ORIGINAL ARTICLE

CONTENTS

Clinical, endoscopic, morphological and microbiological characteristics of diverticular disease in patients with metabolic disorders

Hanna A. Dorohavtseva[1], Andrey E. Dorofieiev[2], Mykhailo S. Myroshnychenko[3]

[1] FEOFANIYA CLINICAL HOSPITAL OF THE STATE ADMINISTRATION OF AFFAIRS, KYIV, UKRAINE

[2] UKRAINIAN MILITARY MEDICAL ACADEMY, KYIV, UKRAINE

[3] KHARKIV NATIONAL MEDICAL UNIVERSITY, KHARKIV, UKRAINE

ABSTRACT

Aim: The aim of the study was to identify the clinical course and endoscopic activity features in patients with uncomplicated diverticular disease (UDD) associated with diabetes mellitus (DM), overweight, and obesity and perform an analysis of the gut microbiome and morphological characteristics of the colonic mucosa in such patients.

Materials and Methods: 259 patients with UDD, hospitalized in the Department of Gastroenterology of Feofaniya Clinical Hospital of the State Administration of Affairs during the period of 2020-2024, were included in the study. Among all patients with DD included in the study, 43 had no metabolic disorders (MD) (DM, overweight, obesity), while 216 presented with varying degrees of MD. All patients underwent total colonoscopy with assessment of endoscopic activity of diverticular inflammation using the Diverticular Inflammation and Complication Assessment (DICA) score. The clinical course of DD was evaluated according to the classification proposed by the German Society of Gastroenterology, Digestive and Metabolic Diseases and the German Society of General and Visceral Surgery in 2021. The microbiome analysis was conducted only in 172 patients who had the financial means to undergo this test. During endoscopic examination of the colon in all patients, mucosal biopsies were obtained from the diverticular orifice. Histological, histochemical, and immunohistochemical methods were used. The obtained digital indicators in the groups were analyzed using statistical methods.

Results: This study evaluated clinical, endoscopic, morphological, and microbiological characteristics of DD in patients with metabolic disorders. A recurrent course of diverticular inflammation was observed more frequently in patients with metabolic dysfunctions. Endoscopic assessment of inflammatory activity correlated with histological changes of colon mucosa and alterations in mucin expression (MUC2 and MUC4). Microbiological analysis revealed a reduction in butyrate-producing flora (*Akkermansia muciniphila*, *Faecalibacterium prausnitzii*) with predominance of *Bacteroidetes* in metabolic disorder patients.

Conclusions: The clinical, morphological, microbiological and endoscopic features of DD identified by the authors highlight pathophysiological links between metabolic dysfunction (DM, overweight, obesity) and DD progression.

KEY WORDS: diverticular disease, clinical and endoscopis features, diabetes mellitus, obesity, gut microbiota, colon mucosa morphology

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INTRODUCTION

Diverticulosis and DD are common gastrointestinal conditions worldwide, with an increasing prevalence and a significant financial burden on healthcare systems in every country. It is estimated that one in four to five individuals will develop diverticulosis or diverticulitis during their lifetime [1]. Traditionally, DD was considered a disease of the elderly; however, over the past decades, its incidence has risen among younger individuals. Contributing factors of DD include population aging, Westernized diet, sedentary lifestyle, overweight and obesity, as well as the widespread use of screening colonoscopy. Certain comorbidities, particularly DM, may promote diverticula formation and influence the inflammatory activity and clinical course of DD.

Epidemiological data on the prevalence of DD in patients with DM remain inconsistent. Danish cohort study demonstrated a slightly higher incidence of DD among patients with type 2 diabetes (0.76 vs. 0.54 events per 1000 person-years) compared to non-diabetic individuals, with the risk increasing with longer disease duration. However, after adjusting for body mass index (BMI), DM was paradoxically associated with a significantly lower risk of DD, suggesting that patients with lower BMI carry a reduced risk. One possible explanation is lifestyle modification required in diabetes management [2], as well as metformin use, which has been shown to reduce the risk of acute diverticulitis [3].

