REVIEW ARTICLE

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Certain ethical issues that arise when using 3D bioprinting technology

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ABSTRACT

Aim: Theoretical and applied study of the ethical issues that arise when using three-dimensional printed bioproducts and their significance for the development of principles for the application of additive manufacturing technologies in medicine.

Materials and Methods: Various methods of scientific knowledge make up the methodological basis of on interdisciplinary approach, which includes a set of methods that allow us to investigate the technological, legal and social aspects of the application of 3D bioprinting, its potential, limitations and ethical challenges.

Conclusions: Ethical principles are one of the foundations for ensuring the provision of proper medical care and medical services with the use of three-dimensional printed bioproduct technologies at an appropriately high level, and are directly related to strict adherence to the principles and standards of additive manufacturing and bioethics, which are imposed on all participants (be it a doctor a 3D designer, a manufacturer of a 3D bioprinter, etc).

KEY WORDS: bioprinting, bioethics, informed consent, bio-ink, three-dimensional printed bioproducts, additive manufacturing

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INTRODUCTION

Among modern breakthrough technologies, three-dimensional printed bioproduct technologies occupy a significant area. In addition to widespread research on intellectual property rights, risks and professional responsibility, morality and religion, bioethics issues play an equally significant role, the urgent solution of which may affect the further application of additive technologies in medicine. In general, problematic issues of the application of innovative technologies and bioethics have already been the subject of our scientific research [1, 2]. At the same time, the relevance of the study lies in identifying ethical issues when using three-dimensional bioprinting technologies. This is primarily due to the fact that ensuring and guaranteeing the right to life and proper medical care, society expects their proper, professional and responsible implementation, which is impossible without ensuring high standards of bioethics in additive manufacturing.

The issue of determining the essence of ethical aspects that arise when using three-dimensional printed bioproducts has been the subject of research by many foreign scientists. Among the scientists who have investigated individual aspects of this issue, it is appropriate to single out the works of F. Gilbert, Z. Jin, J. Kim, L. Lategan, P. li, M. Munsie, A. Recum, M. Rizzo, E. Salvaterra, A. Siddique, Q. Yan, R. Veeravalli, N. Vermeulen, D. Williams, and others. At the same time, a comprehensive study of of the ethical issues that arise when using three-dimensional printed bioproducts and methods of their resolution was virtually disregarded by the scientists.

AIM

The aim of the article was a theoretical and applied study of the ethical issues that arise when using three-dimensional printed bioproducts and their significance for the development of principles for the application of additive manufacturing technologies in medicine.

MATERIALS AND METHODS

Various methods of scientific knowledge make up the methodological basis of on interdisciplinary approach, which includes a set of methods that allow us to investigate the technological, legal and social aspects of the application of 3D bioprinting, its potential, limitations and ethical challenges. Thus, the comparative legal method was used to compare the legislative norms and approaches to regulating 3D bioprinting in different countries. The system-complex method gave us the opportunity to

analyze the essence of informed consent, sources of biomaterials and availability of technologies, as well as the impact of these technologies on social perceptions of medicine and scientific progress. The following other methods were used in the study, in particular: dialectical, analysis and synthesis, formal-logical etc.

REVIEW AND DISCUSSION

INTRODUCTION TO THE CONCEPT OF ADDITIVE TECHNOLOGIES

3D printing is one of the most innovative technologies of our time, and 3D bioprinting is revolutionizing the medical technology industry, the essence of which has already been the subject of our scientific research. The technology is even called the megatrend of the fourth industrial revolution [3].

3D bioprinting is an advanced application of additive manufacturing, which involves the layer-by-layer creation of a tissue or organ using a bioprinter using instructions from computer graphics software [4]. It is defined as the process of applying biocompatible materials layer by layer to create tissues that can mimic the properties of living cells. The creation of tissue constructs is carried out by combining computer-aided design with computer-aided manufacturing to carefully transform the corresponding biomaterials and bio-inks into tissue substitutes, which at the same time provides significant control over their structure, reproducibility, and functional accuracy. This technology offers the simultaneous printing of different cell types in specific spatial locations, making it prime for use in regenerative medicine [5].

