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Magnesium and its Alloys as Biomaterial for Bone Repair: Advances, Challenges and Future Direction in Mechanical and Tissue Engineering Research

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Abstract: Interest in the application of biodegradable bone screw is driven by the increasing knowledge on biomedical materials and tissue engineering field. Currently, various polymeric- as well as metallic-based materials have been used as degradable bone screw. Biodegradable material is a desirable feature for bone screw since the goal is that it uses as a temporary structure holding a growing bone tissue until the bone fracture has sufficiently healed. Among others, magnesium and its alloys have a potential chance to serve as biodegradable bone screw applications, as it has mechanical properties similar to natural bone, lightweight, and biocompatible approved. This article aims to report current development and future potential use of magnesium-based metal for bone screw application. Techniques on manufacturing process, mechanical performance, and biocompatibility assessment of magnesium and its alloys are highlighted.

Keywords: Magnesium; Bone tissue; Manufacturing process; Biocompatibility assessment.

1. Human Bone Tissue

Bone is an open cell composite material composed of a complex vascular system and a significant fraction of protein-related materials. Bone also like other connective tissues, which has cells, fibers and a matrix. In bone, the extracellular matrix is calcified and the fibers, which are collagen, are very highly ordered. At the architectural level, bone is made up of two types of different tissues tightly packed together. The outer shell is of dense compact or cortical bone, while the inner core is comprised of porous cellular, cancellous or trabecular bone. Although both bone types comprise the same composition, each one contains different proportions of the organic and inorganic materials, degree of porosity and organization. The porosity of cortical bone is 5-10%, while in cancellous bones the porosity ranges between 75% and 90% [1,2]. The cells of the bone are developed into one of three main structures, osteoblasts, osteoclasts or osteocytes [3].

Cortical bone is highly dense and contains cylindrically organized osteons, also known as Haversian system, ranges between 10 to 500 μm. It is notable that the Haversian canal is composed of blood vessels in parallel to the long axis of the bone. These blood vessels are interconnected with

vessels on the surface of the bone through perforating canals [4,5]. Contrary to cortical bone, cancellous bone is highly porous, consisting of an interconnected network of trabeculae which is about 50-300 μm in diameter. Figure 1 illustrates the basic architecture of the bone [4].

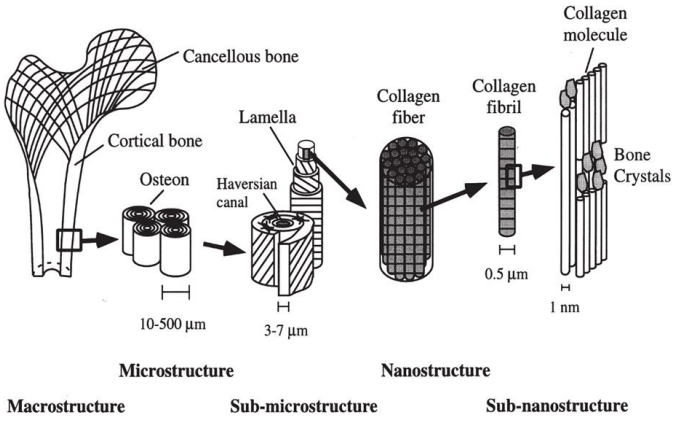

Figure 1. Basic structure of human bone tissue

Bone-related illnesses and fractures are pressing healthcare concerns, particularly among elderly individuals [6]. These conditions are often the result of trauma, congenital abnormalities, tumours, or various diseases and frequently necessitate surgical treatment. As the population continues to age, the incidence of such issues is expected to rise. For instance, Canada reports approximately 30,000 hip fractures annually, with up to 6,000 fatalities associated with these injuries [7-9].

To address bone defects, bone grafts and substitutes play a crucial role in both reconstruction and regeneration of damaged bone tissue [10]. In North America and Europe, over a million bone grafting surgeries are conducted every year. These grafts support bone growth and restore structural integrity to damaged areas. There are three main categories of bone grafts used in clinical settings: autografts, allografts, and synthetic alternatives [10,11].