The association between DD and metabolic disorders is further supported by genetic studies. Genome-wide

association studies suggest a causal relationship between type 2 diabetes, higher BMI, smoking, and increased risk of DD [4]. Mendelian randomization analyses demonstrated that genetic predisposition to type 2 DM is associated with higher risk of DD [5].

DM clearly induces physiological changes in the colonic wall that favors diverticula formation. Most importantly, colonic motility is impaired [6]. Autonomic diabetic neuropathy leads to delayed colonic transit and increased retrograde movements, promoting stasis and elevated intraluminal pressure [7]. Furthermore, accumulation of advanced glycation end-products in extracellular matrix proteins, such as collagen and elastin, increases tissue stiffness, reduces elasticity, and disrupts cell-matrix interactions [8]. Both increased intraluminal pressure and these structural wall alterations are central to diverticula formation.

DM also worsens the course of acute diverticulitis. Patients with DM exhibit more advanced inflammation according to Hinchey classification and higher complication rates. They are more frequently subjected to surgery (46.9% vs. 15.5% in non-diabetics) and have longer hospital stays [9]. Interestingly, DM increases the risk of diverticular bleeding in acute diverticulitis but does not significantly influence the risk of abscess formation, bowel obstruction, or colectomy. Moreover, complicated diabetes is associated with longer hospitalizations and higher healthcare expenditures related to diverticular disease [10].

The mechanisms underlying the more severe clinical course of DD in the context of metabolic disorders are multifactorial. Experimental animal studies demonstrated that DM disrupts intestinal barrier function, leading to reduced mucus layer thickness, impaired tight junction integrity, and development of "leaky gut." These changes are accompanied by low-grade chronic inflammation, severe dysbiosis with predominance of proinflammatory Proteobacteria, and Paneth cell depletion [11]. A defective mucosal barrier allows translocation of bacterial wall components, such as lipopolysaccharides, which activate Toll-like receptor 4. This receptor triggers downstream signaling cascades that stimulate production of proinflammatory cytokines, including TNF-α, IL-6, IL-8, and IL-12, resulting in both local and systemic inflammation [12].

Most available scientific publications have focused on the clinical course of acute and complicated diverticulitis in diabetic patients.

AIM

The aim of the study was to identify the clinical course and endoscopic activity features in patients with UDD associated with DM, overweight, and obesity and perform an analysis of the gut microbiome and morphological characteristics of the colonic mucosa in such patients.

MATERIALS AND METHODS

259 patients with UDD, hospitalized in the Department of Gastroenterology of Feofaniya Clinical Hospital of the State Administration of Affairs during the period of 2020-2024, were included in the study. The cohort comprised 101 men and 158 women. All patients had BMI calculated, and all underwent total colonoscopy with assessment of endoscopic activity of diverticular inflammation using the DICA score.

The clinical course of DD was evaluated according to the classification proposed by the German Society of Gastroenterology, Digestive and Metabolic Diseases and the German Society of General and Visceral Surgery in 2021 [13]. According to this classification, patients were divided into the following groups: diverticulosis as an incidental finding during screening colonoscopy; acute uncomplicated diverticulitis (without pericolic phlegmonous reaction); chronic forms of DD: symptomatic uncomplicated DD and recurrent course (recurrent inflammation within one year).

The microbiome analysis was conducted only in 172 patients who had the financial means to undergo this test. The intestinal microbiome was assessed by qRT-PCR using primers targeting the 15S rRNA gene. Quantitative determination of bacterial taxa was performed by qPCR with primers specific for *Firmicutes*, *Bacteroidetes*, *Akkermansia muciniphila*, and *Faecalibacterium prausnitzii*, as well as universal bacterial primers (Table 1).

Clinical specimens were processed with a lysis buffer in the presence of silica particles as sorbent. This procedure resulted in the disruption of cell membranes, viral envelopes, and other biopolymeric complexes, leading to DNA release. In the presence of the lysis buffer, the liberated DNA bound to silica particles, while other components of the lysed clinical material remained in the solution and were removed by centrifugation and subsequent washing. The addition of elution buffer caused the transfer of DNA from the silica surface into the solution, which was separated from the sorbent particles by centrifugation. As a result, highly purified DNA free of PCR inhibitors was obtained, ensuring high analytical sensitivity of the amplification reaction.

