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3D Printed Composite Structures for Bone Repair and Drug Delivery Application

Joshua C. William[1], Mahamudu H. Mtebwa[1], Regina P. Mtei[2], Innocent J. Macha[†]

[1]Department of Mechanical and Industrial Engineering, College of Engineering and Technology, University of Dar es Salaam.
[2]Department of Chemistry, University of Dar es Salaam.
[†]Corresponding email: imacha@udsm.ac.tz

ABSTRACT

Due to the increase in traffic accidents, industrial contingencies, and natural disasters, there is a high demand for bone regeneration biomaterials. Although bone can regenerate and self-repair, it is difficult to do so when the defect area exceeds the critical repair area due to trauma, tumour resection, or congenital diseases. The traditional methods for bone repair are autograft, allograft, and xenograft. However, these methods have flaws and limitations, such as complications in the donor bone area, a limited number of donors, rejection, and infectious diseases. However, in recent years, the use of additive manufacturing technologies in bone tissue engineering has increased. Three-dimensional printing (3DP) is gaining popularity among the various technology options due to its ability to directly print porous composite with designed shape, controlled chemistry, and interconnected porosity. Some of these inorganic composites are biodegradable and have proven ideal for bone tissue engineering, with the ability to deliver growth factors or drugs to specific sites. The purpose of this study is to discuss recent advancements in 3D printed bone tissue engineering composite, as well as current challenges and future directions. Studies related to tissue engineering applications, specifically, orthopaedics were emphasized. The future perspectives and possible research areas have been potentially proposed.

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INTRODUCTION

Bone tissue comprises two parts; the spongy inner part has more than 50% volume porosity (Susmita et al., 2013). However, the outer part of the bone is closely packed with a porosity of about 3–5% (Burr, 2019), controlled through relationships between the cells that constitute the bone, osteoblast, and osteoclast (Kim et al., 2020). Osteoblasts predominantly form new bone, while osteoclasts break down old bone tissue (Berendsen, 2015; Kular et al., 2012). Such a dynamic process involving osteoclasts and osteoblasts is known as bone remodelling and is responsible for maintaining a healthy bone (KenkreBassett, 2018). Bone is capable of regenerating and healing itself. However, the body cannot fully recover substantial segmental bone losses independently. In most cases, a bone graft is required to resume normal operations (Kiernan et al., 2018; Winkler et al., 2018). The common bone-healing treatments are autograft, allograft, and xenograft (Shrivats et al., 2014). However, these techniques often have limitations and drawbacks, such as issues with the donor bone area, a shortage of donors, rejection, varying rates of implant degradation from newly formed tissue, and infectious diseases (Dhawan et al., 2019; Ibrahim, 2018). Although both techniques have received much attention, their shortcomings have made it necessary to look for the ideal bone graft development. Bone tissue engineering has attracted research attention since the 1980s (Wang et al., 2011). Currently, the main objective is to develop an alternative method for bone grafts using a scaffold from a biocompatible material loaded with cells and bioactive growth factors that can potentially replace traditional tissue grafts (Chocholata et al., 2019). Various scaffolds have been created and tested to meet the chemical, physical, and mechanical requirements for safety while simulating the restored bone (Roseti et al., 2017). To create scaffolds for bone repair, many techniques have been used, such as solvent casting and particle leaching (SCPL) (Poomathi et al., 2020), chemical or gas foaming (Eltom et al., 2019), microsphere sintering, freeze drying, thermally induced phase separation, and electrospinning (Weigel et al., 2006), This method has been applied in some cases quite frequently. However, most of these methods cannot be used to build scaffolds with designed porosity for particular flaws since they do not allow for exact control of pore size, shape, and interconnectivity in the scaffold (Khorshidi et al., 2016). Bone scaffolds with well-tunable properties can be designed using additive manufacturing (AM) techniques (Meng et al., 2020). A variety of AM methods exist, for example, 3D printing (3DP), solid freeform fabrication (SFF), and rapid prototyping (RP) (Arifin et al., 2022). These methods use computer-aided design (CAD) software or 3D object scanners to direct hardware to deposit material, layer upon layer, in precise shape (Li et al., 2022).