This technology is one of the most promising technologies being implemented in tissue engineering and regenerative medicine. As a widespread and fundamental biomanufacturing technology that uses various biological components (such as cells, growth factors, proteins, and biomaterials), this technology can create 3D models, replacement organs, and other therapeutic products. Bioprinting has already shown incredible growth and has become a technology that can overcome the current limitations of tissue engineering and regenerative medicine. It also has the potential to develop personalized implants that can be a solution to the organ shortage crisis. 3D bioprinted tissue models can also be a platform for high-throughput toxicological screening and drug discovery [6].

Thus, the first human organ transplant obtained using 3D printing was a trachea, which was implanted in an infant with a congenital defect [7]. And an implanted bionic ear printed on a 3D printer had better hearing sensitivity than the human ear [8].

Unlike the traditional use of 3D printing to create acellular scaffolds, 3D bioprinting requires different technical methods, such as biomicroscopy, autonomous self-assembly, and mini-tissue building blocks, to create 3D structures with mechanical and biological properties suitable for the deposition of living cells and the restoration of tissue and organ functions. Cells, bio-inks, and bioprinters are all necessary components of the bioprinting process, and each of them has biological, technological, ethical, and other challenges related to cost and clinical effectiveness. As a result, a number of difficulties arise in integrating 3D bioprinting into widespread clinical practice [9].

ETHICAL ISSUES OF INFORMED CONSENT AND SOURCES OF BIOINKS IN THE APPLICATION OF 3D PRINTED BIOPRODUCTS TECHNOLOGIES

Research and commercialization are advancing at such a rapid pace that issues related to the technology, in terms of ethics, policy, regulation, and public acceptance, are not being adequately addressed. Although identifying the ethical, legal, and social aspects of this technology at an early stage is not only part of our social responsibility but also a benefit for the future of the technology itself [10].

Thus, 3D bioprinting technology raises a multitude of ethical issues, among which, in this study, we will consider such as informed consent and sources of bio-inks.

A fully informed consent process will minimize the risk of harm and possible ethical violations [11]. Informed consent is a legal doctrine based on the fundamental ethical principle of the patient's autonomy to make free and informed decisions about medical treatment or research involving their body. Although informed consent for medical treatment is a consolidated practice worldwide and is characterized by different processes and forms of decision-making depending on the purpose of the clinical intervention or research, there is currently no standard procedure for obtaining informed consent for 3D procedures. This is mainly due to the current lack of specific regulations regarding this technology and opens up several avenues for developing informed consent models for bioprinting that are based on respect for the autonomy of the donor and/or the patient involved in the process [12].

E. Salvaterra identifies certain ethical issues that informed consent for medical 3D printing faces. First, the unknown behavior of materials incorporated into the recipient's body requires that the patient be informed of the potential risks of developing teratoma or other diseases not foreseen at the time of transplantation.

Furthermore, it is necessary that the patient or their legal representatives be informed of the difficulty of terminating participation in current protocols by requesting the removal of bioconstructs after their transplantation. Specific information should also be provided on the methods used to ensure the protection of the confidentiality of all subjects involved in biomanufacturing during the collection, storage, and use of personal data collected during the bioprinting process [12].

3D bioprinting using appropriate bio-inks has become a major tool for fabricating 3D biomimetic complex structures that mimic physiological functions [13]. Bio-inks are a combination of living cells and a compatible scaffold, such as collagen, gelatin, silk, alginate, or nanocellulose. The exact material depends on the patient and the function [14]. The bio-inks themselves are used in the printing process to create 3D structures and consist of a mixture of living cells and biomaterials that provide support for the cells after printing [15]. Bio-inks can be defined as any natural or synthetic materials used in bioprinting and designed to interact with a biological system [16]. Bio-inks, which are the most important component, refer to cell aggregates deposited on or within scaffolds or cell constructs that can consist of bioactive components and biomaterials [5].

