Review Article

Updates in the Use of 3D Bioprinting in Biomedical Engineering for Clinical Application: Review Article

Abstract:

Three-dimensional (3D) printing is one of the most well-liked new innovative and promising manufacturing techniques, which has demonstrated tremendous potential for the creation of biostructures in tissue engineering, particularly for bones, orthopaedic tissues, and related organs. In contrast to the conventional use of 3D printing to create cell-free scaffolds, 3D bioprinting requires various technical methods, such as biomimicry, 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 function. Cells, bioinks, and bioprinters are all necessary components of the bioprinting process, and each one of them has biological, technological, ethical, and cost- and clinically-effectiveness-related issues. As a result, there will be several difficulties in integrating 3D bioprinting into widespread clinical practise. Currently, there are multiple applications for 3D bioprinting such as in surgery, cardiovascular system, musculoskeletal and even in drug screening. All of which will be discussed in this review.

Key words: Three-dimensional printing, 3D Bioprinting, Biomedical Engineering, 3D Bioprinting in Clinical Application

Introduction:

One of the most well-liked new innovative and promising manufacturing techniques, three-dimensional (3D) printing, has demonstrated tremendous potential for the creation of biostructures in tissue engineering, particularly for bones, orthopaedic tissues, and related organs. With the right choice of biomaterials and appropriate bioprinting techniques, it is possible to obtain the desired biological, structural, and mechanical qualities for 3D-printed constructions, maybe even when combining additive and conventional manufacturing (AM and CM) processes. A wider variety of acceptable 3D-printed materials are still needed, as well as better printing resolution (particularly at the nanoscale level), speed, and biomaterial compatibility. [1]

As a cutting-edge technique to restore the functional components of injured tissues and organs, the capacity to regenerate tissue has grown in importance. Utilizing in vitro and in situ techniques, tissue engineering is a branch of regenerative medicine that tries to regenerate certain tissues and reestablish normal biological functions. The implantation of (a) scaffolds alone, (b) isolated cells and other bioactive molecules, or (c) a combination of cells implanted within or on scaffolds to model the body's natural extracellular matrix (ECM) and support tissue engineering are examples of the classical approaches to tissue engineering. Each strategy has a variety of benefits and possible applications. [2-6].

In contrast to the conventional use of 3D printing to create cell-free scaffolds, 3D bioprinting requires various technical methods, such as biomimicry, 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 function. 3D bioprinting has a number of benefits over conventional 3D printing, including precise cell dispersion, high-resolution cell deposition, scalability, and affordability. But there are still obstacles in the way of the widespread use of 3D bioprinting in various areas, including medicine. To mention a few, there is a dearth of printable biomaterials, and scalability and printing speeds might be enhanced with new printing technologies. [1]

A number of businesses worldwide are actively working to improve bioprinting by extending the types of materials and enhancing technological approaches, even though in vivo work in regenerative medicine is still in the very early stages of research with full organ transplant seen as the long-term goal. [7]

Study rational:

In order to enhancing technological approaches, even though in vivo work in regenerative medicine is still in the very early stages of research with full organ transplant seen as the long-term goal.

Study objectives:

The objective of this study was to summarize the updates in use of 3D Bioprinting in biomedical engineering for clinical application in health care facilities.

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Materials and Methods:

Study Design: Review article.

Study duration: Data was collected during the period from 1– 29 September, 2022.

Data collection: PubMed and EBSCO Information Services were chosen as the search databases for the publications used within the study, as they are high-quality sources. PubMed being one of the largest digital libraries on the internet developed by the National Center for Biotechnology Information (NCBI) which is a part of the United States National Library of Medicine. Topics concerning the updates in in use of 3D Bioprinting in biomedical engineering for clinical application in health care facilities, published in English around the world. The keyword search headings included “Three-dimensional printing, 3D Bioprinting, Biomedical Engineering, 3D Bioprinting in Clinical Application" and a combination of these was used. References list of each included study was searched for further supportive data. Double revision of each member’s outcomes was applied to ensure the validity.

During articles selection, studies was doubled-reviewed, and their results to assure that we enroll the studies related to the objective of our study, and to avoid or minimize errors in the results.

Data management and analysis:

No software was utilized to analyze the data. The data will be extracted based on specific form that contains (Author’s name, year of publication, study type, objective and outcomes).

Mapping and interpretation

The reviewers used charts to define the identified concepts and map the range and nature of the phenomena. The review explored associations between the themes to help clarify the findings. The review were mapped and interpret findings in line with the review objectives and emerging themes.

Surgical Applications:

When planning operations, 3-DP may help surgeons have a better grasp of complicated anatomy. It may also enable the creation of personalised or patient-specific implants and surgical guidance, which might eventually save the time spent in the operating theatre. While 3-DP may have advantages like faster operating times and lower costs, it may also have drawbacks including material reactions and longer planning times. The following criteria have been used to categorise 3-DP surgical applications: [7-10]

- Anatomical models
- surgical tools
- implants, and prostheses
- splints and external fixators.

