OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

Biomaterial Scaffolds in Bone Tissue Engineering: Evaluating Potential for in vivo and in vitro application through Biocompatibility, Hydrophilicity and Mechanical Properties

Sahana Kumar
sahanakumar0809@gmail.com

ABSTRACT

Bone tissue engineering (BTE) offers an effective solution for skeletal repair, particularly when the body's natural regenerative capacity is insufficient. Central to this field is the development of biomaterial scaffolds that can replicate the structural and functional complexity of bone while supporting cell attachment, proliferation, and differentiation. This paper provides a comprehensive review of the mechanical and biological performance of commonly used scaffolds, including natural and synthetic polymers, bioceramics, bioactive glasses, and metals, evaluating their potential for clinical application in both in vivo and in vitro settings. By comparing properties such as biodegradability, bioactivity, osteoinductivity, hydrophilicity, and mechanical strength, the paper underscores the limitations of monolithic scaffold systems. It also highlights the promise of hybrid and composite materials. By integrating advanced fabrication techniques and functionalization strategies, next-generation scaffolds may overcome existing challenges, paving the way for personalized solutions in regenerative medicine.

INTRODUCTION

Bone tissue engineering has been a field of interest for the last decade and has immense potential for research impact. Bone disorders are also of significant concern due to the rising median age of our population. Thus, advancements in this field may help combat the loss or deterioration of skeletal tissue resulting from disease, aging, or injury, and improve quality of life [1]. This field comprises an engineering component focused on the construction of suitable scaffolds that meet specific structural requirements, as well as a stem cell component that enables the in vivo implementation of cell-seeded scaffolds to differentiate and regenerate bone tissue. Modern medicine most often relies on casts and sling-type apparatus to treat hairline fractures [2], as the bone's innate regenerative capacity can heal a defect <6mm *sua sponte* [3]. However, BTE is the path chosen when the body is unable to regenerate tissue due to the scale of the trauma, tumor, or fracture [4].

May 2026
Vol 7. No 1.

All tissue engineering fields require the triad of scaffolds, cells, and stimulation. Scaffolds may be natural polymers, synthetic polymers, metals, bioceramics, bioglass, hybrid materials composed of two or more substances, or nanomaterials [5]. These scaffolds must be both structurally sound and interact with the extracellular matrix (ECM). Some scaffolds mimic the ECM and thus include components such as collagen, fibronectin, etc., which are components of the ECM [6]. This makes them less histologically active in the body, reducing the risk of an immune response and allowing regeneration to proceed appropriately.

As for cells involved in the tissue engineering process, they fall into 3 main categories: stem cells, progenitor cells, and differentiated cells [7]. Stem cells are seeded onto scaffolds. Generally, mesenchymal stem cells (MSCs) are used for bone tissue engineering [8], [9], although at times pluripotent stem cells (PSCs) or induced pluripotent stem cells (iPSCs) may be used. These cells can differentiate into new bone cells, thereby initiating bone regeneration. These cells are aided by stimulation with growth factors, mechanical stimuli (stress, compression, osmosis, and surface topography), or electrical stimuli, as shown in Figure 1 [7].

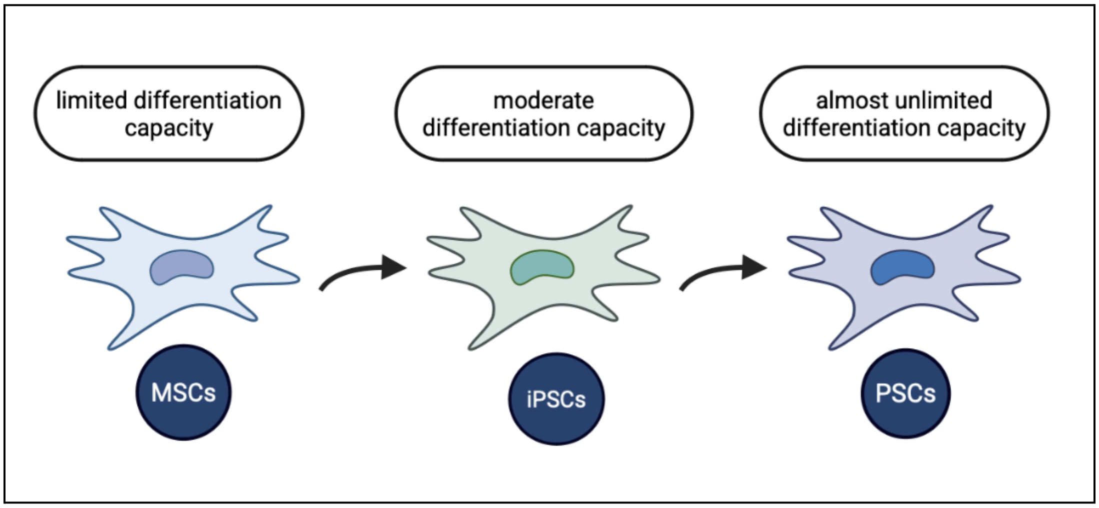


Figure 1. Schematic of the differentiation potential of main stem cell types used in BTE. Own source - Created with BioRender.com.

The importance of appropriately positioning a scaffold to enter the body is paramount, as it serves as the vessel for cell seeding and implantation at the injury site [10]. Any fault in the engineering of the scaffold, that is, the event that the scaffold lacks even one of the properties required to carry out its primary functions (to encourage cell seeding and prevent immune response) may result in the rejection of an implant at worst, along with the multitude of problems that arise from it, and a lack of any bone tissue regrowth at best.

Therefore, an appropriate scaffold must be selected and tailored to the nature of the trauma to achieve the best possible outcome for the patient. BTE scaffolds must be osteoinductive, osteoconductive, and osteogenerative for the former to occur. Osteoconductivity is the extent to which the scaffold type can facilitate cell seeding and growth. On the other hand, osteoinductive materials differentiate mesenchymal stem cells (MSCs) from neighboring tissues into osteoblasts, which secrete the organic components of the bone matrix [11], thereby promoting bone formation. Biocompatibility refers to the ability of the scaffold not to trigger an immune response once implanted into the body [3]. The purpose of every scaffold is to achieve optimum angiogenesis, i.e., formation of blood vessels. Scaffold architecture determines the extent of angiogenesis, which, in turn, affects nutrient transport and cell spread [5].

Previous studies demonstrated the effects of different scaffolds on bone tissue regeneration. These revolved around measuring the properties of the scaffolds and thus determining their suitability [12], [13]. However, large-scale literature reviews evaluating the strengths and limitations of many scaffold types, including natural, synthetic, and nanomaterial scaffolds, have not been published. Thus, this narrative review focuses on the mechanical and biological properties of commonly used BTE scaffolds and evaluates their potential for in vivo applications. Bone tissue engineering scaffolds have made significant advances in efficacy over the past decade [14]. Nevertheless, the presence of degradation byproducts and insufficient mechanical strength and cellular interactions remain to be improved. It has been proposed that overcoming these problems requires the use of novel biomaterials, advanced fabrication techniques, and tailored regulatory strategies [15].

METHODS

This review was conducted as a narrative synthesis of peer-reviewed literature examining biomaterial scaffolds in bone tissue engineering, with a focus on their biological performance, mechanical integrity, and hydrophilicity. To ensure a comprehensive understanding of the field, multiple electronic databases, including PubMed, ScienceDirect and Scopus, were searched using combinations of keywords such as "bone tissue engineering," "biomaterial scaffolds," "polymeric scaffolds," "ceramic scaffolds," "composite scaffolds," "nanomaterials," "biocompatibility," "mechanical properties," and "hydrophilicity." The search was unrestricted by publication year to ensure the inclusion of both foundational studies and the most recent advancements. Only articles written in English and reporting experimental data were considered.

Studies were included if they provided detailed evaluations of scaffold materials in vitro or in vivo, covering aspects such as scaffold composition, fabrication methods, cellular-level interactions, and outcomes in animal models. Both cellular studies, using stem cells or progenitor cells seeded onto scaffolds, and animal studies assessing bone regeneration, osseointegration, or scaffold degradation were incorporated. Exclusion criteria removed editorials, conference abstracts lacking primary data, and studies with insufficient methodological detail or focus on non-bone tissue applications.

For each included study, relevant information was extracted regarding scaffold type, composition, fabrication technique, experimental model, and outcomes related to biocompatibility, hydrophilicity, and mechanical properties. The mechanical properties considered included compressive strength, elastic modulus and tensile strength, while biological outcomes encompassed cytotoxicity, cell adhesion, proliferation, differentiation, and angiogenesis. The studies were then organized into categories based on scaffold material - natural polymers, synthetic polymers, bioceramics, bioactive glasses and metals.

Within each category, data were synthesized to compare trends in material performance and highlight the strengths and limitations emerging across different experimental settings. Figures and tables were used to summarize the key properties in order to provide a clear representation of scaffold performance across the included studies.

The reliability of the findings was supported by prioritizing studies with clearly described, reproducible experimental protocols. Additionally, validity was considered by cross-referencing the results across multiple independent studies and noting any inconsistencies arising from variations in scaffold preparation, measurement techniques or experimental models. Where present, limitations such as small sample sizes and variations in in vivo models were considered during interpretation of the findings.

This methodology allowed for a flexible review of over 100 studies, encompassing both fundamental and recent developments in scaffold design. By integrating information on biological performance, mechanical properties, and hydrophilicity, the review identifies critical gaps in knowledge and areas where next-generation scaffolds may provide enhanced functionality. The approach ensures that the evaluation has its basis in evidence while setting the stage for the subsequent discussion of scaffold properties, comparative performance, and potential clinical applications.

STRUCTURE AND FUNCTION OF BONE TISSUE

The activity of four highly specialized types of bone tissue cells, osteoblasts, osteoclasts, osteocytes, and bone lining cells, ensures that remodeling consistently occurs in the body to balance bone resorption and formation (see Fig. 2) [15]. Meanwhile, the macroscopic structure of bone tissue arises from the repeated assembly of micro- and nanoscale units [5].

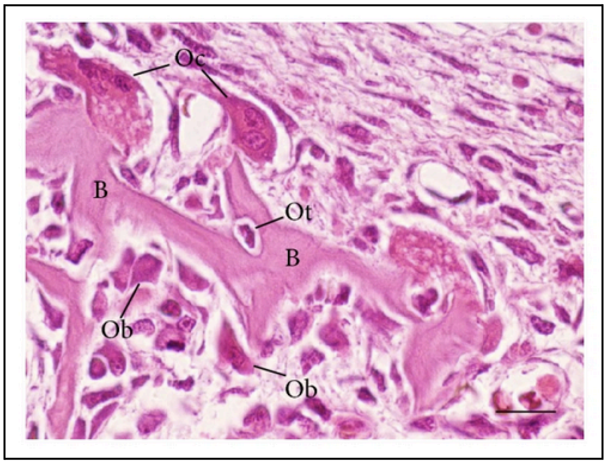


Figure 2. Hematoxylin and Eosin (H&E) staining indicates a light micrograph of portions of the alveolar bone of rats. HE-stained section showing a portion of a bony trabecula (B). Polarized osteoblasts (Ob) and giant multinucleated osteoclasts (Oc) on the bone surface with osteocytes (Ot) surrounding the bone matrix. This image is obtained from [16].

Osteoblasts

Osteoblasts contribute to bone formation, a process known as osteogenesis or ossification, and comprise 4-6% of total bone cells [17]. They arise from pluripotent stem cells (PSCs) and synthesize the bone proteins required for hemostasis, including [3]: osteonectin, γ-carboxyglutamic acid proteins, proteoglycans, osteopontin (OPN), osteocalcin (OCN), and alkaline phosphatase (ALP).

Osteoblasts are also responsible for the synthesis of growth factors, mainly transforming growth factor β (TGF- β), insulin-like growth factors I and II (IGF-I and IGF-II) and bone morphogenetic proteins (BMPs) [7], [3], [18] Matrix vesicles secreted by osteoblasts, which are present in the ECM, are essential as they provide an environment for the nucleation of calcium phosphates [19]. These cells also indirectly regulate osteoclast formation by cell-cell contact, paracrine signaling, and cell-bone matrix interactions. Structurally, osteoblasts are cuboidal or polygonal in shape and are situated in matrix boundaries and aggregate along bone surfaces in the periosteum and endosteum. As their primary function pertains to protein secretion, they include an extensive rough endoplasmic reticulum (rER), the Golgi apparatus, vesicles, and mitochondria. In addition, osteoblasts secrete procollagenases, enzymes that are cleaved into collagenases and used by osteoclasts to degrade collagen fibers [17].

