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Raising the Bar: Progress in 3D-Printed Hybrid Bone Scaffolds for Clinical Applications: A Review

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Abstract

Damage to bones resulting from trauma and tumors poses a significant challenge to human health. Consequently, current research in bone damage healing centers on developing three-dimensional (3D) scaffolding materials that facilitate and enhance the regeneration of fractured bone tissues. In this context, the careful selection of materials and preparation processes is essential for creating demanding scaffolds for bone tissue engineering. This is done to optimize the regeneration of fractured bones. This study comprehensively analyses the latest scientific advancements and difficulties in developing scaffolds for bone tissue creation. Initially, we clarified the composition and process by which bone tissue repairs itself. The review summarizes the primary uses of materials, both inorganic and organic, in scaffolds for bone tissue engineering. In addition, we present a comprehensive study of the most recent advancements in the mainstream techniques used to prepare scaffolds for bone tissue engineering. We also examine the distinct advantages of each method in great detail. This article thoroughly examines potential paths and obstacles in bone tissue engineering scaffolds for clinical applications.

Keywords

3D-implants, biocompatibility, clinical applications, regenerative medicine

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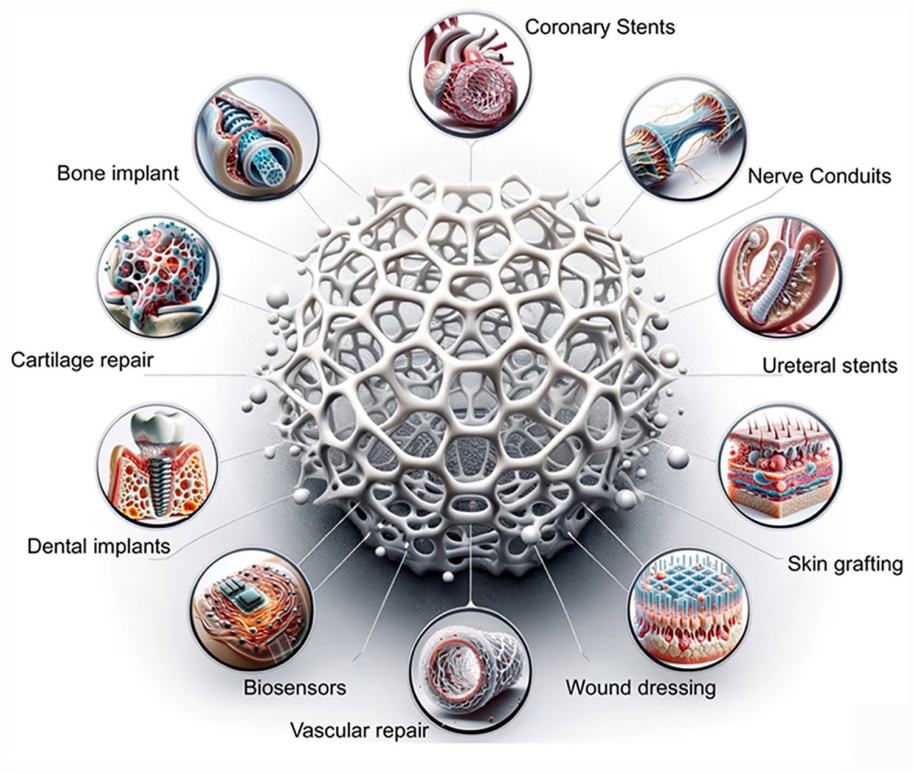
Graphical Abstract



Introduction

Three-dimensional (3D) printing, or additive manufacturing, is a cutting-edge technique that enables the production of 3D items by building them layer by layer, using a digital design as a blueprint[1–4]. The process commences with a digital file, such as a computer-aided design (CAD) model, serves as a blueprint for the desired object[5,6]. The computerized model is segmented into thin, cross-sectional layers, then printed or deposited using various materials and techniques[7,8]. Multiple 3D printing techniques are available, each with unique features and materials that can be used[9,10]. Widely used methods include fused deposition modeling (FDM), stereolithography (SLA), selective laser sintering (SLS), and binder jetting. In addition, ceramics are utilized in 3D printing, which has significantly progressed in various industries, such as electronics and healthcare. Ceramic powders are employed in ceramic 3D printing[11,12].

Hybrid materials (HMs) denote one of the most emergent material classes at the edge of technological advancements[13]. Material properties achieved via a synergetic combination of more than one component on the molecular scale make HMs attractive for several applications[14]. There are several approaches to the classification of HM. They can be based on the source of origin, bonding, properties, and formation route, and highly favored materials in 3D printing[15]. Commonly utilized materials include PCL, PLA/HA, PCL/GelMA, Silk Fibroin/Bioactive Glass, Chitosan/β-TCP, and PLGA/Collagen. Every hybrid variety has unique attributes, such as its durability, flexibility, resistance to temperature changes, and ease of printing[16,17]. 3D printing utilizes metal as a substitute material[18].

Metals such as cobalt-chrome, titanium, stainless steel, and aluminum are usually cast-off in additive manufacturing[19,20]. Durable metal components are produced through the layer-by-layer fusion of metal powders utilizing selective laser melting (SLM) or electron beam melting (EBM) techniques in metal 3D printing[21]. In addition, ceramics are used in 3D printing, which has advanced uses in industries including electronics and healthcare. Ceramic powders are used in ceramic 3D printing[22].

