYOMAS

Of great importance in the pathogenesis of uterine leiomyomas is given to the central mechanism of regulation of menstrual function. It is believed that the basis of the development of leiomyomas of the uterus is the syndrome of psychoemotional stress, which leads to the disruption of adaptive-compensatory responses at different levels of the circulatory system of the hypothalamus-pituitary-ovary-uterus due to the violation of macro and microcirculation and tissue hypoxia. Emotional shocks or craniocerebral traumas often (in

73% of patients) are found in premorbid background in patients with leiomyoma of the uterus [10].

Violations of the functional state of the hypothalamic-pituitary system lead to changes in the cyclic secretion of the gonadotropin nucleus gonadotropin releasing-hormone (GnRH), as a result - the rates of peak exacerbations of luteinizing hormone (LH) and follicle stimulating hormone (FSH) increase substantially beyond the ovulatory, which can be observed in different phases of the menstrual cycle. Data on the content of blood in patients with LH and FSH in the presence of uterine leiomyomas are ambiguous, indicating several pathogenesis of uterine leiomyomas and corresponds to the assumption about possible (as an option of one of the ways) damage to the limbicoreticular structures of the brain that precede the development of the disease.

The largest number of studies is devoted to the study of estrogen-progesterone relationships in patients with leiomyoma of the uterus. There are also ambiguous data: possible variants of absolute, relative or combined hypertrophy; biphasic (2/3 cases) or single-phase (1/3 cases) menstrual cycles; with signs of progesterone deficiency (more often) or at elevated baseline gestagenic stimulation (less often). Significant prevalence of cases of systemic and local hyperestrogenism, rhythm changes and displacement of estrogen secretion peaks, estrogen conjugation disorders, qualitative changes in the concentration of various metabolites of these hormones, with the advantage of the formation of active substances in a proliferative relationship with metabolic fractions such as, for example, 16-α-Hydroxyestron and others.

Comparing the concentration of steroid hormones in the systemic and local (uterine vessels) streams in patients with leiomyoma of the uterus and endometrial hyperplasia, the researchers concluded that the myomatous nodes and the hyperplastic processes of the endometrium can serve as stimulators of relative local hyperteriogenicity and contribute to the formation of a false circle by type of stimulation of consumption, that is, the greater the mass of myometrium and endometrium, the greater the estrogen-consuming substrate, which is an active regulatory factor in the tumor system, is the tumor carrier [11].

The activity of the specific receptive state and the density of the receptor distribution of various sex hormones in the tumor (uterus) and, especially in the tumor itself, determines the final result of the hormonal action. In myomatous uterus, the higher activity of estrogen receptors compared with progesterone: the amount of bound estradiol reaches 60-65%, whereas in the normal uterus - only 37% [12]. Consequently, the content of estradiol and progesterone in the myometric uterus is higher than in normal myometrium, but lower than in the endometrium. Dependence of the content of the receptors of estradiol and progesterone on the magnitude and rate of growth of myomatous nodes was revealed: the highest content of estradiol receptors and the smallest - progesterone receptors were detected in nodes of large sizes with pronounced signs of proliferation; in the case of prolonged existence of myomatous nodes without a tendency to increase, the increase in the concentration of progesterone receptors in both the tissues of the host and in myometrium, while the content of estrogen receptors is relatively low, and in nodes it is lower than in the cells of myometrium surrounding them [10].

Under the influence of treatment with progestogens, increased receptor activity of all tissues [9]. However, it should be noted that in the case of rapid growth of uterine leiomyomas, as well as with the size of a leiomyomatous uterus in the size of 12 and more weeks of pregnancy, degenerative degenerative changes in the receptor apparatus occur, that the proliferative process (local or diffuse) loses sensitivity to the effects of hormones medication correction, which makes the latter inappropriate. Low-dose oral contraceptives, although not increasing the risk of developing uterine leiomyomas, do not prevent the growth of already existing nodes of the uterine leiomyomas.

Three pathogenetic variants of the development of leiomyomas of the uterus according to the level of primary lesions and perimondal background are commonly known:

The 1st variant is caused by violations of the function of the hypothalamic-pituitary system (with an increase or decrease in the production of gonadotropins);

2nd – develops against the background of impaired ovarian function due to inflammatory, atrophic and other changes;

3rd – occurs on the background of violations of the structure and function of the receptor apparatus of the uterus, which was usually the result of abortions, manual and instrumental studies of the uterus, the long-term use of the intrauterine devices (IUD), chronic metroendometrites.

However, it should be kept in mind that primary lesions may occur at any level, at any age and under the influence of numerous damaging factors on a different premorbid background, but sooner or later will necessarily induce the development of the disease all three levels, indicating that that the leiomyoma of the uterus is a systemic disease, not a local one. In his presence, psycho-vegetative, vegetative-vascular and metabolic-endocrine disorders are often observed.

The commonality of certain disorders in the regulation of the functional state of various organs of the

reproductive system leads to a frequent combination of uterine leiomyomas with hyperplastic processes, including endometrial cancer, endometriosis, ovarian polycystic ovary, fibro-cystic mastopathy, and other variants of hormone-dependent breast pathology, as well as cervical diseases (including dysplasia and neoplasia), with pathology of the thyroid gland, adrenals and other endocrinopathies with metabolic disorders. This circumstance emphasizes the necessity of oncological alertness and conducting of a comprehensive examination for the active detection of pre-tumor, benign and malignant neoplasms of various localizations in organs of the reproductive system, as well as related somatic diseases, especially of the liver, intestines, cardiovascular and urinary systems, in patients under dispensary supervision over leiomyomas of the uterus.

MUTUAL INFLUENCE OF UTERINE LEIOMYOMAS AND PREGNANCY

It is known that during pregnancy the growth of nodes of uterine leiomyomas is accelerated; Pregnancy contributes to a violation of hemodynamics in the tumor and, as a result, hemorrhages in the node, swelling of the tumor, necrobiosis and necrosis of the nodes, rupture of the capsule, secondary local and generalized suppurative complications. On the other hand, pregnancy with leiomyoma of the uterus is aggravated by various complications in the 1-st, 2-nd, 3-rd trimesters and in childbirth [8]. Thus, in the early stages of pregnancy, the likelihood of not being worn (due to the violation of the migration processes and the implantation of the pond egg in the localization of nodes near the isthmic parts of the fallopian tubes) increases; In the 1st and 2nd trimesters (due to increased tonus and excitability of myometric myometric biopsy, as well as hormonal dysfunctions), the risk of involuntary miscarriage is increased. Later leiomyoma of the uterus can cause premature birth, placental insufficiency, abnormalities in placental placement, formation of false posture and fetal pregnancy. Occasionally placement of nodes, especially in the cervical orthopedic region of the uterus, may become a barrier to birth per vias naturalis. Often, there is a weakness of labor, untimely departure of around-vegetative waters, hypoxia of the fetus in childbirth, and in the third period of childbirth, the delay of detachment of the placenta and its parts and hypotonic bleeding. In the postpartum period, women with leiomyoma of the uterus also significantly increase the risk of hypotonic bleeding, uterine subinvolution, endometritis, and damage to the trophic nodes of the uterine leiomyomas.

It occurs as a result of the fact that the cells of the uterus spontaneously begin to actively share. The causes of this phenomenon are not fully understood, but it is established that it is stimulated by hormones and is connected with all with increased secretion of estrogens [9] However, the normal content of estrogen and progesterone in the blood does not always clearly indicate the absence of leiomyomas. This is due to the fact that local changes in the level of estrogen in the uterus are not reflected or very slightly reflected in the content of hormones in this group in the blood [10].

However, from 25 to 50, the chances of getting it are quite large. It appears only in the reproductive period, when the ovaries produce estrogens. While ovaries are functioning, leiomyoma grows, at best - is in a stable condition. In postmenopausal leiomyomas no longer occur, and those small nodes, which by that time have already been in women, begin to decrease in size [11]. The fact that leiomyomas began to occur more often is connected with the obvious way of life - with high tempo, high loads. Especially sharply this probability grows during pregnancy, inflammatory processes of genital organs and general decrease of immunity [12].

Leiomyoma of the uterus can provoke hereditary predisposition, problems with the menstrual cycle, infertility, miscarriage, metabolic disorders (obesity, diabetes mellitus), multiple abortions, besides that, scientists have recently discovered that there is a direct relationship between leiomyoma uterus and stress [11]. The uterine leiomyoma predominantly runs asymptomatic, but sometimes women may be disturbed by excessive bleeding during menstruation, cycle disorders, abdominal pain or lower back. there are some signs that a woman may suspect in my uterus. Significant bleeding can lead to anemia, the tumorous node can compress adjacent organs, and sometimes there is pain, problems with urination, there are constipation [10].

If leiomyoma is not completely immersed in the wall of the uterus, then it is possible torsion of "legs"; in this case, a woman is at risk of necrosis of the tumor, its inflammation and rupture; from the outside it is manifested by bleeding, acute abdominal pain and a sharp increase in temperature.

Other problems of leiomyomas are problems with conception, pregnancy and delivery [9]. To determine the size of leiomyomas, an analogy with pregnancy is used. The treatment of leiomyomas depends on the age and the patient's plans. If during many years, leiomyoma does not increase, and the woman is not going to get pregnant, most doctors propose to treat the tumor conservatively. Hormonal drugs can slow down and, in some cases, stop tumor growth. Young women who want to have a baby, doctors advise not to delay the operation.

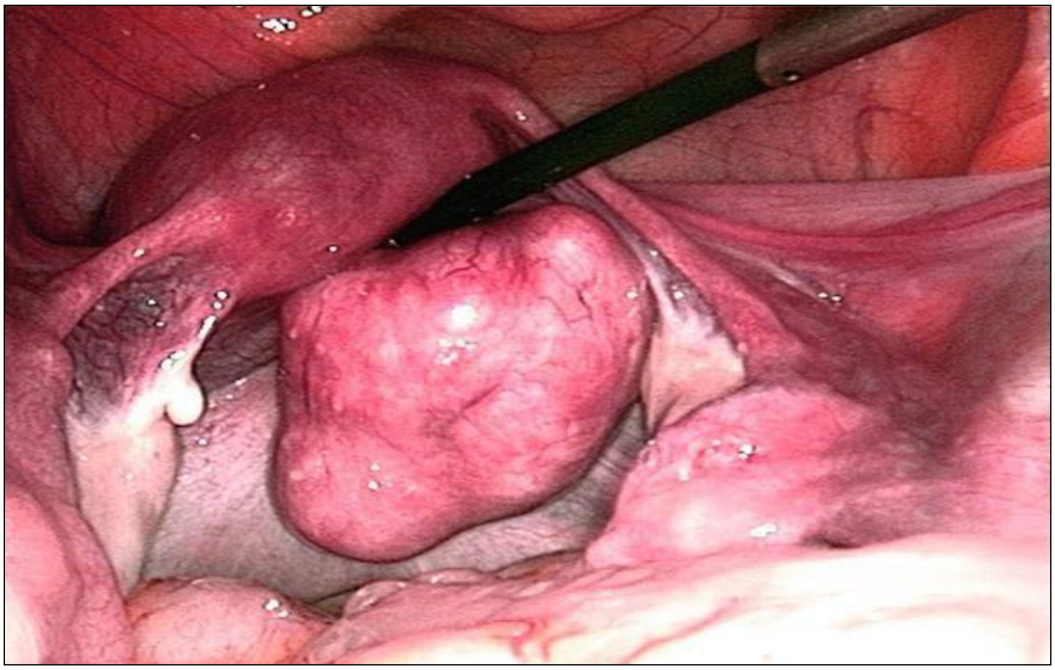

Fig. 2. The type of uterine leiomyoma during the review laparoscopy of patient O., 41.

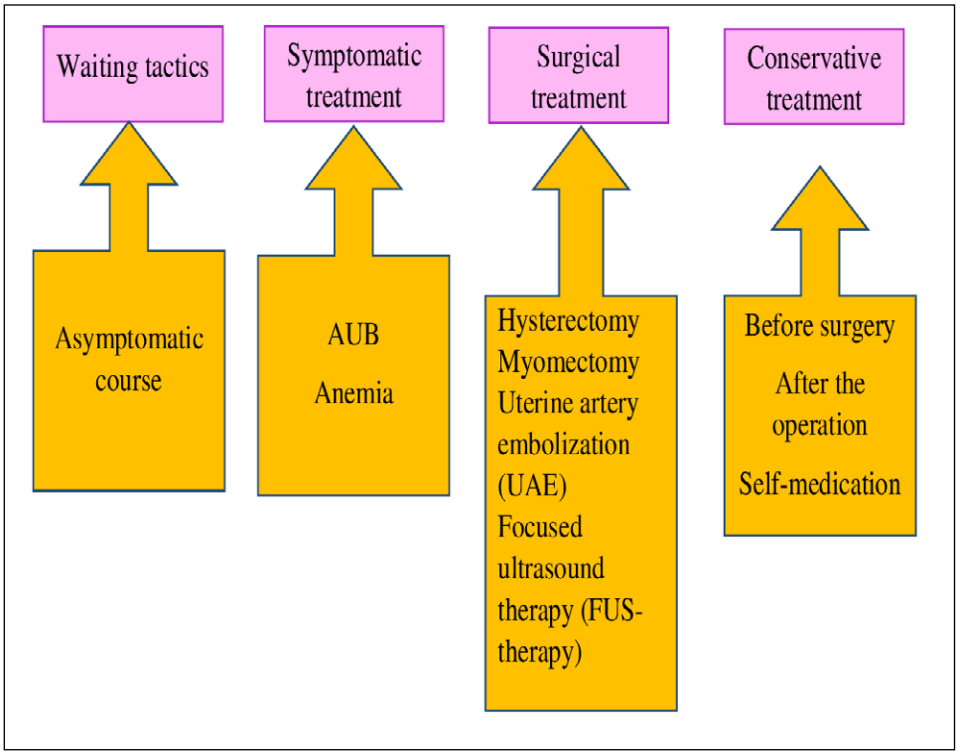

Fig. 3. Modern management of uterine fibroids

Organ-preserving surgery is a myomectomy, when only the nodes themselves are cut out: the uterus is not damaged while normal pregnancy is possible [8]. If the tumor nodes are very large, or too much, then you have to remove the entire uteru.

The impact on reproductive health is often accompanied by infertility, miscarriage, placental dysfunction (distress and growth retardation, pregnancy loss), a high probability of surgical delivery with removal of the uterus [14].

According to the recommendations of authoritative international publications [15], modern management of uterine fibroids involves both conservative and surgical treatment (Fig. 3).

It should be noted that treatment tactics should be selected individually based on the following factors:

- presence and severity of symptoms;
- the patient's desire to receive radical treatment;
- the desire to preserve childbearing function;
- the importance of preserving the uterus;
- infertility associated with deformation of the uterine cavity;
- complications during a previous pregnancy related to leiomyoma.

CONCLUSIONS

1. 80% of women between the ages of 30 and 40 have a high risk of developing uterine leiomyoma, which is the cause of infertility in 20-30% of cases.
2. In the tactics of patient management, an individual approach prevails with a combination of surgical and conservative methods of treatment, taking into account the age of the patients, their reproductive history, and the presence of concomitant genital and somatic pathology.
3. The use of modern conservative and operative methods of uterine leiomyoma treatment makes it possible to reduce the number of its complications, preserve the uterus and reproductive function of a woman, increase the effectiveness of uterine leiomyoma treatment, and the quality of life of patients.

REFERENCES

1. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. Hum Reprod Update. 2016;22(6):665-686. doi: 10.1093/humupd/dmw023 DOI
2. Tatlici TK, Cetin N, Korpe B et al. Association between uterine leiomyoma andfragmented QRS waves: a prospective case-control study. Rev Assoc Med Bras. 2024; 3;70(4):e20231359. doi: 10.1590/1806-9282.20231359. DOI
3. Balulescu L, Brasoveanu S, Pirtea M et al. The Impact of LaparoscopicMyomectomy on Pregnancy Outcomes: A Systematic Review. J Pers Med. 2024;14(4):340. doi: 10.3390/jpm14040340. DOI
4. Laily A, Nair I, Shank SE et al. Enhancing Uterine Fibroid Care: Clinician Perspectives on Diagnosis, Disparities, and Strategies for Improving Health Care. Womens Health Rep (NewRochelle). 2024;27;5(1):293-304. doi: 10.1089/whr.2023.0113. DOI
5. Kiesler ZG, Hunter MI, Balboula AZ et al. Periostin's role in uterine leiomyomadevelopment: a mini-review on the potential periostin poses as a pharmacological interventionfor uterine leiomyoma. Arch Gynecol Obstet. 2024;309(5):1825-1831. doi: 10.1007/s00404024-07435-z. DOI
6. Thanasa A, Thanasa E, Grapsidi V et al. Emergency Surgical Treatment of a LargePedunculated Subserosal Uterine Leiomyoma With Torsion: A Rare Cause of Acute Abdomen. Cureus. 2024;16(1):e52136. doi: 10.7759/cureus.52136. DOI
7. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG. 2017;124(10):1501–1512. doi:10.1111/14710528.14640. DOI
8. Yilmaz BD, Bulun SE. Endometriosis and nuclear receptors. Hum Reprod Update. 2019;25(4):473–485. doi: 10.1093/humupd/dmz005. DOI
9. Török P, Póka R. Diagnosis and treatment of uterine myoma. Orv Hetil. 2016;22:157(21): 813 -819.
10. AlAshqar A, Patzkowsky K, Afrin S et al. Cardiometabolic risk factors and benign gynecologic disorders.Obstet Gynecol Surv. 2019;74(11):661–673. doi: 10.1097/OGX.0000000000000718. DOI
11. Peregrino PFM, Lorenzo Messina M, Santos Simões R et al. Review of magnetic resonance-guided focused ultrasound in the treatment of uterine fibroids. Clinics (Sao Paulo). 2017;72(10):637–641. doi: 10.6061/clinics/2017(10)08. DOI
12. Laughlin-Tommaso SK, Fuchs EL, Wellons MF et al. Uterine fibroids and the risk of cardiovascular disease in the coronary artery risk development in young adult women's study. J Womens Health (Larchmt) 2019;28(1):46–52. doi: 10.1089/jwh.2018.7122. DOI
13. Fartushok TV, Semenyna HB, Yurchyshyn OM, Komissarova OS. Ways to improve natural fertility.Wiadomości Lekarskie. 2021;74(1):144-149. doi:10.36740/WLek202101128. DOI
14. Mashal R.D., Spiegelman D. et al. Genes, Chromosom. Cancer. 1994;11:1–6.
15. Fujii S, Hirose R, Ichigo S et al. Expression of progesterone receptor form A and B mRNAs in uterine leiomyoma. Tumor Biology. 2018;19(2):126–131. doi: 10.1159/000029983. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Experience in implementing effective programs of colorectal cancer screening for the development of an appropriate model in Ukraine – a literature review

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ABSTRACT

Aim: To explore the potential for preventing cancer development through CRC screening programmes.

Materials and Methods: A number of foreign articles, international guidelines were analysed using PubMed, Google Scholar, Web of Science, and information from national government websites about the aspects of CRC screening programmes in countries with high rates of participation of the average-risk population as well as the stages of their implementation for national colorectal cancer screening program development in Ukraine.

Conclusions: The final goal of CRC screening is to decrease mortality by detecting disease at an early stage, which increases treatment effectiveness and provides a better prognosis, as well as reducing incidence in the long term. This decrease in CRC incidence is the result of massive detection of early asymptomatic cases before they progress to later stages.

KEY WORDS: model, public health, colorectal cancer, screening, cancer prevention, fecal immunochemical test

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide. More than 85% of CRC cases occur in high- and upper middle income countries. However, in lower middle- and low income countries, there is an insufficient level of detection of CRC, as a result, there is a gradual increase of mortality rates from this disease.

However, CRC can be treated if detected at an early stage. By removing polyps and pre-cancerous lesions during colonoscopy it is possible to prevent the development and progression of the disease. The high incidence of CRC and its late detection is a threat to the public health that requires systemic solutions at the national level.

AIM

To explore the potential for preventing cancer development through CRC screening programmes.

MATERIALS AND METHODS

A number of foreign articles, international guidelines were analysed using PubMed,Google Scholar, Web of Science, and information from national government websites about the aspects of CRC screening programmes in countries with high rates of participation among average-risk population as well as the stages of their implementation for the prospective design of a national CRC screening programme in Ukraine. Articles and reviews were selected which contained information of existing CRC screening programmes and their successful variants. The publications were analysed using a non-systematic review method with the aim of compiling a brief overview of the collected information.

REVIEW AND DISCUSSION

In 2022, CRC is the third most common oncological disease worldwide among men (1,069,446 cases, 10.4% of all cases) and women (856,979 cases, 8.9% of all cases) [1] (Fig. 1).

More than 85% of CRC cases occur in high- and upper-middle income countries (according to the World Bank classification): 41.9% in high income countries and 43.3% in upper middle income countries and 81.7% of deaths (37.1% in high income countries and 44.6% in

Rank	Cancer site	Number of cases	Percent
1	Lung	1 572 045	15,2%
2	Prostate	1 467 854	14,2%
3	Colorectum	1 069 446	10,4%
4	Stomach	627 458	6,1%
5	Liver	600 676	5,8%
-	Others	4 974 131	48,2%

Number of new cases in 2022, males, all ages

Rank	Cancer site	Number of cases	Percent
1	Breast	2 296 840	23,8%
2	Lung	908 630	9,4%
3	Colorectum	856 979	8,9%
4	Cervix uteri	662 301	6,9%
5	Thyroid	614 729	6,4%
-	Others	4 325 410	44,8%

Number of new cases in 2022, females, all ages

Rank	Cancer site	Number of cases	Percent
1	Lung	2 480 675	12,4%
2	Breast	2 296 840	11,5%
3	Colorectum	1 926 425	9,6%
4	Prostate	1 467 854	7,3%
5	Stomach	968 784	4,8%
-	Others	10 835 921	54,2%

Number of new cases in 2022, both sexes, all ages

Fig. 1. Top 5 most frequent cancers. Number of new cases worldwide in 2022.

upper middle income countries). In contrast, 14.8% of CRC cases occurred in lower middle- and low income countries (13.2% in lower middle income countries and 1.6% in low income countries) and 18.3% of deaths (15.9% in lower middle income countries and 2.4% in low income countries)[1] (Fig. 2).

The incidence rates of CRC in high- and upper middle income countries are 30/100,000 and 20.1/100,000, while the mortality rates of CRC in these countries are 10.2 and 9.0/100,000, respectively. Meanwhile, the incidence rates in lower middle- and low-income countries are: 8.1 and 8.0/100,000, while mortality rates are 4.6/100,000 for lower middle income countries and 5.6/100,000 for low income countries. This reflects the limited access to healthcare services, absence of screening programmes in these countries, and low detection rates of disease, which leads to higher mortality rates[1,2] (Fig. 3).

However, CRC can be treated if detected at an early stage. The overall 5-year survival rate for CRC diagnosed at stage I is 90%, and for metastatic stage IV, this figure drops to 10%. In Europe, on average, only 13-15% of patients are diagnosed with pre-cancer or at stage I, more than 55% of cases are diagnosed at stages III – IV, of which 24% are still diagnosed at late stage IV [3,4] (Table 1).

Polyps and precancerous lesions can be removed during colonoscopy, preventing the development and progression of the disease. The cost of screening is less than for treatment, ranging from 3,000€ for stage I treatment, to up to 170,000€ for a late stage treatment[4]. Overall, the average difference in the cost of treatment for early and late stages of CRC is tenfold between 4,000€ and 40,000€[5].

The high incidence of CRC and its late detection is a problem for public health that requires systemic solutions at the national level. Performing screening only for symptomatic patients do not provide the required results in the management of the disease burden, therefore, organised population-based screening is designated for population of certain age group with no symptoms of the disease, which is a potential solution of this problem[6-11]. Screening programmes should be accessible, safe, and integrated into the healthcare system at an economically reasonable price. Thus, effectiveness, quality and accessibility are the key requirements for screening programmes[12,13]

The Council of the European Union (EU) recommends that CRC screening programmes have to be implemented with systematic monitoring of quality at all levels[14,15]. The programmes are financed from budget or by reimbursement through health insurance[16].

In Austria, a population-based screening programme has been implemented in the federal state of Burgenland since 2003. In the rest of the country, screening is opportunistic. As part of the opportunistic screening, gFOBT is offered annually, and colonoscopy is offered once every 10 years[16].

The population programme in the Wallonia-Brussels was launched in 2009 and in the Flanders in 2013. Since 2016 Wallonia-Brussels replaced gFOBT with FIT. Patients with a positive test result are informed through the treating physician to have colonoscopy [17].

In Lithuania, the population based programme started in 2009 in two regions, and became nationwide in 2014. Invitations are sent via primary healthcare centres[16].

In 2019, the Romanian Colorectal Cancer Screening Programme (ROCCAS) was launched, by the Ministry of Health and the National Institute of Public Health, funded by the European Social Fund, that lasted 60 months until the end of 2023 and consisted of two phases. The first phase was to create the organisational and legal framework to implement the CRC screening programme. The second phase consisted of the pilot testing of the programme in 4 of 8 regions of Romania. By September 2023, 169,052 people were invited to screening in all four regions. The preliminary results revealed a high rate of FIT acceptance, between 89% and 99%, with a good rate for FIT return ranging 79-95%. All the information about the patient (demographics, comorbidities, antithrombotic medication), the procedure (findings, preparation,

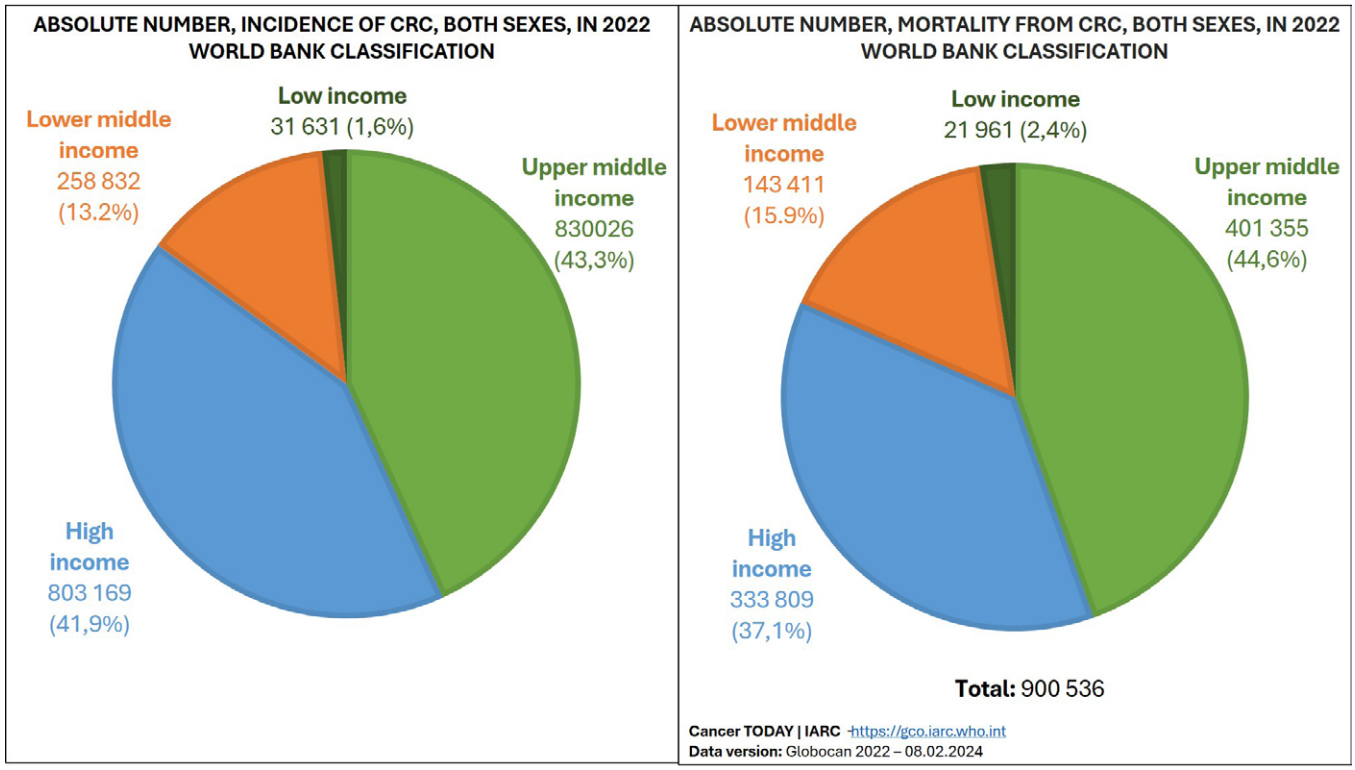

Fig. 2. Incidence and mortality data in countries according to their income levels _ World Bank classification_ in 2022.

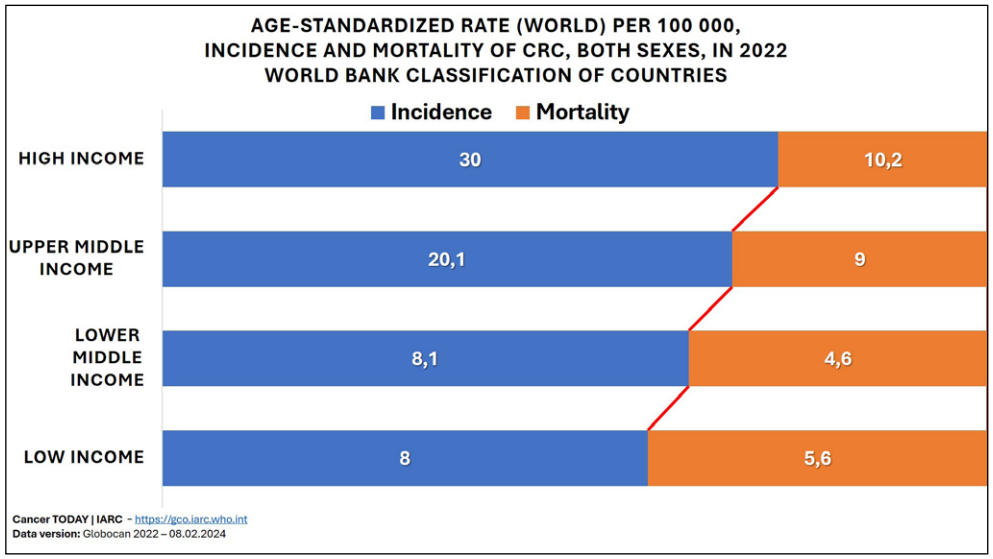

Fig. 3. Age-standardised incidence and mortality rates from CRC per 100_000_ both sexes_ in 2022 in countries according to their income (World Bank classification).

therapeutic approach, adverse events, sedation), histopathology results were collected in a standardized format in the Electronic Screening Record System according to the EU General Data Protection Regulation. The results of the ROCCAS programme have confirmed the effectiveness of CRC screening at the national level, and will be implemented in Romania in 2024[18].

In Poland, CRC is the third most common cancer among the population. In 2022, the estimated mortality rate in Poland was 30/100,000 women and 64.3/100,000 men, while the incidence rate is 53/100,000 women and 104.8/100,000 men [19].

The National CRC Screening Programme started in 2000 and is funded by the Ministry of Health of Poland and the National Health Fund within the framework of the National Cancer Strategy. The programme includes two types of screening: population-based targeted screening (through personal invitation letters) and opportunistic screening [20]. As part of the CRC screening, it is possible to undergo colonoscopy every 10 years. Participants are people aged 55-64 years (regardless the presence of clinical symptoms). Opportunistic screening includes four target groups: (1) people aged 50-65, regardless of family history; (2) people aged

Table 1. 5-year survival rates of patients with colorectal cancer per stage and the proportion of patients diagnosed per stage.

	Stage I	Stage II	Stage III	Stage IV
5-year survival rate	90%	75%	70%	10%
Rate of diagnosed patients	13%	31%	32%	24%

40-49 who have a first-degree relative diagnosed with CRC; (3) people aged 25-49 from a family with Lynch syndrome; (4) people aged 20-49 from a family with familial adenomatous polyposis syndrome. [20].

Despite improvements of CRC screening programme implemented by 2021, participation rate remains low. In 2018, less than 15% of those who received a personal invitation underwent a colonoscopy, which is lower than the 23-70% achieved in other EU countries[21,22].

To involve people to take part in screening tests, a national campaign called "Planning for a long life" was implemented as part of the National Cancer Strategy 2020-2030[22], which includes information campaigns promoting the importance of screening, including CRC, promoting people to participate and informing them about risk factors, symptoms and prevention strategies through media. In addition, the programme includes educational campaigns involving primary care physicians and nurses to inform the population at the local levels about the importance of screening and to spread information materials about screening programmes.

The results of a recent study in Poland demonstrated that the inclusion of primary health care staff in the organisation of a CRC screening programme was found to be a key factor in increasing the level of participation. Especially important factors were invitations in the form of a personal letter or phone call from primary care staff [21].

The programme improves the knowledge and skills of medical staff, with a particular focus on screening. The competence of medical staff is an irreplaceable element that allows for an early diagnosis of CRC. It is important to ensure continuous professional development by creation of training programmes of different levels of detalisation. Collaboration between oncologists and doctors of other specialties and precise detection of disease will speed up the diagnosis and treatment. By the end of 2024, the Public Health Centres would also invite Polish citizens to undergo screening. Due to the National Cancer Strategy, it is planned to increase the rate of the target population covered by CRC screening from 18% to 30%, and by the end of 2027, it is planned to increase this figure to 45%. From 2028, the use of high-definition endoscopes will become an obligatory technical requirement for colonoscopy. Improvements to the existing cancer data collection system have to ensure efficient data exchange, verification and access to the collected information for decision-making at early stages of the disease [22].

The pilot programme "Prevention 40 PLUS", which started in July 2021 consists of a diagnostic package of tests that also includes a FIT. The purpose of this programme is to involve people over 40 years old to preventive examinations

Thus, thanks to the efficient organisation Poland has made significant progress in the early detection of CRC and prevention of its development in asymptomatic individuals.

Every year, about 13,000 people are diagnosed with CRC in the Netherlands, of whom about 5,000 dies. The 5-year survival rate for this pathology is 65%, but it depends on which stage the disease was detected. According to WHO data, the mortality rate from CRC in the Netherlands in 2022 was 30.3/100,000 women and 43.8/100,000 men, while the incidence rate was 79.2/100,000 women and 117.4/100,000 men [19].

In the Netherlands, the national CRC screening programme (Bevolkingsonderzoek Darmkanker) was launched in 2014, and the implementation process from pilot studies to full integration took about 13 years. Its phased realisations allowed to build the required capacity for screening and treatment within the healthcare system.

On behalf of the Dutch Ministry of Health, Welfare and Sport, the screening programme is funded by the Population Screening Centre of the National Institute of Public Health. The costs of diagnosis, treatment and surveillance are part of the insurance package. The legal framework of the screening programme are: the Public Health Act and the Population Screening Act.

People aged 55-75 years are invited to participate in the screening programme every two years. Each participant receives an individual FIT test kit to take a stool sample at home. This test uses antibodies against human globin, which allows for quantitative measurement of haemoglobin in the material[23]. The advantage of FIT over gFOBT is its higher sensitivity and specificity, and its use does not require dietary or medication limitations [24,25]. The sample is sent by mail to the designated laboratory in a return package.

Implementation of the CRC screening programme at the local level is entrusted to five regional screening organisations that are responsible for programme execution, coordination and quality. These organisations have signed agreements with:

- laboratories;
- colonoscopy centres;
- the national postal operator of the Netherlands (PostNL);
- the FIT-kit packing centre;
- a transport company;
- FIT manufacturer;

The screening organisations are responsible for:

- selecting and reviewing the list of the target group;
- inviting and reminding the target group to undergo the screening;
- sending the FIT to the participants;
- informing about the results and guiding the patient for further diagnostics, if necessary;

Laboratory diagnostics specialists, endoscopists and pathologists undergo accredited learning and advanced training to be allowed to work within the CRC screening programme. According to the protocol, the laboratories and its employees are audited every three months. There is a programme of continuing professional development for GPs on the basic principles of the screening programme. The content of the educational programmes is updated every two years [26].

Individuals of the target group are invited biennially, resulting in approx. 2.2 million invitees each year. The personal data is obtained from the Personal Database (Basisregistratie Personen). Citizens receive an invitation package, which contains invitation letter, information folder, reply envelope, FIT test kit with instructions for use. If the invitee didn't respond, the screening organisation sends reminder per invitation set. If the invitee remains unwilling to participate, a new invitation is sent after two years, unless they have reached age 75. They may also unsubscribe from the current round or the entire program via phone, email, or the client portal [27].

The participant sends a sample of the material in a reply envelope by post to the laboratory, which is the starting point for the screening. The laboratory receives and performs analysis of the sample and sends the results digitally within 48 hours. If the screening laboratory determines the stool sample as unsuitable for the test, the Screening Organisation sends a new invitation set to the participant. If the result is negative, the participant is informed of this and will be invited to participate in the screening programme again in two years. If the FIT test is positive, the participant will be informed and scheduled for a colonoscopy. The participant can change or cancel his/her previous visit (time and/or place) via client portal or by phone. If a colonoscopy is cancelled for medical reasons, this is recorded in the ScreenIT system, indicating when the examination will take place (from 2-10 years, till the age of 75) or will not at all, depending on the reason for not having it [27].

If a patient refuses to undergo colonoscopy a CT colonography can be performed and the results will be sent to the GP and the patient. After a positive CT colonography, it is recommended to undergo colonoscopy. When pathology is detected during colonoscopy, histological samples are sent to a certified laboratory. The results are registered in ScreenIT via nationwide network and registry of histo- and cytopathology to monitor the results of the screening programme and are provided to the participant in written form within 15 working days after the procedure. In case of a cancer diagnosis, treatment is usually started within four weeks [27].

Before the screening programme was launched, 17% of patients were diagnosed at stage I, and thanks to screening, this figure increased to 48% [27]. In 2017, a study was performed in the Netherlands, where among people from the target group 55-75 years old – 42% had adenomatous polyps – people who had absolutely no complaints about their health and considered themselves to be absolutely healthy. 70% of those who were invited took part in the primary screening with FIT, which is the highest rate in the world for screening programme [28-31]. 97.6% of patients with a positive FIT wanted to be consulted before having a colonoscopy. After consultation, they agreed to undergo the procedure, which confirms its importance.

