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REVIEW ARTICLE

Future of Bioprinting in Healthcare: A Review

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ABSTRACT

Tissue damage and degeneration are common pathological phenomena in higher organisms, specifically in mammalians. However, the traditional method of organ transplantation is a gold standard treatment option for life-saving, dependent upon a donor's availability. The scarcity of organ donors and the risk of graft rejection is mainly associated with adverse immune responses. Additive manufacturing, such as bioprinting, is one of the most advanced and state-of-the-art techniques that are being utilized for generating tissue engineering construct and in-vitro disease models. Three-dimensional bioprinting associate in creation of extracellular matrix (ECM), such as microenvironments for cells and computer-aided design (CAD) modification of planned tissue morphology. Herein, formulation of suitable bio-ink composition with optimized gelation kinetics for *in-situ* immobilization of cells with high cell viability is the utmost priority for bio-fabrication. This review elaborates on the most current opportunities and prospects for efficiently implementing bioprinting to restructure medical and technological practices and their applications in the healthcare industry.

Keywords: 3D bioprinting, Bio-inks, Tissue reconstruction, Tissue engineering.

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INTRODUCTION

The revamp of the manufacturing industry is related to the advent of additive manufacturing or 3D printing technology. The introduction of new materials and even metals for developing complex, sturdy, lightweight, functional parts have contributed to the transformation as it is quicker than traditional methods. Here, 3D parts are generated methodically, layer by layer. In addition, this technology creates hard physical replicas of anatomical structures in healthcare sectors. Also, the customization of a prosthesis for patients with special needs and the production of prototypes of medical devices become possible with this method. The 3D printing approach became revolutionary gaining particular concern. Regardless of its manufacturing source,[1] 3D printing technique has expanded to healthcare research and prompted the improvement in various medical devices, prosthetics and models. Over the past century, surgery has transformed with emerging technologies like microsurgery, transplantation, and robotics. Thus, the need for proper planning and preparation has increased due to surgical scope and complexity. The issues in reconstructive and transplantation surgery methods are as follows. It comprises donor organs and tissues availability, injury combined with tissue yield, and potential difficulties linked to immunosuppression.[2,3] Patient-specific data can be extracted using 3D printed software like CT guided, laser scanning or magnetic resonance imaging (MRI) to produce customized and tailored tissue implant model.[1] It may lead to personalized healthcare by incorporating biological elements into this technology. Further, surgery can be aided by 3D printing technology, in which bio-ink can be directly transferred over the wound side for healing. Royal college of surgeons called bioprinting a forthcoming of surgery by seeing its diverse application in the healthcare field.[4] The technology of bioprinting of 3D printing covers mechanical engineering, materials science and human by incorporating this in the healthcare to generate an unique and modified choice for the patients.[5,6] Bioprinting may overcome any requirement for contributor's organs for replacement surgery as well as offer less pain in restoration.[7] Usually, the bioprinting method is built up of three major steps, as depicted in Figure 1.[8-10] First, at the pre-bioprinting stage, computer-aided design (CAD) software designs the prototype of tissues with the guidance of medical images.[11] Next, the physical bioprinting step includes different composition of bio-ink by selecting a concise and

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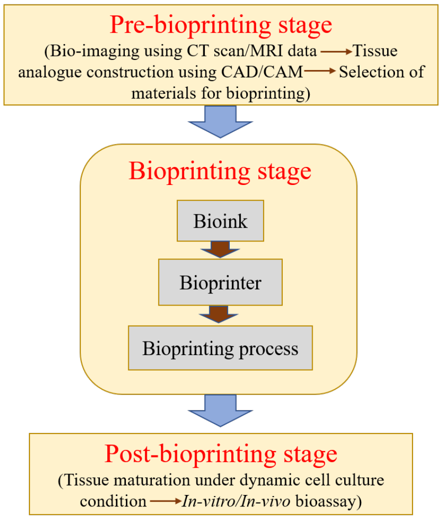

Figure 1: Schematic of major stages involved in 3D bioprinting process.