Osteoclasts

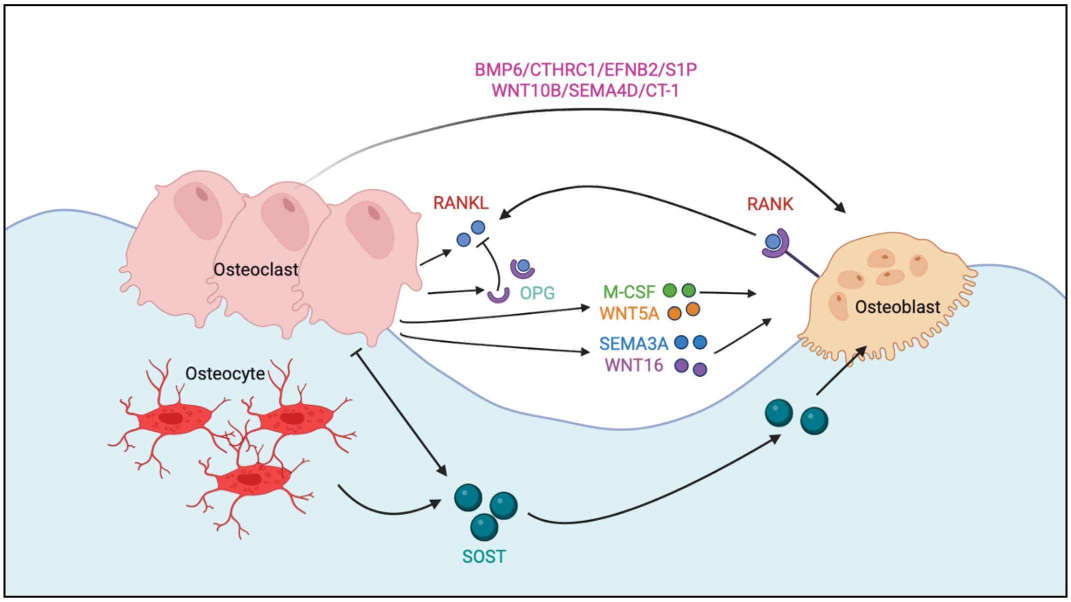


Figure 3. Interaction of enzymes in osteoblasts and osteoclasts, leading to balanced bone resorption and formation. Own source - Created with BioRender.com

Osteoclasts are multinucleated cells derived from hematopoietic progenitor cells and participate in bone resorption [20]. They differentiate as per the process described in Figure 3, when exposed to macrophage colony-stimulating factor (M-CSF) and the receptor activator of the NF-κB ligand, RANKL, which are secreted by osteoblasts and osteocytes [21]. When mature, osteoclasts degrade the extracellular bone matrix by creating a sealing zone including an actin ring circled by a ruffled border [20]. Among other substances, osteoblasts disassemble collagen in the ECM using enzymes, as previously stated. The activity of osteoclasts and osteoblasts must be stable for the maintenance of healthy bone tissue throughout the body's lifetime. In the event of imbalances, diseases such as osteoporosis or osteopetrosis can develop [11].

Osteocytes

Osteocytes regulate the activity of osteoblasts and osteoclasts (i.e., bone formation and resorption), the former through interaction of signaling pathways and the latter through direct perilacunar remodeling [22]. They are often targeted in therapy for bone diseases due to their regulatory tendencies. Osteocytes are terminally differentiated cells from the osteoblast lineage. As illustrated in Figure 4, at the beginning of the formation process, approximately 20% of maturing osteoblasts are surrounded by the ECM, forming a mineralized material composed primarily of type I collagen [23]. This is referred to as an osteoid, which contains pre-osteocytes. These channels allow nutrients and oxygen from blood vessels, as well as signaling molecules, to pass virtually uninterrupted from one cell to another [24]. This structure ensures that cells deep in the bone matrix can effectively communicate with cells they are not in direct contact with [22].

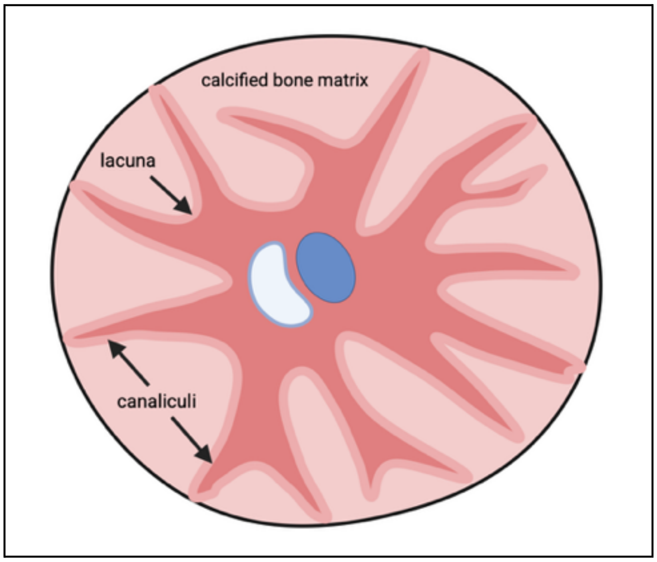


Figure 4. Embedding in the ECM results in a syncytium of pre-osteocytes, interconnected via long cell processes that exist in channels (canaliculi) in the bone matrix. Own source - Created with BioRender.com

Osteocytes possess the ability to sense any pressure placed on the bone and, consequently, respond to these stimuli by deploying osteoblasts and osteoclasts [16]. Thus, the research community widely accepts the concept of the osteocyte as a 'mechanostat' [25], much like the sinoatrial node is often given the moniker 'natural pacemaker of the heart'.

Bone lining cells

Bone lining cells (BLCs) are quiescent (inactive), post-mitotic cells with an osteoblast lineage [26]. They are thought to remove the demineralized matrix on the bone surface before formation through osteoblasts [27]. However, accepted markers or effective selective isolation techniques for BLCs are exceedingly rare. Following the administration of intermittent parathyroid hormone and basic fibroblast growth factor (FGF2) or exposure to high-dose γ-radiation, bone lining cells are a source of active osteoblasts [28]. This osteogenic potential suggests that BLCs may be developed in the future as a viable source of osteoblasts, along with MSCs. The formation or function of bone lining cells is not clearly defined, and research is ongoing to better understand their processes [29].

Macroscopic bone structure

Bone tissue can be classified into two categories: cortical and trabecular bone. Cortical bone, also known as compact bone, is the type of bone that composes about 80% of the human skeleton [30]. Its role is to provide support and strength to the body and is characterized by high density and low porosity [31]. The internal microstructure of cortical bone is a series of concentric cylindrical *osteons* running parallel to the bone's long axis [32]. Osteons include a central Haversian canal with rings of lamellae, which are 5-7 µm wide [7]. In long limb bones, compact bone surrounds trabecular bone, which is highly cancellous (porous), rarely achieving more than a 30% volume fraction (Figure 5). However, in flat bones such as the skullcap, a sandwich-type arrangement is more often seen. This bone type is most often found at the ends of long bones to provide cushioning. Rather than the rigidly organized structure of cortical bone, trabecular bone forms a lattice of interconnected rods and plates known as *trabeculae.* These allow the creation of multiple spaces filled with red bone marrow, which performs hematopoiesis (blood cell production) [33], [30].

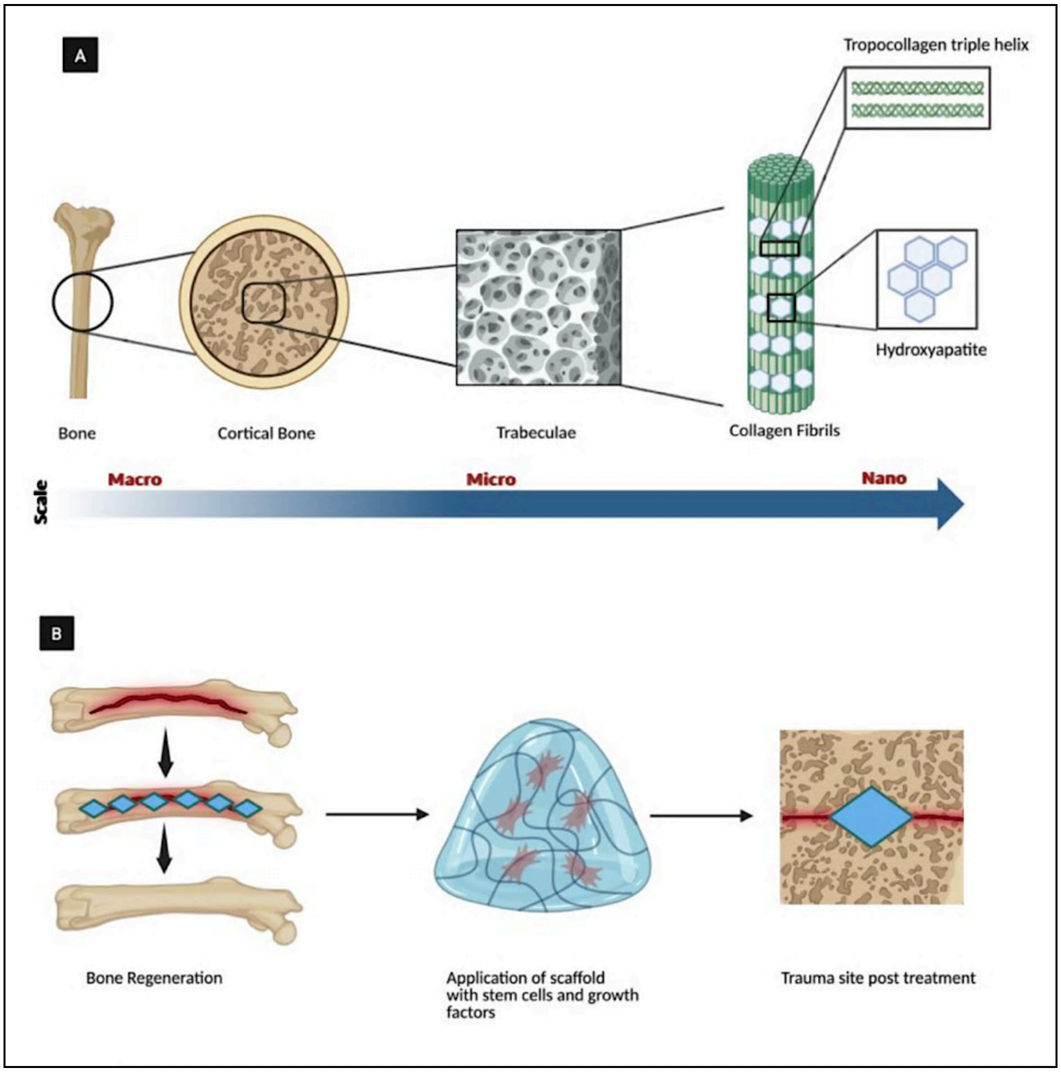


Figure 5. Hierarchical structure of bone tissue, from the nanoscale to the microscale to the macroscale. Own source - Created with BioRender.com

Extracellular bone matrix

The ECM is a three-dimensional, dynamic environment with well-regulated mechanical and biochemical properties [6]. It is considered the fourth element in bone tissue engineering, apart from cells, stimulation, and scaffolds. Both organic (40%) and inorganic (60%) compounds are present in the ECM. However, these percentages vary by age, sex, and other factors. The former is primarily composed of type I collagen (90%) and non-collagenous proteins (10%) and is synthesized by osteoblasts [34]. Inorganic compounds in the ECM can be attributed to a single material, hydroxyapatite (HA, $Ca5(PO4)3OH$), which is deposited via biomineralization. As HA significantly resembles the minerals present in human bones and teeth, it is both biocompatible and osteoinductive, making it suitable for bone fillings and injectable bone substitutes [35]. In bone, the matrix facilitates cell adhesion and proliferation as well as responses to growth factors and differentiation. These activities primarily regulate bone tissue's functional characteristics. Bone ECM is increasingly playing a vital role in bone tissue engineering as more biomaterial scaffolds aim to replicate its properties [36]. These ECM-based scaffolds have been shown to be superior at guiding tissue formation at the implantation site, and their osteoinductive, osteoconductive, and osteogenic potential is garnering increasing attention [37]. Regarding the overall structure of bone tissue, Weiner and Wagner proposed a seven-level hierarchical model in 1998. This has been revised and remains widely accepted in understanding bone composition [38]. The sequence is as follows: bone tissue, cancellous and cortical bone, haversian canals, parallel collagen fiber bundles, mineralized collagen fiber bundles, micron-scale mineralized collagen fibers, and ultimately nanoscale HA and collagen.

