MATERIALS USED IN 3D PRINTING FOR BONE DEFECTS: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: *This systematic review discusses various materials used in repair of bone defects using 3D printing technology. The advantages, disadvantages and various properties of these materials have been highlighted in this systematic review.*

Materials and methods: *A structured search of literature using major data bases like PubMed and Google Scholar were performed. Articles that fulfilled the predefined inclusion and exclusion criteria were appraised with respect to the key objectives of the review.*

Results: *More research should be done in the field of bioinks for treating bone defects as this technique has many unexplored areas. The existing materials have major potential of being modified to further improve quality of treatment and ease of printability/manufacture. This will eventually enhance the overall quality of treatment.*

Conclusion: *Treating bone defects with 3D printing has proven to be very successful. Many materials under these main 4 categories have been used as bioinks alone and in conjugation with other materials. Treating bone defects with 3D printed materials helps in achieving desired properties along with excellent aesthetics and outstanding postoperative results by increasing success rates. With that being stated, calcium phosphate composites have shown the most potential in treating bone defects via 3D printing. Their properties and results are ideal because of their similarity to the composition of natural bone.*

Keywords: *Bone defects, Bone tissue engineering, Bone regeneration, 3D printing techniques, 3D printing materials.*

INTRODUCTION

A bone defect is the absence of bone tissue in an area of the body where bone should be ordinarily present (1). Trauma, congenital malformations, and tissue resection due to malignancy are the most common causes of significant bone deformities (2). Bone defects are frequently associated with serious soft-tissue injuries as well (muscles, tendons, joints, etc.) as a result of trauma or injury. Large bone defects do not heal on their own (3). The aim of treating bone defects is to achieve rehabilitation, reconstruction and regeneration and this is difficult due to the complexity of tissue specific requirements and structural anatomy (4). For surgeons, the challenge is to avoid amputation while yet delivering optimal functional results (3) and to provide an effective, aesthetic and personalized treatment of every patient (4). Due to advancements in stem cell biology, innovative biomaterials, 3D bioprinting and tissue engineering shows promise for the treatment of major bone deformities (5). There are numerous 3D bioprinting techniques available. Fused deposition manufacturing (FDM) is a technique in which a molten material is extruded in a layer-by-layer manner to construct a 3D structure (4). Stereolithography (SLA) uses lasers to solidify light cure polymers layer by layer (6). Selective laser sintering (SLS) technology in 3D printing utilizes a powder material which is sintered in layers to create a structure (7). Inkjet

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bioprinting is done via hydrogel droplets which are ejected with acoustic, thermal or electromagnetic forces along with cells or other biological molecules [8]. Another type, extrusion bioprinting is done by extruding viscous cell slurries through pumps screws or pneumatic systems [4]. Laser assisted bioprinting also uses a hydrogel like inkjet printing but in this the hydrogel solution is vaporized using laser technology [9]. This is a systematic review going through the various materials used for this purpose.

MATERIALS AND METHODS

A comprehensive, structured literature search of published articles was conducted. Reporting Items for Systematic Reviews were used to conduct the study.

Data Sources

In December 2021, a systematic review was carried out using PubMed and Google Scholar using the Boolean descriptors and operators: (bone defects OR tissue engineering for bone defects), (3D printing OR robocasting) AND (3D printing techniques OR 3D printing materials). 74 articles were screened after removal of duplicate articles. Screening was carried out by reading the abstracts of these articles and 44 articles were finally selected that fulfilled the eligibility criteria.

Exclusion and inclusion criteria

All original full papers published in English language in the last 10 years, focusing on bone tissue engineering, 3D printing techniques for bone defects and the materials used in 3D printing were included. Papers written in languages other than English, older than last 10 years and which did not focus on the 3D printing techniques and materials used for 3D printing were excluded.

Materials used in 3D printing of bone defects

Bone tissue engineering has evolved and advanced rapidly since last decade as a result of the requirement for development materials for bone repair that have close similarity to natural structure and function of natural bone tissue and are non-immunogenic. Different biomaterials are used to treat bone defects. Synthetic materials are preferred by researchers because they provide a wide range of sources, changeable characteristics (tailored treatment), and no risk of disease transmission for bone tissue engineering using various techniques such as 3D printing, electrospinning, phase separation, freeze drying, solvent casting etcetera [10]. However, focusing on 3D printing and the materials used in it for bone defects are as follows:

