



Metal additive manufacturing of lattice-based orthopedic implants: A comprehensive review of requirements and design strategies

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ABSTRACT

This scoping review synthesizes recent advancements in the design and manufacturing of metallic additively manufactured lattice-based orthopedic implants. The review begins with an in-depth discussion on material selection, exploring the range of metals suitable for orthopedic applications, and progresses to detail the evolution of design methodologies, which now incorporate bio-inspired concepts and data-driven models such as inverse design. These innovative approaches significantly enhance the customization and functionality of bone implants, offering unprecedented opportunities for tailored patient care.

Additionally, the review analyzes the current standards and regulations that govern the development and implementation of these implants in clinical settings. It outlines the necessary steps and considerations for compliance, emphasizing the importance of these frameworks in ensuring the safe and effective transition of lattice-based orthopedic implants from theoretical models to practical solutions in healthcare.

By bridging the gap between cutting-edge research and clinical application, this review aims to serve as a crucial resource for researchers, engineers, and medical professionals. It not only encapsulates the state-of-the-art in implant technology but also highlights the collaborative efforts required to advance the field and overcome existing challenges. The ultimate goal is to pave the way for next-generation bone implants that are highly effective, safe, and optimized for individual patient needs.

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The Scope of This Paper

This paper aims to provide a comprehensive guide for engineers involved in the design and development of additively manufactured metal lattice-based orthopedic implants, with a focus on mechanical, biological, and clinical requirements. The goal is to offer clear solutions to common design challenges by reviewing metallic lattice-based orthopedic implants produced using additive manufacturing methods. The broad field of knowledge and expertise covered by the authors is a strength of the article, which will hopefully represent a valuable reference for researchers in the field. Fig. 1 provides an overview of the review structure. After introducing the concept in Section 1, Section 2 discusses the guidelines for material selection, offering a detailed introduction to the available metallic materials and their respective advantages and disadvantages. Section 2 further discusses new trends in metallic biomaterials to functionalize the surface and geometry of the implant. Section 3 then explores the additive manufacturing techniques currently employed in the biomedical field. In Section 4, we delve into the biological, mechanical, and clinical requirements for designing optimal implants, including a review of existing studies. Section 5 presents practical guidance on applying these requirements to achieve and optimize the ideal implant design. This section further addresses emerging trends in implant design methodologies including bio-inspired and machine-learning design approaches. Lastly, Section 6

provides a practical guideline from idea toward industry for metallic implants based on relevant standards and regulations.

1. Introduction to bone implants

Despite the appreciable self-healing abilities of bone tissue, in certain instances they are not sufficient for a complete recovery and surgical interventions are needed [5]. Osteoarthritis, osteonecrosis, childhood diseases, skeletal disorders, and bone-damaging traumas resulting in fractures and defects in the skeletal system are examples of these cases. Therefore, autograft or allograft interventions are carried out if the bone tissue is fractured or degenerated by inflammatory or age-related diseases [6]. However, also these bone grafts are not free from issues such as the need for multiple operations, quality and properties of the donor-site, and the risk of infections [7]. To prevent these risks, artificial bone implants have been introduced.

Bone implants are medical devices used to heal bone fractures or to aid the bone formation. Bone implants need a surgical procedure to be placed into the body and are designed to be integrated into the human body to fix, support, reproduce, or improve the functions of human tissues. Bioimplants are defined as such when stay into the human body for more than 30 days [8]. The bone implant market is experiencing a rapid growth, it was valued at USD 4.54 Billion in 2023, and the Global

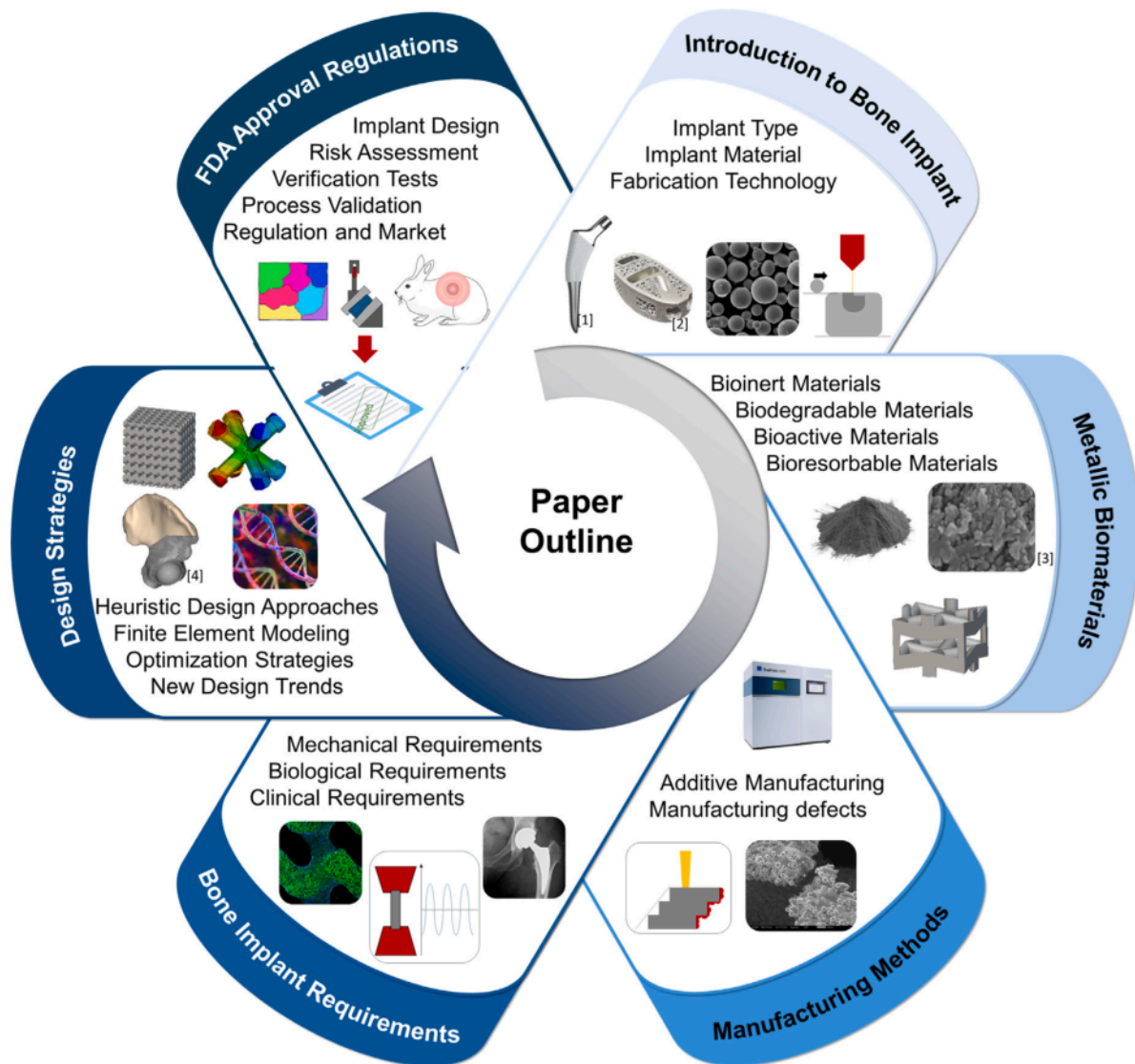


Fig. 1. Paper outline. Hip implant image adapted from [1], spinal implant image adapted from [2], SEM image of Hydroxyapatite coated on titanium alloy surface adapted from [3], topology-optimized custom pelvic lattice-based implant image adapted from [4].

Bone Implant industry is projected to grow from USD 5.65 Billion in 2024 to USD 9.82 Billion by 2032 [9]. This is usually explained by the growing and aging population leading to a continuous increase of bone tumors, skeletal deformities, and consequently increasing demands for bone implants. A further contribution to this growth comes from sport-related injuries [10–12]. Orthopedic implants fall into two categories: permanent load-bearing bone implants, such as total hip and knee replacements, which serve as solutions for osteoarthritis, rheumatoid arthritis, post-traumatic arthritis, osteonecrosis, joint deformities or congenital conditions, and failed previous implants; and temporary fracture fixation devices, including plates, screws, pins, wires, and nails. A thorough understanding of the mechanical, biological, and clinical requirements is essential for the successful design and optimization of load-bearing orthopedic implants under physiological conditions in the human body [13], which is the scope of this paper.

Thanks to the great business opportunity, artificial bone implants market is steadily growing. The United States, followed by Germany, is the largest world exporter of medical devices. North America holds the highest percentage of the global hip and knee replacement market and is expected to maintain the largest market share in the upcoming years [14]. It is estimated that over the period from 2015 until 2025, only the global hip arthroplasty market will increase from around 5.2

billion to over 9.3 billion U.S. dollars. In 2019, the United States registered the highest (over 40 thousand US dollars) cost for a hip replacement, conversely, Poland the lowest cost at around five thousand U.S. dollars [15].

1.1. Implant type

The main types of permanent orthopedic implants, by application, have been classified into hip-, knee-, spine-, and dental orthopedic implants, but interesting examples of prostheses are present also in cranial and maxillofacial surgery [13,16]. Temporary products like orthopedic screws, plates, and interlocking nails (rods), are also widely used for a correct placement of the above-mentioned devices. The choice among the wide range of prostheses available in the market is made by the surgeon, based on the patient's clinical picture. Several factors can influence this decision, including age, gender, body weight, which may require stronger materials, presence of allergies to some of the metals in the prosthesis, and the type of pathology affecting the bone (some prostheses are better suited to treat some pathologies than others) [17–20].

1.2. Implant material

Permanent orthopedic implants are designed to function within the human body for the patient's lifetime. Metals, ceramics, and polymers are commonly used, with material selection depending on the intended working conditions and specific applications. Materials for biomedical implants must exhibit no toxicity, good biocompatibility, and osteointegration, promoting the adhesion and proliferation of cells to their surfaces [21,22]. Moreover, in some cases, they must withstand static as well as dynamic mechanical loads in harsh environment, responsible for wear [23,24], fatigue, and corrosion degradation [25–27]. The presence of a corrosive environment is known to enhance the wear/fatigue degradation, due to the synergistic effect of different damage mechanisms, leading to a more rapid failure of implants [28–30].

Metals, i.e., the materials considered in this review paper, are the far most used, thanks to the high mechanical strength, fracture toughness, and ductility, making them excellent candidates for load-bearing orthopedic implants [29,31,32]. The corrosion resistance of metals and alloys is generally lower compared to polymers and ceramics. However, the most important metallic biomaterials, i.e., stainless steels, Co-based alloys, Titanium and Ti-based alloys can passivate, forming a thin and compact protective surface oxide layer providing excellent surface durability [33,34]. Moreover, metallic biomaterials in these categories have received approval from the US Food and Drug Administration and are commonly used in orthopedic implants [13]. Magnesium alloys, on the other hand, belong to the last generation of degradable biomaterials. Their corrosion resistance is low, thought to act as a temporary structure, which enables them to degrade and allow native tissue to integrate with [35].

1.3. Fabrication technology

Biomedical metallic implants and products have been produced using different manufacturing processes including casting [36] and plastic deformation processes, like hot forging and hot rolling [37,38]. Examples of cast and forged prostheses are available for Ti and Co-based alloys. Both processes allow the production of bulk components and, due to technical and economic limitations, they are produced in standard sizes and shapes. Even though most of the implants on the market are still produced by these traditional methods, the rapid expansion of Additive Manufacturing (AM) opened the way to the introduction of customized devices with unique properties [39]. Now, AM techniques like Powder Bed Fusion (PBF) [40–42] and Binder Jetting (BJ) [43,44] permit to produce personalized prostheses, designed to the needs of the patient. Moreover, thanks to their design freedom, they allow the fabrication of porous lattice structures, characterized by improved osteointegration properties. The introduction of pores in the implant mimics the cancellous part of the bone structure [45,46], including the possibility of a Functionally Graded Porous Structure (FGPS) reproducing the transition from the cortical to inner cancellous bone region [47]. Although the cost of implants produced by AM is still higher than that of implants produced by traditional methods, the aforementioned benefits combined with the lower costs associated with large-scale productions of AM components will likely facilitate their widespread use.

2. Metallic biomaterials

Biomaterials, whether synthetic or natural, are designed to interact with biological systems for medical use, such as tissue repair or drug delivery [48,49]. As the first interface in touch with human tissue they must be cytocompatible, non-toxic and ideally biodegradable. Having suitable mechanical properties like tensile strength, stiffness, and structural features such as size, shape, and porosity for specific applications, as well as stability in physiological conditions are other essentials to

maintain their function. Metals, the main focus of the present work, are commonly used for load-bearing implants in orthopedic surgeries [31].

Stainless steel, titanium and cobalt-based alloys are among the commonly used metals and alloys in medical devices. Their strength and durability make them ideal for applications ranging from fracture fixation to joint prostheses in orthopedics, cardiovascular surgery, maxillofacial surgery, and dentistry. However, while metals excel in mechanical properties, they are more susceptible to corrosion compared to materials like polymers and ceramics. Other biomaterial categories such as polymers, ceramics, composites, and nanocomposites offer distinct advantages in various medical applications but may lack the mechanical properties required for load-bearing implants [50].

A summary of the mechanical properties of the most common metallic biomaterials, besides those of the human bone, is shown in Table 1.

Although the use of metals in medical applications dates back to ancient times, it was only with the development of aseptic surgical techniques in the 1860s that metal implants became successful [52,66]. In orthopedic surgery, the selection of metallic biomaterials depends on the patient's clinical requirements [66,67]. 316L stainless steel, Co–Cr alloys, Ti alloys, Ta alloys and shape memory alloys (SMAs) are commonly chosen for fracture fixation and bone remodeling due to their enduring stability under highly reactive *in vivo* conditions and superior mechanical properties [53,68–72]. Balakrishnan et al. [73] refers to these bioinert materials as the first generation of metallic biomaterials. The second generation of metallic biomaterials includes bioactive and biodegradable materials that promote bone tissue regeneration and healing through degradation or by being coating with bioactive coating. Third generation biomaterials refer to materials in the form of temporary three-dimensional porous structures that actively stimulate tissue regeneration. Below, the most significant metallic materials for the orthopedic sector from these three generations will be discussed.

2.1. First generation: Bioinert materials

2.1.1. Stainless steel

Stainless steels (ISO 5832-1:2019 [74]) are frequently selected for implants because of the presence of chromium that can generate a stable passive surface oxide film, providing effective protection against corrosion attacks [75]. Austenitic stainless steel, namely 316L, stands out as a widely utilized alloy in the production of surgical implants and instruments thanks to its cost-effectiveness, ease of fabrication, and accessibility to a broad patient base [51]. ASTM recommends Type 316L for implant fabrication due to its low carbon content, which reduces the formation of chromium carbide, lowering the risk of intergranular corrosion and enhancing corrosion resistance, especially in chloride-containing body fluids [76]. Due to its overall biocompatibility and resistance to corrosion, it is frequently employed in internal fixation, namely screws and plates to provide provisional support, anticipating full bone tissue regeneration, with the ability for surgical removal once the healing process is complete [77,78]. Nevertheless, its vulnerability to stress cracking and corrosion by chlorides confines this steel to being used as temporary implants, such as steel plates. Pathote et al. [75] focus their attention on the improvement of the biocompatibility and surface properties of 316L by the deposition of a tantalum coating. Another important problem due to pitting corrosion is the release of nickel that seems to promote mutagenic and genotoxic activities, as well as conditions like eczema, skin itching, and, in certain instances, cancer [79,80]. The necessity to reduce the nickel content brings about the development of Ni-free 316L [81].

2.1.2. Co–Cr alloys

Another bioinert metallic biomaterials are the cobalt-chromium (Co–Cr) alloys, known for their high strength and composed mainly of Co and Cr, exhibit excellent high-temperature oxidation resistance and biocompatibility [53,82]. They can develop a passive layer of

Table 1

Mechanical properties of common metallic biomaterials and human bone.

Material	Yield strength (MPa)	Elastic modulus (GPa)	Biocompatibility	Applications	Ref.
Metallic biomaterials					
Stainless Steel	190–690	200–210	High	Temporary fixtures (plates, screws), total hip replacement	[51,52]
Co-based alloys	310–1586	210–253	Low	Total joint replacements (wrought alloys), dentistry castings	[52,53]
Ti-based alloys	585–1060	55–110	High	Stem and cup of total hip replacements with CoCrMo or ceramic femoral heads, other permanent devices (nails, pacemakers)	[52,54–56]
Tantalum alloys	138	185	High	Wire sutures for plastic surgery and neurosurgery, a radiographic marker	[31,57,58]
NiTi alloys	70–690	28–83	Good	Orthodontic dental arch wires, vascular stents, vena cava filter, intracranial aneurysm clips, contractile artificial muscles for an artificial heart, catheter guide wires, orthopedic staples	[59–62]
Mg alloys	21–460	40–45	High (biodegradable)	Ligatures for bleeding vessels, cardiovascular, musculoskeletal, and general surgery, cardiovascular stents and bone implants	[31,63,64]
Human bone [65]					
Cortical bone					
Longitudinally load	tensile: 78–151 compression: 131–224	17–20	–	–	
Transversally load	tensile: 51–66 compression: 106–131	6–13	–	–	
Cancellous bone	50–10	0.05–0.1	–	–	

chromium oxide in human body fluid, even in chloride-rich environments [76,83]. Indeed, the alloy classification for medical purposes is ASTM F75 Co–Cr alloy [84]. Co–Cr alloys have been widely utilized in weight-bearing implants such as artificial hip and knee joints since the 1930s. However, issues such as stress-shielding and bone resorption can occur due to their higher modulus of elasticity, density, and hardness compared to bone tissue. In addition, despite their benefits, Co–Cr alloys exhibit lower biocompatibility and osseointegration compared to titanium potentially due to more toxic byproducts of their corrosion, leading to inflammation and implant failure [83,85]. As a result, they are often preferred for implants that do not directly interface with bone, such as spinal fixation rods. Challenges related to wear and corrosion post-implantation have restricted their use, particularly in procedures like total hip replacement and knee implantation.

2.1.3. Ti alloys

Titanium alloys, renowned for their exceptional mechanical properties and ability to bond effectively with surrounding bone tissue, have been instrumental in advancing implant stability since the late 19th century [55,86–88]. In addition, their widespread use in the orthopedic implant sector stems from their compatibility with Magnetic Resonance Imaging (MRI) scans [89]. The remarkable biocompatibility of titanium arises from the formation of a dense inert TiO₂ oxide layer on its surface that remains stable in body fluids and provide antibacterial properties to the implant surface, although they have poorer tribological properties compared to Co–Cr alloys due to lower hardness [85,90,91]. Therefore, titanium alloys may undergo inflammation due to loss of integrity in harsh conditions, such as exposure to reactive oxygen species like H₂O₂ and hydroxyls [85]. Since the 1970s,

titanium and its alloys have seen extensive utilization in diverse orthopedic applications, including artificial joints, trauma devices, and spinal fixation systems, owing to their outstanding biocompatibility, corrosion resistance, and high specific strength. Three different generations of titanium alloys can be defined. The first generation includes Commercially Pure Titanium (CP-Ti), Ti–3Al–2.5 V, and Ti–6Al–4V [92]. CP-Ti, introduced in the 1940s, initially served non-load-bearing, corrosion-resistant purposes. Later, Ti–3Al–2.5 V was incorporated as an orthopedic implant material, even with poor wear resistance limitation. Ti–6Al–4V, successfully developed in 1954, demonstrated high strength and a 50% increase in mechanical strength compared to CP-Ti, enabling its use in load-bearing implants like fracture fixation plates, hip stems, and screws. However, the necessity to diminish or substitute elements like aluminum (Al) and vanadium (V), which are suspected to pose health risks to patients, along with the need to adjust the alloy stiffness to match that of bone, has motivated researchers to pioneer a new generation of titanium alloys. This emergence of low or non-toxic Ti alloys, classified as the second generation, involves replacing toxic vanadium with elements such as niobium (Nb) and iron (Fe), leading to the development of alloys like Ti–5Al–2.5Fe and Ti–6Al–7Nb [93–98]. Despite these advancements, disparities in elasticity with human bone persist. The third generation introduces β type Ti alloys with high strength, low elastic modulus, and corrosion resistance, rendering them more suitable for internal implants. Examples include Ti–15Mo, Ti–20Mo–6Zr–2Fe, Ti–35Nb–7Zr–5Ta, Ti–24Nb–4Zr–8Sn, Ti–15Mo–5Zr–3Al and Ti–15Mo–3Nb–3Al–0.2Si characterized by low elastic modulus of around 50 GPa, high tensile strength, and excellent corrosion resistance [99–102]. Considering UNI EN ISO standards for surgical implant, only four of these titanium alloys are reported, namely unalloyed titanium

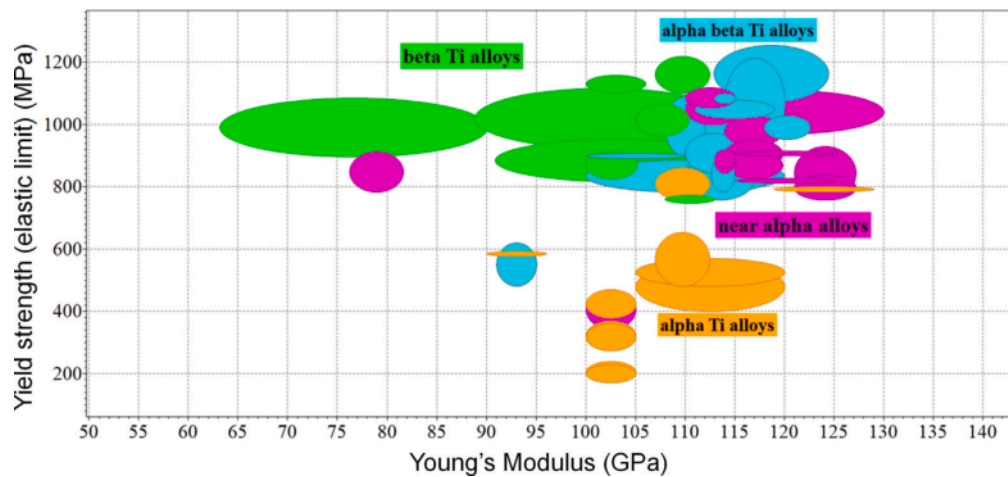


Fig. 2. Yield strength vs. Young's modulus of the different classes of Ti alloys produced by GRANTA EduPack 2021 R1.

(ISO 5832-2:2018 [103]), wrought Ti-6Al4V (ISO 5832-3:2021 [104]), wrought Ti-6Al-7Nb (ISO 5832-11:2014 [105]) and wrought titanium Ti-15Mo-5Zr-3Al (ISO 5832-14:2019 [106]). Differently, considering ASTM standards for biomedical application additionally Ti alloys are present such as Ti-6Al-7Nb (ASTM F 1295-16 [107]), Ti-3Al-2.5 V (ASTM F3046-21 [108]), Ti-15Mo (ASTM F2066-23 [109]) and Ti-12Mo-6Zr-2Fe (ASTM F1813-21 [110]). Graph of yield strength vs. Young's modulus of the different classes of titanium alloys is reported in Fig. 2.

