

REVIEW ARTICLE

CONTENTS

New solutions in transplantology and graft acquisition

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ABSTRACT

In view of rapid advancements in the field of transplantology, emerging solutions in tissue procurement for transplantation became a crucial area of research. Tissue transplantation plays a notable role in improving the quality of life for patients afflicted with various ailments, and the increasing number of transplants necessitates the exploration of innovative procurement methods. This study examines a new direction in transplantology, placing focus on innovative approaches to tissue procurement and discussing the commonly used method of "ex mortuo," i.e., retrieving organs from deceased donors. Given the growing demand for organs, the paper discusses the innovative approach slowly emerging as 3D bioprinting. The paper discusses the key challenges associated with the use of this method in transplantology, including issues of biocompatibility, vascularization, and integration with the immune system. The paper also discusses the latest scientific achievements in the field, such as the first transplants of bioprinted organs, demonstrating the practical application of this technology in medicine. It is also the analysis of the ethical, social, and legal aspects related to these new solutions. The article provides a comprehensive overview of the latest trends in transplantology and presents a holistic view of the current state of knowledge and prospects for development in this pivotal area of medicine.

KEY WORDS: transplantology, xenotransplantology, 3D bioprinting, biotechnology

Wiad Lek. 2024;77(6):1284-1290. doi: 10.36740/WLek202406126 DOI

INTRODUCTION

Transplantation is a complex process involving the transfer of cells, tissues, and organs from one organism to another and stands as one of the most effective therapies for patients facing unrepairable failure of vital organs [1]. In recent decades, there has been dynamic development in the field of transplantology, contributing to the improvement of patients' quality of life but also presenting new challenges associated with organ procurement.

Despite medical advances, the growing deficit in transplant availability has become a key issue in contemporary transplantology [2, 3]. Statistical data indicate an increasing disparity between the number of patients awaiting transplantation and the available pool of potential donors. To address these challenges, experts from various medical fields are seeking innovative solutions in organ procurement. Exploration of novel methods and technologies, such as xenotransplantation, 3D bioprinting, or the use of artificial intelligence, has become a pivotal area of research to address this complex problem.

AIM

The purpose of this paper is to review the problems of obtaining cells, tissues and organs for transplantation, to analyze the new method of obtaining transplantation materials that is 3D bioprinting, and to evaluate the ethical aspects, potential profits and risks of this process.

REVIEW

TRANSPLANTOLOGY – CURRENT STATE

Statistical data on organ transplants serve as an indicator of the challenges currently faced by this medical field. The number of patients awaiting transplants significantly exceeds the available pool of donors, which highlights the urgent need for effective strategies development to increase organ availability.

According to data published on the Statistica platform in 2022, 157,494 organ transplants were performed worldwide, representing an increase of 27,813 transplants compared to 2021 [2].

In Poland, as per data available, in 2023 there were 523 deceased donors whose organs were suitable for transplantation, along with 94 living donors [3]. The number of essential tissue transplants performed that year was 1,746, with 20,874 individuals on the waiting list. An analysis of these data shows that in Poland, about 8% of those in need receive an organ for transplantation. Despite a demonstrated increase in the number of transplants performed in Poland, with a rise of 730 procedures between 2007 (922 transplants) and 2023 (1,652 transplants), the number of recipients still exceeds the number of donors.

These presented numbers unequivocally underscore the cruciality of the ongoing development in the field of transplantology and the necessity of exploring new sources for organ and tissue procurement.

HISTORY OF TRANSPLANTOLOGY

Transplantation has a rich history with roots in distant eras, although today it is mainly associated with advances in modern medicine.

Archaeologists have unearthed ancient Egyptian surgical techniques in papyrus scrolls, dating as far back as 2000 years BC considered the earliest attempts at transplants [4].

Similar achievements were noted in ancient Indian and Chinese civilizations, where artifacts indicate pioneering attempts at tissue and organ transplantation [5]. Dates around 600 BC,based on archaeological findings, suggest that in ancient India, the first attempts at skin grafting were made. These ancient experiments undeniably contributed to the development of the medical field, uncovering new possibilities and raising awareness about what was feasible in the realm of surgical interventions. Attempts at transplants persisted in medical awareness for centuries. However, during the medieval and Renaissance periods, this knowledge was overshadowed by the lack of precise anesthesia methods and a limited understanding of the immune system, impeding progress in the field.

The 19th century brought some advancements, but it was the 20th century that became truly a breakthrough for transplantology. In 1902, French surgeon Alexis Carrel successfully performed the first vascular transplants, earning him the Nobel Prize [4].