Autografts involve harvesting bone from one site in a patient's body and transplanting it to another. While this method is highly successful, it requires an additional procedure, which can lead to complications at the donor site [12]. Allografts, in contrast, use bone from a deceased donor or a living individual, eliminating the need for a second surgery on the recipient but typically yielding lower success rates. Synthetic bone substitutes, made from ceramics, polymers, or composite materials, are used to bridge bone gaps and stimulate new growth. Their key advantage lies in mass production and avoidance of donor-site complications [13].

Traditional bone repair methods—autografts and allografts—have limitations. Autografts, often considered the gold standard, are costly but rich in live bone-forming cells and supportive biological factors [14]. They offer the necessary triad for bone regeneration: osteogenesis, osteo-induction, and osteo-conduction. However, the quantity of bone that can be harvested is limited, and the procedure can cause donor site pain and structural damage, along with difficulties in shaping the harvested tissue [14,15].

Allografts offer benefits such as reduced hospital time, lower costs, and sufficient supply, but they come with challenges including immune rejection, risk of disease transmission, size mismatch, and lower mechanical integrity [16]. Despite their use, these methods don't always lead to ideal outcomes, and the global shortage of suitable donor tissues limits broader application [17]. To overcome these obstacles, synthetic bone graft substitutes have been explored. An ideal substitute should be biocompatible, biodegradable, cost-efficient, and mimic the structural and functional properties of natural bone. However, no single solution has yet fully met these criteria [18,19].

In response, bone tissue engineering has emerged as a promising alternative. This multidisciplinary field integrates biomaterials, biological signals, and living cells to foster bone regeneration. Successful bone implants must not only have the correct chemical composition but also replicate the physical and mechanical traits of natural bone. While dense metal implants are common, they often cause problems such as stiffness mismatch with natural bone and instability due to poor integration with surrounding tissue [20].

To address this, engineered 3D scaffolds, constructed from biodegradable polymers or ceramics that are used as platforms for cultivating bone-forming cells in vitro [21-23]. Recently, more minimally invasive methods have been developed using injectable systems [24]. Injectable hydrogels, such as collagen, alginate, or fibrin, have been investigated to deliver cells for bone repair [25]. However, many of these materials cannot conform to irregular bone defects or fit into complex 3D mold designs.

Tomonori Matsuno (2010) introduced a novel injectable composite scaffold using β-TCP beads combined with alginate. This system offers immediate gelation upon injection and is well-suited to filling irregular bone cavities. The scaffold serves both as a structural framework for bone-forming cells and as a delivery vehicle for growth factors. Uniform $CaCl_2$-coated β-TCP beads were selected to improve mechanical properties. In vivo studies showed that this composite promoted bone-like tissue formation even without added osteogenic agents. Nonetheless, the mechanical strength achieved was relatively low—approximately 69.0±4.6 kPa—compared to natural bone, which may lead to bone resorption and eventual implant loosening due to inadequate load-bearing capacity [26]. Hence, ensuring strong load transfer and stable fixation remains a priority in implant design. Current advancements in tissue engineering are exploring porous materials that better replicate the structure of natural bone. Given that bone is naturally porous, this approach is supported by physiological reasoning and holds promise for the next generation of orthopaedic materials.

2. Porous Metal Properties for Bone Substitute

Porous metal implants serve as structural supports that facilitate tissue and cell adhesion, proliferation, and differentiation, ultimately aiding in the regeneration of healthy bone or soft tissue to restore function [27]. For these implants to be effective, they must meet several key criteria: mechanical compatibility, biocompatibility, bioactivity, controlled degradation (particularly for resorbable materials), favorable cellular response, and well-defined architectural features—including pore size, porosity, and surface characteristics [28,30]. During the healing or regeneration process, the implant must maintain both mechanical strength and biological functionality [31-33]. The essential properties required for bone scaffolds can be grouped into three major categories, i.e., mechanical, structural design, and biocompatibility (including biodegradation) as presented below.

2.1. Mechanical Properties

Implants used in structural bone repair must offer sufficient mechanical support to preserve the volume and stability of the tissue, thereby enabling successful regeneration [34,35]. These implants must be robust enough to withstand physiological loads without fragmenting or releasing particles, and they must not cause mechanical damage to surrounding tissues, whether soft or hard [36]. The mechanical properties most critical to match are stiffness, strength, and fatigue resistance.