Cells, bioinks, and bioprinters are all necessary components of the bioprinting process, and each one of them has biological, technological, ethical, and cost- and clinically-effectiveness-related issues. As a result, there will be several difficulties in integrating 3D bioprinting into widespread clinical practise. Selection of Cell Source Challenges The origins of both cell sources and bioink materials may lead to additional discussion within the healthcare environment. First, as with the pig valves now used in clinical practise, cells utilised to construct basic tissue structures like heart valves may theoretically be obtained from either animals or people. The bulk synthesis of tissue for surgical use from animal sources is presumably possible, however the material comes from allogenic origins impose a danger of xenotransmission of disease. [11]

Cells from either patient or adult stem cells are used to create a bio-ink that may be used to manufacture live tissues. A dissolvable gel or scaffold that can support cells and mould them into the correct form to achieve the intended function holds these components together. To achieve a perfect fit into the target tissue, current advanced imaging technologies, such as CT, allows the fabrication of precise CAD models for 3D printing. In the past several years, there have been reports of the construction of various kinds of thick tissues in a variety of forms, with the eventual goal of printing entire organs or body parts for organ donation. Organ transplant difficulties including extended waiting times for a donor or immunological rejection of the transplanted organ may be avoided by harvesting stem cells from transplant recipients and printing them into a replacement organ. Recent experiments have shown that 3D tissue bioprinting can produce organ-level structures including bone, cornea, cartilage, heart, and skin. [12-19]

In plastic surgery and repair procedures, artificial adipose tissue structures can be employed for soft tissue rebuilding. In 2015, Pati et al. used a multi-nozzle device to bioprint flexible dome-shaped structures with tailored porosity within a PCL framework using decellularized adipose tissue (DAT) matrix encapsulating human adipose tissue-derived mesenchymal stem cells (hASCs) as bioink. A mouse implantation experiment revealed that the structure facilitated positive tissue infiltration, constructive tissue remodelling, and the creation of adipose tissue rather than causing persistent inflammation or cytotoxicity after implantation. [20,21]

Advances in imaging have improved patient care in neurosurgery by enabling doctors to see tiny and complicated structures inside the nervous system. When designing a method, 3-DP has the ability to provide a better visual representation of the connections between complicated components. Due to the complicated architecture of the spine and the fragile components that surround it, 3-DP models and other tools that assist surgeons in planning and precisely carrying out operations may also help patients receive better care. According to reports, the advantages of employing 3-DP, such as decreased operating time and perioperative blood loss, rose along with case complexity. It has been observed that 3-DP surgical guides can reduce operation risks. The creation of anatomical models tailored to each patient, the invention of tools for diagnosing and treating neurosurgical disorders, and the creation of biological tissue-engineered implants are all examples of how 3-DP is used in neurosurgery. [7]

Cardiovascular Applications:

In order to treat cardiovascular disorders and create tissues and organs with ample blood supply, the vasculature performs a function in the movement of nutrients and metabolic waste. Although the process of bioprinting the vasculature in vitro has advanced significantly, it is still difficult to produce particular vascular characteristics for various tissues. According to L. Bertassoni et al., a vascular network bioprinted using methacrylated gelatin (GelMA) has improved metabolic transport, cellular survival, and endothelial monolayer development. D. Kolesky et al. reported employing the sacrificial bioink of Pluronic F127, which was later liquefied and removed at a lower temperature to create open vascular channels as tiny as 45 m, for the direct inclusion of the smaller size of vascular channels into bioprinted tissues. [1, 22-24]

Using a gelatin hydrogel and a unique technique, Hasan et al. created multi-layered blood arteries on a microfluidic device. In three to five days of maturation, the researchers were able to produce the physical structure of the vessels while guaranteeing the correct positioning and proliferation of the endothelial cells within the vessel walls. Similar achievement was achieved by Bertassoni et al. when they used agarose in a crosslinked hydrogel to create a printed blood artery that was in vitro cultivated with endothelial cells. While the direct implantation of bioprinted items is one method, others have looked at using bioprinting to speed up the body's normal processes. Gaebel et al. successfully bioprinted a cardiac patch that was placed on rat myocardial infarction zones and cultured with mesenchymal stem cells and endothelial cells. The in vivo success of this preclinical investigation showed the potential application of 3D bioprinting to enhance angiogenesis and aid in the regeneration of the heart tissue after a myocardial infarction. [2, 25-27]

Aho et al. used feline cardiomyocytes HI.1 cardiac muscle cells and an alginate hydrogel to create cardiac tissue with a beating cell response. In order to enhance crosslinking, layers of CaCl2 were printed into an alginate hydrogel precursor solution to create the tissue. According to the findings, cardiac cells adhered to the alginate successfully imitated the native cardiac ECM. Under light electrical stimulation, the printed heart tissues displayed contractile characteristics. [28]