The first attempts at xenotransplantation were described in scientific literature in 1905. However, interest in animal transplantology waned due to the discovery of immunological barriers related to organ rejection [4]. A revival of research in this area became possible with the introduction of immunosuppressive drugs, opening a new chapter in the history of xenotransplantology.

After World War II, the development of immunosuppression, or agents inhibiting immune reactions, opened new possibilities in the field of transplants. In 1954, Dr. Joseph Murray conducted the first successful kidney transplant between twins [6]. Over the subsequent decades, the scope of transplantation expanded to various organs, from the liver to the heart.

Modern transplantology is a field which dynamically evolves. Technologies such as xenotransplantation (organ transplantation from animals) and tissue engineering open new horizons [7, 8, 9]. Despite challenges related to a shortage of suitable donors, transplantology remains an important area of medicine, which offers hope for new treatment possibilities and improvement of the quality of patients' lives.

CURRENT METHODS OF ORGAN PROCUREMENT

Nowadays, the primary sources of organ procurement involve donations from living donors or post-mortem transplants [10]. Two prevalent donor selection systems exist globally, namely the French opt-out model and the American-Canadian opt-in model [11].

The first, based on the presumption of consent [11], implies that organs are retrieved from a deceased person only if they did not express opposition during their lifetime. Individuals who object to organ retrieval after death are required to report this stance in a specified manner, in accordance with the laws of the respective country. This model is enforced in various countries, including France, Austria, Finland, Belgium, and Poland.

The opt-in model requires obtaining the patient's consent for organ or tissue retrieval after death [11]. Typically, this consent is formally expressed through written statements, such as a donor card carried by the patient. In the absence of such a document, non-consent does not automatically hinder organ transplantation; there is a possibility to determine the deceased's actual position or to make the procedure contingent upon obtaining the consent of the closest family members. According to information published on the European Parliament's website, such legal regulations have been introduced, for example, in Cyprus, Denmark, and Germany. All these countries, except for Germany and Ireland, have also implemented official donor registries.

Currently, standard methods of organ procurement not only require an understanding of the technological aspects of these procedures but also consideration of the ethical implications. The processes of acquiring organs and tissues for transplantation raise fundamental questions about individual autonomy, respect for human life, and a societal approach to medical issues.

At the same time , the global demand for transplants continues to increase medical advancements and rising life expectancy.

CHALLENGES ASSOCIATED WITH CURRENT METHODS

Currently, there are several challenges and issues associated with the field of transplantology that require attention and the search for innovative solutions.

This field presents ethical dilemmas related to organ retrieval from donors, both deceased and living. The focus should be on ensuring adequate ethical standards, respecting patient autonomy, and minimizing risks to donors. In addition to the tissue procurement issues described above, there are also medical challenges.

One of the main problems is matching the donor to the recipient based on tissue compatibility [12]. The highest laboratory standards will increase the chances of a successful transplant. However, compatibility alone is not sufficient. It is important to pay attention to the selection of the size of the organ according to the needs of the individual [13]. Pediatric patients constitute a special group that particularly requires organs of appropriate size, presenting a unique challenge, especially for organs with limited availability.

It is also worth emphasizing that the development of modern immunosuppression methods, surgical techniques, and progress in cell and genetic research open new perspectives but concomitantly generate new challenges and questions related to the safety and effectiveness of procedures. Therefore, further research, technological innovations, and international collaboration are crucial to effectively address current challenges and improve the efficiency of transplant procedures.

NEW DIRECTIONS IN PROCURING TRANSPLANT MATERIAL – 3D BIOPRINTING

3D bioprinting, as a revolutionary technology in the field of medicine, opens new perspectives in organ procurement for transplantation [14]. This method relies on an advanced process that integrates cells, growth factors, and biomaterials to create precise structures resembling natural tissues. The use of special materials called bioinks, containing live cells and carriers, allows for the layer-by-layer deposition of material and the creation of complex structures.

THE PROCESS OF 3D BIOPRINTING

The process of 3D bioprinting consists of three key stages: pre-bioprinting, bioprinting, and post-bioprinting. Each of these stages plays an important role in creating functional and biocompatible tissue structures ready for transplantation.

Pre-bioprinting is a key for obtaining precise models and selecting appropriate materials [15]. The initial step involves obtaining a biopsy of the organ to be reconstructed. Technologies such as computed tomography (CT) and magnetic resonance imaging (MRI) enable the acquisition of detailed images of tissue structure. Using tomographic reconstruction, the obtained images are transformed into 3D models, which form the basis for further bioprinting processes.