Recent research has highlighted the potential of bio-tolerant refractory metals such as Nb and Ta as alloying elements in titanium (Ti) for biomedical applications, particularly in orthopedic implants. Ti/Nb and Ti/Ta systems offer promising biocompatibility due to their ability to stabilize the Ti β phase, enhancing their suitability for use in implants.

Ti-Nb alloys are known for their excellent workability, high strength, and superior osseointegration, with an elastic modulus of 63–70 GPa when incorporating 40–45 wt% Nb [111–113]. The addition of Sn to the Ti-Nb system has further reduced the elastic modulus, enhancing its suitability for biomedical applications. Ti-Nb-Sn alloys have gained attention as promising materials for orthopedic implants, effectively balancing strength and elasticity. By optimizing β -phase stability and microstructure, these alloys achieve a significantly lower Young's modulus ($\sim 31.5 - 36$ GPa) while maintaining mechanical strength. Recent advancements, such as alloying design to stabilized β phase, oxygen solute strengthening and Goss texture refinement, have led to the development of a Ti-Nb-Sn-O alloy with a Young's modulus of 33.5 GPa and a yield strength of 650 MPa [114].

Tantalum (Ta) is one of the most biocompatible alloying elements in titanium alloys, enhancing both corrosion resistance and β -phase stability while reducing the elastic modulus [115]. As a result, Ti-Ta alloys have been extensively studied over the past two decades [116, 117]. When Ta content is increased to 30 wt%, it results in a $\sim 40\%$ increase in strength and a $\sim 50\%$ reduction in elastic modulus, with only a minimal reduction in elongation ($\sim 1\%$) [118]. Additionally, the formation of $\text{Ta}_2\text{O}_5/\text{TiO}_2$ passive layers on the alloy surface significantly improves its biological response, further enhancing its potential for use in biomedical implants [115, 119]. The significant differences in melting point and density of tantalum (Ta) create challenges in achieving a uniform Ti-Ta alloy, often requiring complex processing. To address this, Wu et al. [120] proposed replacing Ta with TaH_2 in laser additive manufacturing. Due to its higher reactivity and lower structural stability, TaH_2 enhances diffusion within the titanium matrix, minimizing the formation of unincorporated Ta particles and improving microstructural uniformity. This approach not only enhances mechanical performance but also simplifies production, making Ti-Ta alloys more practical for biomedical applications. Nevertheless, given the

high density of the targeted implants, the use of too much Ta, which has a very high density (16.65 g/cm^3), poses a challenge. This issue could be addressed by considering Ti/Nb/Ta ternary alloys, which contain a lower amount of Ta and include Nb, a metal with a lower density (8.57 g/cm^3) [121]. However, these alloys do not inherently exhibit significant antibacterial properties. To overcome this limitation, Cu, Ag and Zn could be incorporated into the alloys, leveraging their bactericidal effects to enhance the antibacterial properties of the materials [122–126].

In parallel, β -Ti-based shape memory alloys (SMAs), such as Ti-13V-3Al, exhibit self-adaptability through their shape memory effect and superelasticity, making them suitable for hard-tissue implants. However, improving wear and corrosion resistance remains a key research focus. One promising approach involves interstitial hydrogen (0.3–2.0 at%), which acts as a β -stabilizing element to enhance alloy properties. The (Ti-13V-3Al)99.2H0.8 composition demonstrated optimal mechanical and wear performance, while 2.0 at.% H provided superior corrosion resistance due to Ti_2O_3 film formation [127]. Similarly, Li et al. [128] explored interstitial nitrogen addition in biomedical Ti2448 to enhance strength and corrosion resistance. Their findings reveal that higher N content refines the microstructure, improves mechanical properties, and strengthens the passivation layer. The Ti2448-0.2N alloy demonstrated the best performance, with increased strength, elongation, and corrosion resistance due to TiN and ZrN formation. This method presents a promising strategy for developing high-performance titanium alloys. Further advancements include titanium-based high-entropy phase memory alloys (HE-SMAs), developed by Hua et al. [129], as potential orthopedic implant materials. These alloys exhibit superior mechanical strength, wear and corrosion resistance, and biocompatibility compared to conventional titanium alloys. Notably, the $\text{Ti}_{49}\text{Zr}_{20}\text{Hf}_{15}\text{Al}_{10}\text{Nb}_6$ HE-SMA demonstrates good superelasticity (3.8% recovery strain), high strength (yield strength of 1187 MPa and ultimate tensile strength close to 1240 MPa), and enhanced wear resistance, making it a promising candidate for advanced biomedical applications. To further improve wear behavior, Ti-based HEAs have been reinforced with TiC and TiB [130, 131]. For instance, research on TiNbZrTaMo HEAs with *in situ* TiC and TiB additions has demonstrated improved mechanical strength, tribological performance, and biocompatibility, making them promising candidates for next-generation wear-resistant implants [130].

2.1.4. Ta alloys

Another important metallic bioinert material is tantalum (Ta). It has been integrated into orthopedic practices since the 1940s, boasting remarkable attributes such as biological inertness, corrosion resistance, and biocompatibility, which have been consistently demonstrated over

the past eight decades [58,132,133]. Its widespread use in porous Ta technology, such as socket cups for primary hip replacement and pads for hip and knee defect sites, has been validated through extensive long-term follow-up studies, affirming its safety and efficacy. Furthermore, Ta has exhibited favorable outcomes as an instrument for intervertebral fusion. Nevertheless, challenges arise from its high density and melting temperature, leading to elevated inventory costs with conventional processing methods. To address these limitations, current researchers are alloying Ta with elements like Ti and Mo to enhance mechanical properties, and corrosion resistance as well as reduce processing challenges [46] (see Section 2.1.3).

2.2. Second generation: Biodegradable and bioactive materials

2.2.1. Biodegradable alloys

As mentioned before, the mechanical compatibility of the implant and surrounding bone is a crucial concept in orthopedics. Implants with a high Young's modulus can lead to bone loss in implantation site due to the stress-shielding phenomenon, necessitating removal surgeries following the bone healing process or due to functional issues. To address this issue, there is a growing interest in degradable materials [134]: these materials can gradually break down within the body, reducing the need for removal surgeries after the healing process. This not only minimizes surgical risks but also lowers overall healthcare costs associated with additional procedures. Recent advancements have led to the development of biodegradable materials, including alloys made from magnesium (Mg), iron (Fe), and zinc (Zn). These materials are particularly promising due to their biocompatibility, which means they can be safely absorbed by the body, controlled degradation rates that match the healing process, while still have sufficient mechanical strength to support bone regeneration [64,135–138]. Recent studies explore advancements in magnesium alloys for biomedical applications, focusing on key aspects such as microstructure, mechanical properties, and manufacturing techniques for bone implants [139,140]. Despite the significant advantages these alloys offer, challenges persist regarding the precise control of their degradation rates, the enhancement of their mechanical properties, and the improvement of their biological compatibility. Several strategies have been proposed to address these challenges, including the incorporation of biocompatible elements such as calcium, zinc, and strontium, which enhance both mechanical strength and degradation behavior, as well as coatings designed to regulate degradation rates. Among binary alloys, Mg–Zn stands out as a promising biodegradable material for orthopedic and cardiovascular applications due to its balanced mechanical properties, controlled degradation, and biocompatibility [141]. Unlike Fe-based alloys [142], which degrade too slowly, or Zn-based alloys [143], which exhibit increased strength but strain-softening behavior, Mg–Zn achieves an optimal balance of corrosion resistance and biofunctionality. The presence of Zn helps regulate Mg's degradation while actively supporting bone metabolism and cellular processes.

Building on this, ternary alloys such as Mg–Zn–Ca and Mg–Zn–Sr demonstrate further improvements when subjected to ultrafine grain refinement, offering enhanced corrosion resistance and mechanical performance [139]. Furthermore, recent studies have emphasized the potential of AM in producing customized magnesium-based implants tailored to specific bone defects [144–147]. As will be discussed in more detail in Section 3, AM technology enables the fabrication of complex, lightweight structures that closely replicate the mechanical properties of natural bone, while also reducing material waste by utilizing only the precise amount of material required. However, significant challenges remain in the application of AM to magnesium alloys. Mg powders are highly reactive and flammable, requiring specialized handling, oxidation treatments, and careful control during fabrication. Additionally, only a limited number of Mg alloys are suitable for biomedical use, and many commercially available powders do not meet

the necessary standards for biocompatibility and mechanical properties. High-temperature AM methods face challenges such as oxidation, evaporation of alloying elements, and energy inefficiency, while low-temperature methods struggle with issues related to binder systems and sintering. Furthermore, post-processing techniques for Mg implants are still in the early stages, and their impact on mechanical properties and biodegradation remains insufficiently understood. Moreover, Mg implants, especially in load-bearing applications, may experience early failure due to fatigue and degradation in the body, necessitating further investigation to improve their clinical applicability. Another key point is the role of biological modeling in predicting the *in vivo* behavior of magnesium alloys, which could provide valuable insights for optimizing their clinical use. The development of multi-element alloys, along with advancements in surface treatments and manufacturing processes, holds promise for addressing the current challenges and making magnesium alloys a viable option for next-generation orthopedic implants.

2.2.2. Bioactive materials: Surface functionalization

Metallic materials are inherently bioinert and lack intrinsic bioactivity; however, surface functionalization can confer bioactive properties, enhancing their integration with biological tissues [148–150]. This approach has led to the development of advanced metallic biomaterials engineered to improve interactions with the physiological environment. Various surface modification techniques have been investigated, including electrophoretic deposition, plasma or radiofrequency sputtering, ion beam sputtering, laser ablation, and hot isostatic pressing [151,152]. Among these, bioactive coatings play a pivotal role in promoting osteoconduction, osteoinduction, and osteogenesis, thereby facilitating bone formation and implant integration. Materials such as ceramics, polymers, composites, and bioactive glasses have been extensively studied for their capacity to stimulate bone regeneration. While HA-based and antimicrobial coatings containing silver or iodine have been successfully implemented in clinical applications [153–155], many other bioactive coatings remain in development. Optimizing deposition techniques, including AM, electrospinning, and chemical vapor deposition, is critical to ensuring strong adhesion, controlled bioactivity, and mechanical stability. Future advancements in surface functionalization will focus on refining drug delivery systems within coatings, improving biocompatibility and mechanical durability, and integrating bioactive molecules to achieve localized therapeutic effects, ultimately reducing the risk of implant failure. A recent study by Xu et al. [156] introduced a multifunctional coating developed via the Layer-by-Layer (LBL) self-assembly technique. This system incorporates titanium dioxide nanorods (TN), copper ions (Cu^{2+}), polydopamine (PDA), graphene oxide (GO), and the antimicrobial peptide KR12, forming a bioactive surface with dynamic responsiveness. The controlled release of Cu^{2+} and KR12 provides antimicrobial effects, regulates inflammation, stimulates angiogenesis, and promotes osteoblast activity. By integrating antimicrobial, anti-inflammatory, angiogenic, and osteogenic functionalities, this PGK-CuTN coating significantly enhances implant integration, reducing complications and improving bone regeneration. Beyond bioactive coatings, alternative strategies such as chemical modifications, thermochemical treatments, and etching techniques can promote the formation of a thin titanium oxide layer, which facilitates the deposition of a dense, bone-like apatite layer under physiological conditions. Given the crucial role of surface properties in biocompatibility, further exploration of functionalization strategies will be presented in Section 4.2, with particular attention to antibacterial approaches (Section 4.2.1.2) and their role in implant-bone adhesion and bone regeneration (Section 4.2.2 and Section 4.2.3).

2.3. Third generation: Bioactive and bioresorbable porous structures

Third-generation biomaterials combine bioactivity with biodegradability, utilizing bioresorbable and bioactive porous structures to enhance tissue regeneration. A significant innovation in this domain is

the incorporation of porous components, which help in decreasing the stiffness mismatch between metallic implants and bone. These porous structures can be produced through two main methods: random-structured foams and architected lattice materials with meticulously designed periodic geometries. While foams exhibit a random pore distribution, they offer limited control over cell morphology. On the other hand, architected lattice materials, namely metamaterials, provide greater design flexibility, enabling the precise customization of mechanical and biological properties for optimized implant performance [157]. Lattice metamaterials, in particular, are geometrically engineered to achieve specific mechanical properties, such as reduced stiffness and even a negative Poisson's ratio, characteristics that can promote cell proliferation by interacting with biological systems at the molecular level [22,158]. By replicating the complex architecture of natural bone, these structures effectively reduce stress shielding and encourage tissue ingrowth, both of which are critical in preventing implant loosening [159,160]. Among the most promising advancements in this field is AM, which enables the creation of highly complex, interconnected architectures and curved channels. This significantly enhances the biocompatibility of metallic implants [161]. The most promising AM technologies will be discussed in the Section 3.1. Architected lattice structures are typically classified into two main categories: strut-based lattices and Triply Periodic Minimal Surface (TPMS)-based lattices. Strut-based lattices consist of repeated unit cells in space, made up of unidimensional struts that converge at nodes in various topological patterns.

A systematic categorization of unit cells in this context can be established using Maxwell's criterion [157,162]. In this group, of particular interest are auxetic structures, characterized by a negative Poisson's ratio, which proves advantageous when the implant is subjected to stress that might lead to detachment from the bone [163–167].

For instance, Dongxu Chen et al. [168] performed a study on metallic auxetic meta-biomaterials, introducing an innovative design that combines re-entrant geometries, responsible for the negative Poisson's ratio (NPR), with internal structures exhibiting a positive Poisson's ratio (PPR), i.e., conventional geometries that contract laterally when stretched. These internal PPR substructures are strategically inserted inside the re-entrant cells to act as reinforcement elements. Their purpose is to hinder the movement of the re-entrant nodes under load, thereby increasing the yield strength without significantly affecting the overall performances of the structure. This hybrid design led to a significant increase in yield strength, up to 44.7%, while maintaining the elastic modulus in the range of the human bone (0.65–5.17 GPa). In addition, the auxetic behavior (NPR) of the material was preserved in all configurations, demonstrating the potential for load-bearing orthopedic implants where both strength and stiffness are critical. In contrast, TPMS-based structures offer a high surface area and permeability, which support cell attachment and angiogenesis. In a recent study, Zhou et al. [169] investigated three TPMS structures, namely Gyroid, Diamond, and Primitive, made from Ti64-5Cu alloy with fixed porosity, fabricated using laser powder bed fusion to identify optimal materials and designs for orthopedic implants. Their evaluation of the permeability, flow properties, corrosion resistance, and antibacterial performance of these structures revealed that the Gyroid structure exhibited 42% higher material transport than the Diamond structure. Consequently, the Gyroid structure was found to be more suitable for orthopedic implants due to its ability to promote bone cell growth and better match the modulus of bone. Additionally, TPMS structures exhibit impressive fatigue resistance, up to 60% of the yield strength, due to the absence of notches that typically degrade fatigue life [170–173].

Recent studies have increasingly focused on the development of Functionally Graded Porous Structures (FGPSs) to replicate the natural porosity gradient of cancellous bone, thereby enhancing both mechanical performance and biological integration [42,163,174–179]. Naghavi et al. [180] explore a porous Ti-6Al-4V hip implant made with Laser Powder Bed Fusion (LPBF), using a functionally graded hybrid TPMS

lattice combining gyroid and diamond geometries. This design reduces stress shielding by 70% and bone loss by 60% compared to solid implants, while optimizing stiffness and improving osseointegration. Issues related to the fatigue performance of implants are still under investigation. Similarly, Gandhi et al. [181] highlight the benefits of functionally graded porosity in TPMS-based structures, emphasizing its role in improving stress distribution and mechanical stability. By closely mimicking the natural porosity gradient of bone, graded TPMS structures promote superior bone integration and exhibit enhanced fatigue resistance and load-bearing capacity, making them particularly suitable for long-term orthopedic implant applications.

Notably, as shown in Fig. 3 the thickness and density variations of cortical and cancellous bone in different parts of each bone can be addressed using functionally graded porous structures [42]. These structures improve the overall compatibility of the final design with host tissue.

3. Manufacturing methods

Various manufacturing processes such as forming, injection molding, casting, extrusion, stamping, and machining are crucial for fabricating prostheses and orthopedic implants [182]. Each process requires specialized tooling [183] and can lead to material wastage, especially in machining complex geometries like prostheses [184]. AM techniques allow for precise control over the complex geometries and architectures of lattice structures, enabling designs that are not possible with traditional manufacturing methods [185].

3.1. Additive manufacturing technologies

AM processes are classified under ISO/ASTM 52900:2021 [186] into seven main categories: material extrusion (MEX), material jetting (MJT), binder jetting (BJT), powder bed fusion (PBF), directed energy deposition (DED), sheet lamination (SHL), and vat polymerization (VPP). Of these, four are suitable for metal fabrication, with PBF being the most widely used for producing porous-structured implants, a key feature in orthopedic applications [90,143,181,187,188].

These techniques involve depositing a layer of metallic powder on a build plate and selectively melting a precise cross-section by means of an energy source. PBF methods include Laser Powder Bed Fusion (L-PBF) for laser-based systems in controlled environments, and Electron Beam Powder Bed Fusion (EB-PBF) for electron beam systems in vacuum chamber setup.

The quality of PBF products depends on various factors, including material choice, equipment, and key processing parameters like layer thickness, power settings, scanning speed, and scanning strategy [189–191]. These parameters significantly influence microstructure, anisotropy, internal defects, and surface roughness of final products [185,192]. Dias et al. [193] highlight the predominant use of L-PBF and Ti-6Al-4V in the production of lattice components for load-bearing implants.

Additive manufacturing offers significant advantages, not only in the fabrication of complex structures but also in the production of multi-material components. This approach enables the optimization of mechanical properties through the creation of material gradients, enhancing implant performance and long-term durability. In the context of metallic-metallic multi-material systems, Jiang et al. [194] explored the production of a Ti-based gradient heterogeneous alloy transitioning from Ti6.5Al3.5Mo1.5Zr0.3Si to Ti6Al4V using multi-wire arc additive manufacturing (MWAAM) technology. Their study provides valuable insights into fabricating gradient heterogeneous alloys for advanced applications, with a focus on controlling properties in the transition region between different alloys. In a more recent study, Jiang et al. [195] investigated the use of WAAM to create multi-materials that optimize the performance of final components

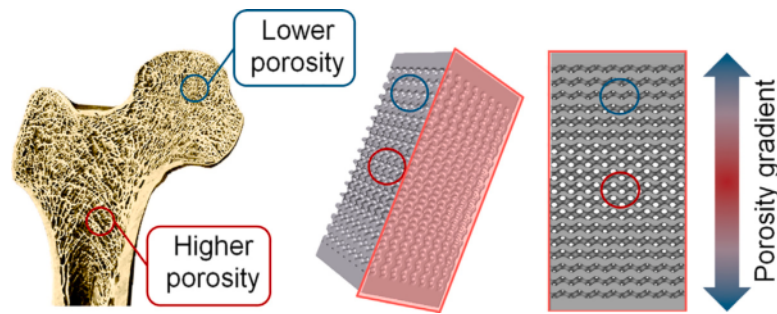


Fig. 3. Functionally graded porous structures mimicking bone anatomy.

for biomedical applications. Specifically, they examined a NiTi-Ti-6Al-4V heterogeneous alloy with a Nb interlayer, aiming to combine the superelasticity and shape memory of NiTi with the strength and biocompatibility of Ti-6Al-4V. The Nb interlayer prevents the direct mixing of alloy elements and reduces the formation of brittle Ti_2Ni phases. By optimizing the WAAM process, they achieved a 53.3% improvement in mechanical properties, particularly in tensile and compressive strength, compared to traditional welding. Despite these advancements, challenges such as weak adhesion and phase evolution in the interlayer remain. Nonetheless, this approach presents a promising method for manufacturing multifunctional metallic components, although further research and evaluation are necessary for optimization. Building on these advancements, companies specializing in additive manufacturing are increasingly focusing on developing specialized machinery tailored for multi-material metal 3D printing. For instance, Aerosint (Belgium) has pioneered a recoater system that enables the simultaneous use of multiple metal powders during the printing process. This innovative approach may facilitate the creation of components with varied material properties within a single part.

3.2. Manufacturing defects

While AM offers promising potential for producing implants, the quality of manufacturing is crucial for the overall success of prosthetic devices. Defects in AM products are extensively studied, with a focus on minimizing them. Davoodi et al. [90] categorizes the manufacturing defects into geometric and microstructural types. Geometric deviations, such as shrinkage, residual stresses, and surface roughness, often arise from improper process parameters, thermal distortion, and laser trajectory, affecting dimensional accuracy [90,191]. These deviations are particularly problematic in lattice structures, where strut defects like thickness variations, and cross-section shape mismatches are common, which often influence local stress concentration [196,197]. Moreover, defects like stair-stepping and balling can further impact surface quality, with rougher downward-facing surfaces and smoother upward-facing surfaces [90].

Microstructural defects, including internal voids and porosities, are another issue, arising from original feedstock-related pores or processing-induced pores such as metallurgical pores, lack-of-fusion, and keyholes [90,198]. These defects contribute to stress concentration, reduced fatigue resistance, and decreased mechanical properties. Additionally, the AM process can cause spatially variable material properties due to thermal gradients, leading to residual stress and further weakening of the structure [199].

As the most favorable method in manufacturing medical devices, optimizing L-PBF parameters to achieve high-quality lattice structures, is essential for medical devices where geometric accuracy directly impacts performance. Variations in these parameters affect defect formation within the lattice, including keyhole and lack of fusion defects, as well as surface quality issues due to energy input disparities [200,201]. Studies by Wang et al. [202] and Bobbert et al. [203] further highlight the role of process parameters not only on the internal defects but

also in altering the microstructure of materials like Ti-6Al-4V, with differing impacts on grain shape and size within lattice structures. These variations underscore the complexity in achieving consistent surface finish and manufacturing accuracy, posing challenges to the predictability of lattice production. It is well known that geometric inaccuracies can result from incorrect parameter settings, compromising mechanical performance [204,205]. Based on this, controlling the orientation of struts is crucial as it profoundly influences both the morphology and mechanical performance of lattice structures. Different orientations result in varied thermal histories during fabrication, impacting heat transfer efficiency and causing irregularities like the “stair-case effect” [206,207]. Surface texture in L-PBF is influenced by deposition characteristics and the presence of partially melted powder particles, leading to surface defects and porosity [208,209]. Different strut angles impact tensile properties, highlighting the importance of analyzing local stress and strain [207,210,211].

Additionally, surface topography, influenced by building angles, significantly affects lattice responses, crucial for biomedical applications [212]. Based on the literature, the surface quality of a single strut decreases from vertical to horizontal printing orientations, with lower angles resulting in reduced accuracy and increased variability among specimens. These variations negatively affect fatigue performance, worsened by the miniaturized size which reduces tensile properties due to a higher surface-to-volume ratio, resulting in decreased yield strength and ultimate tensile strength compared to wrought components [207]. In summary, additive manufacturing is transforming the field of orthopedic implants by enabling the production of complex, patient-specific designs that traditional manufacturing methods cannot achieve.