During endoscopic examination of the colon, mucosal biopsies were obtained from the diverticular orifice. Biopsy samples were fixed in 10% neutral buffered formalin (pH 7.4) for 24-48 hours. After fixation, tissue processing was performed using an *Excelsior AS* processor (Thermo Fisher Scientific, UK), followed by paraffin embedding with the *HistoStar* embedding system

Table 1. Characteristics of bacterial primers

Target flora	Primer sequences
Bacteroidetes	798ebF AAACTCAAAKGAATTGACGG (Forward) cfb967R GGTAAGGTTCCTCGCGTAT (Reverse)
Firmicutes	928F-Firm TGAAACTYAAAGGAATTGACG (Forward) 1040FirmR ACCATGCACCACCTGTC (Reverse)
Akkermansia muciniphila	CAGCACGTGAAGGTGGGGAC (Forward) CCTTGCGGTTGGCTTCAGAT (Reverse)
Faecalibacterium prausnitzii	GGAGGAAGAAGGTCTTCGG (Forward) AATTCCGCCTACCTCTGCACT (Reverse)
Universal	926F AAACTCAAAKGAATTGACGG (Forward) 1062R CTCACRRCACGAGCTGAC (Reverse)

Source: compiled by the authors of this study

Table 2. Clinical features of DD in the examined patients

	DD	%	DD-MD	%	DD+MD	%
Acute diverticulitis	23	8.9	10	23.3	13	6.0
Recurrent diverticulitis	55	21.2	3	7.0	52	24.1
Diverticulosis	47	18.2	17	39.5	40	18.5
Symptomatic uncomplicated DD	134	51.7	13	30.2	111	51.4
Total	259	100	43	100	216	100

Source: compiled by the authors of this study

(Thermo Fisher Scientific, UK). Serial histological sections of 2–3 μm thickness were prepared and stained with hematoxylin and eosin. Periodic acid-Schiff (PAS) reaction was also carried out.

Immunohistochemical analysis was performed on adhesive slides (*Super Frost Plus*, Menzel, Germany). For antigen epitope retrieval, citrate buffer (pH 6) and EDTA buffer (pH 8) were used. The HRP UltraVision Quanto detection system and DAB Quanto chromogen (Thermo Fisher Scientific, USA) were applied. Immunohistochemistry was performed with mouse monoclonal antibodies against MUC2 (clone Ccp58, Master Diagnostica, Spain) and MUC4 (clone 8G7, Master Diagnostica, Spain).

The slides were examined with a *ZEISS Primostar 3* microscope (Carl Zeiss, Germany) equipped with an integrated digital color camera, and a *BRESSER Science TFM-301 Trino* microscope with a *BRESSER Full HD* camera (Bresser GmbH, Germany).

Statistical analysis was performed using *STATISTICA 12* (StatSoft Inc.). Data accumulation, correction, and systematization, as well as visualization of results, were performed with *Microsoft Excel 2015*. Descriptive statistics and variation analysis were applied. Pearson's Chi-square (χ^2) test was used to evaluate differences in categorical variables. For small sample sizes (≤5), Fisher's exact test was applied. A significance threshold of $p<0.05$ was considered statistically significant, with a confidence level not lower than 95%.

RESULTS

Among 259 patients with DD included in the study, 43 (16.6%) had no MD (DD-MD), while 216 (83.4%) presented with varying degrees of MD (DD+MD) (58 (26.9%) patients – DM, 158 (73.1%) patients – overweight or different grades of obesity. Patients with DD were predominantly individuals over 60 years old with a mean age of 65.6±1.45 years. In all groups the number of women was greater ($p<0.05$) than the number of men (Fig. 1).

In all groups diverticula were predominantly localized in the left colon (Fig. 2). Single and multiple diverticula were detected in patients of all groups. The number of cases with single and multiple diverticula did not differ ($p>0.05$) in all groups (Fig. 3).

In patients with DD and MD, a recurrent course of diverticular inflammation was significantly more common – 52 (24.1%) vs. 3 (7.0%) in patients without MD ($p<0.05$). Symptomatic uncomplicated DD was also more frequently diagnosed in patients with metabolic disturbances – 111 (51.4%) vs. 13 (30.2%) ($p<0.05$). At the same time, acute diverticulitis was identified in 10 (23.3%) patients with normal BMI and without DM, compared to 13 (6.0%) in the comparison group ($p<0.05$) (Table 2).