good-resolution bioprinter for better bioprinting with better cytocompatibility and design flexibility.[10,11] Finally, using bioreactor mechanical and chemical conditions of a biological body can be easily mimics, known as the post-bioprinting stage.[12-14] The future trend to develop biomimetic organs may comprise new digital technology and advanced sensors in bioprinting, which may also align 3D bioprinting with the certainty of industry 4.0 for modern therapies, medical devices, engineered tissue and organs in the healthcare industry. However, the exploration is separate from the discovery of advanced bioprinting materials and their different printing parameters and the combination of both approaches will help to create future printed organs. One such possibility comprises using hydrogel with electrical conductivity for interfacing cells in the bio-printed models to provide biochemical and biophysical stimulation. This review outlines the possible application of bioprinting in tissue engineering and regenerative medicine as well as encompasses the recent trends aiming to identify this technology's key role in the future of healthcare.

Types of Bioprinters

Different bioprinting techniques depend on separate principles and material needs, which also consider their advantages and disadvantages. The technology of bioprinting in healthcare can be classified into three major types according to principle of operation: photocuring-based, extrusion-based and droplet-based.[15] Various types of bioprinting are shown in Figure 2.

Inkjet Bioprinting

This bioprinting method is contactless, where bio-ink droplets ejection occurs under pressure.[16] This technique can be of two types drop-on-demand (DOD) or continuous. The nonstop inkjet bioprinters operate with continuous bio-ink release. On the other hand, DOD types use pressure pulses created by electrostatic, piezoelectric, and thermal to eject droplets.[17] A thermal inkjet bioprinter has a thermally controlled actuator that comprises an electrical heat unit for vapor bubble formation through the vaporization of bio-ink solution. Eventually, the expansion of the vapor bubble owing to pressure leads to a rapid explosion, which generates a pulse pressure for ejecting a bio-ink droplet without affecting cell viability.[18] As, the bio-ink droplet releases as its chamber volume change suddenly,[19] cell viability sustains in this method without facing any issues. Electrostatic actuator-based inkjet bioprinters operate in a similar way, a voltage is applied as a pulse between an electrode and a pressure plate to cause the deflection in the pressure plate. During the elimination of the pressure plate voltage, it returns to the initial form and ejects droplet of bio-ink with high cell viability and 80–95% yield[20] and provide a better printing resolution owing to their fine control over the droplet ejection.[21]

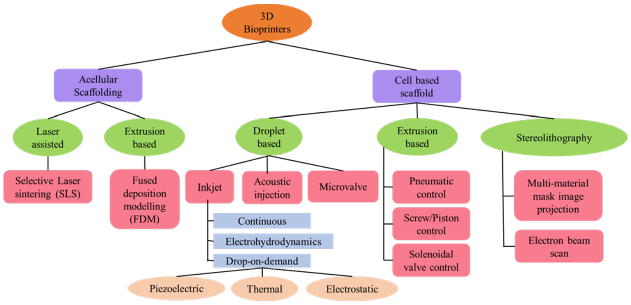

Figure 2: Classification of various bioprinting methods

Droplet-based Bioprinting

This process droplet ejects by an electrochemical valve control technique; a magnetic field is generated due to voltage pulse. The bio-ink fluid chamber pressure exceeds the surface tension, generating a droplet.[22] It uses low-range pneumatic pressure producing less damage to the cells than piezoelectric bioprinting. Hence, it provides outstanding spatial resolution suitable for tissue engineering and regenerative medicine applications, which has better cell viability at a low cost.[17]

Laser-assisted Bioprinting

The utilization of laser pulses for inducing microbubbles is a unique feature of laser-assisted bioprinting. First, a beam of laser is pulsated towards the junction of the marked substrate as well as the layer of absorption. Then, the resulting thermal volatilization forms a microbubble that expands to eject a droplet.[23] Due to its nozzle-free structure this method is very useful for highly viscous bio-inks[24] without any clogging issue. Also, the nozzle-free, non-contact procedure protects the cellular construct from shear stress causing better cellular viability with high resolution of printing.[25] However, the viability of cells decreases a bit owing to the pulsed laser technology.[26] Laser-assisted bioprinting is costly and complex and leads to various operative problems.[27]

Extrusion-based Bioprinting

This bioprinting scheme produces continuing filaments with constant extrusion force in the case of single droplets.[28]

Table 1: Comparison of different bioprinting methods.