4. Bone implant requirements

Designing bone implants begins with understanding the clinical condition of the target bone, influenced by both defect-related and patient-related factors. Key considerations include the trauma site, bone defect size, loading conditions, and structural properties of the bone, such as vascular density, porosity, and cartilage presence. After morphological, physicochemical, and mechanical assessments, the material undergoes extensive *in vitro* and *in vivo* testing. This refinement process leads to clinical trials and ultimately, market delivery of the product [213].

Moreover, understanding bone implant design requirements is crucial in AM technology, as it directly impacts the functionality, longevity, and biocompatibility of the implant. AM enables the fabrication of complex geometries, porous structures, and patient-specific designs that enhance osseointegration and reduce stress shielding. However, optimizing implant performance requires a deep understanding of mechanical properties, material behavior, and biological interactions under physiological conditions. By integrating engineering principles with biomedical requirements, AM can revolutionize bone implant design, leading to more effective and personalized orthopedic solutions.

This section of the paper provides a guideline on the material design requirements for an effective load-bearing orthopedic implants.

4.1. Mechanical requirements

In AM of lattice-based structures, the primary and most critical requirement for load-bearing orthopedic implants is meeting mechanical demands to facilitate tissue integration with the prosthetic device. The design of lattice-based bone implants requires meticulous attention to a range of mechanical requirements to guarantee their optimal performance within the human body's biomechanical environment. Essential considerations include preserving structural integrity, enhancing fatigue strength, minimizing stress-shielding, and addressing implant subsidence [214]. These objectives are crucial for promoting the durability, stability, and integration of porous implants with the surrounding bone tissue. A summary of these fundamental aspects of mechanical requirements is provided below.

4.1.1. Structural integrity and fatigue resistance

Despite the stiffness reduction advantage provided by AM products, recent studies have highlighted the porous architecture as a significant source of implant failure due to device fracture. In this regard, it is important to note that the Food and Drug Administration (FDA) has not yet delivered comprehensive standards and normative guidelines for the commercialization of additive manufacturing medical products [215]. Major concerns regarding the use of lattice structures primarily revolve around their fatigue properties. A standard for mechanical testing is yet to be fully defined, and numerous investigations still need to be conducted to ensure the safety and efficacy of these innovative medical devices [215].

Fatigue is the process of progressive, localized permanent structural change occurring in a material subjected to conditions that produce fluctuating stresses and strains. This can culminate in cracks or complete fracture after a sufficient number of fluctuations [216]. Therefore, the fatigue resistance of metal lattice-based implants is crucial for their application in bone replacements, where they must withstand the physiological time-varying loads of the human body [160,217]. Fatigue typically manifests in localized regions rather than across the entire component, with these areas subject to high stresses and strains from external load transfer, abrupt geometric transitions, residual stresses, and material imperfections. This is particularly significant in porous implants, where the inherent architecture and manufacturing flaws create localized stress conditions that do not necessarily reflect the overall behavior of the component. Consequently, predicting the fatigue strength of a component, especially one with intricate and imperfect geometry, based solely on global properties like stiffness and static strength can be extremely challenging [157].

The fatigue life of a component is influenced by the level of stress applied and can be divided into two main regimes: Low Cycle Fatigue (LCF) and High Cycle Fatigue (HCF). LCF is characterized by high stress levels that cause plastic deformation in each cycle, predominantly driven by crack propagation. In contrast, HCF occurs under lower stress levels, resulting in mainly elastic deformation, where the life of the fatigue is largely governed by crack initiation. Generally, the structural integrity against fatigue is evaluated using a suitable fatigue criterion. This criterion can generally be formulated as Equation (1) [218]:

$$s \leq S_{all} \quad (1)$$

Here, s represents a function indicating the criticality of the loading conditions, often expressed in terms of stresses or strains and thus dependent on geometry (generally at the “macroscopic” level) and applied loads. S_{all} , on the other hand, reflects the material's response relative to the application and depends on factors such as the material properties, expected fatigue life, environmental conditions, manufacturing technologies, and inherent uncertainties.

The specific formulation of the fatigue criterion is generally tailored to the type of component, its intended application, and adheres to national and international regulations. General recommendations

for fatigue assessment can be found in mechanical engineering textbooks [218] and professional guidelines [219]. It is widely recognized that fatigue strength is influenced by a multitude of factors, which are integrated into suitable modifications of Eq. (1). These factors can be grouped into several categories: (1) Load History Effects: This includes the frequency, wave shape, mode of loading, mean stress, variable amplitude, and multiaxial loading. (2) Geometry and Size Effects: These encompass size-related factors and stress concentration effects due to geometric discontinuities. (3) Manufacturing Effects: Factors such as microstructure, surface finish, residual stresses, and thermo-mechanical treatments fall into this category. (4) Environmental Effects: Elements like corrosion, fretting, and temperature also play crucial roles in determining fatigue strength.

Certain effects, such as mode of loading, size, surface finish, and temperature, are commonly integrated into Eq. (1) using Marin's modifying factors, which apply multiplicative adjustments based on empirical data and theoretical analysis [218]. In the context of porous implants, particularly influential factors include mean stress, size effects, surface finish, and the interaction between corrosion and fatigue. The mean stress effect is commonly illustrated using a Haigh diagram, which plots the oscillatory stress amplitude, s_a , against the mean stress, s_m , using constant life lines [180]. In this particular instance, Fig. 4 displays the results from fatigue tests described in Murchio et al.'s study [210] that investigated the mean stress effect on the fatigue strength of miniaturized specimens designed to resemble the struts commonly used in strut-based lattice metamaterials. The diagram in Fig. 4a includes several empirical relationships that correlate alternating stress to mean stress level, juxtaposed with experimental data. Below each curve in the diagram, the region represents infinite life ($N_f > 10^7$), while the region above indicates finite life. Similar plots are reported in the literature for tests undertaken on lab-scale specimens composed with a certain number of unit-cells, however, these investigations are limited only to the compression-compression fatigue regime.

The size effect on fatigue generally exhibits a trend opposite to that observed in conventional fully solid materials [210]. Specifically, the submillimeter dimensions of the structural elements in porous components present significant manufacturing challenges, particularly concerning manufacturing precision and surface finish [220]. The trend depicted in Fig. 4b clearly shows that the fatigue strength tends to decrease as the diameter of the strut decreases. Similar observations have also been reported for lab-scale specimens featuring porous architecture [221]. Based on these observations, it can be stated that size and surface finish effects can be hardly considered separately as done conventionally with two distinct Marin's modifying factors.

At the lattice structure scale, two different categories of lattice topologies are gaining interest in the development of porous prosthetic devices, TPMS and auxetic. Considering firstly the TPMS cells, the fatigue performances of these lattice structures is remarkable, thanks to their continuous geometry able to limit the critical locations encountered in the nodal locations of strut-based topologies [222]. To improve fatigue performances, TPMS lattice can be tailored, performing an oculte selection of the cell topology [181,223], or generating a porosity gradient in the specimens [181]. Moreover, to mitigate the manufacturing induced defects and thus increase the fatigue resistance, post-processing operations can be performed such as Hot Isostatic Pressing (HIP) and sandblasting [181], or chemical etching [224]. The usage of these lattice structures topology is already impacting the development of prosthetic devices, as in remarkable case studies on hip prosthetics [225,226] or spinal ones [227].

Cells with auxetic properties are of interest in the field of lattice porous prosthetic for their valuable characteristic of reducing the stress-shielding effect. However, researchers studying these structures found valuable fatigue properties given by the geometrical nature of these components. Given the bending dominated nature of these topologies, it was found that their resistance is comparable to the one expressed by

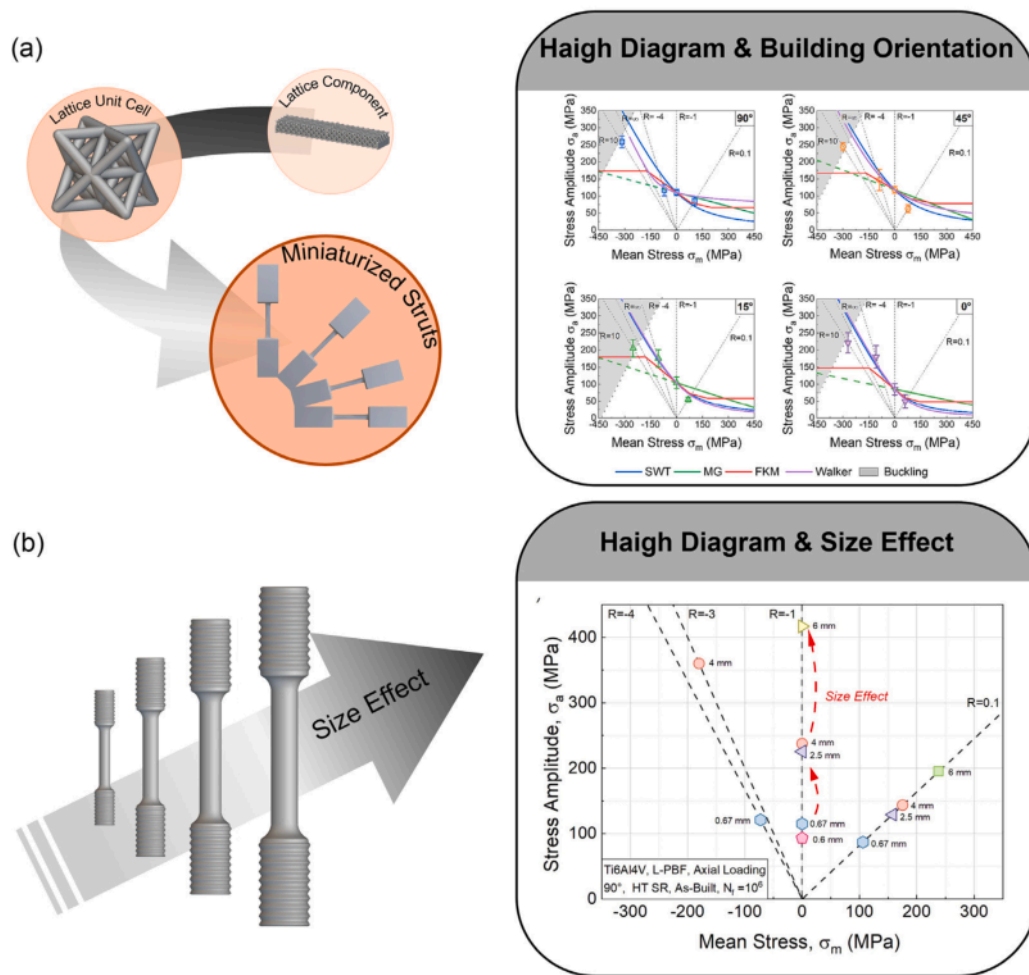


Fig. 4. (a) On the left, a schematic representation of the top-down approach employed in [210] for fatigue characterization of sub-unit miniaturized specimens extracted from strut-based lattices. On the right, Haigh diagrams at 10^7 cycles for L-PBF Ti-6Al-4V thin strut specimens tested at four different building orientations (90° , 45° , 15° , and 0° with respect to the job plate). Fatigue data were gathered for four stress ratios: $R = 0.1$ (tension-tension), $R = -1$, $R = -4$, and $R = 10$ (compression-compression). (b) On the left, a schematic representation illustrating the size effect, showing specimens with varying nominal diameters. On the right, Haigh diagrams from [210] displaying fatigue data at 10^7 cycles for different stress ratios and L-PBF Ti-6Al-4V specimens of varying nominal sizes, manufactured with consistent printing and heat treatment parameters.

Source: Figures adapted from [210].

stretching dominated cells [166], allowing the development of auxetic porous prosthetic devices [228] for spinal applications.

As evident in the mentioned practical examples, the intricate inter-relationship of lattice structures geometry, cannot be adequately addressed using traditional methods codified in fatigue design guidelines. Therefore, typically, numerical simulations are required to accurately determine the stress-strain state within the lattice. These simulations often model the actual, rather than nominal, geometry to also account for surface finish effects on stress evaluation. Further details will be provided in Section 5.2.

An indispensable validation step of fatigue design is fatigue testing, wherein implant prototypes are subjected to time varying loads, in laboratory environment and under uniaxial loading. For instance, six mechanical tests, including static axial compression, compression-shear, torsion test, dynamic axial compression, compression-shear, and torsion test are prescribed by FDA per the methods described in ASTM F2077-24 [229]. In each test, devices are fixtured into a load frame and a static or dynamic load or torque is applied. Cyclic tests are run until device failure occurs or the device reaches 5 million cycles without failure [230–233]. Partial and total hip replacements are in general fatigue tested according to the standard ISO 7206-4 [234]. The implant prototype is distally fixed through mounting in a curable epoxy resin or artificial bone [180,235] and oriented at 10° adduction within the

coronal plane and at 9° flexion within the sagittal plane. The femur head is loaded through a low friction device attached to a uniaxial testing machine.

In addition to *in vivo* tests on implant prototypes, research into the impact of the physiological environment on the fatigue strength of lattice cellular materials has been limited. Notably, preliminary tests on additively manufactured Ti-6Al-4V structural alloy, as documented in Borrego et al. study [236], have shown that fatigue crack growth rates are significantly faster in a NaCl solution than in air. This highlights that fatigue testing, particularly when conducted under conditions that closely represent the actual geometry and loading scenarios, is an indispensable component of validating fatigue design.

The fatigue design process is inherently iterative, integrating both analysis and testing. Solely relying on fatigue testing is not a comprehensive strategy, as it should serve primarily to verify product durability rather than underpin the entire design process [237]. Likewise, relying exclusively on analytical models is insufficient, especially for safety-critical components, as current fatigue life models and software may not encompass all necessary complexities. A robust fatigue design necessitates both analysis and testing. A detailed and iterative analysis, paired with optimization, facilitates the development of prototypes that closely mirror the final product, potentially diminishing the scope and cost of further testing.

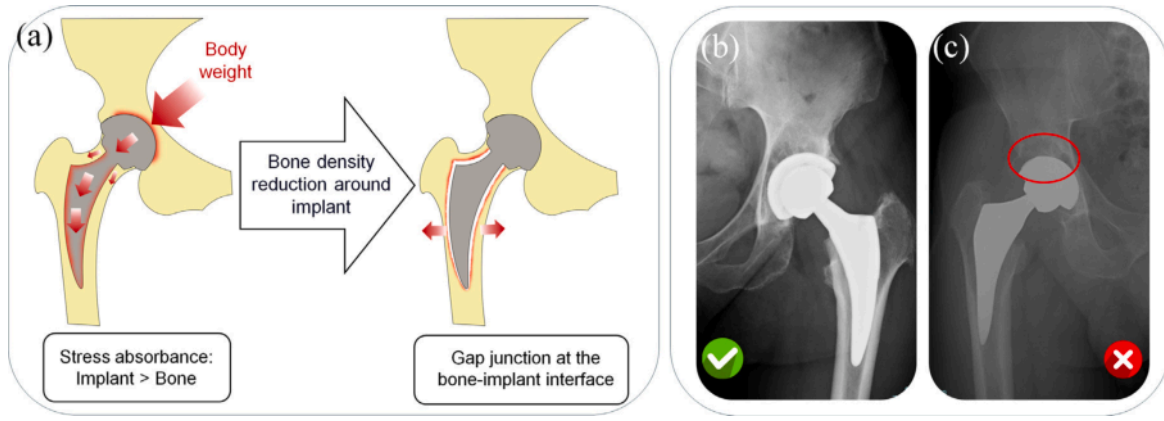


Fig. 5. (a) Stress-shielding effect; (b) Radiograph showing proper bone integration into the implant cap; (c) Radiograph showing poorly integrated acetabulum (The radiolucent area indicated by red circle signifies loosening of the implant cap). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.1.2. Stress-shielding minimization

A significant concern with commercially available orthopedic implants is the stress-shielding effect (Fig. 5a) [238]. This occurs when the implant is considerably stiffer than the original bone, generating a mismatch in mechanical properties that alters the load distribution, causing the synthetic component to bear most of the load. This imbalance prompts bone cells to reorganize the bone topology, leading to bone formation or resorption as it adapts to the novel loading condition. This natural phenomenon can be critical for implant stability since often results in the loss of a significant part of the cortical bone [238]. Consequently, the mechanical performance of the remaining bone diminishes, increasing the risk of implant loosening and bone fractures, ultimately necessitating implant revision (Fig. 5b–c). Fortunately, additive manufacturing offers a solution by enabling the fabrication of lattice-based structures, which reduce the Young's modulus by decreasing material mass. With careful design of specific struts and sheets, these structures help minimize stress shielding, enhancing implant performance.

Literature addresses this issue, particularly focusing on hip implants following total hip arthroplasty (THA) procedures. In this field, the unmatched reference is given by the work of Huiskes et al. [238], where the process of bone remodeling is driven by the natural behavior of the bone to fulfill Equation (2):

$$S_{\text{implant}} - S_{\text{ref}} = 0 \quad (2)$$

Where S_{implant} and S_{ref} are respectively the average strain energy density (SED) normalized on the bone density of the remaining bone after surgery and of the intact bone. This is nevertheless not sufficient to describe bone remodeling, since this effect is triggered by a minimum mismatch between the post-surgery and the intact strain energy density. This activation threshold also known as “dead-zone”, is computed as $(1 \pm s)S_{\text{ref}}$ where s is parameter calibrating this effect, which ranges from $s = 0.35$ to $s = 0.75$ depending on bone reactivity. Turner et al. [239], suggest $s = 0.60$ after a two-years follow up study. The remodeling rule can therefore be proportional to Eq. (3):

$$\frac{d\rho}{dt} = \begin{cases} S_{\text{implant}} - (1-s)S_{\text{ref}} & \text{if } S_{\text{implant}} < (1-s)S_{\text{ref}}, \\ 0 & \text{if } (1-s)S_{\text{ref}} \leq S_{\text{implant}} \leq (1+s)S_{\text{ref}}, \\ S_{\text{implant}} - (1+s)S_{\text{ref}} & \text{if } S_{\text{implant}} > (1+s)S_{\text{ref}}, \end{cases} \quad (3)$$

A direct measurement of bone strain is experimentally performed by Arabnejad et al. [159] with the Digital Image Correlation (DIC) technique.

In recent years, various authors have addressed the stress-shielding problem, referencing Huiskes and introducing the Stress Shielding Index (SSI) for bones with constant density and minimal strain [240].

This index is a measurement based on Von Mises stresses defined as Eq. (4) [241]:

$$SSI = \frac{\sigma_{\text{implant}} - \sigma_{\text{ref}}}{\sigma_{\text{ref}}} \quad (4)$$

$$\sigma_{\text{ref}} = \frac{\sum_{e=1}^{N_{e,r}} \sigma_{VM,e}}{\sum_{e=1}^{N_{e,r}} V_e}, \quad \text{and} \quad \sigma_{\text{implant}} = \frac{\sum_{e=1}^{N_{e,i}} \sigma_{VM,e}}{\sum_{e=1}^{N_{e,i}} V_e} \quad (5)$$

Where $\sigma_{VM,e}$ is the Von Mises stress of the element e , V_e the element volume, and N_e is the number of elements in the region of interest. This approach is followed by different authors [4,180,242], with minor changes in the algebraic sum in Eq. (4). The usage of porous devices is surely beneficial in this sense, reducing the stiffness mismatch provided by bulk prosthetic devices. Practical implementations can be addressed in Section 5.3.

4.1.3. Implant subsidence minimization

Minimizing implant subsidence is crucial for ensuring the stability and longevity of implants. Subsidence, or the sinking of an implant into surrounding bone, can lead to complications such as loosening, instability, and discomfort. Orthopedic surgeons address this by designing implants that promote secure fixation and even load distribution. They evaluate biomechanical forces acting on the implant and bone, tailoring surgical techniques to minimize stress at the implant–bone interface [243]. Precise placement and alignment, supported by advanced tools like surgical guides or navigation systems, choosing biomaterials with suitable mechanical properties, promoting osteointegration, designing patient-specific implants, and postoperative rehabilitation techniques are strategies to reduce subsidence and enhance stability of implant [244].

Subsidence is a significant post-operative complication in orthopedic implants, particularly in spinal fusion and total hip arthroplasty (THA), where implants endure high load distribution and substantial stiffness differences relative to adjacent tissues. As a result, numerous studies aim to match the mechanical properties of surrounding tissues, often through the introduction of porous structures or the selection of suitable materials [245–249]. The following discussion will focus on spinal fusion and THA, where the incidence of subsidence has been highlighted in numerous studies.

Intervertebral body fusion devices consist of single or multiple components, made of materials such as titanium and polymers that are intended to be placed within the intervertebral body space, from the cervical region to the lumbosacral spine. They are typically used in conjunction with graft materials injected into the center of the window (Fig. 6a) to address spinal diseases and promote bone regeneration [250]. There are open-source designs with additive manufacturing

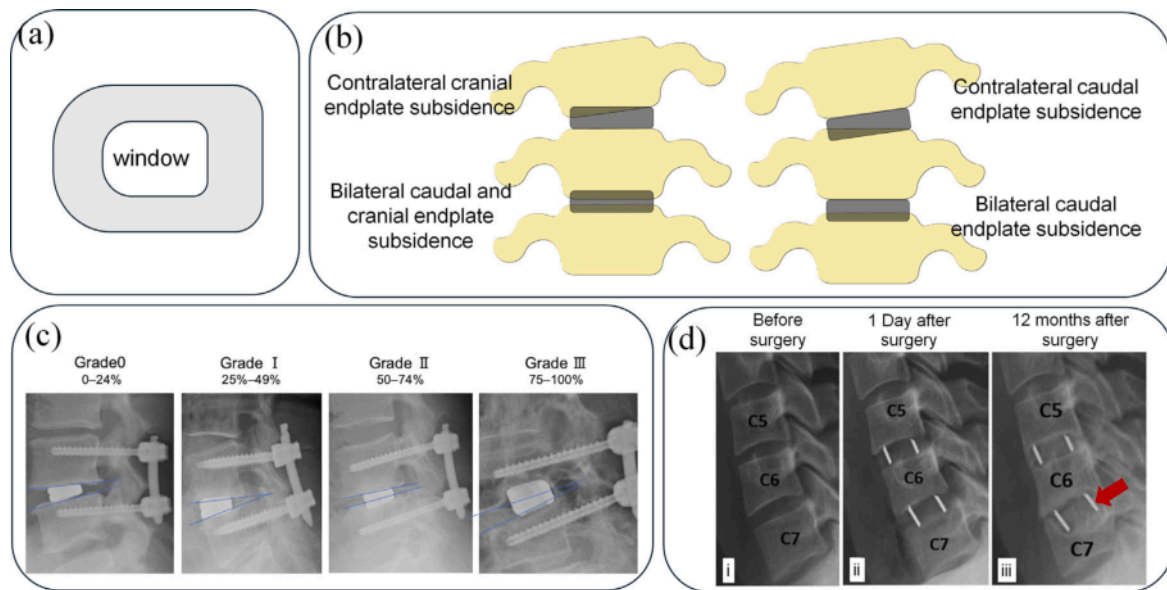


Fig. 6. (a) A simplified design of intervertebral body fusion devices; (b) Types of subsidence based on [260]; (c) Radiographs showing examples of the cage subsidence grades. Adapted from [261]; (d) Radiographs showing case of cage subsidence after 12 month follow-up. Adapted from [262].

technologies, which are intended to assist in the validation of the manufacturing process and benchtop mechanical performance assessments on the FDA webpage [251]. However, many studies have revealed that fusion cages can undergo subsidence over time, leading to a collapse of the intervertebral space. This can result in complications such as cage dislocation or non-union with instability at the incision site, referred as implant subsidence (Fig. 6b, c). Therefore, improving the surface roughness, surface morphology, as well as mechanical properties of cages has become a key area of research to tackle subsidence complications [252]. Interbody fusion cage subsidence is a significant challenge in spinal fusion surgery, leading to compromised fusion rates and poor patient outcomes, including an increased risk of revision [243,244,253–255]. In a systematic review, Shen et al. [256] identified factors contributing to cage subsidence, including age, osteoporosis, endplate injury, and over-distraction of the intervertebral space.