The human skeletal system functions as a fundamental framework, offering structural support and safeguarding the organism[23,24]. Nevertheless, various causes, such as the natural process of aging, physical injuries, or medical conditions, can contribute to the diminished strength or impairment of bones, ultimately resulting in substantial health complications[25,26]. Lately, there has been an increasing fascination with advancing novel techniques for identifying, measuring,

and identifying diseases through various means[27]. To properly treat bone illnesses and injuries, it is necessary to utilize tissue engineering and regenerative medicine procedures[28]. One practical approach in biomedical applications is the utilization of bone scaffolds. These scaffolds are like a 3D framework for tissue regeneration and promote the development of new tissues and bones[29]. Because bone tissue is self-repairing and regenerating, minor flaws typically disappear independently. However, when bone abnormalities grow more significant than a critical size barrier (about >2 cm), the healing process is inadequate and frequently fails to mend[30–32]. Every year, 4 million people worldwide need bone replacement surgery or grafts[33,34]. As a result, treating bone abnormalities effectively is crucial from a clinical standpoint[35,36]. In clinics, bone grafting is a mainstay. Depending on the circumstances, the defect site can heal successfully using different grafts[37,38].

Customized solutions for individual patients: 3D printing produces bone scaffolds tailored to each patient's needs[39]. This individualized strategy optimizes the efficacy of the treatment, enhancing bone rejuvenation consequences and minimizing the likelihood of problems[40]. Biocompatibility: 3D-printed bone scaffolds can be fabricated using biocompatible materials, such as bioceramics or biodegradable polymers, which are highly compatible with the human body[41]. These compounds enhance cell attachment, proliferation, and differentiation, aiding the regeneration of new bone tissue[42]. This article concisely summarizes the recent advancements in the research and enhancement of 3D printing methods for producing scaffolds utilized in bone tissue engineering[43].

Critical Requirements for 3D Printed Scaffolds

3D printing has significantly transformed the field of tissue engineering and regenerative medicine, specifically in the field of bone scaffolds[44,45]. Researchers can develop scaffolds that imitate the form and function of genuine bone by using biomaterials, advanced 3D printing technology, and detailed design procedures[46,47]. Scaffolds provide customized mechanical characteristics, such as rigidity, durability, and adaptability, together with interconnected porous structures that improve the infiltration of cells and the exchange of nutrients[48,49]. 3D-printed bone scaffolds are an excellent choice for patients requiring bone regeneration as long as they fulfill the criteria of biocompatibility, scaffold structure, sterilization, and regulatory compliance[19,50]. These scaffolds offer individualized bone repair, tissue regeneration, and enhanced quality of life. To achieve this objective, the initial and most crucial stage is thoroughly comprehending the requirements[51,52]. They are given in Table 1.

While there have been thorough examinations of scaffolds made from metal, ceramic, and polymers, more research is needed on hybrid scaffolds for advanced therapeutic purposes[62,63]. It is imperative to thoroughly investigate how hybrid scaffolds might effectively address crucial therapeutic requirements[64,65]. This encompasses a brief comprehension of their function in biomimetics, accurate bone regeneration, focused drug administration, tumor therapy, and infection treatment[66,67]. Exploring the incorporation of biomimetic characteristics into these scaffolds remains an unexplored domain, and conducting research is crucial to enhance compositions for more efficient bone regeneration[68,69]. Furthermore, there are unexplored possibilities in regulated drug administration, targeted treatments, and infection control[70,71].

The Mechanism for Repairing Bone Tissue

The bone tissue repair and healing process is intricate and consists of several phases[72,73]. These stages primarily include inflammation and the formation of a blood clot, the recruitment and multiplication of stem cells, the development of blood vessels, the specialization of mesenchymal stem cells (MSCs), and the final phase of tissue remodeling[74,75]. Fractures disrupt a specific area of the blood vessels and nearby tissue, creating a hematoma and the following inflammatory phase. Within 24 hours following the fracture, the soft matrix at the hematoma site attracts immune cells to facilitate an inflammatory response[76,77]. After some time (week), the hematoma and inflammatory response are resolved, and the hematoma site is replaced by granulation tissue[78,79]. Following the inflammatory and hematoma phase, many cells, including osteoblasts and endothelial cells, become active at the location of the defect. In addition to the proliferation of stem cells, angiogenesis occurs throughout the bone tissue healing process[80,81]. Many blood vessels in bone are crucial for bone regeneration Fig. 1. The process of ultimate bone remodeling is a physiological phenomenon significantly influenced by the interaction between osteoblasts and osteoclasts[82,83]. An essential objective is to integrate the attributes and principles of each step in bone tissue restoration with scaffolds, enhancing the performance of the scaffold materials through targeted alterations to attain superior and more effective outcomes in treating bone abnormalities[84].

The Scaffold Structure Design Ensures Safety and Efficiency on Construction Sites

A 3D model of the scaffold can be created and transformed into a printable setup like Stereolithography (STL)[85,86]. Customized scaffold shapes could be generated via CAD software based on specific patient structural anatomical data about the lesion[87,88]. A 3D model is created by analyzing the anatomical data of the affected area, which is collected using computed tomography (CT) or magnetic resonance imaging

Table 1. Biomedical Application and Properties of Hybrid Scaffolds for Clinical Application.