Bioprinters	*Inkjet*	*Laser*	*Extrusion*	*Microfluid*	*Fused deposition modelling*	*Stereolithography*
Cost of printing	Low	High	Fair	Low	Low	High
Printing speed	Fast	Medium	Faster	Fast	Faster	Slower
Resolution	100 mm	30 mm	141 to 300 mm	100 μm	50 to 500 μm	75 μm
Mechanical attributes	Poor	High	Poor	Medium	Good	High
Porosity (%)	33 to 60	Less than 90	Greater than 40	Less than 45 to 60	40 to 75	50 to 80

It uses highly viscous bio-inks to print concentrated cells, dispensing the ink by mechanical force such as a screw, piston, gas, pressurized air, etc.[29] Different types of extrusion-based bioprinter are mentioned below:

• • *Pneumatic-Driven Extrusion*

This technique air compressor is used to give a pneumatic force having two configurations: valve-based or valve-free. There is a connection between the sterilized air pump and the bio-ink-filled nozzle,[30] in case of pneumatical extrusion based bioprinter bio-ink extruded as filamentous structure with shear-thinning properties. Valve-free pneumatic-driven one is comparatively simple, and valve-based extrusion is chosen for highly precise applications suitable for printing cell-laden bio-ink.[31,32]

• • *Mechanical Micro-extrusion*

Extrusion based bioprinter with a nozzle size of less than 1 mm, is known as a micro-extrusion based inject printer.[33] Mechanically controlled extrusion can be piston-based or screw-driven. The electrical pulse controlled piston for pushing the highly viscous bio-ink-like synthetic and natural polymers through the nozzle head.[34] Therefore, this bioprinting method becomes perfect where the cellular density is higher, but low printing resolution limits its application.[35,36]

• • *Photocuring-based Bioprinting*

The benefit of bioprinting of photo-curing type is to harden and form layer-by-layer of bio-ink to attain 3D structures. Different types of photocuring-based bioprinters are as follows:

• • *Stereolithography (SLA)*

This SLA technology utilizes precise control of lighting to solidify photosensitive polymers. The laser scans a 2D pattern for each layer deposition by passing over through a point-to-point path.[37] Then, the vertical shift of the printing platform deposits the ink for each layer.[38]

• • *Digital Light Processing*

The method has a similarity with SLA techniques but the light scanning mode is different. In this case, the light is directed on the surface layer one time rather than point-to-point. DLP also offers a reasonable processing time with a fast fabrication methodology.[39] It produces higher cell viability due to its lower dependency on mechanical forces. The construction of complex tissue configurations with this method offers high resolution of printing by introducing proper photo-initiators to the bio-ink. Accumulating the UV exposure is the concern of this type of bioprinters because it directly impacts cell viability. The current development of tissue engineering approach is very much aided by considering various additive manufacturing methods. 3D bioprinting is one of them in which different types of bioprinter can be used based on the demand and application perspective that we have previously described followed by the schematic of different bioprinting technology, as described in Figure 2.

One of the greatest parts of the healthcare sector is covered by the techniques involved in tissue engineering. Understanding tissue engineering using 3D printing is difficult due to the complexity of cellular viability, printing resolution, vascularisation, and Hullbert's tissue ingrowth concept. The different printing techniques have distinguished features, advantages, and limitations described in Table 1.

Types of Bio-ink

The fabrication technology and the selection of biomaterials is also based on understanding the problem, application site, load bearing capacity and tissue engineering approach. As our body hierarchy is very irregular based on the location and load-bearing capacity it is required to select the proper biomaterials to serve the need of fabrication Mostly bio-inks can be formulated using ceramic, metal, and thermoplastic polymer. These materials need more organic solvents, temperature or cross-linkable products, and they are unsuited with the biomaterials and the cells. Thus, mimicking real organs and tissues becomes difficult for 3D printing technology.[40] Hence, bio-ink which is printable, stable, insoluble in the culture medium, biodegradable, non-toxic, cellular adhesive, etc., becomes fit for 3D bioprinting. Tissue engineering uses 2D and 3D hydrogel scaffolds, offering nutrient permeability, various water-soluble blends, and oxygen.[41] The details comparison 3D printing technology and use of different biomaterials has been described in the following Table 2.