Three-dimensional (3D) printing and working principle

Several techniques have been used to create 3D scaffolds—standard fabrication techniques such as freeze-drying, gas generation, phase separation, and salt leaching. Tissue engineering has fast advanced thanks to 3D printing, an additive manufacturing technology, to replace and repair damaged tissues (Haleem et al., 2020). The 3D printing (3DP) method combines biological sciences with engineering technology to print scaffolds that frequently include the osteogenic cells necessary for healing along with the growth factors that will aid in osteo-differentiation and angiogenesis to hasten the healing process and serve as alternatives to traditional tissue graft procedures (Yazdanpanah et al., 2022). With the use of computer-aided design, this method may turn digital impulses into actual objects (CAD), computer-aided manufacturing (CAM), computer numerical control (CNC), laser technology, and computed tomography (CT) (Chen et al., 2020). Combined with these technologies, digital imaging and communications in medicine (DICOM), such as magnetic resonance imaging (MRI) and computed tomography (CT), can be converted into acceptable types recognized by 3D printers (Mitsouras et al., 2015). This technology makes designing and developing medical implants and devices easily possible. It increases the efficiency and quality of innovation in medicine, dentistry, cardiology, bone tissue engineering, research, food, agriculture, automobile, architecture, aerospace, and other fields. The main focus of this study is the application of 3D printing technology in bone tissue engineering.

METHODS AND MATERIALS

3D printing is a process used to make three dimensional solid objects from successive layers of materials, each of which is successively solidified. The technology was originally used for rapid prototyping but has been adapted for numerous applications including in orthopaedic surgery. While use for making complete structures is relatively new and therefore still in experimental stages, the ability to print composite structures could allow for improved clinical application as well as novel research opportunities. The following literature review examines recent advancements in 3D printing constructs for orthopaedic applications. Recent articles from relevant literatures were reviewed for a wide range of composite structures.

3D-printed bone scaffold

Figure 1 depicts using a 3D bio-printing method to create ideal bone structural scaffolds with greater control over pore morphology, size, and porosity (An et al., 2015). The technology produces adaptable solid free-form structures with exceptional freedom in material selection and geometry for growing irregular tissues (Giannitelli et al., 2014). An ideal 3D scaffold should have high porosity, interconnecting pore networks, and stable, sufficient pore sizes to promote cell migration and infiltration (LohChoong, 2013). These parameters—which affect cell adhesion, proliferation, and distribution—are crucial parts of the scaffold geometry that permit vascularization and nourishment (Zhang et al., 2018). Choosing a suitable material is also essential when designing a scaffold. For optimum tissue regeneration, biocompatible scaffolds with comparable degradation rates to tissue regeneration are advised (Pina et al., 2019). The scaffold must have the necessary mechanical properties to provide temporary structural support until new tissue forms after being implanted (Eltom et al., 2019). The scaffold must possess crucial morphological qualities, such as being highly porous, enabling nutrition transmission and tissue ingrowth, and biocompatible and biodegradable (Wei et al., 2020). To fulfil these needs, tissue engineering scaffolds are usually made to resemble the extracellular matrix (ECM) in nature (Yamaoka, 2019; Yi et al., 2017). Generally, biodegradable porous materials are used to create bone scaffolds, which offer mechanical support during bone regeneration (Ghassemi et al., 2018).

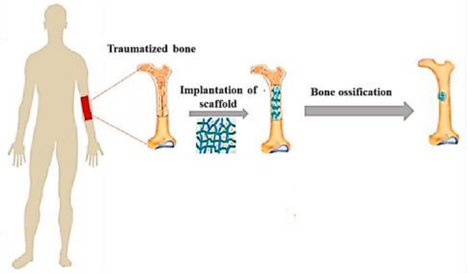

Figure 1: Scaffold promotes tissue and cells repair of the defective bone (Cao et al., 2020)

Over the past few decades, research in bone tissue engineering has sparked innovation in new materials, processing methods, and applications (Montoya et al., 2021). Scaffold materials for desired osteogenesis, angiogenesis and structural support have risen tremendously (Bose et al., 2012). Contemporary scaffold construction techniques have made it possible to create biodegradable scaffolds with controllable porosity and customized properties (Collins et al., 2021). Natural bone has outstanding mechanical qualities because it has an architectural structure with accurate and deliberately constructed interfaces that spans nanoscale to macroscopic scales (Gong et al., 2015).

Biomaterials for bone tissue engineering

Bone tissue engineering aims to create biomaterials that can replace conventional grafts with the correct biochemical and physical properties (Awad et al., 2020; Black et al., 2015; L. Wang, 2016). It can also be used to replace or improve bone by fusing the bone with the surrounding tissues. Since these biomaterials are essential to the 3D printing of bone substitutes, it is necessary to comprehend their properties and use them appropriately (Haleem et al., 2020). This section examines metallic, polymeric, ceramic, and nano biomaterials used in 3D printing to create bone grafts and substitutes.