In 2022, 2102881 people were invited to participate in the CRC screening programme. The coverage rate of the target group was 93.2%. 67943 people (4.7% of invited) had a positive result of FIT and were sent for colonoscopy. Out of them, 56847 people (83.7%) underwent the procedure. The participation rate in colonoscopy was higher among those who were first invited to the programme (86.5%), compared to those who participated in the programme again (83.3%). Perhaps this is due to the lower age of first-time participants. During colonoscopy, 2243 cases of CRC (3.9%) and 14373 of advanced adenomas (25.3%) were detected. In 29.2% of patients with a positive test result, colonoscopy revealed colorectal pathology – the indicator of positive predictive value[32].

The Dutch government set clear goals, expecting that by 2031 the screening programme will save 2,400 lives per year, with the estimated cost of the screening programme at €2,200 per year of life gained, which shows that the cost of screening is reasonable for the healthcare system by increasing life expectancy and reducing healthcare spendings [3,26].

In Slovenia, CRC is the second most common cancer by incidence and mortality. In 2022, the mortality rate from CRC in Slovenia was 36.2/100,000 women and 79.3/100,000 men, while the incidence rate was

68.6/100,000 women and 136/100,000 men[19]. The change in CRC incidence in Slovenia is caused by the implementation of the national CRC screening programme Svit. Since 2010, the overall incidence of CRC has been decreasing annually by 3.0% among men and 2.1% among women. In contrast, before the introduction of the screening programme in 1999-2008, it increased by an average of 3.6% per year among men and 3.4% among women[33].

The screening programme reached participation rate of 64.63% (59.38% men and 69.60% women), with 5,9% of citizens having a positive test result, of which 92% underwent colonoscopy. Today, 49% of patients are diagnosed in stage I, which is a significant success [3,34]. Since 2011, Slovenia has recorded a decrease of new cases of CRC. This is mainly due to the removal of precancerous lesions during colonoscopies [33].

When the Svit programme started in 2008, a communication strategy based on the theory of planned behaviour and informed decision-making was implemented. The advertising agency created the programme's style and design, whose ideas and approaches proved to be successful. In particular, the materials avoided frightening messages, motivating the target group to participate in the programme. Attention was focused on a wide audience through communication activities, since the topic of digestion and excretion is still a delicate one for the society. Therefore, in order to increase the level of participation in the screening programme, it is crucial to stimulate an open discussion of the topic. The majority of the population needs to modify their behaviour, reconsider their attitude to health and acquire new skills[35].

The Svit programme was established by the Ministry of Health and organised as a Centre for Early Detection of Cancer at the National Institute of Public Health. The goals, structure and execution of the programme are described in the Rules for the Implementation of National Screening Programmes for the Early Detection of Pre-Cancerous Conditions and Cancer and in National Cancer Control Plan. The Svit programme is funded by the Health Insurance Institute of Slovenia. On the basis of the Health Care and Health Insurance Act and Health Databases Act, it obtains data on the target population from the Central Population Register and the Health Insurance Institute of Slovenia. The acquired information is protected in accordance with the Personal Data Protection Act [35].

The high quality of the Svit programme, its accessibility are the result of the involvement of a large numerous specialists. The programme is organised by the National Institute of Public Health and consists of the following teams:

- in-house mailing service;
- laboratory;
- call centre;
- analyses and quality control;
- information technology.

The programme involves healthcare professionals throughout Slovenia: pathologists, endoscopists, GPs and healthcare professionals who provide consultations at Svit contact points. They cooperate with the regional units of the National Institute of Public Health, which are responsible for the promotion, implementation and coordination of the programme in their region. A special role is played by the media, which is an important partner in raising awareness and informing the public about CRC [35].

Presentation events are organised for citizens at the local level to inform them about the screening programme, boosting public awareness and prompting social discussion on off-limited topic. The population avoids talking about digestion, referring to existing stereotypes. This is one of the main reasons for late treatment. Therefore, attention is also paid to inform children and adolescents who are not burdened with various prejudices and taboos. School events promote open discussion of the problem and understanding of the importance of proper digestion, which will encourage the younger generation to pay more attention to their health [35].

Lectures and presentations with inflatable colon model and information materials are provided to employers and employees to promote health awareness and knowledge about prevention. These measures have been well accepted by employers, as they decrease the incidence of CRC among the workforce, providing economic benefits [35].

People aged 50-74 years who are covered by compulsory health insurance in Slovenia are eligible to participate in the Svit programme. About 600,000 residents are invited to undergo screening every two years. The process of engaging citizens is a step-by-step process: first, they receive an invitation to participate in the screening programme along with participating statement, which they have to sign and send to the central office. The Svit programme's internal post service processes an average of about 3,000 shipments per working day [35].

The difference in numbers between those who agree to participate in the programme and those who actually send samples for analysis after receiving the test kits is insignificant. In 2018, among those who were invited to participate in the screening programme, 64.63% agreed, of whom more than 92% sent samples. The participation rate of men is on average 10% lower than

that of women, therefore, additional informational campaign is being conducted to promote men's participation in the screening programme[35].

Those who have responded to the invitation are sent a test kit for two stool samples by post. The samples are analysed in the Svit Programme laboratory to maintain quality standards, and the results are recorded digitally Before carrying out the test, the applicant's data is cross-checked with the data in the information system. If the sample does not meet the criteria for the analysis, it is excluded and the person is informed of the type of error. Samples received by the laboratory must be analysed within 14 days from the date of sampling. During the implementation of the screening programme, only 3% of samples were collected incorrectly by participants. After phone call or counselling at the Svit contact point, in the chosen personal physician practice or during a visit from the community care nurse, the proportion of persons with inappropriate sent samples is approximately 0.3%. The samples are tested for the presence of antibodies to human haemoglobin. If the level of haemoglobin is exceeded in at least one of the two samples, the test is considered as positive[35].

The results are sent by mail directly to the participant and his/her GP. Individuals with a positive result are referred for a colonoscopy, which is carried out in accredited centres.The contact centre staff is responsible for communication with the target group and for giving information to participants about the following steps. They are the link between the accredited colonoscopy centres and participants, coordinating examination schedules and sending instructions on how to prepare for the procedure. The contact centre staff plays an important role in motivating people to undergo the examination, and as a result, 92% of people with a positive test result undergo colonoscopy[35].

The analysis of the questionnaires shows a very high level of satisfaction of the participants with the professionalism of the medical staff. Respondents rate the work on a scale from 1 to 5, with 1 being the worst and 5 being the best, with an average score of 4.7 for doctors and 4.8 for nurses. More than 91% of respondents agreed to undergo a colonoscopy again if necessary.

The Svit programme foresees the involvement of people with physical disabilities to the screening programme. For example, people with limited mobility are provided with home care by a nurse, most colonoscopy centres are equipped with ramps and lifts, and there is also an option of preparing for the examination in a hospital. People with cognitive disorders are provided with illustrated instructions of how to participate in the programme. Besides, a support is provided to involve them in the programme, through cooperation with medical staff in various institutions. People with hearing disabilities are provided with instructions in printed form. In the media information about screening is available in sign language with subtitles, and people with visual disabilities can listen to the instructions in audio.

The role of GPs has a significant impact on increasing the level of engagement in the screening programme. Providing information to the population by GPs, recognition of potential obstacles and assistance in resolving them creates more possibilities for the patient, as GPs have the highest level of trust among citizens. To further involvement of the target group to participate, a communication algorithm (reminder system) was developed to ensure regular screening.

GPs are informed about the coverage rate and the results of their patients. Notification of a positive result is sent to the GPs one day before the result is sent to the participant, and notification of a negative result is sent to the GPs within a year. Three times a year, all GPs receive a list of people who did not participate in the programme.

The programme participants need not only the involvement but also the survaillance after receiving a result that confirms pathology. This can cause anxiety, so it is important to explain to them what this means and what their current cancer risks are. If colonoscopy is cancelled for medical reasons, the GP can choose an alternative method to determine the cause of hidden blood in the stool, such as CT colonography.

CONCLUSIONS

The ultimate goal of CRC screening is to reduce mortality by detecting pathology at early stages, which increases the effectiveness of treatment and gives a better prognosis, as well as reducing morbidity in the long term.

Countries that have implemented an organised population-based CRC screening programme have seen an increase in incidence (mainly due to the detection of early stages of CRC) in the first years after the implementation of the screening programme, followed by a gradual decrease (both in early and late stages of CRC) in the future [36]. Screening has increased the number of detected asymptomatic cases, which without screening might have been undetected until symptoms appeared, which may take years.

After the implementation of the screening programme, the incidence of CRC is reduced compared to its implementation before, by detecting and removing polyps and precancerous lesions, which leads to a decrease in the incidence of CRC in the long term [37-39]. This reduction in CRC incidence is the result of a

massive detection of early asymptomatic cases before they progress to advanced stages.

The implementation of a CRC screening programme is a task that requires the involvement of the state's resources and the creation of an appropriate informational and technical infrastructure, primarily an electronic database of the target population, the development of the system of invitations and reminders about the stages of screening and results tracking, as well as continuous monitoring of each stage of screening to identify weaknesses within the healthcare system and make the necessary corrections.

REFERENCES

1. Bray F, Laversanne M, Sung H et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-263. doi: 10.3322/caac.21834. DOI
2. A short guide to cancer screening. Increase effectiveness, maximize benefits and minimize harm. Copenhagen: WHO Regional Office for Europe. 2022. https://iris.who.int/handle/10665/351396. [Accessed 25 June 2024]
3. Digestive Cancers Europe. Roadmap for Colorectal Cancer Screening in Europe. Digestive Cancers Europe; 2019https://www.digestivecancers.eu [Accessed 25 June 2024]
4. Cardoso R, Guo F, Heisser T et al. Proportion and stage distribution of screen-detected and non-screen-detected colorectal cancer in nine European countries: an international, population-based study. Lancet Gastroenterol Hepatol. 2022;7(8):711-723. doi:10.1016/S2468-1253(22)00084-X DOI
5. Kanavos P, Schurer W. The dynamics of colorectal cancer management in 17 countries. Eur J Health Econ. 2010;10(1):S115-S129. doi:10.1007/s10198-009-0201-2. DOI
6. Florence B et al. "Systematic review of colorectal cancer screening guidelines for average-risk adults: Summarizing the current global recommendations."World J Gastroenterol. 2018;24(1):124-138. doi: 10.3748/wjg.v24.i1.124. DOI
7. Helsingen LM, Kalager M. Colorectal Cancer Screening – Approach, Evidence, and Future Directions. NEJM Evid. 2022;1(1):EVIDra2100035. doi:10.1056/EVIDra2100035. DOI
8. Jodal HC, Helsingen LM, Anderson JC et al. Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis. BMJ Open. 2019;9:e032773. doi:10.1136/ bmjopen-2019-032773. DOI
9. Schreuders EH, Ruco A, Rabeneck L et al. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015;64(10):1637-1649. doi:10.1136/gutjnl-2014-309086. DOI
10. Shaukat A, Levin TR. Current and future colorectal cancer screening strategies. Nat Rev Gastroenterol Hepatol. 2022;19(8):551. doi: 10.1038/s41575-022-00661-3. DOI
11. Larsen MB, Njor S, Ingeholm P, Andersen B. Effectiveness of Colorectal Cancer Screening in Detecting Earlier-Stage Disease-A Nationwide Cohort Study in Denmark. Gastroenterology. 2018;155(1):99-106. doi:10.1053/j.gastro.2018.03.062. DOI
12. Ebell MH, Thai TN, Royalty KJ. Cancer screening recommendations: an international comparison of high income countries. Public Health Rev. 2018;39:7. doi:10.1186/s40985-018-0080-0. DOI
13. Kuipers EJ, Rösch T, Bretthauer M. Colorectal cancer screening--optimizing current strategies and new directions. Nat Rev Clin Oncol. 2013;10(3):130-142. doi:10.1038/nrclinonc.2013.12. DOI
14. Moss S, Ancelle-Park R, Brenner H; International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Evaluation and interpretation of screening outcomes. Endoscopy. 2012;44(3):SE49-SE64. doi:10.1055/s-0032-1309788. DOI
15. Lönnberg S, Šekerija M, Malila N et al. Cancer screening: policy recommendations on governance, organization and evaluation of cancer screening. European Guide on Quality improvement in Comprehensive Cancer Control. 2017, pp.39–76. https://cancercontrol.eu/archived/guide-landing-page.html [Accessed 25 June 2024]
16. Ponti A, Anttila A, Ronco G et al. Cancer screening in the European Union. Report on the implementation of the Council Recommendation on cancer screening (second report). Brussels: European Commission. 2017. https://screening.iarc.fr/EUreport.php [Accessed 25 June 2024]
17. Tran TN, Hoeck S, De Schutter H et.al The Impact of a Six-Year Existing Screening Programme Using the Faecal Immunochemical Test in Flanders (Belgium) on Colorectal Cancer Incidence, Mortality and Survival: A Population-Based Study. Int J Environ Res Public Health. 2023;20(2):1654. doi:10.3390/ijerph20021654 DOI
18. Gheorghe C, Bunduc S. The Colorectal Cancer Screening Program in Romania – ROCCAS – is Ready for the Implementation at National Level. J Gastrointestin Liver Dis. 2023;32(4):427-430. doi:10.15403/jgld-5329. DOI
19. Estimates Of Colorectum Cancer Incidence And Mortality In 2022 (for EU-27). https://ecis.jrc.ec.europa.eu/ [Accessed 25 June 2024]
20. Gac A, Kędzior KJ, Pogorzelczyk K et al. Patients' Expectations and Preferences for the Organizational Conditions of the Colorectal Cancer Screening Programme in Poland: A Qualitative Analysis. Healthcare (Basel). 2023;11(3):371. doi:10.3390/healthcare110303711. DOI

21. Trebenda E, Cipora E, Sygit K et al. Demographic and social chosen health behaviours among people over 55 years of age in the field of chronic disease prevention on the example of colorectal cancer. Pielęgniarstwo w Opiece Długoterminowej. Long-Term Care Nursing. 2021;6(1):35-50. doi:10.19251/pwod/2021.1(4). DOI
22. Act of 26 April 2019 on the National Oncology Strategy. Journal of Laws 2019; item 969. [Ustawa z dnia 26 kwietnia 2019 r. o Narodowej Strategii Onkologicznej. Dz.U.2019; poz.969] https://www.gov.pl/web/zdrowie/narodowa-strategia-onkologiczna-nso [Accessed 25 June 2024] (Polish)
23. Telford J, Gentile L, Gondara L et al. Performance of a quantitative fecal immunochemical test in a colorectal cancer screening pilot program: a prospective cohort study. CMAJ Open. 2016;4(4):E668-E673. doi:10.9778/cmajo.20160047. DOI
24. Forbes N, Hilsden RJ, Heitman SJ. The appropriate use of fecal immunochemical testing. CMAJ. 2020;192(3):E68. doi:10.1503/cmaj.190901. DOI
25. Soraya GV, Nguyen TC, Abeyrathne CD et al. A Label-Free, Quantitative Fecal Hemoglobin Detection Platform for Colorectal Cancer Screening. Biosensors (Basel). 2017;7(2):19. doi:10.3390/bios7020019. DOI
26. Ministry of Health, Welfare and Sport. National Institute for Public Health and the Environment Framework for the execution of colorectal cancer screening 2021. https://www.rivm.nl/sites/default/files/2021-01/Framework%20execution%20Dutch%20CRC%20screening%20%282021%29_0.pdf [Accessed 25 June 2024]
27. Toes-Zoutendijk E, Kooyker AI, Elferink MA et al. Stage distribution of screen-detected colorectal cancers in the Netherlands. Gut. 2018;67(9):1745-1746. doi:10.1136/gutjnl-2017-315111. DOI
28. Ministry of Health, Welfare and Sport. National Institute for Public Health and the Environment. Monitoring and Evaluation of the Colorectal Cancer Screening Programme 2017. https://www.rivm.nl/en/media/100661 [Accessed 25 June 2024]
29. Ministry of Health, Welfare and Sport. National Institute for Public Health and the Environment. Monitoring and Evaluation of the Colorectal Cancer Screening Programme 2021. https://www.rivm.nl/en/documenten/monitor-colorectal-cancer-2021 [Accessed 25 June 2024]
30. van der Vlugt M, Grobbee EJ, Bossuyt PM et al. Adherence to colorectal cancer screening: four rounds of faecal immunochemical test-based screening. Br J Cancer. 2017;116(1):44-49. doi:10.1038/bjc.2016.399. DOI
31. Krul MF, Elferink MAG, Kok NFM et al. Initial Impact of National CRC Screening on Incidence and Advanced Colorectal Cancer. Clin Gastroenterol Hepatol. 2023;21(3):797-807.e3. doi:10.1016/j.cgh.2022.08.046. DOI
32. Ministry of Health, Welfare and Sport. National Institute for Public Health and the Environment Monitoring and evaluation of the colorectal cancer screening programme 2022. https://www.rivm.nl/en/documenten/monitoring-colorectal-cancer-screening-2022 [Accessed 25 June 2024]
33. CRRS. Cancer in Slovenia. Annual report. Ljubljana: Institute of Oncology Ljubljana, Epidemiology and Cancer Registry, Cancer Registry of Republic of Slovenia. 2019. https://www.onko-i.si/en/cancer-registry/slovenian-cancer-registry [Accessed 25 June 2024]
34. Tepeš B, Mlakar DN, Stefanovič M et al. The impact of 6 years of the National Colorectal Cancer Screening Program on colorectal cancer incidence and 5-year survival. Eur J Cancer Prev. 2021;30(4):304-310. doi:10.1097/CEJ.0000000000000628. DOI
35. National Institute of Public Health. The Svit Programme – 10 Years of Colorectal Cancer Screening in Slovenia. Ljubljana. 2019. https://www.program-svit.si/wp-content/uploads/2019/10/SVIT-10-LET-ANG-Elektronska.pdf [Accessed 25 June 2024]
36. Breekveldt ECH, Lansdorp-Vogelaar I, Toes-Zoutendijk E et al. Colorectal cancer incidence, mortality, tumour characteristics, and treatment before and after introduction of the faecal immunochemical testing-based screening programme in the Netherlands: a population-based study. Lancet Gastroenterol Hepatol. 2022;7(1):60-68. doi:10.1016/S2468-1253(21)00368-X. DOI
37. Cardoso R, Guo F, Heisser T et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. Lancet Oncol. 2021;22(7):1002-1013. doi:10.1016/S1470-2045(21)00199-6. DOI
38. Chiu HM, Jen GH, Wang YW et al. Long-term effectiveness of faecal immunochemical test screening for proximal and distal colorectal cancers. Gut. 2021;70(12):2321-2329. doi:10.1136/gutjnl-2020-322545. DOI
39. Selva A, Torà N, Pascual E et al. Effectiveness of a brief phone intervention to increase participation in a population-based colorectal cancer screening programme: a randomized controlled trial. Colorectal Dis. 2019;21(10):1120-1129. doi:10.1111/codi.14707. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Legal principles of using special medical and psychiatric knowledge in criminal proceedings: Ukrainian context and international standards

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ABSTRACT

Aim: This article aims to determine the standards of interaction of medical professionals, psychiatrists, and psychologists with participants in criminal proceedings during the implementation of various forms of use of special knowledge, as well as update their adherence in medical practice and criminal procedural activities.

Materials and Methods: As empirical material, the decision of the ECHR, the practice of the Ukrainian courts, the results of scientific research by scientists, dedicated to the related subject of research, were used. In order to realize the set goal, the authors used a whole complex of general scientific and special methods of cognition, namely: system-structural method, method of generalization, dogmatic method, analysis and synthesis, methods of analysis of quantitative indicators, etc.

Conclusions: The use of medical and psychiatric knowledge must be carried out in compliance with a number of legal principles. All participants in criminal proceedings are required to comply with them. The main criteria for the use of special knowledge include: the validity of the grounds for the implementation of certain forms, the impartiality and independence of the person entrusted with the examination or other form, the rule of law, the inadmissibility of disclosing the secret of the pre-trial investigation, the right to receive another independent opinion.

KEY WORDS: crime; human rights; physical examination; forensic medical examination; investigative actions

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INTRODUCTION

Modern trends in criminality indicate that violent crimes are increasingly the result of neurocognitive and mental disorders. Such disorders lead to aggressive, inadequate, and sometimes sadistic behavior of a person. The socially dangerous consequences of such behavior consist of causing physical and moral harm to the victim. This actualizes the need for timely provision of competent medical, psychological, and sometimes psychiatric assistance to victims and suspects. Investigating such criminal offenses is also impossible without the qualified support of doctors, psychiatrists, and psychologists. The legal and organizational basis for the participation of experts and specialists in criminal proceedings is currently unresolved. This is the situation based on the principles of their interaction with the investigator, the prosecutor, the attorney, etc. This direction of scientific research is determined by the need to develop an optimal balance between ensuring the rights of a person who has become a criminal proceedings participant and providing criminal justice with objective scientific knowledge in the context of gathering evidence and proving certain circumstances of a court case.

AIM

This article aims to determine the standards of interaction of medical professionals, psychiatrists, and psychologists with participants in criminal proceedings during the implementation of various forms of use of special knowledge, as well as update their adherence in medical practice and criminal procedural activities.

MATERIALS AND METHODS

As empirical material, the decision of the ECHR, the practice of the judicial bodies of Ukraine, the results of scientific research by scientists, dedicated to the related subject of research, were used. These are, in particular, 16 decisions of the ECHR. Judicial decisions of the courts of general jurisdiction of Ukraine, adopted during

2014-2023, in violent crimes, as well as the results of research by scientists from Europe and other countries of the world, were also subjected to systematic analysis. Such empirical material was chosen for the purpose of improving the legal tools of the best practices for the observance and restoration of violated human rights and legitimate interests. The results of research in the fields of medicine, psychiatry, criminology and criminology are also taken into account. Open data from the Unified State Register of Court Decisions was also subjected to statistical analysis.

In order to realize the set goal, the authors used a whole complex of general scientific and special methods of cognition, namely: system-structural method, method cognitive realization, methods of analysis and synthesis, methods of analysis of quantitative indicators.

Methods of analysis and generalization were used for textual analysis of decisions of the ECHR and courts of Ukraine. The method of comparison contributed to the comparison of the results obtained by us and the data reflected in the studies of scientists selected by us based on the subject of the study.

The system-structural method, as well as the synthesis, made it possible to determine second principles that are universal in nature and must be observed in the context of the application of medical and psychiatric knowledge in criminal proceedings. Dogmatic, comparative-legal, logical and generalizing methods, as well as the method of legal analysis, were also used to formulate the research conclusions.

REVIEW AND DISCUSSION

The expert and a specialist are the subjects authorized to use special knowledge according to the Ukrainian doctrine of criminal procedural law. In violent crimes forensic medical experts, psychiatrists, and psychologists in criminal proceedings most often keep such procedural statuses. The prosecution and the defense have the right to receive qualified specialist and expert assistance. Such a guarantee contributes to implementing parties' equality and competitiveness principles in criminal proceedings.

In addition, Recommendation No. R (87) 18 of the Committee of Ministers of the Council of Europe defines prosecutorial, investigative, and judicial bodies that need the help of experts should use the help of specialists in such fields as psychology, medicine, psychiatry, accounting, economics, finance, and forensic medicine in a sufficient volume to face the growing technical complexity of crimes and ensure the collection of evidence [1]. The most important thing is that the participation of an expert and a specialist is connected with the objective realization of a person's right to a fair trial, which is proclaimed in Art. 6 of the European Convention on Human Rights (after this – the Convention) and other conventional guarantees [2]. In addition to conventional guarantees, it is also necessary to consider several other legal and organizational principles.

1. The validity of appointing expert studies, collecting confidential medical data, and conducting investigative actions. To fulfill the requirements of convection regarding the fairness and impartiality of the court, the Criminal Procedure Code of Ukraine defines the grounds for which the examination is mandatory and regulates the compulsory participation of specialists in certain investigative (search) actions. When deciding whether to involve competent specialists in criminal proceedings, it is necessary to determine whether sufficient grounds exist.

The involvement of specialists must be justified in cases where confidential medical information will be collected, regardless of whether they contain a specific medical diagnosis (see Surikov v. Ukraine, No. 42788/06) [3]. Such information includes information about a person's mental state. The disclosure of such information will be recognized as a violation of the right to privacy guaranteed by Art. 8 of the Convention [2]. Given this, the collection of such information by state authorities in the absence of sufficient grounds is subject to violation of Article 8 of the Convention [2].

The validity of the grounds for the appointment of a psychiatric examination is a debatable issue. Increasingly, scientists pay attention to the fact that the presence of behavior disorders in a person, his aggressiveness, and neurolinguistics disorders become factors that provoke a person to commit violent crimes [4;5]. Scientists indicate that murderers with mental disorders are 3.19 times more motivated by revenge than non-disordered and undiagnosed offenders [6]. An analysis of 70 cases based on the facts of the murders in Iraq gave reasons to state that almost 40% of the killers did not have mental illnesses, more than 17% had personality disorders, nearly 33% had mental disorders, and 9% had neurotic disorders [7]. Psychotic symptoms are reported in 11% of US criminals, including 18% of mass murderers who did not use firearms and 8% of those who did [8]. 49 out of 79 French citizens who committed murders were diagnosed with paranoia, which is a mental disorder, but this did not excuse them from legal responsibility [9].

A separate group of persons, the psyche of which should become the subject of a psychiatric examination in the event of their committing violent crimes, are persons who have committed violent crimes and have a syndrome of dependence on alcohol, narcotic drugs, or psychotropic

substances. This is explained by the fact that the use of these substances and means weakens or in general paralyzes the inhibitory processes of the psyche, and therefore, personality and behavior disorders develop more quickly in such persons. In particular, L. Eriksson, S. Bryant, S. McPhedran, P. Mazerolle, R. Wortley received a favorable conclusion after testing 302 people convicted of murder in Australia. The researchers found that 38.8% of people had a high level of alcohol problems, and 30.8% had drug problems. At the same time, a large proportion of criminals who committed murders abused these substances in the year preceding the crime [10].

As for the practice of Ukraine, during 2014-2023, on average, 7.46% of criminal proceedings on violent crimes are sent to court annually, with a request for the application of coercive measures of a medical nature. The data we obtained correspond to other studies conducted by Ukrainian scientists. As for those convicted of murder, 14% of such persons had mental and behavioral disorders due to the use of alcohol, or narcotic drugs (syndrome of dependence on alcohol, opioids, amphetamine, etc.), 8% of the accused were in a state of simple alcohol intoxication, 4% of persons had a syndrome alcohol dependence (chronic alcoholism), 2% of persons had an emotionally unstable personality disorder, 2% suffered from a mental illness, 1% of the defendants had a personality and behavior disorder due to organic brain damage, and 1% had clinical signs of post-traumatic stress disorder [11]. This shows that the specific weight of persons who took the lives of other people while being in a state of insanity or another morbid state of mind is quite significant. In our opinion, such practice indicates the need to revise the presumption of mental health, which operates in Ukraine.

We agree that individuals' criminal responsibility and legal capacity may vary depending on the legal situation. When applying for a forensic psychiatric examination of these patients with mental comorbidities, the patients should not be biased in terms of their level of cognitive competence, and each case should be evaluated individually [12]. At the same time, we believe that the grounds for appointing forensic psychiatric examinations in criminal proceedings should be expanded at the level of national legislation. A person suffering from a mental disorder has a double role in the judicial process: he or she is an interested person and, at the same time, the main object of the judicial investigation [13; 14]. The national legislation of Ukraine should be supplemented with the grounds for the appointment of a forensic psychiatric examination. Yes, in the case of the suspect receiving injuries to the head and spine, brain discoloration, or damage to the spinal cord, as well as in the case of committing a violent crime by a person who was under the influence of alcohol or drugs or who was under the supervision of a narcologist. This approach corresponds to the principles of adaptation and integration into the social life of people diagnosed with psychopathology, as well as the provision of emergency psychiatric care [15].

Adherence to the validity of the grounds is also required during investigative (search) actions. Exhumation of the body of the deceased is a common investigative action in which medical professionals participate. In the context of the validity of the grounds for conducting an examination or investigative (search) actions related to the application of special medical knowledge, it should be taken into account that the exhumation of a person's body without the voluntary consent of relatives can also be recognized as a violation of the right enshrined in Article 8 of the Convention [16]. In this regard, it is also important to enshrine a legal mechanism in the national legislation, which provides for obtaining consent from relatives to conduct this investigative (search) action.

Considering the diversity of methods that suspects resort to, during the investigation there is a need to examine the suspect's body, which is connected with examining his body cavities. A systematic analysis of the provisions of the Criminal Procedural Code and separate Judgements of the ECHR allows us to conclude that the physical integrity of a person is covered by the concept of "private life" protected by Article 8 of the Convention for the Protection of Human Rights and Fundamental Freedoms (hereinafter referred to as the Convention) [2] and concerns the most intimate aspects of private life, and compulsory medical intervention, even insignificant, constitutes an interference with this right (Decision "X and Y v. the Netherlands" [17]), but such interference is usually justified in accordance with Clause 2 of Art. 8 of the Convention as urgency to prevent a crime ("Tirado Ortiz and Losano Martin v. Spain" [18]) or as the only possible way to save a person's life.

However, any recourse to coercive medical intervention to obtain evidence of a crime must be convincingly justified by the facts. This is especially relevant when a procedure involves gaining access to a person's body cavities to extract evidence.

2. *Independence and impartiality of judicial experts and specialists.* One of the legal bases of activity and interaction of participants in criminal proceedings with experts is their independence and unpredictability. The ECHR rules that the procedural guarantees that ensure their formal and factual independence and unpredictability are the independence of the judicial expert from the persons involved in the events that became the subject of the trial [18].

The independence requirement is essential when obtaining medical opinions from experts, who must have formal and factual independence from those involved in the events (see Bačić v. Croatia, no. 41108/10, § 95, November 13, 2012) [19]. In its practice, the ECHR has determined that the demonstration of the unpredictability of a court-appointed expert in specific characteristics may lead to a violation of the principle of equality of parties admitted to a fair trial (see Bonisch v. Austria, May 6, 1985) [20]. In addition, such a factor as the procedural position/status of the expert and his role in the relevant proceedings should be obtained (see Sara Lind Eggertsdóttir, cited above, § 47, and Letinčić, mentioned above, § 51) (para. 60 of the judgment) [21, 22], his relations with other participants in criminal proceedings. Any doubts about the unpredictability of the expert and specialist leave the public's trust in the judicial system at risk; therefore, "visibility" is essential [23].

In Ukrainian realities, when the investigator or the defense engages an expert, it isn't easy to implement the requirements for checking the excellence and independence of the expert. When the decision on the appointment of expertise is sent, the head of the expert institution or the head of the relevant department of this institution reviews it and actually determines the executor. Therefore, the exact verification of the expert's incomparability is carried out at the stage of familiarization with the received opinion, and the defense side in other cases – at the stage of familiarization with the materials by Art. 290 of the CPC of Ukraine [24]. This practice requires verification of findings at all stages of criminal proceedings.

3. Inadmissibility of disclosing the secret of the pre-trial investigation. One of the legal bases for the use of an expert's special knowledge is the secrecy of a pre-trial investigation or the principle of the inadmissibility of disclosing information of criminal proceedings, which imposes on the expert the duty not to disclose without the permission of the party to the criminal proceedings, which involved him or the court. He knew this information in connection with the performance of the duties assigned to him. The possibility of their disclosure is allowed only with the written permission of the investigator or prosecutor within the limits determined by the latter (the decisions "Bédat v. Switzerland", "Sellami v. France") [25, 26].
4. Rule of law. Regarding the forced hospitalization of a person in a psychiatric institution, clear and effective guarantees against arbitrariness must necessarily be provided, given the vulnerability of persons suffering from mental disorders and the need to give excellent reasons to justify any restrictions on their rights (see the decision of 2 May 2013 in the case "Zagidulina v. Russia," application No. 11737/06, paragraph 53) [28]. This applies to forced treatment and inpatient psychiatric examinations. The task of the court is not to re-evaluate the above conclusions, which were drawn up by professional psychiatrists and which contain opposite conclusions, and to decide which of them were correct and which were incorrect. However, its task is to verify whether the national courts have examined the relevant findings with the necessary care and whether they have correctly justified their decision regarding the compulsory treatment of the applicant in a psychiatric institution (see the decision in the case "Raudevs v. Latvia", application No. 24086/03, paragraph 71) [29].

Most studies suggest that people with mental disorders and illnesses are hospitalized longer than necessary to fulfill two functions: 1) to care for and treat the patient (for their own sake, as well as to reduce future risk); and 2) to protect society from harm by the offender. Clinical experience and research show that safe forensic services are not always the most effective when patients remain in overly restrictive conditions for too long, no longer needing or benefiting from the services offered [30]. For example, among the 1.2 million population of North London in 1999, the average length of stay in non-forensic beds was 79 days, while for forensic beds the figure was 1367 days. Overall, 23.4% of general psychiatric patients were in for more than one year and 17.9% for more than 5 years, while the corresponding figures for forensic patients were 81.2% and 39.1% respectively [31].

5. Principle of legality. This principle requires that all actions carried out by experts and specialists comply with legal regulations. It is also important that the same principles guided all experts and specialists and that their conclusions were without contradictions or disagreements.

In this context, the presumption of mental health should be addressed. The mandatory basis for the appointment of a forensic psychiatric examination is the presence of a person with a disorder of mental activity or a mental illness, which is certified by a relevant medical document (Part 1 of Article 509 of the Criminal Procedure Code of Ukraine) [24]. In 64% of the criminal proceedings we analyzed, it became the basis for a forensic psychiatric examination appointment. The ECHR indicates that a person cannot be considered "mentally ill" and deprived of liberty if three minimum conditions are not met. First, this objective examination must reliably show that the person has a mental illness; secondly, the mental disorder must be such that it causes the forced detention of a person in a psychiatric

hospital; thirdly, the need for continued detention in a psychiatric hospital depends on the persistence of such a disease (see the decision in the case "Winterwerp v. the Netherlands", paragraph 39, Series A No. 33) [27].

It is also important that all experts follow the same approach when formulating their conclusions. The scientific literature indicates that such approaches are not unambiguous. For example, scientists who evaluated the approaches of experts in France to establish the mental state of murder suspects diagnosed with schizophrenia indicated the presence of several inconsistencies. Such disagreements between experts are at the level of forensic interpretation and discussing the relationship between pathology and offense. Scientists stated that the differences are often associated with personal beliefs or different schools of thought that influence the interpretations and conclusions of experts. According to their approach, it is necessary to strengthen training, increase experience, and ensure knowledge exchange between professionals [32].

Scientists from Brazil indicate that the key points in ensuring a unified approach when conducting a psychiatric examination are detailed knowledge of psychopathological concepts inherent in legal capacity, standardization of the examination, use of psychometric indicators developed specifically for forensic psychiatry (in particular, those that assess exclusively legal capacity), and concise drafting of the expert opinion. Other key points are the preferential use of established scientific terms, the avoidance of jargon and buzzwords in the expert report, and the simultaneous assessment by professionals with the same education and experience in the field [33].

Such discrepancies may lead to different legal consequences in similar cases. Therefore, a position is being formed according to which inter-expert reliability in forensic psychiatric/psychological matters is the basis for the court to regularly receive the opinions of several experts to reduce the risk that a single expert opinion may be misleading [34]. The use of different approaches is contrary to the principles of law since the law requires that the same legal procedure be applied to everyone. In this regard, all approaches of experts and specialists must be based on scientific provisions, and their application and activities in general must comply with legal principles.

As a positive example of developing unified approaches to solving expert tasks, we can cite the "Rating Scale of Criminal Responsibility for the Mentally Ill (RSCR)", developed by Chinese scientists. Its essence is that the scale includes eighteen items, namely: criminal motivation, aura before the offense, incitement to the crime, time and place and selectivity of the object and instrument of the crime, emotions during the crime, evasion of responsibility for the offense, concealment of the truth during the investigation, disguise, understanding the nature of the crime, assessment of the consequences of the crime, impairment of vitality, impairment of study or work, impairment of insight, impairment of reality testing and impairment of self-control. This scale can be applied to all cases and is easy to use, according to the results of its application, in almost 89% of cases; similar conclusions were obtained in the cases studied [35].

6. *Guarantee of obtaining another independent opinion.* It is important to guarantee the opportunity for patients to get a second opinion from independent experts. This principle also included in the UN Principles for the Protection of Persons with Mental Illness and the Improvement of Psychiatric Care (see paragraph 63). It is an essential guarantee against possible arbitrariness when making decisions regarding the continuation of the application forced treatment (see the decision in the case "X v. Finland," application No. 34806/04, paragraph 169, ECHR 2012, and the decision in the case "M. v. Ukraine" (M. v. Ukraine), item 66) [36, 37]. The same principles should be observed when using medical knowledge, particularly when conducting forensic examinations. This approach is consistent with the principle that no evidence has a predetermined force.

CONCLUSIONS

The use of medical and psychiatric knowledge must be carried out in compliance with several legal principles. All participants in criminal proceedings are required to comply with them. The main criteria for the use of special knowledge include the validity of the grounds for the implementation of certain forms, the impartiality and independence of the person entrusted with the examination or other form, the rule of law, the inadmissibility of disclosing the secret of the pre-trial investigation, the right to receive another independent opinion.

The practice of many European countries and others is still not perfect and does not always fully agree with convection principles. That is why certain norms need revision and improvement. The grounds for the appointment of psychiatric examinations and the interpretation of the presumption of mental health, and approaches to assessing a person's insanity need revision. After all, behavioral disorders against the background of alcohol and drug addiction, neurocognitive disorders, and others are increasingly becoming a factor characterizing a person convicted of a violent crime.