AN OVERVIEW OF BONE TISSUE ENGINEERING

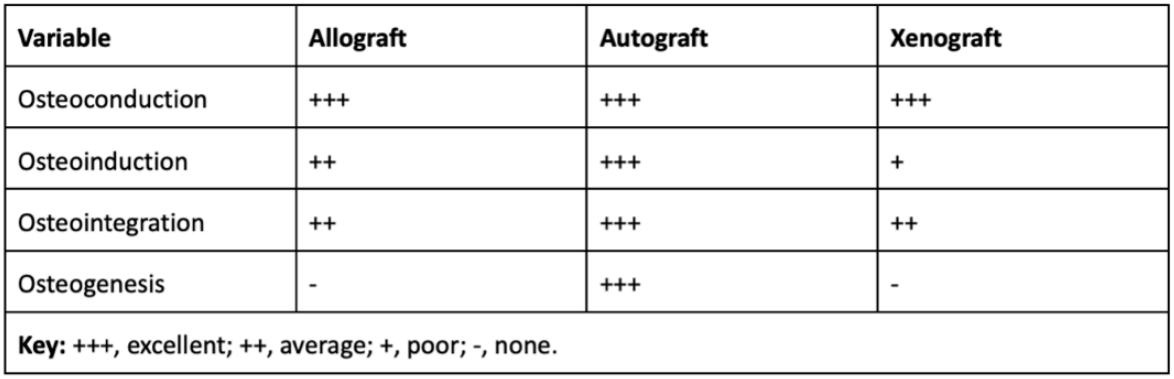
Historical ‘gold standard’ methods for minor traumas

As stated before, non-invasive methods are generally used for minor bone injuries. For slightly larger traumas, bone grafting is required, which can be classified into three subtypes: autografts, allografts, and xenografts. Grafting may involve replacing missing bone tissue with material from the patient’s own body, or an artificial, synthetic, or natural substitute [39]. Autografts have the lowest risk of immunological rejection because they use bone tissue from the patient’s own body. Therefore, they are currently seen as the gold standard for treatment of trauma. Cancellous autografts are commonly harvested from the iliac crest, femur, proximal tibia, calcaneum, olecranon, and distal radius, according to Nashi and Kagda [4]. Although autografts are useful for filling out bone defects and providing a scaffold for bone formation, they lack the ability to provide structural support [40].

Alternatively, allografts from a donor of the same species as the recipient can be used if the patient’s own bone is not viable. These can be harvested from the pelvis, ribs, fibula, or femur. While they can provide structural support that autografts cannot, and the risks of donor-site morbidity and limited graft volume are reduced, evidence for their superiority over technologies such as locking plates (LP) is limited [41], [42]. Regardless, allografts are often used in conjunction with locking plates for fracture treatment.

The final graft type, the xenograft, is an attractive alternative to autografts and allografts because of its large donor supply and reduced risk of transmitting human disease. However, several clinical studies completed involving porcine xenografts have not yet yielded an approach that allows them to integrate with host tissue and avoid rejection [43]. As a result, xenografts are not considered promising candidates for bone therapy.

Table 1. Osteoconduction, osteoinduction, osteointegration, and osteogenesis in allografts, autografts, and xenografts. Source: [39].



Variable	**Allograft**	**Autograft**	**Xenograft**
Osteoconduction	+++	+++	+++
Osteoinduction	++	+++	+
Osteointegration	++	+++	++
Osteogenesis	-	+++	-
Key: +++, excellent; ++, average; +, poor; -, none.			

While autografts, allografts, and xenografts have traditionally been relied upon for the repair of large defects, technological advances have enabled the use of tissue engineering in conjunction with stem/progenitor cells [1].

Key materials used in BTE

Stem cells and progenitor cells

Recent advancements in tissue engineering generally call for the use of stem cells. Stem cells contribute to osteogenesis, osteoinduction, angiogenesis, and mineralization, which are critical for bone regeneration. These must be physically, chemically, and biologically stimulated for regular proliferation and differentiation into osteoblasts, osteoclasts, and osteocytes to occur [44]. In bone tissue engineering, postnatal or adult cells, which can be isolated from almost any tissue, are most often used over perinatal stem cells such as placental or umbilical cord SCs [45]. The focus of most recent studies lies on the following adult stem cells: bone marrow mesenchymal stem cells (BMMSCs), muscle-derived stem cells (MDSCs), adipose-derived stem cells (ADSCs), dental pulp-derived stem cells (DPSCs), and induced pluripotent stem cells (iPSCs), among others, due to their distinctive ability to differentiate into osteogenic lineages [46].

Efficient *in vitro* differentiation of stem cells in TE must follow specific and well-defined protocols that reduce the likelihood of differentiation into divergent lineages [47]. This process includes the integration of an osteogenic differentiation medium containing a combination of factors promoting bone formation, such as the cellular growth regulator dexamethasone, ascorbic acid-2-phosphate for collagen I synthesis, and β-glycerophosphate, which is necessary for mineralization. Differentiation is then monitored by observing the expression of osteoblast-specific alkaline phosphatase (detection within 14 days) and osteocalcin (marker used after +14 days) [48]. The entire process is underpinned by several signaling pathways.

A study by Gao et al. (2024) suggests that BTE requires stem cells from both the donor and the host to differentiate into osteoblasts and, consequently, to synthesize type I collagen, after which mineralization occurs to form bone. Post this, stem cell-derived *extracellular* vesicles can deliver osteogenic materials to the cell. Allogeneic use of this model is very promising due to its reduced risk of immune response. Stem-cell specific scaffolds have also been identified to optimize the environment for bone regeneration [49].

Growth factors

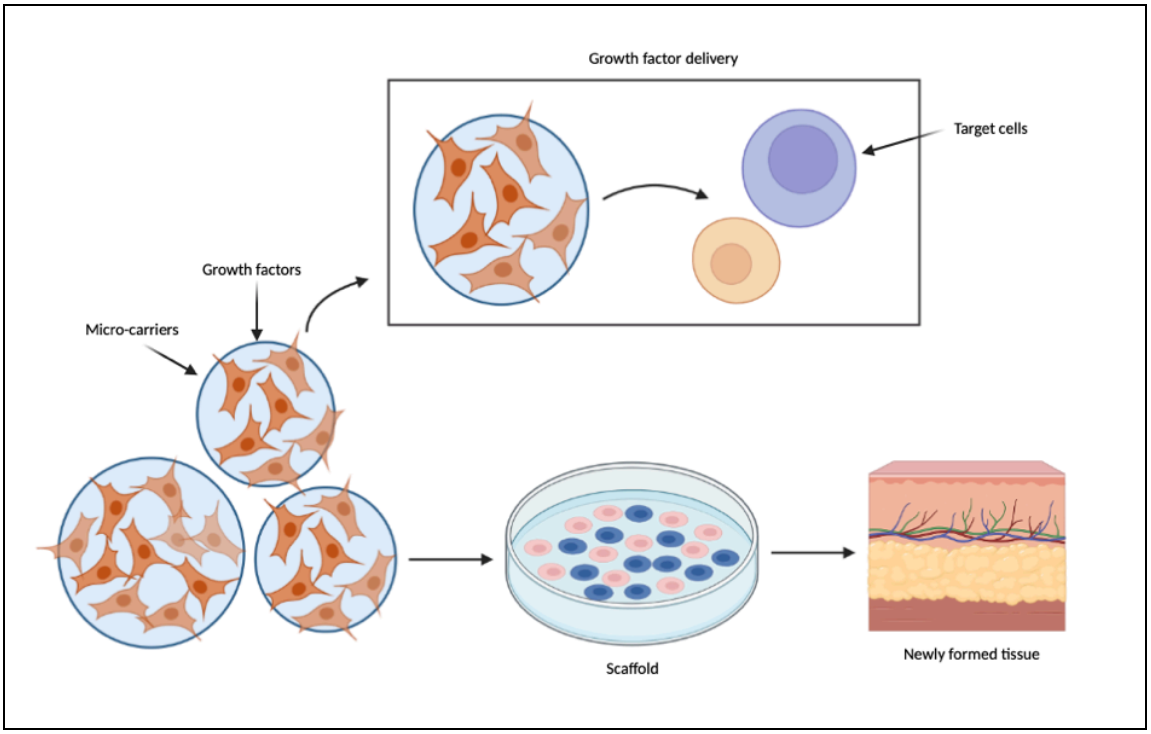


Figure 6. General pathway for growth factor delivery. Own source - Created using BioRender.

As shown in Figure 6, growth factors are used in BTE to enhance stem cell growth and differentiation. While they are naturally released during and after trauma and can also be exogenously delivered to aid healing in non-union defects, controlled release is not yet possible [50]. There are three main roles of the growth factor: (1) Osteoinduction and osteogenesis, carried out by factors such as bone morphogenetic proteins (BMPs) [51], (2) Cell recruitment and migration, done through chemotactic agents like stromal cell-derived factor 1 (SDF-1), VEGF and platelet-derived growth factor (PDGF) which recruit endogenous stem cells to the site of injury and then facilitate their retention and (3) Scaffold integration and neovascularization (development of blood vessels) are also promoted by growth factors at the injury site, which ensures that nutrients are delivered, and waste products removed for effective regrowth [52].

BIOMATERIALS AS KEY COMPONENTS OF BTE

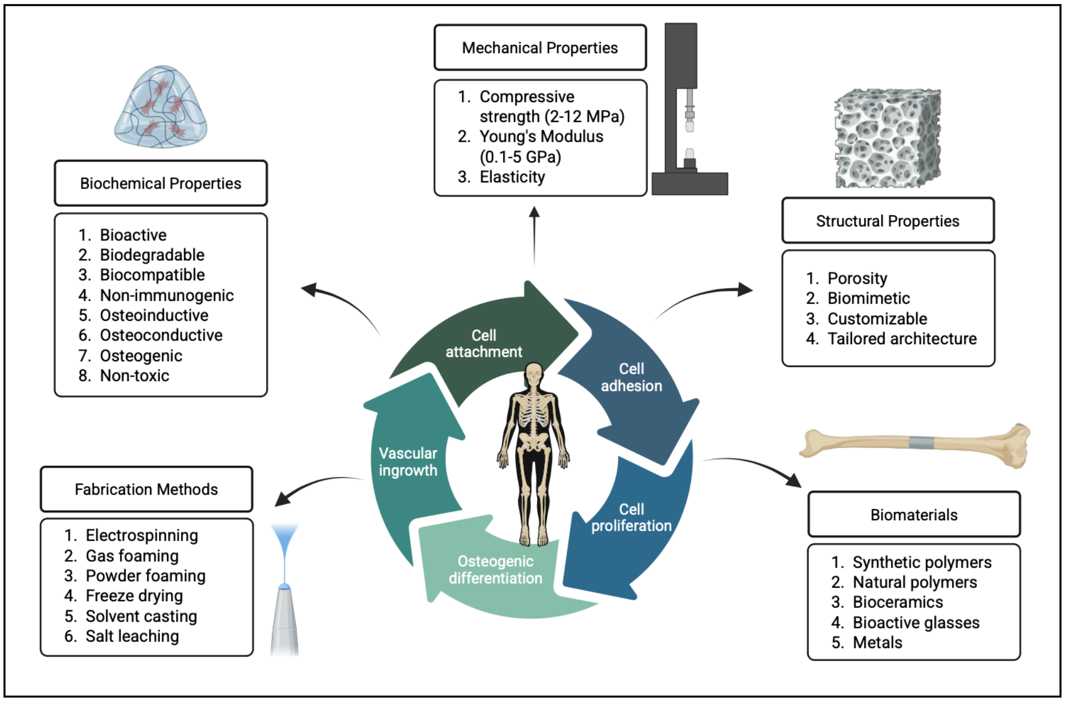


Figure 7. Properties of an ideal bone tissue engineering scaffold. Own source - Created using BioRender.