Advancing our knowledge in regenerative biomaterials and their roles in new tissue formation has great potential in the fast-growing field of regenerative medicine. Selection of biomaterials play a pivotal role in the success of tissue regeneration using 3D printing technology. Synthetic biomaterials produced good mechanical support but osteo-interaction with the native tissue after implantation limits its application. Conflicting to that natural polymeric scaffold supports tissue in and on growth until sufficient new tissue is formed to serve the functionality of the newly fabricated diseased model. Therefore, advanced biomaterial is needed to mimic the 3D tissue microenvironment with structural integrity for cell accommodation, formation of new tissue,

Table 2: Overview of various material based additive manufacturing techniques in tissue engineering applications.

Materia used	*Types of Bioprinter*	*Pros*	*Cons*	*Application*	*References*
Polymers (ABS, PC, PLA, etc.)	Fused deposition bioprinter	Reasonable machines, Fast fabrication, Cost-effective, Patient-specific, Good accuracy, Generate suitable voids in scaffold for bone tissue ingrowth	Anisotropy, Poor surface morphology, Suitable for some thermoplastic polymers, Medium resolution, Difficulty in fabricating small-diameter structures	PCL)/hydroxyapatite (HA) based analogues of goat femur having good biocompatibility and osteogenic potential PMMA-based craniofacial reconstruction	42
Metal-based slurry incorporated with including Fibrin, pluronic, Chitosan, Hyaluronic acid,	Robocasting/Direct ink writing	The combination of biomaterials is less restricted, Support processing in a range of temperature, Suitable for live cell printing	Limited resolution and printing accuracy, Post-processing is needed to improve mechanical stability, Inferior built speed as compared to SLA and other fabrication methods	Beta TCP-based mandibles, skull implant structures implanted in rabbit	43,44
Metal-based biomaterials	Selective laser machining (SLM)/Electron beam melting (EBM)	Powder usage gives support; Post-processing is not required, Feasible manufacturing process at the industrial level, Less porosity in printed Material High mechanical strength	Non-uniform microstructure, Rough topology, Costly, Spacious bulky machines Average ductility, Expensive, Bulky machines	Titanium and Ti6Al4V-based maxillofacial alveolar orbital wall implanted in the human Ti and Ti6Al4V-based Skull and chest implanted in the human	45
Synthetic/Natural Polymer	Inkjet printing	Remarkable cell adhesion, proliferation as well as osteogenic potential, Low cost, Good accuracy Fast build rate, Can make clear parts,	This technique cannot print metals, Generate brittle structures, Inappropriate for load-bearing applications	α-TCP based construct for craniofacial bone defects, bone bridging. PEEK-based scapula in human HA-based skull implants in human	46
Photosensitive polymers	Stereolithography (SLA)/Digital light processing (DLP)	Can make clear parts, Vulnerability of live cells are maintained, High resolution and precision Suitable for printing small or medium-sized single parts,	Time-consuming post-processing Comparatively slower Process than SLA Availability of photo initiators are significantly limited	HA-based skull implants in human	47
Ceramic based	Pneumatic driven extrusion based bioprinter	Complex geometry with higher mechanical strength	Extrusion nozzle clogging	Fabrication of dental implant like mandible	48

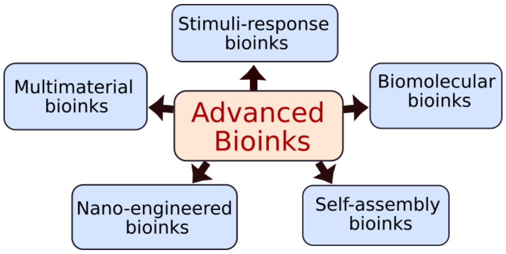

Figure 3: The schematic diagram for the classification of advanced bio-inks.

and development in load-handling conditions. The following section overview the advancement of biomaterials and bio-ink formulation towards future directions of bioprinting in healthcare application.

- *Advanced Bio-inks*

The printing strategy and properties of bio-inks depend on physicochemical and biological characteristics. Consequently, advanced bio-inks may increase the production of printable models, and can manifest shear-thinning attributes.[49] They are classified into five groups as depicted in the following Figure 3.