The next step is isolating cells from the obtained biopsy and multiplying them. Then, they are mixed with the appropriate material, providing nutrients necessary to keep the cells alive. The second stage, bioprinting, involves placing a fluid mixture of cells, matrix, and nutrients called bioinks into the printer cartridge [15]. Based on medical scans of patients, it is determined where to precisely place the bioprinted tissue precursor. During the bioprinting process, the precursor tissue matures, and the cells merge into a three-dimensional structure that mimics the original tissue. Various methods, such as magnetic 3D bioprinting, photolithography, stereolithography, or direct cell extrusion, are used in 3D bioprinting to manufacture biological constructs. Ensuring the stability and viability of cells during the manufacturing process, especially in creating more complex structures like organs, is a key challenge.

The final stage, post-bioprinting, focuses on maintaining the mechanical integrity and functionality of the printed 3D object [15]. To achieve this, mechanical and chemical stimulation sending signals to cells to control tissue remodeling and growth is necessary. Bioreactor technologies enable rapid tissue maturation, vascularization, and enhance the transplant's survival capability. Bioreactors provide convective transport of nutrients, create microgravity environments, and allow for pressure regulation inside the model. The post-bioprinting process has a decisive impact on the final stability and functionality of the bioprinted object, making it ready for potential transplantation.

SAMPLE STRUCTURES FROM 3D BIOPRINTING

3D bioprinting, as a modern technology, plays a notable role in producing various organs and tissues, opening new horizons in transplantology.

In medical practice, 3D bioprinting has already been successfully utilized for the production of 2D tissues, such as skin, and tubular organs like blood vessels, trachea, and urethras [14, 17, 18, 19]. While some successes have been achieved, challenges persist in accurately reproducing the structure of the epidermal layer in the skin, ensuring protection against immunological rejection of the graft, and maintaining high standards of execution to preserve the functionality of tubular tissues. This is crucial for reducing the risk of phenomena such as stenosis or thrombosis, which is a foundation to the effectiveness of transplants.

Scientists have achieved no less success in creating more advanced structures such as non-tubular hollow organs like the urinary bladder [19]. Organs with such structures represent another level of complexity that can be created using 3D bioprinters. Creating a fully functional three-dimensional structure of an organ that ensures proper urine voiding requires precision and complex interactions with other systems in the body.

Solid organs like the kidney pose the most challenging task for scientists so far [21]. Achieving an organ structure that corresponds to biological complexity, as well as ensuring adequate vascularization and innervation, presents key challenges. Issues related to immunological rejection and long-term functionality require special attention.

Although the heart, as the most complex organ, remains beyond the reach of current capabilities, researchers at Tel Aviv University have made a breakthrough by 3D printing a rabbit-sized heart using human cells [22, 23]. While the printed heart does not beat, it represents a promising step towards new methods of treating heart diseases.

As 3D bioprinting technology advances, it is necessary to approach each type of tissue with an individual strategy, considering its biological specificity. Continuous research and adaptation of solutions are essential to counter potential complications and adapt to advancing scientific and technological knowledge. The quality of printed models remains an issue to be addressed , particularly in terms of their comparison with a living organism. Furthermore, additional research and technological development are needed for bioprinting to replace animals in clinical studies.

ISSUES SURROUNDING THE USE OF 3D BIOPRINTING IN TRANSPLANTATION

The introduction of 3D bioprinting into the field of transplantology brings revolutionary perspectives but also presents a series of challenges for researchers, doctors, and medical institutions.

The first key obstacle involves ensuring adequate networking mechanisms for materials that facilitate the embedding process in bioprinters [14]. These materials must be both printable for precise structure creation and biocompatible for long-term use in transplants. The diversity of cells, varying in size and shape, poses a challenge in controlling the printing process. Materials need to be tailored to different cell types, and their characteristics, such as size and shape, must be considered in the construction process. Nanoscale features like ridges and grooves additionally impact cell adhesion, proliferation, and morphology. Achieving short-term stability is crucial for maintaining the initial mechanical properties of tissue structures. However, these constructions must also undergo controlled degradation, enabling natural remodeling as 3D bioprinted tissues develop in vivo. 3D bioprinting in transplantology must address issues related to controlling the cellular microenvironment, precise construction, and maintaining structural stability to create effective and long-term functioning organs for transplantation.