Bone tissue engineering scaffolds must support cell growth and provide a stable, osteoconductive matrix that mimics the body's ECM. They must also have specific mechanical and biochemical properties that render them immunologically unresponsive and withstand wear and tear until cell seeding and bone regrowth are complete. Therefore, biomaterials that possess all these characteristics are ideal as BTE scaffolds and are widely used in regenerative medicine [53]. Figure 7 details these requirements as well as a host of fabrication methods commonly used to produce BTE scaffolds. A biomaterial refers to a substance engineered to interact with biological systems to replace, repair, or augment a body part. They possess a high degree of biocompatibility by definition and can be natural, synthetic, hybrid (a mixture of both), composite (including a part of the ECM), bioceramics and bioglasses, or carbon nanomaterials [54]. As discussed previously, scaffolds, along with cells and stimulation, are part of the tissue engineering triad and are vital for conducting BTE appropriately.

Natural Polymers

Natural polymers are large biomaterials derived from living organisms. Of these, those frequently used in BTE and in research studies include collagen, gelatin, chitosan, alginate, and silk fibroin. Natural polymers can be further classified into three groups: nanofibers, hydrogels, and microspheres, each with its own fabrication methods [55].

Nanofibers are widely used for their ability to mimic the ECM at the nanoscale and improve adhesion, proliferation, and differentiation of stem cells [56]. The main technique used to formulate nanofibers is electrospinning, which enables the scaffolds to have a high surface area, porosity, and tightly controlled fiber diameter and orientation [57]. The electrospinning process involves electrical fields that draw charged threads of polymer solutions or melts into nanofibers and relies on the principle that a charged liquid droplet will deform into a Taylor cone when subjected to a strong field, then eject a charged jet of liquid. This jet then thins because of electrostatic repulsion and solvent evaporation, leaving a nanofiber [58]. The advantages of this method include a high surface area-to-volume ratio, adjustable parameters to control properties, improved tensile strength, and versatility in the range of polymers that can be processed with it [59].

Secondly, hydrogels are valued for their ability to encapsulate cells and bioactive molecules (e.g., growth factors) and to provide a semipermeable medium that facilitates metabolite diffusion, which is essential for promoting osteogenesis [60]. Hydrogels have been developed that respond to external stimuli, such as temperature and pH, but further research is required to investigate their implications for controlled drug delivery [61]. Although they mimic the ECM and degrade in a controlled manner, hydrogels alone cannot meet the mechanical strength standards of native bone and are thus usually used as hybrids with hydroxyapatite or graphene oxide [62].

Microspheres, as the name suggests, are microscale spherical structures that encapsulate growth factors and other molecules at the site of the defect or trauma. They enable controlled release to stimulate osteogenesis and angiogenesis [63]. Emulsion remains the primary technique for fabrication, in which a dispersed phase containing the material to be encapsulated is created within an immiscible phase. High shear forces and emulsifiers are often used to stabilize these emulsions. After emulsion formation, the droplets are solidified into microspheres via solvent evaporation (if a volatile organic solvent is present) and cross-linking [64]. Factors such as viscosity, interfacial tension, solvent volume ratio, and agitation speed can greatly affect microsphere properties, posing a challenge, as even an insignificant change can yield a product that is not fit for purpose [65].

Synthetic Polymers

Synthetic polymers differ from natural polymers in that they are synthesized from petroleum oil, while the latter are extracted from animal feces or degraded organic matter. They may be classified as (i) hydrophobic, (i.e., polyethylene (PE), polypropylene (PP), polymethyl methacrylate (PMMA)); (ii) more polar systems (i.e., polylactic-glycolic acid (PLGA)); (iii) water-swelling materials (i.e., polyhydroxy ethyl methacrylate (PHEMA)); and (iv) water-soluble materials (i.e., polyethylene glycol (PEG)) [66]. Synthetic polymers are highly tunable and provide predictable, reproducible properties. This is a primary reason for the FDA approving more synthetic polymers than natural ones. The main disadvantage of this scaffold type is the disproportionate environmental impact of waste generated during manufacturing, as most plastics are non-biodegradable [67]. Although synthetic polymers have enormous mechanical potential, they are also less flexible and less biocompatible than natural scaffolds. Additionally, osteoconductivity and cellular adhesion properties are not strong enough to use them alone for bone regeneration.

As a result, most current research in BTE focuses on the regenerative potential of natural-synthetic hybrid scaffolds, which offer the synergistic benefits of both [68]. Using either alone often leads to a trade-off between mechanical strength and biocompatibility, both of which are essential properties. Chitosan has been blended with various synthetic polymers, including PMMA, PEG, PCL, and PLA. PCL is a non-toxic aliphatic polyester with a low degradation rate [69]. It is hydrophobic, which hinders cellular activity, but studies on PCL-alginate scaffolds have shown that alginate significantly increases water absorption [70]. One of the most widespread synthetic polymers is PLGA, a copolymer of PLA and PGA. It has been used in the field for its variable degradation rate, which ranges from weeks to months depending on the monomer ratio. There is still significant room for improvement, as the amorphous structure and poor osteoconductivity limit its use in load-bearing applications. As a result, bioceramics such as hydroxyapatite are increasingly being integrated into PLGA [71].

Bioceramics

Bioceramics are mineral fillers commonly used in BTE for applications such as coatings on commercial metallic implants. Zirconia, for example, is a bioceramic that is exceedingly popular in dental applications for its high strength and aesthetic properties. However, hydroxyapatite (HA) and beta-tricalcium phosphate (β-TC) remain the bioceramics of choice for BTE. These materials possess a high degree of biocompatibility and bioactivity, and their similarity to the minerals in bone tissue itself lessens the risk of immune response [72]. The disadvantages of the two primary bioceramics – HA and β-TC lie in their low and high resorption rate, respectively. While HA can limit the rate of bone regeneration, the latter may be unable to support the scaffold for a sufficient period before reverting to the former state [73]. Many of the overall repairs in BTE are dental, and bioceramics, primarily HA, are the scaffold type of choice for this application due to the properties discussed above. As with the combination of natural and synthetic polymers to form composite scaffolds, HA-polymer or BGs-polymer scaffolds have also gained momentum [74]. These composites exhibit more mechanical strength and customizability than often brittle bioceramics, and more bioactivity than polymers. Bioceramics can be processed using conventional solvent casting, freeze-drying, and particulate leaching, but newer additive manufacturing (AM) methods include 3D printing and electrospinning, the latter of which has already been covered.

Bioceramics can be broadly classified into three categories based on their interaction with host tissue: bioinert, bioactive, and biodegradable. Each plays a distinct role in bone tissue engineering depending on the clinical requirement, location, and desired immune response [75]. Bioinert bioceramics, such as alumina (Al_2O_3) and zirconia (ZrO_2), are characterized by their high stability and minimal interaction with the surrounding biological environment. They do not form any chemical or biological bonds with the host tissue, making them suitable for load-bearing applications where long-term mechanical stability is prioritized over integration. However, their inertness limits their ability to bond to bone, so their applications are largely confined to joint replacements and dental implants, where wear resistance and low reactivity are critical. Despite these limitations, advancements in surface texturing and doping have shown potential to improve osseointegration without compromising their inert nature [76]. Biodegradable bioceramics are those that progressively degrade in the physiological environment, ideally at a rate that matches new tissue formation. Their degradation is mediated through both physicochemical dissolution and cellular resorption, providing a temporary scaffold that is eventually replaced by native bones. The resorbability of these ceramics offers a clear advantage in applications where the long-term presence of foreign material is undesirable [77]. Finally, bioactive bioceramics have emerged as a field of their own in BTE research.

Bioactive glass

In contemporary regenerative medicine, bioactive glass has transformed drug delivery. While it has traditionally been used for sutures and to fill bone defects, bioactive glass is emerging as a key area of future research. Bioglass®, a product pioneered by Hench, is widely regarded as the best current biomaterial for chemically bonding to host bone and promoting osteogenesis [78]. In an *in vivo* study on rat bone, c*irca* 1969, Hench et al. recognized its ability to bond chemically to silicate-based glass materials. These materials came to be termed 'bioactive', or causing a biological response at the bone surface, which resulted in bone tissue and bioactive glass bonding. While the original composition included 45% SiO2, 24.5% Na2O, 24.5% CaO, and 6% P2O5, bioactive glasses have been developed that contain other elements in the silica matrix, such as fluorine, magnesium, strontium, iron, silver, boron, potassium, or zinc [79]. It is widely accepted that, for bioactive glasses to bond, they must react with body fluids and form a hydroxycarbonate apatite (HCA) layer, after which cellular reactions continue. These materials can control the release of drugs from the silica matrix, stimulate cell proliferation and adhesion, and, in turn, promote the synthesis of essential proteins. More recently, they have been used to create 3D bone models, and their fabrication method is being investigated to achieve greater control over scaffold formation [80].

Metals

Metals are highly regarded in BTE for their mechanical strength, which is comparable to that of synthetic polymers. As a result, they are routinely used in alloys, especially those of titanium, cobalt, tantalum, and magnesium, in varying ratios. Their high elasticity, resistance, ductility, and stability make them attractive options for BTE. Despite these myriad strengths, metals also have a high Young's modulus, indicating that they are too stiff and resist elastic deformation on the application of force [81]. This detracts from their ability to facilitate cell seeding. The toxicity of their ions and the presence of particle release may also have negative implications for the body. Ti_6Al_4V titanium alloys are favored in clinical practice at present, as the addition of aluminum compensates for the poor strength of pure titanium, which limits its widespread use [82]. Titanium-based alloys are mostly used in total joint replacement and fracture fixation but run the risk of loosening in osteoporotic bones. Magnesium-based alloys are biodegradable and exhibit suitable plasticity and mechanical strength, helping patients avoid secondary surgery after implantation, as is the case with several metal implants [83].

A certain study demonstrated the biocompatibility of Mg^{2+} scaffolds in rabbit femurs, providing more *in vivo* evidence supporting their use in humans [84]. Mg-Cu alloys are also found to have osteogenic and angiogenic properties in an *in vitro* model of mouse pre-cranial osteoblasts and human umbilical vein endothelial cells, respectively [85]. Metal scaffolds are unique in that some have both anabolic and catabolic effects; that is, they can both promote and inhibit cell proliferation and the osteogenesis that follows. Strontium has been shown to regulate the function of osteoblasts and osteoclasts through the BMP-2/Smad1 and OPG/RANKL signaling pathways, and it can even promote MSC differentiation. In recent years, nanotechnology has shown promise as a BTE mechanism, enabling the development of materials that can overcome challenges in cell proliferation and differentiation in current biomaterials. While multiple types of biomaterials have been used in nanoparticles, silver nanoparticles (Ag NPs) are widely used in the orthopedic field for their antibacterial, antifungal, antiviral, anti-inflammatory, and osteoinductive effects [86]. Metal nanocomposites with both antibacterial and osteogenic abilities have also been developed.

COMPARATIVE ANALYSIS OF BIOMATERIAL SCAFFOLD TYPES

This section discusses each property required to construct a suitable BTE scaffold by biomaterial type and evaluates the usefulness of each, based on mechanical strength, biochemical properties and hydrophilicity, alone and in conjunction with other materials.

Biochemical properties

The main biochemical properties desirable for a BTE scaffold are biodegradability, bioactivity, and biocompatibility. Biodegradability is typically assessed through in vitro degradation tests in simulated body fluids (SBF) or phosphate-buffered saline (PBS), where weight loss, pH changes, or ion release are monitored over time, while is measured by the formation of a hydroxycarbonate apatite (HCA) layer on the scaffold surface after immersion in SBF, confirmed via SEM, XRD or FTIR [87]. A microscale approach typically involves live/dead staining, fluorescence microscopy, or quantitative assays (e.g., MTT or Alamar Blue) after seeding osteoblasts or stem cells onto the scaffold [88].