Increasing societal expenses of the spinal degenerative disc diseases (DDD) and escalating trend of low back incidences among adults [257–259], makes fusion surgery useful to treat patients by fusing adjacent vertebrae.

The sinking phenomenon in case of fusion cage subsidence, occurs around an implanted spinal device resulting in the loss of intradiscal height. In terms of subsidence, there is not only ASTM F2077-24 [229] offer general guidance for mechanical evaluation, but also the ASTM F2267-24 [250] provides a specific evaluation procedure with a test setup for the subsidence test on the intervertebral body fusion devices.

As previously discussed, stress shielding is a significant concern in many post-surgery scenarios involving conventional metal implants which leads to an uneven load distribution at the interface of implant and bone (Section 4.1.2). In the case of fusion cages, stress is primarily concentrated on the main body of the device, which can result in unacceptable subsidence and graft resorption [263]. To address this issue, extensive research has focused on designing interbody cages with optimal materials and architecture to create a conducive environment for successful fusion outcomes. Steffen et al. [264] has shown that a wide-open window design, allowing more graft bone to be in direct contact with the adjacent endplates, offers biological advantages. Kanayama et al. [265] found that larger contiguous pore sizes were more effective in mitigating stress shielding. Adl Amini et al. [266] conducted a 6–12 month follow-up study and demonstrated that 3D-printed porous titanium cages are less likely to cause subsidence compared to PEEK-based

cages after lateral lumbar interbody fusion. The emergence of porous titanium devices, facilitated by advancements in additive manufacturing technology, presents a promising solution to reduce cage stiffness and mitigate the risk of subsidence while maintaining favorable osseointegration properties. Various porous titanium interbody fusion cages have been developed, incorporating design modifications aimed at optimizing the cage's architecture and surface textures [244,253–255]. Additionally, Tunc et al. [267] demonstrated that PLLA bioresorbable fusion cages, compared to titanium cages, could enhance fusion due to their reduced stiffness after six months, thereby facilitating new bone growth. For the main body of the cage, Faizan et al. [268] found that larger cages were better able to bear functional loading, resulting in a lower risk of subsidence. More recently, Toop et al. [269] assessed that 3D-printed porous titanium cages, compared with solid cages, protected patients against subsidence by more closely matching the modulus of human bone. Overall, there is strong evidence suggesting that an optimized fusion cage design should avoid stress shielding, allowing the graft to receive the mechanical stimulus necessary for it to heal and fuse directly with the vertebral endplates.

Subsidence occurs in all orthopedic implants, not just intervertebral cages. Regarding hip implants, cementless femoral stems are widely used in primary total hip arthroplasty (THA) for their ability to engage with the metaphysis and transfer load proximally while maintaining bone integrity. Successful implantation requires achieving primary fixation of the femoral stem, ensuring osseointegration, and maintaining its position over time. Leiss et al. [270] documented femoral stem subsidence after primary THA using various stem designs, finding that subsidence rates were notably higher in the enhanced recovery group compared to the partial weight-bearing group when using a collarless cementless femoral stem. However, these differences, while statistically significant, may not be clinically relevant due to the minor absolute values observed. Nonetheless, while there is research on porous interbody fusion cages, studies specifically addressing porous femoral stems and their influence on subsidence are notably absent from literature.

4.1.4. Corrosion and wear resistance

As it is well known, implant stability is influenced by both strength and the integration with surrounding tissues. This integration is enhanced as bone tissue grows into a porous metal matrix, securing the implant. Further properties must be investigated to understand this integration process. One of these parameters is biocorrosion, which,

unlike typical corrosion, affects implant osseointegration due to the body's corrosive environment. This necessitates the study of corrosion properties alongside mechanical properties and fabrication methods. Biomedical materials experience corrosion when exposed to body fluids, primarily due to corrosive substances such as chloride ions and proteins. Within the body, orthopedic implants undergo chemical reactions involving metal oxidation and reduction of oxygen to hydroxide ions. Fretting corrosion poses a common concern in load-bearing orthopedic implants, resulting from cyclic loading and minor movements at interfaces, which can generate debris, raising concerns about potential toxicity and inflammation. For example, even with a perfect interlocking design, micro-movements in total hip implants can lead to fretting corrosion. Most metallic orthopedic implants possess passive layers on their surfaces, which significantly inhibit general corrosion. The formation and stability of these oxide layers are influenced by the strength of the electric field and can be compromised, leading to dissolution.

Notably, AM offers precise control over microstructure, as well as high repeatability and controllability of morphological and mechanical properties. This reduces defects such as surface pores, porosity, and segregation, which can accelerate corrosion. Despite these considerations, the corrosion behavior of lattice-based metallic biomaterials is still not well-studied [271].

Ebrahimi et al. [272] investigated the effects of pore size and heat treatment on the compression and corrosion behaviors of Ti-6Al-4V sheet-based gyroid structures fabricated by L-PBF in a phosphate-buffered saline (PBS) at 37 °C. They highlighted that the superior corrosion resistance in the heat-treated lattice structures was due to the microstructural change from acicular α' martensite to $\alpha + \beta$ phases. This improvement is justified because α' martensite, being a higher-energy, non-equilibrium phase, reduces corrosion resistance [273]. Conversely, in Ti-based alloys, the β phase demonstrates a greater capability to form a stable protective oxide film compared to the α and α' phases promoting corrosion resistance [274]. Considering the effect of pore size ranging from 600 to 1200 μm , greater corrosion resistance was achieved by increasing the pore size. In a different study by Longhitano et al. [275], the electrochemical behavior of EB-PBF Ti-6Al-4V solid and lattice structures with pore sizes of 500, 700, and 900 μm in PBS at 37 °C was evaluated. The lattice structures exhibit a higher susceptibility to pitting attacks, but these occur at a high potential of 2.25 V, which exceeds typical in-service potential values. Electrochemical Impedance Spectroscopy (EIS) revealed thicker native oxide layers after 168 h of immersion for the lattice structures, confirming good protective properties. Overall, the study concluded that Ti-6Al-4V lattice structures demonstrated satisfactory corrosion resistance suitable for biomedical implants, though further research is needed on topology-specific corrosion mechanisms. Corrosion resistance could be influenced not only by pore size but also by the specific lattice geometries. Puttonen et al. [276] investigated the impact of size and geometry on localized corrosion in 316L lattices fabricated via L-PBF, focusing on gyroid and diamond structures. They observed that significant corrosion occurred only in the smaller lattice samples (0.323 mm thickness) of both geometries when exposed to 3.5 wt% NaCl, although this corrosion was passivated within a week. No discernible differences were observed between the two distinct geometries. Corrosion was attributed to surfaces with cavities and partially molten powder. Despite visible pitting, the mass losses were minimal (8–19 mg) and were not related to the size or geometry of the unit-cell. Micro-computed tomography ($\mu\text{-CT}$) analysis indicated mass loss due to detachment or corrosion of trapped powder, without penetration into denser materials. Another study on the corrosion resistance of 316L lattice structures was made by Ravichander et al. [277] highlighting different behavior depending on the geometry. In this research, TPMS structures exhibited superior corrosion resistance compared to solid samples, despite having larger exposed areas. For instance, the diamond lattice showed a notably higher pitting potential of 0.234 V, outperforming other TPMS types

such as Fischer (0.042 V) and IWP structures (0.008 V). Conversely, the solid sample had a considerably lower pitting potential of -0.029 V compared to all TPMS structures. EIS indicated that TPMS lattices had higher overall impedance, with the diamond lattice achieving $0.261 \text{ M}\Omega \text{ cm}^2$, suggesting effective passivation. Charge transfer resistance (R_p) was significantly greater for TPMS structures ($0.049 \text{ M}\Omega \text{ cm}^2$) than for solids ($0.034 \text{ M}\Omega \text{ cm}^2$), underscoring their enhanced corrosion resistance. This study highlights the potential of 316L TPMS lattices for applications requiring durable corrosion protection, although further investigation is necessary to explore specific corrosion mechanisms related to lattice topology. More recently, Munyensanga et al. [271] investigated the corrosion resistance of solid samples and three different lattice structures, namely gyroid, rhombic dodecahedral (RH) lattice, and a hybrid of minimal surface and strut lattices (BD.05), in CoCrMo alloy. Their results underscored the superior corrosion resistance of lattice structures compared to solid samples. Notably, gyroid and BD.05 structures exhibited promising corrosion resistance (R_p), with gyroid at $0.028 \text{ M}\Omega \text{ cm}^2$ and BD.05 at $0.023 \text{ M}\Omega \text{ cm}^2$, compared to RH lattice at $0.018 \text{ M}\Omega \text{ cm}^2$ and solid samples at $0.006 \text{ M}\Omega \text{ cm}^2$. This confirms the superior corrosion resistance of structures based on TPMS.

Another important property that must be considered for implant stability is wear resistance. Wear in bone implants results from mechanical actions like sliding or rolling, which can lead to device failure or the release of particles causing adverse biological reactions [117]. Selecting appropriate biomaterials for the worn part is crucial for implant integrity. In hip joints, titanium alloy femoral heads exhibit the highest wear (74.3%) against UHMWPE, while Co-Cr-Mo alloys have the lowest wear. Surrounding tissues of titanium prostheses accumulate more metal debris compared to Co-Cr-Mo and 316L SS implants [278]. Aseptic loosening necessitates revision surgeries in 10%–20% of metal head and polymer cup joint replacements within 15–20 years, with wear debris causing inflammation, tissue damage, and compromised functionality. Load-bearing joints like the hip and knee have a friction coefficient of about 0.02 and a wear factor of $106 \text{ mm}^3/\text{N}$ [55]. Implant materials' friction coefficients usually range from 0.16 to 0.05, depending on contact materials and lubrication [117]. Shifting from polymer to metal or ceramic cup materials reduces wear and revision surgeries. Metal-on-metal (MoM) prostheses exhibit significantly less wear than metal-on-polyethylene bearings but raise concerns about long-term release of toxic particles due to both surface wear [279]. Ceramic-on-ceramic materials offer less wear due to their strength and crack resistance, though some experience early failures from aging [280]. Interest grows in alumina-zirconia composites leveraging both materials' toughness. However, implant success assessment requires long-term use, complicated by disparities between *in vivo* and *in vitro* wear testing rates [281]. The wear resistance becomes an even more critical parameter in lattice-based AM products. AM enables the fabrication of lattice-based structures that evenly distribute mechanical loads, reducing localized wear on implant surfaces. Longhitano et al. [275] investigated the tribological performance of cubic lattice structures produced by AM with varying porosities (500 μm , 700 μm , and 900 μm), comparing them to solid samples using a ball-on-plate reciprocating sliding setup at room temperature. The dry wear tests revealed similar specific wear rates across all porosities, although potential measurement inaccuracies stemmed from plastic deformation at the interface between the bulk material and pores. They identified abrasive and adhesive wear as the primary mechanisms of material removal. Additionally, the study explored the tribocorrosion behavior, observing that post-sliding repassivation restored the initial protective properties of the surfaces. The presence of PBS altered the oxide composition and morphology, resulting in increased coefficients of friction (COF) but reduced volume loss. These findings highlight the intricate interactions among surface properties, electrochemical responses, and environmental conditions in elucidating wear mechanisms in additively manufactured titanium alloys. Not only the combination of wear and corrosion, but also the combined effects of cyclic loading

and corrosive body fluids accelerate the degradation of biomaterials. Therefore, corrosion fatigue resistance is crucial and influenced by alloy composition, surface conditions, and microstructure [282]. Dynamic loading in corrosive environments poses challenges compared to static conditions. Current research endeavors focus on optimizing processing techniques, developing surface treatments, and enhancing biocompatibility to improve medical device performance and ensure extended lifetimes for titanium implants, especially in the case of lattice-based implants.

4.2. Biological requirements

Biocompatibility stands as the foundation of biomaterial engineering, denoting “the ability of a material to perform with an appropriate host response in a specific application” [213]. In an orthopedic implant, achieving biocompatibility depends on ensuring not only mechanical compatibility, but also biological and histological compatibility within the device lifetime [46]. The goal is to prevent infection and minimize implant-related inflammation while promoting the migration of mesenchymal stem cells (MSCs) from host tissue to the implant. This includes ensuring a favorable surface for cell adhesion, providing a nutrition system, promoting the deposition of extracellular matrix (ECM) proteins and minerals onto the scaffold to initiate tissue formation, and ultimately ensuring tissue vascularization to maintain the functionality of the substitute organ or tissue. AM plays a crucial role in meeting these biological demands by enabling precise control over implant architecture, surface topography, material composition, and controllable biocorrosion. AM allows for the fabrication of porous structures that mimic natural bone, enhancing vascularization and bone ingrowth. By integrating biological considerations with AM capabilities, metallic implants can be tailored to optimize not only mechanical performance, but also long-term biological compatibility and longevity, ultimately improving patient outcomes.

The biological response of the body to an implant is primarily influenced by its surface, making the bone-implant interface a critical topic in this field. At this interface, complex physical and chemical interactions occur between the implant surface and bone tissue. Modifications to surface geometry at the micron, sub-micron, and nanoscale levels can enhance implant anchorage, reducing the risk of implant loosening and the need for revision surgeries. The timeline for achieving osseointegration varies across materials, surface designs, and patient-specific conditions that may affect the healing process [283].

This section summarizes the key biological requirements for successful implantation and review solutions proposed in the literature to optimize bone-implant integration. We began by discussing strategies to control infections following implantation surgery, aiming to reduce the risk of septic loosening. Next, we explored approaches to minimize chronic inflammation, which is crucial for preventing aseptic loosening. We then delved into cellular behavior around the implant, focusing on host tissue responses such as adhesion and proliferation. Finally, we provided a detailed explanation of strategies to promote osseointegration and osteogenic differentiation. Overall, we aim to address the body's potential reactions after implantation and offer solutions to effectively manage these challenges.

4.2.1. Infection control

Periprosthetic infection (PI) occurs in 0.5% to 9% of knee, hip, and ankle total joint replacements, making it one of the failures for arthroplasty [284]. PI is a set of interactions between bacteria or fungi, and the host immune response. A minimal microbial presence can initiate PI, then the organisms can adhere to the surfaces of the implant, produce extracellular polymeric substances (EPS), and form biofilms. Biofilm matures with growth in cell number, enhanced intercellular communication, and merging of smaller colonies. Once the biofilm reaches a critical size, individual bacteria or fragments of the biofilm

detach from the surface and propagate the infection, causing implant-associated infections (IAI) [285]. The cost of treating IAI in the US by 2020 was reported more than \$1 billion [286].

The interaction between bacteria and metal implants is categorized into four steps: adhesion, colonization, biofilm formation, and proliferation [284]. The literature suggests two main strategies for preventing IAIs: (1) reducing the chance of bacterial adhesion or inactivating their ability to produce EPS and (2) preventing the accumulation and colonization of attached bacteria.

Fig. 7 shows the strategies to control infection on a metallic implant. We discuss these strategies in the current section.

4.2.1.1. Antibacterial treatment: The most common approach to preventing IAIs has traditionally been antibacterial treatments aimed at preventing bacterial accumulation and biofilm formation. Diluted antibiotic drugs incorporated into cement or bone graft during surgery are employed to control protein adhesion and the formation of EPS at this stage [284,285]. Vancomycin [287–289], gentamicin [290], tetracycline [291], minocycline [292], cefotaxime sodium [293], and chlorhexidine [294] are among the antibiotics that have demonstrated effective antibacterial properties on titanium-based implants. However, despite the effectiveness of antibiotics in many cases, bacterial resistance, and genetic transfer pose challenges [285].

The alternative approach is employing antimicrobial metal ions like silver (Ag^+) [295], copper (Cu^{2+}) [296] and zinc (Zn^{2+}) [297] in the form of coatings or nanoparticles, which have demonstrated the ability to inhibit bacterial growth on metal alloys [285]. Metallic nanoparticles, which can take the form of nanospheres, nanosheets, nanoplates, nanotubes, and nanorods within the size range of 1–100 nm, are known to exhibit potential antibacterial activity. This efficacy is attributed to their large surface-to-volume ratio, which increases membrane permeability and disrupts microorganism's cell integrity [297,298]. Additionally, they can inactivate DNA replication or other cellular components through the production of reactive oxygen species (ROS) at the site, capable of damaging bacterial membranes [286,299,300]. The drawback of metal ion coatings is their potential cytotoxic effects on host tissue if the concentration exceeds a certain threshold [285]. Even though certain ions may be effective at preventing bacterial growth at very low concentrations (low Minimum Inhibitory Concentration), they can be harmful or fatal to humans at relatively low doses as well (small Median Lethal Dose), making them toxic to the body. Another disadvantage of incorporating antibacterial metal ions into the implant structure is the potential of a decrease in fatigue and corrosion resistance in cases that they are impurity in the substrate metal [284]. For instance, the addition of Cu and Ag to titanium alloys was proved to decrease ductility and increase galvanic corrosion in this alloy [284].

4.2.1.2. Antibacterial surface engineering: The low efficiency of antibacterial drugs once biofilms form, and the toxicity associated with antibacterial metal ions, have led scientists to develop a new approach aimed at preventing bacterial attachment, known as antifouling surface treatment [301]. The bacterial adhesion process is highly dependent on the chemical and physical properties of the substrate surface. Nano- and micro-scale roughness, topography, stiffness, hydrophilicity (wettability), and static charge of the surface play crucial roles in this aspect [284].

Conventional engineered surfaces were initially designed to be non-adhesive or cell-repellent. However, a drawback of this design is its prevention of both bacterial and human cell attachment. With the growing demand for surfaces that are bactericidal yet allow cell adhesion, as well as recent advancements in fabrication techniques, scientists began exploring the impact of surface texture on bacterial behavior [302]. Surface texture is influenced by factors such as geometry, height, width, depth, and spacing of surface patterns. High-aspect-ratio structures like nanopillars and nanotubes can hinder bacterial attachment through membrane rupture or reduced adhesion forces [303]. In contrast, depending on the shape, size, and depth of the channels, microwells and

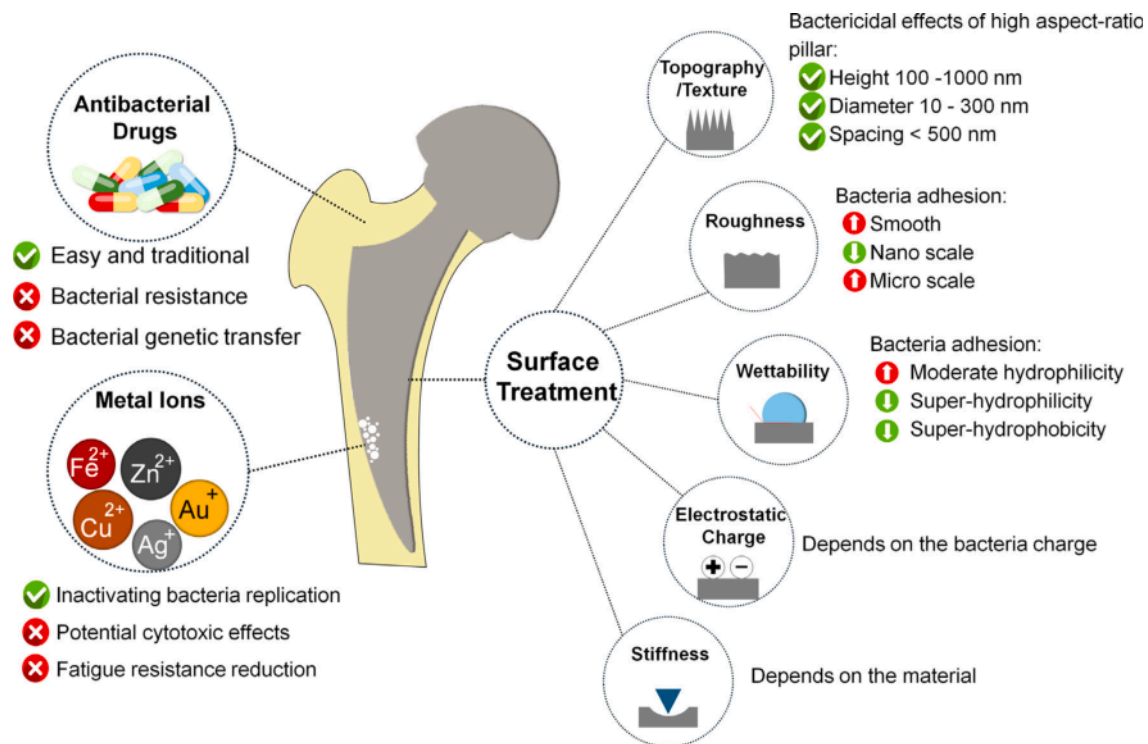


Fig. 7. Summary of infection control strategies on a metal implant.

microgrooves can either isolate bacteria and hinder colonization or provide shelter against shear forces, thereby increasing the chances of colonization [303]. In a systematic review of 46 studies, Modaresifar et al. [302] narrowed the optimal dimensions of surface patterns for exhibiting bactericidal effects to a range of 100–1000 nm in height, 10–300 nm in diameter, with a spacing of less than 500 nm, which is still far from a practical optimum.

Moreover, enhancing surface roughness by incorporating irregular nano- and micro-scale peaks and pits has been shown to reduce bacterial attachment by decreasing the available surface area for adhesion [303,304]. Bacteria are more likely to attach to smooth surfaces ($R_a < 0.2$ nm) than to those with nanoscale roughness ($R_a = 0.2 - 6$ nm) [303]. Smooth surfaces provide a larger area for strong adhesion, while the tips of nanofeatures cause surface tension on bacterial membranes, ultimately resulting in rupture [305]. As nano roughness increases ($R_a = 6 - 100$ nm), bacterial deposition on the surface increases again [303,306]. It is worth noting that bacteria can eventually overcome attachment barriers even on unfavorable surface topographies. To counter this, Lee et al. [307] propose using dynamic substrates made from shape-memory materials and flexible surface features instead of static surface topographies on implants. Most studies show that micro-scale roughness generally increases bacterial adhesion, as the rougher surface enhances adhesion forces and provides valleys that protect bacteria from shear forces during washing (Table 2). However, highly rough surfaces can also trap bacteria, preventing their direct contact with others and preventing colonization, depending on the surface topography [303].