Scaffold type	Materials	3D printing technology	Pore Size (μm)	Mechanical properties	Biological properties	Growth factors	Degradation rate (months)	Applications	Ref
Scaffold 1	PLA/HA	Fused deposition modeling	300–500	Compressive Strength: 5 MPa	Supports osteoblast proliferation	BMP-2	6–12	Bone tissue engineering	[53]
Scaffold 2	PCL/GelMA	Stereolithography (SLA)	100–300	Elastic Modulus: 50 MPa	Enhances vascularisation	VEGF, TGF*-β1	12–18	Cartilage regeneration	[54]
Scaffold 3	PLGA/collagen	Selective laser sintering	200–400	Tensile Strength: 10 MPa	Promotes cell adhesion and growth	FGF*-2	4–6	Soft tissue engineering	[55]
Scaffold 4	PEGDA/HAp	Digital Light Processing	250–350	Flexural Strength: 15 MPa	High biocompatibility	IGF*-1	3–5	Dental implants	[56]
Scaffold 5	Silk fibroin/ bioactive glass	Inkjet Printing	150–250	Shear Modulus: 20 MPa	Stimulates osteogenic differentiation	BMP*-7	8–10	Bone grafts	[57]
Scaffold 6	Chitosan/β-TCP*	Extrusion Bioprinting	200–500	Compressive Modulus: 6 MPa	Antibacterial properties support chondrocyte growth	PDGF*, TGF-β3	3–6	Cartilage and bone regeneration	[58]
Scaffold 7	Alginate/GelMA	Micro Extrusion	100–200	Young's Modulus: 1–2 MPa	Supports angiogenesis, biocompatible	VEGF, bFGF*	1–3	Vascular tissue engineering	[59]
Scaffold 8	PEEK*/carbon nanotubes	Melt Extrusion	400–600	Elastic Modulus: 5–10 MPa	Enhanced mechanical properties support osteogenesis	BMP-2, IGF-1	Less than 24	Load-bearing orthopedic implants	
Scaffold 9	Hyaluronic acid/ PLGA	Electrospinning	50–150	Compressive Strength: 3 MPa	Promotes wound healing, supports fibroblast activity	EGF, PDGF	2–4	Skin tissue engineering	[60]
Scaffold 10	PVA*/ hydroxyapatite	Direct Ink Writing	150–350	High tensile strength: 80 MPa	Osteoconductive, supports osteoblast proliferation	BMP-4	6–8	Bone defect repair	[61]

*TGF-β1: Transforming growth factor beta 1*FGF: fibroblast growth factor*IGF: Insulin-like growth factor *PDGF: platelet-derived growth factor *bFGF: basic fibroblast growth factor *EGF: epidermal growth factor *β-TCP: beta-tricalcium phosphate *PEEK: polyether ether ketone *PVA: polyvinyl alcohol.

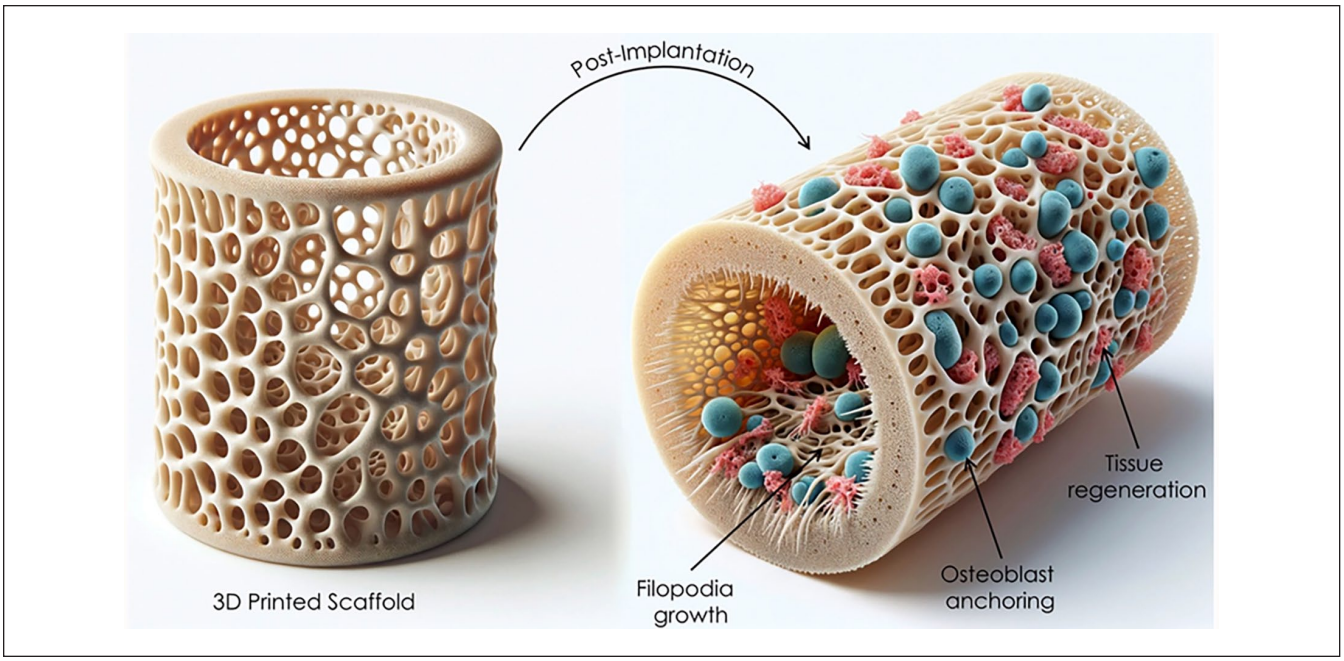


Figure 1. Schematic illustration of bioactive response of 3D-printed scaffolds during physiological immersion.