Natural polymers are among the most biocompatible and bioactive biomaterials used today for BTE scaffolds. They are inherently resemblant to the ECM and can contain specific cell-signaling molecules that are anti-inflammatory and promote cell attachment, proliferation, and differentiation. Their low immunogenicity allows them to easily integrate with host bone tissue and begin the regenerative process [55]. Bioceramics are another biomaterial type that exhibits excellent tissue integration and low immune response. While natural polymers are similar to the ECM in chemical structure, bioceramics mimic the mineral composition of native bones. Bioceramics are classified as either bioinert, biodegradable, or bioactive. The latter can bond directly with both cancellous and cortical tissues to form a single entity, bringing the bone as close as possible to its original state. Bioinert bioceramics do not offer an advantage in terms of bioactivity, but they interact minimally with surrounding tissue and are unlikely to elicit immune responses, such as inflammation. Lastly, biodegradable bioceramics are gradually reabsorbed by the body, dissolving as the bone slowly heals. For example, calcium phosphates such as β-TCP release calcium and phosphate ions, which are naturally present in the body [78].

Bioceramics are both osteoconductive and osteoinductive, especially when certain dopants are applied [3]. Bioactive glasses share the likeness of bone minerals with bioceramics but have the added benefit of being extremely bioactive, as evidenced by their name. The HA layer formed upon implantation promotes protein adsorption, accelerates the release of beneficial ions, and increases osteoconductivity. Multiple bioactive glasses are already FDA-approved and used clinically. While little research has compared the biological properties of bioactive glass and natural polymers, bioactive glass has been widely accepted as more bioactive than natural polymers [89]. On the other hand, synthetic polymers are generally biocompatible but have limited bioactivity. They may also cause local acidity and inflammation from breakdown products, though these are non-toxic (e.g., lactic acid from PLA, which is naturally metabolized by the body) [90]. Most are hydrophobic, severely limiting their cell adhesion and, consequently, their clinical potential. Lastly, metals are the least ideally suited for BTE in terms of biocompatibility when used alone. Titanium alloys are biocompatible, high-strength, corrosion-resistant but lack osteoinductive and antibacterial properties. Other metals, such as cobalt-chromium, steel, and magnesium alloys, are prone to corrosion byproducts despite their biocompatibility [82].

Mechanical properties

Mechanical properties are measured using compression, tensile, or three-point bending tests, depending on scaffold geometry. The key parameters include compressive strength, Young's modulus, and fracture toughness, which are assessed using a universal testing machine (UTM) according to ASTM standards. When referencing porosity, it is important to note the relationships governing porosity, elastic moduli, and tensile strength. An increase in porosity leads to a decrease in the other two properties, simply stated, although the true relationship is complex and follows a power-law model [91]. Interconnectivity of the pores in a scaffold is crucial for enabling tissue and vascularization, with minimum requirements for open porosity and pore size (e.g., >50% open porosity and pores >=100 μm) being necessary for tissue ingrowth [92]. These pore characteristics, along with the overall porosity, also influence bioactivity by increasing the specific surface area available for mineralization. The strongest biomaterial in BTE is metal, with a tensile strength (Young's modulus) and density that far exceeds the capacity of native bone. This generally causes it, when used alone, to take on most of the load-bearing capabilities and lead to the atrophy of surrounding bone tissue, as per multiple studies. For instance, the modulus of elasticity (GPa) of cancellous bone, the softer and less dense bone type, is 3.2 ~ 7.8, while that of the closest metal to it, magnesium, ranges from 41 to 45 [93].

Bioactive glass's mechanical properties are highly dependent on the specific composition, method of fabrication, and extent of crystallization to glass-ceramics. As a result, they are highly customizable and in high clinical demand, as previously stated, given that multiple models are FDA-approved. Commercially trademarked bioactive glass, Bioglass 45S5, is formed by 45% SiO_2, 24.5% Na_2O, 24.5% CaO, and 6% P_2O_5. Meanwhile, Perioglass has shown promise in clinical trials for the treatment of periodontal defects in generalized aggressive periodontitis. Research comparing the direct foaming method with glass-slurry foaming has also been conducted, demonstrating the range of mechanical properties achievable. For the methods, the mean compressive strength ranged from 0.53 to 0.68 MPa and 0.8 to 0.92 MPa, and the mean total and interconnected porosities ranged from 88% to 93% and 76% to

86%, respectively [94]. Bioactive glass has a lower fracture toughness than cortical bone but is similar to that of some porous materials.

Meanwhile, the strength of bioceramics is comparable to that of human trabecular bone at similar porosity, meaning fewer secondary methods are required to enhance its properties. This makes it an attractive option for bone regeneration. Bioceramics are hard and brittle, but their properties can be tuned to specifications. The combination of bioceramics and bioactive glass yields glass-ceramics with improved strength, lower porosity, and greater fracture resistance. Synthetic polymers are also tunable and offer much greater control and consistency in the gradation of mechanical properties than natural polymers. Monomers influence the characteristics of the polymer, such as crystallinity, molecular weight, and boiling points. For elasticity, the length and degree of entanglement of the polymer chains and the presence of crosslinking, as in elastomers, all play a part [95]. Porosity-wise, porogen concentration, freezing temperatures, and the addition of water affect the polymer. Lastly, natural polymers are widely known to be less firm and elastic mechanically, but the same factors that affect the properties of synthetic polymers also hold in common.

Hydrophilicity and swelling behaviors

Hydrophilicity is typically evaluated by measuring water contact angles; lower angles indicate greater wettability. Swelling behavior is assessed by immersing dry scaffolds in PBS or water, measuring their weight gain over time, and calculating the swelling ratio as a percentage of the initial dry weight. Both properties play a central role in determining the success of a scaffold in bone tissue engineering, as they govern fluid uptake, nutrient transport, and overall cellular interactions. They, however, vary significantly across the different materials used in scaffold design [96]. Natural polymers, including chitosan, collagen, gelatin, and agarose, are inherently hydrophilic due to the presence of polar functional groups such as hydroxyl and amine moieties. This strong affinity for water results in high swelling capacity, facilitating cell attachment, migration, and nutrient exchange [97]. For example, chitosan-fluorapatite hybrid scaffolds studied by Iqbal et al. exhibited equilibrium water content values as high as 95%, compared to significantly lower values in hydroxyapatite-loaded analogues, due to chitosan's hydrophilic groups binding to less reactive ceramic surfaces [98]. Agarose/nanocrystalline apatite scaffolds have also been shown to exhibit high hydrophilicity, which improves preosteoblastic cell adhesion, as confirmed by contact angle and MTT assays. While beneficial biologically, excessive swelling in natural polymers can lead to shape distortion and compromise mechanical integrity, requiring careful tuning or blending with more stable phases.

Synthetic polymers such as polycaprolactone (PCL), polylactic acid (PLA), and their copolymers are generally hydrophobic, with water contact angles of 80–90°, which can hinder cell attachment and proliferation. A study incorporating wollastonite into a PLA-PCL blend reported a decrease in water contact angle from 89° to 49°, significantly enhancing hydrophilicity and thus improving osteoblast compatibility [99]. Similarly, the addition of titanium dioxide nanoparticles to PVA-based scaffolds resulted in a hydrophobic shift (contact angle increasing from 93° to 120°), attributed to increased crosslinking density and reduced availability of hydrophilic domains [100].

Bioceramics, particularly calcium phosphate-based materials such as hydroxyapatite (HAp) and tricalcium phosphate (TCP), represent a middle ground between natural and synthetic polymers and are moderately hydrophilic. Their swelling behavior is not governed by polymer chain dynamics but rather by the absorption of water onto their porous or microporous surfaces. In a study evaluating ceramic-loaded collagen methacrylate hydrogels, TCP and lithium-aluminum-silicate (LAP) ceramics exhibited stable swelling over 7 days of PBS immersion, preserving gel integrity while maintaining sustained bioactivity [101]. The key advantage of bioceramics lies in their ability to facilitate osteoconduction without undergoing dimensional changes upon water uptake, making them stable yet biologically effective as scaffold constituents.

Bioglasses, such as the well-characterized 45S5 Bioglass, exhibit excellent surface hydrophilicity due to their highly reactive silicate network. Upon exposure to physiological environments, rapid ion-exchange processes lead to the formation of a hydroxycarbonate apatite (HCA) layer, which is critical for bonding to bone. Although they do not swell in the polymeric sense, their interaction with water allows them to function. The reactivity of bioglass surfaces contributes to excellent initial wettability, which facilitates protein adsorption and subsequent cell attachment. While data on bioglass swelling is limited, their performance in hydrophilic environments is well documented, particularly when integrated into composite scaffolds, where their wettability can enhance the surrounding polymer matrix [91].

Metals, in contrast, exhibit minimal to no swelling and are generally hydrophobic. Titanium and magnesium alloys used in BTE are surface-inert in their raw state, requiring post-processing techniques such as plasma oxidation or protein grafting to improve wettability. These modifications reduce the water contact angle and promote cell adhesion, but the bulk material remains unswellable [102]. Their lack of swelling is not inherently a disadvantage for load-bearing roles, but it limits their use as standalone scaffolds that require cellular infiltration and nutrient diffusion.

Table 2. Summary of the hydrophilic, mechanical, and biochemical properties of natural polymer, synthetic polymer, bioceramic, bioglass, and metal scaffolds and their limitations for use in bone tissue engineering

Property	Natural Polymer	Synthetic Polymer	Bioceramic	Bioglass	Metal
Biodegradability	High; degrades naturally via enzymatic activity	Tunable; can be designed to degrade at controlled rates	Varies; TCP resorbable, HA less so	Generally non-biodegradable, but can dissolve in body fluid depending on composition	Generally non-biodegradable; some (e.g., Mg alloys) degrade in vivo

Biocompatibility	Excellent; mimics ECM; supports cell adhesion and proliferation	Good; may require surface treatment to enhance cell interaction	High; supports osteoconduction and integration	Excellent; strong cellular response due to ionic dissolution products	High; inert but may cause stress shielding and require coatings
Bioactivity	Moderate; may need to be used in a hybrid	Inherently low; surface modification improves bioactivity	High; especially calcium phosphates like HA and TCP	Very high; forms HCA layer and stimulates cell responses	Low; not inherently bioactive unless surface treated
Tensile Strength	Low	Moderate to High (depends on polymer type)	Low to moderate; brittle in nature	Low to moderate; brittle	Very high; best for load-bearing roles
Elasticity	High elasticity; soft and flexible	Tunable; elastomers can be highly flexible	Low; stiff and brittle	Low; brittle and fragile under tensile stress	Low to moderate; typically, stiffer than bone
Load bearing	Poor; unsuitable alone for load bearing	Moderate to good; tunable for mechanical needs	Moderate; brittle fracture behavior	Poor to moderate; not suitable alone for load bearing	Excellent; high load-bearing capability
Hydrophilicity	High; absorbs water easily	Low to moderate; can be improved with additives	Moderate; absorbs fluid at surface level	High; excellent surface wettability	Low; generally hydrophobic, requires surface treatment
Swelling Capacity	High; can swell excessively	Tunable; depends on crosslinking and hydrophilicity	Minimal swelling; dimensionally stable	Very low; not polymeric, but highly reactive in fluid	None; no swelling behavior
Osteoconductivity	Moderate; can support bone cell growth	Low; needs modification	High; supports bone ingrowth	High; promotes bonding and bone formation	Low; not osteoconductive without coating

Osteoinductivity	Possible with functionalization	Generally poor	Moderate except for doped ceramics	Moderate; can be doped for osteoinductivity	Very low; inert unless biofunctionalized
Customizability	Good; natural sources, but harder to control properties	Excellent; can be synthesized with specific properties	Moderate; sintering and shaping required	Moderate; properties depend on composition and fabrication method	Moderate; advanced processing (e.g., 3D printing, alloying) required
Clinical Use	Widely used for soft tissue regeneration and drug delivery	FDA-approved for various implants;	Used in dental, orthopedic applications	Approved in several clinical applications (e.g., Bioglass® 45S5)	Standard in orthopedics (e.g., titanium, stainless steel, magnesium)
Limitations	Weak mechanical strength, fast degradation	Hydrophobic, may not promote cell adhesion	Brittle, not suitable for high-stress sites	Fragile; poor mechanical strength	Risk of stress shielding, corrosion (for some alloys), non-degradable

DISCUSSION

Despite considerable progress in scaffold development, a fundamental limitation remains: no single biomaterial class can adequately meet the complex and often competing requirements of bone tissue engineering. Metals, while unmatched in strength, are inherently hydrophobic and incapable of supporting cellular growth unless extensively modified. Bioglasses and bioceramics offer superior bioactivity and wettability but are brittle and mechanically unsuitable for high-stress environments. Natural polymers exhibit excellent biological properties due to their hydrophilicity and biodegradability but lack structural integrity. Lastly, synthetic polymers bridge specific gaps with tunable properties and consistency, yet their poor hydrophilicity and cell-interaction capabilities limit their use as BTE scaffolds. Consequently, the most effective scaffolds are those that combine two or more materials in hybrid or composite configurations. Importantly, the enhanced performance of composite scaffolds arises not only because of the coexistence of complementary bulk properties but also from the interfacial interactions between biomaterials that improve protein adsorption and load distribution.