When the stiffness of an implant is significantly greater than that of native bone, it can lead to stress concentration in the bone, potentially resulting in bone degradation or failure. Conversely, if the implant is too flexible, stress can accumulate within the implant itself, leading to mechanical failure or bone resorption due to underuse. This phenomenon, known as stress shielding [37], disrupts normal bone remodelling and impedes healing. A weakening of the bone–implant interface can lead to the development of fibrous tissue, which increases relative motion between the implant

and bone under load. This instability often causes patient discomfort and, over time, necessitates revision surgery [38,39].

2.2. Structural Design

For metallic implants to effectively support bone regeneration, they must possess a porous architecture. Features such as pore size, porosity, and interconnectivity significantly influence cell penetration, vascularization, and nutrient exchange [40,41]. A scaffold must enable cell seeding, migration, extracellular matrix deposition, and the transport of oxygen and nutrients to and from the implant site. High porosity, typically ranging between 50–90%, along with pore sizes in the optimal range of 100–500 μm, has been shown to promote cell ingrowth and vascularization [42,43].

2.3. Biocompatibility and Biodegradation

Biocompatibility is a critical non-mechanical requirement for any bone implant. A biocompatible material can remain in contact with bodily tissues without causing significant adverse reactions. This property encompasses more than toxicity; it includes all negative biological effects caused by the material [44,45].

An ideal scaffold must be osteoconductive, promoting the attachment, proliferation, and matrix formation of bone cells on its surfaces and within its pores. It should also possess osteo-inductive capabilities, which involve recruiting progenitor cells and encouraging new bone formation through biochemical signaling. Furthermore, successful implants must support angiogenesis—the formation of new blood vessels—within a few weeks of implantation to ensure proper oxygen and nutrient delivery [46].

While metallic scaffolds provide structural support, they should not remain in the body indefinitely. Long-term presence can lead to complications such as stress shielding, interfacial instability, and mechanical or electrochemical degradation, all of which may result in adverse biological reactions [47]. Depending on the clinical approach, scaffolds may be pre-seeded with osteoprogenitor cells before implantation, or they may be implanted directly into the defect site [48]. In either case, the material should degrade safely and at a rate that aligns with the pace of natural tissue regeneration [49].

Biodegradation and corrosion resistance is a vital consideration when selecting metallic materials for implants. The human body contains fluids that are inherently corrosive, and as a result, metallic implants are prone to degradation over time. Corrosion can lead to the release of toxic metal ions, compromise implant integrity, and shorten the device's lifespan. These effects may necessitate additional surgical procedures and pose broader risks to patient health [50].

3. Porous Metals for Biomedical Applications

Biocompatible porous metals are widely used in orthopaedic surgery as scaffold materials to replace damaged bone or to support bone regeneration in defect sites. These materials not only provide mechanical stability but also facilitate tissue integration by promoting bone ingrowth, thereby enhancing the fixation between the implant and the host bone. When designing new porous metallic scaffolds, several critical factors must be taken into account. The material must be non-toxic and biocompatible [51]. In addition, the scaffold should possess high porosity and a structural architecture that closely mimics the cancellous (spongy) bone, which is essential for nutrient exchange and tissue infiltration. Due to the mechanical reliability and biological compatibility of the porous metals, currently the most commonly investigated porous metals for orthopedic use are including: Titanium (Ti), Tantalum (Ta), and Magnesium (Mg) based metals, that will be presented in the following chapter.

3.1. Porous Titanium

Titanium and its alloys have gained considerable attention in the medical field, particularly for dental and orthopedic applications, thanks to their favorable mechanical performance (e.g., high strength and toughness), excellent biocompatibility, and chemical inertness [50,52]. In recent years, extensive research has focused on developing porous titanium scaffolds to better match the elastic modulus of native bone and enhance the biological integration at the bone–implant interface [53].

Various fabrication techniques exist for creating porous titanium structures, including metal powder sintering, the space-holder technique, freeze casting, and additive manufacturing. Other researcher has been introduced a modified sponge replication method that produces highly porous structures with interconnected pores, which are ideal for promoting vascularization and tissue ingrowth [54]. This method was further enhanced by combining it with anodization, which resulted in elongated pore formation that increased compressive strength, along with a bioactive nanoporous TiO_2 surface coating to further improve biocompatibility.