Bacterial adhesion and biofilm formation are believed to be under the impact of surface wettability as well. Wettability is associated with the quantity of hydrogen bonds and other acid–base interactions [303]. Studies show moderately hydrophobic surfaces favor bacterial adhesion by decreasing bacterial velocity through stretching and unfolding the outer membrane proteins, leading to a more stable attachment. The hydrophilic polysaccharide inner layer of the bacteria membrane then facilitates an irreversible bond with the substrate [303,304]. For most metal surfaces, increasing the water contact angle (WCA) to about

95 degrees enhances bacterial growth and biofilm formation (Table 2). However, beyond a certain WCA threshold, bacterial adhesion decreases due to the superhydrophobic effect. Superhydrophobic surfaces are as effective as superhydrophilic surfaces in resisting bacterial adhesion. Superhydrophilic substrates form a hydration layer that hinders bacterial attachment, while superhydrophobic surfaces trap an air layer, creating a barrier against bacterial adhesion [303].

Another factor influencing bacteria adhesion on a material surface is electrostatic surface charge [304]. Bacteria typically carry a negative charge in liquid environments, thus negatively charged substrates can repel bacteria and inhibit their settling on the surface [330,331]. Conversely, positively charged surfaces promote bacteria adhesion in most cases. However positive surface can also be the case for a phenomenon known as “contact-killing” which can compromise the integrity of bacteria membranes and disrupt their cell walls [303,332]. Kao et al. [333] conducted an experiment using layer-by-layer polyelectrolyte assembly method demonstrating that both positively and negatively charged titanium screws could potentially reduce the risk of infection by *P. aeruginosa* and bacterial colonization on implants *in vitro* and *in vivo* stages. Consequently, literature has documented both a decrease [334–336] and an increase [332,337] in the adhesion of gram-negative bacteria to negative surfaces.

Stiffness also plays a significant role in bacterial adhesion and biofilm formation [338–340]. Research on the relationship between bacterial adhesion and surface stiffness has yielded inconclusive results, with various studies reporting conflicting relationships depending on the material, possibly due to changes in the bulk material’s properties such as wettability, roughness, density, and viscosity [341,342]. Consequently, further investigation will be required to clarify this correlation.

4.2.2. Minimizing inflammation

Fig. 8 presents a schematic of biochemical processes that occur immediately after implantation surgery, highlighting two perspectives: the immune system response and the recruitment of stem cells by the body to facilitate healing.

Table 2

Summary of bacterial adhesion studies on metal implants.

Parameter range (unit)	Material	Bacteria species	Result - correlation with bacteria adhesion	Ref.
Nano roughness (nm)				
Ra = 0.16 – 0.21	Titanium	<i>S. aureus</i> and <i>P. aeruginosa</i>	Insignificant	Truong et al. 2015 [305]
Rq = 25.2 – 986	Stainless steel 304	<i>E. coli</i>	Positive	Bohinc et al. 2016 [308]
Rq = 11.58 – 17.99	YSZ coated titanium	<i>E. coli</i> and <i>S. aureus</i>	Positive	Kaliaraj et al. 2016 [309]
Ra = 2 – 6	Stainless steel 304 and Stainless steel 316	<i>S. aureus</i> and <i>S. xylosus</i>	Positive	Azelmad et al. 2017 [310]
Ra = 45.2 – 172.5	Stainless steel	<i>P. aeruginosa</i> and <i>S. aureus</i>	Negative	Wu et al. 2018 [311]
Ra = 113 – 463	Stainless steel 316L	<i>E. coli</i> and <i>S. aureus</i>	Positive	Kumar S. et al. 2019 [312]
Ra = 143 – 463	Ti-6Al-4V		Positive	
Ra = 10.33 – 120.05	Ti-6Al-4V	<i>S. mutans</i>	Positive	Jhong et al. 2020 [313]
Ra = 20 – 280	Nitinol (NiTi)	<i>E. coli</i> and <i>S. aureus</i>	Positive	Jang et al. 2023 [314]
Micro roughness (μm)				
Ra = 0.09 – 8.14	Stainless steel 316L	<i>S. aureus</i> and <i>S. epidermidis</i>	Negative	Bagherifard et al. 2015 [315]
Ra = 0.31 – 0.80	Titanium	<i>E. coli</i>	Negative	Lorenzetti et al. 2015 [304]
Ra = 0.2 – 2.7	Titanium	<i>E. coli</i>	Insignificant	Chen et al. 2016 [316]
Ra = 0.283 – 10.835	Ti-6Al-4V	<i>S. sanguinis</i>	Positive	Annunziata et al. 2017 [317]
Ra = 0.09 – 2.98	Titanium	<i>S. epidermidis</i>	None	Wassmann et al. 2017 [318]
		<i>S. sanguinis</i>	Positive	
Ra = 0.10 – 0.45	Titanium	<i>S. mitis</i>	Positive	Huang et al. 2019 [319]
Ra = 0.017 – 0.363	Titanium	<i>S. mitis</i>	Positive	Huang et al. 2019 [320]
Ra = 0.68 – 2.34	Ti-6Al-4V	<i>S. mutans</i>	Positive	Jhong et al. 2020 [313]
Ra = 0.02 – 0.13	Titanium	<i>S. mutans</i>	Insignificant	Hjerpe et al. 2021 [321]
Ra = 0.01 – 0.04	Cobalt-chromium (CoCr)			
Ra = 0.78 – 10.33	Copper coated stainless steel 316L	<i>E. coli</i>	Highest adhesion at Ra = 1.34 μm	Alhussein et al. 2023 [322]
Hydrophobicity (°)				
WCA = 31.9 – 74.3	Titanium	<i>S. aureus</i>	Positive	Chan et al. 2017 [323]
WCA = 45.7 – 72.6	Ti-6Al-4V			
WCA = 65.2 – 106.5	Titanium	<i>S. epidermidis</i>	Positive	Wassmann et al. 2017 [318]
WCA = 27.1 – 82.9	Beta titanium alloy (TNZT)	<i>S. aureus</i>	Positive	Donaghy et al. 2020 [324]
Super hydrophobicity (°)				
WCA = 49 – 96	Stainless steel 304	<i>E. coli</i>	Negative	De Giorgi et al. 2017 [325]
WCA = 84.2 – 94.3	Silane-coated stainless steel 316L	<i>S. aureus</i>	Negative	Zouaghi et al. 2018 [326]
WCA = 88.5 – 102	Stainless steel 316L	<i>E. coli</i> and <i>S. aureus</i>	Negative	Kumar S. et al. 2019 [312]
WCA = 83 – 96	Ti-6Al-4V			
WCA = 95.3 – 114.5	Ti-6Al-4V	<i>S. aureus</i>	Positive	Sarker et al. 2019 [327]
WCA = 30 – 150	Titanium	<i>S. mutans</i>	Negative	Souza et al. 2020 [328]
WCA = 67.6 – 176.3	Titanium	<i>Pseudomonas sp.</i> and <i>Bacillus sp.</i>	Negative	Manoj et al. 2020 [329]

Immediately after implantation, the implant surface is coated with water molecules followed by proteins, which, along with cytokines from damaged cells, trigger a foreign body reaction (FBR). Immune system cells are then recruited to the site to manage the response through phagocytosis. Regardless of the foreign material type, macrophages defend the body against pathogens [343]. However, if macrophages cannot clear the foreign material, it can lead to frustrated phagocytosis,

chronic inflammation, formation of foreign body giant cells (FBGC), and fibrous encapsulation [344]. This involves the development of a fibrous capsule by fibroblasts around the implant, preventing proper bone contact, physically isolating the device, potentially disrupting its functionality, causing patient discomfort, and disconnecting cell-seeded implants from nutrient support and eventually complete failure of implantation [344,345].

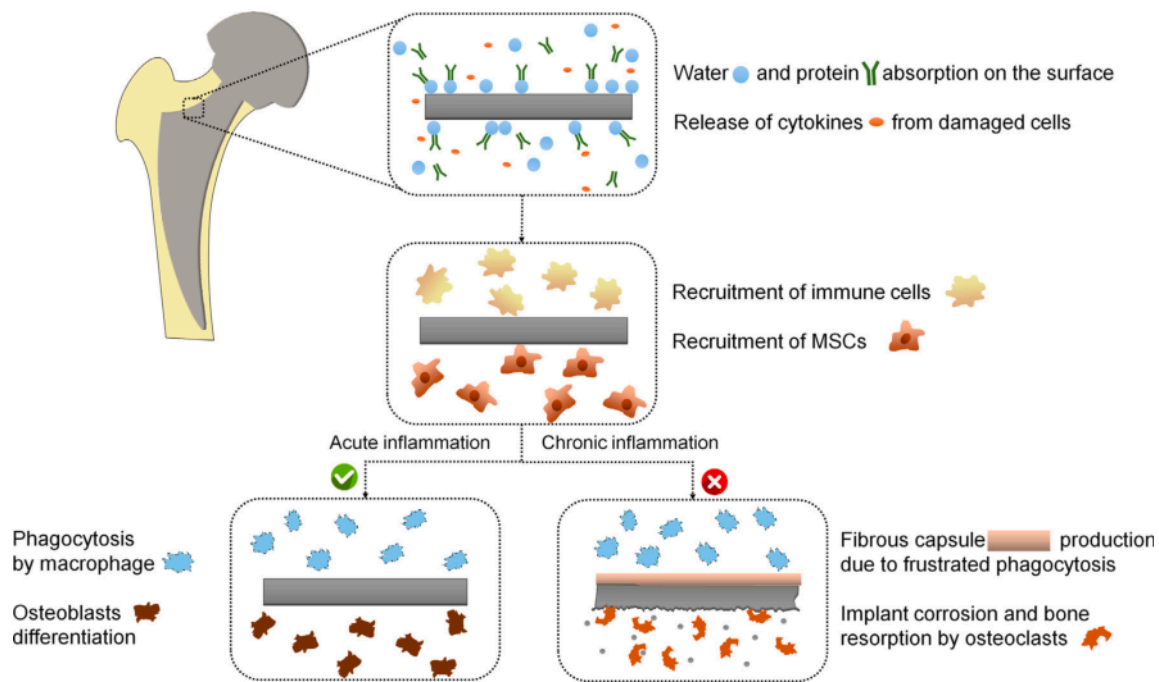


Fig. 8. Schematic process of wound healing after implantation surgery on the surface of the implant.

For successful osseointegration, MSCs must differentiate into osteoblasts and osteocytes, leading to new bone formation, initiated by an early pro-inflammatory response [345]. Another possible scenario upon activation of macrophages in chronic inflammation is that the release of cytokines and inflammatory mediators at the surgery site promotes the differentiation of osteoclasts instead of osteoblasts, contributing to osteolysis [285,343,346]. Osteoclasts start a bone resorption process on host tissue, resulting in aseptic loosening, and long-term failure of implant [285,343].

During the inflammation phase, macrophages begin to generate ROS, which decreases the pH in biofluids and initiates potential corrosion of the metal surface. The implant surface can oxidize in the corrosive body fluid, releasing ions into periprosthetic areas [91]. The *in vivo* corrosion of permanent load-bearing implants is a significant concern, as the release of heavy metal ions can shorten implant lifespan and affect patient health. Non-essential ions like nickel, chromium, cobalt, vanadium, and aluminum can reach toxic levels in the body and cause adverse effects such as dermatitis, neurological toxicity, and Alzheimer's disease [83]. In a study by Bigueti et al. [347] the *in vivo* effect of titanium alloy corrosion was investigated. Corroded cpTi and Ti64 screws proved to trigger a prolonged FBR with chronic inflammation lasting up to 21 days. Corrosion led to osteolysis and bone loss, and corroded implants predominantly induced an M1-type inflammatory response, hindering healing and osseointegration. For this reason implants must endure a highly corrosive environment immediately following surgery, especially during the initial stages of inflammation. There is evidence indicating that specific types of macrophages can also exhibit corrosive behavior toward metal implants, contributing to ion release [348]. Additionally, osteoclasts have also been reported to induce corrosion in metal implants, a phenomenon known as inflammatory cell-induced corrosion (ICIC) [85]. For these reasons, achieving successful osseointegration first requires balancing the FBR to avoid chronic inflammation and fibrotic encapsulation.

Moreover, tribocorrosion resulting from repeated movements in orthopedic implants generates wear debris (Section 4.1.4), which can elicit an inflammatory response in the host tissue [349]. In this process, mechanical loading removes the passive film on the metal surface, exposing the underlying active metal to bodily fluids. This exposure significantly accelerates the corrosion rate – a phenomenon known

as wear-accelerated corrosion – which is a major contributor to joint degradation [350]. The macrophage activation to digest this wear debris causes periprosthetic inflammation with the same mechanism described as the paragraph above. Aseptic loosening, resulting from infection-free inflammation due to particles released from the implant over time, is the leading cause of failure in orthopedic implants, accounting for over 70% of hip revisions and more than 44% of knee revisions [343].

Optimal material selection for implant manufacturing, which can withstand chemical factors such as exposure to corrosive bodily fluids and oxidative environments post-inflammation, as well as mechanical stressors like micro-motion, friction, vibration, and fatigue from repetitive motion, is key to avoiding infection-free failures [349]. The general guidelines for choosing metallic biomaterial are discussed in Section 2. As previously mentioned, titanium and Co–Cr alloy alloys are among the most favored metals for orthopedic applications due to their ability to form a stable passive layer in body fluids, protecting the implant from biocorrosion.

Apart from the material selection, several studies have attempted to improve the corrosion resistance of metal implants with various surface treatments that offer potential benefits such as osteointegration, antibacterial activity, and friction reduction as well as corrosion resistance (see Section 4.1.4). Surface modifications of titanium implants such as alterations in roughness [351], TiO₂ nanoparticle (NP) coating [352], plasma electrolytic oxidation (PEO) coating [353], and surface hydrogenation [354] have been demonstrated to impact the activation of the immune system. Laser-induced surface topography on AM Ti-6Al-4V has been shown to impact passivation behavior and enhance corrosion resistance [355].

Lattice design parameters were introduced as another important factor in dealing with the corrosion resistance of AM metallic implants. Munyensanga et al. [271] investigated the corrosion resistance of AM porous CoCrMo implants with TPMS gyroid and rhombic dodecahedron (RH) lattice structures. Electrochemical testing in simulated body fluid (SBF) compared these designs to a solid sample and a mixed geometry of both unitcells (BD.05). Results showed that corrosion resistance generally increased with surface area. BD.05 exhibited better corrosion resistance than RH, similar to gyroid, though still lower than the solid sample. The study also emphasized the critical role of manufacturing

and post-processing in influencing corrosion behavior, highlighting the need to optimize these factors for improved implant performance. In another study, the *in situ* corrosion behavior of Ti-6Al-4V alloys with cellular structures, fabricated via EBM, was studied in PBS [356]. Results showed that as pore depth increased, H^+ and Cl^- concentrations rose while surface potential declined. Despite this, the internal surfaces remained passivated after 14 days of immersion at $37^\circ C$, regardless of pore depth. At the deepest pores, a thinner passive film with higher donor density formed, likely due to limited oxygen supply and chloride ion adsorption within the pores.

Bio-tribocorrosion resistance is specifically required for implants connected to joints because they undergo relative motion, which leads to metal-on-metal rubbing. Addressing tribocorrosion due to the patient's needs in clinical situations is complex. As the passive films on the native surface degrade due to abrasion and oxidation during the relative motion of the surrounding joints. Ideally, the contact of the fresh surface with the medium should trigger the formation of a fresh passive film, which protects it from further corrosion and wear [357]. In the case of THA, MoM devices are favored for younger patients due to their higher wear resistance, superior mechanical properties, and greater stability, which accommodate a broader range of motion and high-impact activities [285]. Cases of osteolysis are fewer in MoM implants compared to polymeric-coated implants, possibly because metal ions are smaller and more easily phagocytized and removed [343]. However, metal ion release can elevate concentrations in blood serum for up to 10 years post-implantation, leading to issues such as nerve damage, gray-green tongue spots, and hearing loss [85,285]. Consequently, MoM hip replacements have not been FDA-approved in the US since 2016 [285].

To mitigate complications, polymeric materials have gained popularity due to their lower friction coefficient, which reduces wear debris in contact with the metal components [285]. However, macrophages may struggle to digest large polymer debris molecules, releasing inflammatory mediators and initiating the formation of granulomatous tissue rich in activated macrophages [343].

A comparison of the bio-tribocorrosion behavior of selectively laser melted (SLM) Titanium-25% Niobium and conventionally manufactured Ti-6Al-4V under inflammatory conditions revealed superior performance and biocompatibility of Ti-25Nb [357]. This is attributed to SLM-induced compressive residual stresses, a smoother worn surface, denser Nb oxide layers, and the low toxicity of niobium. However, there remains a significant gap in the literature regarding the bio-tribocorrosion behavior of additively manufactured lattice-based metallic implants, which is yet to be thoroughly explored.

4.2.3. Cell adhesion and proliferation

Cell adhesion is essential for initiating cellular processes such as migration, proliferation, and differentiation, and eventually tissue formation [358]. The key to successful bone repair lies in the rapid recruitment, adhesion, and spreading of reparative cells, followed by the deposition of extracellular matrices. Various growth factors and cytokines are employed to influence host cell infiltration.

Physical guidance can also promote bone repair by affecting cell behaviors such as adhesion and migration direction [359]. Features on the surface of the implant including topography, roughness, wettability, stiffness, surface energy, and charge can significantly influence protein adsorption and cell adhesion [358]. The interaction of cell membrane receptors with external molecules, specifically adsorbed proteins on the implant surface, triggers a cascade that rearranges the cytoskeleton, and results in different cellular responses [360,361]. Highly ordered nanotube [362] and nanogrooves [363], nanopits [364], and nanopillars [365] are just a few examples of surface topography enhancement to achieve efficient cell adhesion, migration, and osseointegration on metal implants. Factors such as aspect ratio, spacing and depth of each pattern proved to have a role in increasing or decreasing of cell

adhesion response, although the exact amount of each value is still inconclusive [302].

Regarding roughness, nano-scale surface roughness is considered beneficial for promoting cell attachment as it closely mimics the natural topography of tissue surfaces [366], facilitates optimal cellular interaction [358,360], and offers an expanded area for mechanical anchoring of cells [361]. For instance, nano-scale pits and pillars ($R_a \approx 30 - 40$ nm), due to their abundant protein adsorption, enhance cell motility by providing more protein ligands for filopodia, whereas larger dimensions, the tops of the pillars and the bases of the pits resemble a flat surface until the edges are reached [367]. In a sub-micron scale, smooth surfaces ($R_a < 0.5$ μm) tend to attract fibrotic cell adhesion, whereas rougher surfaces ($R_a > 0.5$ μm) are conducive to pre-osteogenic cell attachment, thereby reducing the likelihood of fibrous tissue formation and implant loosening [361,368]. A recent study compared the viability behavior of osteoblast and fibroblasts on Ti discs and concluded micropores (5 – 10 μm) enhance osteoblast adhesion while nanopores (1 – 5 nm) improve fibroblast adhesion and viability significantly [369]. Micro-scale roughness has been reported to exert positive or negative effects on cell adhesion and morphology [358,360]. Table 3 suggests that micro-roughness up to a certain level ($R_a \approx 20 - 25$ μm) improves cell adhesion in most cases. The reason according to Jahani et al. [370] is creating small shelters for cells, aiding in their attachment and growth. Lerebours et al. [368] believe that since osteoblast size is in the range of 20-25 μm , higher roughness cannot trigger mechanosensing of this cell. However, beyond this point, increased roughness can result in deep pits that trap cells, isolating them from others and rendering them inactive [367,370]. Rahmati et al. [360] highlighted contradictions in how surface roughness affects different materials and cell types, but still believe that designing biomaterials with multiscale surface roughness at both micro- and nano-scales can enhance cell responses. A roughness gradient improves interactions between various cell or protein types on the surface. Despite extensive research, the optimal roughness for successful implant design remains inconclusive due to conflicting arguments. Some researchers argue that although increased roughness provides more surface area for cell anchorage and a better 3D environment for cells, it also leads to more friction, wear debris generation, and inflammation [370].

Another factor that can affect cell adhesion is material stiffness. Material stiffness acts as a mechanical stimulus that cells convert into biochemical responses through the mechanotransduction process. When studying the effects of stiffness on cell behavior, we must consider the challenges posed by the synergistic interactions of stiffness, topography, and material composition, which are difficult to isolate. Additionally, cells may respond differently to stiffness levels based on their type and the stiffness of their natural tissue environment. Consequently, the results can be specific to the material, cell type, and application [360]. Cells can detect a mismatch between the stiffness of natural tissue and an implant, recognizing it as a foreign body [360]. Therefore, it is crucial to mimic the stiffness of the target tissue to activate beneficial cellular behaviors.

The surface wettability of the implant can affect cell adhesion through surface protein adsorption on different functional groups. Generally, hydrophilic surfaces are believed to promote better cell adhesion due to optimal protein adsorption [358,366,367,380]. They enhance protein adsorption and cell adhesion due to higher surface energy and the presence of specific chemical groups such as -OH, -COOH, and -NH₂, which increase the possibility of Ca-P deposition that stimulates the biomineralization process [381]. Surface energy, defined as the measure of unsaturated bond energy at a material's surface, plays a crucial role in cell adhesion. High surface energy promotes cell adhesion and spreading, while low surface energy can inhibit cell attachment [358].

In contrast, hydrophobic materials tend to enhance monocyte adhesion compared to hydrophilic materials [359]. Super-hydrophobic surfaces (contact angle $> 150^\circ$) often hinder cell attachment due to

Table 3Comparative *in vitro* studies on metal implants.

