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

Ali Hamad Mohammed Al-Mansour [a*], Abdullah Nasser Gvin Al Rizk [b], Hamad Mohammed Shaman Al-Mansour [b], Hadi Salem Faraj Al Mahamed [b], Hussain Saleh Muidh Al Sharmah [b], Ali Mohammed Al-mahamed [c], Jaber Mohammed Al-hattab [d] and Fahad Mohammed Hamad Almansour [e]

[a] Biomedical Engineering, Maternity and Children Hospital, Saudi Arabia.
[b] Medical Devices Technician, Khabash General Hospital, Saudi Arabia.
[c] Biomedical Engineering, Maternity and Children Hospital, Saudi Arabia.
[d] Medical Devices Technician, Maternity and Children Hospital, Saudi Arabia.
[e] Medical Device Technician, Eradah Complex for Mental Health Najran, Saudi Arabia.

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Review Article

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**Corresponding author;*

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. 3D printing for the medical industry was considered a lofty pipe dream. Time and money, though, made it a reality. Today's 3D printing technology has a significant possibility to assist pharmaceutical and medical corporations in developing more specialised pharmaceuticals, enabling the quick creation of medical implants, and transforming how doctors and surgeons approach surgical planning. In today's practise of precision medicine and for individualised therapies, patient-specific anatomical models that are 3D printed are becoming increasingly helpful tools. 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 are 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.

Keywords: Three-dimensional printing; 3D Bioprinting; biomedical engineering; 3D bioprinting in clinical application.

1. 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]. 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. 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.

2. EVOLUTION, PROCESS AND CLASSIFICATION OF 3D BIOPRINTING

The ability to 3D bioprint fully functional organs for transplant is currently not very plausible. But there is no denying that bioprinting methods have advanced tremendously. Several pioneers, including Vladimir Mironov, Gabor Forgacs, and Thomas Boland, saw the natural fusion of technologies, such as cell patterning and others, such as commercial inkjet printing, decades ago for the purpose of developing living structures that may one day be used in human organ transplantation 3, 4.

Fig. 1 shows a chronology of the development of bioprinting technology up to the present.

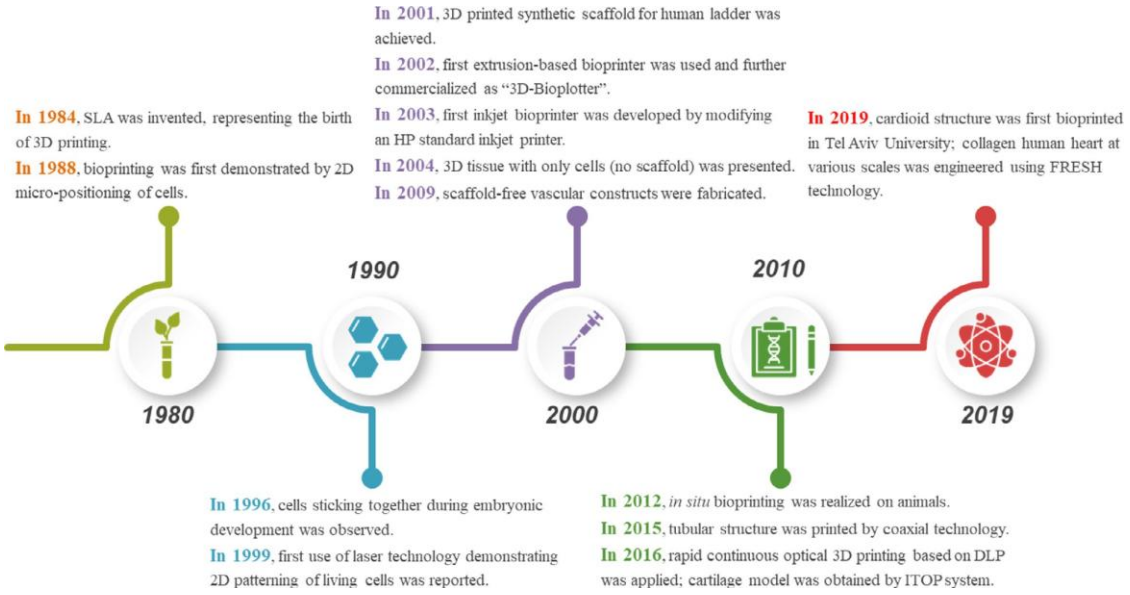

Fig. 1. A timeline for the evolution of bioprinting technology up to state-of-the-art 3