3.2. Porous Tantalum

Tantalum is another promising metal for orthopedic implants due to its excellent resistance to corrosion and demonstrated bioactivity in vivo [55,56]. It forms an appetite-like layer when immersed in simulated body fluids, which aids in forming a strong biological bond with bone. Both in vitro and animal studies have confirmed that porous tantalum supports bone tissue infiltration and secure mechanical fixation [57,58].

In addition to its excellent biocompatibility and bioactivity, tantalum offers a low elastic modulus, high surface friction, and outstanding osseointegration characteristics [59–61]. Despite these advantages, processing tantalum remains challenging due to its extremely high melting point (3017°C) and strong affinity for oxygen. These factors make it difficult to fabricate using traditional manufacturing techniques.

3.3. Porous Magnesium (Mg)

Magnesium and its alloys are exceptionally light, with densities ranging from 1.74 to 2.0 g/cm^3, significantly lower than that of titanium alloys (approximately 4.4–4.5 g/cm^3) and comparable to natural bone (1.8–2.1 g/cm^3). Magnesium exhibits better fracture toughness than ceramics and has an elastic modulus (41–45GPa) that closely matches bone, helping to reduce stress shielding. However, pure magnesium corrodes rapidly in chloride-rich physiological environments due to its low standard electrode potential (–2.37V) [62,63].

As the fourth most abundant cation in the human body—after calcium, potassium, and sodium—magnesium plays a critical role in many physiological processes. The human body contains approximately 24 grams of magnesium, with about half stored in bone and muscle, while only 1% resides in extracellular fluid [63]. Magnesium is essential for intracellular processes such as DNA stabilization, cell proliferation, apoptosis, and genomic repair [64,65]. It is primarily transported between intra- and extracellular compartments via diffusion which have been presented elsewhere [66]. The intracellular magnesium concentrations remain tightly regulated and can be affected when extracellular levels drop below 0.2 mmol/L [67].

One significant advantage of using magnesium as a biomaterial is its biodegradability, which may eliminate the need for a second surgery to remove the implant. Recent developments in magnesium–calcium (Mg-Ca) alloys have shown promise as biodegradable materials for orthopaedic applications, with successful in vitro and in vivo performance. Although concerns have been raised regarding the potential toxicity of magnesium degradation products, studies indicate that excess magnesium is efficiently excreted in urine [68]. The degradation behaviour of magnesium is influenced by its alloy composition and occurs through electrochemical corrosion processes in aqueous environments.

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3.4. Biodegradation of Magnesium

Compared to other metals, magnesium is known for its bioresorbable properties. Its first use in orthopedic applications where magnesium plates have been applied for fracture fixation [69]. However, these early attempts failed due to rapid corrosion and gas formation, with implants dissolving in under eight days [69,70].

Further studies were conducted by Seelig [71], who implanted chemically pure magnesium in animals. These experiments also reported gas formation and the appearance of magnesium salts at the implantation site. Modern in vitro analyses have identified the by-products of magnesium degradation as hydrogen gas and magnesium hydroxide ($Mg(OH)_2$) [72]. The hydrogen is released faster than surrounding tissues can absorb, leading to temporary gas pockets beneath the skin. Although these pockets and the residual magnesium are clearly visible within two weeks post-implantation, they typically resolve as the material is fully resorbed and integrated with surrounding tissue.

In physiological saline, magnesium and its alloys degrade through electrochemical reactions, with the specific corrosion pathways influenced by the presence of alloying elements. Understanding and controlling these reactions is key to developing safe and effective biodegradable magnesium-based implants. The electrochemical reaction of magnesium corrosion is as follows [72,73]:

$$Mg(s) + 2H2O \rightarrow Mg(OH)2(s)+H2(g) \quad (1)$$

$$Mg(s) + 2Cl{-}(aq) \rightarrow MgCl2 \quad (2)$$

$$Mg(OH)2(s) + 2Cl{-}(aq) \rightarrow MgCl2 + 2OH{-}(aq) \quad (3)$$

In the initial corrosion reaction (1), magnesium reacts with water to form magnesium hydroxide ($Mg(OH)_2$), which appears as a gray film on the metal surface. This process is also accompanied by the release of hydrogen gas bubbles. Additionally, magnesium can directly react with chloride ions, resulting in the formation of magnesium chloride ($MgCl_2$), as shown in reaction (2). Magnesium chloride can also form through the interaction of $Mg(OH)_2$ with chloride ions, as illustrated in reaction (3) [73]. Since $MgCl_2$ is highly soluble in bodily fluids, the protective layer of $Mg(OH)_2$ is disrupted, leading to accelerated degradation. Consequently, magnesium-based implants may lose their structural strength before the surrounding tissue has fully healed.