Metallic Biomaterials

Since the seventeenth century, metal has been used to create implants. Metals can be used to build structures that can withstand heavy loads without suffering severe elastic deformations or permanent deformation because of their solid elastic moduli and suitable yield points (Hosseini et al., 2012; Kassanos et al., 2021). Metal devices provide good to outstanding resistance to the diversity of external and internal conditions found in orthopaedic practice if proper care is taken during production, surface polishing, and handling (Bose et al., 2018). Metallic screws were first used in load-bearing systems such as hip and knee prostheses and internal and external bone fracture fixation, as shown in Figure 2 (Bazaka et al., 2021).

Table 1 depicts the mechanical properties of common metals, which are solely determined by their properties. To ensure that the implant material's properties are not changed or harmed over time, it is essential to research and consider a number of metal implant features, including biocompatibility, corrosion resistance, mechanical properties, and fatigue resistance (Xiang et al., 2022).

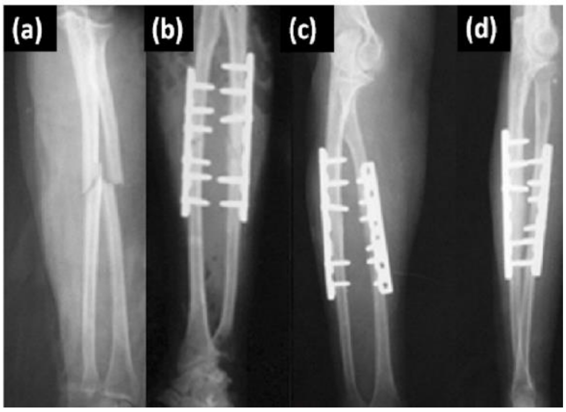

Figure 2: Preoperative X-ray of the forearm shows fracture of both bones; (b) immediate postoperative X-ray following locking compression plate and; (c) X-ray after ten months of follow-up shows fracture union (Saikia et al., 2011).

Table 1: Mechanical properties of metals materials in orthopaedics

Metals	**Tensile strength (MPa)**	**Modulus (GPa)**	**Reference**
CP-Titanium	240–550	105	(Thouas, 2015)
Cobalt-Chromium-Molybdenum	897–1192	220	(ASTM, 2012)
Titanium-6Aluminium-7Niobium	860	105	(Gepreel, 2015)
Stainless steel 316L	465–950	200	(Navarro et al., 2008)
Titanium-5Aluminum-2.5Iron	900	110	(Chen, 2019)
Titanium-3Aluminum-2.5Vanadium	690	100	(Ijaz et al., 2020)

On the other hand, metallic implants have several drawbacks due to their high elastic modulus, which causes stress shielding (SavioBagno, 2022). Metallic implant ions are a major cause for concern regarding adverse effects. As a result, several surface reaction strategies have recently been released. Surface topography and chemical composition both have an impact on surface responsiveness. Plasma treatments, grit or sand blasting, and other surface topographical modifications are possible (Damiati et al., 2018). A variety of coatings, including hydroxyapatite, titanium oxide, and nitride, have been used to improve surface characteristics (Aviles et al., 2020; Xue et al., 2020)

Polymeric Biomaterials

Poly-methylmethacrylate, silicone, polyurethane, ultra-high molecular weight polyethene, and polyurethane have all been used in orthopaedic applications, as shown in Figure 3 (RameshSivaramanarayanan, 2013). These polymers' mechanical properties are shown in Table 2. UHMWPE is a popular polymer for orthopaedic implants due to its high mechanical strength, low wear rate, and biocompatibility (Hussain et al., 2020). Although ultra-high molecular weight polyethene (UHMWPE) has been used for a decade, wear debris osteolysis remains a concern (Kandahari et al., 2016). Numerous kinds of research have been conducted to understand better the wear mechanism and the osteolysis caused by wear debris (Shahemi et al., 2018).