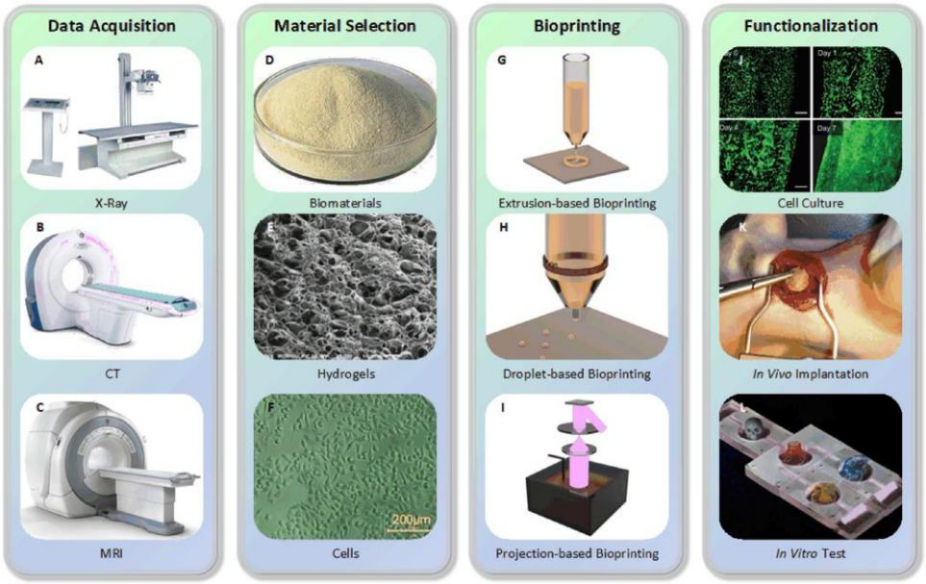

Fig. 2. The process of 3D bioprinting can be classified into four steps 3

Table 1. Various Types of 3D Bioprinted Tissues and Organs, Which Have Undergone In vivo Evaluation or Printed *in vivo* [4]

Tissue Type	Bioprinting System	*In vivo* Testing	Cell Viability	Features
Bone	Modified HP DeskJet 550C printer	Incubated for 1 week in osteogenic medium and implanted subcutaneously in immunodefecient mice for 8 weeks	–	Highly mineralized tissue observed after 8 weeks and generation of hard tissue within the construct after 18 weeks
	Laser-induced forward transfer (LIFT)	Printed *in vivo* on calvaric defective site of mice	–	Mature and immature bone after 1 month and fully repaired bone tissue after 3 months
	Laser-assisted and Electrospinningbioprinting	Cell number analysis in 4 and 8 weeks in NOD-SCID mice	20,000 cells in day 1, greater cell viability in LBL sites	Dense and thick fibrous tissue was observed in the LBL sites, whereas a thinner fibrous tissue was presented in the CSS samples
	Custom designed ITOP with pneumatic extrusion syringes	Cultured in osteogenic media for 10 days, implanted in a calvarial bone defect region of Sprague Dawley rats for 5 months	91 *6* 2% after 1 day	Newly formed vascularized bone tissuethroughout the implants
Skin	Pressure driven extrusion system	Analysis after 7 and 14 days of bioprinting on immunodeficient mice	Large number at day 1	AFS cell- and MSC-treated wounds had more areas of closed wound and wound area contraction, thicker tissue generation and neovascularization observed
	Laser-assisted bioprinting	Incubated overnight in submerged condition and implanted subcutaneously in nude mice	–	Vascularization from wound beds and edges observed, differentiation of keratinocytes
	Bio-electrospraying method	Submerged in culture media for 24 h and subcutaneously implanted in mice	–	No significant impairment of construct for *in vivo* engraftment
Cartilage	Hybrid system (electrospinning and inkjet)	2 weeks *in vitro* culture and 8 weeks subcutaneous implantation in immunodeficient mice	81.58 *6* 3.46% After 1 week	Dense and well organized collagen formation, rounded chondrocytes with lacunae
	Custom designed ITOP with pneumatic extrusion syringes	Implanted in the dorsal subcutaneous space of athymic micefor 1 and 2 months	91 *6* 8% after 1 day	Increasing GAG content to that of native cartilage tissue, vascularization at the periphery