Currently, sources of cells for bioprinting include adult stem cells and human embryonic stem cells. The use of the latter cells is particularly controversial because it involves the destruction of human embryos, which raises moral and ethical questions about the value and sanctity of human life. Conversely, the use of adult stem cells and induced pluripotent stem cells may be considered more ethically acceptable because it does not involve the destruction of embryos. Some scientists view the embryo as a being with the same moral rights as an adult or a child, arguing from religious and moral perspectives that life begins at the moment of conception, making the embryo a person with rights and interests that need to be protected. Therefore, removing cells from a blastocyst to create an embryonic stem cell line is tantamount to committing murder. However, until proven otherwise, unless the blastula attaches to the uterine wall, it cannot develop into a child. Moreover, it is quite reasonable to argue that the embryo acquires a true "moral person" at the stage of development after fertilization. This is an eternal debate, the resolution of which is unlikely to be achieved [17]. However, according to domestic legislation, a person has a civil legal capacity at the moment of his birth (part 2 of article 25 [18]).

It should also be remembered that the commercial use of embryonic cells is taboo. The protection of human rights in the field of biomedical research is based on two principles, namely: informed consent and confidentiality. The use of bioprinting may endanger health (e.g. organs) or quality of life (e.g. reproductive organs). The possible commercialization of bioprinting may also raise ethical issues. The point is the safety, quality, and effectiveness of bioprinting technologies that respect human rights and dignity [19].

One of the ethical issues related, in particular, to the use of stem cells in 3D bioprinting is the origin of these biomaterials and focuses on the distinction between autologous and allogeneic stem cells. While the use of autologous stem cells raises well-known issues related to patient safety (e.g., the risk of oncogenicity), the processing of allogeneic stem cells raises additional questions regarding the perception of a new identity (or personhood) by the recipient of the engineered cells (development of consent procedures that clarify the complex stage of biomanufacturing, protection of confidentiality and intellectual property rights arising from biomanufacturing) [12].

It is difficult to foresee in advance the side effects of implantable devices printed on a 3D printer since it is only possible to analyze how they react in the body after they have been implanted. This impasse can be overcome by using autologous cells, which are specifically adapted to the patient and cannot be tested on any other patient. However, even with the use of autologous cells, the risk of side effects will not be completely eliminated, and there will still be a need for standardization of the materials for manufacturing. In addition, it would be impossible to conduct clinical trials, since it would be unethical to first test this patient-adapted material on another population of non-specific subjects if these treatments are not life-saving. Moreover, great attention should be paid to the long-term outcome of the implants [7].

There are other issues that may affect the moral acceptability of using bio-inks from non-autologous cells. For example, the use of stem cell bio-inks obtained from donors who have been coerced into donating their cells, or donors who are unable to give informed consent to the use of their cells (e.g., unconscious patients in intensive care units). In this regard, a trusted person, such as a family member, may be able to make arrangements on behalf of such a person. In any case, potential donors and their families should fully understand the risks and have sufficient information to justify their expectations. The use of bio-inks from autologous cells can often be considered ethically understandable because they are derived from the patient's body [20]. Equally important, as autologous induced pluripotent stem cell lines may outlive their donors and potentially be used for proj-

ects not planned at the time of tissue/cell collection, it is important to routinely seek permission for research or other use throughout the life of the donor and/or project, avoiding the need to re-contact the donor for consent at a later date [21].

Bioprinting using stem cells poses a risk of abnormal cell growth, potentially exposing the recipient to the risk of developing cancer or other adverse effects, such as zoonotic diseases from non-human stem cells [22]. Furthermore, when using xenogeneic cells, patients should be fully informed about the source of the cells in the informed consent, as they may not agree to the use of cells from certain animal species (e.g., porcine) for religious reasons.

It is also essential that bio-inks demonstrate biocompatibility and, where appropriate, biodegradability by reproducing the natural microenvironment of tissues. Bio-inks should be chemically modified to meet the specific requirements of different tissue types. Finally, they should have the potential for large-scale production, minimizing batch-to-batch variations [23]. Biocompatibility of bio-inks for 3D bioprinting refers to the ability to perform the desired function that will support appropriate cellular activity, including cell viability, adhesion, proliferation, and differentiation, to promote tissue regeneration without causing any systems [24].