- *3D Bioprinting of Multi-material Bio-inks*

This type of bio-ink is currently at the development stages where various materials are combined together[48] like alginate was added with calcium ions to enhance the appetite formation at the implant and tissue interface.[49] Recently, Yanga *et al.* printed cartilage tissue using collagen-integrated alginate bio-inks.[50]

- *Stimuli-responsive Bio-inks*

Dynamic and stimuli-responsive bio-inks offer an opportunity for developing 4D bioprinting to mimic the true biological microenvironment of printed tissue model. These smart hydrogel-printed materials alter their functionality with outside stimuli, like water[51] magnetic field,[52] temperature, light, and pH.[53,54]

- *Bio-inks of Self-assemble Type*

The self-assembling materials ides in bioprinting has recently become relevant to fabricating larger anatomical shapes.[55] This self-assembling, scaffold-free bioprinting technology offers to create of nanofibrous, shape-morphing hydrogel for forming a 3D network such as ECM[56] and promote greater cellular viability.

- *Biomolecular Bio-inks for 3D Printing*

Despite efforts to develop a cell-printed structure, the cell-material interaction is still challenging for bioprinting. The complex interactive relation has motivated scientists to offer natural microenvironment conditions. Therefore, it led to the use of living tissue materials like a bio-ink.[57] (dECM) The decellularized extracellular matrix (dECM) is the most suitable technique to solve this issue as it can replicate almost entirely needs of the extracellular matrix (ECM).[58] The dECM-based bio-inks comprise the tissue decellularization by cells removal by keeping intact the ECM. After that the deformation of the ECM occurs into a powder and mixed in a cell-friendly solution to develop the bio-ink. The bio-inks have no requirement for crosslinking, also the adjacent gel can be degraded by them.[59] As the materials suffer from mechanical strength, we use tunable bio-inks with many material attributes to solve such issues. Also, these hydrogels have essential characteristics: biocompatibility, biodegradability, and permeability to nutrients, which attract particular concern.

- *Nano Engineered bio-inks for 3D Printing*

The mechanical strength and structural integrity are the limitations in case of polymer-based materials of a 3D printed constructs. Thus, to overwhelm this problem, few scientists mixed different biomolecules to the matrix of the polymer for improved integrity with the native tissue owing to better cytocompatibility and osteo-integrity.[60] In the last three decades, these nanoengineered hydrogel materials offers greater potential in 3D bioprinting[61] which has been described in the following section:

- Nanoparticle-reinforced Polymeric Hydrogel

Nanoparticles like carbon dots, carbon nanotubes, and graphene-integrated polymer composite hydrogel printed scaffold are having better structural network and mechanical properties such as stiffness, creep resistance, fracture toughness and young's modulus.[62] Adding those specific nanoparticles based on aspect ratio, shape, and size distribution may lead to many desired characteristics, i.e. bioactivity, electrical conductivity, photo responsiveness, fluorescence properties, etc., during tissue engineering application.[63]

- Fiber Reinforced Composites using Polymers

Recently, composites of polymerised fibers have gained particular concern for application in tissue engineering. In general, the hydrogel properties can be enhanced with fiber to help cell binding. As hydrogels are mechanically weak, and fibers have a compacted structure, their combination (fibrous and a gelatinous) can provide new mechanical attributes, and biomimicking aspects for optimized scaffold functionality.[64] Later, the addition of nanofibers to the cell-laden bio-ink for manipulating scaffold features is proposed by Narayanan *et al.*.[65] Rapid evolution of regenerative biomaterials recently helped release controlled growth factor which works dependently with the biomaterial to get better functionalities and tailored biological properties during *in-vivo* and *in-vitro* conditions. Therefore, the diversified application of bioprinting has been briefly described in the following section based on cellular viability, tissue integrity, mechanical stability for the variation in body location and functionality.