REFERENCES

1. Recommendation no. R (87) 18 of The Committee of Ministers to Member States Concerning the Simplification of Criminal Justice. https://rm.coe.int/16804e19f8 [Accessed 15 July 2024]
2. United Nations. European Convention on Human Rights. 1950. https://www.echr.coe.int/documents/d/echr/convention_ENG [Accessed 28 July 2024]
3. Sprava «Surikov proty Ukrayiny». Zayava № 50264/08. Rishennya vid 26 kvitnya 2017 roku [Case of Surikov v. Ukraine. Application no 50264/08. Judgment of 27 April 2017]. https://hudoc.echr.coe.int/#{%22itemid%22:[%22001-192315%22]} [Accessed 28 July 2024] (Ukraine)
4. Meijers J, Kuin NC, Scherder EJA, Harte JM. Characteristics of forensic psychiatric patients with a neurocognitive disorder. BJPsych Open. 2024;10(3):e117. doi:10.1192/bjo.2024.712 DOI
5. O'Loughlin A. Law and Personality Disorder: Human Rights, Human Risks, and Rehabilitation. Oxford University Press. 2024. doi: 10.1093/9780191875434.001.0001. DOI
6. Hachtel H, Nixon M, Bennett D et al. Motives, Offending Behavior, and Gender Differences in Murder Perpetrators With or Without Psychosis. J Interpers Violence. 2021;36(7-8):3168-3190. doi: 10.1177/0886260518774304. DOI
7. Hummadi BF, Al-Kadhimi FA, Al-Mashhadani GA. Criminal responsibility among murderer presented to forensic committee in Al-Rashad training hospital/ forensic department. Indian Journal of Forensic Medicine and Toxicology. 2020;14(1):462-468.
8. Brucato G, Appelbaum P, Hesson H et al. Psychotic symptoms in mass shootings v. mass murders not involving firearms: findings from the Columbia mass murder database. Cambridge University Press. 2021. https://www.cambridge.org/core/journals/ps ychological-medicine/article/abs/psychotic-symptoms-in-mass-shootings-v-mass-murders-not-involving-firearms-findings-from-the-columbia-mass-murder-database/50514607ADF1AC2ECEB43369B 6153E34 [Accessed 28 July 2024]
9. Bouthier M, Mahé V. Paranoid personality disorder and criminal offense. Encephale. 2019;45(2):162-168. doi: 10.1016/j.encep.2018.07.005. DOI
10. Eriksson L, Bryant S, McPhedran S et al. Alcohol and drug problems among Australian homicide offenders. Addiction. 2021;116(3):618-631. doi: 10.1111/add.15169. DOI
11. Husieva V, Oderiy O, Petrova I et al. Features of the investigation of premeditated murders committed by persons with mental disorders in the practice of Ukraine. Amazonia Investiga. 2021;10(46):109-117. doi: 10.34069/AI/2021.46.10.10. DOI
12. Boylu ME, Taşdemir İ, Doğan M, Duran A. "What is important in forensic psychiatric evaluation in people with Down syndrome? A sample from Türkiye", Journal of Intellectual Disabilities and Offending Behaviour. 2024;15(1/2):1-13. doi: 10.1108/JIDOB-11-2023-0008. DOI
13. Tatsiy VY, Tyshchenko OI, Titko IA. Mental health of a person as a criterion of personal participation in the trial during criminal proceedings. Wiad Lek. 2020;73(12):2737-2742. doi: 10.36740/WLek202012207. DOI
14. Sacchetin BF. Periculosidade: uma proposta de ressignificação do conceito à luz da reforma psiquiátrica. [Dangerousness: a proposal for redefining the concept in light of psychiatric reform]. Revista Eletrônica Direito e Sociedade – REDES. 2023;11(3). doi:10.18316/redes.v11i3.7962. (Portuguese) DOI
15. Antar AY. Guilty or not guilty by reason of insanity? a comparative study of murderers referred for psychiatric examination by court order. Health Justice. 2023;11(35):1-20. doi: 10.1186/s40352-023-00230-z. DOI
16. Case of Solska and Rybicka v. Poland. Application no. 30491/17, 31083/17. Judgment of 20 September 2018. https://hudoc.echr.coe.int/eng#{%22itemid%22:[%22001-186135%22]} [Accessed 28 July 2024]
17. Case of X and Y v. the Netherlands. Application no.8978/80 Judgment of 26 March 1985. https://hudoc.echr.coe.int/eng?i=001-57603 [Accessed 28 July 2024]
18. Case of Tirado Ortiz and Lozano Martin v. Spain. Application no. 43486/98. Decision of 15 June 1999. https://hudoc.echr.coe.int/eng?i=001-5635 [Accessed 15 July 2024]
19. Case of Bačić v. Croatia. Application no. 3742/02. Judgment of 16 December 2004. https://hudoc.echr.coe.int/eng?i=001-67778 [Accessed 28 July 2024]
20. Case of Bonisch v. Austria. Application no. 8658/79. Judgment of 6 May 1985. https://hudoc.echr.coe.int/eng?i=001-57443 [Accessed 28 July 2024]
21. Case of Sara Lind Eggertsdóttir. Application no. 31930/04. Judgment of 05 July 2007. https://hudoc.echr.coe.int/eng?i=001-81433 [Accessed 28 July 2024]
22. Case of Letinčić v. Croatia. Application no. 7183/11. Judgment of 03 August 2016. https://hudoc.echr.coe.int/eng?i=001-162422 [Accessed 28 July 2024]
23. Case of Riepan v. Austria. Application no. 35115/97. Judgment of 15 June 2000. https://hudoc.echr.coe.int/eng?i=001-5364 [Accessed 28 July 2024]
24. Zakon Ukrayiny № 4651-VI. Kryminal'no-protsesual'ni kodeksy Ukrayiny. [Law of Ukraine No. 4651-VI. Criminal Procedure Codes of Ukraine]. Verkhovna Rada of Ukraine. 2012. https://zakon.rada.gov.ua/laws/show/4651-17 [Accessed 28 July 2024] (Ukrainian)
25. Case of Bédat v. Switzerland. Application no. 56925/08. Judgment of 29 March 2016. https://hudoc.echr.coe.int/eng?i=001-161898 [Accessed 28 July 2024]

26. Case of Sellami v. France. Application no. 61470/15. Judgment of 17 March 2021. https://hudoc.echr.coe.int/eng?i=001-206518 [Accessed 28 July 2024]
27. Case of Winterwerp v. the Netherlands. Application no. 6301/73. Judgment of 24 October 1979. https://hudoc.echr.coe.int/eng?i=001-57597 [Accessed 28 July 2024]
28. Case of Zagidulina v. Russia. Application no. 11737/06. Judgment of 02 May 2013. https://hudoc.echr.coe.int/eng?i=001-119043 https://hudoc.echr.coe.int/eng?i=001-119043 [Accessed 28 July 2024]
29. Case of Raudevs v. Latvia. Application no. 24086/03. Judgment of 17 March 2014. https://hudoc.echr.coe.int/app/conversion/pdf/?library=ECHR&id=001-139268&filename=001-139268.pdf&TID=ihgdqbxnfi [Accessed 28 July 2024]
30. Völlm B, Bartlett P, McDonald R. Ethical issues of long-term forensic psychiatric care. Ethics Med Public Health. 2016;2(1):36–44. doi:10.1016/j.jemep.2016.01.005. DOI
31. Sharma A, Dunn W, O'Toole C, Kennedy GG. Cross-sectional length of stay in adult and forensic psychiatry beds. Int J Ment Health Syst. 2015:9:25. doi: 10.1186/s13033-015-0017-7. DOI
32. Guivarch J, Piercecchi-Marti M-D, Glezer D, Chabannes J-M. Differences in psychiatric expertise of responsibility for schizophrenic persons accused of murder: study with experts of the Court of Appeal of Aix-en-Provence. L'encephale. 2016;42(4):296-303. doi: 10.1016/j.encep.2015.08.001. DOI
33. Meyer LF, Valença AM. Factors related to bias in forensic psychiatric assessments in criminal matters: A systematic review. Int J Law Psychiatry. 2021:75:101681. doi: 10.1016/j.ijlp.2021.101681. DOI
34. Svensson O, Andiné P, Bromander S et al. Experts' decision-making processes in Swedish forensic psychiatric investigations: A case vignette study. Int J Law Psychiatry. 2024:92:101947. doi: 10.1016/j.ijlp.2023.101947. DOI
35. Cai W, Zhang Q, Huang F et al. The reliability and validity of the rating scale of criminal responsibility for mentally disordered offenders. Forensic Sci Int. 2014:236:146-50. doi: 10.1016/j.forsciint.2013.12.018. DOI
36. Case of X v. Finland. Application no. 34806/04. Judgment of 03 July 2012. https://hudoc.echr.coe.int/fre#{%22itemid%22:[%22002-6410%22]} [Accessed 28 July 2024]
37. Sprava «M. proty Ukrayiny». Zayava № 2452/04. Rishennya vid 19 kvitnya 2012 roku [Case of M. v. Ukraine. Application no 2452/04. Judgment of 10 April 2012]. http://consultant.parus.ua/?doc=08JE97C55C [Accessed 28 July 2024] (Ukrainian).

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Microbial infection disease diagnosis and treatment by artificial intelligence

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ABSTRACT

Aim: The main objective of this study was to examine current perspectives on initiatives to identify viable approaches for more accurate diagnosis of infectious diseases.
Materials and Methods: Indexed databases, such as EMBASE, Scopus, and PubMed/Medline, and online searches were performed. Cross-referencing of important articles led to additional references. This study reviews important clinical applications and provides an overview of several Artificial intelligence algorithms used in diagnosis of diseases caused by pathogenic microorganisms.
Conclusions: Artificial intelligence technologies could be used in nearly every area of medicine. Before these new technologies may be used in actual clinical settings, more carefully planned clinical trials are required.

KEY WORDS: Microbial, Infection, Artificial Intelligence

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INTRODUCTION

The term artificial intelligence (AI), first coined in 1956, refers to digital systems that attempt to solve problems and continuously improve their data processing skills by using algorithms that mimic human intellect. These days, artificial intelligence has expanded too many industries and started to help them thanks to the rise in data entry, the usage of more potent coding languages, and the application of sophisticated algorithms [1]. This implies that they should also play a bigger role in bacterial epidemiology. For instance, at major hospitals, machine learning algorithms can forecast patients' likelihood of contracting Clostridium diffusible infection in advance, enabling medical staff to take proactive precautions before an infection happens [2, 3]. Contact tracing in the emergency room can be done more quickly and effectively with real-time locator devices than with tracing techniques that depend on electronic medical data. This maximize the utilization of time and money while significantly increasing the number of potentially susceptible individuals identified. Selling hospitals and payers on the usefulness of sophisticated microbiology diagnostics is one of the largest problems facing the clinical microbiology community. It would be highly beneficial to provide explicit guidance on how to identify and demonstrate treatment value [4, 5]. There are two technologies used in medicine: visual and artificial intelligence, the latter of which is related to web design. These features include electronic health records, appointment scheduling, prescribing, drug interactions, imaging and osteoporosis, and score systems for diagnosis and verification. Conversely, physical components include post-operative technical support, social assistive technology used in elder care, rehabilitation, and televiewing [6, 7]. Artificial intelligence is the imitation of human intelligence via the use of computers. This new science explores and creates ideas, methods, instruments, and strategies to duplicate, improve, and broaden human knowledge. Machine learning, a branch of artificial intelligence, allows machines to learn tasks by identifying patterns in data. Neural networks are adaptable mathematical models that can use a range of methods to express intricate relationships in big data sets. Artificial intelligence,

particularly its variations like as deep learning and convolutional neural networks (CNNs), is currently the most used machine learning technique. Data is sent to the input layer, which uses a hidden multi-layer algorithm to process it. The outcomes are displayed in the results. Instead of being a straightforward neural network with one or a few convolutional layers between the input and output layers, deep learning may be thought of as a computational process with several hidden layers. The hidden layers can be piled endlessly to create a machine with greater sensitivity and accuracy as processing power increases [8].

AIM

This study sought to investigate how AI can raise the degree of individualized treatment and the precision and effectiveness of clinical diagnosis in light of the potential obstacles to its clinical deployment. It was based on a careful examination of existing literature and findings from recent studies. By providing medical professionals with an in-depth understanding of how AI can be used to diagnose and treat infectious diseases, by working together to advance the use of AI to combat infectious diseases, and by providing patients with more accurate and efficient healthcare , this will not only be important in improving global public health.

MATERIALS AND METHODS

METHODOLOGY AND INTEGRATION OF THE SEARCH

Indexed databases, such as EMBASE, Scopus, and PubMed/Medline, were separately searched in English only, without regard to time constraints. Cross-referencing of important articles led to additional references. This study reviews important clinical applications and provides an overview of several Artificial intelligence algorithms used in diagnosis of diseases caused by pathogenic microorganisms.

REVIEW AND DISCUSSION

USING ARTIFICIAL INTELLIGENCE TO DIAGNOSE MICROORGANISMS

Every diagnostic method, from sample collection to identification and susceptibility testing, poses challenges to traditional microbiology. Improper sample processing causes problems and can lead to incorrect conclusions [9]. The presence of antibiotics in clinics makes the process of cultivating and isolating germs more difficult and prone to false negative results (Fig.1-2). The inherent delay in traditional microbiological detection can result in antibiotic resistance through empirical therapy by letting diseases deteriorate [10]. The early detection of pathogens and the development of successful prevention measures depend on AI algorithms' ability to quickly and accurately identify trends and abnormalities in large microbial datasets [11, 12]. Artificial intelligence's predictive modeling predicts microbial activity based on historical data, which aids in improving treatment approaches, anticipating illness outbreaks, and better understanding patterns in antibiotic resistance [13].

STRUCTURE AND ROLE OF ARTIFICIAL INTELLIGENCE IN CLINICAL MEDICINE

Artificial intelligence in healthcare can be separate into two collection depending connected how it works: visual and physical [14]. The term "physical AI" describes devices that may help with and carry out a range of useful functions, such as surgery and the deployment of robots in medical procedures. Virtual artificial intelligence includes any program that can process, analyze, and pass on with other inclination connected to a system (Fig.3). More precisely, artificial intelligence computes data and provides a deterministic response using two methods. AI software may be able to make accurate decisions about a patient's health and treatment in "real-time" thanks to machine learning (ML), which is the capacity of an AI system to develop suitable algorithms that generate decisions and/or predictions based on the data generated [15]. This method, known as the "flow chart technique," mimics how a doctor would compile information from a patient's medical history and clinical test results. AI programs can also use a more complex type of flow chart.

MONITORING AND IDENTIFYING EMERGENCIES

By gathering and examining data on risk factors, clinical outcomes, and patterns of disease transmission, AI can also be a helpful tool in case analysis. Healthcare practitioners might use this to pinpoint high-risk groups, track the transmission of illnesses, and anticipate any outbreaks. This tends to maximize resource use while improving early intervention tactics [16]. Thus, as has been emphasized throughout history, detection and management of disease outbreaks are critical. Conventional surveillance techniques require manual data collection, which eventually results in underreporting or delays in the reporting of infectious

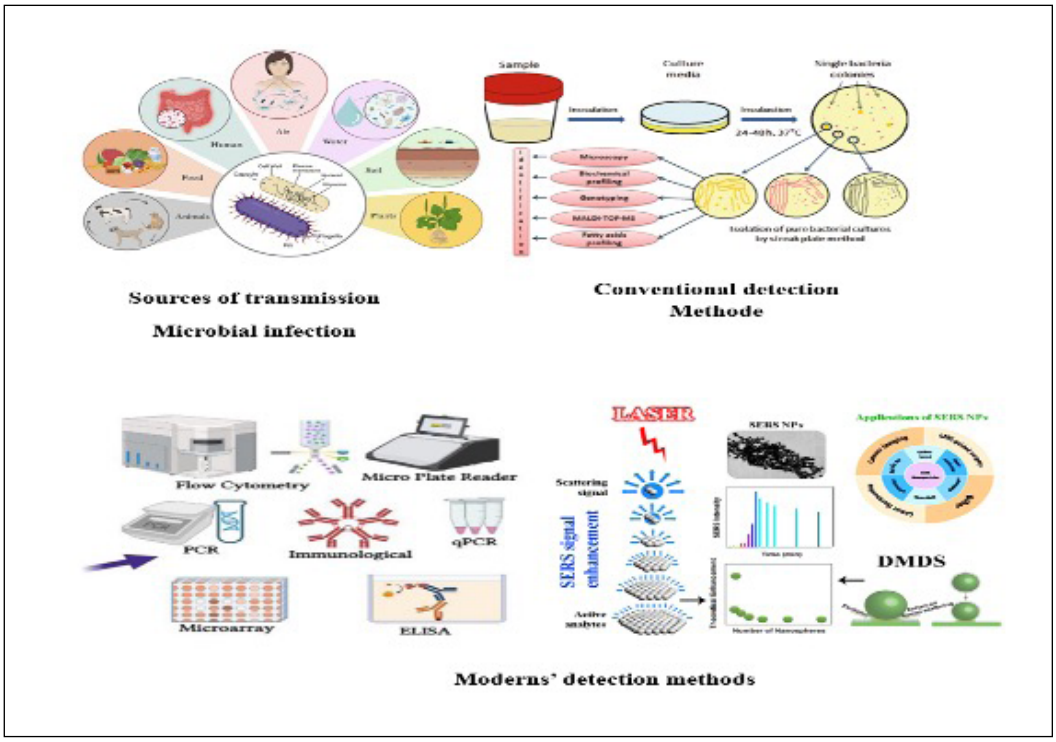

Fig. 1. Flow chat of future diagnostics microbial infection identification of diseases by traditional methods of detection and current (modern methods of identification).

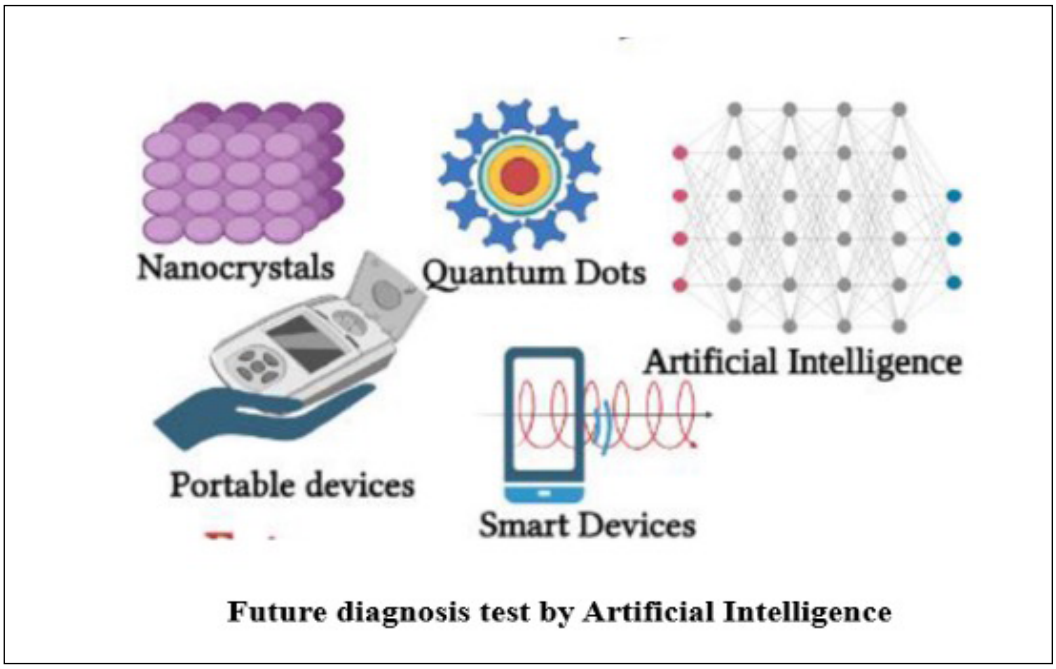

Fig. 2. Flow chat of future diagnostics microbial infection identification of diseases by Artificial Intelligence.

disease cases. AI-based surveillance systems, on the other hand, automatically gather information from social media and medical records while evaluating real-time data streams to improve public health response and situational awareness [17]. At the extremely least, machine learning-based alert systems have been created that detect deviations in disease rates or the ways infectious diseases are spread, alerting health authorities to potential outbreaks [18]. AI has shown great potential in the tract of learned profession imagination, which is essential for diagnosis. Profound eruditeness systems, a different kind of artificial intelligence, have demonstrated accuracy in analyzing medical pictures, including X-ray and histopathology CT scans. All things considered, the application of AI in TDM may lead to improved patient outcomes. Improve the precision and effectiveness of medical care delivery to lower medical expenses. It is anticipated that AI will become more significant in TDM as it develops [19].

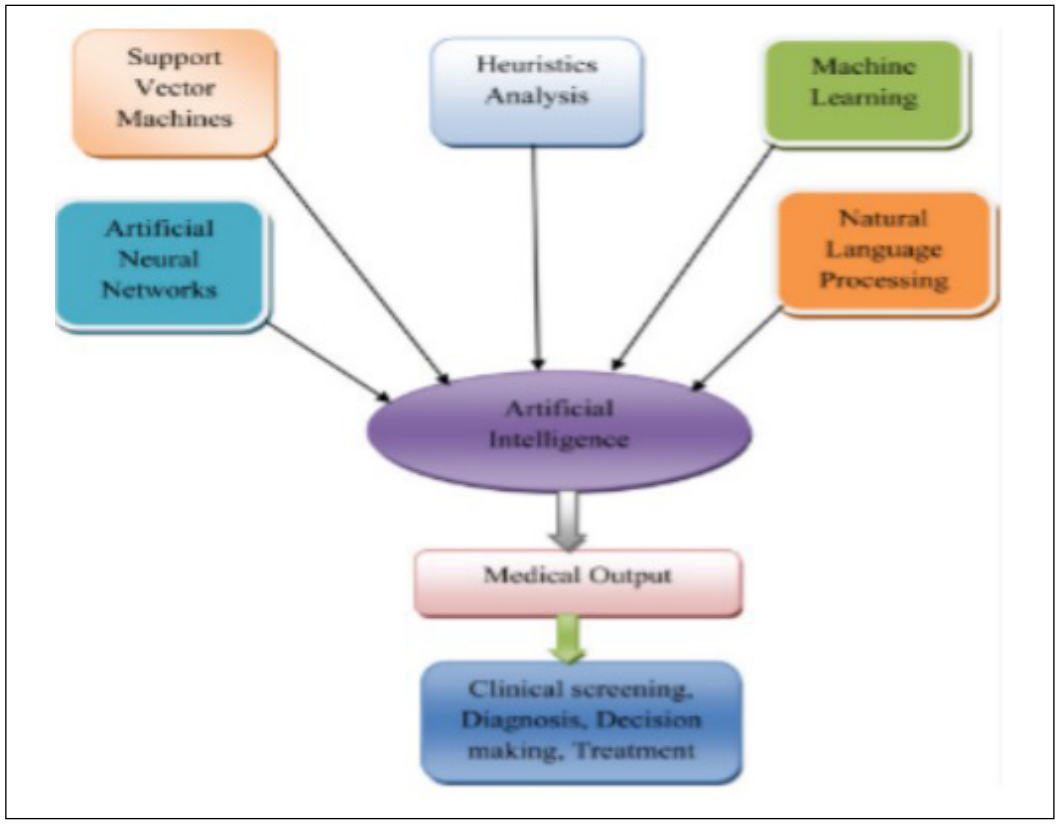

Fig. 3. Structure and functions of artificial intelligence in clinical medicine.

RISKS, ETHICS, AND LEGAL ISSUES RELATED TO AI IN MEDICAL FIELD

Developing AI technology for use in healthcare, safe practices, services, and policies is costly and risky. It is becoming more and more crucial to safeguard the financial interests of AI and data-driven healthcare advances [20]. Previously, vital signs such as blood pressure, heart rate and glucose levels could only be monitored by medical personnel [21], however, the ongoing collecting of this data is now made possible by contemporary mobile applications. The ethical issues surrounding the application of AI technology must be addressed, particularly those pertaining to patient autonomy, informed consent, and abuse of data privacy and confidentiality [22]. The GDPR introduces comprehensive data protection legislation within the EU, causing a shift in data protection globally, whereas HIPAA primarily protects sensitive health information processed by lawful organizations [23-26]. The introduction of AI into the healthcare system may distort patient data and affect important medical examination results. Cyber-attacks have increased [27]. Certain cyber threats can be identified and avoided with the use of predictive algorithms. A comprehensive examination of cyber security and the cyber risk environment of healthcare systems is necessary to protect data privacy and preserve system integrity [27]. It is possible to mitigate the risk of relying solely on one solution by utilizing multiple reliable AI algorithms. Artificial intelligence in healthcare offers numerous benefits, including process simplification, increased productivity, time and resource savings, support for research, and a reduction in medical stress, despite concerns about data privacy and security breaches. The impact of digital technologies on healthcare supply chain stakeholders was assessed using an epistemological framework for ethical assessment that places a high priority on ethical awareness, transparency, and accountability [28].

CUSTOMIZATION OF TREATMENT

AAI can provide creative answers for monitoring epidemics and providing individualized care. Algorithms in microbial identification powered by artificial intelligence have shown impressive accuracy and efficacy in identifying pathogenic microorganisms from a variety of clinical samples [29]. These algorithms swiftly and accurately diagnose infections by analyzing massive databases of genomic, proteomic, and clinical data, enabling healthcare to create individualized treatment programs [30]. Epidemic surveillance has been greatly enhanced by the quick identification and analysis of trends in epidemiological data. AI systems can identify new epidemics, monitor the spread of illnesses, and identify possible hotspots by processing and analyzing real-time data from several origin, including medical

records, and environmental detector. During infectious disease emergencies, this proactive approach helps containment and mitigation efforts by enabling prompt intervention measures. Essentially, artificial intelligence in microbial diagnosis and epidemic monitoring plays a critical role in protecting public health globally in addition to improving healthcare by optimizing treatment approaches [31].

CONCLUSIONS

The methods for diagnosing microbial infectious diseases have evolved from serological techniques to advanced molecular approaches [32,33]. Today, AI has become a powerful tool applicable across all fields of life. AI-driven predictive analytics can improve the accuracy, efficiency, and cost-effectiveness of clinical laboratory testing and disease detection. As AI is incorporated, the method for diagnosing microorganisms is changing. It makes it possible to identify pathogens quickly and accurately, identify antibiotic resistance early, and develop better diagnostic methods. AI is also crucial for drug research, outbreak detection, early disease diagnosis, and individualized treatment. Consequently, there have been significant improvements in healthcare results and public health benefits. But as AI becomes more prevalent in medical decision-making, ethical concerns like patient privacy, algorithmic biases, data security, transparency, accessibility, and human oversight must be addressed. Further improvements in illness prevention and treatment are now acceptable due to the development of AI in microbiological detection, which also ensures ethical and equitable healthcare practices.

REFERENCES

1. Kandilci M, Yakıcı G, Kayar MB. Artificial Intelligence and Microbiology. Experimental and Applied Medical Science. 2024;5(2):119 – 128. doi:10.46871/eams.1458704. DOI
2. Oh J, Makar M, Fusco C et al. A generalizable, data-driven approach to predict daily risk of Clostridium difficile infection at two large academic health centers. Infect. Control Hosp. Epidemiol. 2018;39:425–433. doi: 10.1017/ice.2018.16. DOI
3. Tilton CS, Johnson SW. Development of a risk prediction model for hospital-onset Clostridium difficile infection in patients receiving systemic antibiotics. Am. J. Infect. Control. 2019;47:280-284. doi: 10.1016/j.ajic.2018.08.021. DOI
4. Miller MB, Atrzadeh F, Burnham C-AD et al. Clinical utility of advanced microbiology testing tools. J Clin Microbiol. 2019;57(9):10-11282. doi:10.1128/JCM.00495-19. DOI
5. Salazar BM, Balczewski EA, Ung CY, Zhu S. Neuroblastoma, a paradigm for big data science in pediatric oncology. Int J Mol Sci. 2016;18(1):37. doi:10.3390/ijms18010037. DOI
6. Hamet P, Tremblay J. Artificial intelligence in medicine. Metabolism. 2017;69:S36-S40. doi:10.1016/j.metabol.2017.01.011. DOI
7. Abdi J, Al-Hindawi A, Ng T, Vizcaychipi MP. Scoping review on the use of socially assistive robot technology in elderly care. BMJ Open. 2018;8(2):e018815. doi:10.1136/bmjopen-2017-018815. DOI
8. Jartarkar SR. Artificial intelligence: Its role in dermatopathology. Indian J Dermatol Venereol Leprol. 2023;89(4): 549-552. doi: 10.25259/IJDVL_725_2021. DOI
9. Franco-Duarte R, Cernáková L, Kadam S et al. Advances in chemical and biological methods to identify microorganisms – From past to present. Microorganisms. 2019;7(5):130. doi: 10.3390/microorganisms7050130. DOI
10. Uddin TM, Chakraborty AJ, Khusro A et al. Antibiotic resistance in microbes: History, mechanisms, therapeutic strategies and future prospects. J. Infect. Public Health. 2021;14:1750-1766. doi: 10.1016/j.jiph.2021.10.020. DOI
11. Agbehadji IE, Awuzie BO, Ngowi AB, Millham RC. Review of big data analytics, artificial intelligence and nature-inspired computing models towards accurate detection of COVID-19 pandemic cases and contact tracing. Int. J. Environ. Res. Public Health. 2020;17:5330. doi:10.3390/ijerph17155330. DOI
12. Rabaan AA, Alhumaid S, Al Mutair A et al. Application of artificial intelligence in combating high antimicrobial resistance rates. Antibiotics. 2022;11:784. doi:10.3390/antibiotics11060784. DOI
13. Hamet P, Tremblay J. Artificial Intelligence in Medicine. Metab. Clin. Exp. 2017;69:S36–S40. doi: 10.1016/j.metabol.2017.01.011. DOI
14. Krishnan G, Singh S, Pathania M et al. Artificial Intelligence in Clinical Medicine: Catalyzing a Sustainable Global Healthcare Paradigm. Front. Artif. Intell. 2023;6:1227091. doi:10.3389/frai.2023.1227091. DOI
15. Beam AL, Kohane IS. Big Data and Machine Learning in Health Care. JAMA. 2018;319:1317-1318. doi: 10.1001/jama.2017.18391. DOI
16. Yang W, Olson DR, Shaman J. Forecasting Influenza Outbreaks in Boroughs and Neighborhoods of New York City. PLoS Comput. Biol. 2016;12:e1005201. doi:10.1371/journal.pcbi.1005201. DOI
17. Liu JYH, Rudd JA. Predicting drug adverse effects using a new Gastro-Intestinal Pacemaker Activity Drug Database (GIPADD). Sci Rep. 2023;13(1):6935. doi:10.1038/s41598-023-33655-5. DOI
18. Subramanian M, Wojtusciszyn A, Favre L et al. Precision medicine in the era of artificial intelligence: implications in chronic disease management. J Transl Med. 2020;18(1):472. doi:10.1186/s12967-020-02658-5. DOI

19. Gerke S, Minssen T, Cohen G. Ethical and legal challenges of artificial intelligence-driven healthcare. Artif Intell Healthc. 2020, pp.295–336. doi:10.1016/b978-0-12-818438-7.00012-5. DOI
20. Cohen IG, Mello MM. HIPAA and protecting health information in the 21st Century. JAMA. 2018;320(3):231. doi:10.1001/jama.2018.5630. DOI
21. Yuan B, Li J. The policy effect of the General Data Protection Regulation (GDPR) on the digital public health sector in the European Union: an empirical investigation. Int J Environ Res Public Health. 2019;16(6):1070. doi:10.3390/ijerph16061070. DOI
22. Alotaibi S, Mehmood R, Katib I et al. A Big Data Analytics Tool for Healthcare symptoms and Diseases Detection using Twitter, Apache Spark, and machine learning. Appl Sci. 2020;10:1398. doi:10.3390/ app10041398. DOI
23. Al-Mistarehi A-HM, Mijwil M, Filali Y et al. Artificial Intelligence Solutions for Health 4.0: Overcoming Challenges and Surveying Applications. MJAIH. 2023. doi: 10.58496/MJAIH/2023/003. DOI
24. Radanliev P, De Roure D. Epistemological and bibliometric analysis of Ethics and Shared responsibility—health policy and IoT Systems. Sustainability. 2021;13(15):8355. doi: 10.3390/su13158355. DOI
25. Radanliev P, De Roure D, Ani U, Carvalho G. The ethics of shared Covid-19 risks: an epistemological framework for ethical health technology assessment of risk in vaccine supply chain infrastructures. Health Technol (Berl). 2021;11(5):1083–91. doi: 10.1007/s12553-021-00565-3. DOI
26. Ransbotham S, Candelon F, Kiron D et al. The Cultural Benefits of Artificial Intelligence in the Enterprise. MIT Sloan Management Review and Boston Consulting Group. 2021. https://sloanreview.mit.edu/projects/the-cultural-benefits-of-artificial-intelligence-in-the-enterprise/ [Accessed 12 December 2024]
27. Rigby MJ. Ethical Dimensions of Using Artificial Intelligence in Health Care. AMA Journal of Ethics. 2019;21(2):121-124. doi: 10.1001/amajethics.2019.121. DOI
28. Rutala WA, Weber DJ. Best practices for disinfection of noncritical environmental surfaces and equipment in health care facilities: A bundle approach. American Journal of Infection Control. 2019;47:A96–A105. doi: 10.1016/j.ajic.2019.01.014. DOI
29. Bohr A, Memarzadeh K. The rise of artificial intelligence in healthcare applications. Artificial Intelligence in Healthcare. Elsevier, Amsterdam, the Netherlands. 2020. doi:10.1016/B978-0-12-818438-7.00002-2. DOI
30. Vora LK, Gholap AD, Jetha K et al. Artificial intelligence in pharmaceutical technology and drug delivery design. Pharmaceutics. 2023;15:1916. doi: 10.3390/pharmaceutics15071916. DOI
31. Agrebi S, Larbi A. Use of artificial intelligence in infectious diseases. Artificial Intelligence in Precision Health. Elsevier, Amsterdam, the Netherlands. 2020. doi: 10.1016/B978-0-12-817133-2.00018-5. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

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REVIEW ARTICLE

CONTENTS

Medical confidentiality as an element of privacy vs. public interest in crime disclosure: striving for balance

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ABSTRACT

Aim: This article aims to raise awareness and stimulate scientific discussion on the issue of protecting medical confidentiality during criminal proceedings, with the goal of further improving legal tools to ensure compliance with the standards of the European Court of Human Rights (hereinafter referred to as the ECHR) in this field.

Materials and Methods: In preparing the article, the following issues were addressed: the provisions of international legal acts; the legal positions of the ECHR related to the protection of medical confidentiality in criminal proceedings; and scientific research in this field. The methodological basis of the research includes the method of generalization, methods of analysis and synthesis.

Conclusions: The right to confidentiality regarding health status may be restricted during criminal procedural activities in forms prescribed by law. Such a restriction will be considered lawful and justified in a democratic society, provided that the interference meets the set of criteria established by the practice of the ECHR. The storage of biological material outside the scope of criminal proceedings is, in some cases, justified to safeguard public interests in a democratic society; however, under certain conditions, it may conflict with the principles of the presumption of innocence and the right to privacy.

KEY WORDS: medical secret and confidential medical information, collection of biological samples, privacy, investigative actions, ECHR practice, criminal process

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INTRODUCTION

Criminal procedural activities are often associated with intrusions into the sphere of human rights and fundamental freedoms. One such example is the disclosure of medical information without the patient's consent. Therefore, achieving a fair balance between the public interest in investigating criminal offenses to hold perpetrators accountable and the individual's right to confidentiality of health information as part of the right to privacy is impossible without establishing certain guidelines. Searching for such guidelines for states that uphold European values is entirely justified in the practice of the ECHR.

AIM

This article aims to raise awareness and stimulate scientific discussion on the issue of protecting medical confidentiality during criminal proceedings, with the goal of further improving legal tools to ensure compliance with ECHR standards in this field.

MATERIALS AND METHODS

The basis for the preparation of the article was international legal acts (in particular: the Convention on Human Rights and Biomedicine (1997); the International Code of Medical Ethics (1949); the Declaration on the Promotion of Patients' Rights in Europe (1994); the Convention for the Protection of Human Rights and Fundamental Freedoms of (1950)), as well as empirical material – the judicial practice of the ECHR. The selection of specific ECHR rulings was determined by their significance in assessing the legality of intrusions into the right to respect for private and family life through the disclosure of information constituting medical confidentiality. A total of 9 ECHR decisions were analyzed. Supplementary materials included rulings of national courts in Ukraine and scientific articles by domestic and foreign scholars. During the investigation, a combination of general scientific and specific methods of cognition was used, including the method of generalization, and methods of analysis and synthesis. The generalization method was employed in studying

ECHR practice to formulate criteria for the legality of disclosing health-related confidentiality in light of convention standards. The methods of analysis and synthesis facilitated the identification of key motives in the ECHR's positions, which subsequently allowed for the development of a comprehensive understanding of generally accepted standards for protecting medical confidentiality in criminal proceedings.

REVIEW AND DISCUSSION

International legal instruments guarantee everyone the right to confidentiality of health information (Article 10 of the Convention on Human Rights and Biomedicine of April 4, 1997; the International Code of Medical Ethics (1949); and the Declaration on the Promotion of Patients' Rights in Europe of 1994). The ECHR considers medical information as part of the right to respect for private and family life, which is protected under Article 8 of the Convention for the Protection of Human Rights and Fundamental Freedoms of 1950 (hereinafter referred to as the Convention): "The Court has held that the protection of personal data, not least medical data, is of fundamental importance to a person's enjoyment of his or her right to respect for private and family life as guaranteed by Article 8 of the Convention. Respecting the confidentiality of health data is a vital principle in the legal systems of all the Contracting Parties to the Convention. The disclosure of such data may dramatically affect an individual's private and family life, as well as his or her social and employment situation" [1].

It should be noted that at the level of national legal regulation, the legislator has adopted European values and established mechanisms for protecting health-related confidentiality. At the same time, this right is not absolute and may be restricted by the state in certain areas to achieve public objectives. One such example is criminal procedural activity.

The provisions of the Criminal Procedure Code (hereinafter referred to as the CPC) of Ukraine prohibit the questioning of medical workers and other individuals who, in the course of their professional or official duties, have become aware of a person's illness, medical examinations, evaluations, and their results, as well as intimate and family aspects of a person's life—information constituting medical confidentiality (para. 4, part 2, Article 65 of the CPC of Ukraine). Similar prohibitions are provided for in the criminal procedure laws of other European countries (e.g., Article 72 of the Estonian CPC, Article 53 of the German CPC, and Articles 155 and 157 of the Austrian CPC). However, in Ukrainian judicial practice, there have been cases where courts have granted motions from parties in criminal proceedings to summon medical workers for questioning as witnesses [2-4] or issued orders to compel the attendance of medical workers, despite the prohibition established by part 3 of Article 140 of the CPC of Ukraine [5-7].