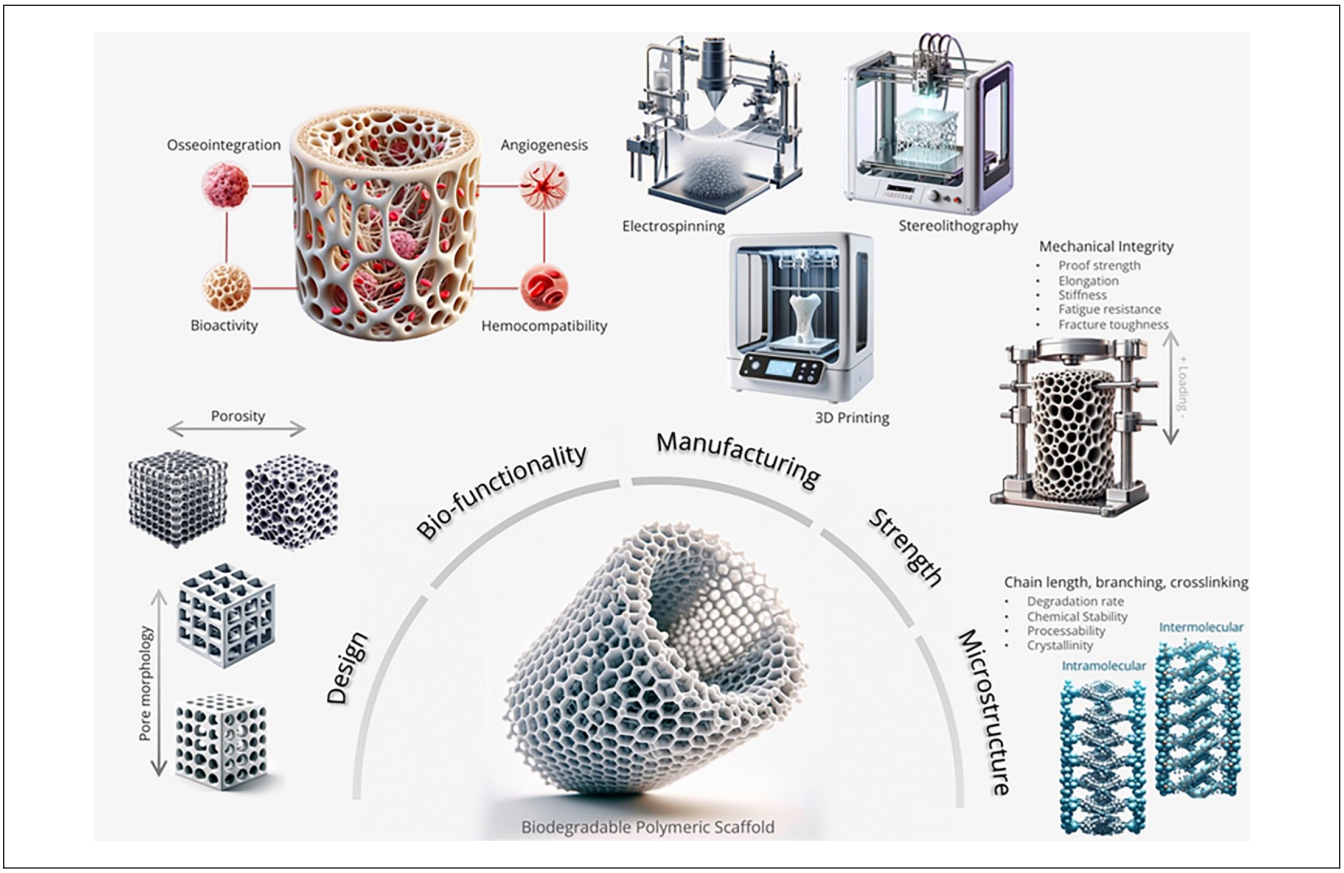


Figure 2. Multifaceted evaluation parameters, including design, functionality, manufacturing, mechanical integrity, and microstructure, are required for the development of an ideal scaffold.

(MRI)[89]. Med CAD design and interfaces, inverse engineering surfaces, and STL-triangle shape model converting procedures are various approaches to creating CAD models from therapeutic pictures[90]. Scaffolds and porous architecture are essential in tissue regeneration as they maintain tissue volume, fulfill temporary mechanical roles, and transport biofactors[91]. An effective scaffold will integrate mechanical functionality with the delivery of biofactors, facilitating a gradual transformation from scaffold to regenerated tissue as the previous scaffold breaks down[92].

Consequently, the scaffold structure should imitate the inherent properties of genuine bone, including interconnecting pores[93,94]. The scaffold's porosity is crucial for cell intrusion, nutrition exchange, and tissue amalgamation. Researchers can use 3D printing to design and fabricate pores of varying sizes and forms[95–97]. Fig. 2 explains the different properties required to construct the 3D scaffolds including their design, (shape, pore size, morphology) biofunctionality, (hemocompatibility, bioactivity, angiogenesis and osteointegration) manufacturing (electrospinning, SLA and 3D printing) strength (mechanical integrity, poor strength, stiffness, load bearing capacity and toughness) microstructures (degradation rate, chemical stability, processibility and crystallinity).

Tissue Engineering

Tissue engineering is a promising therapy option that uses engineering concepts to alleviate tissue damage[98,99]. The field consists of three essential elements: scaffolds, cells, and growth factors. Bioreactors play a vital role in tissue engineering[3,100]. The ideal scaffolds function as structural reinforcement for damaged tissue, transforming the growth factors produced by cancer cells into stimuli that promote tissue regeneration. Conventional approaches to treating tissue injury have faced substantial challenges throughout the years[101].