Patients with DD demonstrated disturbances in the population of butyrate-producing bacteria. A normal level of *Akkermansia muciniphila* was found in 19.4% (n=29) of patients with MD and in 45.5% (n=10) of patients with normal BMI ($p<0.05$). A re-

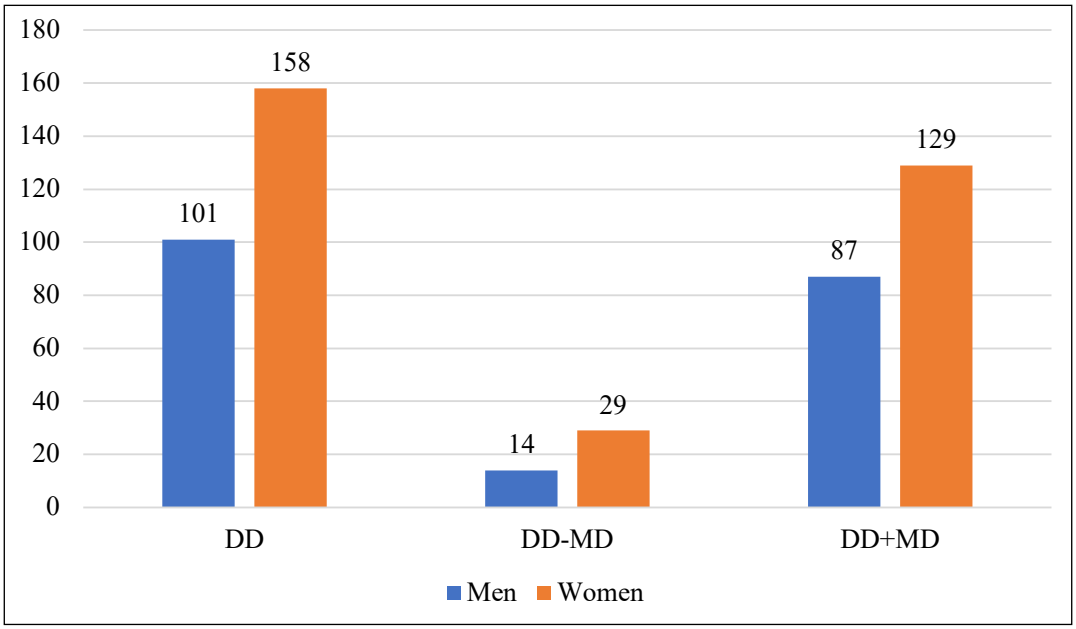

Fig. 1. Gender characteristics of patients with DD
Source: compiled by the authors of this study