When considering magnesium for biomedical use, several physiological and safety aspects must be assessed. These include cytotoxicity, sensitization, irritation, genotoxicity, implant response, chronic toxicity, and potential carcinogenic effects [74]. The biodegradability and cytocompatibility of lotus-type porous magnesium were also investigated by others [75,76], with used a porous structure with an average pore diameter of 170μm, was designed to facilitate efficient cell ingrowth and fluid transport. The porous material was fabricated using metal/gas unidirectional solidification under pressurized hydrogen conditions [75].

The study evaluated corrosion resistance, mechanical degradation, and biocompatibility, using dense pure magnesium as a reference. Results showed that the lotus-type porous magnesium exhibited a lower hydrogen release rate and reduced mass loss during immersion in simulated body fluid (SBF) compared to the compact version. However, higher concentrations of magnesium ions released from the porous scaffold led to increased osmotic pressure, which can influence cell viability. Despite this, in vitro cytotoxicity tests confirmed that the porous magnesium remained safe for cellular applications. The authors concluded that lotus-type porous magnesium is a promising candidate for biodegradable scaffolds in tissue engineering, offering a suitable balance of degradation rate and biocompatibility [76].

4. Manufacturing Process for Porous Metals

Authors should discuss the results and how they can be interpreted in perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

4.1. Basic Metallic Foam Method

Porous metal scaffolds can be fabricated through a range of traditional and advanced processing techniques, depending on the intended application. The effectiveness of these scaffolds in bone regeneration depends on selecting the right material and design, the manufacturing approach, and any potential surface treatments.

Although several methods exist for producing metallic foams, only a limited number are appropriate for creating porous magnesium. Both liquid-state and solid-state processes have been employed successfully to manufacture magnesium scaffolds. In one study, Komer et al. explored a liquid-phase technique where molten magnesium was injected at high speed into a dual-cavity permanent mold [77]. The first cavity contained a blowing agent powder (MgH_2), which mixed with the molten metal before it entered the second cavity. This process produced magnesium foam with closed-cell pores and an irregular pore structure [78,79]. Another approach by Yamada et al. involved casting using a porous template [80].

This method began by pouring plaster slurry into an open-cell polyurethane (PU) foam to form a template. After the plaster set, the PU foam was eliminated through heating at 500°C, leaving behind a porous plaster structure that mimicked the original foam. Molten magnesium was then vacuum-infiltrated into the plaster template, which was later removed using water spraying [81]. Figure 2 displays optical micrographs of both the original PU foam and the resulting magnesium foam. Additionally, magnesium foams can be produced using powder metallurgy techniques [82] or via the GASAR process—a solidification method involving a metal/gas eutectic system to produce lotus-type porous magnesium [75,82]. However, these conventional techniques generally offer limited control over key scaffold features such as pore size, geometry, interconnectivity, spatial distribution, and internal channel design.

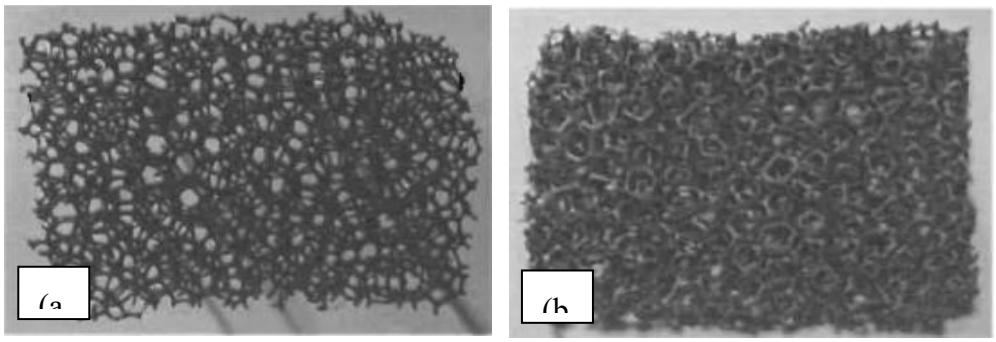

Figure 2. Images of (a) polyurethane foam and (b) resulting magnesium foam.