Recent progress in bone tissue engineering has integrated growth factors and other biomolecules into scaffolds to direct cell behavior during the regeneration of organs and tissues[102,103]. In the past 20 years, advances have been achieved in developing and applying biological scaffold materials[46,104]. The three primary components of bone tissue engineering are bone progenitor cells, bone growth factors, and scaffolds[90,105]. These elements work together to promote cell adhesion, maintain cell function, and imitate the natural process of bone tissue regeneration[106,107]. The scaffold must serve as a transient template for cell regeneration of new bone tissue while also being capable of degradation to allow for replacement by the newly formed bone tissue[108,109]. The scaffold's primary function is to create an ideal microenvironment for cells, facilitating new tissue production and distribution of nutrients between the cells and their surroundings[110].

Bone Scaffold Formation

Temporary constructs known as porous scaffolds facilitate the regeneration of bone tissue by providing an appropriate environment. They promote cell attachment, growth, specialization, and migration to the injury site[111,112]. Scaffolds are essential to tissue engineering because they offer the best extracellular matrix (ECM) for progenitor cell proliferation and differentiation[113]. These cells can enter the scaffold and start the development, differentiation, multiplication, and migration processes because they react to biochemical and physical cues in their environment[114,115]. When the environment is favorable, the cells secrete ECM and produce new tissues[116]. The best scaffolds have strong adhesion to bone-forming cells, biodegradability, robustness, and consistency in their mechanical properties[117]. The cells must be able to move toward the scaffold, stick to it, and multiply. Another essential feature is the scaffold's connected porosity, which permits precise cell development and spreading inside the porous structure[118].

This facilitates efficient angiogenesis in the surrounding tissue. The objective of constructing bone scaffolds is to produce an environment demonstrating biophysical, biomechanical, and biochemical features responsible for cell growth, specialization, and viability. Polymers, ceramics, and metals are the primary categories of biodegradable materials that have lately been examined in clinical and research settings[119,120]. Therefore, a scaffold is a crucial element in tissue engineering, and to fulfill its essential function, it must possess the features mentioned above[121].

Clinical Applications of 3D-printed Scaffolds

Wound and Infection Healing

A wound is a disruption or break in the skin caused by physical or thermal damage or a pathological cause[122]. The nature and severity of wounds vary depending on their underlying etiology, clinical manifestations, healing processes, or anatomical location[123]. Regardless of their characteristics, wounds pose a significant healthcare challenge in the development of chronic diseases as they can raise healthcare expenses and complicate both internal and external health[124]. Wound healing involves a range of well-coordinated molecular processes, including hemostasis, inflammation, proliferation, and remodeling[125].

Using 3D scaffolds with stem cell delivery has shown great potential in regenerative medicine. Wang et al. explained the examples of cell types include bone marrow mesenchymal stem cells, human umbilical cord perivascular cells (HUCPVC), and amniotic fluid-derived cells[126]. Stem, endothelial progenitor, and circulating angiogenic cells (CACs) are frequently studied. Haki et al. utilize early endothelial progenitor cells (EPCs), also known as CACs, derived from peripheral blood mononuclear cell fraction and can be used locally to address nonhealing diabetic foot

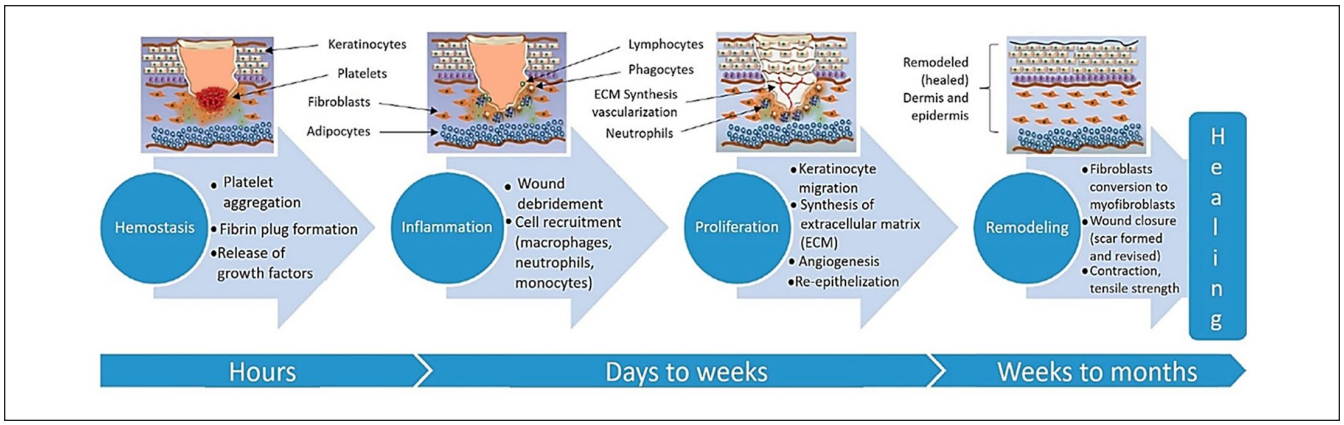


Figure 3. Mechanism of wound healing from hours to months adopted with permission[122].

ulcers[127,128]. Lv et al. does the augmentation in the formation of new blood vessels and a higher proportion of wound healing was noted when a scaffold made of collagen was used to transfer CACs to a diabetic rabbit ear wound (specifically, an ulcer produced by alloxan)[129]. A 3D membrane scaffold, derived from a freeze-dried conditioned medium of bone marrow mesenchymal stem cells (FBMSC-CM), effectively expedited wound healing and improved the formation of new blood vessels (neovascularization) and the growth of epithelial tissue (epithelialization) by enhancing the presence of nourishing elements in the wound area[130,131]. Fig. 3 explains the phenomena of wound healing for a long time and how hemostasis occurs due to 3D implant scaffolds, the formation of new cells, and epithelisation leading toward the remodeling of skin or wound repair.