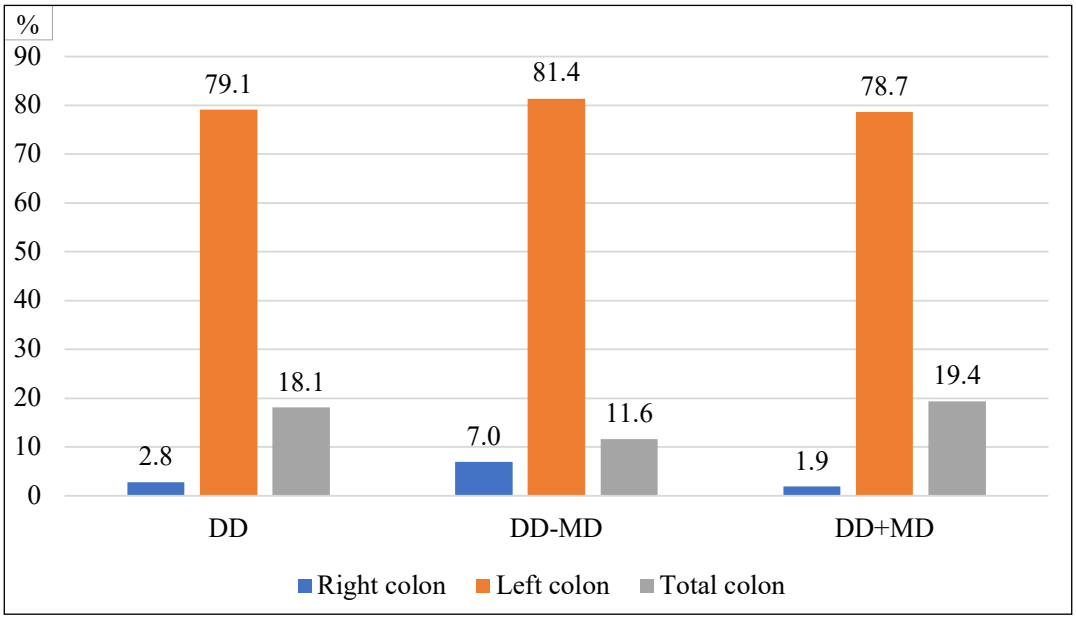

Fig. 2. Localization of diverticula in patients with DD
Source: compiled by the authors of this study

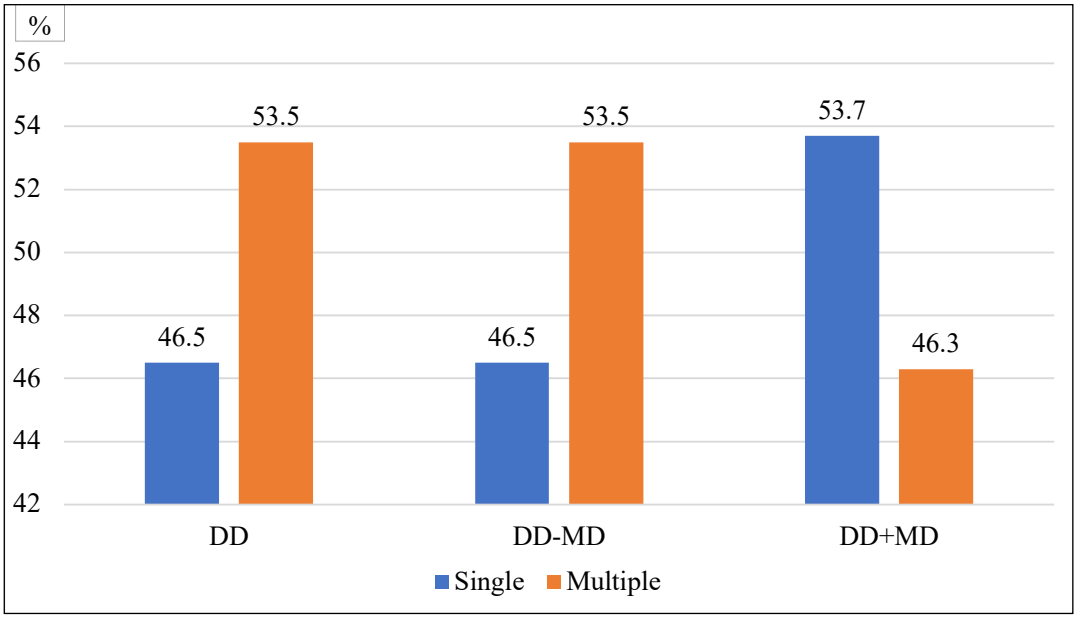

Fig. 3. Number of diverticula in patients with DD
Source: compiled by the authors of this study