Tissue Engineering Application

Organ and Tissue Regeneration Bioprinting

The human body needs regeneration or transplantation after severe damage by trauma or diseases. There must be more than existing tissue engineering methods to generate organs and tissues for use in medical purpose excluding testing of drugs. The availability of donors and immune reactions become challenging for the organ transplantation method.[66]

The dissimilar configuration of gradients, ECM and natural tissue play an essential character in cell differentiation, proliferation, and migration.[67] In tissue engineering, bioprinting targets to produce complicated, functional and well-vascularized structures of tissues of varied fit of compositions for clinical uses in the future. The desired tissue is developed from computer-aided manufacturing/computer-aided design tools depending upon the CT or MRI images from the patients.[57] The printed tissues provide cells with essential cues and enable vascular network production. The structure of the target tissue influences the bio-inks choice and the printing methods. The current tissue engineering and regenerative medicine development uses bioprinting survey restoration, regeneration and replacement of injured and damaged blood vessel, neural tissue, heart, cartilage, bone and skin. Stem cells or tissue-specific bio-inks can produce bioprinted tissues.[58] This section discusses the existing studies and 3D bioprinting applications for soft and hard tissue fabrication.

Hard Tissue

- *Bone and Cartilage*

The most important part of the skeletal tissue is bone. It is made up of a difficult composite of organic matrix and minerals.[52] Despite its self-healing and self-regeneration properties, we need bone implant when the damage size crosses the critical defect size of bone. Cartilage is the linking tissue comprising proteoglycans and collagen.[68] Hyaline cartilage found between joints is essential in reconstructing bone tissue.[69] 3D bioprinting uses thermoplastics like polycaprolactone (PCL) and PLA to generate cartilage tissues. Other than grafts technology, it is possible to mimic the complex architecture of bone tissue like the mandibular, skull, knee, hip etc. can be reconstructed through different Bioprinting techniques. Datta *et al.* developed bioprinted constructs using alginate and poly-amino acids for bone tissue engineering applications. The developed constructs showed good cellular and mechanical properties for bone applications.[70]

- *Dental Applications*

Bioprinting is also popular for recent dental applications such as direct crowns and bridges, surgical drill guides, denture bases, etc.[71] Using High-resolution 3D bioprinting digital orthodontic models can be accurately regenerated. Dental applications include various biomaterials like spheroids, cell aggregates, composite materials, ceramics, etc. Later, Han *et al.* developed three-dimensional patient-specific dentin–pulp using hydrogel of fibrin-based.[72] Hence, the dental implants future should be benefited through 3D bioprinting.

Soft tissue

- *Skin*

Skin bioprinting is a proposed in situ approach in which the cells that are pre-cultured can be sprightly delivered at the targeted wound to grow cells in the normal surrounding. However, the exploration of the skin *in-situ* bioprinting in inadequate, compared with the skin *in-vitro* bioprinting experiments, that are extensively present in the literature.[73] Different kinds of cells are incorporated into bio-inks to produce fully functionalized skin graft. Lee *et al.* generated a graft of skin, layered printed constructs using adult human skin elements like epidermal keratinocytes and dermal fibroblasts in between collagen layers.[74] Other bio-inks like gelatin, fibrinogen, alginate, decellularized ECM can also be used to improve cellular viability during skin tissue printing. Datta *et al.* bioprinted constructs using alginate and honey for would healing skin tissue engineering applications. They showed good cellular activities and matched the mechanical strength of the skin.[10]

- *Cardiovascular Tissue Construct*

Cardiac tissue structures can be fabricated using bioprinting which can promote heart functionality and facilitate cardiovascular tissue regeneration. It also requires mechanical robustness with flexibility and vascularization to deliver nutrition supplies and optimal oxygen in case of tissue engineering approach with 3D bioprinting technology.[75,76] Scientists have mixed 3D bioprinting techniques with common tissue engineering methods to portray vasculature *in-vitro* structures for general design of heart valves and cardiac tissue. Hence, bioprinting is the future in case of heart transplantation of any designed model.

- *Neural Tissue*

The Peripheral nervous system (PNS) has natural healing and regeneration process for minor injuries. However, surgery is required for bigger ones. The (CNS) central nervous system is more difficult in nature.[77] Xu *et al.* is 2005 used thermal bioprinter of inkjet type for printing cells suspended of motoneuron nerve tissue using rat embryonic in phosphate-buffered saline (PBS).[78] Distribution of cells through bioprinting and neuron differentiation can have the potential in case of neural tissue redevelopment for medical applications.