Another equally important aspect is the precise reproduction of the physiological state of cells in vivo, which is crucial for preserving their function after transplantation [14]. Control over cell proliferation poses another challenge, where too little can lead to the loss of construct viability, and too much can result in excessive proliferation or apoptosis. The proliferation time of cells is significant for both the initial colonization of the construct and the long-term tissue homeostasis. This issue requires precise regulation of the proliferation rate, achievable through various methods such as viral transfection or the use of small molecules.

The potential rejection of transplanted constructs by the host's immune system is an obstacle that researchers can overcome through the use of autologous cell sources or tolerance induction strategies [14]. In cases of diseases or disorders preventing invasive surgical procedures, as well as when isolated cells do not fulfill desired functions, the use of stem cells becomes a promising alternative. Cells of this type, especially embryonic and induced pluripotent stem cells, show potential for self-renewal.

The sizes and complexity of the organ model structure for transplantation pose a challenge in the 3D bioprinting method [24]. The heart represents one of the largest technical problems in achieving the synchronization of heart chamber movements. Ensuring rhythmic heart function without the risk of thrombosis and heart failure is a significant challenge. The precise control of each cell and the appropriate density of blood vessels in the heart structure are crucial. Disturbances in movement synchronization can lead to irregular heart rhythm, affecting its performance. Bioprinted tissues are subject to the risk of immunological rejection, similar to traditional transplants. It is necessary to construct structures that not only minimize immune reactions but also ensure compatibility with the recipient's body [14, 25]. Therefore, proper modulation of the immune system becomes a key aspect in 3D bioprinting.

The introduction of 3D bioprinting into transplantology is not only a step into the future but also a challenge that requires the collaboration of scientists, doctors, and funding institutions to effectively overcome technical, physiological, and financial obstacles.

DISCUSSION

The overview of the presented information on new solutions in transplantology and organ procurement reveals the dynamic development of this branch of medicine while shedding light on existing challenges [5].

The positive effects of advancements in transplantology can be observed, open perspectives for more effective treatment of diseases involving the failure of vital organs and beyond. The mentioned 3D bioprinting method seems to be a promising alternative to traditional transplants, which bring hope for increased organ and tissue availability for patients [15].

The most significant ethical issue concerning the use of the described method is the costs associated with research and production, which may result in limited accessibility for the broader community. Consequently, there is a risk that modern treatment methods will become available primarily to individuals with higher socioeconomic status. It is worth considering what steps should be taken to ensure fair access to transplants for different social groups. A less-discussed issue at the current research stage but equally significant is that research on 3D bioprinting brings challenges related to the use of biological materials and patient safety. Striking a balance between technological progress and ethical standards becomes a key challenge, requiring transparency, fairness, and responsibility in the research process. In the long term, the success of 3D bioprinting in transplantology will depend not only on the clinical effectiveness of the products but also on skillfully addressing these ethical challenges [8, 10].

The frequently emphasized issue in this paper is the increasing number of patients awaiting transplants, which requires not only modern technological solutions but also a focus on public education, the elimination of cultural barriers, and the adaptation of the law to current realities. The presumed consent model appears as a potential compromise, respecting individual autonomy while stimulating the field's development. However, there is a need to increase public awareness in this regard [22].

In summary, despite challenges related to donor shortages, modern approaches to transplantology offer hope for a future where innovative technologies, new procurement methods, and societal awareness will enable more effective life-saving and improve the quality of medical care. Key to this will be the continuation of scientific research, interdisciplinary collaboration, and active societal engagement in transplant-related processes [25].

CONCLUSIONS

Transplantology is a dynamically evolving field of medicine. It offers hope for effective therapy for many diseases, especially those characterized by the failure of vital organs.

Despite numerous benefits resulting from advancements in this medical field, the most significant challenge remains the process of obtaining transplant materials. The current number of patients awaiting a transplant far exceeds the availability of potential donors. To adress this challenge, it is essential to increase public awareness through education, social campaigns, and encourage consent to organ donation during one's lifetime. Continuing scientific research, developing new methods and technologies, and adapting the law to contemporary needs appear valuable. This will enable the creation of more efficient and sustainable systems for organ procurement, storage, matching, and transplantation.

Looking into the future of transplantology, emerging solutions such as the 3D bioprinting described in this paper seem to be a promising alternative to ex mortuo transplants, bringing hope for improved organ availability. The development and standardization of modern solutions hold promise for facilitating life-saving procedures and improving the quality of life for patients who would otherwise be limited to symptomatic treatment.

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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

RECEIVED: 28.03.2024
ACCEPTED: 30.05.2024