Tumor Therapy

3D scaffolds represent a promising solution in tumor therapy by providing a controlled and replicable microenvironment for studying cancer progression and testing treatments [111]. Many 3D scaffolds are used to treat tumors like novel bioceramic scaffolds. These scaffolds can be engineered to mimic the ECM of tumors, allowing for more accurate modeling of tumor growth, invasion, and metastasis [115]. By incorporating bioactive molecules, such as drugs, growth factors, or genetic material, 3D scaffolds can deliver targeted therapies directly to the tumor site, potentially enhancing the efficacy and reducing the side effects of conventional treatments [129]. Moreover, Fig. 4 explains the mechanism of how local sites of proteins and membranes are being damaged by the heat-generated functional scaffolds, leading to apoptosis and cell death. As a result, scaffolds exhibiting superior photothermal or magnetothermal properties are highly effective as localized treatment agents. The ability to personalize these scaffolds based on patient-specific tumor characteristics facilitates the development of tailored therapeutic strategies, paving the way for more effective and individualized cancer treatments[125,129].

Cartilage and Spine Injury

Cartilage is a soft bone with a minimal capacity for regeneration. When a lesion, such as osteoarthritis, is created, more innovative explanations are needed. Lan et al.[132] employed a scaffold using human nasal and chondrocytes using type 1 collagen. The scaffold was implanted in the mouse skin, and after 9 weeks, the printed cartilage regenerated its original shape and size. Cell viability decreased during the construction of the 3D structure. Similarly, after subcutaneous implantation, Beketov et al.[133] produced the scaffold using the bio-ink consisting of 4% collagen and chondrocytes. The cartilage tissue contains a high amount of COL2 and glycosaminoglycan (GAG).

A spine injury can be caused by accidents, swelling, dislocation, extrusion, and ischemia, leading to the damage of irreparable nerve cells. Neural stem cells (NSC) and their spatial distribution in the spinal cord is the route toward its successful repair again. Liu et al.[134] used different HMs to prepare the scaffold, such as bio-ink containing the mixed NSCs, hyaluronic acid derivatives, and chitosan. After implantation in the rats, it restored the locomotor abilities, called viability, and renewed axons. Similarly, another study explained how 3D-generated scaffolds with the help of gelatin combined with oligodendrocytes and NSCs improved motor skills and the production of new axons and neurons after implantation[28,135].

Heart Disease and Liver Failure

Decrease of cardiac fibrosis, cardiomyocyte hypertrophy, and increase of vascular formation using the 3D-constructed scaffold to treat the congenital heart disease of right ventricle failure in the rat model by using the bio-ink containing progenitor cells laden cardiac ECM gelatin and neonatal human c-kit[136]. Similarly, to produce elongated cells that can contract, embedding the printed construct between 2 layers of rat omentum over a week using hydrogel with

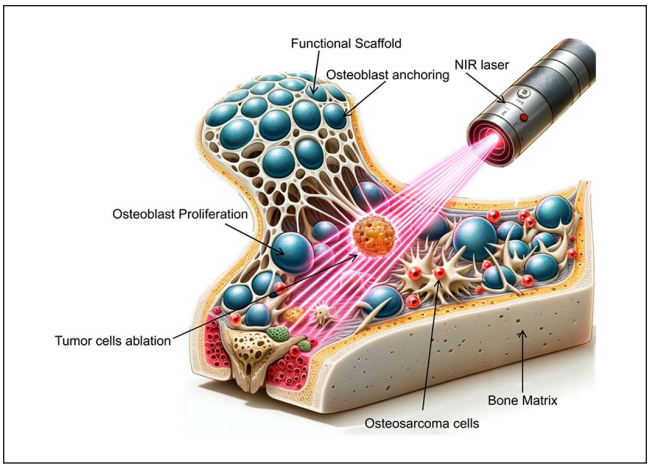


Figure 4. Schematic illustration of a bifunctional scaffold with significant potential for clinical use in bone tumor therapy. The scaffold demonstrates pronounced capabilities for both regenerating bone tissue and treating tumors.

iPSCs differentiated into cardiomyocytes and patient-specific endothelial cells[137].

Human hepatocytes and methacrylate gelatin bio-ink were used to treat liver failure in mice. A 3D scaffold constructed stimulated liver cells' vascularization and normal function[138]. However, scaffolding in the mouse liver damage increased albumin expression and accelerated cell proliferation by using the 3% alginate hydrogel with induced hepatocyte cells[139]. In addition, Table 2 explains the present challenges and their solution provided by 3D technology.