- *Liver*

Human liver performs metabolic operations and detoxification.[79] It comprises vascular networks and hepatic lobules, where vascularisation is the key point during liver transplantation.[80] Collagen and glycosaminoglycan facilitates the liver's self-regeneration.[81] Li *et al.* in 2009 discussed an analysis of liver tissue regeneration by encapsulating hepatocytes in chitosan, gelatine and alginate[82] and adipose-derived stromal tissue in alginate, fibrinogen, and gelatine hydrogel for structure in vasculature. Robbins *et al.* fabricated a liver by syringe-based extrusion printer that was totally working properly for 28 days.[83] The total liver model with the complicated network of biliary and vascular structures was bioprinted successfully[84] which prove bioprinting has a great potential in case of liver tissue regeneration.

Other Organs and Tissues.

The bioprinting method is analysed to implement many more soft tissues such as muscles and tendons that may offer structural support and integrity in case of skeletal tissue

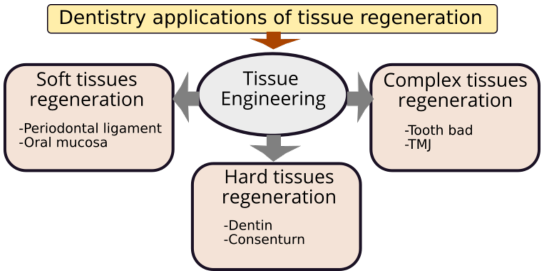

Figure 4: Different tissue engineering techniques using 3D bioprinting

regeneration. Many researchers have used several biomaterials to produce such tissue for example renal tubular tissue of the kidney was modelled using 3D bioprinting.[85] This technology can also be used to regenerate airway, lungs, ear, nose, throat and corneal tissue.[86,87]

Efficacy of Therapeutic Drug Using Drug Delivery

Bio-inks can be used to fabricate the complete organoid model in which drug and different growth factor can be targeted. Therefore, use of 3D bioprinting personalised drug loaded cross-linkable bio-ink can be formulated to check the drug efficacy the disease side in a particular manner.[88] Further this finding also improves the pathway of toxicology analysis and drug screening in bioprinted models of tissue.

Tumor Modelling

A tumor microenvironment can be produced with 3D bioprinting for the interaction of tumor cells with the neighbouring cells. Using tumor modelling, we can generate a microenvironment in an *in-vitro* condition for analysing drug response, tumor monitoring and progression. Either animals or cell cultures of monolayer type do the orthodox method of cancer or tumor modelling. Though, monolayer cultures absence the difficult communications happening with the animal models and the natural tissue that is different in response than human tissue. Therefore, analysis using bioprinted tumor models can be more justified and feasible to understand its response to the biological model.[89] As bioprinting techniques are explored further, the generation of complex biological systems to investigate disease interactions at the cellular level and on the surrounding tissue can be realized.[90] In Figure 4 various tissue engineering techniques using 3D bioprinting are depicted.

Future of Bioprinting

3D and 4D bioprinting will dominate the regenerative medicine in healthcare sector in the upcoming days. Vascularisation in the case of human tissue and organ transplantation played a vital role in clinical practice. The incorporation of vascular network can be stimulated by the tissue environment and the cellular viability during bioprinting. Furthermore, models of human-on-a-chip models can be established by means of microfluidics in organ-on-chip models to investigate the drug reactions in different organs at a time.[91] Bioprinting could help to understand interlinked vascular networks and system operations. To analyze the tests using bioprinting, we need to improve by using 3D microscopy, culture networks such as non-invasive monitoring systems and bioreactors. In the coming days, bioprinting can also support patients of diabetic by printing tissues of the pancreas islet to fight against immune responses.[9] The environment for personalized medicines and therapies can be studied using different pharmacodynamics. The signal of the electrical transport in the hydrogels can provide a detailed disease investigation related to electrically energetic organs. In brief, bioprinting to create human organs and tissue, evaluating treatments and drugs, and understanding disease appliances, etc., allows further exploration. Also, there is an increase in non-clinical bioprinting applications. For instance, worldwide organ shortages can be met with the development of soft robotics. This type of robotics can also make testing new cosmetic, chemical, and pharmaceutical products on animals more reluctant. Researchers are trying to develop complex human tissues to create 3D models for cancer-like critical illnesses. Such unique use may direct to personalized treatment for complex diseases. The ongoing development and application in this field will realize the solid complex organs "made to order" soon. Smart bio-inks using novel biomaterials can generate customized scaffolds which support cellular growth have been developing for the last two decades. From 2014 onwards, many companies of 3D bioprinting R&D and start-ups spinouts the total market. Commercialization has advanced this original machinery and created a predictable market price. 3D bioprinted items gained a market price of about $680 million in 2016, while the industry reported projected development to extent $1.9 billion by 2027.