Parameter range (unit)	Material	Surface treatment method	Assay type	Result	Ref.
Nano roughness (nm)					
Sq = 1 – 100	Ti-6Al-4V	Nanoparticle deposition	<i>In vitro</i>	The highest number of adhering cells was observed for Sq roughness of 30 nm	Solar et al. 2015 [371]
Ra = 1.8 – 105.6	Titanium	Polishing	<i>In vitro</i>	Negative relation with osteoblast cell attachment, proliferation, and calcification ability	Migita et al. 2017 [372]
Ra = 98.3 – 157.4	Titanium	Machining, sandblasting, etching	<i>In vitro</i>	Moderate roughness affects osteoprogenitor cell adhesion, proliferation, and differentiation	Martinez et al. 2020 [373]
Micro roughness (μm)					
Ra ≈ 20 – 170	Ti-6Al-4V	Blasting + etching	<i>In vitro</i>	Positive relation with osteoblast differentiation	Cheng et al. 2014 [374]
Ra = 0.32 – 10.57	Titanium	Yb:YAG laser vs. Polishing	<i>In vitro</i>	Positive relation with osteoblast activity and differentiation	Mariscal-Muñoz et al. 2016 [375]
Ra = 0.05 – 4.02	Titanium	Sand blasting + chemical polishing	<i>In vitro</i>	Negative relation with osteoblast proliferation Ra = 1 – 2 μm is the optimum value for differentiation	Andruxhov et al. 2016 [376]
Sq = 2.81 – 16.68	Ti-6Al-4V	Polishing, sandblasting, etching, anodization	<i>In vitro</i>	Not significant	Hatamleh et al. 2018 [377]
Ra = 8.7 – 19.2	Ti-6Al-4V	Laser beam	<i>In vitro</i>	Positive relation with cell number and covering rate	Lerebours et al. 2019 [368]
Ra = 0.452 – 3.37	Ti-6Al-4V	Nd-YAG laser	<i>In vitro</i>	Positive relation with cell viability, cell morphology and cell spreading area	Rafiee et al. 2020 [378]
Ra = 5 – 70	Ti13Nb13Zr	Polishing, etching, grinding, machining	<i>In vitro</i>	Positive relation with initial cell attachment. Positive relation with cell proliferation up to Ra = 28 μm	Jahani et al. 2021 [370]
Ra = 0.3 – 1.4	Ti-6Al-4V	Sandblasting, acid-etching	<i>In vitro</i>	Negative relation with osteoblast proliferation. Positive relation with osteoblast differentiation	Stoilov et al. 2022 [379]

strong protein interactions that unfold and denature them [367,382] or because of trapped air that reduces available surface area [358, 383]. However, some studies have reported improved cell adhesion on super-hydrophobic surfaces of materials like copper and certain polymers [383,384]. The effects of super-hydrophilic surfaces (contact angle < 5°) are more debated. Some studies suggest they inhibit cell adhesion by attracting water molecules that prevent protein binding [367]. In contrast, others argue that superhydrophilicity does not correlate with protein adsorption or cell attachment capacities at all [385].

The surface charge of the implant significantly influences cell adhesion, with positively charged surfaces being preferred over negatively charged ones [358]. At physiological pH, most proteins are negatively charged and tend to adhere to positively charged surfaces. Initially, cells prefer positively charged surfaces but will spread over negatively charged areas if conditions are favorable, likely due to protein matrix formation [366]. Surface charge affects cell behavior by altering chemical functional groups, regulating protein adsorption,

binding to integrins, and influencing specificity, thereby governing cell adhesion [358].

The final strategy to enhance cell adhesion involves surface functionalization with bioactive molecules. This approach aims to (1) prevent the adsorption of proteins that lead to nonspecific cell attachment, potentially causing fibrotic tissue formation or bacterial adhesion; (2) promote the adherence of desired cell types, such as osteogenic progenitor cells and osteoblasts; and (3) guide immune cell responses to modulate inflammation during bone healing [361].

Biomolecules such as vitronectin, fibrinogen, type I collagen, laminin, and fibronectin rapidly adsorb onto material surfaces, forming a protein layer that facilitates cell adhesion through specific RGD sequences [358]. Osteoblastic cells anchor to these sequences, thus functionalizing biomaterials with RGD sequences enhances their recognition and adhesion [366]. Despite challenges with protein degradability and extraction difficulties, using the RGD sequence for surface modification has shown significant promise due to its specific cell recognition capability [358]. Additionally, immobilizing growth factors like bone morphogenetic protein (BMP) and basic fibroblast growth

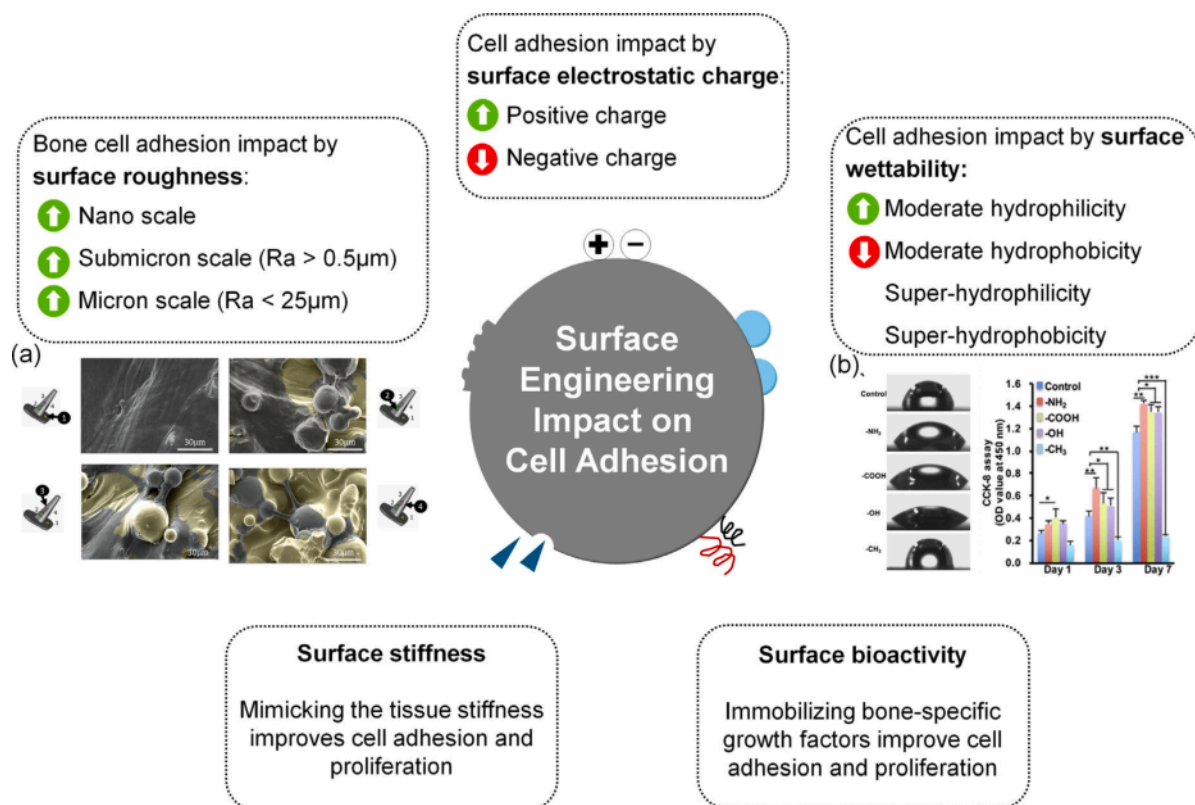


Fig. 9. Surface feature impact on cellular response. (a) Surface roughness impact on cell spreading. Adapted from [368]. (b) Surface wettability impact on cell proliferation. Adapted with permission from [386].
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factor (bFGF) on material surfaces can effectively regulate osteoblast adhesion [358].

Fig. 9 illustrates the key surface features of a metallic implant that can promote cellular adhesion and proliferation, as discussed in this section.

Studying cell adhesion on metals is advantageous due to their extensive use in orthopedics. Metal surfaces, with high surface energy, typically enhance cell adhesion [358]. Hallab et al. [387] found that cell adhesion strength on metal materials is about five times greater than on polymers. The nano-morphology of metal surfaces also influences cell behavior [358]. Additionally, metals naturally form a thick, uniform oxide layer on implant surfaces, which can increase oxygen content. This higher oxygen content enhances protein adsorption, including albumin and fibrinogen, thereby improving cell adhesion [388].

The surface texture of AM metal, even without any surface treatments, has proven advantageous for cell adhesion [389]. The ideal micro-roughness, attributed to partially melted powder on the surface, and submicron roughness induced by the laser beam, can be a reason for this advantage [368].

4.2.4. Osteogenic differentiation and osteointegration

MSCs are among the first to colonize implant surfaces, proliferating and migrating in all directions. Under biochemical and biomechanical stimuli, they differentiate into osteoblasts, which secrete a collagen-rich matrix that calcifies and mineralizes to form new bone. Surface topography and bulk porosity can modulate osteogenic differentiation of stem cells, ideally guiding them to penetrate deeper parts of the

implant for complete integration. Successful integration creates a bone-implant interface similar to natural bone, eliminating the need for bone cements [361]. Bone cements have several disadvantages, such as implant loosening, osteoporosis due to poor osteointegration, and tissue necrosis from high exothermic temperatures [390,391]. Additionally, these pores provide a void for the development of blood vessels, a process known as vascularization [392]. Achieving natural bone-implant integrity is crucial to addressing these issues.

Surface roughness at both micro [375,393] and nano [394] scales are crucial for an implant's osteogenic properties, as they promote the formation and mineralization of the ECM. Nanoscale modifications can significantly influence integrin conformation and clustering, affecting the organization of signaling proteins in focal adhesions [394]. Research suggests that an average surface pore diameter of 20 ± 5 nm, about twice the size of an integrin head, can impact integrin orientation and conformation [394]. TiO_2 nanotubes with diameters of 15 – 30 nm have been shown to provide the optimal scale for integrin clustering and focal contact formation, emphasizing the importance of controlling surface feature sizes to achieve predictable cellular outcomes [395]. Moderate nano-roughness and nano-pores encourage better cell responses compared to smooth surfaces, and irregular surface organization is more conducive to osteogenic lineage differentiation than ordered structures [361]. In comparison to nano-scale features with a diameter range of 25–35 nm (anodizing-heat treatment) on a Ti-6Al-4V implant, submicron surface features in a range of 100 – 200 nm (alkali-acid-heat and acid-alkali treatments) showed more hydroxyapatite formation which resulted in significantly higher bone formation rate [396].

Table 4

Comparative porous/non-porous studies from 2014–2024 on metal lattice for bone regeneration (Abbreviations: ND, not defined).

Ref.	Material	Pore size range (μm)	Porosity range (%)	Unit cell geometry	Assay type	Result
MacBarb et al. 2017 [406]	Titanium	300	60	Triangular	<i>In vivo</i>	AM porous outperformed nonporous plasma-sprayed implant in bone ingrowth
Bandyopadhyay et al. 2017 [407]	Titanium	200 – 300	25	ND	<i>In vivo</i>	AM porous outperformed nonporous in early stage osseointegration and interfacial bonding to the surrounding tissue
Li et al. 2019 [408]	Ti-6Al-4V	100 – 700	50	TPMS	<i>In vivo</i>	AM porous outperformed nonporous in osteointegration capability
Huang et al. 2020 [409]	Titanium	200 – 400	ND	ND	<i>In vivo</i>	AM porous outperformed nonporous in both ingrowth and ongrowth total bone formation
Tikhilov et al. 2020 [410]	Titanium	100	ND	Irregular beams	<i>In vivo</i>	AM porous outperformed nonporous in integration of bone, muscle, blood vessels, and minimal amount of fibrous tissue
Bai et al. 2020 [411]	Ti-6Al-4V	800	70	Dodecahedron	<i>In vitro</i>	AM porous outperformed nonporous in MSCs cell proliferation and osteogenic differentiation
Suresh et al. 2021 [398]	Ti-6Al-4V	400	ND	Hexagonal	<i>In vitro</i>	AM porous outperformed nonporous in MC3T3-E1 cell proliferation and osteogenic differentiation

Micro-rough surfaces, on the other hand, increase the surface area, allowing for a stable mechanical interlocking between the implant and the newly mineralized bone matrix, enhancing mechanical stability and strength, as well as promoting osteogenic differentiation [361]. Reducing surface roughness to less than 10 μm using different treatments showed a significant improvement in cell viability and bone ingrowth compared to as-built AM Ti-6Al-4V implants [397]. A common belief is that moderately rough surfaces with $R_a = 1 - 2 \mu\text{m}$ are beneficial in osteoblast response, although some studies also show an improving bone response up to $R_a = 3 - 4 \mu\text{m}$ [398]. An increase in bone-implant interface area and mechanical stability was reported to be the reason for better osteointegration and bone-bonding [397,398]. Interestingly incorporating a hybrid nano-/micro- topography pattern can promote bone formation for two reasons. Micro-topography provides the initial cell adhesion and proliferation, and nano-topography regulates protein conformation and signal transduction, resulting in osteogenic cell differentiation [397]. In other words, combining surface roughness at various scales (micro, submicron, and nanometer) significantly improves osteointegration by mimicking the hierarchical architecture of natural bone [361,399]. Regarding surface topography, nanotubes [400–402] and nanopores [403,404] surface treatments are among the most common approaches to enhance the osteogenic properties of metal implants. Various methods have been researched to achieve these nanopatterns, including sonication, sandblasting, solvothermal techniques, plasma oxidation, lithography, etching, and anodization [405].

Besides the surface characteristics, it is crucial to ensure that the bulk properties of the implant are suitable for tissue integration. Traditional solid materials are becoming less favored, with a shift toward porous materials. Porosity is essential for osteointegration, influencing cell behavior and implantation success (Table 4). While surface pores on an implant are crucial to prevent surface occlusion, internal material porosity facilitates the penetration of nutrients and oxygen throughout the implant, preventing potential tissue necrosis [358]. Parameters such as pore geometry and size play significant roles in these outcomes.

The impact of pore geometry on cell and tissue behavior has been extensively studied for optimizing tissue engineering. Geometric design by impacting surface curvature activates certain biomolecules, signaling the cells and influencing bone remodeling and healing [412]. Cells

are believed to possess the ability to detect local curvature at a millimeter scale [413]. Rumpler et al. [412] propose that tissue development follows a trajectory that reduces local surface tension by regulating curvature at each point. Their curvature-driven model suggests that cells elongate the cytoskeleton in the presence of concave surfaces. Cellular growth begins at acute-angled corners of the pores, with cells in zero-curvature sections waiting for neighboring points to achieve suitable curvature. Cell expansion then proceeds toward the center of curvature to reduce local curvature, resulting in a rounded surface regardless of the initial pore geometry. Over time, tissue formation fills the remaining space, progressing toward the center [412,413].

The presence of acute-angle pores in scaffolds serves a dual purpose: it facilitates cell bridging over corners, enhancing cell proliferation, and once the pores become circular, it regulates cell growth to prevent excessive surface occlusion. This design helps maintain scaffold permeability in 3D environments, crucially preventing tissue necrosis in the scaffold core [414]. Diamond, octahedron, and tetrahedron unit-cells are frequently utilized in implementing strut-based lattice structures (Table 5). While diamond unit-cells often outperform cubic, tetrahedron, and octahedron unit-cells in various studies, irregular random lattice designs are reported to be more conducive to bone integration and vascularization compared to diamond lattices (Table 5).

Triple Minimal Periodic Surface lattices are another beneficial pore geometry discussed in the literature, which mimics the zero-curvature found in trabecular bone [164]. Providing a large surface area facilitates cell deposition and bone cell differentiation, while highly interconnected pore design allows oxygen and nutrient permeability to assist in better tissue bonding [415]. TPMS lattice design has been reported to enhance *in vivo* bone ingrowth, resulting in promising bone-implant bonding by simulating bone architecture [408]. Araya et al. [416] examined the *in vivo* and *ex vivo* performance of bio-inspired Ti-6Al-4V lattice structures produced via the PBF-LB technique, with a focus on their biomechanical behavior and osseointegration in horse bone tissue. The study found that precise geometry in Gyroid structures and surface modifications achieved through chemical etching notably enhanced the mechanical performance, evidenced by increased yield strength and improved stress distribution, which contributed to

stronger biomechanical interlocking. The well-organized strut architecture of Gyroid lattices demonstrated superior mechanical resilience and more consistent bone ingrowth compared to Stochastic lattices, underscoring the importance of lattice design in promoting osteogenesis and ensuring long-term implant stability.

Another critical factor in achieving a strong bond between the implant and tissue within an optimal timeframe is pore size. Pore size along with porosity, shape, and connectivity influence permeability and fluid dynamics within scaffolds, impacting the delivery of oxygen and nutrients for cell maintenance [415]. Macro pores within the material are essential for cell migration and proliferation, while micro-pores, especially at the nanometer scale, are advantageous for collagen fiber and ECM formation [358]. Balancing permeability accelerates tissue formation around and inside the implant [422,444].

From an *in vitro* perspective, cell seeding efficiency – which ensures cells effectively attach to the scaffold surface rather than passing through its pores – has an inverse relationship with pore size and implant permeability. As pore size increases, permeability rises, but cell attachment decreases [414,432]. Smaller pores, apart from having favorable curvature, enhance cell-seeding efficiency by reducing flow velocity through the scaffold, giving cells more time to adhere [430]. Several studies have shown that there is an optimal lower limit for pore size, suggesting that designing scaffolds with pores smaller than 300 μm may not be effective for biological responses [418,433,445]. However, investigations into bone cell proliferation on metal implants consistently show a direct correlation between pore size and cell proliferation [392,414,418,435]. Studies indicate that scaffolds with a pore size of approximately 700 μm , which enhance nutrient diffusivity, exhibit the highest and most favorable proliferation compared to other pore sizes within the 400–1100 μm range [392,432,433,436]. Excessively large pores do not provide enough surface area for cells to adhere to the struts and neighboring cells, leading to reduced cell signaling and proliferation. Hence, beyond a certain pore diameter, permeability is no longer the dominant factor in promoting proliferation; instead, the lack of a curvature-driven mechanism necessary for cell attachment and growth becomes a limiting factor [433]. Regarding osteogenic differentiation, research indicates that in larger pores ($\sim 1000 \mu\text{m}$), cells attach to a single strut and receive limited stimuli. In contrast, smaller pores (not less than 300 μm) allow cells to adhere to multiple struts, providing diverse stimuli [414,446].

Micro-CT evaluations of *in vivo* studies reveal that larger pore sizes facilitate greater cell migration and deeper tissue infiltration, enhancing bone ingrowth [432,447]. Ran et al. [432] found that 900- μm pores allowed deeper bone infiltration compared to 700 and 500 μm pores. However, scaffolds with 700 μm pores showed more favorable outcomes in terms of trabecular thickness, trabecular number, and total bone tissue generation compared to those with 500 or 900 μm pores. Studies identify an optimal pore size for bone ingrowth and implant stability, typically between 500 μm and 800 μm (Table 5) [447,448].

Larger pores facilitate deeper tissue penetration into implants, while smaller pores show significant osteogenic potential based on bone gene expression levels [432–434,446]. Therefore, a gradient porous pattern resembling the natural bone tissue structure has gained more attention due to its ability to improve bone tissue regeneration by promoting migration, osteogenic differentiation and mineralization of the ECM altogether (see Section 2.3) [90,449]. Peripheral larger pores offer wider pore throats, thus promoting increased bone ingrowth depth within a functionally graded scaffold and smaller central pores to optimize cell deposition [433,439,447].

Porosity mostly influences the biomechanical compatibility of the implant with the host tissue, rather than a direct effect on cellular responses [415]. However, we cannot overlook the role of porosity in the permeability of the implant. Table 5 shows *in vitro* studies demonstrated that higher porosity promotes greater osteogenic differentiation. Additionally, *in vivo* studies have reported improved osteointegration with higher porosity implants (Table 5). Recent research suggests that a porosity of around 60%–70% of the implant volume is particularly beneficial for osteoblast differentiation and bone tissue integration (Table 5).

4.3. Clinical requirements

After the primary evaluation of an orthopedic implant, which focuses on mechanical and biological requirements, a design is established to meet essential functional and physiological demands. However, achieving a successful implant is not solely dependent on its mechanical strength or biocompatibility. Clinical considerations play an equally crucial role, ensuring that the implant is safe, effective, and compliant within practical applications. These clinical requirements are instrumental in translating a technically sound design into a reliable medical product that can be successfully utilized in clinical settings. A simplified flowchart of AM process is shown in Fig. 10. Effective collaboration between medical engineers and surgeons is crucial to establish a well-designed workflow. This collaboration is essential for navigating the logistical and regulatory aspects of technology development, ensuring both safety and effectiveness. In this section, we explored the key clinical requirements of additive manufacturing for surgical implants including regulatory standards compliance, cleanliness and sterilization, implantation requirements, and implant removal considerations.

4.3.1. Removing manufacturing material residues and sterilization

AM of metal medical implants often leave behind material residues. The removal of residual materials from the manufacturing process is critical to ensuring the safety, performance, and regulatory compliance of the final product. Residues such as unmelted powder and other contaminants can adversely affect the biocompatibility and mechanical properties of implants. Additionally, effective sterilization is essential to eliminate microbial contaminants, safeguarding patient health and meeting medical standards. This section explores the challenges and methods for residue removal and sterilization in metal AM for medical implants, with a particular focus on porous structures and their importance in ensuring clean and reliable medical devices.

Final device performance and material properties can be highly influenced by post-processing steps, such as removal or cutting from the build plate, annealing treatment, sandblasting, cleaning, and sterilization process [451,452]. Although AM technology facilitates the creation of complex geometries, porosity and interconnective networks, it can raise difficulties in post-processing.

For instance, a highly porous AM structure of spinal fusion cages requires cutting and removal from the build plate. Various polishing techniques should be evaluated, as they may increase the difficulty of the cleaning and sterilization process. During cleaning, as mentioned above, loose powder particles, either from the powder bed or from the polishing process, can become trapped in internal structures that are far from the surface or in blind pores that do not fully penetrate the devices. Therefore, it is crucial to validate that these issues are mitigated to levels that do not adversely affect the safety and effectiveness of the device.

ASTM F3335-20 [453] considers the powder detachment after implantation of the medical device as a risk factor. Additionally, the standard provides residue assessments, including visual inspection, microscopy, spectroscopy, μCT [454] or measuring of releasing residues [455]. In this context, residues are defined as particulates remaining on the parts after manufacturing and post-processing, including starting material, blast media, and other debris.

Furthermore, the subsequent process, sterilization, is crucial to mitigate the risk of infection with implantable medical devices and is significantly affected by their complex geometries. Depending on the materials and processes involved, various sterilization methodologies can be employed, such as autoclaving (ISO 17665-1 [456]), gamma radiation (ISO 11137 [457]), and ethylene oxide (EtO) gas (ISO 11135 [458]). For example, EtO is used in this stage to ensure better sterility for internal complex structures. According to ISO 10993-7 [459], there is a limit on EtO residuals. Additionally, the worst-case scenarios, including the greatest number of residual materials and a combination of the

Table 5

Comparative biocompatibility studies on metal lattice for bone application (Abbreviations: ND, not defined).