a. Data acquisition. X-ray, computed tomography (CT), magnetic resonance imaging (MRI), and other scanning and reconstruction methods, as well as direct use of computer-aided design (CAD) software, can all be used to create 3D models. Then, using specialised software, 3D models would be cut into 2D horizontal slices with adjustable size and orientation. The various bioprinting techniques would further transform these data into particles or filaments.
b. Material selection. Cells, growth factors, hydrogels, and other materials should be carefully selected in accordance with the needs of printed structures and methodologies. The combination of these biomaterials is technically referred to as bioinks, though they are typically just thought of as cell-filled hydrogels. To ensure biocompatibility, printability, and mechanical property—which will be covered in more detail in the last section of this review—the choice of bioinks is essential.
c. Bioprinting. Before bioprinting, appropriate configuration of printing parameters needs to be confirmed. And observation during printing process is necessary to make adjustment when encounters any problems.
d. Functionalization. After printing, to make dispersed cells forming connections and generating some functions of natural tissue/organ through physical and chemical stimulation is the target.

3. 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].

4. 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].

5. 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]

5.1 *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].

5.2 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].

5.3 Challenges, Applications and Future Perspective

Many problems still need to be resolved in tissue engineering despite all the advancements made over the years. There are two main types of challenges: 1) Biomanufacturing, which entails the 3D fabrication of the cells and biomaterials, and 2) in vivo integration, which entails integration and functionality upon implantation. Nozzle clogging in nozzle-based fabrication technologies is one difficulty in the fabrication

process. The length of the fabrication process can vary depending on the application. In these circumstances, the printing precursor must be homogenous and have the necessary viscosity and shear thinning qualities to prevent nozzle clogging. 41 Another difficulty is that for effective transplantation, the 3D constructions must be sufficiently hard and sturdy mechanically. For instance, when repairing hard tissue, the scaffolds' elastic modulus must be high enough to keep their intended porosity and structural integrity while being implanted. Any newly generated tissue will likely fail due to scaffold deformation if the scaffold is unable to maintain its structure and offer mechanical support [34-43].

Due to its variety and numerous potential uses, 3D bioprinting is currently growing quickly toward becoming a significant business. The market for 3D printing is expected to grow from $2.2 billion in 2012 to $10.8 billion in 2021. Several businesses are presently developing 3D bioprinting products for tissue engineering uses like bone, breast, cartilage, and liver tissue. One of the businesses that has already created commercially available bioprinted products is Tissue Regeneration Systems. This business creates bioprinted PCL-based remedies made specifically for each patient to fix skeletal flaws [44].

"The two main categories of bioprinting applications are 1) tissue regeneration and regenerative medicine and 2) biomedical applications. Applications of bioprinted constructs like vascular grafts, skin, neurons, bone, and liver are discussed in the first group, while drug discovery and biopreservation are covered in the second group" [45].

It goes without saying that during the past ten years, bioprinting has undergone steady change, and this trend appears to be holding. It will soon be possible to print more complicated 3D constructions as bioprinting resolution and quality improve with more research being done on the subject. Natural organs are frequently extremely intricate structures made up of various tissues, ligaments, and other components, each of which serves a specific purpose. The biofabrication of intricate constructs that precisely mimic natural organs become feasible as bioprinting technology develops. The precise fabrication of multi-material 3D constructs can also increase the structural complexity of the bioprinted products [46].

An effective method for creating organs with ualityies in multiple places is the simultaneous deposition of materials with various physical and chemical properties. With the help of multimaterial bioprinting, it is possible to modify the concentration of growth factors, cell adhesion, and disintegration rate in various areas of the printed product. Another advantage of this strategy is the ability to load various cell types on compatible biomaterials and in various zones, closely simulating the diversity and activity of naturally occurring cells [47].