A further limitation arises from the methodological variability across studies on this topic. Mechanical properties are frequently reported across different porosity thresholds and fabrication techniques, which restricts the precision of comparison between studies. Similarly, biological performance is evaluated using differing in vitro systems and animal defect models that vary significantly in anatomical site, scale and regenerative capacity. These inconsistencies complicate the establishment of definitive performance hierarchies between biomaterial types and weaken the translational reliability of the findings. Therefore, until greater standardisation in both experimental design and reporting of data is achieved, determining the superiority of scaffold designs will remain inherently dependent on the context despite the breadth of existing literature.

For instance, triphasic constructs integrating polymers with bioactive ceramics and glasses demonstrate a synergistic balance of mechanical performance, hydrophilicity, and bioactivity [103]. Additionally, scaffolds combining PLA, PCL, and wollastonite not only support angiogenesis and osteogenesis but also address issues of brittleness and poor water uptake observed in monolithic scaffolds. Surface modifications, such as alkaline hydrolysis or plasma treatment, can improve the hydrophilicity of otherwise inert polymers and metals, thereby enhancing their compatibility in mixed-material systems. Future directions include the development of spatially graded or zonal scaffolds that mimic the hierarchical nature of bone, with mechanically robust cores surrounded by hydrophilic, bioactive interfaces [104]. Advances in additive manufacturing enable precise placement of diverse materials, opening opportunities for multi-phase, stimuli-responsive scaffolds that can adapt to the healing environment. Furthermore, biofunctionalization with ion-doped bioceramics, such as copper- or zinc-enriched diopside, can confer antibacterial and pro-angiogenic properties, extending scaffold functionality beyond structural support [105]. Innovative scaffolds capable of responsive swelling or drug release in response to local stimuli, such as pH or temperature, are also an emerging frontier, enabling dynamic interaction with the host tissue [106]. Despite these advancements, challenges related to reproducibility, long-term safety and regulatory approval remain significant barriers to clinical translation.

CONCLUSION

This review explored the landscape of biomaterial scaffolds used in bone tissue engineering, focusing on their biocompatibility, mechanical properties, and potential clinical applications. A detailed comparison of natural polymers, synthetic polymers, bioceramics, bioactive glass, and metals reveals that each material class offers distinct advantages, ranging from superior cell adhesion to robust load-bearing capacity. However, these benefits are often accompanied by corresponding drawbacks, such as inadequate mechanical strength in natural polymers or poor bioactivity in metals. The data presented affirm that no singular biomaterial currently meets all the necessary criteria for an ideal BTE scaffold. As such, integrating complementary materials into composite scaffolds offers a viable solution, enabling the simultaneous fulfilment of biological and structural requirements. Collectively, this paper underscores the critical importance of scaffold selection in ensuring the success of regenerative strategies and highlights the growing sophistication with which materials science and biomedical engineering converge in the pursuit of functional bone regeneration.

REFERENCES

[1] S. Bose, M. Roy, and A. Bandyopadhyay, "Recent advances in bone tissue engineering scaffolds," *Trends Biotechnol*, vol. 30, no. 10, pp. 546–554, Oct. 2012, doi: 10.1016/J.TIBTECH.2012.07.005/ASSET/35F94F17-9336-40FE-B57A-A6894AE6223A/MAIN.ASSETS/GR3.SML.

[2] M. Coon, M. Denisiuk, D. Woodbury, B. Best, and R. Vaidya, "Closed Fracture Treatment in Adults, When is it Still Relevant?," *Spartan Med Res J*, vol. 7, no. 1, p. 28060, Feb. 2022, doi: 10.51894/001C.28060.

[3] T. M. Koushik, C. M. Miller, and E. Antunes, "Bone Tissue Engineering Scaffolds: Function of Multi-Material Hierarchically Structured Scaffolds," Apr. 05, 2023, *John Wiley and Sons Inc*. doi: 10.1002/adhm.202202766.

[4] N. Nashi and F. H. Kagda, "Current concepts of bone grafting in trauma surgery," *J Clin Orthop Trauma*, vol. 43, p. 102231, Aug. 2023, doi: 10.1016/J.JCOT.2023.102231.

[5] A. G. Abdelaziz *et al.*, "A Review of 3D Polymeric Scaffolds for Bone Tissue Engineering: Principles, Fabrication Techniques, Immunomodulatory Roles, and Challenges," *Bioengineering*, vol. 10, no. 2, Feb. 2023, doi: 10.3390/BIOENGINEERING10020204.

[6] X. Lin, S. Patil, Y. G. Gao, and A. Qian, "The Bone Extracellular Matrix in Bone Formation and Regeneration," *Front Pharmacol*, vol. 11, p. 757, May 2020, doi: 10.3389/FPHAR.2020.00757.

[7] R. Dimitriou, E. Jones, D. McGonagle, and P. V. Giannoudis, "Bone regeneration: Current concepts and future directions," *BMC Med*, vol. 9, May 2011, doi: 10.1186/1741-7015-9-66.

[8] Z. Peng, T. Zhao, Y. Zhou, S. Li, J. Li, and R. M. Leblanc, "Bone Tissue Engineering via Carbon-Based Nanomaterials," *Adv Healthc Mater*, vol. 9, no. 5, Mar. 2020, doi: 10.1002/ADHM.201901495.

[9] H. Zhao *et al.*, "Harnessing electromagnetic fields to assist bone tissue engineering," Dec. 01, 2023, *BioMed Central Ltd*. doi: 10.1186/s13287-022-03217-z.

[10] T. Ghassemi, A. Shahroodi, M. H. Ebrahimzadeh, A. Mousavian, J. Movaffagh, and A. Moradi, "Current Concepts in Scaffolding for Bone Tissue Engineering," *Archives of Bone and Joint Surgery*, vol. 6, no. 2, p. 90, Mar. 2018, doi: 10.22038/abjs.2018.26340.1713.

[11] X. Chen, Z. Wang, N. Duan, G. Zhu, E. M. Schwarz, and C. Xie, "Osteoblast-Osteoclast Interactions," *Connect Tissue Res*, vol. 59, no. 2, p. 99, Mar. 2017, doi: 10.1080/03008207.2017.1290085.

[12] S. Kalidas and S. Sumathi, "Mechanical, biocompatibility and antibacterial studies of gelatin/polyvinyl alcohol/silkfibre polymeric scaffold for bone tissue engineering," *Heliyon*, vol. 9, no. 6, p. e16886, Jun. 2023, doi: 10.1016/J.HELIYON.2023.E16886.

[13] K. Zhou, F. A. Azaman, Z. Cao, M. Brennan Fournet, and D. M. Devine, "Bone Tissue Engineering Scaffold Optimisation through Modification of Chitosan/Ceramic Composition," *Macromol 2023, Vol. 3, Pages 326-342*, vol. 3, no. 2, pp. 326–342, Jun. 2023, doi: 10.3390/MACROMOL3020021.

[14] A. R. Amini, C. T. Laurencin, and S. P. Nukavarapu, "Bone Tissue Engineering: Recent Advances and Challenges," *Crit Rev Biomed Eng*, vol. 40, no. 5, p. 363, 2012, doi: 10.1615/CRITREVBIOMEDENG.V40.I5.10.

[15] S. Farjaminejad *et al.*, "Advances and Challenges in Polymer-Based Scaffolds for Bone Tissue Engineering: A Path Towards Personalized Regenerative Medicine," *Polymers (Basel)*, vol. 16, no. 23, Dec. 2024, doi: 10.3390/POLYM16233303.

[16] R. Florencio-Silva, G. R. D. S. Sasso, E. Sasso-Cerri, M. J. Simões, and P. S. Cerri, "Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells," *Biomed Res Int*, vol. 2015, p. 421746, 2015, doi: 10.1155/2015/421746.

[17] J. P. Henry and B. Bordoni, "Histology, Osteoblasts," *StatPearls*, May 2023, Accessed: Jul. 24, 2025. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK557792/

[18] A. G. Kurian, R. K. Singh, K. D. Patel, J. H. Lee, and H. W. Kim, "Multifunctional GelMA platforms with nanomaterials for advanced tissue therapeutics," *Bioact Mater*, vol. 8, p. 267, Feb. 2021, doi: 10.1016/J.BIOACTMAT.2021.06.027.

[19] T. Hasegawa *et al.*, "Matrix Vesicle-Mediated Mineralization and Osteocytic Regulation of Bone Mineralization," *Int J Mol Sci*, vol. 23, no. 17, p. 9941, Sep. 2022, doi: 10.3390/IJMS23179941.

[20] J. Kodama and T. Kaito, "Osteoclast Multinucleation: Review of Current Literature," *Int J Mol Sci*, vol. 21, no. 16, p. 5685, Aug. 2020, doi: 10.3390/IJMS21165685.

[21] G. Borciani, G. Montalbano, N. Baldini, G. Cerqueni, C. Vitale-Brovarone, and G. Ciapetti, "Co–culture systems of osteoblasts and osteoclasts: Simulating in vitro bone remodeling in regenerative approaches," *Acta Biomater*, vol. 108, pp. 22–45, May 2020, doi: 10.1016/j.actbio.2020.03.043.

[22] M. Prideaux, D. M. Findlay, and G. J. Atkins, "Osteocytes: The master cells in bone remodelling," *Curr Opin Pharmacol*, vol. 28, pp. 24–30, Jun. 2016, doi: 10.1016/J.COPH.2016.02.003.

[23] T. Hasegawa *et al.*, "Matrix Vesicle-Mediated Mineralization and Osteocytic Regulation of Bone Mineralization," *Int J Mol Sci*, vol. 23, no. 17, p. 9941, Sep. 2022, doi: 10.3390/IJMS23179941.

[24] H. C. Anderson, "Vesicles associated with calcification in the matrix of epiphyseal cartilage," *J Cell Biol*, vol. 41, no. 1, pp. 59–72, 1969, doi: 10.1083/JCB.41.1.59.

[25] J. M. Hughes *et al.*, "The Central Role of Osteocytes in the Four Adaptive Pathways of Bone's Mechanostat," *Exerc Sport Sci Rev*, vol. 48, no. 3, p. 140, Jul. 2020, doi: 10.1249/JES.0000000000000225.

[26] T. L. Andersen, P. R. Jensen, T. T. Sikjaer, L. Rejnmark, C. Ejersted, and J. M. Delaisse, "A Critical Role of the Bone Marrow Envelope in Human Bone Remodeling," *Journal of Bone and Mineral Research*, vol. 38, no. 6, pp. 918–928, Jun. 2023, doi: 10.1002/JBMR.4815.

[27] V. Everts *et al.*, "The bone lining cell: Its role in cleaning Howship's lacunae and initiating bone formation," *Journal of Bone and Mineral Research*, vol. 17, no. 1, pp. 77–90, Jan. 2002, doi: 10.1359/JBMR.2002.17.1.77;REQUESTEDJOURNAL:JOURNAL:15234681;WGROUP:STRING:PUBLICATION.