Table 2: Mechanical properties of polymeric materials in orthopaedics

Polymer	Tensile strength (MPa)	Modulus (GPa)	Reference
Poly-methyl methacrylate (PMMA)	48-76	3-5	(Najeeb et al., 2016)
Polylactide (PLA)	32.2	0.35-3.5	(Luthringer et al., 2014)
Polycaprolactone (PCL)	23	0.21-0.44	(Luthringer et al., 2014)
Chitosan	34-44	1.1-1.4	(Luthringer et al., 2014)
Polyglocolide (PGA)	60 - 99.7	6-7	(Luthringer et al., 2014)
UHMWPE	20-30	0.5-1.3	(KurtzDevine, 2007)

Resorption of bone around the implant occurs concurrently with the formation of vascularized granuloma at the implant-bone interface (Nussvon Rechenberg, 2008). The appearance of granulomas is a body response to clean up the worn particles. Because the primary issue with using UHMWPE as acetabular cups is the weakening of interfacial adhesion between tissue and implant (due to wear debris), significant efforts have been made to improve UHMWPE wear resistance (Goodman et al., 2020; Lei et al., 2019).

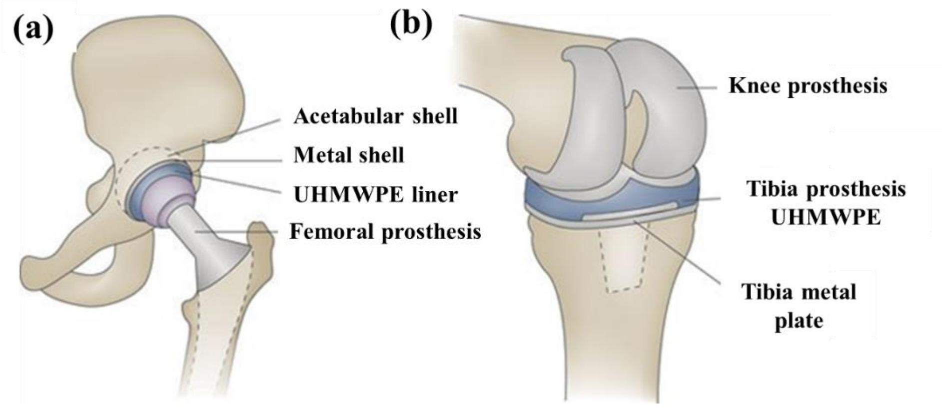

Figure 3: Schematics of typical joint implant devices. (a) A hip replacement (b) A knee replacement prosthesis (Cobelli et al., 2011)

Oxidation during sterilization is another cause of UHMWPE implant failure (Bistolfi et al., 2021). Even though disinfecting the implant in an inert environment and other medical interventions such as gas plasma and ethylene reduce oxidation of UHMWPE, high-intensity radiation exposure causes free radicals to form in the crystalline phase of UHMWPE (Bracco et al., 2017). When these free radicals react with dissolved oxygen, they cause oxidative embrittlement, which reduces the implant's mechanical properties. To prevent oxidative embrittlement of UHMWPE, vitamin E as an antioxidant is suggested (Bistolfi et al., 2021; Bracco et al., 2017).

Ceramic Biomaterials

Ceramic materials have several advantages that make them ideal for orthopaedic implants. They have a hard surface, high mechanical stiffness, low elasticity, low thermal expansion, and chemical-physical refractoriness, but their properties are also influenced by the composition and particle size of the starting powder (Chen et al., 2021; Affatato, 2019; Mhadhbi et al., 2021). Ceramic scaffolds are widely used in bone regeneration procedures because they are highly biocompatible, rarely elicit an immune response, and rarely cause fibrous tissue to form around the scaffold; instead, they are osteoinductive due to their high ability to recruit cells from the biological environment and promote osteogenic differentiation (Dolcimascolo et al., 2019; Donate et al., 2020; Gao et al., 2022). Despite these advantages, the use of ceramics in tissue engineering applications is restricted due to their fragility and slow degradation (Baino et al., 2015). Table 3 displays the mechanical properties of various ceramics used in orthopaedic applications.