Cetola et al. suggested a method for creating a hybrid vascular graft in 2010. Specifically, they employed a blend of electrospinning and fused deposition modelling methods to create a poly-L-lactide (PLLA)/poly—caprolactone (PCL) scaffold that releases heparin. By electrospinning PLLA/heparin scaffolds into a tubular form, they were produced. The exterior layer of the tubes was then armoured with a single coil of PCL to enhance mechanical qualities. Following the seeding of the scaffolds with human mesenchymal stem cells, the morphology, mechanical tensile strength, cell survival, and differentiation were evaluated. This hybrid graft maintained the endothelial differentiation and proliferation of the implanted human mesenchymal stem cells and had a stress-strain profile similar to that of a human thoracic artery. [29,30]

Utilizing spider silk, which promotes the growth of new heart muscle tissue, is one of the creative methods for cardiac tissue regeneration. Hydrogels are produced by spider silk. The 3D printing technique may be used to create tissue-like structures from this premium material. These hydrogels contain living cells that can give the cardiac cells functional stability. The proteins found in spider silk that provide structural and mechanical strength are of particular interest to researchers. Using 3D printing, a research team at the University of Bayreuth under the direction of Professor Thomas Scheibel successfully created a "bioink" or hydrogel by combining spider silk with mouse fibroblast cells. When the gels pass through the printer head and onto an extrusion surface, they quickly transition from a fluid to a solid state. This understanding has been utilised to successfully create cardiac muscle tissue utilising cardiomyocytes and scaffolds made of spider silk. The outcomes demonstrated that bioengineered spider silk provides a successful foundation for the recovery of cardiac muscle tissue. [31,32]

Musculoskeletal Applications:

Both non-biological and biological 3D printing, as well as CM, which includes gas foaming, salt leaching, and dry freezing, have similar ground in the engineering of making artificial bones. Bioprinting offers the distinct benefit of being able to precisely manipulate biological structures and mechanical characteristics among all manufacturing techniques now in use. The best composition for the repair and replacement of substantial bone defects was created using cement powder to create biphasic calcium phosphate (BCP) scaffolds including hydroxyapatite and tricalcium phosphate (TCP). The BCP scaffolds' attained structural correctness exceeded 96.5%. According to F. Pati et al., human nasal inferior turbinate tissue-derived mesenchymal stromal cells (hTMSCs) produced mineralized ECM that was used to decorate 3D bioprinted scaffolds made of PCL, PLGA, and b-tricalcium phosphate (b-TCP). [1]

In vivo Bioprinting: The direct patterning of de novo tissue onto the target area of the body, such as chronic skin wounds or bone defects, is one of the potential uses for 3D bioprinting. The topology of printed tissue may be tailored to match the wound or defect with the use of medical imaging so that heterotypic cellular structures, hydrogels, and soluble components can be properly deposited inside the flaws. This strategy, known as in situ bioprinting or intraoperative bioprinting (IOB), would reduce the distance between the implant and host interfaces and offer clearly defined structures within regions of irregular topographies during the healing process, which can efficiently recruit desired cells from surrounding tissues where the patient's body acts as a natural bioreactor. [12]

Since cartilage is a tissue that cannot naturally renew, bioprinting of cartilage has become more important over time. Because of this, bioprinting is essential to reducing the problems caused by cartilage deterioration. Cui et al. grew a bioink made of chondrocytes and PEGDMA in a bioreactor for six weeks after depositing it onto a 3D biopaper plug using inkjet bioprinting. After incubation, they discovered that the cartilage construct had less collagen I and more collagen II than a naturally occurring cartilage piece. This demonstrates the cartilage cells' appropriate maturation and development over the incubation period. [12,33].

Medications Screening:

A cutting-edge method for creating drug screening systems is 3D bioprinting. Bioprinting may consistently distribute cells onto a microdevice surface, which is extremely desirable for testing and screening the interactions between cells and the tested medications. This is in contrast to traditional manual screening procedures. To create a drug testing platform for the liver using alginate-encapsulated immortalised hepatocytes, R. Chang et al colleagues created a pneumatically-driven, extrusion-based bioprinter. This method can distinguish the drug metabolism capability beneficial for screening effectiveness and toxicity for the agent of interest and simulates the in vivo microenvironments of various mammalian tissues. According to other research, skin disease-causing cells may be incorporated into biomaterials to create skin tissue via 3D bioprinting. In this manner, the pathophysiologies of skin illnesses might be studied using skin tissue printed with pathogenic cells. In order to investigate possible pharmacological effects on tissues, bioprinting might potentially be utilised for cell seeding during the creation of organ-on-a-chip devices, which imitate routes of regular organ activities. [1]

Conclusion:

The utilizations of three-dimensional (3D) printing in medicine has long way to goal. Indeed, there are no limitations on how far this technology can be utilized. From creating 3rd Models for educational and preoperational purposes up to creating full organs to be transplanted. Creating synthetic organs could solve massive transplanting issues such as lack of number of doners of these organs and also will reduce the risk of immune system rejection of the organ. Research and development should increase in order to unlock the full-scale potential of this technology in medicine.

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