[28] I. Matic *et al.*, "Quiescent Bone Lining Cells Are a Major Source of Osteoblasts During Adulthood," *Stem Cells*, vol. 34, no. 12, p. 2930, Dec. 2016, doi: 10.1002/STEM.2474.

[29] A. M. F. S. Mohamed, "An Overview of Bone Cells and their Regulating Factors of Differentiation," *Malays J Med Sci*, vol. 15, no. 1, p. 4, 2008, Accessed: Jul. 27, 2025. [Online]. Available: https://pmc.ncbi.nlm.nih.gov/articles/PMC3341892/

[30] A. Zhang, S. Zhang, and C. Bian, "Mechanical properties of bovine cortical bone based on the automated ball indentation technique and graphics processing method," *J Mech Behav Biomed Mater*, vol. 78, pp. 321–328, Feb. 2018, doi: 10.1016/J.JMBBM.2017.11.039.

[31] E. Vigmond, "Encyclopedia of Biomedical Engineering | ScienceDirect," vol. Volume 1, 2019, Accessed: Jul. 26, 2025. [Online]. Available: http://www.sciencedirect.com:5070/referencework/9780128051443/encyclopedia-of-biomedical-engineering

[32] P. N. Soucacos, E. O. Johnson, and G. Babis, "An update on recent advances in bone regeneration," *Injury*, vol. 39, no. SUPPL.2, Sep. 2008, doi: 10.1016/S0020-1383(08)70009-3.

[33] J. D. Currey, "Bone and Natural Composites: Properties," *Encyclopedia of Materials: Science and Technology*, pp. 776–781, Jan. 2001, doi: 10.1016/B0-08-043152-6/00149-2.

[34] G. Zhu *et al.*, "Bone physiological microenvironment and healing mechanism: Basis for future bone-tissue engineering scaffolds," *Bioact Mater*, vol. 6, no. 11, p. 4110, Nov. 2021, doi: 10.1016/J.BIOACTMAT.2021.03.043.

[35] J. Ramier *et al.*, "From design of bio-based biocomposite electrospun scaffolds to osteogenic differentiation of human mesenchymal stromal cells," *J Mater Sci Mater Med*, vol. 25, no. 6, pp. 1563–1575, Jun. 2014, doi: 10.1007/S10856-014-5174-8/FIGURES/6.

[36] B. N. Brown and S. F. Badylak, "Extracellular matrix as an inductive scaffold for functional tissue reconstruction," *Transl Res*, vol. 163, no. 4, p. 268, 2013, doi: 10.1016/J.TRSL.2013.11.003.

[37] P. You *et al.*, "Composite bioink incorporating cell-laden liver decellularized extracellular matrix for bioprinting of scaffolds for bone tissue engineering," *Biomaterials Advances*, vol. 165, p. 214017, Dec. 2024, doi: 10.1016/J.BIOADV.2024.214017.

[38] S. Weiner and H. D. Wagner, "The material bone: Structure-mechanical function relations," *Annual Review of Materials Science*, vol. 28, no. 1, pp. 271–298, Aug. 1998, doi: 10.1146/ANNUREV.MATSCI.28.1.271/CITE/REFWORKS.

[39] V. T. Athanasiou, D. J. Papachristou, A. Panagopoulos, A. Saridis, C. D. Scopa, and P. Megas, "Histological comparison of autograft, allograft-DBM, xenograft, and synthetic grafts in a trabecular bone defect: an experimental study in rabbits.," *Med Sci Monit*, vol. 16, no. 1, pp. BR24-31, Jan. 2010.

[40] B. Baroli, "From natural bone grafts to tissue engineering therapeutics: Brainstorming on pharmaceutical formulative requirements and challenges," *J Pharm Sci*, vol. 98, no. 4, pp. 1317–1375, 2009, doi: 10.1002/JPS.21528.

[41] B. J. Hartigan and R. L. Makowiec, "Use of bone graft substitutes and bioactive materials in treatment of distal radius fractures," *Fractures and Injuries of the Distal Radius and Carpus: The Cutting Edge*, pp. 241–245, Dec. 2008, doi: 10.1016/b978-1-4160-4083-5.00025-1.

[42] A. R. Gazdag, J. M. Lane, D. Glaser, and R. A. Forster, "Alternatives to Autogenous Bone Graft: Efficacy and Indications," *Journal of the American Academy of Orthopaedic Surgeons*, vol. 3, no. 1, pp. 1–8, Jan. 1995, doi: 10.5435/00124635-199501000-00001.

[43] D. N. Bracey *et al.*, "A porcine xenograft-derived bone scaffold is a biocompatible bone graft substitute: An assessment of cytocompatibility and the alpha-Gal epitope," *Xenotransplantation*, vol. 26, no. 5, Sep. 2019, doi: 10.1111/XEN.12534.

[44] J. M. Seong, B. C. Kim, J. H. Park, I. K. Kwon, A. Mantalaris, and Y. S. Hwang, "Stem cells in bone tissue engineering," *Biomedical Materials*, vol. 5, no. 6, p. 062001, Oct. 2010, doi: 10.1088/1748-6041/5/6/062001.

[45] R. Augustine, M. Gezek, V. K. Nikolopoulos, P. L. Buck, N. S. Bostanci, and G. Camci-Unal, "Stem Cells in Bone Tissue Engineering: Progress, Promises and Challenges," *Stem Cell Rev Rep*, vol. 20, no. 7, pp. 1692–1731, Oct. 2024, doi: 10.1007/s12015-024-10738-y.

[46] X. Gao, J. J. Ruzbarsky, J. E. Layne, X. Xiao, and J. Huard, "Stem Cells and Bone Tissue Engineering," *Life*, vol. 14, no. 3, p. 287, Feb. 2024, doi: 10.3390/life14030287.

[47] E. Kalaiselvan *et al.*, "Bone Marrow-Derived Mesenchymal Stem Cell-Laden Nanocomposite Scaffolds Enhance Bone Regeneration in Rabbit Critical-Size Segmental Bone Defect Model," *J Funct Biomater*, vol. 15, no. 3, p. 66, Mar. 2024, doi: 10.3390/JFB15030066/S1.

[48] W. Liang *et al.*, "Current status of nano-embedded growth factors and stem cells delivery to bone for targeted repair and regeneration," *J Orthop Translat*, vol. 50, pp. 257–273, Jan. 2025, doi: 10.1016/J.JOT.2024.12.006.

[49] W. Mende, R. Götzl, Y. Kubo, T. Pufe, T. Ruhl, and J. P. Beier, "The Role of Adipose Stem Cells in Bone Regeneration and Bone Tissue Engineering," *Cells*, vol. 10, no. 5, p. 975, May 2021, doi: 10.3390/CELLS10050975.

[50] É. R. Oliveira *et al.*, "Advances in Growth Factor Delivery for Bone Tissue Engineering," *Int J Mol Sci*, vol. 22, no. 2, p. 903, Jan. 2021, doi: 10.3390/IJMS22020903.

[51] L. Zhan *et al.*, "Advances in growth factor-containing 3D printed scaffolds in orthopedics," *BioMedical Engineering OnLine 2025 24:1*, vol. 24, no. 1, pp. 1–23, Feb. 2025, doi: 10.1186/S12938-025-01346-Z.

[52] L. M. Caballero Aguilar, S. M. Silva, and S. E. Moulton, "Growth factor delivery: Defining the next generation platforms for tissue engineering," *Journal of Controlled Release*, vol. 306, pp. 40–58, Jul. 2019, doi: 10.1016/J.JCONREL.2019.05.028.

[53] M. J. Yaszemski, R. G. Payne, W. C. Hayes, R. Langer, and A. G. Mikos, "Evolution of bone transplantation: Molecular, cellular and tissue strategies to engineer human bone," *Biomaterials*, vol. 17, no. 2, pp. 175–185, 1996, doi: 10.1016/0142-9612(96)85762-0.

[54] A. Garimella, S. B. Ghosh, and S. Bandyopadhyay-Ghosh, "Biomaterials for bone tissue engineering: achievements to date and future directions," *Biomed Mater*, vol. 20, no. 1, Jan. 2024, doi: 10.1088/1748-605X/AD967C.

[55] S. Saurav *et al.*, "Harnessing Natural Polymers for Nano-Scaffolds in Bone Tissue Engineering: A Comprehensive Overview of Bone Disease Treatment," *Current Issues in Molecular Biology 2024, Vol. 46, Pages 585-611*, vol. 46, no. 1, pp. 585–611, Jan. 2024, doi: 10.3390/CIMB46010038.

[56] L. Guo *et al.*, "The role of natural polymers in bone tissue engineering," *Journal of Controlled Release*, vol. 338, pp. 571–582, Oct. 2021, doi: 10.1016/J.JCONREL.2021.08.055.

[57] S. Pramanik, S. Kharche, N. More, D. Ranglani, G. Singh, and G. Kapusetti, "Natural Biopolymers for Bone Tissue Engineering: A Brief Review," *Engineered Regeneration*, vol. 4, no. 2, pp. 193–204, Jun. 2023, doi: 10.1016/J.ENGREG.2022.12.002.

[58] M. Pandey, G. R. Suman, and K. Deshmukh, "Electrospinning and nonelectrospinning techniques for the fabrication of nanofibers: Mechanisms, process parameters, and key technical challenges," *Functionalized Nanofibers: Synthesis and Industrial Applications*, pp. 1–30, Jan. 2023, doi: 10.1016/B978-0-323-99461-3.00011-X.

[59] X. ; Yan *et al.*, "Functionalization of Electrospun Nanofiber for Bone Tissue Engineering," *Polymers 2022, Vol. 14, Page 2940*, vol. 14, no. 14, p. 2940, Jul. 2022, doi: 10.3390/POLYM14142940.

[60] M. R. Singh, S. Patel, and D. Singh, "Natural polymer-based hydrogels as scaffolds for tissue engineering," *Nanobiomaterials in Soft Tissue Engineering: Applications of Nanobiomaterials*, pp. 231–260, Jan. 2016, doi: 10.1016/B978-0-323-42865-1.00009-X.

[61] L. Parmentier and S. Van Vlierberghe, "Natural hydrogels for bone tissue engineering," *Tissue Engineering Using Ceramics and Polymers, Third Edition*, pp. 743–770, Jan. 2022, doi: 10.1016/B978-0-12-820508-2.00009-X.

[62] J. He *et al.*, "Chitosan-coated hydroxyapatite and drug-loaded polytrimethylene carbonate/polylactic acid scaffold for enhancing bone regeneration," *Carbohydr Polym*, vol. 253, p. 117198, Feb. 2021, doi: 10.1016/J.CARBPOL.2020.117198.

[63] Z. Feng, X. Su, T. Wang, X. Sun, H. Yang, and S. Guo, "The Role of Microsphere Structures in Bottom-Up Bone Tissue Engineering," *Pharmaceutics 2023, Vol. 15, Page 321*, vol. 15, no. 2, p. 321, Jan. 2023, doi: 10.3390/PHARMACEUTICS15020321.

[64] P. Couvreur, M. J. Blanco-Prieto, F. Puisieux, B. Roques, and E. Fattal, "Multiple emulsion technology for the design of microspheres containing peptides and oligopeptides," *Adv Drug Deliv Rev*, vol. 28, no. 1, pp. 85–96, Oct. 1997, doi: 10.1016/S0169-409X(97)00052-5.

[65] Z. Cai *et al.*, "Microspheres in bone regeneration: Fabrication, properties and applications," *Mater Today Adv*, vol. 16, p. 100315, Dec. 2022, doi: 10.1016/J.MTADV.2022.100315.

[66] F. Donnaloja, E. Jacchetti, M. Soncini, and M. T. Raimondi, "Natural and Synthetic Polymers for Bone Scaffolds Optimization," *Polymers (Basel)*, vol. 12, no. 4, p. 905, Apr. 2020, doi: 10.3390/POLYM12040905.

[67] R. K. Gupta, P. Guha, and P. P. Srivastav, "Natural polymers in bio-degradable/edible film: A review on environmental concerns, cold plasma technology and nanotechnology application on food packaging- A recent trends," *Food Chemistry Advances*, vol. 1, Oct. 2022, doi: 10.1016/j.focha.2022.100135.