5.4 Laser-assisted Bioprinting

"The notion of laser-induced forward transfer serves as the foundation for laser-assisted bioprinting (LAB) (LIFT). The thin biomaterial layer is ejected onto the predetermined location by high-energy laser pulses that form high-pressure bubbles in it. A pulsed laser beam, a focusing mechanism, a ribbon, an energy-absorbing layer, and a biomaterial layer are all components of a LIFT system. The thin energy-absorbing layer, which is often made of metal, is supported by the transparent ribbon, and the biomaterials must be in a liquid or gel state to spread over the metal layer. When energy is deposited to eject materials, the energy absorption layer acts as an energy conversion layer. Each element of the system, such as the laser's energy, frequency, and viscosity, has the potential to affect the resolution of the printed material" [48,49].

"High-energy laser pulses have little influence on cell viability or function, and selective writing of several cell types is achievable. LAB can precisely arrange small droplets of biomaterial (a few hundred femtoliters in size). Furthermore, high cell densities (up to 50 million cells mL21) and hydrogel precursors with any desired viscosity can be produced. Because there is no nozzle, this approach can have exact control over the deposition of high-viscosity material" [50].

"The use of lasers, especially those utilizing UV light, can have negative effect on cells. Therefore, tests should be carried out on cells or recipient tissue for in situ and in vivo bioprinting. The fine printing resolution of LAB also means a slow printing speed which may not be suitable in some cases where rapid fabrication is required because of dehydration" [51].

5.5 Extrusion-based Bioprinting

"Because of its versatility and cost, extrusion-based bioprinting (also known as direct ink writing) is the most extensively used method of 3D bioprinting. Extrusion-based bioprinting, as opposed to single droplet printing, produces continuous filaments via continuous extrusion force. This method may be used to print a wide range of biomaterial viscosities and cell concentrations. As a result, researchers favour extrusion-based bioprinting to create tissue architectures with adequate mechanical properties. Furthermore, coaxial and multi-material bioprinting can be used in conjunction with extrusion-based bioprinting for a variety of purposes" [52].

"Extrusion-based bioprinting, in theory, extrudes bioink (typically from a syringe) via a nozzle using mechanical or pneumatic force to generate continuous micro filaments, which are then deposited on a receiving substrate and finally stacked into desired structures. The substrate might be solid (for example, a culture dish), liquid (for example, growth media), or substance produced from gel. After configuration, the nozzle route is often produced by software using digital models. Temperature, nozzle diameter, extrusion pressure, movement speed, extrusion speed, path interval, and other parameters would all have an impact on the final bioprinted structures. Common extrusion-based bioprinting can be divided into pneumatic, piston, and screw-driven actuation types of liquid dispensing systems" [53,54].

"Extrusion-based bioprinting is a dependable technique for fabricating biomaterials when using appropriate bioinks, particularly for hydrogels with shear-thinning and quick crosslinking capabilities. The final bioprinted formation would be affected by nozzle diameter, bioink viscosity, nozzle movement speed, bioink extrusion speed, extrusion pressure, substrate surface characteristics, and so on. Extrusion-based bioprinting is widely employed by researchers all over the world due to its versatility, economy, and capability for printing porous materials" [55].

"Because extrusion-based bioprinting is the most practical, cost-effective, and widely used method, there are multiple commercial extrusion-based bioprinters on the market. In our opinion, printing scaffolds using FDM and then transferring cells is not genuinely bioprinting technology. As a result, the 3D Bioplotter®, which was capable of cell-laden bioprinting, may be considered the world's first commercial 3D bioprinter. It was invented by a University of Freiburg research group and quickly commercialised by EnvisionTEC" [52]. "It can print not just cell-laden hydrogels like gelatin, fibrin, alginate, and agarose, but also hard polymers and inorganic ceramic materials like PCL, hydroxyapatite (HA), and tricalcium phosphate (TCP) particles to create non-bioabsorbable scaffolds. Another significant bioprinter was the NovoGen MMX BioprinterTM, which was invented in 2009 by Organovo" (which was formed in Delaware, USA, in 2007). "This small apparatus, which could be placed on any clean bench, included two nozzles for extruding cells, hydrogels, scaffolds, or supporting matrix. This device was first used to bioprint tissue spheroids with an agarose hydrogel support framework. After the printing process, tissue spheroids bonded together and matured into a tissue-like organisation, and the agarose was removed. For the time being, this company no longer sells bioprinters; instead, it has evolved into a platform that offers technical services such as in vitro tests, disease models, and safety tests" [52-56].

6. 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.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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