Table 3: Mechanical properties of ceramic materials used in orthopaedics

Material	Tensile strength (MPa)	Modulus (GPA)	Reference
Magnesium-67Zirconium28Calcium5	675 - 894	48	(Luthringer et al., 2014)
Hydroxyapatite	40-200	70-120	(Luthringer et al., 2014)
Bioglass (45S5)	42	35	(Fiume et al., 2018)
Beta-Tri-calcium phosphate (β-TCP)	18-130	23.4 - 84.8	(Wang et al., 2004)

Metals, ceramics, and plastics make femoral heads for hip replacements and wear plates for knee replacement (Merola et al., 2019). One of the concerns with alumina ceramic implants was their low fracture toughness. However, it was overcome by increasing purity, lowering porosity and grain size, and improving manufacturing techniques (Al-Sanabani et al., 2014). In hip replacements, alumina is used as the femoral head with a metallic femoral stem and UHMWPE as an acetabular cup opposing articulating surface (SinghGangwar, 2021). Several studies focus on other materials as an alternative to alumina (Taeh et al., 2022). Apart from alumina, zirconia, as a potential material for application in orthopaedics, was published in 1969. The first publication on the design of zirconia ball heads for total hip replacement was reported in 1988 (Piconi et al., 2003). The polymorphic structure of zirconia, its complex surface, low thermal conductivity, and large thermal expansion coefficient make it an excellent material for dental and hip implants (Piconi et al., 2003), as shown in Figure 4. It is a perfect candidate for prostheses and bone grafting due to its high breaking load and biocompatibility (Ding et al., 2021).

Novel nanocomposite systems and composite materials

3D-printed composite scaffolds have previously been utilized for many applications owing to their low production costs and potential to construct intricate parts (Varma et al., 2020). Despite the enormous success of today's bone implants for joint replacement, there is still a need for the development of materials that are more biocompatible, last longer in the body, and have a wide range of applications, as well as the blending of different materials with unique properties for the generation of high-performance composites (Mbundi et al., 2021).

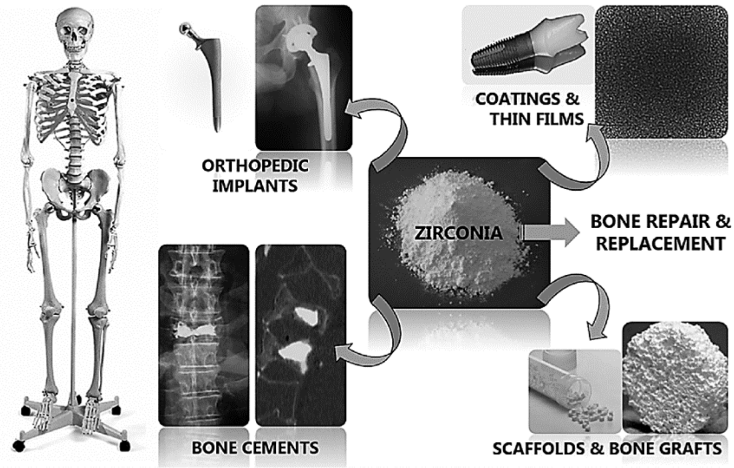

Figure 4: Biomedical uses of zirconia ceramics in modern bone replacement and repair applications (Afzal, 2014)

Recently the fabricated nanocomposite scaffolds outperformed conventional composite scaffolds in terms of mechanical, thermal, and chemical properties, as well as cell proliferation and differentiation in regenerative medicine (Cernencu et al., 2022).

(Goodarzi et al., 2019) and his colleagues created a collagen/beta-tricalcium phosphate (β-TCP) nanoparticles scaffold, and the results showed that the presence of (β-TCP) particles embedded in the collagen matrix could promote mesenchymal stem cell (MSC) differentiation to osteoblasts with higher alkaline phosphate activity and higher mechanical strength of the scaffold compared to pure collagen scaffold. More importantly, in vivo subcutaneous vascularization increased significantly when collagen/(β-TCP) was compared to pure collagen. Furthermore, (Joseph et al., 2020) worked on the development of scaffold-based hydroxyapatite (HAP)-bacterial cellulose (BC) nanocomposites, and it was discovered through Fourier transmission infrared studies that the HAP crystals with low crystallinity synthesized on the bacterial cellulose contain carbonate, similar to natural bone.

Moreover, carbon fibres have excellent mechanical properties and are biocompatible. They have reinforced ultra-high molecular weight polyethylene in total hip replacement components (Akgul et al., 2019). Polymethylcrylatecrylate (PMMA), polypropylene and polysulphone, polyethylene, polybutylene terephthalate, and PEEK (polyetheretherketone) carbon fibre composites have all been investigated for potential load-bearing applications (Li et al., 2015). Several efforts have been made to reinforce bioceramics with carbon fibres to improve composites' bioactivity and mechanical properties for orthopaedic applications (Abbas et al., 2021).