Unit cell geometry	Pore size range (μm)	Porosity range (%)	Assay type	Result	Ref.
Studies on unit cell geometry					
Tetrahedron vs. Octet truss	500 vs. 770	56 vs. 70	<i>In vivo</i>	Bone ingrowth: Octet truss > tetrahedron (due to higher porosity)	Arabnejad et al. 2016 [417]
Tetrahedron vs. Octahedron	500 & 1000	62 – 84	<i>In vitro</i>	Cell spreading: Octahedron > Tetrahedron	Zhao et al. 2018 [418]
Diamond (regular, irregular, gradient) vs. Tetrahedral	450	63	<i>In vitro</i>	Higher osteogenic proliferation (ALP): Diamond-gradient	Wang et al. 2018 [419]
			<i>In vivo</i>	New bone formation: Diamond-regular $\approx$ Diamond-irregular > Diamond-gradient > Tetrahedral	
TPMS (Gyroid vs. Diamond)	490 – 1100	ND	<i>In vitro</i>	No significance in cell viability and proliferation	Liu et al. 2020 [420]
Octadens vs. Gyroid vs. Dode	1000	ND	<i>In vivo</i>	No significance in bone generation	Lim et al. 2021 [421]
Diamond vs. Circular-pore cube vs. Tetrahedron vs. Cubic	650	65	<i>In vivo</i>	New bone formation: Diamond > Tetrahedral Cube > Cubic > Circular	Deng et al. 2021 [422]
Diamond vs. Irregular	800 – 1000	86.3 – 94.2	<i>In vitro</i>	Optimum proliferation and osteogenic differentiation: Irregular design	Wang et al. 2021 [423]
			<i>In vivo</i>	Optimum bone generation and vascularization: Irregular design	
TPMS (Gyroid vs. Diamond vs. Schwarz Primitive)	276 – 700	30 – 50	<i>In vitro</i>	Metabolic activity: Schwarz (700 μm , 50%) > Gyroid (429 μm , 49%) and Diamond (276 μm , 31%)	Soro et al. 2022 [424]
Diamond vs. Rhombic Dodecahedron	~400	~70	<i>In vitro</i>	Depending on the material (Ta and Ti), each can be the optimum geometry	Huang et al. 2022 [425]
5 types of cuboid units	330 – 805 graded	40 – 80	<i>In vitro</i>	No significance on proliferation	Tan et al. 2022 [426]
Diamond vs. Irregular YM	600 – 900	65	<i>In vitro</i>	Optimum viability: Diamond design	Wang et al. 2023 [427]
			<i>In vivo</i>	Higher bone integration force: YM-random	
Multi-morphology (Primitive and Gyroid)	0 – 1800 graded	50 – 70	<i>In vitro</i>	Higher number of cells: Multi-morphology-graded	Yu et al. 2023 [428]
TPMS Gyroid vs. auxetic bow-tie	340 – 1400	28 – 66	<i>In vitro</i>	Higher metabolic activity: TPMS (900 μm pore size)	Emanuelli et al. 2025 [222]
Studies on pore size (μm)					
Diamond	200 – 1000	ND	<i>In vivo</i>	Optimum bone ingrowth: 500 – 800 μm range	Hara et al. 2016 [429]
Diamond	300 – 900	65	<i>In vivo</i>	Optimum bone ingrowth: 600 μm	Taniguchi et al. 2016 [430]
Diamond	300 – 700	34 – 51	<i>In vitro</i>	Optimum adhesion and proliferation: 300 – 400 μm range	Li et al. 2016 [431]
Diamond	300 – 400	34	<i>In vivo</i>	No implant dislocation and good depth of bone ingrowth	

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Table 5 (continued).

Tetrahedron & Octahedron	500 vs. 1000	62 – 84	<i>In vitro</i>	Optimum cell adhesion and growth: 1000 μm	Zhao et al. 2018 [418]
Interconnected channels	400 – 800	ND	<i>In vitro</i>	Optimum cell viability: 800 μm	Ran et al. 2018 [432]
			<i>In vivo</i>	New bone formation: 800 > 600 > 400 μm . Optimum bone-implant fixation at 600 μm	
Diamond	400 – 1100	66.2 – 71.5	<i>In vitro</i>	Optimum proliferation at 650 μm . Larger pores reduce differentiation	Ouyang et al. 2019 [433]
			<i>In vivo</i>	Optimum bone ingrowth: 650 μm	
Octahedral	500 – 700	70 & 80	<i>In vitro</i>	Optimum proliferation and osteogenic differentiation: 500 μm	Chen et al. 2020 [434]
			<i>In vivo</i>	Optimum bone ingrowth: 500 μm	
Trabecular-like irregular	800 – 1000	ND	<i>In vitro</i>	Optimum proliferation and osteogenic differentiation: 1000 μm	Wang et al. 2020 [435]
Diamond	660 – 860	58 – 85	<i>In vitro</i>	Optimum proliferation: 660 μm	Pei et al. 2020 [413]
			<i>In vivo</i>	Optimum bone generation: 860 μm	
Diamond & Irregular	800 – 1000	86.3 – 94.2	<i>In vitro</i>	Optimum proliferation and osteogenic differentiation: 1000 μm	Wang et al. 2021 [423]
			<i>In vivo</i>	Optimum bone generation: 1000 μm	
Cubic	400 – 900	70	<i>In vitro</i>	Proliferation and osteogenic differentiation: 700 > 900 > 400 μm	Zhang et al. 2022 [436]
			<i>In vivo</i>	Osteointegration: 700 > 900 > 400 μm	
Diamond	200 – 500 (normal vs. graded)	62 – 80	<i>In vitro</i>	Graded porous offers cell retention and diffusion	Wysocki et al. 2016 [437]
Rhombic Dodecahedron	200 – 600 (graded)	65	<i>In vitro</i>	Cellular activity varies across graded structure	Nune et al. 2017 [438]
BCC	Dense-In vs. Dense-Out (600 – 1000)	~50	<i>In vitro</i>	Dense-In shows higher cell proliferation and colonization	Onal et al. 2018 [439]
Studies on porosity (%)					
Bone CT scan template	177 – 653	15 – 70	<i>In vitro</i>	Higher porosity shows higher osteoblast maturation but lower proliferation	Cheng et al. 2014 [374]
ND	ND	0 – 20	<i>In vitro</i>	No significance in cell proliferation	Roy et al. 2016 [440]
Bone CT scan template	563 $\pm$ 2	0 vs. 67	<i>In vitro</i>	Osteogenic differentiation factors significantly increased on porous sample	Cheng et al. 2017 [441]
			<i>In vivo</i>	Osteointegration significantly increased on porous sample	
Trabecular-like irregular	400 – 100	48.83 – 74.28	<i>In vitro</i>	Porosity higher than 63.5% showed higher viability and better osteoblast differentiation result	Liang et al. 2019 [442]
Octahedral	500 – 700	70 vs. 80	<i>In vitro</i>	Optimum proliferation and osteogenic differentiation: 60%	Chen et al. 2020 [434]
			<i>In vivo</i>	No significance in bone ingrowth	

(continued on next page)

Table 5 (continued).

Cubic	700	40 – 90	<i>In vitro</i>	Proliferation: 70% and 90% > 40%. Osteogenic differentiation: 70% > 90% > 40%	Zhang et al. 2022 [436]
			<i>In vivo</i>	Osteointegration: 70% and 90% > 40%	
Trabecular-like irregular	450 – 800	60 – 80	<i>In vitro</i>	Best cell adhesion: 60%. Higher proliferation and osteogenic differentiation: 70% and 80%	Jiao et al. 2023 [443]
			<i>In vivo</i>	Best osteointegration: 70%	

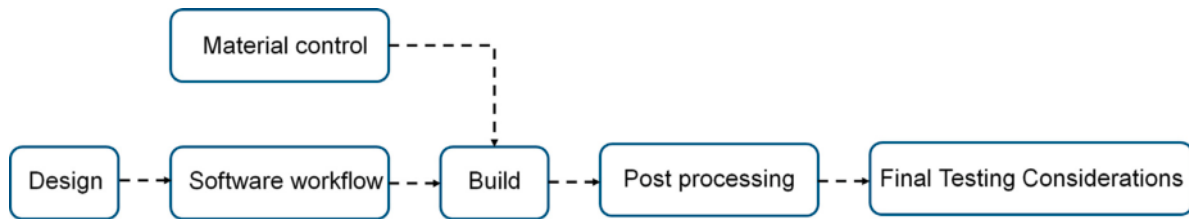


Fig. 10. A simplified flowchart of the AM process based on [450].

largest surface area, greatest porosity, and most internal voids, should be considered in the assessment of the sterilization process.

Overall, cleaning and sterilization residual assessments should be conducted on final finished devices that have undergone all other processes. These tests should include the most complex cases to ensure the safety and effectiveness of the medical devices.

4.3.2. Implantation requirements

Hip and knee replacement surgeries are among the most common elective orthopedic procedures, with approximately 790,000 knee and 544,000 hip prostheses implanted annually in the United States. When including replacements of minor joints such as the shoulder, elbow, and ankle, as well as revision and re-implantation surgeries, the total number of procedures reaches several million each year. These figures are projected to increase as the population continues to age [460]. Over time, advancements in the design of prostheses have led to significant improvements in clinical and functional outcomes. Enhanced materials and advancements in prosthetic tribology have contributed to the durability of these implants, resulting in fewer adverse reactions and side effects for patients.

The primary goals of joint replacement surgery are to alleviate pain and correct issues such as limping, whether caused by pain or mechanical dysfunction. Additionally, the surgery aims to restore an acceptable, and ideally complete, range of joint motion, correct deformities across various planes (axial, sagittal, coronal, or rotational), and reestablish normal limb length in cases where degenerative diseases have caused discrepancies. Achieving these objectives enables patients to carry out daily activities more effectively and enhances their overall quality of life [461,462].

Prosthetic implants must support both physiological loads, such as those encountered during walking and weight-bearing activities, and para-physiological loads, including intense physical work or sports. This support should be provided with minimal friction to reduce wear and maintain implant longevity. The implant must also ensure a wide range of motion, ideally comparable to that of a native joint, while maintaining stability. Moreover, biocompatibility is crucial; the implant should not induce harmful reactions, either locally or systemically, due to the release of potentially toxic substances or ions [463,464]. For instance, issues regarding ion release from MoM-THA, have developed pseudotumors in the surrounding soft tissues of some patients [465]. Elevated levels of cobalt and chromium ions in the blood, observed in some cases, pose potential risks to vital organs such as the liver. These findings underscore the importance of ongoing monitoring

and further research to enhance the safety and efficacy of prosthetic implants [466].

An orthopedic surgeon performing primary knee or hip arthroplasty expects the prostheses to meet specific mechanical and functional requirements. One critical factor is the three-dimensional microscopic structure of the implant, which should closely resemble the porosity of trabecular bone. This lattice structure offers significant advantages over solid configurations, balancing strength with reduced weight. Additionally, it promotes tissue regeneration and facilitates the diffusion of oxygen and nutrients, enhancing integration with the patient's bone tissue [467].

At a macroscopic level, the prosthetic design must allow for maximum joint mobility while minimizing weight and bulk. Reducing the load transmitted to surrounding bone is crucial to prevent bone resorption and implant failure. Various factors, including prosthesis geometry and design, influence load transfer and bone remodeling. For instance, standard straight stems in THA often reduce load on the proximal femur, shifting it to the distal region and leading to bone resorption in the proximal part. In contrast, certain short stems provide a more balanced stress distribution, improving femoral loading and reducing bone loss. However, it is important to note that short hip arthroplasty (SHA) stems vary significantly in design, impacting periprosthetic bone remodeling differently [468].

The prosthesis must adapt to various anatomical morphologies of the acetabulum, femur, and tibia. Designing a single implant suitable for all patients is challenging due to anatomical variations, which may compromise primary stability and biomechanical restoration. Custom-made implants, designed based on CT scans, address these challenges effectively. Although they are approximately 30% more expensive than standard implants, custom THAs have demonstrated high survival rates and positive functional outcomes, particularly in complex cases [469].

Stable anchoring of prosthetic components to the bone is essential for successful arthroplasty. In THA, most acetabular cups are implanted using a press-fit technique, where the cup's diameter is typically 1 to 4 mm larger than the last ream used [470]. While this method generally does not require additional fixation, cups with 2 or 3 holes can accommodate screws for added stability if necessary. In complex or revision cases, multi-hole cups are preferred to ensure secure fixation [471].

The implant's elastic modulus should closely match that of bone to prevent stress shielding, and it must exhibit lasting resistance to applied stresses, including tensile and fatigue forces. Moreover implant must provide uniform load distribution to the bone tissue.

Preserving patient bone stock is another critical consideration. Recent femoral stems are designed to be thinner proximally and shorter distally compared to conventional stems, preserving more bone in the metaphyseal region. Additionally, lateral stem shoulders are often inclined to preserve as much bone as possible [470].

Finally, prostheses must resist wear and corrosion while avoiding the release of harmful metallic ions, ensuring long-term safety and functionality for the patient. Providing minimum friction between implant and bone is the strategy that has been used to tackle this problem. In the past years, in hip arthroplasty, bimodular stems seemed to offer a solution for controlling leg length, anteversion, and neck shaft-angle. Despite these benefits, in time these implants have caused many mechanical failures due to dissociation of modular components, corrosion, and metal ion release [472]. Consequently, single-block femoral stems, which combine the shaft and neck, are now preferred. The availability of various neck lengths, anteversion angles, and neck-shaft angles allows surgeons to tailor the implant to individual patient needs.

From a biological perspective, several factors are critical in ensuring the success of knee and hip prostheses. First, the materials used in the implants, such as steel, chrome-cobalt, titanium, polyethylene, and polymethylmethacrylate, must be biocompatible to prevent adverse reactions at the bone-prosthesis interface. Additionally, the implant should possess strong osteointegration capabilities to promote stable and long-lasting integration with the patient's bone tissue.

One of the most significant challenges in orthopedic surgery is implant-related infection, a leading cause of prosthesis failure. Despite advancements in surgical techniques, facilities, and the routine use of systemic antibiotic prophylaxis, periprosthetic joint infection (PJI) remains a major concern [473]. Current registry data indicate a rising incidence of PJI, with infection rates ranging from 2% to 5% for primary implantations and doubling in revision surgeries. To mitigate this risk, various strategies are being developed and evaluated, including the use of antibacterial coatings on implants. Their implementation represents a promising approach to addressing this persistent clinical issue and improving overall patient outcomes [474]. These innovative coatings have demonstrated potential in reducing the incidence of early post-surgical infections following joint replacement and osteosynthesis [473].

From a surgical standpoint, several key factors contribute to the success of knee and hip arthroplasty. First, the tools required for implant preparation and component placement must be easy to handle to ensure efficient and precise surgical execution. Additionally, a wide range of prosthetic designs is essential to accommodate diverse anatomical variations and meet the specific needs of patients, considering factors such as age, weight, activity level, and psychological expectations.

Precise and accurate preoperative planning plays a crucial role in optimizing surgical outcomes. Effective pre-surgical planning helps predict the appropriate implant size and positioning, while also allowing the surgical team to anticipate potential challenges [475]. The integration of 3D printing technology has significantly enhanced this process by providing detailed anatomical information. Surgeons can create scale models for preoperative evaluation, which improves comprehension and facilitates personalized approaches. This advancement has led to reduced surgical time, minimized bleeding, lower risks, faster decision-making, and quicker patient recovery [476].

Another critical consideration is the mechanical design of the prosthetic implant, which should allow for easier removal if reoperation or re-implantation becomes necessary. This feature is particularly important in revision surgeries, where efficient extraction of the existing implant can impact the overall success of the procedure [477]. Finally, the availability of navigation systems or robotic-assisted surgical technology provides an additional layer of precision and control, further enhancing the accuracy of implant placement and overall surgical outcomes [478].

4.3.3. Implant removal in revision

As mentioned before, the progressive increase in primary prosthetic implants, expanding surgical indications, and an aging population have led to a growing demand for arthroplasty revision surgeries. According to major arthroplasty registries, the risk of revision within 10 years is approximately 5%, with the Australian Joint Replacement Report indicating a 5.5% revision rate within the same period [468]. Revision procedures can range from simple implant removal to more complex interventions, such as removal and replacement with a prosthetic spacer in cases of infection or the implantation of a new prosthesis. The primary reasons for revision surgery include joint instability, mechanical failure (such as implant wear, loosening, or breakage), infection, periprosthetic fractures involving implant mobilization, and persistent pain [479].

A critical aspect of all prosthetic revision surgeries is the removal of the existing implant, which can be a complex process involving several surgical steps. These steps may include:

- Separation of prosthetic components (polyethylene-metal, ceramic-metal, metal-metal, etc.);
- Interruption and separation of the prosthesis' anchorage to the bone (metal-bone interface, cement-bone interface, etc.);
- Physical removal/separation of the prosthetic element from the bone;
- Removal of any remaining materials or particles (debris or inflammatory reactions to them).

Prosthetic implants must be designed not only for safe and durable implantation but also to facilitate removal without causing significant local damage. The removal process often leads to some degree of bone stock depletion, which can increase tissue trauma, blood loss, and surgical duration—factors that pose additional risks to the patient. Greater damage to bone stock may necessitate more invasive revision procedures and larger, more complex prostheses [480].

Advances in prosthetic design now allow for the replacement of large joint segments, including adjacent bone structures. However, orthopedic surgeons prefer to minimize bone stock damage during revision surgery. The goal is to use prosthetic designs that are as similar as possible, in terms of invasiveness, to the primary arthroplasty implants, ensuring better outcomes and preserving as much native bone as possible [464,481].

As examples, in hip and knee prosthetics, it is essential that each designed implant includes mechanisms to facilitate safe and efficient revision procedures.

For hip prosthetic revision, a well-designed liner removal system is crucial. Polyethylene liners can typically be removed with cutting instruments, such as osteotomes, or by anchoring them to a screw thread. Ceramic liners, however, are more challenging to extract. Utilizing a high-frequency drill on the outer diameter of the acetabular shell induces vibrations that can separate the tapered metal-ceramic interface. Should this approach prove unsuccessful, it may be necessary to fracture the ceramic liner, albeit with the risk of generating sharp fragments within the joint [482,483]. Including grooves in ceramic liners would greatly facilitate their removal by providing hook-up points for extraction tools.

Disrupting and releasing the prosthesis-bone or prosthesis-cement interface of the acetabular cup requires specialized tools, such as chisels, curved blades, or multiple K-wires that follow the contour of the acetabular shell [484,485]. Additionally, the acetabular cup should feature lateral hooking sites, preferably threaded, at its outer border to anchor removal tools effectively.

For the modular neck of the femoral prosthetic stem, a dedicated removal system allows for replacing only the modular neck if it becomes worn or damaged, thereby avoiding the more invasive procedure of replacing the entire femoral stem [486]. Systems designed to disrupt and

release the stem-bone or stem-cement interface should include chisels or flexible blades that closely follow the variable shapes of different femoral stems. Furthermore, the stem should have hooking mechanisms to facilitate extraction with specialized tools. Cement removal from the femoral canal can be performed using mechanical systems, such as long chisels or elastic tools, or physical systems like ultrasound, which mobilize residual cement while minimizing damage to cancellous and cortical bone.

In knee prosthetic revision, liner removal is generally straightforward and can be achieved using an osteotome to separate it from the metal back. Disrupting and releasing the prosthesis-bone or prosthesis-cement interface of the femoral and tibial components involves the use of chisels, curved blades, or oscillating and reciprocating saws that closely match the implant's shape. Once the interface is released, component removal is typically uncomplicated and facilitated by extractors that anchor to specific parts of the prosthetic components. Similar to hip revisions, cement removal from the distal femur and proximal tibia relies on mechanical tools, such as chisels and elastic instruments, or physical methods like ultrasound to safely mobilize residual cement while preserving the bone structure [487,488].

In conclusion, successful prosthetic revisions require careful consideration of both implant design and the tools necessary for safe removal and replacement. Effective surgical systems for extracting implant components are essential to minimize damage to surrounding bone structures and preserve patient bone stock. Additionally, incorporating design features like grooves and threaded hooking points enhances the efficiency of revision procedures. As prosthetic designs continue to evolve, focusing on these elements will contribute to less invasive surgeries, reduced complications, and better long-term outcomes for patients undergoing joint revisions.

5. Design strategies for manufacturing metal implants

The design of prosthetic devices is inherently complex, requiring the careful integration of mechanical functionality, biological compatibility, and clinical applicability. When these devices are fabricated using metal additive manufacturing (MAM), the design process becomes even more challenging, not only due to the expanded geometric freedom and customization potential MAM enables, but also to its process-specific constraints, such as anisotropic material properties, surface roughness, and internal defect control. These characteristics necessitate a fundamental reconsideration of conventional design strategies in favor of approaches that are explicitly informed by, and tailored to, the capabilities and limitations of MAM. Accordingly, this chapter aims to provide a comprehensive overview of practical design methodologies for MAM lattice-based orthopedic implants. It is structured into five main sections. The first introduces heuristic design principles and outlines a formalized workflow, highlighting how these must evolve within the MAM context. The second explores numerical simulation techniques for the mechanical characterization of architected cellular materials. The third presents the role of topology optimization in enhancing material efficiency and structural performance, taking full advantage of the design freedom offered by MAM. The fourth section addresses fatigue modeling strategies, which are particularly critical given the surface and size sensitivities inherent to AM-produced lattices. Finally, the chapter concludes by examining emerging trends in artificial intelligence and biomimetic design, two promising approaches that naturally complement the data-rich and geometry-flexible nature of metal additive manufacturing.

5.1. Heuristic design approaches

The design process of an implant is complex and strictly dependent on the implant type and on the mechanical and biological requirements specific to the location and the patient. Despite the diversity in prosthetic designs and requirements, certain general guidelines are

Table 6

Design approaches in porous prosthetic devices.

Design approach	Implant type	Ref.
Biomimicry	Spinal	[230,489–492]
	Hip	[235,493–495]
Porous Redesign	Spinal	[254,496,497]
Structural Optimization	Various	[498–500]

applicable across all of them. Designers often follow the same core principles when addressing these challenges, including biomimicry, adaptation of existing geometries, and targeted property optimization. Table 6 presents examples of each of the adopted solutions.

The core idea is underpinned by the desire to restore the body's functionality by mimicking the healthy parts of the human body. Several elements in the body are characterized by the presence of a symmetric similar counterpart, formally described as contralateral, which is studied by designers and replicated to restore the functionality of the missing or damaged part. The same idea is shared by researchers designing implants characterized by mimicking human bones' shape and porosities. The shape is therefore a direct copy of the healthy human body, without considering the mechanical functionality of the component. Several examples are available in literature in this sense, and often the presence of gradient in the lattice porosity is driven by an observation of the natural shape and topology of the healthy counterpart. Other authors address this problem with a different formulation, trying to design an implant to restore the geometry of a healthy body, such as the distance between the vertebrae in spinal diseases [489]. A second design approach for porous implants revolves on the implementation of lattice structures in the geometry of an already commercially available product. This approach relies on the clinical experience of the re-designed prostheses including the benefit of the porous geometry.

The final approach involves using structural optimization algorithms, including topology optimization and multi-objective topology optimization. Imposing a variation in the characteristics of the porous material allows the device to meet different requirements coming both from the mechanical and biological fields [491]. The advantages of this method obtained thanks to topology optimization are well-documented in the literature; therefore, this topic is discussed in detail in Section 5.3. Given this framework, attention will be devoted to the description of a formal design process, as presented in Ullman's book [501] specifically focused on porous implants. This can be used as a roadmap by readers to address the design problem.

Firstly, it has to be considered that the design of porous implants is a complex and multidisciplinary process, it is therefore mandatory to address this challenging task with a proper design team, characterized by a different background and a set of competencies that range from medicine to material science to mechanical engineering. Once the design team is defined, the design problem must be clearly stated, selecting the target implant to be designed or redesigned and clearly limiting the components on which the actions should be taken. Once these preliminary tasks are completed, the function, the requirements and the engineering specifications of the implant need to be understood. To formally collect this information, the functional decomposition process and the development of a Quality Function Deployment (QFD) chart is suggested [502]. Based on the information in these documents, a conceptual design phase can be defined. In this phase, different possible solutions for each function are developed in a draft form using multiple expressions. Once this stage is completed, multiple design concepts are mixed and combined to obtain different possible geometries of which include all the desired functions. This step is also known as a divergent step. A convergent phase is then addressed, where the different concepts are compared and evaluated to identify the best solution for the prosthetic device. Then a detailed design



Fig. 11. Workflow originally suggested by [501] for designing mechanical components which can be effectively adapted for the design of implants.