Hybrid Scaffolds

Hybrid scaffolds are a promising field of study because they combine multiple materials to create improved features better suited for various tissue engineering applications. PCL/collagen scaffolds have been employed to fabricate artificial human skin[145,146]. The resulting material gains muscular tensile strength by combining collagen with a small amount of PCL. This makes it helpful in creating scaffolds perfect for human skin tissue engineering[147,148]. Recent investigations indicate that NPs are widely utilized in biomedical applications, including biosensing of metabolites, drug delivery, bioimaging, anti-biofilm, and antibacterial applications [149,150]. A study utilized PCL combined with titanium oxide, which has antibacterial properties and is coated with collagen to create a wound dressing material with antibacterial capabilities[103,151]. A different research study utilized human endometrial stem cells (hEnSCs) by introducing them into a PCL/collagen scaffold to create an innovative structure for skin engineering[152]. Due to the endometrium's remarkable regenerative ability, this nanofiber was suggested to stimulate angiogenesis without needing growth hormones. This indicates its potential for repairing skin tissue during wound healing[153]. A composite of poly L-lactide (PLLA) and chitosan was created to preserve the essential properties of both materials. PLLA possesses high mechanical strength but is not conducive to cell growth[154].

On the contrary, chitosan demonstrates favorable tissue regeneration capabilities, but it lacks sufficient strength[58,105]. Consequently, collagen was utilized to construct scaffolds with funnel-shaped structures with pores, enabling the cells to proliferate and establish connections beneath the surface [77]. Subsequently, the collagen funnels were positioned onto a PLLA mesh to create hybrid scaffolds. Animal experiments have demonstrated that applying these hybrid scaffolds to seed fibroblast cells can improve the repair of incisional lesions[17,52,126]. Combining chitosan and silk nanofibrils has been utilized to create nanocomposite scaffolds that demonstrate excellent resistance to high temperatures and impressive mechanical durability[126]. The nanocomposites share a comparable composition with the ECM, so they can produce a more sophisticated biomaterial for skin engineering[155]. An article has described a bilayer nanocomposite scaffold made from silk fibroin, gelatin, and oxidized alginate. This scaffold has a structure comparable to the ECM and has the potential to be used in regenerative medicine and skin engineering[156]. The efficacy of hybrid collagen scaffolds containing ZnO-curcumin nanocomposites was assessed to promote accelerated wound healing and minimize scarring[157]. An 80% cell viability was recorded, indicating a favorable cell growth and attachment level. Experiments conducted on live albino rats showed an increase in the expression of TGF-β3 and a notable recovery of burnt wounds without scarring[158]. A separate research project involved the creation of a nanocomposite scaffold using chitosan and PVA. This scaffold was infused with photogenic iron oxide nanoparticles (FeO NPs) to investigate their effects on diabetic wounds associated with anemia[159]. The FeO NPs were synthesized using a leaf extract obtained from Pinus densiflora. The FeO NPs exhibited favorable anti-diabetic and antioxidant effects in biological experiments and antibacterial solid capabilities[160]. The in vitro wound healing experiment demonstrated enhanced cellular proliferation by HEK 293 cells. These data indicate that this composite scaffold could be used for treating diabetic wounds, pending a thorough in vivo assessment[161,162]. Table 3 summarizes various hybrid polymers utilized as scaffolds for applications in wound healing and skin tissue engineering[163].

Future Perspectives

The application of 3D printing in bone tissue engineering is now undergoing extensive research and exploration. The primary benefit of this technology is its capacity to regulate the arrangement of fibers, leading to scaffolds that exhibit superior performance due to their optimized structure and function at many scales[168]. Despite the advancements in 3D printing technology, certain constraints still impede the application of

Table 2. Detailed Table with Additional Clinical Challenges and Their 3D Printing Solutions.

Clinical challenges	Description	3D printing solution	References
Complex Bone Structures	Bones have intricate shapes and internal structures that are difficult to replicate accurately.	3D printing allows precise control over the shape and internal architecture, creating patient-specific, complex structures.	140
Biocompatibility and Integration	Ensuring the material is biocompatible and integrates well with native bone tissue.	3D printing uses biocompatible materials and creates surface textures that promote better tissue integration.	75
Mechanical Strength	Regenerated bone must have sufficient mechanical strength to withstand physiological loads.	3D printing customizes scaffold properties for optimal mechanical strength and porosity.	141
Vascularization	The formation of blood vessels within the scaffold is essential for supplying nutrients and removing waste.	3D-printing designs scaffolds with channels and pores that facilitate vascularization and can incorporate growth factors or cells.	93
Customization and Personalization	Each bone defect is unique, requiring personalized treatment approaches.	3D printing produces patient-specific implants based on imaging data, ensuring a perfect fit and better functional outcomes.	2,4
Cost and Accessibility	Traditional methods are often expensive and time-consuming, limiting accessibility.	3D printing can reduce custom implants' cost and production time, making personalized treatments more accessible.	142
Infection Risk	Implantation can introduce infections, complicating healing and regeneration.	3D printing can incorporate antimicrobial agents into the scaffold material, reducing infection risks.	143
Healing Time	Long healing times can result in complications and prolonged recovery periods.	3D-printed scaffolds can be designed to release growth factors that accelerate bone regeneration and healing.	10
Osteoinductivity	The ability of a material to induce bone formation is critical for successful regeneration.	3D printing allows for the incorporation of osteoinductive agents into the scaffold, promoting new bone growth.	144
Structural Stability	Ensuring the scaffold maintains its shape and functionality over time is crucial.	3D-printed scaffolds can be designed with optimal degradation rates, balancing structural stability with tissue regeneration.	90
Supply Chain and Scalability	Manufacturing and delivering custom implants on a large scale can be challenging.	3D printing enables on-demand, localized production of implants, improving supply chain efficiency and scalability.	104

tissue engineering scaffolds in practical medical settings. For instance, the selection of printing materials is restricted[169]. It is essential to consider the physiochemical qualities of the materials, such as rheology (flow behavior), wetting performance, and melting point[170].