Limitations of This Technology

The selection of optimal biomaterials is essential at the pre-bioprinting stages for healthcare tissue. Despite the widespread use of polymers in tissue engineering and 3D bioprinting, these materials lack suitable cytocompatibility causing undesirable cellular interactions.[92,93] Too much biological activity can lead to annoying cellular interactions and premature osteogenic differentiation. As an alternative, novel biopolymer and hydrogels are needed to mimic the nanostructured scaffold that act as an extra cellular matrix during cell proliferation.[94] However, poor structural integrity in these printed scaffold makes them unsuitable for bioprinting.[95] Therefore, optimizing the microarchitecture of these printed structure has attracted particular concern. In a recent study, Atala and colleagues formed combined bio-ink incorporated with tricalcium phosphate for bone bioprinting.[96] Current bioprinting methods are lengthy and incapable of delivering continuous cells for various tissues. The mechanical forces involved in the printing process may change cellular structures that may lead to losses of cell viability.[97] One enormous challenge in bioprinting is the formation of vascular networks in case of functional tissues[98] because their absence limits nutrient flow in engineered tissues that may cause necrosis.[99] Hence, optimizing resolution and speed in bioprinting vasculature is required for cell viability.[100] However, the timely development of tissues with mature, functional vasculature is yet to achieve and creates opportunities for further explorations.

CONCLUSION

The evolution of bioprinting for tissue engineering and regenerative medicine is widespread. Bioprinting methods try to mimic the complexity of tissues and networks in nature. Currently, 3D bioprinting offers extensive use in the healthcare and therapeutic sector. It comprises the potential to regenerate skin and bone and the ability to reconstruct complex tissues and organs. For example, tissues of skeletal muscle and cardiac, and organs such as the liver, kidney, heart, etc., are the upcoming products of bioprinting. Subsequently, some of the crucial tasks that arise during bioprinting are: choosing suitable biomaterial, designing bio-inks, optimizing the printing scheme, proper scaling, and vascularization increase. In the case of cancer research, bioprinting offers better scope to understand the microenvironment of tumor models and microtissue fabrication. The mechanical characteristics of a 3D printed construct are much better than the 2D cellular construction using a cell monolith. Accordingly, biomedical science can be reconstructed. 3D bioprinting can transform the existing model into a developed one just by changing the design morphology and optimizing the fabrication parameters in the healthcare and research industry. Integrating live cells with biological molecules can significantly change the 3D printing applications in surgery, contributing tremendous potential for 3D-printed organoid models. The potential of 3D printing in the case of synthetic tissue analogs is far better than other conventional grafting techniques. A patient-specific model with vascularisation is one of the most outstanding achievements using 3D printing construct. Not only the tissue construct using 3D printing, but we can also create the microenvironment of cancer models, and complex cellular models can be used for therapeutic drug screening under dynamic cell culture conditions. The miscellaneous bioprinting technology applications have conversed on a universal scale, primarily to the generation of complex structures from composite and vessel tissue. The diversification of this technology and the advancement in bioprinting and 3D printing in the following century can make tissue engineering future-proof and create a revolution in the healthcare industry. Since its inception, 3D bioprinting has made great progress toward the goal of functional tissue printing. Despite all challenges, bioprinting has become worthy in the recent ongoing research. greater time, multidisciplinary, and effort will be needed to accomplish this technology's potential in clinical field. Bioprinting has the potential to the development of personalized regenerative medicine. In the future, the prime focuses will be the advancement of novel bioprinting materials with excellent cytocompatibility, better printing resolution with higher mechanical properties. Development of heterogeneous and gradient composite materials are essential for *in-situ* bioprinting. Improvement of the biomaterials can be possible using recombination with bioactive factors with biomolecules. Combining open and closed porous biopinted structures can promote cell proliferation with vascularization. Thereof, bioprinting can be aided by development of various printing materials that will improve the efficacy of printing so that bioprinting will eventually come with a revolution healthcare industry.

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