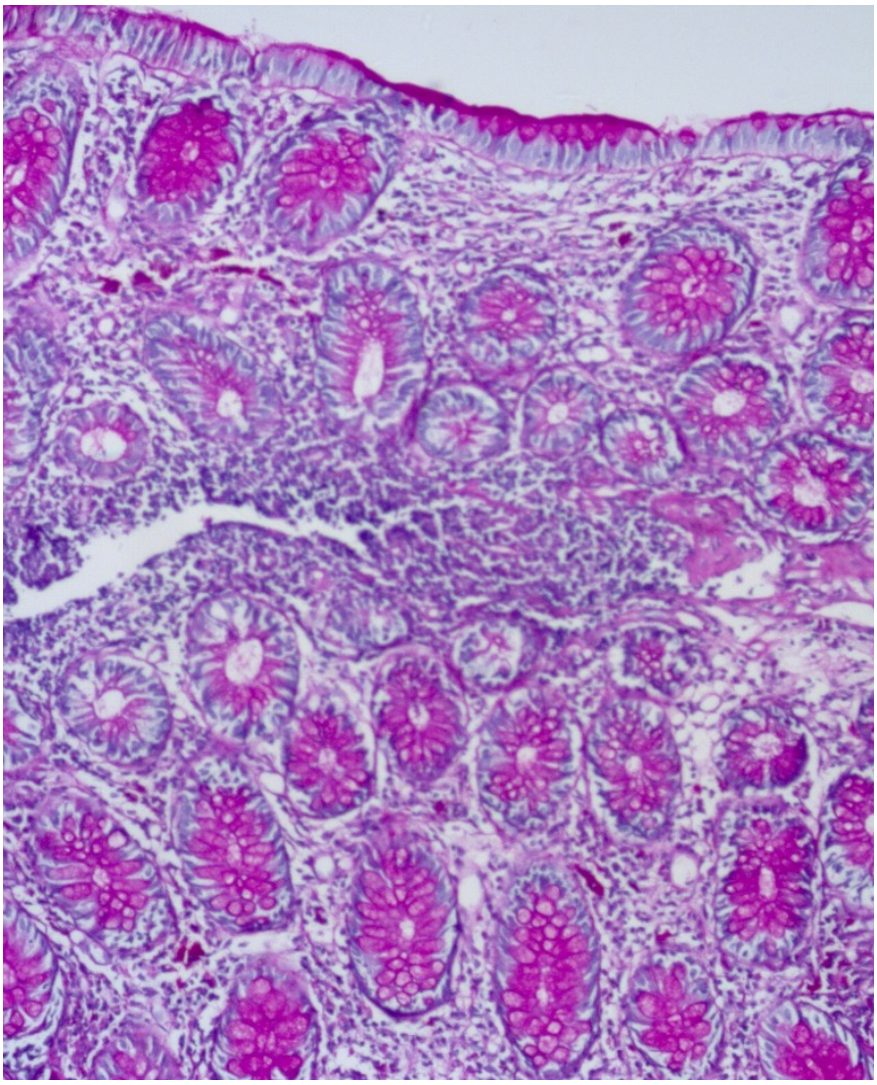

Fig. 4. Decreased PAS reaction intensity in a patient with DD, DM and obesity. PAS reaction, ×100
Picture taken by the authors

duction of *Akkermansia muciniphila* (<10^{10} CFU/g) or its absence was detected in 39.3% (n=59) and 41.3% (n=62) of patients with DM and high BMI, respectively, and in 31,8% (n=7) and 22.7% (n=5) of patients without MD.

A more pronounced deficiency of *Faecalibacterium prausnitzii* (<10^{10} CFU/g) was observed in patients with diverticular inflammation and MD compared to the control group: 41.3% (n=62) vs. 22.7% (n=5).

The *Firmicutes/Bacteroidetes* ratio <1.0 was found in 44.5% (n=10) of patients with DD without metabolic disturbances and in 74.0% (n=111) of patients with MD (p<0.05).

It should be noted that the intensity of colonic mucosal inflammation differed among DD patients of different groups. The mean DICA endoscopic activity score of diverticular inflammation in patients with MD was 1.23±0.23, while in patients with DD without metabolic disturbances it was 0.97±0.35. This correlated with a greater inflammatory intensity on histological examination. Hematoxylin and eosin staining of colonic biopsies in patients with DD and metabolic dysfunction more frequently revealed a denser inflammatory cell infiltrate with neutrophils compared to patients with isolated DD.

A decrease in butyrate-producing microflora in patients with diverticular inflammation caused the alteration of the morphofunctional state of the colonic mucosal barrier. These changes manifested by a reduction in mucus layer thickness, decreased number of goblet cells and their vacuole size, reduced mucus production capacity, as well as alteration in the mucin profile (changes in MUC2 and MUC4 expression). Analysis of PAS reaction demonstrated a decrease in its intensity in DD patients with type 2 diabetes, particularly in combination with obesity (Fig. 4).