The CPC of Ukraine also establishes a procedural order for obtaining a court order to access information that may constitute medical confidentiality (para. 2, part 1, Article 162 of the CPC of Ukraine). In this case, the patient's consent, who entrusted the information, is not required.

At the same time, scholars have repeatedly argued against the unacceptable absolutization of medical confidentiality due to: a) cases where participants in criminal proceedings manipulate their health condition to delay investigative, procedural actions, or judicial proceedings (V. Mykhailenko) [8]; b) the need for the rehabilitation of a deceased participant in criminal proceedings (D. Shynharov) [9]. Some scientists also suggested the possibility of interrogating a medical worker as a witness by a court decision using mechanisms to protect confidential information (for example, by conducting interrogation in a closed court session) [10].

At the same time, to find a fair balance between the objectives of criminal proceedings and the right to confidentiality of health information, it is advisable to rely on the criteria established by the practice of the European Court of Human Rights (ECHR). Therefore, let us examine them in more detail, focusing on the following areas of research: 1) obtaining information about a person's health condition through questioning a medical worker as a witness or obtaining a court order for access to information that may constitute medical confidentiality; 2) interaction between medical workers and the media regarding the health status of patients who may be participants in criminal proceedings; 3) storage of biological material outside the scope of criminal proceedings.

1. *Obtaining information about a person's health condition through questioning a medical worker as a witness or obtaining a court order for access to information that may constitute medical confidentiality.* Interference with the right to respect for private and family life, including the right to confidentiality of health information, is justified if: a) medical information impacts the comprehensive, complete, and objective investigation of the case circumstances (for example, the qualification of a criminal offense) [11]; b) medical information is requested within the framework of criminal proceedings to fulfill its objectives and in relation to individuals who have acquired procedural status in the criminal proceedings, rather than for preventive purposes [2]; c) the pre-trial investigation body has used alternative methods to obtain infor-

mation about the health status before requesting a court order for access to medical documentation [2]; d) the state has ensured the confidentiality of the health information obtained within the framework of criminal proceedings [11, 12].

For example, in the case of Z. v. Finland (Application No. 22009/93), the applicant considered the questioning of doctors as witnesses regarding her health circumstances to be an interference with the right provided under Article 8 of the Convention. The ECHR, in turn, noted that such actions undoubtedly constitute a restriction of the right under Article 8 of the Convention but are justified in a democratic society. The purpose of this measure was solely to obtain information from the doctors about when the applicant's husband knew or had grounds to believe that he was HIV-positive. Their testimony, at the time of the investigation, could have been decisive in determining whether the applicant's husband was guilty of committing only sexual offenses or additionally guilty of attempting intentional murder when the test results indicating his HIV-positive status were already known (para. 102). Moreover, the questioning was conducted before the city court with video recording, and the court had previously decided that the court hearing minutes, including the transcript, were not subject to disclosure. Individuals involved in the process were required to treat the information as confidential and not subject to disclosure (para. 103). In this regard, the ECHR concluded that the various orders requiring the applicant's medical consultants to testify were based on relevant and sufficient grounds aligned with the legitimate aim pursued. There was a reasonable proportional relationship between the measures and the legislative purpose, which did not violate Article 8 of the Convention (para. 105) [11].

In the case of Avilkina and Others v. Russia (Application No. 1585/09), the applicants complained that the prosecutor's office had requested doctors to disclose information from their medical files without their consent and without any criminal investigation justifying such disclosure. As a result, confidential medical information was disclosed [2]. The prosecutor's interference significantly complicated the second applicant's treatment, obstructing the use of alternative non-blood treatment methods, including erythropoietin. The attitude of medical personnel towards her noticeably worsened. Additionally, an article appeared in the media in which one of the doctors openly discussed the second applicant's case. The fourth applicant was unable to consult the medical institution where she had previously been treated due to the threat of repeated disclosure of her medical records (para. 41) [2].

Thus, the ECHR found a violation of Article 8 of the Convention because: 1) the applicants were neither suspects nor accused in any criminal investigation; 2) the prosecutor was merely conducting an inquiry into the activities of the applicants' religious organization following complaints received by his office; 3) the medical facilities where the applicants underwent treatment did not report any alleged criminal behavior to the prosecutor's office; 4) the prosecutor had alternative options besides ordering the disclosure of confidential medical information, such as seeking the applicants' consent or questioning them regarding the matter (paras. 47–48) [2].

2. *Interaction of Medical Personnel with the Media Regarding the Health Status of Patients Involved in Criminal Proceedings.* There have been cases in practice where medical personnel provide comments to the media about the health status of patients involved in criminal proceedings that attract public interest or even share excerpts from medical records (including photographs or video materials) with journalists. Two key questions arise in this context: 1. Does a doctor have the right to take photographs of a patient for medical purposes? 2. In what ways can such materials be used?

According to I. Seniuta, a medical professional, when it is necessary to photograph a patient in order to document clinical results before and after an intervention, must obtain written consent. The statement should include the following key provisions: 1) the patient grants permission for photography for clinical purposes, with the understanding that these images will be placed in their medical records; 2) if the medical professional intends to share these photographs on social media to present their work or publish them at conferences for scientific purposes, the patient must give explicit consent for such publication, specifying the purpose and ensuring that personal identification details are included [13].

In the case of Ageyevy v. Russia (Application no. 7075/10), the applicants, who were accused of failing to fulfill their parental duties, complained that doctors had provided journalists with photographs of their son, information about his health condition, and granted the film crew unrestricted access to the child, including the possibility of further interviews. Subsequently, various national media outlets published articles with titles such as "Mother with a devil's heart," "I was beaten by my Mum," "Mummy beat me up with a hot kettle full of boiling water," "Monster-mummy is facing jail for ill-treatment of child," and "Mummy tortured adopted child," among others (para. 65). The government argued that the photographs, which showed the victim's burns, were taken for medical purposes, and that the media had

received permission to film only in the hospital lobby. However, the ECHR found a violation of Article 8 of the Convention, as such interference was not foreseen by law (para. 183) [14].

3. *Storage of biological material outside the scope of criminal proceedings*. The criminal procedural legislation outlines the procedure for collecting biological samples for forensic examination (part 3 of Art. 245 of the CPC of Ukraine). However, the issue of storage remains unregulated at the level of the CPC of Ukraine. On the other hand, Article 5 of the Law of Ukraine "On the State Registration of Human Genomic Information" stipulates that information about individuals convicted of intentional crimes (the legislator narrows this list to crimes against the foundations of national security of Ukraine, life, health, liberty, honor, dignity, sexual freedom and integrity of the person, property, public safety, the circulation of narcotic drugs, psychotropic substances, their analogues or precursors, crimes against peace, the security of mankind, and international law and order) (clause 3, part 1, Art. 5 of the Law) must be registered, and this information is stored in the Electronic Register for 50 years (part 2, Art. 18 of the Law) (the genomic information is to be stored for 50 years. The biological material, based on which this information has been generated, is destroyed after the person has served their sentence, but no later than the expiration of the retention period set by the manufacturer of the means (systems) for collecting biological samples (para. 2, part 1, Art. 14 of the Law)). The pretrial investigation authorities and the court have the right to use this information for identifying individuals who have committed criminal offenses (part 1, Art. 16 of the Law), and the oversight of human rights compliance is entrusted to the relevant Ombudsman of the Verkhovna Rada of Ukraine (part 1, Art. 19 of the Law) [15].

It should be noted that during the legislative process, the conclusions of the Main Scientific and Expert Department dated May 31, 2021, criticized these provisions due to: 1) excessive storage periods for genomic information; 2) an insufficiently effective control mechanism, since the Verkhovna Rada Commissioner for Human Rights does not have real powers to influence the Ministry of Internal Affairs of Ukraine's system of bodies [16]. Supporting these observations, we would also add that certain provisions of the Law of Ukraine "On the State Registration of Human Genomic Information" may be contradictory from an ethical standpoint in terms of adhering to the principles o f the presumption of innocence and non-interference in private life. Therefore, let us examine some ethical aspects of their relationship (this issue has already been addressed by some scholars [17]).

Scholars highlight five criteria that the ECHR considers when balancing the right to respect for private life (Art. 8 of the Convention) with the storage of biological samples: 1) type of biological samples; 2) severity of the criminal offense; 3) procedural status of the person (acquitted or convicted); 4) presence of previous convictions; 5) age. Moreover, scholars note that these criteria can be used to assess compliance with the principle of presumption of innocence [17].

Considering the conclusions already formed by scholars[17], it should be noted that in the practice of the ECHR, the approach has developed that the mere storage of biological samples cannot be equated with the expression of suspicion [18], and the assumption about a person's involvement in criminal offenses (referring to a tendency towards unlawful behavior) does not fall under the concept of "accusation" as defined in Art. 6 of the Convention [19].

At the same time, the storage of materials of individuals who: (a) were initially suspected of committing a minor crime or (b) had criminal proceedings closed or had a judgment of acquittal become final [18-21], leads to treating them as guilty [18]. On the other hand, the storage of materials of individuals convicted of committing crimes of a certain level of severity is necessary in a democratic society, and therefore does not violate the principle of the presumption of innocence [19, 20].

In its turn, national judicial practice sets its own trends in law enforcement. Unlike the ECHR, Ukrainian courts, when deciding on the storage of samples outside of criminal proceedings, are guided solely by the first criterion – the type of biological samples (in the following, only guilty verdicts are analyzed. It should be noted that when studying law enforcement practice, the authors did not find any acquittal verdicts in which the court decided to keep biological samples in the criminal proceedings. This trend is positive from the standpoint of observing the principles of the presumption of innocence and non-interference in private life). For example, in case No. 344/22140/19, the court, having found the person previously convicted of serious criminal offenses guilty (criminal law qualification: Part 1 of Art. 115, Part 3 of Art. 357, Part 1 of Art. 358, Part 3 of Art. 358, Part 4 of Art. 358, Part 2 of Art. 190 of the Criminal Code of Ukraine) ruled to destroy biological samples, specifically blood samples, buccal epithelium, nail clippings, and hand swabs [22]. It should be noted that this approach contradicts the Law of Ukraine "On the State Registration of Genomic Information," which provides for the storage of biolog-

ical material of convicted individuals until they have served their sentence (paragraph 2, part 1 of Art. 14 of the Law). A similar approach was applied in other cases, both for those previously convicted [23-25] and for those not previously convicted [26, 27], before the adoption of Law No. 2391-IX.

In contrast, fingerprint samples are stored after a conviction has been issued, both for individuals who have been previously convicted [28, 29] and for those who have not been convicted [30-32].

In scientific discourse, these trends are explained by the gradation of biological samples based on the degree of interference with the right to respect for private life, which has developed within the first criterion: (a) highest level – cellular material, as it contains information that not only allows identification of a person but also reveals details about their health and potential diseases, which goes beyond the needs of criminal investigations; (b) medium level – DNA profile, which, while including a more limited amount of private information than cellular material, still provides the possibility of revealing cellular connections or ethnic origin, also going beyond the scope of criminal investigations; (c) lowest level – fingerprint samples, which only allow for identification of a person and do not disclose any other confidential information about them [17].

In summary, the storage of biological material outside the scope of criminal proceedings may conflict with the principles of the presumption of innocence and the right to privacy if the material is stored and used to identify individuals who have committed a criminal offense after an acquittal, the closure of criminal proceedings, or the completion of the punishment by the person from whom the material was collected. On the other hand, the storage of biological material from individuals who have already been convicted and subsequently found guilty of committing serious or particularly serious criminal offenses (for the entire period of serving the sentence – until the conviction is expunged) is necessary in a democratic society and, therefore, largely justified.

It is noteworthy that general issues of medical confidentiality (including some criminal procedural aspects in individual studies) were studied by Daria I. Klepka, Iryna O. Krytska, Anna S. Sydorenko [33], Philip Rieder, Micheline Louis-Courvoisier, Philippe Huber [34], Kristin E. Schleiter [35], Keren Semyonov-Tal [36], D.O. Shynharov [9], T. Korcheva, O. Nevelska-Hordieieva, D. Voitenko [37]. The criminal-legal assessment of the protection of medical confidentiality is highlighted in the dissertation by L. Karpenko [38], and the scientific article by T. Mykhailychenko, O. Horpyniuk, and V. Rak [39]. The administrative-legal context of understanding medical confidentiality was addressed by I.V. Shatkovska [40]. The legal nature of medical confidentiality, as well as the balance between medical confidentiality and criminal justice, was studied by Polish scholars, including Burdziak, Konrad, Kowalewska-Łukuć, Magdalena [41], A. Kaminska-Nawrot, D. Bienkowska, J. Falecki, R. Depczynski, D. Czarnecki [42], A. Pilarska, A. Zimmermann, A. Zdun-Ryzewska [43], K. Michalak [44]. However, the scientific works demonstrate a lack of comprehensive understanding of the implemented convention standards regarding the fair balance between the objectives of criminal proceedings and the confidentiality of health information as part of the right to privacy. This article provides an overview of the main standards established by the case law of the ECHR regarding the protection of medical confidentiality in the course of criminal proceedings. However, this overview is not exhaustive, indicating the need for further research.

CONCLUSIONS

1. The right to the confidentiality of health information may be restricted in the course of criminal procedural activities, specifically in the following forms: a) obtaining information about health status through the interrogation of a medical professional as a witness or obtaining a court order for access to information that may constitute medical confidentiality; b) interaction between medical professionals and the media regarding the health status of patients who may be involved in criminal proceedings; c) storage of biological material outside of criminal proceedings.
2. Interference with the right to the confidentiality of health information as part of the right to respect for private and family life is justified if: a) the medical information affects the comprehensive, complete, and objective investigation of the circumstances of the case (for example, the qualification of a criminal offense); b) the medical information is requested within the framework of a criminal proceeding to fulfill its objectives and pertains to individuals who have acquired a procedural status in the criminal proceedings, rather than for preventive purposes; c) the pre-trial investigation body has used alternative methods of obtaining information about the health status before requesting a court order for access to medical records; d) the state ensures the confidentiality of the health information obtained within the framework of criminal proceedings; e) the dissemination of information about health status is provided by law.

3. The storage of biological material outside of criminal proceedings may conflict with the principles of the presumption of innocence and non-interference with private life if the biological material is stored and used for the identification of individuals who have committed a criminal offense after an acquittal, closure of the criminal case, or the completion of a sentence by the individual from whom the material was taken. However, the storage of biological material from individuals who have already been convicted and are again found guilty of committing serious or particularly serious criminal offenses (for the entire period of sentence – until the conviction is expunged) is necessary in a democratic society and, therefore, largely justified.

REFERENCES

1. Case of Varapnickaite-Mazyliene v. Lithuania. Application no. 20376/05. Judgment of the European Court of Human Rights, 17 April 2012. https://hudoc.echr.coe.int/ukr?i=001-108680 [Accessed 15 October 2024]
2. Case of Avilkina and others v. Russia. Application no. 1585/09. Judgment of the European Court of Human Rights, 07 October 2013. https://hudoc.echr.coe.int/?i=001-120071 [Accessed 15 October 2024]
3. Rishennya Illichivs'koho mis'koho sudu Odes'koyi oblasti vid 04.11.2013 r., sudova sprava № 10000. 501/4507/13-k. [Decision of Illichivsk City Court of Odesa Oblast from November 4, 2013, court case no. 501/4507/13-k]. https://reyestr.court.gov.ua/Review/37074975 [Accessed 15 October 2024] (Ukrainian)
4. Rishennya Izyums'koho mis'krayonnoho sudu Kharkivs'koyi oblasti vid 15.03.2016 r., sudova sprava № 10000. 623/3878/14-k. [Decision of Izium City District Court of Kharkiv Oblast dated 15 March 2016, court case no. 623/3878/14-k]. https://reyestr.court.gov.ua/Review/56474078 [Accessed 15 October 2024] (Ukrainian)
5. Ukhvaloyu Vinnyts'koho mis'koho sudu Vinnyts'koyi oblasti vid 13 lystopada 2012 r., sudova sprava № 10000 vid 13.11.2012r. 206/5574/2012. [Resolution of Vinnytsia City Court of Vinnytsia Oblast from November 13, 2012, court case no. 206/5574/2012]. https://reyestr.court.gov.ua/Review/48448401 [Accessed 15 October 2024] (Ukrainian)
6. Ukhvala Halyts'koho rayonnoho sudu Ivano-Frankivs'koyi oblasti vid 22.05.2013 r., sudova sprava № 10000 vid 22.05.2013 r. 0904/1927/12. [Resolution of Halytskyi District Court of Ivano-Frankivsk Oblast from May 22, 2013, court case no. 0904/1927/12]. https://reyestr.court.gov.ua/Review/50545124 [Accessed 15 October 2024] (Ukrainian)
7. Postanova Holosiyivs'koho rayonnoho sudu m. Kyyeva vid 21.06.2011 r., sudova sprava № 10000. 1-22/11. [Resolution of Holosiivskyi District Court of Kyiv from June 21, 2011, court case no. 1-22/11]. https://reyestr.court.gov.ua/Review/17141094 [Accessed 15 October 2024] (Ukrainian)
8. Mykhaylenko V. The Competition of Rights and Duties when Questioning a Medical Worker as a Witness in Criminal Proceedings Concerning Representatives of the Public Sector of Ukraine (Inspired by Practice) [Konkurentsiia prav ta oboviazkiv pry dopyti medychnoho pratsivnyka yak svidka u kryminalnomu provadzhenni shchodo predstavnykiv publichnoho sektoru Ukrainy (naviiano praktykoiu)]. Academy of the Successful Doctor. 2018. https://docacademy.com.ua/jurist/rights-and-obligations/ [Accessed 15 October 2024] (Ukrainian)
9. Shynharov DO. Ensuring the rights and legitimate interests of individuals during interrogation at the stage of pre-trial investigation [Zabezpechennia prav ta zakonnykh interesiv osib pid chas provedennia dopytu na stadii dosudovoho rozsliduvannia]: thesis for obtaining the scientific degree of Doctor of Philosophy. Yaroslav Mudryi National Law University. Kharkiv. 2017, p.223, (Ukrainian)
10. Abbasova DL. Pravove zabezpechennia ta realizatsiia etychnykh norm u kryminalnomu protsesi Ukrainy [Legal support and implementation of ethical norms in the criminal process of Ukraine]: thesis for obtaining the scientific degree of Doctor of Philosophy. Yaroslav Mudryi National Law University. Kharkiv. 2023, p.312. (Ukrainian)
11. Case of Z. v. Finland. Application no. 22009/93. Judgment of the European Court of Human Rights, 25 February 1997. https://hudoc.echr.coe.int/eng?i=001-58033 [Accessed 15 October 2024]
12. Case of Y.G. v. Russia. Application no. 8647/12. Judgment of the European Court of Human Rights, 30 November 2022. https://hudoc.echr.coe.int/ukr?i=001-218920 [Accessed 15 October 2024]
13. Seniuta I. Analitychne doslidzhennia shchodo obrobky personalnykh danykh u sferi okhorony zdorovia ta dotrymannia prav liudyny v tsii tsaryni [Analytical study on the processing of personal data in the field of health care and compliance with human rights in this area]. Council of Europe project "Supporting the implementation of European standards for the protection of human rights in Ukraine". 2024, p.57. (Ukrainian)
14. Case of Ageyevy v. Russia. Application no. 7075/10. Judgment of the European Court of Human Rights, 09 September 2013. https://hudoc.echr.coe.int/?i=001-118602 [Accessed 15 October 2024]
15. Pro derzhavnu reyestratsiyu henomnoyi informatsiyi pro lyudynu: Zakon Ukrayiny vid 09 lypnya 2022 r. № 2391-IKH. [On state registration of human genomic information: Law of Ukraine dated 9 July 2022. No. 2391-IX]. https://zakon.rada.gov.ua/laws/show/2391-20#Text [Accessed 15 October 2024] (Ukrainian)

16. Vysnovok Holovnoho naukovo-ekspertnoho upravlinnya vid 31.05.2021 shchodo proektu Zakonu Ukrayiny «Pro derzhavnu reyestratsiyu henomnoyi informatsiyi lyudyny» № 4265 vid 26.10.2020. [Conclusion of the Main Scientific and Expert Directorate dated 05/31/2021 on the draft Law of Ukraine "On State Registration of Human Genomic Information" No. 4265 dated 26 October 2020]. http://w1.c1.rada.gov.ua/pls/zweb2/webproc4_1?pf3511=70249 [Accessed 15 October 2024] (Ukrainian)
17. Kaplina OV, Shylo OH, Titko IA. Using the samples of human biological materials in the criminal procedure: the practice of the European Court of Human Rights. Wiad Lek. 2019;72(8):1576-1581.
18. Case of S. and Marper v. the United Kingdom. Applications nos. 30562/04 and 30566/04. Judgment of the European Court of Human Rights, 4 December 2008. https://hudoc.echr.coe.int/eng?i=001-90051 [Accessed 15 October 2024]
19. Case of Peruzzo and Martens v. Germany. Applications nos.7841/08 and 57900/12. Judgment of the European Court of Human Rights, 04 June 2013. https://hudoc.echr.coe.int/eng?i=001-121998 [Accessed 15 October 2024]
20. Case of Van der. Velden v. The Netherlands. Application no. 21203/10. Judgment of the European Court of Human Rights, 31 October 2012. https://hudoc.echr.coe.int/eng?i=001-112547 [Accessed 15 October 2024]
21. Case of M.K. v. France. Application no. 19522|09. Judgment of the European Court of Human Rights, 18 April 2013. https://hudoc.echr.coe.int/eng?i=001-119075 [Accessed 15 October 2024]
22. Vyrok Ivano-Frankivs'koho mis'koho sudu Ivano-Frankivs'koyi oblasti vid 21 kvitnya 2023 r. sudova sprava № 344/22140/19. [Verdict of Ivano-Frankivsk City Court of Ivano-Frankivsk Oblast dated 21 April 2023, court case no. 344/22140/19]. https://reyestr.court.gov.ua/Review/110365782м [Accessed 15 October 2024] (Ukrainian)
23. Vyrok Rozhyshchens'koho rayonnoho sudu Volyns'koyi oblasti vid 12 sichnya 2023 r. sudova sprava № 163/265/22. [Verdict of Rozhyshchenskyi District Court of Volyn Oblast dated 12 January 2023, court case no. 163/265/22]. https://reyestr.court.gov.ua/Review/108360448 [Accessed 15 October 2024] (Ukrainian)
24. Vyrok Ivano-Frankivs'koho mis'koho sudu Ivano-Frankivs'koyi oblasti vid 30 lystopada 2021 r. sudova sprava № 344/17136/21. [Verdict of Ivano-Frankivsk City Court of Ivano-Frankivsk Oblast dated 30 November 2021, court case no. 344/17136/21]. https://reyestr.court.gov.ua/Review/101503618 [Accessed 15 October 2024] (Ukrainian)
25. Vyrok Kozel'shchyns'koho rayonnoho sudu Poltavs'koyi oblasti vid 2 lystopada 2021 r. sudova sprava № 533/929/21. [Verdict of Kozelshchyna District Court of Poltava Oblast dated 2 November 2021, court case no. 533/929/21]. https://reyestr.court.gov.ua/Review/100751914 [Accessed 15 October 2024] (Ukrainian)
26. Vyrok Konotops'koho mis'krayonnoho sudu Sums'koyi oblasti vid 20 hrudnya 2022 r. sudova sprava № 574/121/22. [Verdict of Konotop City District Court of Sumy Oblast dated 20 December 2022, court case no. 574/121/22]. https://reyestr.court.gov.ua/Review/107965856 [Accessed 15 October 2024] (Ukrainian)
27. Vyrok Zhovkivs'koho rayonnoho sudu L'vivs'koyi oblasti vid 5 travnya 2021 r. sudova sprava № 444/972/21. [Verdict of Zhovkva District Court of Lviv Oblast dated 5 May 2021, court case no. 444/972/21]. https://reyestr.court.gov.ua/Review/96714079 [Accessed 15 October 2024] (Ukrainian)
28. Vyrok Novomoskovs'koho mis'krayonnoho sudu Dnipropetrovs'koyi oblasti vid 02 serpnya 2021 r., sudova sprava №183/3740/17. [Verdict of Novomoskovsk City District Court of Dnipropetrovsk Oblast dated 2 August 2021, court case No.183/3740/17]. https://reyestr.court.gov.ua/Review/98698219 [Accessed 15 October 2024] (Ukrainian)
29. Verdict of Amur-Nyzhniodniprovskyi District Court of Dnipropetrovsk dated 2 February 2021, court case no. 199/488/21. https://reyestr.court.gov.ua/Review/94558142 [Accessed 15 October 2024] (in Ukrainian).
30. Vyrok Amur-Nyzhn'odniprovs'koho rayonnoho sudu m. Dnipropetrovs'ka vid 2 lyutoho 2021 r. sudova sprava № 199/488/21. [Verdict of Pavlohrad City District Court of Dnipropetrovsk Oblast dated 28 September 2022, court case no. 185/9564/17]. https://reyestr.court.gov.ua/Review/106568151 [Accessed 15 October 2024] (Ukrainian)
31. Vyrok Obolons'koho rayonnoho sudu m. Kyyeva vid 05.11.2021 r. sudova sprava № 756/225/14-k. [Verdict of Obolonskyi District Court of Kyiv dated 5 November 2021, court case no. 756/225/14-k]. https://reyestr.court.gov.ua/Review/100949094 [Accessed 15 October 2024] (Ukrainian)
32. Vyrok Volodymyrets'koho rayonnoho sudu Rivnens'koyi oblasti vid 15 lypnya 2016 r. sudova sprava № 556/1380/16-k. [Verdict of Volodymyretskyi District Court of Rivne Oblast dated 15 July 2016, court case no. 556/1380/16-k]. https://reyestr.court.gov.ua/Review/59095083 [Accessed 15 October 2024] (Ukrainian)
33. Klepka D, Krytska I, Sydorenko A. Obligation of the disclosure of medical confidential information in criminal proceedings. Wiad lek. 2019;72(12):2602-2608.
34. Rieder Ph, Louis-Courvoisier M, Huber Ph.The end of medical confidentiality? Patients, physicians and the state in history. Med Humanities. 2016. doi: 10.1136/medhum-2015-010773. DOI
35. Kristin E, Schleiter, JD. When Patient-Physician Confidentiality Conflicts with the Law. Virtual Mentor. 2009;11(2):146-8. doi: 10.1001/virtualmentor.2009. DOI
36. Semyonov-Tal K. Keeping medical information safe and confidential: a qualitative study on perceptions of Israeli physicians. Isr J Health Policy Res. 2024;13(1):54. doi: 10.1186/s13584-024-00641-9. DOI

37. Korcheva T, Nevelskaia-Hordeeva E, Voitenko D. Medical privacy: medical, criminally-remedial and the philosopho-legal aspects of its disclosure (review). Georgian medical news. 2020;306:166-171.
38. Karpenko LK. Kryminalno-pravove zabezpechennia likarskoi taiemnytsi [Criminal legal protection of medical confidentiality]: thesis for obtaining the scientific degree of Doctor of Philosophy. Kharkiv National University of Internal Affairs. Kharkiv. 2013, p.205. (Ukrainian)
39. Mykhailichenko TO, Horpyniuk OP, Rak VYu. Medical confidentiality disclosure in cinditions of epidemic threats. Wiad Lek. 2021;11(2):2877-2883.
40. Shatkovska IV. Administratyvno-pravove zabezpechennia likarskoi taiemnytsi v Ukraini [Administrative and legal support of medical confidentiality in Ukraine]: thesis for obtaining the scientific degree of Doctor of Philosophy. National University of Bioresources and Environmental Management of Ukraine. Kyiv. 20106 p.198. (Ukrainian)
41. Burdziak K, Kowalewska-Łukuć M. Psychologist's professional secrecy versus secrecy in criminal proceedings. Probacja. 2023;1:115-131. doi: 10.5604/01.3001.0016.2852. DOI
42. Kaminska-Nawrot A, Bienkowska D, Falecki J et al. Enhancing Human Security: Balancing Medical Confidentiality and Criminal Justice. European Research Studies Journal. 2024;XXVII(2);531-545.
43. Pilarska A, Zimmermann A, Zdun-Ryzewska A. Access to Health Information in the Polish Healthcare System – Survey Research. Int. J. Environ. Res. Public Health. 2022;19(12):7320. doi: 10.3390/ijerph19127320. DOI
44. Michalak K. The essence of medical secrecy according to the Polish law. Prog Health Sci. 2014;4(1):239-244.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

The level of use of cardiovascular interventions in the treatment of patients with acute myocardial infarction in Ukraine

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ABSTRACT

Aim: To investigate the level of use of cardiovascular interventions during the treatment of patients with acute myocardial infarction in Ukraine.

Materials and Methods: Materials: statistical data of the National Health Service of Ukraine for the period 2021-2023 in regional aspect. Methods: bibliosemantic, medico-statistical, of structural-and-logical analysis.

Conclusions: In Ukraine, there is a tendency to increase the level of use of these technologies in the treatment of patients with acute myocardial infarction. Reliable differences in the level of use of cardiovascular interventions in the treatment of patients with acute myocardial infarction across the regions of Ukraine were reveale. A critically low level of use of these technologies is observed in the territories temporarily occupied by Russian troops since 2014 – Donetsk and Luhansk regions.

KEY WORDS: acute myocardial infarction, treatment, cardiovascular interventions

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INTRODUCTION

Myocardial infarction is a serious complication of ischemic (coronary) heart disease and hypertension, which leads to a high level of disability and mortality of the working-age population in most developed countries of the world. This indicator at the age of 50–54 years is 404–367 per 100,000 population [1-3].

A modern effective method of treating patients with myocardial infarction is the use of cardiovascular interventions with stenting of coronary vessels [4]. The use of cardiovascular interventions during the treatment of patients with acute myocardial infarction contributes to increasing the effectiveness of treatment results and reducing patient mortality.

This type of medical care in Ukraine is included in the package of state medical guarantees [5].

AIM

The aim is to investigate the level of use of cardiovascular interventions during the treatment of patients with acute myocardial infarction in Ukraine.

MATERIALS AND METHODS

Object of the study: use of cardiovascular interventions in the treatment of patients with acute myocardial infarction: open stenting of coronary vessels, transcutaneous stenting of coronary vessels, transcutaneous coronary rotational atherectomies. The information base of the study was composed by electronic medical records that were created by doctors when providing medical care under the packages of the medical guarantee program according to the data of electronic health care system

Table 1. Data on patients with acute myocardial infarction, treated in hospitals and experienced cardiovascular interventions, 2021-2023

Area	2021				2022				2023			
	Number of treated patients with acute myocardial infarction	Open stenting of coronary vessels	Percutaneous stenting of coronary vessels	Percutaneous transluminal coronary rotational atherectomies [PTCRA]	Number of treated patients with acute myocardial infarction	Open stenting of coronary vessels	Percutaneous stenting of coronary vessels	Percutaneous transluminal coronary rotational atherectomies [PTCRA]	Number of treated patients with acute myocardial infarction	Open stenting of coronary vessels	Percutaneous stenting of coronary vessels	Percutaneous transluminal coronary rotational atherectomies [PTCRA]
Regions(Oblasts)												
Vinnytsia	1163	5	611	-	1306	2	781	1	1409	-	898	-
Volyn	900	3	434	1	972	1	583	4	1004	4	498	25
Dnipropetrovsk	3945	4	1084	3	4363	-	1566	1	4424	-	2023	116
Donetsk	1741	2	645	1	770	-	133	-	575	-	5	-
Zhytomyr	880	2	302	-	1156	1	558	-	1232	-	734	3
Transcarpathian	824	2	489	-	1017	1	644	-	1100	3	676	2
Zaporizhzhia	2002	3	842	-	1498	-	795	24	1801	-	960	60
Ivano-Frankivsk	1024	1	461	-	1261	7	708	-	1286	9	849	11
Kyiv	1411	1	452	4	1400	4	457	21	2396	4	985	91
Kirovohrad	962	8	278	2	1046	1	370	-	1077	-	542	29
Luhansk	673	-	11	-	130	-	-	-	-	-	-	-
Lviv	2812	5	1049	3	3250	19	1564	3	3557	10	1736	20
Mykolaiv	843	2	306	3	949	-	330	-	1074	-	504	11
Odesa	1578	9	835	19	2213	4	1190	14	2430	6	1403	56
Poltava	1371	6	782	2	1690	4	1012	-	1815	4	1142	31
Rivne	934	-	423	-	1057	1	677	-	1107	5	745	4
Sumy	1106	-	538	-	1185	-	631	1	1081	-	587	54
Ternopil	802	-	303	-	901	2	449	1	924	6	568	4
Kharkiv	2665	14	1017	1	2178	3	501	-	3025	3	1213	19
Kherson	826	7	200	-	411	5	91	-	291	-	121	-
Khmelnytskyi	1175	1	551	-	1300	4	780	-	1514	-	961	68
Cherkasy	1261	-	689	1	1420	-	788	-	1413	1	927	6
Chernivtsi	980	-	373	-	1088	-	579	-	1430	-	727	143
Chernihiv	896	-	376	-	809	-	392	-	968	-	558	27
City of Kyiv	2460	4	790	3	3118	5	1421	7	3243	1	1626	132
Total	32774	75	13051	40	33370	59	15579	70	36933	55	19362	780

Table 2. The level of use of cardiovascular interventions in the treatment of patients with acute myocardial infarction, 2021-2023

Area	2021			2022			2023		
	Number of treated patients with acute myocardial infarction	Number of performed cardiovascular interventions	Percentage of use of cardiovascular interventions, %	Number of treated patients with acute myocardial infarction	Number of performed cardiovascular interventions	Percentage of use of cardiovascular interventions, %	Number of treated patients with acute myocardial infarction	Number of performed cardiovascular interventions	Percentage of use of cardiovascular interventions, %
Regions (Oblasts)									
Vinnytsia	1163	616	59,96	1306	784	60,03	1409	898	70,19
Volyn	900	438	48,87	972	588	60,49	1004	527	52,49
Dnipropetrovsk	3945	1091	27,66	4363	1567	35,92	4424	2139	48,35
Donetsk	1741	648	37,22	770	133	17,27	575	5	0,87
Zhytomyr	880	304	34,55	1156	559	48,36	1232	737	59,82
Transcarpathian	824	491	59,59	1017	645	63,42	1100	682	62,00
Zaporizhzhia	2002	845	42,21	1498	819	54,67	1801	1020	56,64
Ivano-Frankivsk	1024	462	45,12	1261	715	56,70	1286	869	67,57
Kyiv	1411	457	32,39	1400	482	34,43	2396	1076	44,91
Kirovohrad	962	288	29,94	1046	371	35,47	1077	571	53,02
Luhansk	673	11	1,63	130	-	-	-	-	-
Lviv	2812	1057	37,59	3250	1578	48,55	3557	1766	49,65
Mykolaiv	843	311	36,89	949	330	34,77	1074	515	47,95
Odesa	1578	863	54,69	2213	1208	54,59	2430	1465	60,29
Poltava	1371	790	57,62	1690	1016	60,12	1815	1177	64,85
Rivne	934	423	45,29	1057	678	64,14	1107	754	68,11
Sumy	1106	538	48,64	1185	632	53,33	1081	641	59,29
Ternopil	802	303	37,78	901	452	50,17	924	578	62,55
Kharkiv	2665	1032	38,72	2178	504	23,14	3025	1235	40,83
Kherson	826	207	25,01	411	96	23,36	291	121	41,58
Khmelnytskyi	1175	552	46,98	1300	784	60,31	1514	1029	67,97
Cherkasy	1261	690	54,72	1420	788	55,49	1413	934	66,10
Chernivtsi	980	373	38,01	1088	579	53,22	1430	870	60,84
Chernihiv	896	376	41,96	809	392	48,45	968	585	60,43
City of Kyiv	2460	797	32,40	3118	1433	45,96	3243	1759	54,24
Total	**32774**	13166	40,17	**33370**	**15708**	47,07	**36933**	20197	54,69

on the number of treated patients with acute myocardial infarction and patients who underwent cardiovascular interventions for the period 2021-2023 in the regional aspect. The study covers the territories that are controlled by Ukraine during the war against Russian military aggression. *Research methods:* bibliosemantic, medico-statistical (calculation of relative values of the use of cardiovascular interventions in the treatment of patients with acute myocardial infarction), of structural-and-logical analysis.

REVIEW AND DISCUSSION

At the first stage of the study, statistical data were grouped and analyzed across the regions of Ukraine for the period 2021-2023 regarding the quantity of: treated patients for acute myocardial infarction, open coronary stenting, percutaneous coronary stenting, percutaneous transluminal coronary rotational atherectomy [PTCRA]. The obtained results are shown in Table 1.

The analysis of the data presented in Table 1 indicates that the number of acute myocardial infarction patients treated in the country's hospitals during the study period increased by 1.13 times and amounted to 36,933 patients in 2023. At the same time, an increase in the number of hospitalized patients with acute myocardial infarction was registered in 20 (80.0%) regions.

The largest quantiry of these patients was registered in Dnipropetrovsk (4,424), Lviv (3,557), and Kharkiv (3,025) regions and in the city of Kyiv (3,243).

In general, the following dynamics of the use of cardiovascular interventions were registered:

- open stenting of coronary vessels: the number decreased by 1.36 times and amounted to 55 interventions with the largest number being 10 (18.2% of the total number in Lviv region). In 2023, these coronary artery stenting technologies were used in health care institutions in 12 (48.0%) regions of Ukraine;

- percutaneous stenting of coronary vessels: the number increased by 1.48 times and in 2023 amounted to 19,362 interventions. These coronary artery stenting technologies were used in health care facilities in all regions of Ukraine in 2023. The largest number of percutaneous stentings of coronary vessels was performed in Dnipropetrovsk (2023), Lviv (1736) and Odesa (1403) regions and in the city of Kyiv (1626).

- percutaneous transluminal coronary rotational atherectomies: the number increased by 19.5 times and in 2023 amounted to 780 interventions. In 2023, these coronary artery stenting technologies were used in health care facilities in all regions of Ukraine except Vinnytsia, Donetsk, Luhansk, and Kherson regions.

Further, in order to reveal the level of use of cardiovascular interventions in the treatment of patients with acute myocardial infarction, the obtained data were summarized in a general table and the proportion of patients with acute myocardial infarction who underwent cardiovascular interventions was calculated. The obtained results are presented in Table 2.

The analysis of the data presented in Table 2 indicates that, as a whole, the share of acute myocardial infarction patients in Ukraine who were treated with cardiovascular interventions increased by 14.52% and in 2023 amounted to 54.69%.