4.2. Advanced Methods

Rapid prototyping (RP), also referred to as solid freeform fabrication (SFF) or additive manufacturing (AM), represents a group of cutting-edge manufacturing techniques. These methods build objects layer by layer directly from digital data, including Computer-Aided Design (CAD), Computed Tomography (CT), or Magnetic Resonance Imaging (MRI) files. One of the earliest and most successful applications of RP has been in scaffold fabrication, due to the technology's ability to integrate complex designs and produce customized parts with high precision [83].

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The process starts with the creation of a CAD model that defines the scaffold's geometry and porosity. The 3D printing apparatus includes a deposition bed, feed bed, powder spreader, print head, and drying unit. Initially, the print head applies a binder to a layer of loose powder following the CAD model. The deposition bed then lowers while the feed bed rises, and a roller spreads a fresh layer of powder across the binder, which is then dried. This sequence is repeated layer by layer until the complete structure is formed [83]. After printing, ceramic parts can be densified through high-temperature sintering to enhance their mechanical strength. Figure 3 outlines the key steps involved in scaffold fabrication using RP technologies.

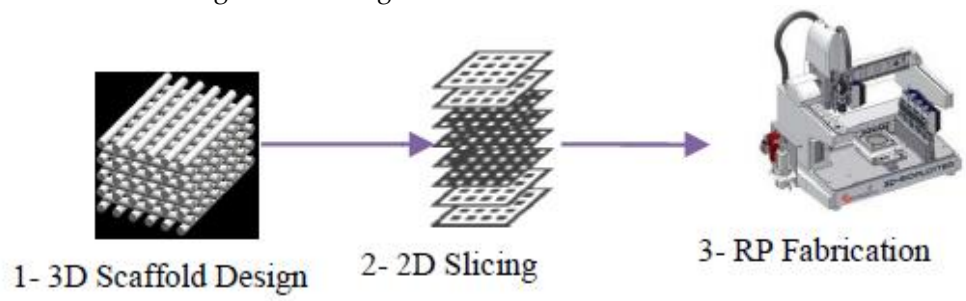

Figure 3. Main steps in scaffold fabrication using RP methods.

Researchers have been introduced methods for producing topologically ordered porous magnesium (TOPM) scaffolds using SFF techniques [84,85]. In their approach, a 3D template made from NaCl, designed with precise, ordered porosity, was fabricated using a simplified method derived from existing RP technologies. This innovative process enabled the creation of TOPM scaffolds with a controlled, interconnected porous structure based on CAD models. The entire fabrication workflow is illustrated in Figure 4.

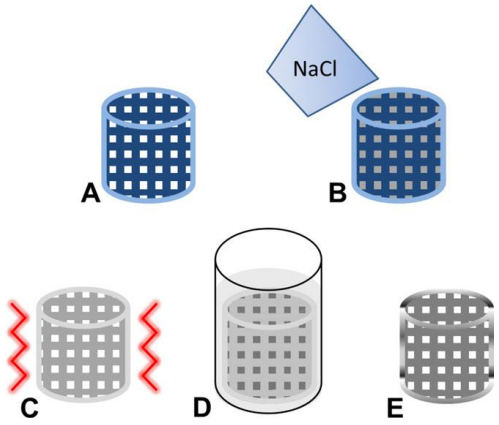

Figure 4. Diagram of the RP-based fabrication process: (**a**) Creation of a polymer RP template; (**b**) Infiltration with NaCl paste; (**c**) Burnout of the polymer and sintering of NaCl; (**d**) Low-pressure magnesium casting into the NaCl mold; (**e**) Final scaffold after dissolving the NaCl.