[68] J. He *et al.*, "Chitosan-coated hydroxyapatite and drug-loaded polytrimethylene carbonate/polylactic acid scaffold for enhancing bone regeneration," *Carbohydr Polym*, vol. 253, p. 117198, Feb. 2021, doi: 10.1016/J.CARBPOL.2020.117198.

[69] R. Auras, B. Harte, and S. Selke, "An Overview of Polylactides as Packaging Materials," *Macromol Biosci*, vol. 4, no. 9, pp. 835–864, Sep. 2004, doi: 10.1002/MABI.200400043.

[70] Z. Pan and J. Ding, "Poly(lactide-co-glycolide) porous scaffolds for tissue engineering and regenerative medicine," *Interface Focus*, vol. 2, no. 3, pp. 366–377, 2012, doi: 10.1098/RSFS.2011.0123.

[71] C. Zong *et al.*, “Biocompatibility and bone-repairing effects: Comparison between porous poly-lactic-Co-glycolic acid and nano-hydroxyapatite/poly(lactic acid) scaffolds,” *J Biomed Nanotechnol*, vol. 10, no. 6, pp. 1091–1104, 2014, doi: 10.1166/jbn.2014.1696.

[72] C. Zhao, W. Liu, M. Zhu, C. Wu, and Y. Zhu, “Bioceramic-based scaffolds with antibacterial function for bone tissue engineering: A review,” *Bioact Mater*, vol. 18, pp. 383–398, Dec. 2022, doi: 10.1016/J.BIOACTMAT.2022.02.010.

[73] P. Diaz-Rodriguez, M. Sánchez, and M. Landin, “Drug-Loaded Biomimetic Ceramics for Tissue Engineering,” *Pharmaceutics*, vol. 10, no. 4, p. 272, Dec. 2018, doi: 10.3390/PHARMACEUTICS10040272.

[74] I. Ielo, G. Calabrese, G. De Luca, and S. Conoci, “Recent Advances in Hydroxyapatite-Based Biocomposites for Bone Tissue Regeneration in Orthopedics,” *International Journal of Molecular Sciences 2022, Vol. 23, Page 9721*, vol. 23, no. 17, p. 9721, Aug. 2022, doi: 10.3390/IJMS23179721.

[75] T. Bedir, E. Altan, K. Aranci-Ciftci, and O. Gunduz, “Bioceramics,” *Stem Cell Biology and Regenerative Medicine*, vol. 74, pp. 175–203, 2023, doi: 10.1007/978-3-031-35832-6_6.

[76] L. Gremillard and J. Chevalier, “Ceramic biomaterials for orthopaedic prostheses,” Techniques de l’Ingénieur. Accessed: Dec. 06, 2025. [Online]. Available: https://www.techniques-ingenieur.fr/en/resources/article/ti589/ceramic-materials-for-orthopedic-prostheses-med7100/v1/orthopedic-prostheses-1

[77] A. El-Ghannam, “Bone reconstruction: from bioceramics to tissue engineering,” *Expert Rev Med Devices*, vol. 2, no. 1, pp. 87–101, 2005, doi: 10.1586/17434440.2.1.87.

[78] L. C. Gerhardt and A. R. Boccaccini, “Bioactive Glass and Glass-Ceramic Scaffolds for Bone Tissue Engineering,” *Materials*, vol. 3, no. 7, p. 3867, 2010, doi: 10.3390/MA3073867.

[79] G. Kaur *et al.*, “Mechanical properties of bioactive glasses, ceramics, glass-ceramics and composites: State-of-the-art review and future challenges,” *Materials Science and Engineering: C*, vol. 104, p. 109895, Nov. 2019, doi: 10.1016/J.MSEC.2019.109895.

[80] S. Mehdi Mirhadi, H. Ghomi, and R. Emadi, “CHARACTERIZATION OF HIGHLY POROUS 63S BIOACTIVE GLASS SCAFFOLDS FABRICATED BY TWO FOAMING METHODS,” *Ceramics-Silikáty*, vol. 59, no. 3, pp. 194–201, 2015.

[81] Y. Mori *et al.*, “A Review of the Impacts of Implant Stiffness on Fracture Healing,” *Applied Sciences 2024, Vol. 14, Page 2259*, vol. 14, no. 6, p. 2259, Mar. 2024, doi: 10.3390/APP14062259.

[82] E. Marin and A. Lanzutti, “Biomedical Applications of Titanium Alloys: A Comprehensive Review,” *Materials 2024, Vol. 17, Page 114*, vol. 17, no. 1, p. 114, Dec. 2023, doi: 10.3390/MA17010114.

[83] L. H. Xu, L. T. Ye, J. Y. Wang, and X. Qiu, “Magnesium-based alloys for bone regeneration and beyond: A review of advances and therapeutic prospects,” *Regen Ther*, vol. 30, pp. 977–983, Dec. 2025, doi: 10.1016/J.RETH.2025.10.010.

[84] J. Ye *et al.*, “3D printed porous magnesium metal scaffolds with bioactive coating for bone defect repair: enhancing angiogenesis and osteogenesis,” *J Nanobiotechnology*, vol. 23, no. 1, Dec. 2025, doi: 10.1186/S12951-025-03222-3.

[85] C. Liu *et al.*, "Biodegradable Mg-Cu alloys with enhanced osteogenesis, angiogenesis, and long-lasting antibacterial effects," *Scientific Reports 2016 6:1*, vol. 6, no. 1, pp. 27374-, Jun. 2016, doi: 10.1038/srep27374.

[86] S. Castiglioni, A. Cazzaniga, L. Locatelli, and J. A. M. Maier, "Silver Nanoparticles in Orthopedic Applications: New Insights on Their Effects on Osteogenic Cells," *Nanomaterials (Basel)*, vol. 7, no. 6, Jun. 2017, doi: 10.3390/NANO7060124.

[87] X. Zhang *et al.*, "Functionalized mesoporous bioactive glass scaffolds for enhanced bone tissue regeneration," *Scientific Reports 2016 6:1*, vol. 6, no. 1, pp. 19361-, Jan. 2016, doi: 10.1038/srep19361.

[88] A. Kurzyk, "Mesenchymal Stem Cell Seeding on 3D Scaffolds," *Methods Mol Biol*, vol. 2429, pp. 417–434, 2022, doi: 10.1007/978-1-0716-1979-7_28.

[89] R. Sreena, G. Raman, G. Manivasagam, and A. J. Nathanael, "Bioactive glass-polymer nanocomposites: a comprehensive review on unveiling their biomedical applications," *J Mater Chem B*, vol. 12, no. 44, pp. 11278–11301, Oct. 2024, doi: 10.1039/D4TB01525H.

[90] Z. Yang, G. Yin, S. Sun, and P. Xu, "Medical applications and prospects of polylactic acid materials," *iScience*, vol. 27, no. 12, p. 111512, Dec. 2024, doi: 10.1016/J.ISCI.2024.111512.

[91] F. Baino and E. Fiume, "Elastic Mechanical Properties of 45S5-Based Bioactive Glass–Ceramic Scaffolds," *Materials 2019, Vol. 12, Page 3244*, vol. 12, no. 19, p. 3244, Oct. 2019, doi: 10.3390/MA12193244.

[92] A. C. Jones, C. H. Arns, D. W. Hutmacher, B. K. Milthorpe, A. P. Sheppard, and M. A. Knackstedt, "The correlation of pore morphology, interconnectivity and physical properties of 3D ceramic scaffolds with bone ingrowth," *Biomaterials*, vol. 30, no. 7, pp. 1440–1451, Mar. 2009, doi: 10.1016/J.BIOMATERIALS.2008.10.056.

[93] Y. Lv *et al.*, "Metal Material, Properties and Design Methods of Porous Biomedical Scaffolds for Additive Manufacturing: A Review," *Front Bioeng Biotechnol*, vol. 9, p. 641130, Mar. 2021, doi: 10.3389/FBIOE.2021.641130/XML.

[94] S. Mehdi Mirhadi, H. Ghomi, and R. Emadi, "Characterisation of highly porous 63S bioactive glass scaffolds fabricated by two foaming methods," *Ceramics-Silikáty*, vol. 59, no. 3, pp. 194–201, 2015.

[95] V. Guarino, F. Causa, and L. Ambrosio, "Porosity and Mechanical Properties Relationship in PCL Porous Scaffolds," *Journal of Applied Biomaterials and Biomechanics*, vol. 5, no. 3, pp. 149–157, 2007, doi: 10.1177/228080000700500303.

[96] P. Ma, W. Wu, Y. Wei, L. Ren, S. Lin, and J. Wu, "Biomimetic gelatin/chitosan/polyvinyl alcohol/nano-hydroxyapatite scaffolds for bone tissue engineering," *Mater Des*, vol. 207, p. 109865, Sep. 2021, doi: 10.1016/J.MATDES.2021.109865.

[97] A. S. Pádua, L. Figueiredo, J. C. Silva, and J. P. Borges, "Chitosan scaffolds with mesoporous hydroxyapatite and mesoporous bioactive glass," *Prog Biomater*, vol. 12, no. 2, pp. 137–153, Jun. 2023, doi: 10.1007/S40204-023-00217-X.

[98] H. Iqbal *et al.*, "Chitosan/hydroxyapatite (HA)/hydroxypropylmethyl cellulose (HPMC) spongy scaffolds-synthesis and evaluation as potential alveolar bone substitutes," *Colloids Surf B Biointerfaces*, vol. 160, pp. 553–563, Dec. 2017, doi: 10.1016/J.COLSURFB.2017.09.059.

[99] J. Wei *et al.*, "Preparation and characterization of bioactive mesoporous wollastonite - Polycaprolactone composite scaffold," *Biomaterials*, vol. 30, no. 6, pp. 1080–1088, Feb. 2009, doi: 10.1016/J.BIOMATERIALS.2008.10.046.

[100] M. A. Ibrahim, G. M. Nasr, R. M. Ahmed, and N. A. Kelany, "Physical characterization, biocompatibility, and antimicrobial activity of polyvinyl alcohol/sodium alginate blend doped with TiO2 nanoparticles for wound dressing applications," *Scientific Reports 2024 14:1*, vol. 14, no. 1, pp. 5391-, Mar. 2024, doi: 10.1038/s41598-024-55818-8.

[101] N. Y. Patrawalla, N. S. Kajave, and V. Kishore, "A comparative study of bone bioactivity and osteogenic potential of different bioceramics in methacrylated collagen hydrogels," *J Biomed Mater Res A*, vol. 111, no. 2, p. 224, Feb. 2022, doi: 10.1002/JBM.A.37452.

[102] H. Li, Y. Cong, S. Zhou, and J. Zhang, "Cutting-Based Manufacturing and Surface Wettability of Microtextures on Pure Titanium," *Materials*, vol. 17, no. 15, p. 3861, Aug. 2024, doi: 10.3390/MA17153861.

[103] M. A. A. Ansari, P. Makwana, B. Dhimmar, R. Vasita, P. K. Jain, and H. S. Nanda, "Design and development of 3D printed shape memory triphasic polymer-ceramic bioactive scaffolds for bone tissue engineering," *J Mater Chem B*, vol. 12, no. 28, pp. 6886–6904, Jul. 2024, doi: 10.1039/D4TB00785A.

[104] F. Liu, H. Mishbak, and P. Bartolo, "Hybrid polycaprolactone/hydrogel scaffold fabrication and in-process plasma treatment using PABS," *Int J Bioprint*, vol. 5, no. 1, p. 174, 2018, doi: 10.18063/IJB.V5I1.174.

[105] X. Huang *et al.*, "Sustained zinc release in cooperation with CaP scaffold promoted bone regeneration via directing stem cell fate and triggering a pro-healing immune stimuli," *J Nanobiotechnology*, vol. 19, no. 1, pp. 207-, Dec. 2021, doi: 10.1186/S12951-021-00956-8/TABLES/2.

[106] H. Wei, J. Cui, K. Lin, J. Xie, and X. Wang, "Recent advances in smart stimuli-responsive biomaterials for bone therapeutics and regeneration," *Bone Research 2022 10:1*, vol. 10, no. 1, pp. 17-, Feb. 2022, doi: 10.1038/s41413-021-00180-y.