The analysis of the use of cardiovascular interventions in the treatment of acute myocardial infarction in the dynamics of the research years showed the following:

- 2021: cardiovascular interventions were used in the treatment of 40.17% of patients with acute myocardial infarction. The largest share of acute myocardial infarction patients treated with cardiovascular interventions was registered in Vinnytsia (59.96%), Transcarpathian (59.59%) and Poltava (57.62%) regions. The smallest share was registered in Luhansk (1.63%), Kherson (25.01%), Dnipropetrovsk (27.66%) regions. In Kyiv, cardiovascular interventions in the treatment of acute myocardial infarction were used in 32.40% of cases;

- 2022: cardiovascular interventions were used in the treatment of 47.07% of patients with acute myocardial infarction. The largest share of acute myocardial infarction patients treated with cardiovascular interventions was registered in Rivne (64.14%), Transcarpathian (63.42%) and Volyn (60.49%) regions. The smallest share was registered in Donetsk (17.27%), Kharkiv (23.14%) and Kherson (23.36%) regions. This technology was not used in Luhansk region. In Kyiv, cardiovascular interventions in the treatment of acute myocardial infarction were used in 45.96% of cases;

- 2023: cardiovascular interventions were used in the treatment of 54.69% of patients with acute myocardial infarction. The largest share of acute myocardial infarction patients treated with cardiovascular interventions was registered in Vinnytsia (70.19%), Rivne (68.11%) and Khmelnytskyi (67.97%) regions. The smallest share was registered in Donetsk (0.87%), Kharkiv (40.83%) and Kherson (41.58%) regions. This technology was not used in Luhansk region. In Kyiv, cardiovascular interventions in the treatment of acute myocardial infarction were used in 54.24% of cases.

The analysis of the impact of the war against Russian military aggression on the frequency of cardiovascular interventions in the treatment of acute myocardial infarction in the regions of Ukraine showed the following:

- *regions of the zone of active hostilities:* Kharkiv region – the number of hospitalized patients with acute myocardial infarction increased by 13.51%, and the level of use of cardiovascular interventions increased

by 2.11%; Sumy region – the number of hospitalized patients with acute myocardial infarction decreased by 2.26%, and the level of use of cardiovascular interventions increased by 1.65%; Zaporizhzhia region – the number of hospitalized patients with acute myocardial infarction decreased by 14.43%, and the level of use of cardiovascular interventions increased by 10.4%; Kherson region – the number of hospitalized patients with acute myocardial infarction decreased by 64.77%, and the level of use of cardiovascular interventions increased by 16.57%;

- *regions close to the zone of active hostilities:* Dnipropetrovsk region – the number of hospitalized patients with acute myocardial infarction increased by 12.14%, and the level of use of cardiovascular interventions increased by 20.69%; Mykolaiv region – the number of hospitalized patients with acute myocardial infarction increased by 27.40%, and the level of use of cardiovascular interventions increased by 11.06%; Odesa region – the number of hospitalized patients with acute myocardial infarction increased by 53.99%, and the level of use of cardiovascular interventions increased by 5.6%; Poltava region – the number of hospitalized patients with acute myocardial infarction increased by 32.39%, and the level of use of cardiovascular interventions increased by 7.23%.

At the time of conducting this analysis, Donetsk and Luhansk regions have a special status, part of their territory has been temporarily occupied since 2014. Since then, the infrastructure of the health care system has been partially destroyed or is located in the territory that is not controlled by Ukraine. Corresponding to the above noted, data from the territories of these regions controlled by Ukraine were subject to analysis.

Donetsk region: the number of patients treated in hospitals for acute myocardial infarction decreased by 3.03 times over the years of the study and amounted to 575 patients; the share of patients who underwent cardiovascular interventions during the treatment process decreased from 37.22% to 0.87%.

Luhansk region: the number of patients with acute myocardial infarction treated in hospitals in the territories subordinated to Ukraine in 2021 amounted to 673, with the use of cardiovascular interventions at the level of 1.63%. In 2022, 130 patients were treated for acute myocardial infarction without the use of cardiovascular interventions. In 2023, patients with acute myocardial infarction in health care facilities in the territories subordinated to Ukraine were not treated on an inpatient basis.

The war against Russian military aggression caused a significant part of the population from the regions of active hostilities and territories close to them to become forced migrants within the country and refugees in other countries. Currently, there is no statistical information on their incidence of acute myocardial infarction.

The use of cardiovascular interventions during the treatment of patients with acute myocardial infarction contributes to increasing the effectiveness of treatment results and reducing patient mortality. With an increase over the years of the study of the proportion of patients with acute myocardial infarction treated with cardiovascular interventions by 14.52% with a level in 2023 of 54.69%, the use of this technology in Ukraine in comparison with European countries [6,7] and the USA [8,9] is insufficient in terms of providing them to patients with myocardial infarction.

So, in Europe and the USA, cardiovascular interventions are performed not only in patients with acute myocardial infarction, but also in 20–30% of patients with coronary heart disease [10]. It is important to compare the use of cardiovascular interventions in Ukraine and other European countries to calculate the number of interventions per 100,000 population. The comparison of the Ukrainian indicator with the "average European" one was first published by the representative of the European Society of Cardiology, Professor P. Widimsky [11]. In 2013, the number of primary stenting in patients with acute myocardial infarction in Ukraine was at the level of 75 patients per 1 million population, which was almost 5 times less than the average European indicator [12].

Subsequently, an increase in the indicator was registered: 2014 – 100 patients per 1 million population [13], 2015 – 132 [14], 2016 – 190 [15], 2017 – 220 [16], 2018 – 286, 2019 – 312, 2020 – 336, 2021 – 391, 2022 – 442 with the European average indicator of 373 [17].

Scientific publications indicate a decrease in the availability and quality of medical care during the war [18,19]. Our study found a significant decrease in the use of cardiovascular interventions during the treatment of patients with acute myocardial infarction in Donetsk and Luhansk regions.

CONCLUSIONS

In Ukraine, an increase is detected in the level of the use of cardiovascular interventions in the treatment of patients with acute myocardial infarction for the period from 2021 to 2023 by 14.52% with a level of use in 2023 of 54.69%. Reliable differences in the level of use of cardiovascular interventions in the treatment of patients with acute myocardial infarction across the regions of Ukraine were revealed. A critically low level of the use of these technologies is observed in the territory of Donetsk and Luhansk regions controlled by Ukraine, a part of which have been temporarily occupied by Russian troops since 2014.

REFERENCES

1. Fuster V, Kelly BB et al. Institute of Medicine (US) Committee on Preventing the Global Epidemic of Cardiovascular Disease: Meeting the Challenges in Developing Countries. Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health. Washington (DC): National Academies Press (US). 2010. doi: 10.17226/12815. DOI
2. Terenda NO, Shulhai AH, Petrashyk YM et al. Impact of certain public health factors on the duration of inpatient treatment of mi patients. Wiad Lek. 2020;73(5):850–856.
3. Slabkyi HO, Koshelia II. Smertnist naselennia Ukrainy vnaslidok khvorob systemy krovoobihu v peredvoiennyi period. [Mortality of the population of Ukraine due to diseases of the circulatory system in the pre-war period]. Ukraina. Zdorovia natsii. 2022;4(70):5–10. (Ukrainian)
4. Park J-S, Jeong S, Lee DH. Recent Advances in Gastrointestinal Stent Development. Clin Endosc. 2015;48(3):209-15. doi: 10.5946/ce.2015.48.3.209. DOI
5. Pakety medychnykh posluh. Zmist ta pidkhid do kontraktuvannia zakladiv okhorony zdorovia. Natsionalna sluzhba zdorovia Ukrainy. [Medical service packages. Contents and guidelines for contracting health care institutions. National Health Service of Ukraine]. Kyiv, 2020, p.59. (Ukrainian)
6. Silber S, Albertsson P, Aviles FF et al. Guidelines for percutaneous coronary interventions: the task force for percutaneous coronary interventions of the European Society of Cardiology. Eur Heart J. 2005;26(8):804-47. doi: 10.1093/eurheartj/ehi138. DOI
7. Gupta M, Chang WC, Van de Werf F et al. International differences in in-hospital revascularization and outcomes following acute myocardial infarction: a multilevel analysis of patients in ASSENT-2. Eur Heart J. 2003;24(18):1640-50. doi: 10.1016/s0195-668x(03)00433-0. DOI
8. Anderson HV, Shaw RE, Brindis RG et al. A contemporary overview of percutaneous coronary interventions. The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). J Am Coll Cardiol. 2002;39(7):1096-103. doi: 10.1016/s0735-1097(02)01733-3. DOI
9. Vakili BA, Kaplan R, Brown DL. Volume-outcome relation for physicians and hospitals performing angioplasty for acute myocardial infarction in New York state. Circulation. 2001;104(18):2171-6. doi: 10.1161/hc3901.096668. DOI
10. Sokolov MYu. Reyestr cherezshkirnykh koronarnykh vtruchan'. Zminy na 2015–2018 rr. – vypadkovyy splesk diyal'nosti chy systemni peretvorennya? [Register of percutaneous coronary interven tions. Are changes for 2015–2018 a casual splash of activi ties or system transformations?]. Sertse i sudyny. 2019;3:12 33. (Ukrainian)
11. Widimsky P, Wijns W, Fajadet J et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J. 2010;31(8):943-57. doi: 10.1093/eurheartj/ehp492. DOI
12. Sokolov MYu. Reyestr cherezshkirnykh koronarnykh vtruchan': rozshyrenyy porivnyal'nyy analiz 2012–2013 rr. [Percutaneous Coronary Interventions Registry: advanced comparative analysis 2012–2013]. Sertse i sudyny. 2014;3:7-20. (Ukrainian)
13. Sokolov MYu. Reyestr cherezshkirnykh koronarnykh vtruchan': rozshyrenyy porivnyal'nyy analiz, reperfuziyna terapiya v Ukrayini, Ohlyad CHKV – 2015. [Percutaneous Coronary Interventions Registry: advanced comparative analysis, reperfusion therapy in Ukraine, Survey PCI – 2015]. Sertse i sudyny. 2015;3:7 29. (Ukrainian)
14. Sokolov MYu. Reyestr cherezshkirnykh koronarnykh vtruchan': porivnyal'nyy analiz 2014–2015 rr. Dynamika rehional'nykh reperfuziynykh merezh v Ukrayini. [Percutaneous Coronary Interventions Registry: comparative analysis of 2014–2015 years. The dynamics of regional reperfusion networks in Ukraine]. Sertse i sudyny. 2016;3:14 34. (Ukrainian)
15. Sokolov MYu. Reyestr cherezshkirnykh koronarnykh vtruchan': rozshyrenyy porivnyal'nyy analiz rezul'tativ 2016 ta 20 17 rr. Vid reperfuziynoho paradoksu do znyzhennya smertnosti. [Register of percutaneous coronary interven tions: expanded comparative analysis of results of 2016 and 20 17. From reperfusion paradox to decrease of mortality]. Sertse i sudyny. 2018;3:9 27. (Ukrainian)
16. Sokolov MYu. Reyestr cherezshkirnykh koronarnykh vtruchan': rozshyrenyy porivnyal'nyy analiz, reperfuziyna terapiya v Ukrayini, Ohlyad CHKV – 2015. [Percutaneous Coronary Interventions Registry: advanced comparative analysis, reperfusion therapy in Ukraine, Survey PCI – 2015]. Sertse i sudyny. 2015;3:7 29. (Ukrainian)
17. Sokolov MYu, Danylchuk IV, Besh DI et al. Reyestr cherezshkirnykh koronarnykh vtruchan': zminy za ostanni roky (2010–2022 rr.). [Registry of percutaneous coronary interventions: changes over recent years (2010–2022)]. Ukrainian Journal of Cardiology 2024;1:7-33. doi: 10.31928/2664-4479-2024.1.733. (Ukrainian) DOI
18. Maksimovich MI, Litvin NA. Current challenges of access to healthcare during the war. Juridical scientific and electronic journal. 2022;9:330-332. doi:10.32782/2524-0374/2022-9/80. DOI
19. Health care during the war: The impact of Russia's full-scale invasion on health care in Ukraine.». International Renaissance Foundation. Agency for Legislative Initiatives.Ukrainian Medical Center. 2023, p.26.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Actual scientific data in comorbid periodontal diseases and heart-vessel pathology

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ABSTRACT

Aim: The aim of this study is to review and analyze contemporary scientific and professional literature to investigate the role of periodontal diseases in the development and progression of cardiovascular diseases. Specifically, this study aims to deepen our understanding of the pathogenetic mechanisms underlying periodontitis in this category of patients and the reciprocal aggravating influence of these pathologies on each other

Materials and Methods: bibliometric and analytical methods applied to data from international scientific sources investigating the role of periodontal diseases in the pathogenesis of cardiovascular diseases.

Conclusions: The growing body of evidence indicates a significant comorbidity between periodontal diseases and cardiovascular diseases. Given the systemic impact of periodontitis on cardiovascular health, there is a pressing need for enhanced periodontal care and further research to better understand this complex relationship

KEY WORDS: periodontitis, cardiovascular diseases, atherosclerosis, microorganisms, risk factors

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INTRODUCTION

The close relationship between oral health and overall health is supported by current epidemiological studies and is increasingly substantiated by modern scientific advancements.

In the context of the global COVID-19 pandemic, the study of the impact of periodontal infection on the development and progression of cardiovascular diseases has become particularly relevant. The pandemic has presented healthcare systems with unprecedented challenges, emphasizing the necessity of comprehensive patient care. Periodontitis, as a chronic inflammatory disease, can significantly impact overall health, particularly in patients with COVID-19 who already have cardiovascular conditions. Such patients require more vigilant monitoring and a comprehensive treatment plan.

Epidemiological studies have demonstrated a strong association between periodontal disease and an increased risk of cardiovascular events, including atherosclerosis, coronary heart disease, and myocardial infarction. Systemic inflammation, endothelial dysfunction, and the translocation of oral pathogens into the circulation are believed to be the primary mechanisms linking periodontal disease to cardiovascular disease. The situation is exacerbated by the frequent underdiagnosis and undertreatment of periodontal infections, which elevates the risk of cardiovascular complications. Considering periodontal health in cardiology patients can significantly improve prognosis and reduce the likelihood of complications.

The urgency of this issue lies in the need to develop effective preventive and therapeutic strategies aimed at improving periodontal health and reducing the risk of cardiovascular disease. This involves integrating dental and medical approaches in patient care and raising awareness among both healthcare providers and patients about the crucial connection between oral health and coronary heart disease.

AIM

The aim of this study is to review and analyze current scientific literature to examine the role of periodontal diseases in the development and progression of cardiovascular pathology. Specifically, this study aims to deepen our understanding of the pathogenetic mechanisms underlying periodontitis and the mutual influence of these pathologies on each other.

MATERIALS AND METHODS

This study utilized bibliometric and analytical methods to systematically review global research examining the association between periodontal diseases and coronary heart disease.

REVIEW AND DISCUSSION

Cardiovascular diseases pose a significant global health burden. In Europe alone, nearly 4 million people die from these conditions annually, accounting for 44% of all deaths [1, 2].

Beyond traditional cardiovascular risk factors, the growing burden on global and regional healthcare systems is exacerbated by new challenges such as air pollution and the uncertain long-term consequences of COVID-19 on cardiovascular disease patterns [3].

Consequently, cardiovascular diseases continue to be a major public health concern. The full-scale war in Ukraine, which began in 2022, has led to a further, dramatic increase in the prevalence of cardiovascular diseases, following the initial surge post-COVID-19. In addition to the existing challenges, the population is now facing extremely high levels of psychological stress, while the destruction of parts of the healthcare infrastructure, disruptions in the supply of medications and medical equipment, and a growing unmet need for medical care have exacerbated the situation [5, 6].

Cardiovascular disease (CVD) is a general term for a group of disorders of the heart and blood vessels. Atherosclerosis (AS) is one of the primary causes of cardiovascular diseases. It is a progressive disease characterized by the accumulation of plaques, consisting of lipids, cellular waste products, and fibrous tissue, in the arterial intima. Traditionally, AS was understood as a disease initiated by the accumulation of low-density lipoproteins within the arterial wall, leading to the formation of atherosclerotic plaques [7].

Subendothelial accumulation of modified low-density lipoproteins (LDL) triggers a chronic inflammatory response. The interplay of oxidative stress, growth factors, cytokines, and the recruitment of monocytic macrophages and smooth muscle cells within this microenvironment ultimately contributes to plaque formation.

AS is a chronic disease that progresses asymptomatically for many years. Clinical manifestations typically arise when advanced atherosclerotic lesions cause significant stenosis or thrombosis, leading to ischemia of the heart (coronary heart disease), brain (ischaemic stroke), or lower extremities (peripheral vascular disease) [8].

Multiple studies have consistently demonstrated a correlation between microorganisms and their toxins and the pathogenesis of atherosclerosis [9].

Chronic vascular inflammation, initiated by endothelial injury, is a complex process modulated by a combination of traditional and emerging risk factors. CVD can be prevented by modifying risk factors for atherosclerosis. Including factors that influence systemic inflammatory burden. Oral diseases, particularly periodontitis, are factors that directly or indirectly contribute to systemic inflammation.

Scientific advancements have revealed increasingly strong associations between periodontal diseases and cardiovascular risk factors [10].

Chronic oral infections, including periodontitis, increase the risk of systemic diseases. A growing body of research points to a bidirectional relationship between systemic diseases and periodontal disease, suggesting that systemic diseases can both contribute to the development of periodontal disease and vice versa [11-13].

Recent studies have introduced a paradigm shift, recognizing dental diseases, especially periodontitis, as a new modifiable risk factor for CVD [14, 15].

A potential mechanism underlying this link is that localized periodontal infection induces a chronic inflammatory state. Periodontal infection can exert both direct and indirect effects on systemic health. Direct mechanisms involve the direct migration of pro-inflammatory bacteria from the oral cavity into the cardiovascular system. Indirect mechanisms operate through the activation of systemic immune responses, leading to a sustained chronic inflammatory state [14].

They describe at least four main pathogenetic mechanisms by which oral inflammation, particularly periodontal infection, influences the development and progression of CVD: (1) bacteremia, where oral bacteria enter the bloodstream and penetrate the arterial wall; (2) systemic inflammation induced by pro-inflammatory mediators released from oral inflammatory foci into the bloodstream; (3) autoimmune reactions against host proteins triggered by the host's immune response to specific components of oral pathogens; and (4) proatherogenic effects caused by specific bacterial toxins released by oral pathogens [16].

A normal oral microbiome forms a structured "biofilm" in which bacterial communities are embedded in an extracellular matrix, providing protection and resistance to the penetration of external agents. Nevertheless, alterations in the quantitative and qualitative makeup of the biofilm, disrupting homeostasis, elicit a complex host immune-inflammatory response. An acute inflammatory response, manifesting as gingivitis, is first observed on both supragingival and subgingival dental plaque. This response is perpetuated by a coordinated effort involving innate immune cells such as resident epithelial cells and fibroblasts, phagocytic cells like

macrophages and neutrophils, as well as complement proteins and neuropeptides. During this phase, cytokines like tumor necrosis factor (TNF-α), interleukin (IL)-1β, and interleukin (IL)-6, secreted by resident cells, play a central role in stimulating the migration of cells to the site of infection. They also enhance the expression of adhesion molecules on the vascular endothelium, facilitating neutrophil recruitment, and promote the production of additional pro-inflammatory cytokines. The removal of plaque results in the resolution of inflammation and the restoration of individual homeostasis. Prolonged dental plaque persistence results in the activation of the adaptive immune system. This involves antigen presentation by lymphocytes, macrophages, and dendritic cells, and is regulated by adaptive immune cytokines like interferon (IFN)-γ, interleukin (IL)-2, and interleukin (IL)-4 [17].

Periodontitis, a remitting chronic inflammation associated with microbes, develops due to the proliferation of pathogenic microorganisms, their toxin production, and their ability to penetrate tissues. Key periodontal pathogens, including Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia, Treponema denticola, and Prevotella intermedia, are anaerobic Gram-negative bacteria. These organisms, upon reaching a critical mass within subgingival biofilm and in the presence of various local and systemic predisposing factors, initiate inflammatory responses [18, 19].

In a dysbiotic subgingival microbiome, the host immune system is chronically activated, primarily by IL-1, IL-8, TNF-α, prostaglandins, and matrix metalloproteinases (MMPs). These inflammatory mediators influence the functions and activity of leukocytes, osteoblasts, and osteoclasts, leading to characteristic destruction of the periodontal ligament, connective tissue, and alveolar bone [20].

The progressive destruction of periodontal tissues, including bone resorption and extracellular matrix degradation, results from a shift in the balance between osteogenesis and osteoclastogenesis in favor of the latter. This is regulated by a complex inflammatory-induced osteoclastogenesis pathway involving the receptor activator of nuclear factor kappa-B (RANK) and its ligand (RANKL), as well as IL-1β, IL-6, and TNF-α. Extracellular matrix (ECM) degradation occurs due to increased regulation of the expression of a family of 23 Zn2+ and Ca2+-dependent enzymes known as matrix metalloproteinases (MMPs). These enzymes are involved in the degradation of gingival and periodontal ligament collagen, which occurs in periodontitis during the catabolism of connective tissue [17].

Specific bacteria from the periodontal pocket can penetrate the epithelial barrier and enter the systemic circulation. Thus, inflammatory mediators from the periodontium enter the bloodstream and activate acute-phase proteins in the liver, such as C-reactive protein (CRP), which further exacerbates systemic inflammation.

Patients with periodontal disease have an average of twice the risk of developing coronary heart disease, including myocardial infarction. The increased risk of systemic diseases in patients with periodontitis may be associated with a higher prevalence and severity of bacteremia caused by oral microorganisms. Such bacteremias are often caused by species such as Streptococcus sanguis and Porphyromonas gingivalis, which can contribute to thrombus formation by promoting platelet aggregation and binding to endothelial cells. We suggest that chronic oral infections, particularly periodontitis, may be a contributing factor in the development and progression of atherosclerosis [21, 22].

Increased vascular permeability results in the leakage of periodontopathogens into the bloodstream. These are transported through the blood vessels to other target tissues. The finding of subgingival plaque microorganisms in the blood of individuals with coronary artery disease provides evidence to support the notion that oral pathogens can translocate from the oral cavity to the arterial system, thereby intensifying the inflammatory response and promoting the development or exacerbation of cardiovascular complications [23].

An increasing number of studies have described the detection of periodontopathogens far beyond their primary localization.

Verica Pavlic and colleagues (2021) utilized polymerase chain reaction to detect the presence of five periodontal pathogens (Porphyromonas gingivalis (P.g.), Aggregatibacter actinomycetemcomitans (A.a.), Tannerella forsythia (T.f.), Treponema denticola (T.d.), and Prevotella intermedia (P.i.)) in subgingival plaque and atherosclerotic plaques obtained from carotid and coronary arteries in patients who underwent aortocoronary bypass grafting and carotid endarterectomy. In atherosclerotic plaques of carotid arteries, P.g., A.a., T.f., T.d., and P.i. were detected in 26.7%, 6.7%, 66.7%, 10.0%, and 20.0% of cases, respectively. In coronary arteries, P.g. was found in 39.3%, A.a. in 25%, T.f. in 46.4%, T.d. in 7.1%, and P.i. in 35.7% of cases. This study not only allowed us to hypothesize a link between periodontopathogenic bacteria and atherosclerosis but also demonstrated a correlation between the detection of five periodontal pathogens in atherosclerotic carotid and coronary arteries and the degree of periodontal inflammation [24].

A nationwide retrospective cohort study in Taiwan investigating the association between carotid atherosclerosis and periodontitis revealed that male patients

with periodontitis had a significantly higher risk of developing atherosclerosis compared to those without a history of periodontitis [25].

Periodontal pathogens have been identified as major risk factors contributing to the pathogenesis of atherosclerosis. This is supported by the results of epidemiological studies, as described in the work of Huang, X., and colleagues (2023). Epidemiological evidence suggests a strong association between periodontitis and an increased risk of atherosclerosis and cardiovascular events. Atherosclerotic plaques contain a variety of periodontal pathogens, including Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Fusobacterium nucleatum. The study delves into the mechanisms by which these pathogens contribute to AS, including endothelial damage, immune response activation, and foam cell formation, highlighting the need for further investigation [26].

Clinical and microbiological research conducted by Mazur I.P. et al. provides evidence of periodontal pathogen DNA in cardiac valve tissue. The study found that 100% of patients with valvular heart disease undergoing cardiac surgery had generalized periodontitis of varying severity. The high level of gingival bleeding on probing (mean ± SD: 2.93 ± 0.07) was likely due to systemic antiplatelet therapy. The study found that 100% of patients had both staphylococci and streptococci in their periodontal pockets and heart valves. The high prevalence of periodontal pathogens identified in both periodontal pockets and excised heart valves using real-time PCR suggests a significant risk of hematogenous spread, transient bacteremia, and infective endocarditis. A significantly higher prevalence of P. gingivalis was observed in both periodontal pockets (86.7±12.4%) and heart valves (60.0±17.8%) ($p < 0.01$). A diverse range of bacteria, including T. denticola (40.0%), T. forsythia (36.7%), P. intermedia (10.0%), and A. actinomycetemcomitans (10%), were identified in heart valves. The presence of periodontal pathogens in aortic and mitral heart valves may contribute to a worsening of heart disease and heart failure [27].

Patients with advanced periodontitis who experience recurrent abscesses are more likely to develop heart failure with reduced ejection fraction. The amount of plaque buildup has also been linked to an increased risk of atrial fibrillation [14, 28, 29].

Hypertension, defined as a systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg, is the most common cardiovascular disease. Prospective studies have shown a significant association between periodontal disease and an increased risk of developing hypertension, with a hazard ratio of 1.68 (95% CI: 0.85-3.35). Patients with periodontal disease had significantly higher mean systolic blood pressure (SBP) [weighted mean difference (WMD) 4.49 mmHg; 95% CI: 2.88-6.11] and diastolic blood pressure (DBP) (2.03 mmHg; 95% CI: 1.25-2.81) compared to those without periodontal disease [30]. Cross-sectional studies have consistently demonstrated a positive association between the extent of tooth loss and the prevalence of hypertension, with individuals experiencing greater tooth loss exhibiting higher systolic blood pressure. A statistically significant association between tooth loss and the development of hypertension has been consistently demonstrated in meta-analyses [31].

CONCLUSIONS

The findings of our review of the current scientific literature support the following conclusions:

- the rising rates of periodontal diseases and cardiovascular diseases, and their associated comorbidities, highlight the urgent need for further research and interventions in public health;
- new data emerging from updated research on the pathogenesis of periodontal disease highlights its systemic implications as an infectious process;
- periodontal care for patients with cardiovascular diseases needs further scientific investigation and practical refinement.

REFERENCES

1. Wilkins E. et al. European cardiovascular disease statistics 2017. European Heart Network. https://ehnheart.org/about-cvd/the-burden-of-cvd/ [Accessed 23 July 2024]
2. Townsend N, Kazakiewicz D, Wright LF et al. Epidemiology of cardiovascular disease in Europe. Nat Rev Cardiol. 2022;19:133–143. doi: 10.1038/s41569-021-00607-3. DOI
3. Nedkoff L, Briffa T, Zemedikun D et al. Global Trends in Atherosclerotic Cardiovascular Disease. Clin Ther. 2023;45(11):1087-1091. doi: 10.1016/j.clinthera.2023.09.020. DOI
4. Adam T, Pano V, Nick T et al. European Society of Cardiology, on behalf of the Atlas Writing Group, European Society of Cardiology: cardiovascular disease statistics 2021. Eur Heart J. 2022;43(8):716–799. doi: 10.1093/eurheartj/ehab892. DOI
5. Rynhach NO, Vlasyk LY. Zminy u strukturi smertnosti v Ukraini: realni ta prohnozovani. [Changes in the structure of mortality in Ukraine: real and forecasted]. Visnyk sotsialnoi hihiieny ta orhanizatsii okhorony zdorovia Ukrainy. 2022;2(92):25-31. (Ukrainian)

6. Mishchenko LA, Sokolova LK. Osoblyvosti perebihu ta likuvannia arterialnoi hipertenzii, tsukrovoho diabetu i khronichnoi khvoroby nyrok u stresovykh umovakh voiennoho chasu. [Peculiarities of the course and treatment of arterial hypertension, diabetes and chronic kidney disease in the stressful conditions of wartime]. Hypertension. 2022;15(3-4):30-38. (Ukrainian)
7. Kong P, Cui ZY, Huang XF et al. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention. Signal Transduct Target Ther. 2022;7(1): 131. doi: 10.1038/s41392-022-00955-7. DOI
8. Perrotta I. Atherosclerosis: From Molecular Biology to Therapeutic Perspective. Int J Mol Sci. 2022;23(7):3444. doi: 10.3390/ijms23073444.
9. Bułdak Ł. Cardiovascular Diseases-A Focus on Atherosclerosis, Its Prophylaxis, Complications and Recent Advancements in Therapies. Int J Mol Sci. 2022;23(9):4695. doi: 10.3390/ijms23094695. DOI
10. Beck J, Garcia R, Heiss G et al. Periodontal Disease and Cardiovascular Disease. J Periodontol. 1996;67:1123-1137. doi: 10.1902/jop.1996.67.10s.1123. DOI
11. Sloboda MT, Minko LIu. Systemni zakhvoriuvannia yak faktor ryzyku prohresuvannia zakhvoriuvan parodonta: (ohliad literatury). [Systemic diseases as a risk factor for the progression of periodontal diseases: (literature review)]. Klinichna Stomatolohiia. 2022;(3):23–30. doi: 10.11603/2311-9624.2022.3.13238. (Ukrainian) DOI
12. Scannapieco FA, Cantos A. Oral inflammation and infection, and chronic medical diseases: implications for the elderly. Periodontol 2000. 2016;72(1):153-75. doi: 10.1111/prd.12129. DOI
13. Nemesh OM, Honta ZM, Slaba OM, Shylivskyi IV. Pathogenetic mechanisms of comorbidity of systemic diseases and periodontal pathology. Wiad Lek. 2021;74(5):1262-1267. doi: 10.36740/WLek202105140. DOI
14. Altamura S, Del Pinto R, Pietropaoli D, Ferri C. Oral health as a modifiable risk factor for cardiovascular diseases. Trends Cardiovasc Med. 2023;23:1050-1738. doi: 10.1016/j.tcm.2023.03.003. DOI
15. Pussinen PJ, Könönen E. Oral health: A modifiable risk factor for cardiovascular diseases or a confounded association? Eur J Prev Cardiol. 2016;23(8): 834-8. doi: 10.1177/2047487316636506. DOI
16. Aarabi G, Heydecke G, Seedorf U. Roles of Oral Infections in the Pathomechanism of Atherosclerosis. Int J Mol Sci. Jul. 2018;19(7):1978. doi: 10.3390/ijms19071978. DOI
17. Di Stefano M, Polizzi A, Santonocito S et al. Impact of Oral Microbiome in Periodontal Health and Periodontitis: A Critical Review on Prevention and Treatment. Int J Mol Sci. 2022;23(9):5142. doi: 10.3390/ijms23095142. DOI
18. Belibasakis GN, Belstrøm D, Eick S et al. Periodontal microbiology and microbial etiology of periodontal diseases: Historical concepts and contemporary perspectives. Periodontol 2000. 2022;00:1-17. doi: 10.1111/prd.12473. DOI
19. Liu Y, Huang W, Wang J et al. Multifaceted Impacts of Periodontal Pathogens in Disorders of the Intestinal Barrier. Front Immunol. 2021;12:693479. doi: 10.3389/fimmu.2021.693479. DOI
20. Luis Muñoz-Carrillo J, Elizabeth Hernández-Reyes V, Eduardo García-Huerta O et al. Pathogenesis of Periodontal Disease. IntechOpen. 2019. doi: 10.5772/intechopen.86548. DOI
21. Haraszthy VI, Zambon JJ, Trevisan M et a;. Identification of periodontal pathogens in atheromatous plaques. J Periodontol. 2000;71(10):1554-60. doi: 10.1902/jop.2000.71.10.1554. DOI
22. Dankevych-Kharchyshyn IS, Vynogradova OM, Malko NV et. al. Periodontal diseases and atherosclerosis (literature review). Wiad Lek. 2019;72(3):462-465.
23. Corredor Z, Suarez-Molina A, Fong C et al. Presence of periodontal pathogenic bacteria in blood of patients with coronary artery disease. Sci Rep. 2022;12(1):1241. doi: 10.1038/s41598-022-05337-1. DOI
24. Pavlic V, Peric D, Kalezic IS et al. Identification of Periopathogens in Atheromatous Plaques Obtained from Carotid and Coronary Arteries. Biomed Res Int. 2021:9986375. doi: 10.1155/2021/9986375. DOI
25. Tong C, Wang YH, Chang YC. Increased Risk of Carotid Atherosclerosis in Male Patients with Chronic Periodontitis: A Nationwide Population-Based Retrospective Cohort Study. Int J Environ Res Public Health. 2019;16(15):2635. doi: 10.3390/ijerph16152635. DOI
26. Huang X, Xie M, Lu X et. al. The Roles of Periodontal Bacteria in Atherosclerosis. Int. J. Mol. Sci. 2023;24(1):2861. doi: 10.3390/ijms241612861. DOI
27. Mazur IP, Vitovskyi RM, Slobodianyk MV. Poshyrenist parodontopatohennoi mikroflory v patsiientiv iz klapannoiu patolohiieiu sertsevo-sudynnoi systemy. [Prevalence of periodontopathogenic microflora in patients with valvular pathology of the cardiovascular system]. Suchasna stomatolohiia. 2018;2:24-30. (Ukrainian)
28. Walther C, Wenzel JP, Schnabel RB et. al. Association between periodontitis and heart failure in the general population. ESC Heart Fail. 2022;9(6):4189–97. doi: 10.1002/ehf2.14150. DOI
29. Struppek J, Schnabel RB, Walther C et al. Periodontitis, dental plaque, and atrial fibrillation in the Hamburg City Health Study. PLoS ONE. 2021;16(11). doi: 10.1371/journal.pone.0259652. DOI
30. Muñoz Aguilera E, Suvan J, Buti J et al. Periodontitis is associated with hypertension: a systematic review and meta-analysis. Cardiovascular Research. 2020;116(1):28–39. doi: 10.1093/cvr/cvz201. DOI
31. Tada A, Tano R, Miura H. The relationship between tooth loss and hypertension: a systematic review and meta-analysis. Sci Rep. 2022;12(1):13311. doi: 10.1038/s41598-022-17363-0. DOI

CONFLICT OF INTEREST
The Authors declare no conflict of interest

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REVIEW ARTICLE

CONTENTS

Epidemiology, treatment and diagnosis of Hepatitis C virus infections

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ABSTRACT

Aim: Studding several aspects of Hepatitis C virus infection, such as epidemiology, prevalence, diagnosis, and outcome of patients with hepatitis C infection.
Materials and Methods: Systematic review of electronic medical records and epidemiological data and risk factors for Hepatitis C virus infection in patients evaluated in relevant studies.
Conclusions: Hepatitis C virus serology and viral genotyping. Hepatitis B may be associated with risk factors such as perinatal infection, kidney disease, dialysis, intravenous or percutaneous drug use, occupational factors, suddenly local population factors of hepatitis transmission and pay children. These young and vulnerable cultures bear the enormous social, economic, and political costs of Hepatitis C virus infection. Therefore, to combat the effects of Hepatitis C at regional and national levels, specific intervention approaches and policies are needed.

KEY WORDS: epidemiology, treatment, diagnosis, Hepatitis C, infections

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ABBREVIATIONS

HCV: Hepatitis C virus
HCC: Hepatocellular Carcinomas
DAAs: Direct-Acting Antiviral Medications
CIAs: Chemiluminescence Assays
NAT: Nucleic Acid Testing
EIAs: Enzyme Immunoassays
ECLs: Electrochemoluminescence Immunoassays
CLIAs: Chemiluminescence Immunoassays
RDTs: Rapid Diagnostic Tests

INTRODUCTION

According to WHO data, about one million new cases of HCV infection are recorded each year, with a 2.2% prevalence. Additionally, patients with HCV are thought to be responsible for 25% of HCC and 27% of cirrhosis globally. This type of infection is very common in poor nations, especially in those groups that were thought to be at hazard of contracting the HCV [1]. Simple population-based disease screening techniques and efficient therapies enable successful interventions to lower the burden of disease and ultimately eradicate viral hepatitis identifies a disabling social problem by 2030. It examines barriers in the 2015, World Health Organization ranking [2]. Chronic HCV infection influences 71.1 million people globally, or 1% (955% CI: 0.8–1.1) of the population, making it a global health issue. Intravenous drug use, hazardous injection procedures in hospitals, and direct blood-to-blood contact through blood transfusions are the most prevalent ways that HCV is transmitted [3]. In 2015, locations were the relative incidence of intercontinental HCV is 23.7 cases per 100,000 people (95% CI 21.3–28.7), or about 1.75 million new infections. There is evidence that about 2.3 million people living with HIV have experienced or are now experiencing HCV harms. HCV genotypes 1(44%) of patients, 3(25%) of patients, and 4 (15%) of patients are responsible for the intercontinental epidemic [4]. Thus, infection has been implicated in HCV pathogenesis, leading to the development of HCV [5]. HIV (human immunodeficiency virus) drug users who freely exchange syringes have seen an increase in HCV infections. When selecting a new therapy technique, several factors need to be considered, including the patient's age, gender, viral genotype, and related disorders. It seems that some preventative interventions are necessary for the high-risk population [6]. Documenting the generality

of HCV ill health in patients, documenting the epidemiology of viral hepatitis in various countries, summarizing pertinent published literature, and estimating the disease's potential burden based on available data were the objectives of the current study. Because this infection's frequency, diagnosis, and treatment should guide future research and aid in infection prevention measures. The majority of HCV infection-related events, including epidemiology, transmission, diagnosis, and patient outcomes, were discussed in this assessment. The citation databases PubMed and Scopus were used to conduct a narrative review search. Hepatitis C epidemiology, transmission, virology, prevalence by itself, and combinations were the keywords. The American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of Liver Disease (EASLD) were also searched [7].

AIM

The aim of this research was to investigate several aspects of HCV infection, such as epidemiology, prevalence, diagnosis and outcomes in patients with hepatitis C infection.