5. Porous Biomaterial and Tissue Integration Challenges.

5.1. Biomaterial-Tissue Vascularization

Bone is a highly vascularized tissue that depends on an intricate blood vessel network for the delivery of oxygen and essential nutrients. For engineered tissues to grow beyond 100–200 μm, the maximum effective diffusion distance for oxygen, and angiogenesis must occur to support cellular viability [86]. Vascularization plays a fundamental role in bone development, remodelling, and healing, and is considered a key initiator in the formation of new bone tissue [87–89]. In the context of bone tissue engineering using porous scaffolds, it is vital for these constructs to facilitate early-

stage formation of functional vasculature. The establishment of new blood vessels within the scaffold reduces the limitations of nutrient and waste transport imposed by diffusion and minimizes the formation of fibrotic encapsulation often associated with the foreign body response (FBR) [90,91].

By mitigating the FBR, efficient nutrient and waste exchange can be maintained, thereby supporting tissue viability within porous scaffolds. This advancement also holds promise for improving the precision of drug delivery systems and enhancing the performance of immune-isolated gene and cell-based implants [92]. Upon implantation, the metabolic capacity of seeded cells is restricted due to insufficient substrate availability (oxygen, glucose, amino acids) and inadequate removal of metabolic byproducts (CO_2, lactate, urea), severely compromising cell survival and the functionality of the engineered tissue [93,94].

Bone formation within grafts is closely tied to the presence of a vascular network. The highest levels of new bone deposition are typically found in regions with robust blood supply [94]. Without vascular integration, nutrient transport relies solely on diffusion, a mechanism only effective over short distances or for low-metabolic-demand tissues such as cartilage. Computational modelling has shown that a scaffold with a thickness of 1 cm and no internal vasculature can support only about 280,000 cells per cm^3 without central necrosis, while native cancellous bone supports roughly 1000 times more [94]. To enable the survival and function of metabolically active tissues like newly forming bone, the development of vasculature that surpasses the diffusion limit is essential.

Thus, engineering large-volume bone constructs necessitates strategies that promote vascularization to meet cellular metabolic demands. A major hurdle in current tissue engineering practices is the inability to generate functional microvascular networks that integrate with the host's circulatory system. Effective therapeutic strategies must therefore focus on guiding neovascularization in biomaterial scaffolds. Various factors influence vascular development, including (i) scaffold architecture (pore size and porosity), (ii) spatial and temporal gradients of growth factor diffusion, and (iii) cellular responses to those gradients such as chemotaxis and chemokinesis [95]. Based on these parameters, extensive efforts have been directed toward understanding and controlling the biological mechanisms that drive angiogenesis, as well as designing scaffolds that support vascularized tissue regeneration.

5.2. Strategies to Enhance Vascularization in Biomaterials

Traditional approaches that rely on post-implantation vascular infiltration have shown limited effectiveness, restricting the clinical application of engineered tissues to thin or avascular structures such as skin or cartilage [96,97]. Therefore, more active strategies have been developed to accelerate and guide the formation of functional blood vessel networks in bone tissue engineering. The following sections summarize key methods, their underlying principles, benefits, and current limitations.

5.2.1. Scaffold Design and Architecture

Historically, scaffold-based bone regeneration has focused on providing mechanical support and a surface for osteogenic cell attachment. However, recent trends emphasize designing scaffolds that can actively support vascularization [98]. Among the most critical scaffold parameters is porosity, which significantly affects cellular behaviour and tissue formation [99,100]. While earlier studies emphasized its impact on osteoblast proliferation and matrix deposition, attention has shifted to its influence on vascular infiltration. Small-pore scaffolds often exhibit hypoxic conditions that favour cartilage formation, whereas larger pores facilitate better oxygen diffusion and promote mesenchymal stem cell (MSC) differentiation into osteoblasts, thereby enhancing osteogenesis [101].

5.2.2. Introducing Angiogenic Growth Factors

Angiogenesis is primarily regulated by soluble growth factors that modulate endothelial cell behavior, including proliferation, migration, and intercellular signalling. Given the interdependence of angiogenesis and osteogenesis, these growth factors play an essential role in both blood vessel formation and bone regeneration processes such as endochondral ossification [102,103]. Key pro-angiogenic factors include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β). Among these, VEGF is recognized as the most potent angiogenic stimulator, capable of inducing endothelial cell proliferation and migration [104–106]. Similarly, bFGF, secreted by various cell types, also promotes these angiogenic processes [107].