In addition, their biological properties should also be considered, including biodegradability, biocompatibility, and cell interaction. Internal faults may arise during printing, leading to subpar mechanical quality in the printed product[171]. To utilize 3D printing technology effectively, it is crucial to thoroughly examine ink materials regarding material selection, design of 3D structures, and function novelty. Furthermore, the printing procedure is essential to optimize the associated parameters for high-quality outcomes[172,173]. Although several fabrication material concerns have not yet been resolved, there is still ample opportunity to investigate beneficial approaches for bone tissue engineering. The current research on repairing infected bones needs a thorough grasp of the repair mechanism in a complicated model of infected bone defects[174,175]. The currently described bone analogs possess only one specific function, and creating bone analogs capable of performing multiple tasks in an integrated manner remains a significant challenge[176]. Vascularization is essential for developing organs in massive bone tissues, as they require a well-developed network of blood vessels to provide nutrients and oxygen. Regrettably, the construction of vascular networks remains a significant obstacle due to the low vascularization of bone tissue[177].

To efficiently address these glitches, it is vital to understand the inherent structural properties of bone tissue and the natural mechanisms involved in bone tissue healing and regeneration, including the impacts and interplay of many factors in infected bone defects[178]. The design of bone tissue engineering scaffolds should aim to replicate the bionic

Table 3. shows the Advantages and Disadvantages of Various Hybrid Scaffold Materials Used in Biomedical Applications.

Material	Advantages	Disadvantages	Ref
PLA (polylactic acid)/ HA (Hydroxyapatite)	–Biocompatible and biodegradable –Good mechanical properties –Promotes bone regeneration and integration	–Slow degradation rate, –Potential for acidic degradation products –Limited cell adhesion without surface modification	53
PCL (polycaprolactone)/ GelMA (gelatin methacrylate)	–Biocompatible and biodegradable –Flexible and elastic –Supports cell adhesion and proliferation –Tunable degradation rate	–Lower mechanical strength compared to some other materials –Possible immune response to gelatin components	97
PLGA (poly[acid])/ collagen	–Excellent biocompatibility –Supports cell adhesion and growth –Tunable degradation rate –Versatile mechanical properties	–Potential for acidic degradation products –Rapid degradation rate can sometimes be too fast	77
PEGDA (polyethylene glycol diacrylate)/HAp (hydroxyapatite)	–High biocompatibility –Tunable mechanical properties –Non–toxic degradation products –Supports osteogenic differentiation	–Limited mechanical strength for load–bearing applications –Requires functionalisation for enhanced cell interaction	163
Silk fibroin/bioactive glass	–Excellent biocompatibility –Supports osteogenesis –Good mechanical properties –Bioactive properties	–Potential brittleness –Limited degradation rate control	164
Chitosan/β-TCP (beta-tricalcium phosphate)	–Biocompatible and biodegradable –Antibacterial properties –Supports bone and cartilage regeneration	–Variable degradation rate –Mechanical properties can be lower than synthetic polymers	77,105,58
Alginate/GelMA (gelatin methacrylate)	–Biocompatible and biodegradable –Supports cell proliferation –Easy to process and print –Promotes angiogenesis	Poor mechanical properties alone –Rapid degradation in physiological conditions	134
PEEK (polyether ether ketone)/carbon nanotubes	Excellent mechanical properties –Biocompatible –Supports osteogenesis –High wear resistance	–Non–biodegradable –Potential toxicity of carbon nanotubes –Expensive and difficult to process	165
Hyaluronic acid/PLGA (poly[acid])	Excellent biocompatibility Supports wound healing Tunable degradation rate Promotes fibroblast activity	Potential for acidic degradation products –Requires stabilization for mechanical integrity	60,166
PVA (polyvinyl alcohol)/ hydroxyapatite	Biocompatible –Supports osteoblast proliferation –Good mechanical properties –Hydrophilic nature	–Non–biodegradable –Potential for rapid swelling and loss of mechanical properties in aqueous environments	167

structure of natural bone tissue. These scaffolds can be enhanced by incorporating inflammatory cytokines, ECM, and ligands. This integration allows for imitating the initial phases of bone regeneration and tissue repair[179–181].

Conclusion

Infected bone injuries and defects are still a core problem for orthopedic surgeons and practitioners. Engineering technologies and biological integration are critical elements in developing bone tissues. This review concisely discusses strategies for addressing bone defects through sustainable hybrid 3D-printed scaffold materials. A fundamental requirement for bone defects is the promotion of tissue regeneration and the stopping of bone infection. Many factors are responsible for this infection therapy, which include antibacterial coatings, bioactive metal ions, anti-infective drugs, and 3D-printed scaffolds that collectively fight against bone issues and treat osteomyelitis by producing the ideal microenvironment for rapid bone growth. Moreover, essential factors like photothermal, electric, and magnetic stimuli can be enhanced to promote bone regeneration during the loading of the 3D porous scaffolds. In tissue engineering, 3D-printed scaffold technology is currently the most reasonable solution for designing scaffolds according to infected patients' complex shape injuries.

Authors Contribution

A.R.K. and N.S.G. wrote the manuscript and collected all the data. F M. O.T, F. T, and R. M.Z they also interpreted the

manuscript's results. H-J. Z. and Z. J. developed the theory and reviewed the manuscript.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Declaration of Conflicting Interests

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