MATERIALS AND METHODS

A recently established procedure for HCV reviews served as the basis for the study's methodology. The main features of this methodology are described below. We conducted a systematic search of PubMed to identify published studies on the prevalence, diagnosis, treatment, and control of HCV in these countries.

REVIEW AND DISCUSSION

GLOBAL EPIDEMIOLOGY OF HCV INFECTIONS

An estimated 71 million people, or 1% of the world's population, were expected to have a chronic HCV infection. However, it was estimated that around 14 million people in the European Union/European Economic Area had a chronic HCV infection, indicating a comparatively higher incidence of 1.5% in this area [10]. An estimated 1.75 million people worldwide were newly infected with HCV in 2015, translating to a global incidence of 23.7 cases per 100,000 people (95% UI: 21.3–28.7). It surpassed the total estimated number of people who died from end-stage HCV infection (N = 399,000) and those who were treated (N = 843,000), which explains why the global epidemic is still spreading [11]. From 1995 to 2006, the government monitored the incidence of HCV in 13 Saudi Arabian administrative provinces. The number of cases reported to the MOH varied significantly by region, with Jizan having the lowest prevalence (0.016%) and Al-Baha and Jeddah having the highest (0.32%) per capita [12]. These findings are consistent with previous KSA investigations. For example, research of 557,815 Saudi citizens in the province of Riyadh revealed a 1.1% anti-HCV prevalence in adults, while blood screening results from 528 blood donors in the Jeddah region showed a 1.7% prevalence of HCV infection [13]. HCV infection seems to be most common in the Middle East and North Africa (MENA) area globally [14]. HCV is a major problem in a few nations in the region, such as Egypt, where the prevalence is 14.7%, and Pakistan, where it is 4.8%.It is yet unclear how widespread the virus is in the nations of the Arabian Gulf [15, 16]. In terms of both population and land area, Saudi Arabia is the biggest nation in the region. Out of the 120 records that contained 442 HCV prevalence measures from this nation, 81 were found in high-risk groups, 32 in intermediate-risk groups, 60 in specific clinical groups, and 269 in general populations [17]. The prevalence of HCV was lower in developed nations like the United States (1.8%), Germany (0.6%), Canada (0.8%), France (1.1%), and Australia (1.1%) than in East Asia or North Africa. HCV prevalences in Indonesia and Pakistan were 2.1% and 6.5%, respectively, while those in China and India, which account for one-fifth of the global population, were 3.2% and 0.9% [18]. According to [19], a study on the prevalence of the HCV in the Iranian population found that just 0.5% of Iranians were infected with the virus, which is low when compared to other neighboring nations like Pakistan (5.1%) as well as caring for the sick.

DIAGNOSTIC TESTS OF HCV

IDENTIFICATION OF ANTI-HCV ANTIBODIES USING SEROLOGICAL TESTING

Detecting HCV infection usually begins with serological testing to find anti-HCV antibodies [20]. Blood antibodies against HCV are usually detected two or three months after virus exposure. Antibody testing for HCV includes chemiluminescence assays (CIAs), enzyme immunoassays (EIAs), and rapid diagnostic tests (RDTs) [21]. Serological assays are frequently used as the first diagnostic technique to check for viral exposure and identify the host immune response (antibodies to HCV) or a viral antigen (HBsAg, HCVcAg) [22]. Hepatitis serological diagnostics based on the immunoassay principle include rapid diagnostic tests (RDTs), laboratory-based enzyme immunoassays (EIAs), and electrochemolumi-

nescence immunoassays (ECLs) and chemiluminescence immunoassays (CLIAs) [23]. Fast throughput, high precision, dependability, and cost-effectiveness are the primary benefits; full automation's technical simplicity for testing facilities suggests a high volume. Rapid diagnostic tests (RDTs) are less expensive than costly tests to use, are readily available, and can use capillary blood, serum, and plasma samples collected from handshakes. In extreme cases, they may also hire trained laypersons or expert demonstrators who do not require equipment using small incisions or venipuncture [24].

MOLECULAR TECHNIQUE FOR SCREENING HCV

An additional layer of blood safety is provided by nucleic acid testing (NAT), a molecular screening method for blood donations that reduces the risk of ITT for recipients. In the case of viral nucleic acids, NAT exhibits high sensitivity and specificity. It amplifies the viral ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) fragments. It reduces the time to infection by detecting HIV, HBV, and HCV earlier than with conventional screening techniques. The use of serological techniques to rectify donations that react improperly is another benefit of NAT, which is essential for donor counseling and information. Targeted NAT technologies help to reduce the window for HIV, HBV, and HCV. It has issues with costly excavation, consumables, infrastructure, and technical know-how, and it is very technical [25]. The frequency and generality of illnesses in the blood donor population, the resources that are available, and the proof of the advantages of using NAT in conjunction with serology testing all affect the necessity for NAT, thus, once the basic transfusion arrangement is complete, including donor withdrawal, donor notification, counseling, and quality-assured sensitive serologic techniques for TTI screening for infectious diseases by transfusion (TTI), included, and the decision to start NAT is considered to have to go [26].

TREATMENT OF CHRONIC HCV

Ribavirin and interferon boosted with polyethylene glycol are used to treat degenerative HCV unhealthiness. Treatment aims to prevent the improvement of cirrhosis and reduce or stop the advancement of fibrosis. It is predicated on indicators of a persistent virological response. In the approaching, a multidrug program might be developed to enhance current treatments. Patients who have a persistent HCV infection should abstain from alcohol. Alcohol consumption is safe for people infected with HCV, despite the lack of a vaccination to prevent infection [27]. Treatments are designed to help patient's live longer, symptom-free lives by preventing the emergence of tuberculosis and delaying or stopping its progression. An objective criterion utilized in the majority of studies to evaluate treatment success is the intervention's long-term results, which are linked to better outcomes, including decreased mortality, readmission risk, and risk of cirrhosis and breast cancer. The decision to continue treatment may be influenced by a number of circumstances, even if the objective is to treat people with chronic HCV infection [28]. A decreased likelihood of responding to treatment is linked to non-modifiable variables, including the degree of liver fibrosis, obesity, advanced age, Black or Latino race, high viral load, and genotype 1. People who are at least eighteen years old, willing to receive treatment, Treatment candidates for HCV infection typically include those who adhere to treatment guidelines, have compensatory cirrhosis or severe liver fibrosis, have abnormal serum alanine transaminase (ALT) values, have normal renal function, and are free of anemia or neutropenia. Baseline blood work should be performed before starting interferon therapy because it has been associated with autoimmune thyroiditis, thrombocytopenia, and leukopenia. This includes assessment of thyroid-stimulating hormone levels, a comprehensive metabolic panel, and a complete blood count. For patients with autoimmune hepatitis, decompensated cirrhosis, ongoing HCV infection and anemia, severe heart disease, untreated severe depression, and renal insufficiency, treatment is not suggested for pregnancy or untreated hyperthyroidism. Since ribavirin (Rebetol) is eliminated by the kidneys and should be administered with caution in patients with renal impairment, blood urea nitrogen and serum creatinine levels should be monitored. More interferons (Albinterferon alfa-2b and consensus interferon) and ribavirin alternatives (taribavirin) are being developed to improve the safety, efficacy, and tolerance of treatment for chronic HCV infection [29]. Phase 3 clinical trials are currently being conducted to examine two novel protease inhibitors: boceprevir and telaprevir multidrug regimens will most likely be utilized in conjunction with ribavirin and interferon in the future [30, 31].

CONCLUSION

HCV treatment as a preventative measure will be a successful means of lowering the burden of Disease linked to HCV in the future as efficient IFN-free DAA regimens become more widely accessible. The current framework for PWID care and prevention must be expanded upon in any approach. Treating HCV as a prophylactic approach is only one aspect of the problem; another is

increasing access to HCV testing and care. A comprehensive approach combining population-based and individual-level strategies will be required to control and ultimately eradicate HCV transmission and illness. To ascertain the best way to distribute services, cost-effectiveness analyses are required.

REFERENCES

1. Alter MJ. Epidemiology of hepatitis C virus infection. World journal of gastroenterology: WJG. 2007;13(17):2436. doi: 10.3748/wjg.v13.i17.2436. DOI
2. WHO: Global health sector strategy on viral hepatitis 2016-2021. https://www.who.int/hepatitis/ strategy2016-2021/ghss-hep/en/. [Accessed 26 March 2024]
3. Moosavy SH, Davoodian P, Nazarnezhad MA et al. Epidemiology, transmission, diagnosis, and outcome of Hepatitis C virus infection. Electronic physician. 2017;9(10):5646–5656. doi: 10.19082/5646. DOI
4. Nguyen LH, Nguyen MH. Systematic review: Asian patients with chronic hepatitis C infection. Aliment Pharmacol Ther. 2013;37(10):921-36. doi: 10.1111/apt.12300. DOI
5. Mondelli MU, Cerino A, Cividini A. Acute hepatitis C: diagnosis and management. J Hepatol. 2005;42(1):108-14. doi: 10.1016/j.jhep.2004.10.017. DOI
6. Roudot-Thoraval F. Epidemiology of hepatitis C virus infection. Clin Res Hepatol Gastroenterol. 2021;45:101596. doi: 10.1016/j.clinre.2020.101596. DOI
7. World Health Organization. Global health sector strategy on viral hepatitis 2016–021. 2016. https://www.emcdda.europa.eu/system/files/attachments/9478/WHO-HIV-2016.06-eng.pdf. [Accessed 26 March 2024]
8. Health Organization. Update recommendations on simplified service delivery and diagnostics for hepatitis C infection. 2022. https://www.who.int/publications/i/item/9789240052697. [Accessed 26 March 2024]
9. Reipold EI, Trianni A, Krakower D et al. Values, preferences and current hepatitis B and C testing practices in low- and middle-income countries: results of a survey of end users and implementers. BMC Infect Dis. 2017;17(1):702.
10. Sallam TA, Tong CYW, Cuevas LE et al. Prevalence of blood-borne viral hepatitis in different community in Yemen. Epidemiology and Infection. 2003;131(1):771–5. doi: 10.1017/s0950268803008653. DOI
11. Al-Waleedi AA, Khader YS. Prevalence of hepatitis B and C infections and associated factors among blood donors in Aden city, Yemen. East Mediterr Health J. 2012;18(6):624-9. doi: 10.26719/2012.18.6.624. DOI
12. Chaabna K, Kouyoumjian SP, Abu-Raddad LJ. Hepatitis C Virus Epidemiology in Djibouti, Somalia, Sudan, and Yemen: Systematic Review and Meta-Analysis. PLoS One. 2016;11(2):e0149966. doi: 10.1371/journal.pone.0149966. DOI
13. Lewis KC, Barker LK, Jiles RB, Gupta N. Estimated prevalence and awareness of hepatitis C virus infection among US Adults: National Health and Nutrition Examination Survey, January 2017– March 2020. Clinical Infectious Diseases. 2023;77:1413–5. doi: 10.1093/cid/ciad411. DOI
14. Zou B, Yeo YH, Le MH et al. Prevalence of Viremic Hepatitis C Virus Infection by Age, Race/Ethnicity, and Birthplace and Disease Awareness among Viremic Persons in the United States, 1999-2016. J Infect Dis. 2020;221(3):408-418. doi: 10.1093/infdis/jiz479. DOI
15. World Health Organization. Global hepatitis report 2024: action for access in low and middle-income countries. Geneva: World Health Organization. 2024.
16. Schröeder SE, Pedrana A, Scott N et al. Innovative strategies for the elimination of viral hepatitis at a national level: a country case series. Liver Int. 2019;39:1818–36. doi: 10.1111/liv.14222. DOI
17. Thursz M, Fontanet A. HCV transmission in industrialized countries and resource-constrained areas. Nat Rev Gastroenterol Hepatol. 2014;11:28–35. doi: 10.1038/nrgastro.2013.179. DOI
18. Shah R, Agyei-Nkansah A, Alikah F et al. Hepatitis C virus in sub-Saharan Africa: a long road to elimination. Lancet Gastroenterol Hepatol. 2021;6:693–4. doi: 10.1016/S2468-1253(21)00224-7. DOI
19. Chevaliez S, Roudot-Thoraval F, Brouard C et al. Clinical and virological features of chronic hepatitis B in the French national surveillance program, 2008–2012: A cross-sectional study. JHEP Reports. 2022;4(12):100593. doi: 10.1016/j.jhepr.2022.100593. DOI
20. Shyamala V. Factors in enhancing blood safety by nucleic acid technology testing for human immunodeficiency virus, hepatitis C virus and hepatitis B virus. Asian J Transfus Sci. 2014;8:13-18. doi: 10.4103/0973-6247.126682. DOI
21. Bruno S, Stroffolini T, Colombo M et al. Italian Association of the Study of the Liver Disease. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007;45(3):579-587. doi: 10.1002/hep.21492. DOI
22. Hung CH, Lee CM, Lu SN et al. Long-term effect of interferon alpha2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. J Viral Hepat. 2006;13(6):409-414. doi: 10.1111/j.1365-2893.2005.00707.x. DOI

23. Strader DB, Wright T, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. Hepatology. 2004;39(4):1147-1171. doi: 10.1002/hep.20119. DOI
24. Backus LI, Boothroyd DB, Phillips BR, Mole LA. Predictors of response of US veterans to treatment for the hepatitis C virus. Hepatology. 2007;46(1):37-47. doi: 10.1002/hep.21662. DOI
25. Rodriguez-Torres M, Sulkowski MS, Chung RT et al. Factors associated with rapid and early virologic response to peginterferon alfa-2a/ribavirin treatment in HCV genotype 1 patients representative of the general chronic hepatitis C population. J Viral Hepat. 2010;17(2):139-147. doi: 10.1111/j.1365-2893.2009.01157.x. DOI
26. McHutchison JG, Lawitz EJ, Shiffman ML et al. IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med. 2009;361(6):580-593. doi: 10.1056/NEJMoa0808010. DOI
27. Cholongitas E, Papatheodoridis GV. Review article: novel therapeutic options for chronic hepatitis C. Aliment Pharmacol Ther. 2008;27(10):866-884. doi: 10.1111/j.1365-2036.2008.03644.x. DOI
28. Njoroge FG, Chen KX, Shih NY, Piwinski JJ. Challenges in modern drug discovery: a case study of boceprevir, an HCV protease inhibitor for the treatment of hepatitis C virus infection. Acc Chem Res. 2008;41(1):50-59. doi: 10.1021/ar700109k. DOI
29. Chen KX, Nair L, Vibulbhan B et al. Second-generation highly potent and selective inhibitors of the hepatitis C virus NS3 serine protease. J Med Chem. 2009;52(5):1370-9. doi: 10.1021/jm801238q. DOI
30. Lewis KC, Barker LK, Jiles RB, Gupta N. Estimated prevalence and awareness of hepatitis C virus infection among US Adults: National Health and Nutrition Examination Survey, January 2017– March 2020. Clinical Infectious Diseases. 2023;77:1413–5. doi: 10.1093/cid/ciad411. DOI
31. Messina V, Pisaturo M, Alessio L et al. Hepatitis C virus (HCV) micro-elimination in the hospital setting: The results of the HCV Caserta hospital project. Journal of Infection and Public Health. 2022;15(5):562-565. doi: 10.1016/j.jiph.2022.04.003. DOI

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CASE STUDY

CONTENTS

Acute coronary syndrome in post-partum period: challenge for differential diagnosis and proper management

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ABSTRACT

The patient was presented with chest pain, new ECG changes indicating ischemia, an increase in troponin and NT pro BNP, elevated D-dimer levels, and wall motion abnormalities on an Echo. A chest computed tomography angiography did not show pulmonary embolism but revealed a sac-like aneurysm of the left anterior descending artery (LAD). The coronary angiogram confirmed an aneurysm of the LAD in 6-7 segments, along with an extended 80% stenosis of the a. intermedia. The interventional cardiology team concluded that the patient required coronary artery bypass grafting (CABG) due to extensive vessel damage. She underwent CABG three months after acute coronary syndrome in an experienced center.

KEY WORDS: Acute coronary syndrome, coronary artery aneurysm, post partum period

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INTRODUCTION

Despite significant improvement in cardiovascular outcomes in the nonpregnant population, maternal mortality due to cardiac disease has not decreased in almost 20 years, especially for acute coronary syndrome (ACS)[1]. Although ACS is rare during pregnancy and postpartum period, it still increases the risk of acute myocardial infarction (AMI) 3- to 4-fold [2]. It accounted for more than 20% of all cardiac deaths in the latest UK triannual enquiry [3]. AMI is often caused by atherosclerotic coronary artery disease (CAD). This risk increases with factors such as smoking, older maternal age, hypertension, diabetes mellitus, obesity, and dyslipidemia. [4,5]. It is expected that the incidence of ACS will increase in the coming years because the pregnant population is becoming older, more overweight, and with more medical co-morbidities [2]. The cause of the higher susceptibility to ACS during pregnancy or early postpartum period is not entirely clear, but it may be due to hormonal influence (especially oestrogen and progesterone), an increase in vessel shear stress caused by pregnancy and labour, as well as hypercoagulability that persists for weeks after delivery [6].

The causes of ACS are more often non-atherosclerotic, including coronary artery dissection, coronary artery spasm, and coronary thrombosis [7]. Chest pain during pregnancy and in the postpartum period can have a wide range of possible causes, but ACS should be considered as one of them. The similarity between pregnancy-related symptoms and those of ACS may lead to a delayed diagnosis. Additionally, ECG changes during pregnancy and postpartum period, which involve inverted T-waves, can further complicate the diagnosis. However, it is worth noting that serum troponins are typically not affected, although they may be found in cases of pre-eclampsia [8].

CASE REPORT

A 35-year-old female presented to our department approximately two weeks postpartum after a term, singleton vaginal delivery with a chief complaint of a squeezing chest discomfort, radiating to both arms, started after physical activity. Associated symptoms were shortness of breath and palpitations at rest. She had no known risk factors for atherosclerotic disease, smoking, alcohol or drugs abuse and no history of any connective tissue disorder or infectious diseases. The course of her pregnancy had been uncomplicated.

On admissiom her respiratory rate was 22/min, heart rate – 90/min, blood pressure – 140/90 mm of Hg, oxygen saturation – 94 % on room air, temp. – 36.6°C, BMI – 28 kg/m2. Chest auscultation did not reveal any obvious abnormal heart murmurs. ECG demonstrated ST segment elevation in II, III, AVF and ST segment depression with T wave inversion in V2-V3 leads (Fig.1). Bedside transthoracic echocardiography showed intra-ventricular septal dyssynchrony and hypokinesia of basal and middle segments of anterior wall of left ventricle with preserved ejection fraction 55 %. Cardiac biomarkers were found to be elevated on the day of admission: high-sensitivity troponin T – 334 ng/l (0-24.5

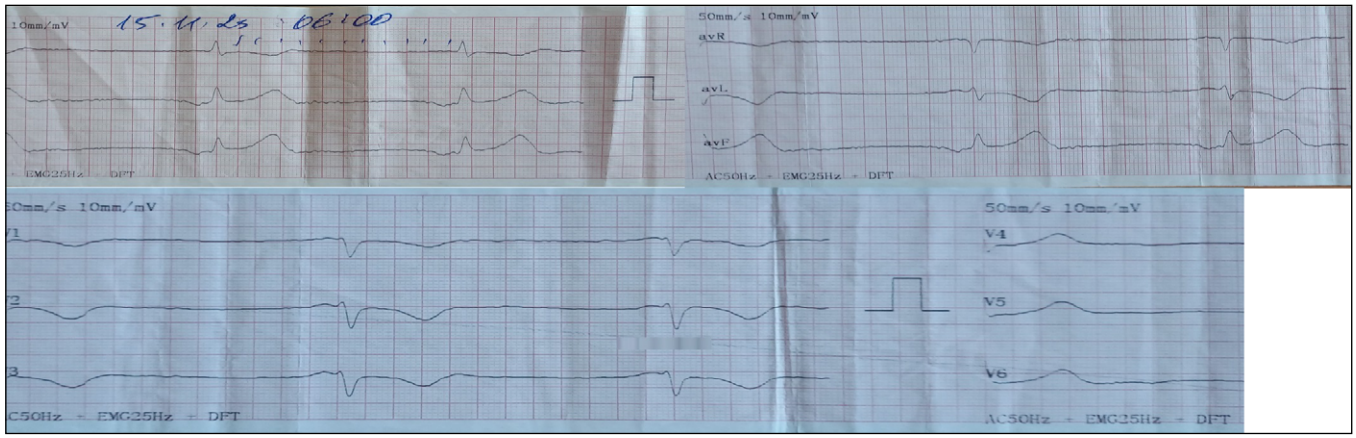

Fig. 1. Initial ECG.

ng/l), NT pro BNP – 700.3 pg/ml (0-125 pg/ml), D-dimer – 3.25 mcg/ml (< 0.5 mkg/ml), C reactive protein 18.92 mg/ml (< 5.0 mg/ml).

The main differential diagnosis were ACS, pulmonary embolism, myocarditis. A chest computed tomography angiography (CTA) did not reveal pulmonary embolism but showed sac-like aneurysm of left anterior descendent artery (LAD) 13 mm in diameter (Fig.2, Fig.3). Coronary angiogram revealed aneurysm of LAD in 6-7 segments, extended 80 % stenosis of a. intermedia and 40 % stenosis of right coronary artery (RCA) in 1 segment (Fig.4).

Upon consultation with cardiothoracic surgery, the interventional cardiology team determined that the patient required coronary artery bypass grafting due to extensive vessel damage. The breastfeeding was discontinued, and she was started on a double anti-platelet therapy.(aspirin 100 mg and clopidogrel 75 mg), enoxaparin 0.6 ml twice daily, nebivolol 2,5 mg, enalapril 5 mg and rozuvastatin 10 mg. In 2 weeks ECG after the event showed resolution of MI pattern (Fig.5). She underwent CABG in 3 monthes after ACS in experienced centre. During follow up the patient remains asymptomatic.

The presence of coronary artery aneurysm (CAA) or ectasia has been associated with poor long-term outcomes irrespective of the presence of concomitant atherosclerotic coronary artery disease [10]. Clinical presentations range from incidental finding on cardiac imaging to ACS [11]. The pathogenesis of CAA is not clear. However, there can be associations between certain risk factors in particular:

- an individual genetic susceptibility in patients with congenital CAA [12].
- systemic connective tissue diseases with vasculitis (e.g., Kawasaki disease, Marfan, and so on)
- atherosclerosis lesion
- iatrogenic CAA caused by intracoronary manipulation (PCI, brachytherapy etc)
- post-infectious CAAs due to infectious direct wall invasion or immune complex deposition [10].

Thrombosis and distal embolization are the most likely causes of an ACS-like presentation in patients with CAA but without underlying coronary artery obstruction or atherosclerosis. Thrombosis usually develops in the aneurysm, which is often asymptomatic. Patients start experiencing symptoms when the thrombus either spreads and blocks the coronary artery, usually proximal to the aneurysm, or breaks apart and gets lodged in a distal artery causing an embolic phenomenon [13].

Coronary aneurysm can be a result of obstructive ischemic coronary artery disease with decreased flow volume. This can lead to exercise-induced myocardial ischemia [14]. The coronary flow reserve is also significantly reduced in coronary aneurysms [15].

Dilatation of the coronary arteries can lead to disturbed coronary flow, which in turn can increase blood viscosity and activate coagulation. This pathophysiological element may cause thrombotic occlusion of ectatic coronary arteries. Another possible mechanism is the elevated level of inflammatory cytokines in CAE subjects, which can activate the coagulation cascade and increase the risk of acute coronary events. [16].

Matrix metalloproteinases (MMPs) have been shown to be involved in the pathogenesis of CAA formation by causing increased proteolysis of extracellular matrix proteins [17]. The MMP-3 5A allele is linked with higher promoter activity for transcription of the gene, and is more frequently seen in patients with CAA and atherosclerosis compared to patients with only coronary atherosclerosis.[18, 20]. The presence of CAA can predict future cardiac events in patients with acute MI. As a result, these patients might benefit from a pharmacological approach to controlling the coagulation cascade [19].

IMAGING OF CAA

Coronary angiography is considered the most reliable diagnostic tool for the detection of CAA. It is also useful

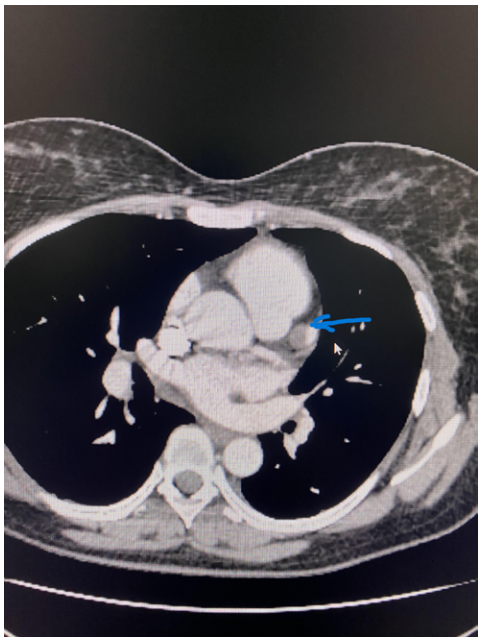

Fig. 2. CT angiography 1.

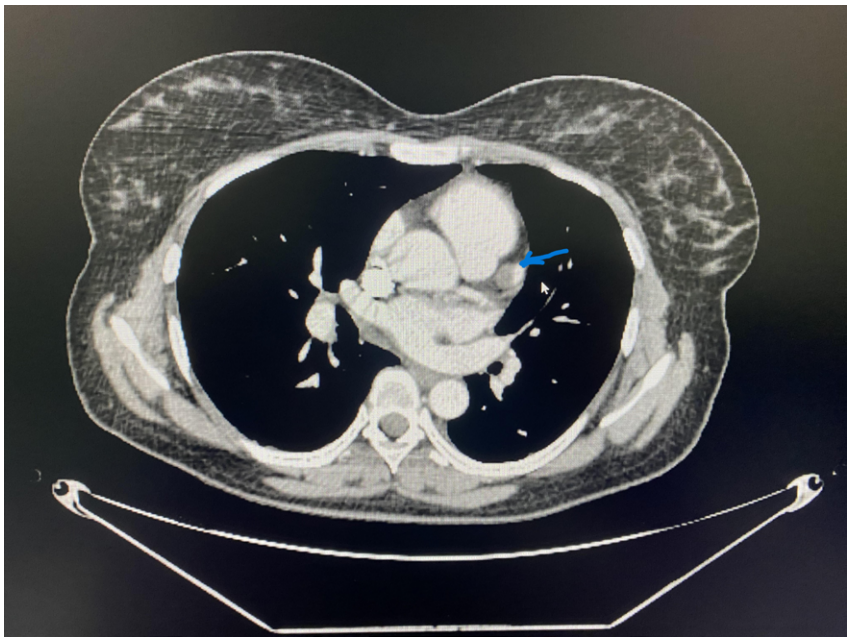

Fig. 3. CT angiography 2.

in determining the optimal strategy for surgical resection. Other imaging modalities include transthoracic echocardiography, ECG-gated CT angiography, MRI and/or MR angiography, and angiographic cardiac catheterization [21]. Proper imaging helps to evaluate aneurysm shape and structure, its morphology (fusiform or saccular), diameter, wall calcification, luminal thrombosis, presence of associated stenosis, origin and termination, monitoring of growth rate, exclude potential complications, myocardial perfusion abnormalities, fistula formation, extrinsic mass compression, rupture and hemopericardium [21]. CT coronary angiography is a highly sensitive tool for detecting CAAs and provides clear visualization of the coronary lumen. It highlights intraluminal thrombi. In our case, it was a superior imaging revealed the cause of ACS in our patient. CT coronary angiography yields a versatile post-processing: maximum intensity projections, curved multiplanar reformations and 3D volume rendering clearly identify the anatomical relationships of the aneurysm with the surrounding structures [20, 22]. Intravascular ultrasound (IVUS) is a highly reliable technique used to produce clear images of the coronary arteries. It provides information about the composition of the lumen and arterial wall structure, making it an effective tool in differentiating between true and false aneurysms caused by plaque rupture. IVUS is considered the "gold standard" technique for this purpose [20, 23].

TREATMENT MANAGEMENT OF CAA

The treatment of CAA involves medical management, surgical resection, and stent placement. However, the appropriate treatment for CAAs depends on the specific clinical situation. Currently, there are no randomized trials to evaluate different management strategies and their outcomes in these patients. Due to a high risk of thromboembolism, antiplatelet and anticoagulant medications should be administered [20]. In our case, the patient received enoxaparin, aspirin and clopidogrel at hospital and was discharged with dual antiplatelet therapy.

Excessive TGF-β and metalloproteinase have been linked to the development and progression of CAAs. Angiotensin II type-1 receptor antagonists can inhibit TGF-β [24]. Statins have been shown to inhibit the secretion of metalloproteinases 1, 2, 3, and 9 from macrophages and vascular smooth muscle cells [20]. Therefore, these drugs may be helpful in treating and preventing the progression of CAA. However, there are currently no long-term randomized data available.

In patients with ACS due to CAA culprit, the emphasis is to restore flow. Percutaneous coronary intervention of an aneurysmal/ectatic culprit vessel had lower procedural success and a higher incidence of no-reflow and distal embolization [10]. In cases where PCI is not a viable option for symptomatic patients, it is recommended to perform surgical excision or ligation of CAA along with bypass grafting of the affected coronary arteries [20, 25]. The surgical treatment of CAA is indicated in cases of severe coronary artery disease, when the aneurysms are located near the bifurcation of large branches, when there is evidence of emboli from the aneurysm to the distal coronary bed resulting in myocardial ischemia, when there is progressive enlargement of a CAA documented by serial angiographic measurements, and when there are complications such as fistula formation, compression of cardiac chambers, or giant

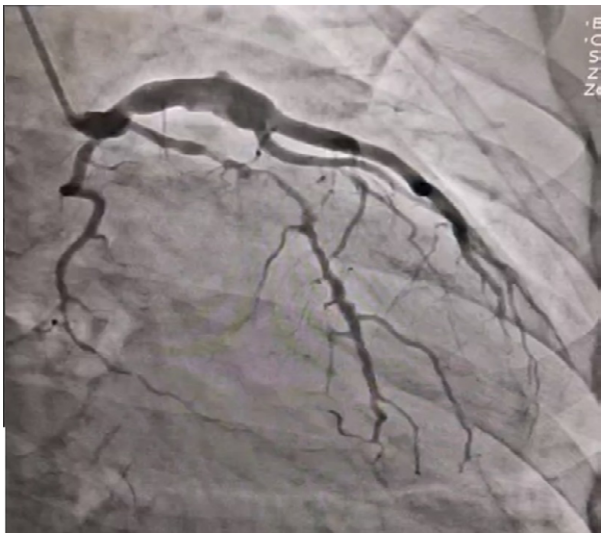

Fig. 4. Coronarography.

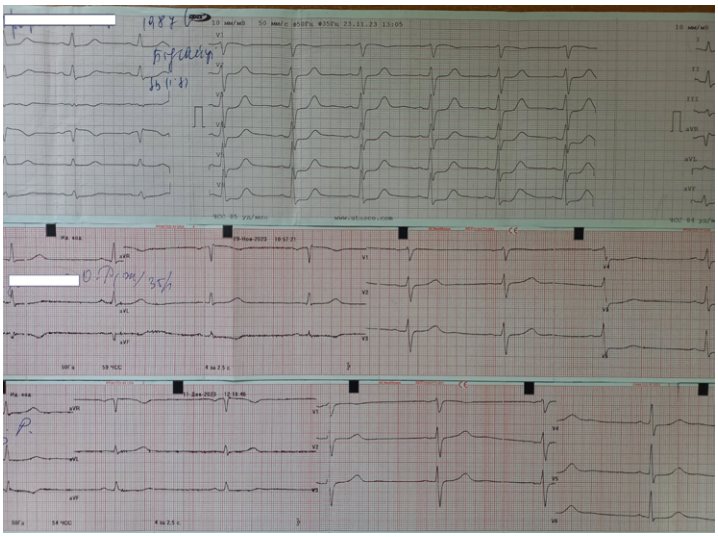

Fig. 5. Follow up ECG.

CAA (dilatation exceeding the reference vessel diameter by more than four times) [20].

CONCLUSIONS

Chest pain during pregnancy or in the postpartum period prompts a broad spectrum of differential diagnoses, and ACS should always be considered. CAA is a rare disorder, which can be presented as a random findings on cardiac imaging or ACS with life-threatening consequences. During the early postpartum period managing of CAA is still a challenge. It's crucial to know variants of clinical presentation, perform accurate imaging assessments and access interventional or surgical treatment to achieve optimal results. To improve patient care and outcomes, it's essential to conduct prospective studies and maintain registries.

REFERENCES

1. Freeman A, Squire G, Herrey A et al. Acute coronary syndromes in pregnancy: a literature review. Obstet Gynecol. 2023;25:101-109. doi:10.1111/tog.12861. DOI
2. Tubaro M et al. The ESC Textbook of Intensive and Acute Cardiovascular Care, 3 edn. The European Society of Cardiology Series. Oxford. 2021. doi:10.1093/med/9780198849346.001.0001. DOI
3. Knight M et al. Examining the impact of introducing ICD-MM on observed trends in maternal mortality rates in the UK 2003–13. BMC Pregnancy Childbirth. 2016;16:178. doi: 10.1186/s12884-016-0959-z. DOI
4. James AH et al. Acute myocardial infarction in pregnancy: a United States population-based study. Circulation. 2006;113:1564–71. doi: 10.1161/CIRCULATIONAHA.105.576751. DOI
5. Ladner HE, Danielsen B, Gilbert WM. Acute myocardial infarction in pregnancy and the puerperium: a population-based study. Obstet Gynecol. 2005;105:480–4. doi: 10.1097/01.AOG.0000151998.50852.31. DOI
6. Saw J et al. Spontaneous coronary artery dissection: prevalence of predisposing conditions including fibromuscular dysplasia in a tertiary center cohort. JACC Cardiovasc Interv. 2013;6:44–52. doi: 10.1016/j.jcin.2012.08.017. DOI
7. Elkayam U et al. Pregnancy-associated acute myocardial infarction: a review of contemporary experience in 150 cases between 2006 and 2011. Circulation. 2014;129:1695–702. doi: 10.1161/CIRCULATIONAHA.113.002054. DOI
8. Morton A, Morton A. High sensitivity cardiac troponin I levels in pre-eclampsia. Pregnancy Hypertens. 2018;13:79– 82. doi:10.1016/j.preghy.2018.04.020. DOI
9. Freeman A, Squire G, Herrey A et al. Acute coronary syndromes in pregnancy: a literature review. Obstet Gynecol. 2023;25:101-109. doi:10.1111/tog.12861. DOI
10. Kawsara A, Núñez Gil IJ, Alqahtani F et al. Management of Coronary Artery Aneurysms. JACC Cardiovasc Interv. 2018;11(13):1211-1223. doi: 10.1016/j.jcin.2018.02.041. DOI
11. Cohen P, O'Gara PT. Coronary artery aneurysms: a review of the natural history, pathophysiology, and management. Cardiol Rev. 2008;16(6):301-4. doi: 10.1097/CRD.0b013e3181852659. DOI
12. Abou Sherif S, Ozden Tok O, Taskoylu O et al. Coronary artery aneurysms: a review of the epidemiology, pathophysiology, diagnosis, and treatment. Front Cardiovasc Med. 2017;5:24. doi: 10.3389/fcvm.2017.00024. DOI

13. Pasha AK, Jokerst CE, Janardhanan R. Myocardial Infarction Related to a Coronary Artery Aneurysm. The American Journal of Medicine. 2015;128(2). doi:10.1016/j.amjmed.2014.10.017. DOI
14. Krüger D, Al Mokhtari NE, Wieckhorst A et al. Evidence of pathological coronary flow patterns in patients with isolated coronary artery aneurysms. Coron Artery Dis. 2008;19:249–255. doi: 10.1097/MCA.0b013e3283030b4b. DOI
15. Kruger D, ElMokhtari NE, Wieckhorst A et al. Intravascular ultrasound study and evidence of pathological coronary flow reserve in patients with isolated coronary artery aneurysms. Clin Res Cardiol. 2010;99:157–164. doi: 10.1007/s00392-009-0100-7. DOI
16. Brunetti ND, Salvemini G, Cuculo A et al. Coronary artery ectasia is related to coronary slow flow and inflammatory activation. Atherosclerosis. 2014;233:636–640. doi: 10.1016/j.atherosclerosis.2014.01.018. DOI
17. Newman KM, Ogata Y, Malon AM et al. Identification of matrix metalloproteinases 3 (stromelysin-1) and 9 (gelatinase B) in abdominal aortic aneurysm. Arterioscler Thromb. 1994;14:1315–20. doi: 10.1161/01.atv.14.8.1315. DOI
18. Lamblin N, Bauters C, Hermant X et al. Polymorphisms in the promoter regions of MMP-2, MMP-3, MMP-9 and MMP-12 genes as determinants of aneurysmal coronary artery disease. J Am Coll Cardiol. 2002;40:43–8. doi: 10.1016/s0735-1097(02)01909-5. DOI
19. Doi T, Kataoka Y, Noguchi T et al. Coronary Artery Ectasia Predicts Future Cardiac Events in Patients With Acute Myocardial Infarction. Arterioscler Thromb Vasc Biol. 2017;37(12):2350-2355. doi: 10.1161/ATVBAHA.117.309683. DOI
20. Sheikh AS, Hailan A, Kinnaird T et al. Coronary Artery Aneurysm: Evaluation, Prognosis, and Proposed Treatment Strategies. Heart Views. 2019;20(3):101-108. doi: 10.4103/HEARTVIEWS.HEARTVIEWS_1_19. DOI
21. Knipe H, Yap J, Buemi F et al. Coronary artery aneurysm. Radiopaedia. 2024. doi:10.53347/rID-37916. DOI
22. Forte E, Inglese M, Infante T et al. Anomalous left main coronary artery detected by CT angiography. Surg Radiol Anat. 2016;38:987–90. doi: 10.1007/s00276-016-1634-9. DOI
23. Sanidas EA, Vavuranakis M, Papaioannou TG et al. Study of atheromatous plaque using intravascular ultrasound. Hellenic J Cardiol. 2008;49:415–21.
24. Loeys BL, Schwarze U, Holm T et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med. 2006;355:788–98. doi: 10.1056/NEJMoa055695. DOI
25. Badmanaban B, Mallon P, Campbell N, Sarsam MA. Repair of left coronary artery aneurysm, recurrent ascending aortic aneurysm, and mitral valve prolapse 19 years after Bentall's procedure in a patient with Marfan syndrome. J Card Surg. 2004;19:59–61. doi: 10.1111/j.0886-0440.2004.02052.x. DOI

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CASE STUDY

CONTENTS

Role of diagnostic laparoscopy in abdominal disorders with uncertain diagnosis: a rare case report

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ABSTRACT

Female patient was hospitalized in the surgical of the Municipal Enterprise "2nd City Clinical Hospital of Poltava City Council" (Poltava, Ukraine) in 2023. The patient underwent a complete general clinical examination, a plain radiograph of the abdominal cavity, fibrogastroduodenoscopy, colonoscopy, ultrasound of the abdominal organs, CT scan of the abdominal organs. Diagnostic laparoscopy was performed to make a final diagnosis.