Osteoprogenitor cells and drug delivery using 3D-printed scaffolds

The biocompatibility of materials governs the interactions between the material and the surrounding biological system of the living tissue (Huzum et al., 2021). However, materials alone are not enough to improve the biocompatibility of 3D-printed scaffolds; growth factors being used (osteoprogenitor) significantly improve scaffold biocompatibility (Do et al., 2015). Drug delivery in scaffolds has also been used to enhance bone growth using 3D-printed scaffolds, as shown in Figure 5 (Bahraminasab, 2020). Site-specific delivery of growth factors and drugs has received significant attention due to the potential for dose reduction, controlled release pattern, and negligible side effects compared to systemic delivery. Maintaining drug loading and release rates in scaffolds is aided by pore size, connectivity, and geometry (Bose et al., 2013; Patra et al., 2018). 3DP technique was used to create different kinds of calcium phosphates scaffold (CaPs): brushite, monetite, and HAP; immersion/vacuum impregnation was used to load vancomycin hydrochloride, ofloxacin, and tetracycline hydrochloride onto these compositions (Kilian et al., 2022). The specific surface area influenced drug absorption, and the release rate of the scaffold followed an exponential pattern. Furthermore, drug immersion in a combined polymer of polylactide-polyglycolide (PLA/PGA) resulted in a delayed release profile (Bose et al., 2013). Again, incorporating polylactic acid (PLA) calcium phosphate scaffold with zinc nanoparticles led to the improved proliferation of tissue (Wang et al., 2021).

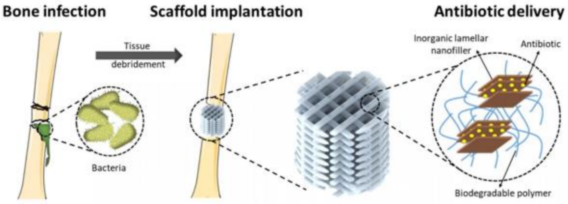

Figure 5: Schematic representation of the antibacterial composite scaffolds (Cámara-Torres et al., 2021)

Medical advancement of 3D printing

The increased utilization of 3D printing in biomedical sciences demonstrates its utility for various research and healthcare applications (Eshkalak et al., 2020). The Wake Forest Institute for Regenerative Medicine performed the first clinical application of 3D-printed organs in 1998, successfully implanting a 3D-printed human bladder into a human (Munoz-Abraham et al., 2016; Sowjanya et al., 2013). This technology is still used in medical applications such as artificial bone scaffolds, blood vessels, nerve tissue, and cartilage (Palmisciano et al., 2021; Saleh et al., 2022). The 3D printing bone scaffold can print porous scaffolds with the required shape and size using the layer-by-layer technique (LiuYan, 2018). Technology is gaining popularity due to its ability to produce customized parts at a lower cost and in less time (Prashar et al., 2022). Due to technological advancements, three-dimensional (3D)-printed organs are a hot topic (Munaz et al., 2016). Recently a Poly-lactide, a versatile material used as a 3D printing filament, bonded with fluorescent dye rhodamine-conjugated and functionalized with poly-amidoamine dendrimers to create a multifunctional scaffold for cell proliferation, gene regulation, and expression (Paolini et al., 2018). 3D Printing has enormous potential in biomedical science, particularly in orthopaedics. Artificial bone grafts can be made using a variety of techniques, including stereolithography, selective laser sintering, fused deposition modelling, ink-jet 3D printing, direct metal laser sintering, selective laser melting, and digital light processing (Suresh, 2021; Li et al., 2022; Kumar, 2022). A summary of 3DP technologies, their advantages and disadvantages, and their common application are shown in Table 4.

Table 4: Advantages and disadvantages of 3DP technologies and application

Technique	Application	Advantages (+) and disadvantages (-)	References
Fused deposition modelling	3D printed skull for anatomy education Femoral condyle defect	3D printed skull for anatomy education Femoral condyle defect	(Chen et al., 2017)
Selective laser sintering	Porous scaffolds for repairing trabecular bone, and Cartilage defect	+Good processing flexibility and complexity; high precision - Complex control of laser printing system; side effects	(Brunello et al., 2016)

		of laser	
Direct metal laser sintering	Segmental bone defects Mandibular implant	+ High-speed, complex geometries can be easily created, high quality - Expensive, implants have a small build size	(Vance et al., 2018)
Selective laser melting	Repair cylindrical bone defect of the lateral femoral condyle, Cortical bone defect	+ A wide range of metals can be used, and post-treatments reduced -Not suitable for well-controlled composite materials; high laser power required	(Guo et al., 2019)
Stereolithography	RP model for a right shoulder injury	+Mature; stable printing process; fast printing speed; High resolution - The limitations of using materials; high cost	(Surmen et al., 2020)
Digital light processing	Bone regenerative applications	+ High quality, fast -Smaller print volumes, expensive	(Schmidleithner et al., 2019)