Furthermore, analysis of mucin expression in the colonic mucosa revealed that patients with symptomatic uncomplicated DD and MD demonstrated reduced and heterogeneous expression of MUC2 and MUC4. In contrast, in DD patients without metabolic disturbances, alteration in mucin expression were minimal (Fig. 5, 6).

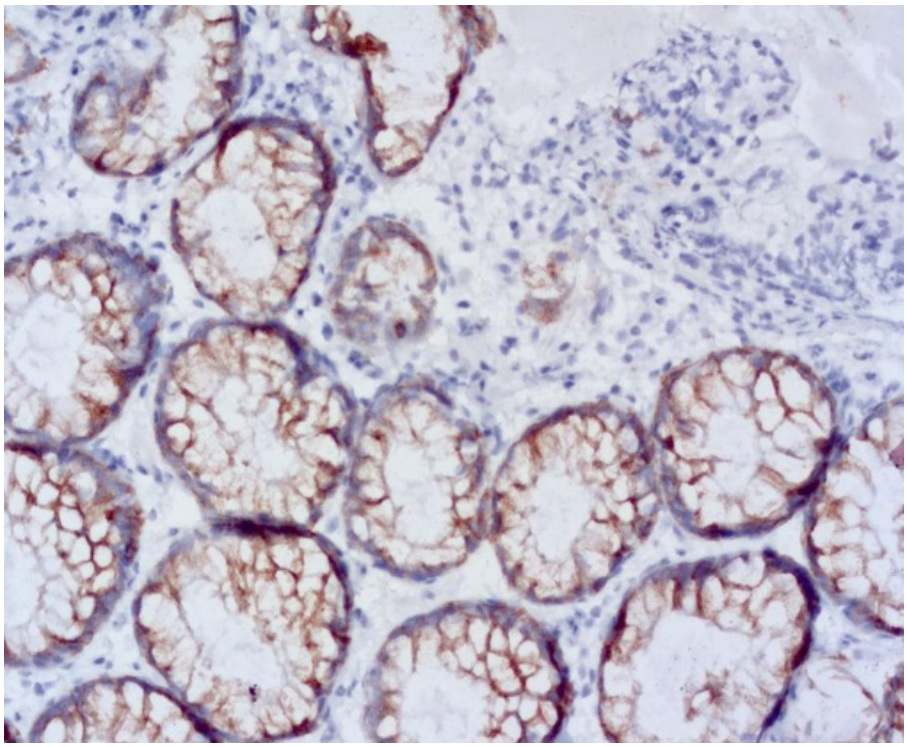

Fig. 5. Reduced and heterogeneous expression of MUC2 in the colonic mucosa of a patient with DD and MD. Immunohistochemical reaction with monoclonal antibody against MUC2, ×200
Picture taken by the authors