A plain radiography of the abdominal cavity revealed no pathology. Ultrasound of the abdominal organs revealed a pelvic mass. A computed tomography scan revealed damage to the pelvic organs in the form of a neoplasm and an enlargement of the left ovary. The preliminary diagnosis was a pelvic tumor, tumor of the left ovary. Diagnostic laparoscopy was performed to make the diagnosis. A rounded formation was defined in Douglas space. The capsule of the formation was opened and pus was released. The abscess wall was opened, and a foreign body (gauze pad) was removed from the cavity. The patient was discharged from the hospital in satisfactory condition on the fifth day after surgery.

The case we examined emphasizes that when assessing the nature of an intra-abdominal neoplasm, it is necessary to remember about foreign bodies, especially in patients after surgical interventions. Diagnostic laparoscopy is a technically advanced and minimally invasive procedure for the diagnosis and treatment of intra-abdominal gossypiboma.

KEY WORDS: foreign body, diagnostic laparoscopy, gossypiboma, abdominal cavity

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INTRODUCTION

Cancer is a major public health problem worldwide and the second leading cause of death in the United States [1]. Cancer accounts for 21% of all deaths in both men and women and is the second leading cause of death after heart diseases. However, it is the leading cause of death among women aged 40 to 79 years and men aged 60 to 79 years [1].

The main criterion for adequate treatment of patients with abdominal tumors is timely identification of the problem and accuracy of clinical diagnosis. That is why a comprehensive examination of the patient at the pre-hospital and hospital stages plays an important role in achieving the final result of treatment [2, 3].

Modern standards for diagnosing abdominal tumors in patients include: ultrasound examination of the abdominal cavity as a screening diagnostic method, magnetic resonance imaging, multislice computed tomography with intravenous contrast [2, 3]. However, the gold standard for diagnosing almost all types of malignant neoplasms is positron emission computed tomography (PET-CT) [4]. Its principle is to visualize the activity of the body at the cellular level, in contrast to Magnetic Resonance Imaging (MRI) and Multi-slice computed tomography (MSCT), which show only the structure of the organ [5, 6].

The main disadvantage of PET-CT in diagnosing tumors in Ukraine is the lack of sufficient necessary equipment to conduct such studies. Now in our country there are only four such tomographs [7]. At the same time, according to the European Association of Nuclear Medicine, for adequate diagnosis of the tumor process, one PET-CT device is needed to examine 1.5-2 million people [5].

In this regard, we proposed to use another method for the diagnosis and treatment of abdominal tumors, namely diagnostic laparoscopy, as an invasive method for diagnosing pathology of the abdominal and pelvic organs [8]. We use this diagnostic method in cases where other methods did not give an accurate result or their data differ significantly from each other. Diagnostic laparoscopy has a number of advantages: small wound

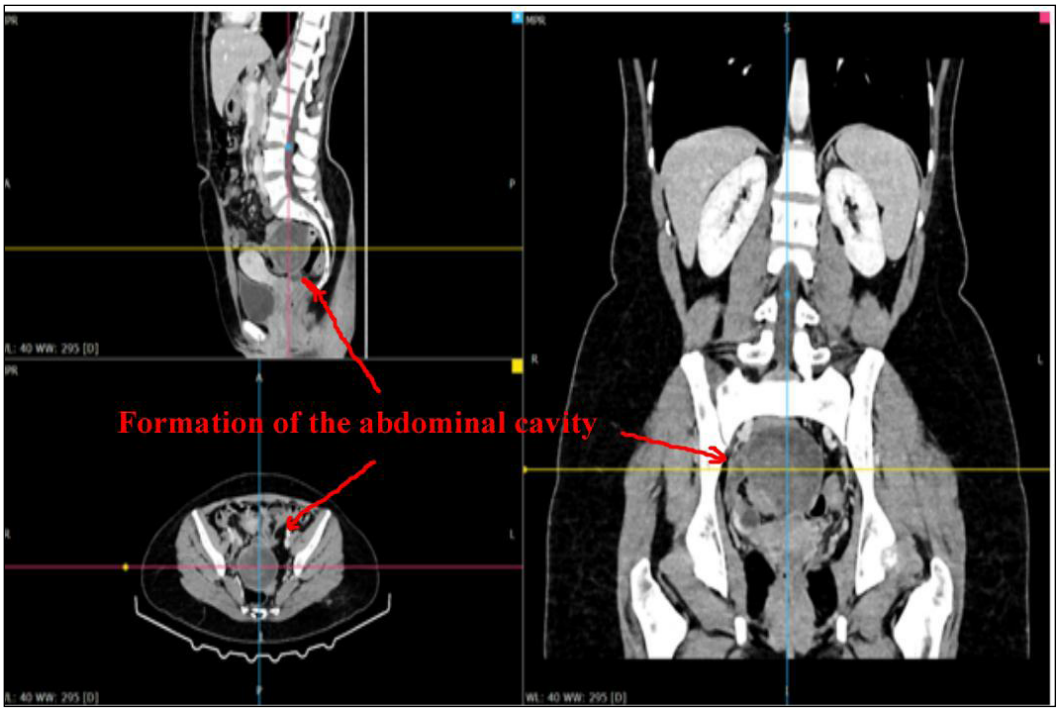

Fig.1. MSCT of the abdomen and pelvis: axial section and frontal section.

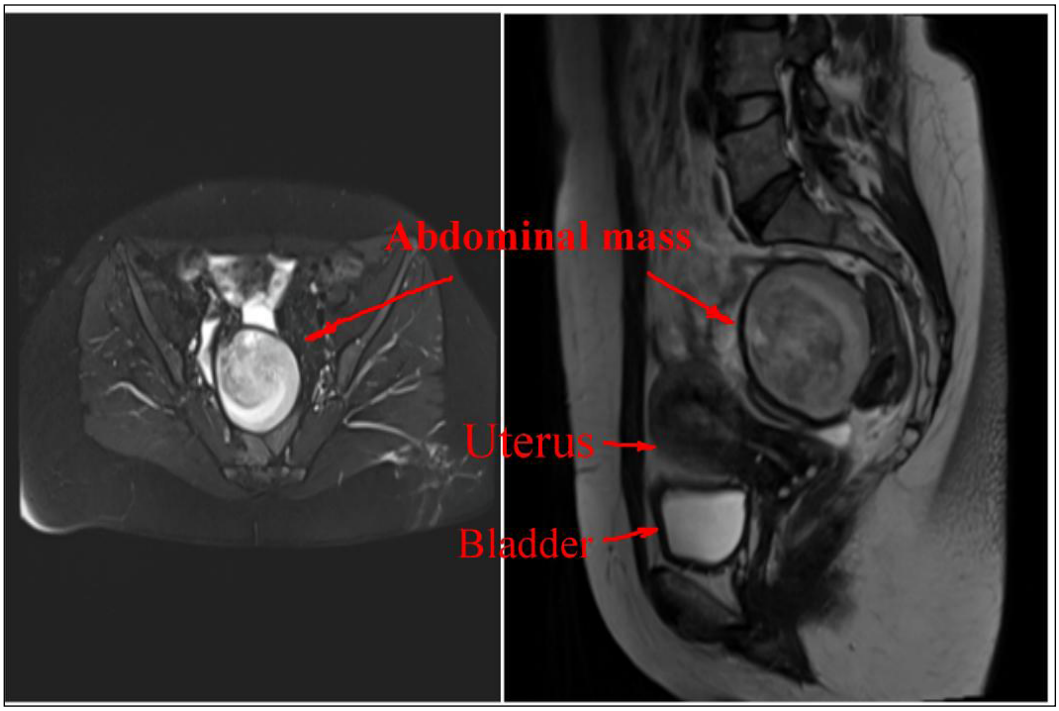

Fig. 2. MRI of the abdominal cavity. Abdominal mass.

sizes, rapid patient recovery, minimal risk of infection, absence of scars, and most importantly, the ability to perform a biopsy during the procedure [9, 10].

In some cases, abdominal tumors have to be differentiated from various foreign bodies, especially in those patients who have previously undergone surgical interventions [11, 12]. This differential diagnosis always causes great difficulties, even when using the entire range of non-invasive studies.

In the United States, more than 28 million surgical procedures are performed annually, and about 1.5 thousand cases of retained foreign bodies are detected among them. Foreign bodies in the abdominal cavity are a serious problem for surgeons and patients, with an average incidence of 0.3-1.0 cases per thousand abdominal surgeries [11]. Foreign bodies may appear immediately after surgery and require emergency surgery or remain undetected for months or years. All foreign bodies can cause various complications: pain, abscess, intestinal obstruction or perforation, gastrointestinal fistula, etc. [12].

Such foreign bodies in the abdominal cavity include gossypiboma [12, 13]. The term gossypiboma

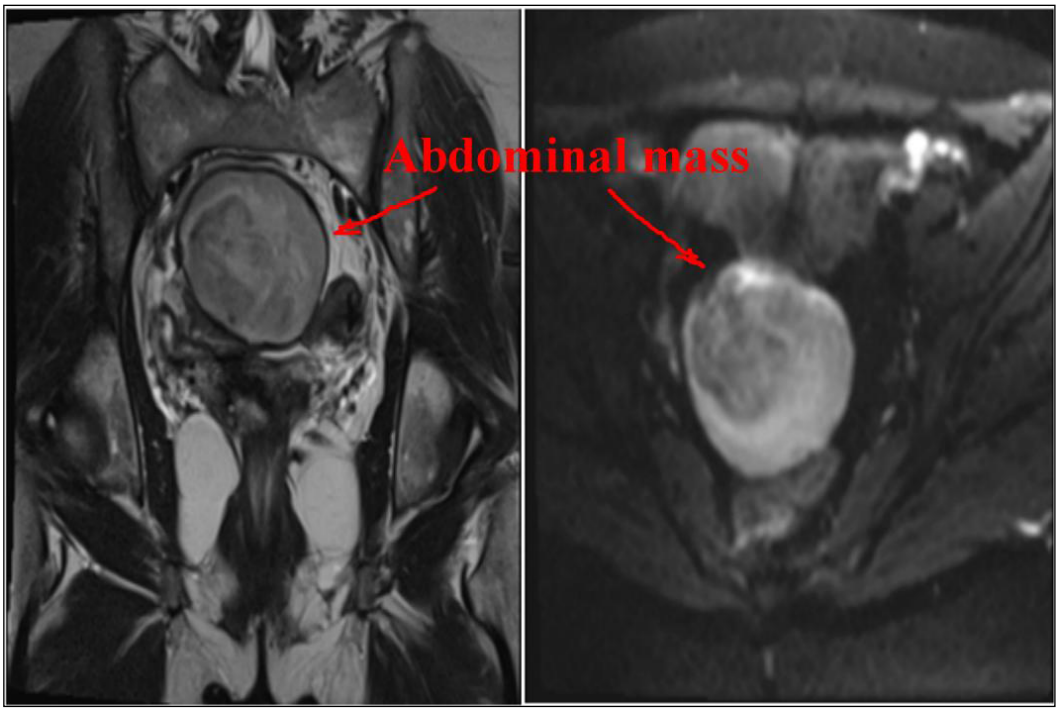

Fig. 3. MRI of the abdominal cavity. Abdominal mass.

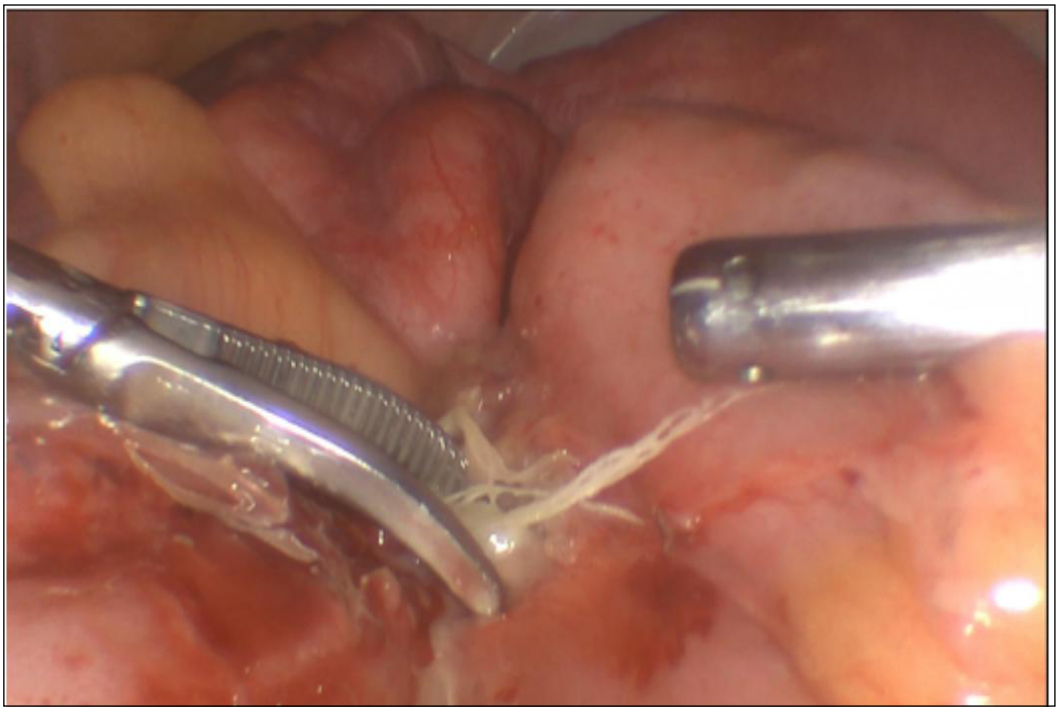

Fig. 4. Per operative images of the changes found in patient M., 39 years old.

was first described by Wilson in 1884 to refer to the unknowing abandonment of a surgical gauge or sponge in a body cavity following a surgical procedure [14, 15]. It is an infrequent but serious surgical complication that is rarely reported due to its medico-legal implications. This usually causes an exudative inflammatory reaction with the formation of an abscess or aseptic fibrosis with the formation of a mass that leads to future complications such as intestinal obstruction [15]. It can appear within a few days, and sometimes even several years after surgery. Gossypiboma is a serious surgical complication that impacts patient safety, cost of care, and can lead to mortality if diagnosis and treatment are delayed. Its clinical manifestations are extremely varied, so diagnosis is quite difficult [16, 17].

Thus, the search and implementation of new informative and reliable non-invasive and minimally invasive methods for diagnosing neoplasms and foreign bodies of the abdominal cavity is now very relevant.

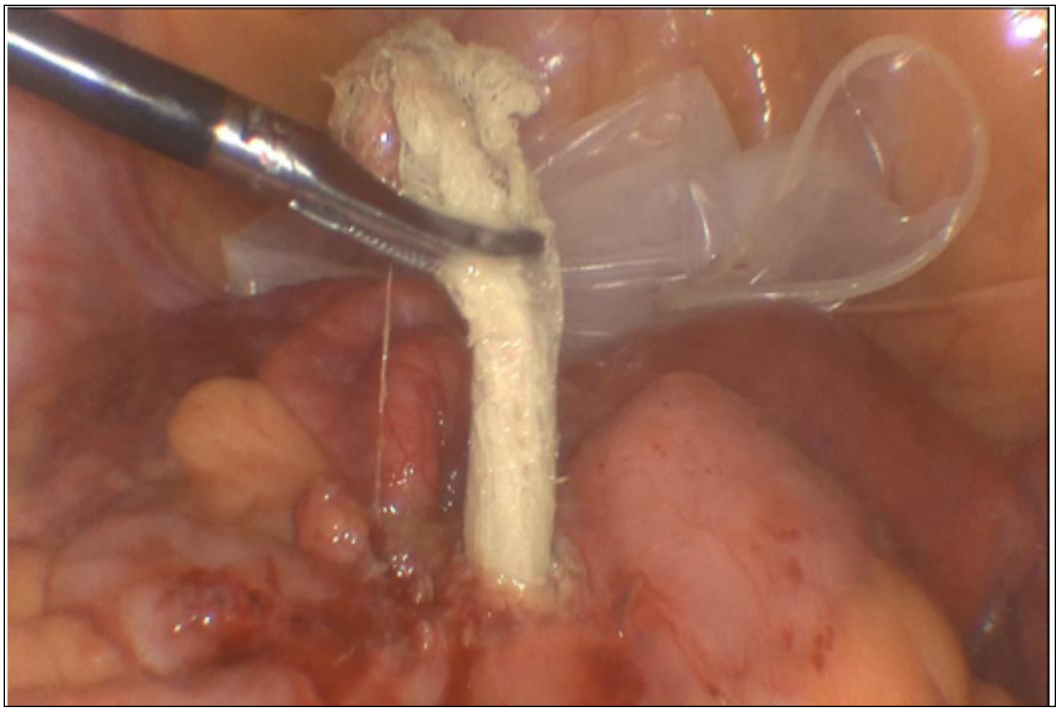

Fig. 5. Per operative images of the changes found in patient M., 39 years old: detected foreign body (gauze wad).

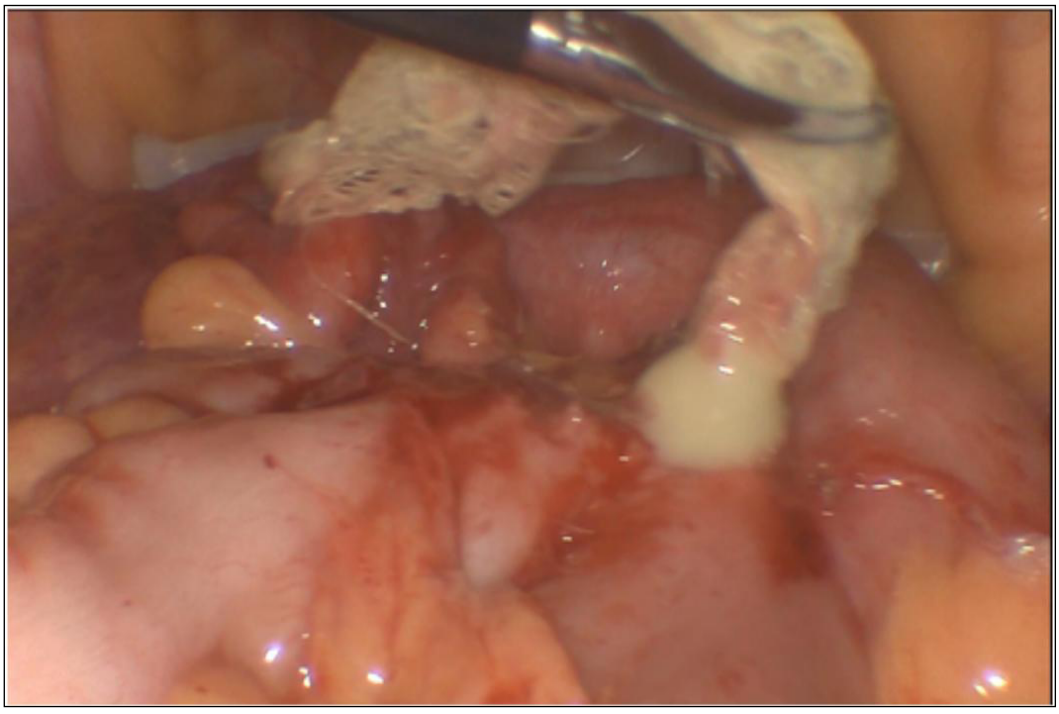

Fig. 6. Per operative images of the changes found in patient M., 39 years old: foreign body with discharge of pus from the abscess cavity.

CASE REPORT

Female patient M., born in 1985, was routinely hospitalized in the surgical of the Municipal Enterprise "2nd City Clinical Hospital of Poltava City Council" (Poltava, Ukraine) in 2023. The patient underwent a complete general clinical examination, determination of tumor markers, serological tests for amebiasis and echinococcus, a plain radiograph of the abdominal cavity, fibrogastroduodenoscopy, colonoscopy, ultrasound of the abdominal organs, CT scan of the abdominal organs. Diagnostic laparoscopy was performed to make a final diagnosis.

The patient complained of constant aching pain in the lower abdomen, predominantly on the left, radiating to the lumbar region, nausea without bloating, fatigue, and weakness for three months. The passage of feces and gases was preserved.

As it became known from the anamnesis, the patient was operated on twice in gynecological departments: in 2019 there was a laparotomy for a cyst of the left ovary with a Pfannenstiel incision, and in 2021 a laparoscopic cystectomy was performed on the left.

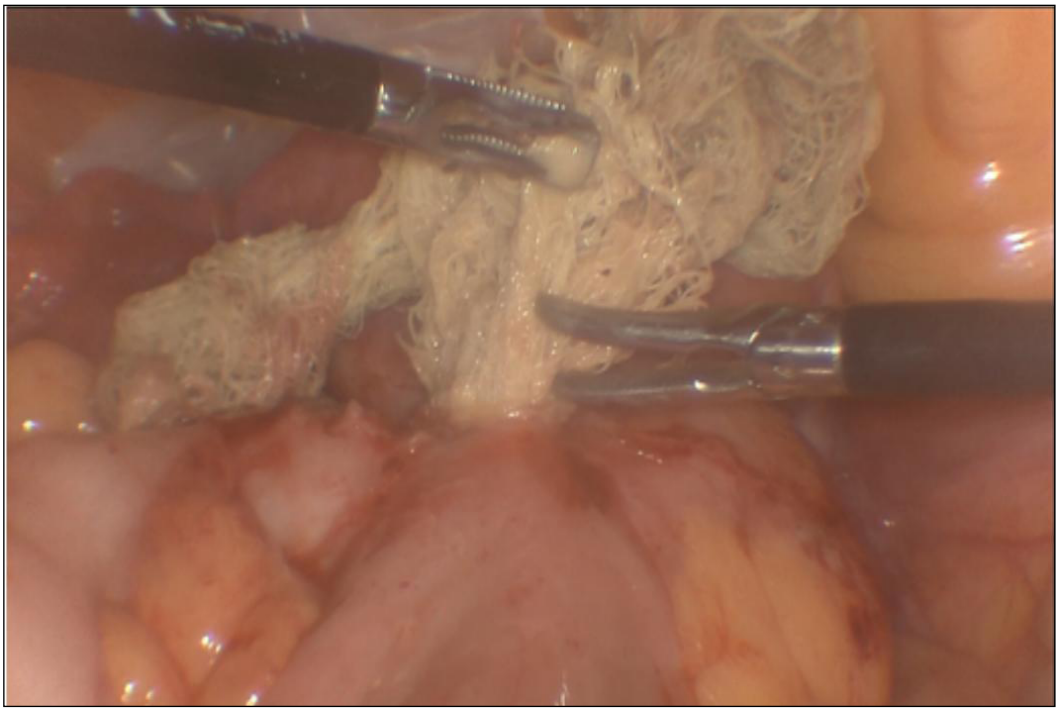

Fig. 7. Per operative images of the changes found in patient M., 39 years old: blunt removal of a foreign body (gauze wad).

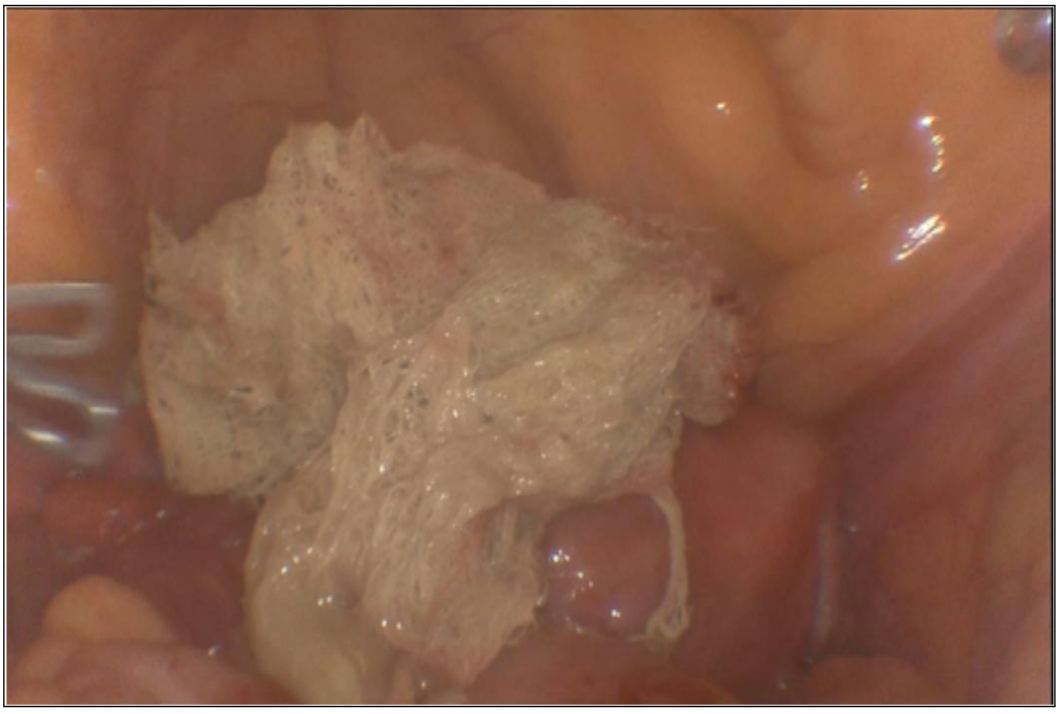

Fig. 8. Per operative images of the changes found in patient M., 39 years old: foreign body (gauze wad) removal.

An objective examination revealed: blood pressure 120/70 mm. Hg, pulse 98 beats per minute, respiratory rate 18 per minute, body temperature 36.8 C. Examination of the abdominal cavity revealed a painful mass in the left lower quadrant and slight tenderness in the periumbilical region. During a laboratory examination, the patient's hemoglobin level was within normal limits, the leukocyte count was 9.2×10^9/l (80% neutrophils), hematocrit – 39%, platelet count – 345×10^9/l. A plain radiography of the abdominal cavity revealed no pathology.

Fibergastroduodenoscopy did not reveal any organic pathology. Colonoscopy revealed erythematous proctitis. When performing an endometrial biopsy, the endometrium is in a disturbed phase of proliferation. When examining tumor markers: CA 125 – 88.4 U/ml, HE 4 – 44.2 pmol/l, ROMA index – 6.28%. Serological tests for amoebiasis and echinococcus were negative. Ultrasound of the abdominal organs showed a pelvic mass of a heterogeneous structure measuring 7.5 by 7.6 cm, small uterine leiomyoma, type 4.

A computed tomography scan revealed a complex localized lesion of the pelvic organs in the form of a

hypodense formation measuring 8.2 by 8 by 7.5 cm with peripheral enhancement and hemorrhagic contents, and an enlargement of the left ovary (Fig.1).

An MRI of the abdominal cavity and pelvis revealed a tumor of the left ovary and adenomyosis of the uterus I-II (Fig.2, Fig.3).

A preliminary diagnosis was made: Mass formation of the pelvis. Tumor of the left ovary. Small uterine leiomyoma.

Due to discrepancies in the results of non-invasive research methods, the patient was offered diagnostic laparoscopy to make a final diagnosis. The patient was warned about possible options for completing the surgical intervention (conversion, bowel resection, surgical sterilization, hysterectomy, etc.). Consent for the operation was obtained.

Elective diagnostic laparoscopy was performed. During the revision operation, it was revealed that the stomach, gallbladder, and liver were without organic pathology. The patient was transferred to the Trendelenburg position. When examining the pelvic organs, the uterus and right appendages were unchanged. The left ovary was enlarged (up to 5 cm) due to a cystic formation, the ovarian tissue was located on the periphery. The left fallopian tube was unchanged. A rounded formation measuring up to 15 cm in diameter was detected in Douglas space. It was densely elastic consistency, limited movable. The loops of the small intestine and the sigmoid colon were tightly fused to it. Viscerolysis was performed using a blunt method and using electrocoagulation, during which the integrity of the capsule of the formation was disrupted, and up to 150 ml of thick, cream-like pus was released (Fig. 4). This situation was previously assessed as a pelvic abscess. The abscess wall was opened up to 2 cm, with a section of foreign body (gauze wad) protruding from the cavity (Fig. 5, Fig. 6, Fig. 7, Fig. 8).

The foreign body was removed from the abdominal cavity in a container. The abscess cavity was opened and drained. After a bacteriological examination of the abscess contents, no bacterial cultures were found.

The course of the postoperative period was uncomplicated. The drains were removed from the abdominal cavity on the fifth day of the postoperative period. The patient was discharged from the hospital in satisfactory condition on the fifth day after surgery.

During follow-up examinations one, three, and six months after surgery, the patient did not present any complaints. When conducting a control ultrasound of the abdominal cavity after three and six months, no pathological formations were detected in the abdominal cavity and pelvis.

Abdominal foreign bodies may not manifest themselves clinically for several months or years, but may be diagnosed by chance [14]. The biggest problem is that this foreign body is often interpreted as a malignancy, which leads to additional problems in the diagnosis and treatment of such patients [12, 14]. Having no specific symptoms, clinical manifestations vary from an asymptomatic course to constant abdominal pain, nausea, vomiting, intestinal obstruction, fistulas, sepsis, and in some cases, diffuse peritonitis [14,16].

According to statistics, the greatest number of cases with foreign bodies left behind occurs precisely in emergency surgery (about 85-90%), which is associated with the increased amount of stress, fatigue of the surgeon, since the operation can be performed at night, or when unplanned events take place during the procedure, etc [12, 13, 17].

A surgical gauzeis the most frequent item that can be left in the abdominal cavity, in contrast to surgical instruments, gloves, which occurs more rarely. Gossypiboma, this term comes from Latin "gossypium" (cotton) and Swahili "boma" (shelter), that means surgical dressing material (gauze wads, tampons, etc.) forgotten in cavities. Women are especially exposed to high risk (63%) since gossypiboma often occurs after gynecological surgery [14, 15, 16].

MSCT with intravenous contrast is the gold standard for the diagnosis of foreign bodies in the abdominal cavity all over the world [2, 3, 7]. In the mentioned above clinical case, none of the additional, non-invasive, diagnostic methods had shown a result "in the direction" of a foreign body, and performing a diagnostic laparoscopy enables to make a clinical diagnosis and carry out surgical treatment without performing a more traumatic "open" surgery [8, 9, 10].

In order to exclude errors and prevent from leaving foreign bodies, close cooperation between the surgeon and the operating nurse is necessary: while the counting of gauze wads, distractions, interruptions or breaks are not allowed, and the counting method must be consistent; the operation is not finished until all gauze wads or instruments have been counted [18, 19, 20].

In order to prevent similar situation, we recommend the use of gauze wads with radiopaque markers, in this case, radiography on the operating table, can help even before the end of the operation. If there are any doubts, repeated revision of the operative field is needed.

CONCLUSSIONS

The case we examined emphasizes that when assessing the nature of an intra-abdominal neoplasm, it is necessary to remember about foreign bodies, especially in patients who have previously undergone surgical interventions. Diagnostic laparoscopy is a technically advanced and minimally invasive procedure for the diagnosis and treatment of intra-abdominal gossypiboma.

REFERENCES

1. Howlader N, Noone AM, Krapcho M et al. SEER Cancer Statistics Review, 1975-2018. National Cancer Institute. 2021. https://seer.cancer.gov/csr/1975_2018/ [Accessed 25 June 2024]
2. Adama S, Balaraba MLAA, Aliou ZO et al. Diagnostic and therapeutic approach to abdominal masses in a country with limited resources. BMC Surg. 2024;24(1):97. doi: 10.1186/s12893-024-02371-w. DOI
3. Akkoca M, Tokgoz S, Yilmaz BK et al. Diagnosis and treatment approaches for intraabdominal masses in adults. Ankara Universities Tip Fakultesi Mesmuasi, Turquie 2017;70(3). doi: 10.1501/Tipfak_0000000987. DOI
4. Joo Hyun O, Lodge MA, Wahl RL. Practical PERCIST: a simplified guide to PET response criteria in solid tumors 1.0. Radiology. 2016;280:576–584. doi:10.1148/RADIOL.2016142043. DOI
5. Pinker K, Riedl C, Weber WA. Evaluating tumor response with FDG PET: updates on PERCIST, comparison with EORTC criteria and clues to future developments. Eur J Nucl Med Mol Imaging. 2017;44:55–66. doi:10.1007/S00259-017-3687-3. DOI
6. Altini C, Lavelli V, Ruta R et al. Typical and atypical PET/CT findings in non-cancerous conditions. Hell J Nucl Med. 2020;23(1):48–59. doi: 10.1967/s002449912005. DOI
7. Dzhuzha DA. Radiation visualization in radiation oncology. Radiation Diagnostics, Radiation Therapy. 2020;3:39-48. doi:10.37336/2707-0700-2020-3-4. DOI
8. Leimkühler M, de Haas RJ, Pol VEH et al. Adding diagnostic laparoscopy to computed tomography for the evaluation of peritoneal metastases in patients with colorectal cancer: A retrospective cohort study. Surg Oncol. 2020;33:135-140. doi: 10.1016/j.suronc.2020.02.010. DOI
9. El Zanati HI, Aboelwafaa WA, Hamza YM. The role of diagnostic laparoscopy in abdominal masses. Int Surg J. 2020;7(4):945-9. doi:10.18203/2349-2902.isj20201370. DOI
10. Yeola ME, Gode D, Bora A. Diagnostic Laparoscopy as an Effective Tool in Evaluation of Intra-abdominal Malignancies. World Journal of Laparoscopic Surgery. 2018;11. 68-75. doi:10.5005/jp-journals-10033-1338. DOI
11. Hempel S, Maggard-Gibbons M, Nguyen DK et al. Wrong-site surgery, retained surgical, items, and surgical fires a systematic review of surgical never events. JAMA Surg. 2015;150(8):796–805. doi: 10.1001/jamasurg.2015.0301. DOI
12. Zejnullahu VA, Bicaj BX, Zejnullahu VA, Hamza AR. Retained surgical foreign bodies after surgery. Open Access Maced J Med Sci. 2017;5(1):97-100. doi: 10.3889/oamjms.2017.005. DOI
13. Sonarkar R, Wilkinson R, Nazar Z et al. Textiloma presenting as a lump in abdomen: a case report. Int J Surg Case Rep. 2020;77:206-9. doi: 10.1016/j.ijscr.2020.10.081. DOI
14. Bairwa BL. Gossypiboma – an unusual cause of surgical abdomen and surgeon's nightmare: A rare case report. Int J Surg Case Rep. 2021;80:105521. doi: 10.1016/j.ijscr.2021.01.015. DOI
15. Ram T, Dahiya D, Naik A. Gossypiboma: case report and review of literature. Int. Surg. J. 2019;6:4148-4151. doi:10.18203/2349-2902.isj20195142. DOI
16. Alemu BN, Tiruneh AG. Gossypiboma: a case series and literature review. Ethiop. Ethiop J Health Sci. 2020;30(1):147-149. doi: 10.4314/ejhs.v30i1.19. DOI
17. Szymocha M, Pacan M, Anufrowicz M et al. Leaving a foreign object in the body of a patient during abdominal surgery: still a current problem. Pol Przegl Chir. 2019;91(6):35-40. doi: 10.5604/01.3001.0013.2024. DOI
18. American College of Surgeons (ACS) Committee on Perioperative Care Revised statement on the prevention of unintentionally retained surgical items after surgery. Bull. Am. Coll. Surg. 2016;101:50(10)-51.
19. Ambulkar R, Ranganathan P, Salunke K, Savarkar S. The World Health Organization Surgical Safety Checklist: An audit of quality of implementation at a tertiary care high volume cancer institution. J Anaesthesiol Clin Pharmacol. 2018;34(3):392–398. doi: 10.4103/joacp.JOACP_328_17. DOI
20. Fencl JL. Guideline implementation: prevention of retained surgical items. AORN J. 2016;104(1):37–48. doi: 10.1016/j.aorn.2016.05.005. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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CASE STUDY

CONTENTS

Case of early uncomplicated multivascular nonobstructive coronary atherosclerosis in young male: novel aspects of noninvasive diagnostic

Yuliya Tyravska, Oleksandr Savchenko, Iryna Melnychuk, Viktor Lizogub
BOGOMOLETS NATIONAL MEDICAL UNIVERSITY, KYIV, UKRAINE

ABSTRACT

This clinical report demonstrates the case of nonobstructive coronary artery disease in a 38-year-old male with the only complaint of an episodical increase in blood pressure. A combination of risk factors raised the suspicion of nonobstructive coronary artery disease. It was substantiated by the modified stress test which consists of electrocardiography, echocardiography, laser Doppler flowmetry, pulse oxymetry, capnometry, lactate measurement, and blood pressure monitoring while cycling. Only afterward, the patient passed over coronary computed tomography angiography, which confirmed the suspected diagnosis precisely. Based on the current case, we aimed to increase the awareness of physicians about nonobstructive coronary artery disease and propose an algorithm for nonobstructive coronary atherosclerosis screening.

KEY WORDS: case report, ischemia with nonobstructive coronary artery disease, atherosclerosis screening, stress echocardiography, endothelial dysfunction

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INTRODUCTION

Ischemia with nonobstructive coronary artery disease (INOCA) has become widespread condition that affects approximately 3-4 million individuals annually. It is defined as less than 50% epicardial coronary artery (CA) stenosis on angiography. A large number of such patients have an asymptomatic course or with atypical pain syndrome and, often, shortness of breath during physical exertion as the only symptom. Unless earlier INOCA was believed to be among benign disorders, up-to-date data demonstrate it is associated with serious cardiovascular outcomes (major adverse cardiovascular events), recurrent hospitalization, additional medical procedures, decline in quality of life, satisfaction with medical care, and mortality especially in patients of older age, with diabetes, hypertension, smoking. Of note, the risk of myocardial infarction and death in patients with 3 non-obstructive CAs is similar to single-vessel coronary obstruction [1].