Inspired by mechanisms observed in tumor angiogenesis, researchers have employed these growth factors to attract host-derived endothelial cells into scaffold pore networks. By delivering VEGF, bFGF, and PDGF—either individually or in combination—effective vascular ingrowth has been demonstrated in several experimental models [108–110].

5.2.3. Micro-scaling Technique

Replicating the intricate architecture of highly vascularized tissues such as bone, liver, and heart remains a significant challenge. To address this, microscale fabrication techniques—including microfluidics, bioprinting, soft lithography, and photolithography—have been used to create biomimetic constructs with defined vascular geometries [111–115]. Microfluidic systems are particularly effective for forming capillary-like networks, while photolithographic approaches allow modular assembly of microvascular structures. Recently, computer-aided rapid prototyping has been employed to fabricate vascularized tissues by printing microchannel networks within three-dimensional hydrogels [115].

Despite these advances, most current vascularization strategies fall short of replicating native vasculature. They often rely on the formation of isolated capillaries without functional integration into the host's arterial system, leading to vessel regression over time. Establishing robust capillary networks within engineered constructs remains a central objective. This can be achieved through various strategies, including: (i) incorporation of angiogenic growth factors to elicit an in vivo response, (ii) co-culturing with mature and progenitor endothelial cells, (iii) embedding microcapillary-like structures into the scaffold design, (iv) exploring endothelial–osteoblast interactions through co-culture systems, and (v) applying microsurgical techniques to enhance vascular integration [116].

While forming capillary-like structures in engineered bone is a major achievement, these vessels often lack long-term stability. Current research therefore focuses on maintaining and stabilizing newly formed vasculature. A critical aspect of this is ensuring that micro-vessels within the scaffold can anastomose with the host’s vascular network. Without this connection, nutrient delivery and waste removal are compromised. At present, technological limitations restrict host vessel connections to a minimum of 1 mm in diameter, which may not suffice for microcirculatory needs. Furthermore, complex tissue defects, such as osteochondral injuries that include both vascular and avascular regions, present additional design and therapeutic challenges [117-118].

5. Future Direction and Challenges.

The development of novel biodegradable materials for bone implant applications is a critical focus in regenerative medicine. These materials must not only satisfy the distinct mechanical and metabolic requirements of both bone and cartilage tissues but also possess the capacity to integrate seamlessly with host bone systems to promote effective bone regeneration. Magnesium and its alloys

have emerged as highly promising candidates owing to their favorable biodegradability, mechanical compatibility with natural bone, and inherent bioactivity [119-120].

Advancements in material processing and surface modification technologies have facilitated the fabrication of magnesium-based biomaterials in both bulk and porous forms, enhancing their suitability for a wide range of orthopedic and maxillofacial applications. Among these, porous magnesium scaffolds offer significant advantages by mimicking the natural architecture of cancellous bone, promoting cell infiltration, nutrient diffusion, and vascular in-growth, which are essential for successful osseointegration and long-term implant performance [121-122].

However, the integration of porous magnesium implants into clinical applications requires further interdisciplinary research to address key challenges, including controlled degradation rates, corrosion resistance, and long-term biocompatibility. Moreover, the biological performance of these materials can be significantly enhanced through the incorporation of strategies that promote vascularization—one of the most critical aspects of tissue regeneration [123].

5. Concluding Remarks.

Emerging design paradigms should emphasize that effective vascularization is not solely dependent on scaffold geometry or porosity, but must also be directed by biochemical and epigenetic cues that govern angiogenesis. Therefore, future research should aim to develop multifunctional porous magnesium biomaterials that are capable of delivering epigenetic signals, growth factors, or gene-modifying agents to actively guide vascular and osteogenic responses. In conclusion, the successful translation of porous magnesium-based implants into clinical practice will rely on a systems-level approach that combines material science, biology, and engineering. Such a framework will pave the way for the next generation of smart biodegradable implants that not only support bone repair but also actively participate in the regenerative process by modulating the host environment in a temporally and spatially controlled manner.

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