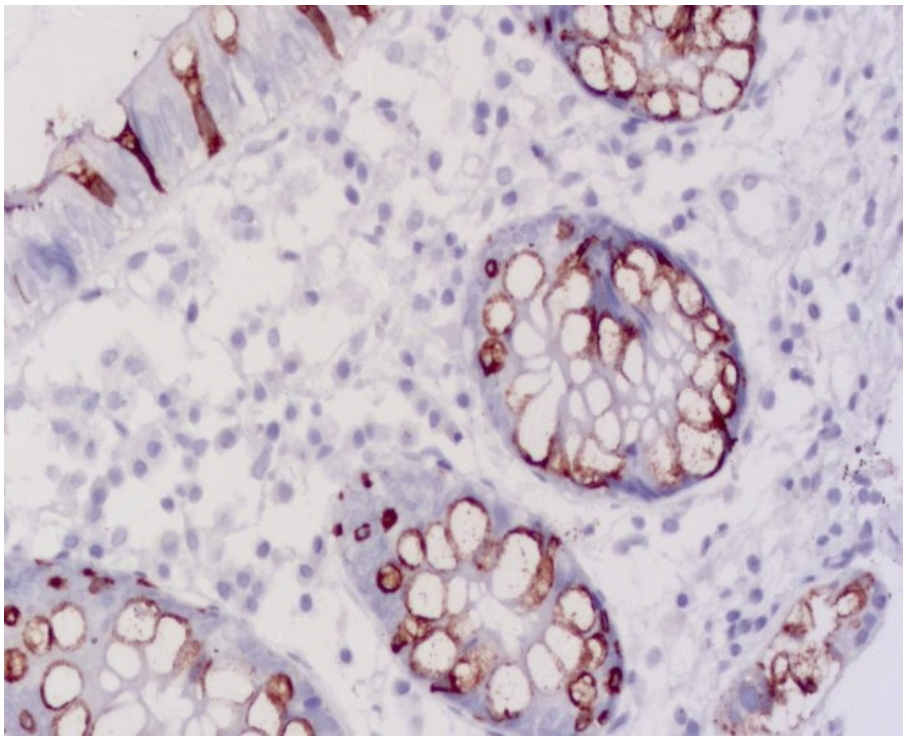

Fig. 6. Reduced and heterogeneous expression of MUC4 in the colonic mucosa of a patient with DD and MD. Immunohistochemical reaction with monoclonal antibody against MUC4, ×200
Picture taken by the authors

DISCUSSION

In patients with DD and MD, distinct clinical, endoscopic, morphological, and microbiological features of the disease course were identified. A recurrent course of diverticular inflammation was more frequently observed in DD patients with metabolic disturbances [14].

Inflammatory activity in patients with diverticula can be assessed endoscopically. Although the endoscopic index of diverticular inflammation is rarely used in routine practice, it is valuable in predicting the risk of recurrence of DD exacerbations [15, 16]. In our study, patients with MD demonstrated higher endoscopic activity of diverticular inflammation compared with those with isolated DD. Increased endoscopic inflammation correlated with more pronounced histological inflammatory activity in patients with DD and metabolic disturbances, as well as altered mucus production and modification of the colonic mucus composition, includ-

ing decreased expression of MUC2 and MUC4. A higher DICA score in these patients may explain the recurrent course of DD in the setting of metabolic dysfunction.

The population of butyrate-producing bacteria in DD patients with metabolic disturbances reflected a general trend towards reduction, consistent with inflammatory conditions of the colon and metabolic dysfunction. A more pronounced deficiency of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* in DD patients with metabolic disturbances indicates a deeper impairment of the morphofunctional state of the colonic mucosal barrier. Reduced numbers of mucus-producing bacteria result in thinning of the mucus layer, decreased size and number of goblet cells with reduced mucus secretion capacity, and altered mucin profile (decreased MUC2 and MUC4 expression) [16-18].

The *Firmicutes/Bacteroidetes* ratio <1.0, reflecting predominance of *Bacteroidetes*, was detected more often in patients with DD and MD compared to patients without MD. Excessive abundance of *Bacteroidetes* has been associated with intestinal inflammation and its severity [14]. By contrast, *Firmicutes* enrichment is more characteristic for obesity and metabolic syndrome. Interestingly, in our cohort, *Bacteroidetes* predominance was observed among overweight and obese patients, supporting the concept of more active diverticular inflammation in this group.

CONCLUSIONS

A recurrent course of diverticular inflammation is more frequent in patients with MD. The level of butyrate-producing bacteria is significantly reduced in DD patients with metabolic disturbances, reflecting impaired morphofunctional status of the colonic mucosa. In patients with DD and MD, *Bacteroidetes* predominate, indicating higher inflammatory activity in the colon. A higher endoscopic index of diverticular inflammation, correlating with the intensity of histological changes and mucus production alterations (decreased MUC2 and MUC4 expression) may underlie the recurrent course of DD in patients with metabolic dysfunction.

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CONFLICT OF INTERESTS

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Mykhailo S. Myroshnychenko
Department of General and Clinical Pathological Physiology
named after D.O. Alpern, Kharkiv National Medical University,
4 Nauky Avenue, Kharkiv, Ukraine
e-mail: msmyroshnychenko@ukr.net

ORCID AND CONTRIBUTIONSHIP

Hanna A. Dorohavtseva: 0000-0002-4080-5992 A C D
Andrey E. Dorofieiev: 0000-0002-2631-8733 B E
Mykhailo S. Myroshnychenko: 0000-0002-6920-8374 D F

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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