INOCA occurrence is tightly associated with microvascular dysfunction [2]. Quiet often, it is manifested by dysfunction of endothelium-dependent vasodilatation of arterioles, associated with insufficient amount of synthesized NO or its non-absorption [3]. However, limited attention is paid to the impact of oxygen, carbon dioxide, and lactate on coronary flow including microvascular [4].

Coronary angiography is the principal method of INOCA diagnosis confirmation [1]. However, it is demonstrated that the effectiveness of computer tomography (CT) as a non-invasive method is not worse than that of invasive angiography [5]. Nevertheless, the cost-effectiveness of both procedures is assessed with questionable results of the patients' risk stratification regarding the necessity of every procedure [6]. Therefore, the non-invasive algorithm of nonobstructive atherosclerosis detection remains one of the most urgent problem [7].

Thus, in this case, we presented the patient with early uncomplicated multivascular nonobstructive coronary atherosclerosis with the establishment of the preliminary diagnosis before providing CT. For this purpose, we applied above-mentioned regularities of microvasculature to improve the technique of stress echocardiography to identify patients with nonobstructive coronary atherosclerosis.

CASE REPORT

PATIENT INFORMATION

Male patient P., 38 years old, visited a cardiologist on an outpatient basis with complaints of episodically increased blood pressure (BP) and with the diary of BP and heart rate (HR) which he kept for 10 days before cardiologist visiting

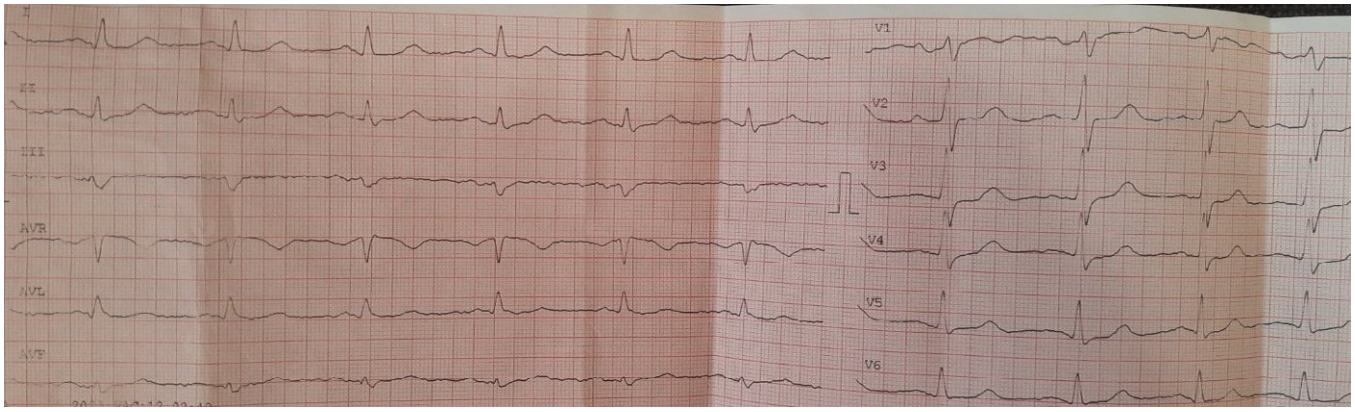


Fig. 1. 12-channel ECG of the patient.

following the recommendations of his colleagues: BP (mmHg) – HR (bpm); 171/122 – 85; 107/73 – 87; 110/75 – 91; 170/112 – 89; 140/109 – 88; 172/114 – 83; 134/99 – 94; 141/97 – 77; 127/94 – 94; 149/100 – 101.

No other complaints, including any discomfort in the heart region, palpitation, or dyspnoe, were mentioned.

HISTORY OF PRESENT ILLNESS

From the anamnesis, the history of such disorders has lasted for not more than 2–3 weeks. The patient associated BP dysregulation with stressful periods at work.

PERSONAL HISTORY

No therapeutical disorders, traumas, surgeries, or allergic reactions were registered. The patient denied harmful habits and any history of medicine intake.

OBJECTIVELY

The general condition is satisfactory with hypersthenic body habitus type and body mass index – 29.8 kg/m^2. The skin and visible mucous membranes are clean. The left border of the relative dullness of the heart is shifted 0.5 cm outward from the left midclavicular line while percussion at the 5th intercostal space. Heart tones are muffled, and regular. No murmurs while auscultation of the heart. Pulse 92 bpm, rhythmic, with satisfactory properties. BP –180/120 mm Hg. No pathological findings were noticed during the physical examination of the lungs, and abdomen. No peripheral edema.

DIAGNOSTIC ASSESSMENT

On the ECG (Fig. 1), sinus regular rhythm was registered, the horizontal position of the electrical heart axis, negative Sokolov-Lyon criteria, and mild diffuse changes of the myocardium with possible signs of hypoxic changes of left ventricular (LV). No other peculiarities.

The patient underwent two-dimensional transthoracic echocardiography (Toshiba Artida, SSH-880CV) (Table 1). The wall thickness and ejection fraction (EF=56%) were normal. Mild enlargement of LV volumes. S-shape interventricular septum. Signs of diastolic dysfunction of LV (type I, impairment of LV relaxation) were also confirmed with pulse wave tissue Doppler imaging. Slightly increased stiffness of left and right CAs. No changes in the local contractility of LV were noticed.

However, while 2D Speckle tracking echocardiography (Toshiba Artida), a significant reduction of global longitudinal strain and local deformation of the myocardium were observed in the 4-chamber view in the apical-lateral and medial-lateral segments, and the 3-chamber view in the apical-lateral and medial-posterior segments (Fig. 2A, B, C).

Consequently, we provided more profound investigations of the patient.

The results of laboratory assessments are aggregated in Table 2. Data of complete blood count with blood differential rate, levels of thyrotropic hormone, triiodothyronine, thyroxine, C-reactive protein, creatinine, uric acid, potassium, magnesium, homocysteine, D-dimer are within normal reference ranges. Dyslipidemia and hyperglycemia are noticed.

Carotid ultrasound registered hemodynamically insufficient local hyperechoic plaque with regular contour along the posterior wall of common carotid arteries bifurcation from the left side (stenosis 44% of diameter and 31% of surface) (Fig. 3A, B).

All collected information hinted to suspect initial non-obstructive atherosclerosis of CAs in the patient. So, the patient passed stress test following modified protocol (Table 3), particularly in addition to ECG registration during bicycling, EchoCG before and after cycling (Table. 4), BP control before the test, after each stage and at 1′, 3′, 5′ of restitution, such parameters as SaO_2 (Fig. 4), $etCO_2$ and lactate were measured as well as Laser Doppler Flowmetry (LDF) was performed before and after stress test (Fig. 5A, B).

LDF-gram before physical exertion demonstrated endothelial dysfunction with the trend of arteriolospasm even without normalization of microcirculation. Four minutes after deflation, improvement in the constant

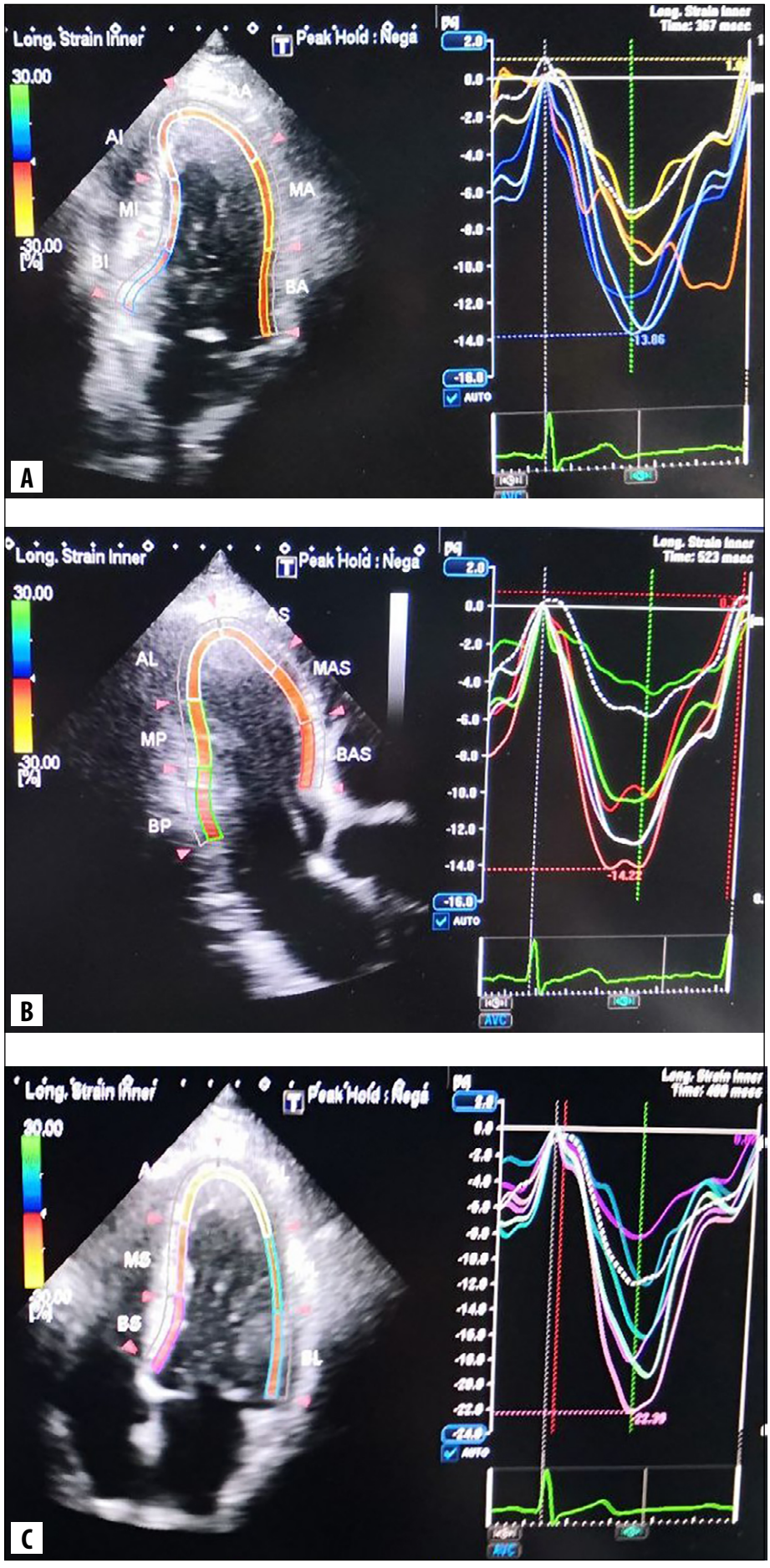


Fig. 2.A) 2D Speckle tracking. 2-chamber view; B) 2D Speckle tracking. 3-chamber view: C) 2D Speckle tracking. 4-chamber view.

Table 1. EchoCG data of the patient at rest

Parameter	Result	Reference range
Diameter of aorta, mm	37	20-37
Aortic valve opening, mm	23	17-25
Left atrial diameter, mm	41.2 *	20-40
Interventricular septum thickness at end diastole, mm	10.2	6-11
Left ventricular posterior wall thickness at end diastole, mm	9.3	6-11
Anterior wall of right ventricular, mm	4.1	< 5
Right ventricular dimension at end diastole, mm	30	9-30
Right atrial diameter, mm	34	20-40
Ejection fraction, %	56	> 55
End-diastolic volume, mL	162.2 *	51-160
End-systolic volume, mL	85.1	14-70
Stroke volume, mL	92.1	30-100
E/ A (peak velocity of early diastolic transmitral flow (m/ s)/ peak velocity of late transmitral flow (m/ s)	0.9 *	1.5-1.6
Deceleration time of early diastolic transmitral flow, ms	228 *	160-220
Isovolumic relaxation time, ms	96	60-100
Peak velocity of diastolic flow, cm/ s	71.3	62-80
Pulmonary artery systolic pressure	25.8	<30

Notes: * - out of reference ranges.

Table 2. Laboratory data of the patient

Parameter	Result	Reference range
Lipidogram		
Cholesterol, mmol/l	5.56 *	<5.2
Triglycerides, mmol/l	2.05 *	<1.7
High density lipoproteins, mmol/l	0.97 *	>1.00
Low density lipoproteins, mmol/l	4.14 *	<3.0
Very low density lipoproteins, mmol/l	0.94	0.26-1.00
Serum glucose, mmol/l	6.4 *	4.11-5.89
Glycated hemoglobin, %	5.7 *	4.5-5.6

Notes: * - out of reference ranges.

component of microcirculation (M=3.60 PPU vs M=4.74 PPU), as well as the variable component of mictocirculation (absence of arteriolospasm on the LDF-gram after stress test with the increase in area under the curve of post-ischemic reactive hyperemia (430 PPU vs 740 PPU) were noticed.

Hence, the stress test was positive. The patient fulfilled 86% of the targeted workload with 87% of targeted HR which indicates high tolerance to physical exertion. Initial atherosclerosis may be suspected in the distal segment of the left anterior descending artery or circumflex artery.

Based on complaints, anamnesis, physical examination, and results of all above-presented laboratory and instrumental investigation we established the diagnosis: Arterial hypertension, I stage, grade 1-2, mild risk (SCORE scale). Coronary artery disease: INOCA (non-obstructive coronary atherosclerosis)? Heart failure I.

To establish the diagnosis precisely the patient was directed to coronary CT angiography. It was visualized combined atherosclerotic plaques in left anterior descending artery, circumflex artery. and right coronary artery, stenosing the vessels up to 25%, 20% and 35%, respectively.

Thus, preliminary diagnosis was confirmed and we established final diagnosis: Arterial hypertension, I stage, grade 1-2, mild risk (SCORE scale). Coronary artery disease: INOCA (multivascular non-obstructive coronary atherosclerosis: left anterior descending artery 25%, circumflex artery 20%, right coronary artery 35%). Heart failure I.

THERAPEUTIC INTERVENTION

It was prescribed nebivolol 5 mg once a day, perindopril 5 mg once a day, rosuvastatin 10 mg once a day, L-arginine 1

Table 3. The protocol of modified stress test of the patient

Stage	Initial (0)	1	2	3	Restitution	Rest
Workload, W	0	50	100	150	30	0
Time, min:s	3:00	3:00	3:00	1:00	3:00	5:00
HR, bpm	67	111	131	142	90	65
BP, mm Hg	120/75	130/80	160/80	190/90	140/75	120/75
ECG	sinus regular rhythm, mild diffuse myocardial changes	-//-	-//-	Upsloping depression up to 0.9 mm in V_{5-6}	As initial	As initial
EchoCG	Normokinesis of all segments in long-axis, short axis, 2Ch-, 4Ch-views	-//-	-//-	Mild hypokinesis in 4Ch-view (apical-lateral segment) and in 2Ch-view (apical-anterior segment)	As initial	As initial
RR, 1/min.	15-20	-	-	18-20	-	15-18
SpO2	95	95	95	96	96	95
etCO2	3.3-3.4	-	-	3.5-3.6	-	3.3
Lactate	1.3	-	-	-	-	7.0
Complaints	-	-	Dyspnoe	Dyspnoe, fatigue in the muscles of legs	Dyspnoe	-

Notes: 2Ch – 2-chamber, 4Ch – 4-chamber.

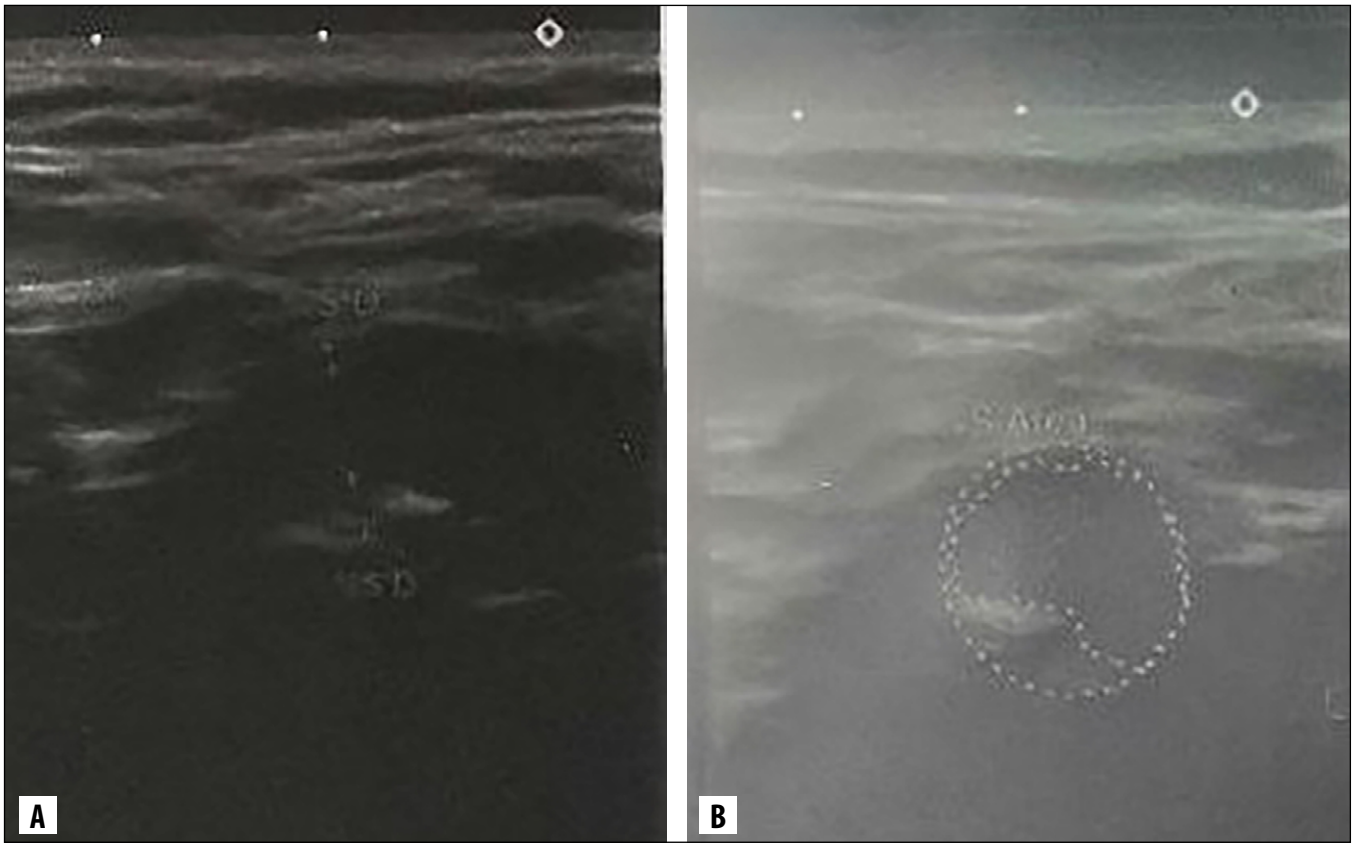
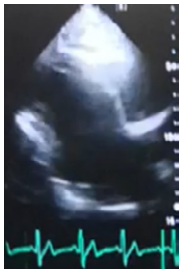
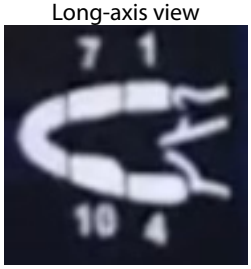
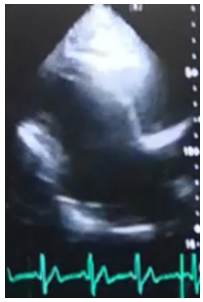
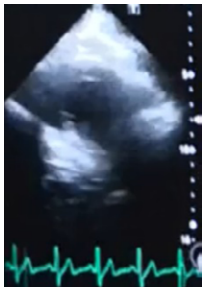
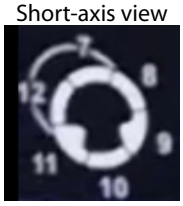
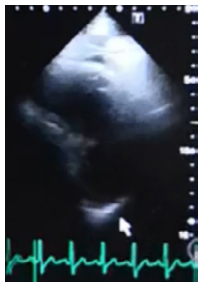
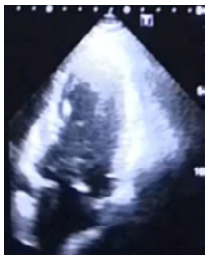
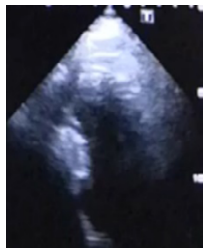
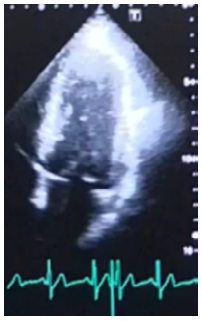
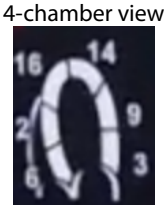
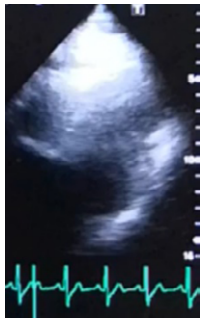


Fig. 3. A) Carotid ultrasound. Common carotid artery; B) Carotid ultrasound. Bifurcation.

spoon 3 times a day, acetylsalicylic acid 75 mg once a day, mild physical activity (walking) regularly.

Despite the fact that the patient had a low pre-test probability of coronary artery disease based on his age, the absence of bad habits (non-smoker), and the typical angina attacks, we took into account other important risk factors for atherosclerosis, namely: the presence of atherosclerotic plaques in the brachiocephalic arteries, hyperlipidemia, an elevated level of glycated hemoglobin and blood glucose, arterial hypertension and increased body mass index. These

Table. 4. EchoCG before and after stress test

Before stress test	Echography views	After stress test
	Long-axis view 	
	Short-axis view 	
	2-chamber view 	
	4-chamber view 	

important risk factors arose suspicion regarding non-obstructive coronary atherosclerosis [1].

Despite the absence of ischemia on the ECG and changes in the regional myocardial contractility according to the standard echocardiogram, the use of the 2d Spackle tracking option, namely, the determination of the longitudinal deformation of the myocardium, allowed us to be more confident in making this diagnosis [8]. In Fig. 3 from the longitudinal strain of the patient is significantly reduced (the reference point is less than 15%) in all coronary artery basins (at least in two adjacent segments). These changes may indicate a violation of perfusion in the subendocardial layer of the left ventricle. The occurrence of a decrease in longitudinal strain in two adjacent segments is linked to the damage of a specific coronary artery [8]. In observed patient it can be suspected multiple vascular damage. To confirm this assumption, we performed modified stress echocardiography on both patients.

From Table 3, the patient cycled 150 W for 1 min, while he did not reach the submaximal HR (88%). The test was stopped due to severe shortness of breath and weakness in the leg muscles. In the course of load steps, single ventricular extrasystoles appeared already at 50 W, and at 100 W, they were joined by supraventricular ones, at 150 W, depression of the ST segment by 0.9 mm appeared in leads V5-6. The graph of SpO2 did not change during all stages and corresponded to the norm. According to etCO2, the initial level was 3.5% at the peak of the load, it fluctuated from 3.8 to

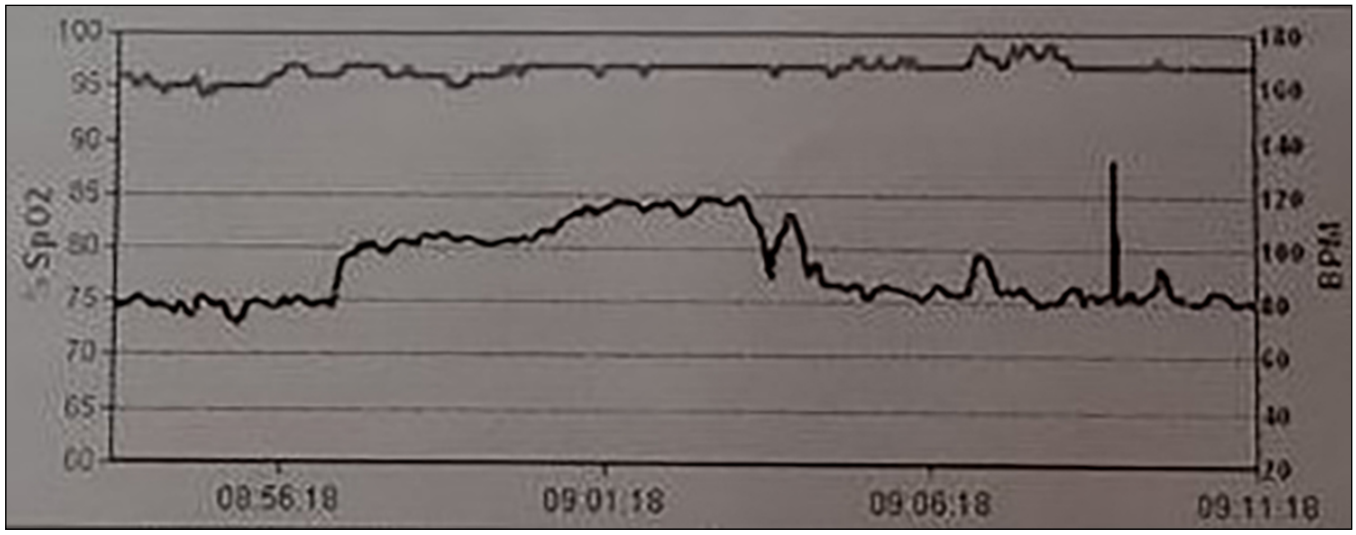


Fig. 4. Pulse oximetry and heart rate while stress test.

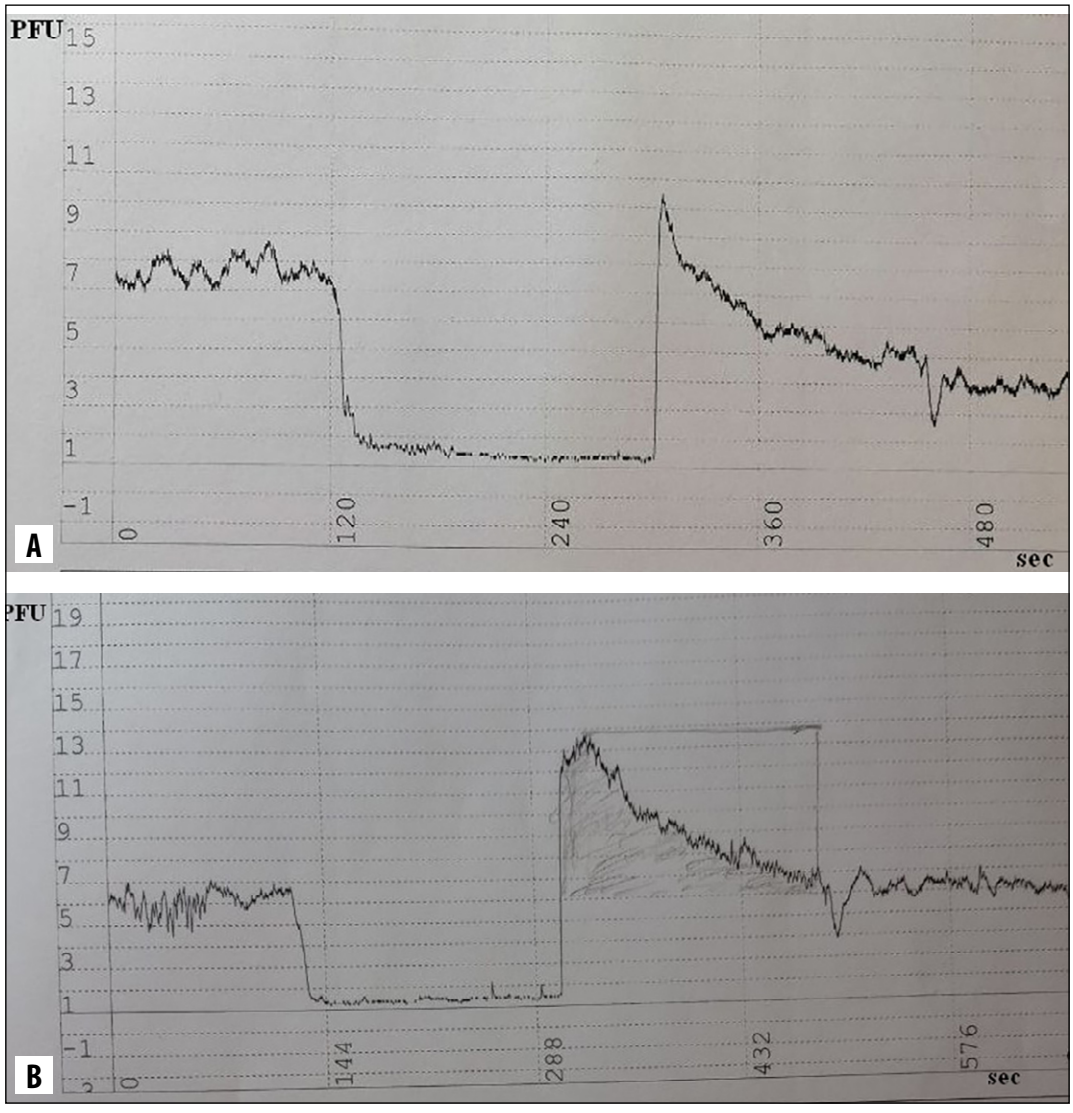


Fig. 5.A) LDF-grams of the patient before stress test; B) LDF-grams of the patient after stress test.

3.5%, and returned to the initial during the restitution period. According to lactate before exercise, it was 1.25 mmol/l, and during the restitution period it increased to 7 mmol/l.

When hypoxemia occurs (the partial pressure of oxygen in the blood decreases), an increase in hydrogen ions, CO_2 and lactate is observed, causing dilation of arterioles, which leads

to an increase in the number of functioning capillaries of the myocardium [9] The same metabolites are formed while myocardial ischemia. At the same time the metabolism of the ischemic myocardium switches from the cycle of tricarboxylic acids to aerobic, and with aggravating of ischemia even to anaerobic glycolysis. At the same time, the level of CO2 decreases and the amount of lactate in the blood increases progressively. But the number of ATP molecules synthesized by the myocardium significantly decrease [10-12].

In turns of the echocardiography data, there was mild hypokinesis in the apical anterior and apical lateral segments at the peak of the load, which corresponds to the lesion of the distal segment left anterior descending artery or circumflex artery. Thus, it can be concluded that the usual stress echocardiography with a visual assessment of regional myocardial contractility has disadvantages due to the subjective assessment that depends on the experience of the operator [13]. However, when analyzing additional options, it is possible to slightly increase the diagnostic value of stress echo for the diagnosis of initial coronary atherosclerosis.

Regarding etCO2 analysis, its increase at the peak of physical exertion may indicate still aerobic glycolysis in the myocardium. Nevertheless, initial coronary atherosclerosis can be suspected especially when lactate has crossed the lactate (anaerobic) threshold of 4 mmol/l. The stenosing coronary atherosclerosis with the transition of the myocardium metabolism to anaerobic glycolysis is diagnosed if the level of etCO2 on the peak of physical exertion has become lower than the initial level, whereas the lactate level is high [14. In addition, such combination may arise the suspicion about the deterioration of the microcirculation of the myocardium due to the spasm of arterioles. Thus. Observed patient is more likely to have initial atherosclerosis according to the results of modified stress EchoCG, eventhough the ECG changes are questionable. Furthermore, we suspected initial nonobstructive atherosclerosis which was confirmed by results of coronary computed tomography angiography with the trend toward arteriolospasm [16]. The results of LDF also suggested the possibility of vasospasm [17].

The prescribed treatment following the wholistic management of the patient taking into account multiple pleiotropic effects of drugs (nebivolol with vasodilation effect [18] and L-arginine with combination of vasodilation and endothelium protection effects [19], rosuvastatin [20], perindopril [21], and acetylsalicylic acid [22]).

CONCLUSIONS

physicians should be aware of INOCA as clinal picture of the latter is divorce and non-specific. The diagnostic at early stages with further appropriate treatment prevents progression of disease including complications. Proposed algorithm of modified stress test may be a promising method for initial atherosclerosis screening in the patients with suspicion of INOCA before coronary computed tomography angiography or coronary angiography.

Informed Consent and Ethical Approval. The patient gave written consent to participate in current observation after the explanation of the purpose and allowed to publish the results of the later with depersonalized data.

REFERENCES

1. Hansen B, Holtzman JN, Juszczynski C et al. Ischemia with No Obstructive Arteries (INOCA): A Review of the Prevalence, Diagnosis and Management. Curr Probl Cardiol. 2023;48(1):101420. doi:10.1016/j.cpcardiol.2022.101420. DOI
2. Crea F, Montone RA. Pathophysiology of coronary microvascular dysfunction. Vascul Pharmacol. 2023;153:107239. doi:10.1016/j.vph.2023.107239. DOI
3. Segers VFM, Bringmans T, De Keulenaer GW. Endothelial dysfunction at the cellular level in three dimensions: severity, acuteness, and distribution. Am J Physiol Heart Circ. 2023;325(2):H398-H413. doi:10.1152/ajpheart.00256.2023. DOI
4. De Backer D. Detailing the cardiovascular profile in shock patients. Crit Care. 2017;21(3):311. doi:10.1186/s13054-017-1908-6. DOI
5. DISCHARGE Trial Group; Kofoed KF, Bosserdt M et al. Comparative effectiveness of initial computed tomography and invasive coronary angiography in women and men with stable chest pain and suspected coronary artery disease: multicentre randomised trial. BMJ. 2022;379:e071133. doi:10.1136/bmj-2022-071133. DOI
6. Darlington M, Gueret P, Laissy JP et al. Cost-effectiveness of computed tomography coronary angiography versus conventional invasive coronary angiography. Eur J Health Econ. 2015;16(6):647-55. doi:10.1007/s10198-014-0616-2. DOI
7. Kwiecinski J, Tzolos E, Williams MC et al. Noninvasive Coronary Atherosclerotic Plaque Imaging. JACC Cardiovasc Imaging. 2023;16(12):1608-1622. doi:10.1016/j.jcmg.2023.08.021. DOI
8. Zhou F, Yuan H, Sun J et al. Two-dimensional speckle tracking imaging cardiac motion-based quantitative evaluation of global longitudinal strain among patients with coronary Heart Disease and functions of left ventricular ischemic myocardial segment. Int J Cardiovasc Imaging. 2024;40(2):351-359. doi:10.1007/s10554-023-02993-w. DOI
9. Grubbström J, Berglund B, Kaijser L. Myocardial oxygen supply and lactate metabolism during marked arterial hypoxaemia. Acta Physiol Scand. 1993;149(3):303-10. doi:10.1111/j.1748-1716.1993.tb09625.x. DOI

10. Rosano GM, Fini M, Caminiti G, Barbaro G. Cardiac metabolism in myocardial ischemia. Curr Pharm Des. 2008;14(25):2551-62. doi:10.2174/138161208786071317. DOI
11. Depré C, Rider MH, Hue L. Mechanisms of control of heart glycolysis. Eur J Biochem. 1998;258(2):277-90. doi:10.1046/j.1432-1327.1998.2580277.x. DOI
12. Kadir AA, Stubbs BJ, Chong CR et al. On the interdependence of ketone body oxidation, glycogen content, glycolysis and energy metabolism in the heart. J Physiol. 2023;601(7):1207-1224. doi:10.1113/jp284270. DOI
13. Picano E, Ciampi Q, Wierzbowska-Drabik K et al. The new clinical standard of integrated quadruple stress echocardiography with ABCD protocol. Cardiovasc Ultrasound. 2018;16(1):22. doi:10.1186/s12947-018-0141-z. DOI
14. Ørn S, van Hall G. Does a normal peripheral lactate value always indicate an aerobic tissue metabolism? Eur J Heart Fail. 2017;19(8):1034-1035. doi:10.1002/ejhf.863. DOI
15. Rossiter HB. The "Anaerobic Threshold" Concept Is Valid in Physiology and Medicine. Med Sci Sports Exerc. 2021;53(5):1089-1092. doi:10.1249/mss.0000000000002548. DOI
16. Premont RT, Reynolds JD, Zhang R, Stamler JS. Role of Nitric Oxide Carried by Hemoglobin in Cardiovascular Physiology: Developments on a Three-Gas Respiratory Cycle. Circ Res. 2020;126(1):129-158. doi:10.1161%2FCIRCRESAHA.119.315626. DOI
17. Stegemann E, Weidmann M, Miyazawa AA et al. Laser Doppler flow for the hemodynamic differentiation of tachycardia. Pacing Clin Electrophysiol. 2023;46(2):114-124. doi:10.1111/pace.14618. DOI
18. Hanif N, Zamir A, Imran I et al. Clinical pharmacokinetics of nebivolol: a systematic review. Drug Metab Rev. 2023;55(4):428-440. doi:10.1080/03602532.2023.2271195. DOI
19. Wang Z, Yang N, Hou Y et al. L-Arginine-Loaded Gold Nanocages Ameliorate Myocardial Ischemia/Reperfusion Injury by Promoting Nitric Oxide Production and Maintaining Mitochondrial Function. Adv Sci (Weinh). 2023;10(26):e2302123. doi: 10.1002/advs.202302123. DOI
20. Vavlukis A, Vavlukis M, Dimovski A et al. Anti-inflammatory and immunomodulatory effects of rosuvastatin in patients with low-to-moderate cardiovascular risk. Acta Pharm. 2021;72(2):303-315. doi:10.2478/acph-2022-0018. DOI
21. Buda V, Andor M, Petrescu L et al. Perindopril Induces TSP-1 Expression in Hypertensive Patients with Endothelial Dysfunction in Chronic Treatment. Int J Mol Sci. 2017;18(2):348. doi:10.3390/ijms18020348. DOI
22. Siwik D, Gajewska M, Karoń K et al. Pleiotropic Effects of Acetylsalicylic Acid after Coronary Artery Bypass Grafting-Beyond Platelet Inhibition. J Clin Med. 2021;10(11):2317. doi:10.3390/jcm10112317. DOI

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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3. The impact of destructive factors of war on the human body and adaptive processes
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5. Mechanisms of formation and development of typical pathological processes, diseases, and their complications
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8. Pathogenetic platform of comorbid pathology
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10. Pathomorphosis of diseases
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Working languages of the conference: Ukrainian, English

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