Challenges and future direction of 3D printed bone tissue engineering composite

The technology of additive manufacturing (AM) is rapidly expanding, resulting in unexpected scientific contexts and dynamics (Giannitelli et al., 2015). Various approaches and concepts for bone engineering of modern constructs with improved properties and functions are described in the existing literature. The only certainty about AM's future is that it will continue to expand and offer new opportunities in the coming years. AM technology, for example, is used to create a 3D scaffold that supports regenerating tissue and transplanted cells and enables the local release of regulatory or therapeutic substances. (SalernoNetti, 2021).

Despite advances in 3D scaffold research, many challenges remain, making it difficult to select a suitable scaffold and biomaterial. Because of their low viability and stability, scaffolds containing cells and growth factors are challenging to store. The long-term release of incapacitated substances does not always result in the desired micro-environmental effects, such as promoting functional recovery or providing trophic or anti-inflammatory support. The following are some of the significant challenges of 3D scaffolding.

i. The process-property optimization of particular materials, such as ceramics, with the mechanical properties of porous scaffolds requires the most attention.
ii. As the porosity increases, the scaffolds' strength will decrease. These scaffolds are weak, making it challenging to work with them during processing.
iii. Design Challenge: create superior scaffolds for a particular application that don't burst and are simple to deactivate by combining various biomaterials with integrated bioactive compounds and varied production techniques.
iv. It is currently unclear how to best optimize scaffolds' structural, biomechanical, and disintegration rates while maintaining good

surface properties to enhance cell interactions and extracellular matrix deposition.

Animal models employed in the bulk of investigations were rats and rabbits. The functioning of synthetic scaffolds in the human body is a significant concern due to the interspecies heterogeneity between animal models and human immunology.

Prospects of 3D Printing in bone tissue scaffold

Because natural and artificial bone tissues are expected to differ, researchers must strike an appropriate balance when integrating different cell types and 3D printing techniques to synthesize the scaffolds. Additionally, the complexity of design constraints limits the efficacy of existing methods, especially when attempting to regenerate clinically relevant size injuries. Some of these constraints can be overcome by employing nanomaterial. Nanomaterials give scaffolds the tunability and flexibility they need to stay in the tissue microenvironment. Furthermore, nanomaterial-based scaffolds can be tailored to the patient's needs using 3D printing technology and image technologies that scan, record, and analyze imaging data of the injury from which the scaffold will be printed. Current advances in 3D printing of bone substitutes using various biomaterials and nanomaterials may pave the way for implementing patient-specific health care. A healthy and adaptable community has increased the opportunity for researchers and clinicians worldwide to implement 3D printing technologies, increasing their potential for use in regenerative medicine.

Moreover, various scaffolds with different forms, such as nanoparticles and microcapsules, have been designed to deliver drugs or proteins. However, most of them burst completely within two days without performing the intended function efficiently (Montiel-Herrera et al., 2015; Rambhia, 2015). Recently, studies have been able to develop the scaffold that takes up to two days to release drugs. For instance, Tao and colleagues created a scaffold of calcium phosphate cement incorporated within bone morphogenetic protein-2 with a decent release rate of 4 weeks (Rothe et al., 2020; Tao et al., 2018). The scaffold comprising calcium phosphate and bone morphogenetic protein-2 improved the in vivo therapy of defective rat bone and boosted the production of critical-size bone (Deininger et al., 2021).

CONCLUSION

Tissue regenerative engineering has undoubtedly advanced; at the moment, most researches are concentrated on composite bone tissue-generated scaffolds with enhanced bioactivity, drug delivery capabilities and appropriate mechanical properties. Additionally, various scanning, printing, and support software tools are used in the most recent breakthrough, additive manufacturing. Images can generate complex shapes for customized scaffolds without cost or effort. Despite substantial achievements, regulatory restrictions prevent using additive manufacturing technology in drug delivery systems in clinical applications. The mass production, quality control, and sterilization of scaffolds still require more research.

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