1. Polymers

A polymer is a substance made up of numerous repeating subunits and consists of macromolecules [11]. Depending on their sources, polymers are classified into synthetic polymers (examples: polyethylene, polypropylene, polystyrene, polyvinyl chloride, synthetic rubber, phenol formaldehyde resin, neoprene, nylon, polyacrylonitrile, Polyvinylbutyral (PVB) and silicone) and natural polymers (examples: hemp, shellac, amber, wool, silk, and natural rubber). Both play important roles in everyday life due to their diverse range of characteristics [11]. Use of polymers in 3D printing is gaining eminence in industry, especially in the surgical and medical fields, due to recent studies on scaffold fabrication for tissue engineering[12].They are available as filaments for fused deposition modelling (FDM), powder-beads for selective laser sintering (SLS), solutions for stereolithography (SLA), and gels for direct ink writing (DIW) [13]. Polymers are biocompatible, have adjustable mechanical properties and degradation rates, and can be dissolved in quickly evaporating organic solvents like dichloromethane, tetrahydrofuran, or dimethyl sulfoxide [14]. The most prevalent polymer 3D printing methods include : extrusion, resin curing, and powder-based procedures [15]. Each process allows for the additive deposition of layers to build parts and fabricates them utilizing distinct processing stages that limit processes to specific material selections and designs [15]. New capabilities in medicine are being enabled by current advancements in polymer 3D printing such as spinal fusion cage, dental model, prosthetic hand, PPEs , sacral surgery planning , and drug-delivering microneedles [12].

2. Ceramics

Ceramics are hard, brittle, chemically inert materials that have been in use for a long time for various applications such as manufacturing of pottery, machinery, electronic devices, biomedical devices etc [25]. Ceramics like calcium phosphate has been used since 1920s for the purpose of encouraging the formation of bone [26]. 1990s Marcus et al and Sachs et al used ceramics for the first time in 3D printing

[25]. Different 3D technologies such as are used for different preprinting forms of ceramics that include bulk solid based, slurry based and powder based forms [25]. The table below shows technologies used for 3D printing of ceramic based materials [25].

3D printing can be used to fabricate both bioinert and bioactive ceramic such as bio active glass[27], beta tricalcium phosphate, calcium silicate and hydroxyapatite based scaffolds [28]. Bioactive ceramics can be used alone or in combination forming a composite like biphasic calcium phosphate, which is formed by combination of tricalcium phosphate with hydroxyapatite [29]. Calcium phosphate scaffolds have shown promising results for bone defects regeneration due to their close resemblance to natural bone structure [30] and are biocompatible, biodegradable and osteo conductive [31]. 3D printing using lithography has been used to make scaffolds of specific pore size with calcium phosphate ceramic[31]. Bioactive ceramics have proven to be helpful in regeneration of defects on the cartilage and its subchondral bone [32]. Research has also shown good potential of hydroxyapatite ceramics for scaffold formation using 3D printing for bone regeneration due to resemblance to mineral component of bone [33]. Hydroxyapatite is highly osteogenic, osteoinductive and biocompatible[33]. Main advantages of ceramics are their closer to normal bone tissue, osteoconductive and osteoinductive properties and can be used in many forms such as granular particles, pastes or in injectable forms. Disadvantages are their hard and brittle nature and less controlled resorption of ceramic scaffolds [29].

3. Composite

Bio glass composite scaffolds have proven to be more favorable in bone tissue regeneration as compared to hydroxyapatite-based scaffolds [34]. Recent studies have shown potential of combination of bioactive ceramics and composite for regeneration of large bone defects [35] . Further research and advancement in 3D printing using bioactive properties of ceramics in combination with other materials can help in more effective bone repair tissue engineering techniques.

4. Collagen

Collagen is a natural protein found in the structure of skin and connective tissue [36]. Collagen is a protein that accounts for one-third of the total protein present in the human body. It is hard, insoluble, flexible, and fibrous in nature. Collagen is a supporting structure that is responsible for cell-to-cell anchorage. Almost 30 types have been discovered so far. Type I collagen is the most abundant type present in the human body followed by type II, III and IV.