ETHICS IN BUSINESS: ADDITIVE TECHNOLOGIES ON THE LINE OF ECONOMIC STRATIFICATION

Another important ethical issue that arises when applying 3D bioprinting technologies is affordability. The cost of 3D bioprinters and starting materials is high, often making the technology unaffordable for many and potentially exacerbating social inequalities. Most available 3D bioprinters are built on modified 3D deposition modeling frameworks that are adapted to apply biocompatible materials and their price ranges from US$13,000 to US$300,000. This makes the biomaterials expensive and creates a barrier to the affordability of bioprinting, given that high manufacturing costs translate into high costs for patients. In an attempt to democratize the technology, prototypes of a cost-effective 3D bioprinter built from recycled materials and off-the-shelf electronics have been reported. This approach, which uses open-source methodology and affordable materials, could make bioprinting more accessible, potentially bringing its benefits to low- and middle-income countries and narrowing the economic gap in healthcare [17].

However, social stratification is still possible in this area. These are expensive scientific and technological solutions that are unlikely to benefit everyone. 3D bioprinting is another game-changer that will not be available to everyone, and certainly not to most in its immediate application. Despite the promise of organs printed "on demand" for everyone, it is likely that the specter of a "social stratification of biofabrication" will arise with those who can afford to pay for their own organs. A tiered system of therapeutic organ replacement is likely intended for those who can afford to pay for their own organs, who live longer; perhaps enjoying a significantly higher quality of life, avoiding the negative physical consequences of taking immunosuppressants. While others will wait until a human organ donor becomes available, they will then be forced to take a punitive drug regimen for the rest of their lives to prevent episodes of rejection of the transplanted organ. Others who cannot afford to pay will make do with "used" organs from another living or deceased donor when they become available (as is done in the current system) [25].

Tissue-engineered medical devices and 3D bioprinting are biomedical applications of additive manufacturing processes for the artificial production of biological tissues. Their goal is to replace damaged tissues and organs. The process of 3D bioprinting is the spatial structuring of biological cells by combining them using a computerized layer-by-layer method. This is necessary for growing living tissues and organs for further use in biological research, in particular, such as regenerative medicine, tissue engineering, and pharmacokinetics [26].

Ethics should become part of the human potential development program. When using technologies in healthcare, both the capabilities of the technologies and the impact and consequences of the technologies on healthcare should be taken into account [19]. The attention of ethicists is not so much on the technology itself as on its application, since it affects people and the environment [19].

The advent of 3D bioprinting technology represents a significant leap forward in the field of medical science, opening up unprecedented opportunities for organ transplantation, regenerative medicine, drug testing and development, and disease modeling. However, the rapid growth and development of this technology has outpaced existing regulatory, legal, and ethical frameworks, resulting in a multitude of bioethical and legal implications that require careful consideration. Safety remains a top priority. As with any medical innovation, the potential risks and adverse effects associated with 3D bioprinting of organs and tissues must be carefully assessed and mitigated [17]. However, in the blind pursuit of innovation, safety cannot be neglected [27].

CONCLUSIONS

The possibility of providing medical care and medical services when using three-dimensional printed bioproduct technologies at an appropriately high level is directly related to the strict adherence to the principles and standards of additive manufacturing and bioethics by all participants. This is due to the fact that, taking into account the specifics of new technologies in the field of 3D bioprinting, we can conclude that not only a doctor who does not have the appropriate experience in the application of such innovative technologies but also one who does not adhere to ethical principles is unable to properly ensure the realization of a person's right to life and health, which is the highest social value in society.

Among the important ethical principles, we can highlight those that are necessary at the pre-preparation stage, namely: informed consent and the suitability of the source of bio-ink as printing materials containing living cells for the creation of living tissues, bones, blood vessels, and even organs. Providing full informed consent by the patient will allow us to avoid further problems that may potentially arise when using any innovative technologies that are at the stage of implementation, including 3D bioprinting technology. Patient awareness of the sources of bio-ink is necessary, since, despite the legislation of the state, there may be moral and religious obstacles for the patient in their use. Thus, an appropriate delineation of ethical standards for 3D bioprinting technologies is useful and necessary for the future of the technology itself.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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