In 3D printing, collagen has been used for treatments related to the skin, heart tissues, vascular tissue, liver tissues, cornea and even the nervous system. But it has proved to be highly successful in printing for treatment of bone defects [36]. For 3D printing, collagen is used in the form of a hydrogel, most of which are produced from type I collagen [37]. Type I collagen is a fibril forming collagen. When mineralized, it is the building unit of bone and therefore, used widely in treating these structures [37]. At normal physiological conditions, i.e. a temperature of 37°C and a neutral pH, the molecules of collagen in solution organize themselves into fibrils [38]. This converts the collagen solution into a hydrogel [38]. The kinetics of this mechanism determine the printability of the collagen bioink. The faster this process is, the better will be the accuracy of printing [38]. The main advantage of using collagen as a 3D printing material is not only its biocompatibility due to its nativity to the human body but also its low immunogenicity [36]. To achieve maximum biocompatibility, collagen should be pure [39]. The main issue with this is that it has inferior mechanical properties [39]. Bioinks in their pure forms and free from any additives have been used very rarely [39]. In the early years it was deduced that to increase the printability of collagen bioinks, it was necessary to increase their storage modulus prior to extrusion [40]. The reason for this was that for direct extrusion bioprinting, the loss modulus lower than the storage modulus was more favorable [40]. Another technique FRESH was also discovered. FRESH stands for freeform reversible embedding of suspended hydrogels [38]. In this supportive hydrogel were also included in the materials as they improved the capability of collagen to be used as a bioink in terms of its printability [38]. The use of a supportive hydrogel for 3D printing with use of collagen, most of the processes occur while in the gelatin slurry stage [38]. This is the secondary hydrogel. The gelatin slurry here acts as a thermos reversible support only temporarily [38]. Sodium alginate has also been used as an additive with collagen type I to produce 3D printed bone [41]. It was seen that these materials have good mechanical strength [41]. To produce a bone structure that is closest to natural bone and composition closely matching that of bone another technique was employed. Deproteinized bovine bone (DBB) powder and hydroxyapatite (HA) were added to collagen [42]. This allowed for the manufactured architecture to be porous [42]. Materials with both the additions showed similar cell proliferation and were highly biocompatible [42]. They had desired mechanical and chemical properties and promoted osteogenic differentiation [42]. Because of these properties these materials are high well suited for use in 3D printing of bone to treat defects of bone. Another modification in this was the addition of calcium deficient hydroxyapatite into collagen bioink [43]. The main advantage of this was that it healed larger or critical sized defects of the bone desirably [43]. Beta Tricalcium phosphate has also shown to produce desired 3D printed structures in conjugation with collagen which can treat bone defects [44]. This material had excellent capability to maintain bone defects and they supported barrier membranes very well [44]. It can hence be observed that collagen allows many possibilities of additives which can improve its quality as a bioink for 3D printed structures to treat bone defects and it is well accepted by the body while possessing desired properties so, it is a material which is highly suitable for this purpose.

RESULTS

Treating bone defects with 3D printing has proven to be very successful. Many materials under these four main categories have been used as bioinks alone and in conjugation with other materials. Treating bone defects with 3D printed materials helps in achieving desired properties along with excellent aesthetics and outstanding postoperative results by increasing success rates.

Table 1. Highlights the printing techniques and measured mechanical properties of some common 3D-printed polymer materials.

Material	Printing technique	Mechanical Properties	References
ABS	Fused deposition modeling (FDM)	TS: 35 MPa; EM: 1300 MPa.	(16) (17)
PC	FDM	TS: 37 MPa; EM: 1000 MPa.	(16)
PEEK	FDM	TS: 58–85 MPa EM: 3000–4100 MPa;	(18)
PETG	FDM	TS: 36–40 MPa;	(19)
PLA	FDM	US: 265 MPa; YS: 205 MPa; ES: 4400 MPa.	(20)
Nylon	Multi jet fusion	TS: 47–48 MPa; EM: 1150–1250 MPa;	(21)
Stratasys: MED 610	Poly jet	EM: 1860–2120 MPa;	(15)
DSM Somos, Inc: Watershed XC 11122	Stereolithography	TS: 37–48 MPa; EM: 2040–2400 MPa;	(22)
EnvisionTEC: E-Shell 600	Stereolithography	EM: 1400–1620 MPa;	(23)
Formlabs: Dental SG	Stereolithography	EM: 1670 MPa;	(24)

Abbreviations: TS- Tensile Strength, EM-Elastic modulus, YS-Yield strength, US-Ultimate strength, FDM-Fused deposition modeling

Table2: 3D printing technologies and their respective abbreviations.

3D printing technologies	abbreviations
Inkjet printing	IJP
Direct ink writing	DIW
Two photon polymerization	TPP
Three-dimensional printing	3DP
Selective laser sintering	SLS
Selective laser melting	SLM
stereolithography	SL
Digital light processing	DLP
Fused deposition modelling	FDM
Laminated object manufacturing	LOM

Table 3: Types of collagen and where it is most abundant in the human body.

Type of Collagen	Body Part/Organ
Type I	Bones, tendons, organs
Type II	Cartilage
Type III	Reticular fibers
Type IV	Basement membrane of cell membranes
Type V	Hair, nails

CONCLUSION

Treating bone defects with 3D printing has proven to be very successful. Many materials under these main 4 categories have been used as bioinks alone and in conjugation with other materials. Treating bone defects with 3D printed materials helps in achieving desired properties along with excellent aesthetics and outstanding postoperative results by increasing success rates. With that being stated, calcium phosphate composites have shown the most potential in treating bone defects via 3D printing. Their properties and results are ideal because of their similarity to the composition of natural bone.

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