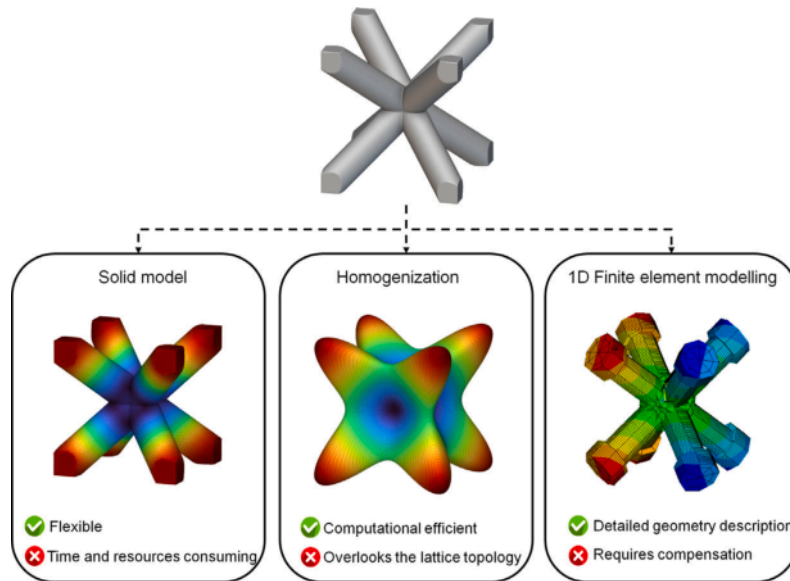


Fig. 12. Modeling technique for lattice structures simulations.

process formally defines the final geometry of the component. The performance of this geometry is then verified against the engineering specifications that were recognized in the QFD chart.

If the design is not satisfactory, iterations on the geometry must be performed based on the information obtained in the verification process. In this phase, some trials may require the manufacturing of a prototype of the implant which is tested according to the requirements and normative. The suggested design path is summarized in Fig. 11.

5.2. Finite element modeling

The design process of an implant cannot be decoupled from the understanding of the mechanical properties of the component, especially when dealing with lattice-based structures. Analytical methods are developed in this regard, such as the Gibson-Ashby model [503], nevertheless, the complex shape and loading condition characteristic of the implants requires a more comprehensive approach. To address this issue, the Finite Element (FE) method can be applied [504]. The following subsection deals with the most common simulation approaches available in literature, focusing on the challenging task of reducing the computational cost. In this framework, attention will be given to the techniques able to include in the modeling process the effect of manufacturing-induced defects. An overview of the FE modeling technique is presented in Fig. 12.

5.2.1. Solid finite element modeling

A common technique for addressing lattice structure geometry is the use of FE models made of solid or brick elements. These elements employ a three-dimensional depiction of the geometry through a meshing process, dividing the lattice geometry into elementary parts – tetrahedral or hexahedral volumes – referred to as elements [505].

Solid FE modeling offers numerous advantages, including precise characterization of component geometry, accurate evaluation of displacement and stress fields, and detailed description of the lattice-bulk interaction. Additionally, it accommodates variations in lattice porosity or topology, providing design flexibility while ensuring precise results. However, describing lattice structure topology can also pose challenges. To tackle this, Fadeel et al. [506] developed an Abaqus extension for lattice structure modeling.

Nevertheless, a complete description of intricate lattice topology comes with a cost. Considering the technology, quadratic elements are commonly used and advised, but the determination of the appropriate mesh size is challenging. There is little agreement among researchers on the mesh dimension needed for a precise description of the lattice properties. To this end, most of the authors address the specific problem through a convergency analysis [507–510]. This solution poses however challenges on the computational requirements. General meshing guidelines are provided by studies [511–513] where at least three elements along the lattice strut's thickness, while Kladovasilakis et al. [514] suggested at least one element along the thickness.

The use of solid modeling in implant design and validation is well-documented in literature [180,254,515], while the complex and extensive model of the spinal column by Song et al. [516] is an example of the capability of the solid FE method.

Despite the critical computational requirements, solid FE models remain the reference in lattice structure simulations given the flexibility and the complete description of the geometry provided. Alternative methods able to reduce significantly the computational effort are available and can be grouped under two main strategies: homogenization and 1D Finite Element Modeling.

5.2.2. Homogenization approach

Conversely to solid FE models, homogenization is a computational technique that treats a non-uniform element as an aggregate entity,

focusing on the global behavior. In the context of lattice structures, this method replaces the lattice with a fictitious solid material possessing equivalent mechanical properties. To do so, only a small portion of the metamaterial, namely the Representative Volume Element (RVE), is analyzed under specific boundary conditions to extract the global behavior. Initially developed to study composite materials, RVE is defined by Hill [517] and further refined by Hashin [518]. According to Hill's definition, the RVE is the smallest material volume that represents on average the global material behavior, incorporating enough sub-unital elements to remain insensitive to loading conditions when computing elastic properties. Hashin contributed to the RVE definition by specifying that it should be statistically homogeneous under the required boundary conditions.

The homogenization technique originated from mathematical theories addressing partial differential equations with rapidly varying parameters [519–522]. Suquet [523] significantly enhanced the method by introducing Periodic Boundary Conditions (PBC) and popularizing the term “homogenization”. PBC are specific constraints able to describe the analyzed material as in an infinite repetition in space of the specified RVE, improving sensibly the accuracy.

In recent years, homogenization has been applied to metamaterials and lattice structures, leveraging their dual-scale nature given by the cell and the global behavior. Therefore, the RVE for regular lattice structures is typically the unit-cell. This technique has been employed for simulating lattice components, including strut-based [524–526] and TPMS lattices [176], and is integral to topology optimization. As deepened in Section 5.3, topology optimization utilizes the relationship between the mechanical properties of lattice structures and relative density to obtain enhanced component design. The core link between lattice relative density and mechanical properties is established through homogenization.

A major advantage of the homogenization method is its computational efficiency: simulating a single lattice cell to represent the entire structure behavior significantly cuts the computational cost. The calculation of the homogenized properties is performed through subsequent solid FE simulations on the RVE, which are combined to obtain the elastic properties of the equivalent fictitious material. The meshing requirements for the RVE are normally more demanding with respect to solid modeling, since a higher degree of accuracy is normally preferred and care is required in obtaining a periodic mesh, able to better incorporate the PBC. Meshing guidelines [511–513] prescribe the usage of at least three elements along the struts' diameter or rely on a case-by-case convergence analysis. Although the computational cost for a solid model of the lattice RVE is significant, it is minimal compared to simulating the entire lattice structure.

As it will be discussed in Section 5.3, the homogenization technique is extensively covered in literature since it is the basic tool involved in topology optimization. Instead the use of homogenization as simulation techniques for lattice structure is not intensive and, with specific regards to implant design or analysis is carried out by Alkhatib et al. [524] and Saviour et al. [498] on hip implants.

The homogenization technique well describes lattice structures macroscopic properties, with the drawback of overlooking the lattice structure topology and local effects. To overcome this problem, Pasquale et al. [527] developed a two-step simulation algorithm, able to simulate the global behavior of the lattice structure to determine the position and the loading conditions of the most critical lattice cell which can be simulated in a more detailed solid sub-model.

Additionally, a second drawback in homogenization usage is related to the usage of PBC and the hypothesis of infinite repeatability of the lattice cell. This is clearly not possible in real components, and so a minimum number of cells to obtain convergence of the mechanical properties is necessary. There is little agreement in this sense, and a lack of a validated method is found. Nevertheless, different contributions addressed the problem, and while Savio et al. [528] achieved convergence using a tensile specimen with $2 \times 3 \times 7$ cells, the

experimental campaign of Moeini et al. [529] set the limit to $8 \times 8 \times 8$ cells. The minimum number of cells is a transversal concern for lattice structure analysis, and it is also worth mentioning the numerical analysis of Galarreta et al. [510] which sets it to 8 while the ISO 13314:2011 standard [530] for compressive tests on porous material set the minimum RVE repetition on the cross-section to 10.

5.2.3. 1D finite element modeling

To mitigate the issues connected to homogenization while keeping a contained computational cost, alternative simulation techniques providing a complete topological description have been developed. To achieve this, 1D model simulation uses one-dimensional finite elements to simulate strut-based lattice structures. The method takes the moves from the observation of the one-dimensional nature of lattice sub-elements. In this approach, lattice struts are modeled as beam or truss elements and nodal junctions as nodes.

In past years, researchers [531–533] focused on the development of an analytical model for stretching and bending-dominated lattice structures, confirming this technique's validity. Nevertheless, method applicability flourished thanks to the usage of FE solvers [512,534–536]. Beam model simulation relies on basic truss and beam theory assumptions: lattice struts are straight, the material is linear and elastic, and the stress state is computed thanks to Timoshenko beam theory in FE simulations.

In beam model simulation, two approaches are proposed, considering stretch-dominated and bending-dominated lattices. Stretch-dominated structures are characterized by negligible bending moments and can be accurately simulated using truss models [531]. For bending-dominated structures, simplified beam modeling fails to accurately capture behavior near the nodes, leading to discrepancies between simulations and experimental results. This is due to the oversimplification of the mechanical behavior of struts converging at idealized zero-dimensional points, ignoring the rigidity of real nodal connections.

To address this, various corrective strategies have been proposed. Luxner et al. and others [534,536–538] suggested increasing nodal stiffness by locally increasing the material elastic moduli. While others [510,512,535] recommended enhancing local stiffness by increasing strut diameter near nodes. Dong et al. [539] introduced a method of incorporating correction factors into the beam element stiffness matrix, comparing beam models to solid models of unitary cells. However, some authors [510,540,541] do not consider the compensation for structures with very low porosity. A summary of the beam model technique can be addressed in Fig. 13.

There is a lack of agreement among the different authors on the compensation coefficients and the length of the lattice struts characterized by the compensation. A study able to generalize this manner is strongly necessary.

Studies have been performed on the convergence of the compensated and non-compensated beam models, suggesting dividing the lattice struts in at least 4 [542], 5 [541], 6 [510] or 10 [511] beam elements. This choice depends on the specific study, cell topology and porosity, while as a general statement, at least 6 elements per strut are suggested.

An extension of this concept is proposed by Ozdemir et al. [543], where the sheet-based TPMS lattice structures are modeled thanks to shell elements.

Compensated beam and truss models offer significant computational efficiency, reducing computation time by orders of magnitude compared to solid models. They also provide a detailed description of lattice topology, enabling direct examination of displacement and stress fields and application of loading conditions and constraints. However, the primary drawback is the need for calibrating compensation parameters, either through experimental tests or solid FE models.

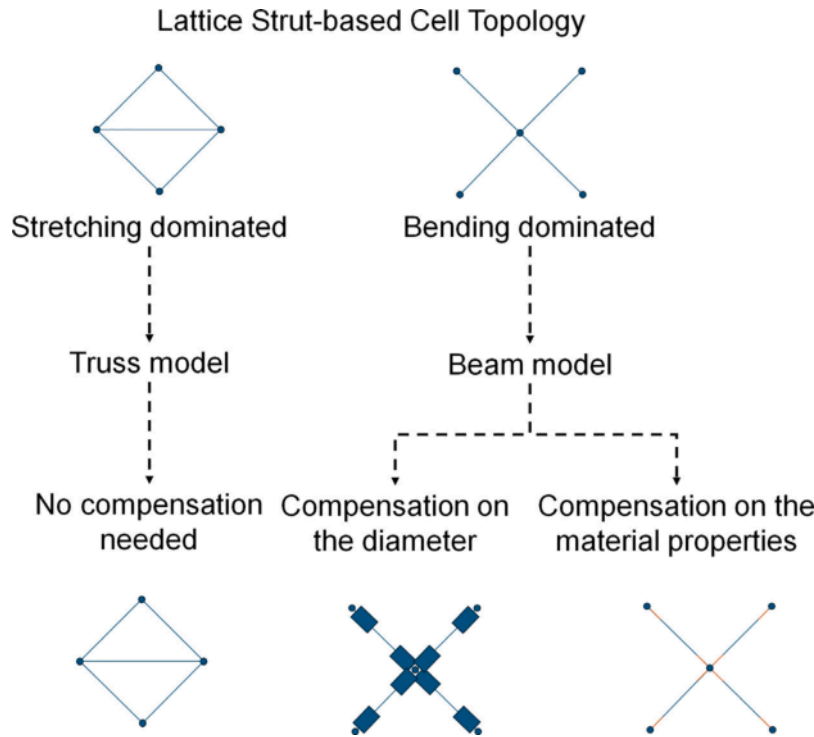


Fig. 13. Conceptual guideline for lattice structure simulation using 1D elements.

Table 7

Techniques for including the manufacturing induced defects in FE simulation of lattice structures.

Simulation technique	Defect addressed	Generative tool	Reference
Solid	Surface defects	Statistical analysis	[510,511,544]
Solid - FCM	Surface defects	Statistical analysis	[545]
Solid	Internal defects	Damage model	[546]
Homogenization	Surface defects	Statistical analysis	[545,547]
Beam models	Surface defects	Statistical analysis	[510,511,548–550]
Beam models	Material properties	Statistical analysis	[548,549]

5.2.4. FE modeling of the manufacturing-induced defects

The topological complexity and thus the computational cost is not the only challenge linked to the simulation of lattice structures. The manufacturing process strictly influences the lattice structure geometry, imposing a deviation from the ideal as-design geometry to an as-build one characterized by geometrical discrepancies. These manufacturing-induced defects alter the geometrical outcome and so the mechanical properties of the analyzed structure.

This challenge cannot be overlooked by the FE models, and research efforts have been made to include these effects in the different simulation techniques. A summary of the proposed approaches is presented in Table 7.

The inclusion of manufacturing-induced defects in the lattice topology is worsening the issues connected to the computational cost of the FE simulation. For this reason, different authors addressed the problem using computational efficient 1D models or a combination of 1D models and solid models [538].

It is also important to mention the possibility of using specific FE theories, such as the Finite Cell Method [551,552] to simulate geometries obtained directly from CT-scan analysis of lattice components. In this sense, Korshunova et al. [545,553–555] show the capabilities of a powerful integration among these tools.

5.3. Design optimization strategies

Given the complex biological and mechanical requirements discussed in the previous sections (Section 4.1 and Section 4.2), heuristic design approaches (Section 5.1) face significant challenges in the designing of effective bone implants. These methods are often unsuitable for a rapid and efficient prototyping of new implants, primarily due to the extensive trial-and-error process needed to satisfy the aforementioned criteria. Over recent decades, structural and multidisciplinary optimization (SMO) techniques have emerged as revolutionary computational methods that transcend the intrinsic limitations of heuristic approaches by offering robust design strategies. When combined with the key manufacturing advantages of additive manufacturing technologies, these strategies are paving the way for the development of next-generation implants, optimized to meet both biological and mechanical criteria, marking tremendous advancements in the orthopedic field [556].

SMO refers to a branch of computational engineering that leverages optimization techniques to efficiently improve the overall design and performances of a structural component [557]. These approaches mainly focus on the definition of the best design parameters that fulfill and adhere to predefined criteria and constraints. SMO can be generally classified into three main categories: sizing optimization (SO), shape optimization (SHO) and topology optimization (TO). SO techniques focus on determining the ideal thickness or cross-sectional distributions for elements like plates, shells, or truss structures. On the other hand, SHO aims to identify the optimal shape within a fixed contour or domain, maintaining the original material connectivity. Unlike SO and SHO, which are constrained to predefined configurations of the design space, TO offers a more flexible approach by allowing for the redistribution of material within a design domain, thereby altering and optimizing both its geometrical features and material connectivity. While the distinctions among these optimization techniques can sometimes blur, TO is often regarded as the most comprehensive approach. It effectively incorporates aspects of both SO and SHO by enabling adjustments in the structural connectivity, shape, and size [557].

The flexibility and wide-ranging applicability of TO, originally developed for structural and civil engineering applications, have led to its growing popularity across various fields. It has indeed extended far beyond its traditional applications to become a valuable tool in sectors like the biomedical orthopedic field.

5.3.1. Topology optimization

The general topology optimization problem has the aim of finding the optimal material distribution (Ω^*) in a given design space (Ω), by its discretization into a set of smaller subspaces (N), that minimizes a cost or objective function (J), under one or more pre-established constraint functions (C_k). The optimization problem can be ruled by a linear or non-linear state equation and the material distribution can be defined as a function of a design variable ($\rho(x)$), a level-set function ($\psi(x)$) or a characteristic function ($\chi(x)$), according to the TO approach employed. Among the most diffused methods for solving SMO and TO problems, it is worth mentioning the solid isotropic microstructure with penalization (SIMP) [558,559], the level-set method (LSM) [560], the evolutionary structural optimization (ESO) [561] and the bi-directional evolutionary structural optimization (BESO) [562] methods. SIMP, sometimes also labeled as density-based optimization, is by far the most employed methodology as recently reported in [557]. Hence, the general formulation for a standard SIMP TO is herein reported in Eq. (6):

$$\min_{\rho \in U_{ad}} J(\rho, u(\rho)) \equiv \int_{\Omega} j(\rho, u(\rho), x) d\Omega \quad (6)$$

$$s.t. \quad C_0(\rho) \equiv \int_{\Omega} c_0(\rho, x) d\Omega \leq 0 \quad (7)$$

$$C_k(\rho) \leq 0, \quad \text{for } k = 1, \dots, m \quad (8)$$

$$\rho_e \in \{0, 1\}, \quad \text{for } e = 1, \dots, N_e \quad (9)$$

$$Ku(\rho) = F \quad (10)$$

The objective function J can be defined by the volume integral of the local function j over the given design space Ω . The cost function J is then subjected to constraint functions such as the volume constraint, C_0 (often expressed as $\sum_{e=1}^{N_e} v_e \rho_e - V_0 \leq 0$ where v_e , ρ_e and N_e are respectively the element volume, the element density and the total number of elements in which the design space has been sampled). In its general formulation, other constraint equations can be incorporated, herein represented by $C_k(\rho)$, where m refers to the number of constraint functions applied. The whole TO problem needs to satisfy the state equation, $Ku(\rho) = F$ (linear as in this case or non-linear), to guarantee the global equilibrium of the system. SIMP is generally referred to as a discrete problem where the elemental density ρ_e can binary assume the value of 0 (void) or 1 (solid), as a result of a penalization iterative scheme. This scheme is ruled by a parameter P (penalty factor) which also allows to linking the design variable, *viz.* density, to the isotropic properties of a materials, E_{ijkl}^0 , through a power law, as shown in Eq. (11):

$$E_{ijkl}(x) = \rho(x)^P E_{ijkl}^0, \quad P > 1 \quad (11)$$

In more advanced formulations of density-based TO approaches, the elemental density variable can be also considered as a continuous scalar value ranging in the interval $0 \leq \rho \leq 1$. The assignment of an “artificial density” to each element of the mesh is necessary to control the microstructure of the design space, which in the case of AM applications and specifically of cellular materials is of paramount importance for their optimal spatial distribution. These approaches are often defined as homogenization-based topology optimization (HBTO), since the assigned density is linked to the homogenized properties of a material. In general, to solve the optimization problem and to iteratively update the design variable, different update schemes can be employed. Among the most adopted algorithms, it is worth mentioning

the Optimality Criteria (OC) [563], the Method of Moving Asymptotes (MMA) [564] and Sequential Quadratic Programming (SQP) [565].

Following this general introductory overview of SMO and TO approaches, the subsequent sections explore applications of different SMO and TO strategies in the orthopedic field, with the aim of reviewing the most common cost and constraint functions applied in the design of bone implants. Furthermore, practical applications mainly through two case-specific studies, *viz.* spinal and hip prosthetic implants, are showcased and overviewed, highlighting and examining the primary advantages and challenges associated with TO in the field.

5.3.2. Cost and constraint functions for bone orthopedic implants

Table 8 comprehensively reviews and summarizes the primary TO strategies, alongside their associated cost and constraint functions, employed in the design of lattice-based orthopedic implants manufactured through metal AM technologies. Standard TO (STO) is acknowledged as an established methodology in the preliminary design phase of bone implants, extensively used to optimize their overall structure. It principally aims at removing unnecessary material, thus creating lightweight implants that, for instance, can mitigate the risk of stress-shielding by lowering the elastic modulus. Nonetheless, while STO provides a quick and effective means for initial device redesign, it faces two significant limitations that hinder its exclusive adoption as an all-encompassing design tool. Firstly, STO often considers a single system loading condition at a time, failing to fully represent the complex array of physiological loading scenarios and the dynamic interactions between the implant and adjacent bone tissue. Secondly, within the field of lattice-based bone implants, the metamaterial introduction is simply given by the infill of the voids left by STO, without undergoing any specialized optimization process. Weighted TO (WTO) introduces a refinement to the STO scheme by incorporating the complex, intricate, and multiple loading conditions characteristic of a realistic physiological model. This approach is exemplified in the studies of Huang et al. [566] and of Lai et al. [2], where the four different loading conditions affecting the lumbar section of the spine – namely flexion, extension, lateral bending, and axial rotation – are integrated into the TO framework, by assigning to each loading condition a specific weight (21.5%, 21.5%, 33%, and 24%, respectively) throughout the optimization process. A condensed scheme of the workflow proposed by Lai et al. [2] is summarized in Fig. 14a. However, similar to STO, also WTO does not facilitate a specific optimization approach for the lattice infill within the device, as it primarily operates at a single-scale level.

Two different approaches can overcome the aforementioned limitation on the lattice infill: the homogenization-based TO (HBTO), shown in Fig. 14b and the multiscale TO, shown in Fig. 14c. In both cases, the optimization scheme assumes the separation of length-scales, so that the patterns at a microscopic scale are consistently smaller than the macroscopic features of the component. This guarantees to perform two consequent optimizations of the design domain either at a global scale, *viz.* the outer framework of the device, and at a local scale, *viz.* the material microstructure expressed as a periodically spaced lattice. HBTO bases its foundation on the homogenization theory (see Section 5.2.2), which allows to look for optimal solutions in a relaxed design space. This is achieved by a simplification of the complex microstructural characteristics (*i.e.*, porous lattices) of the material and their replacement with a simpler and more computational efficient continuous “fictitious” medium of which its elasticity tensor, depicting the “effective” properties of the microstructure, is a function of the design variable (*i.e.*, lattice relative density). The SIMP is hence transformed into an “unpenalized” problem where the relative density of the unit-cell varies continuously from 0 to 1, thus assigning to each scalar value a different homogenized set of material properties. The application of this well-known methodology [584] within the framework of bone implant design is well described by Moussa et al. [574,576], which have shown two practical applications for an optimized design of a cervical fusion cage and for an acetabular cup for a THA. It is however

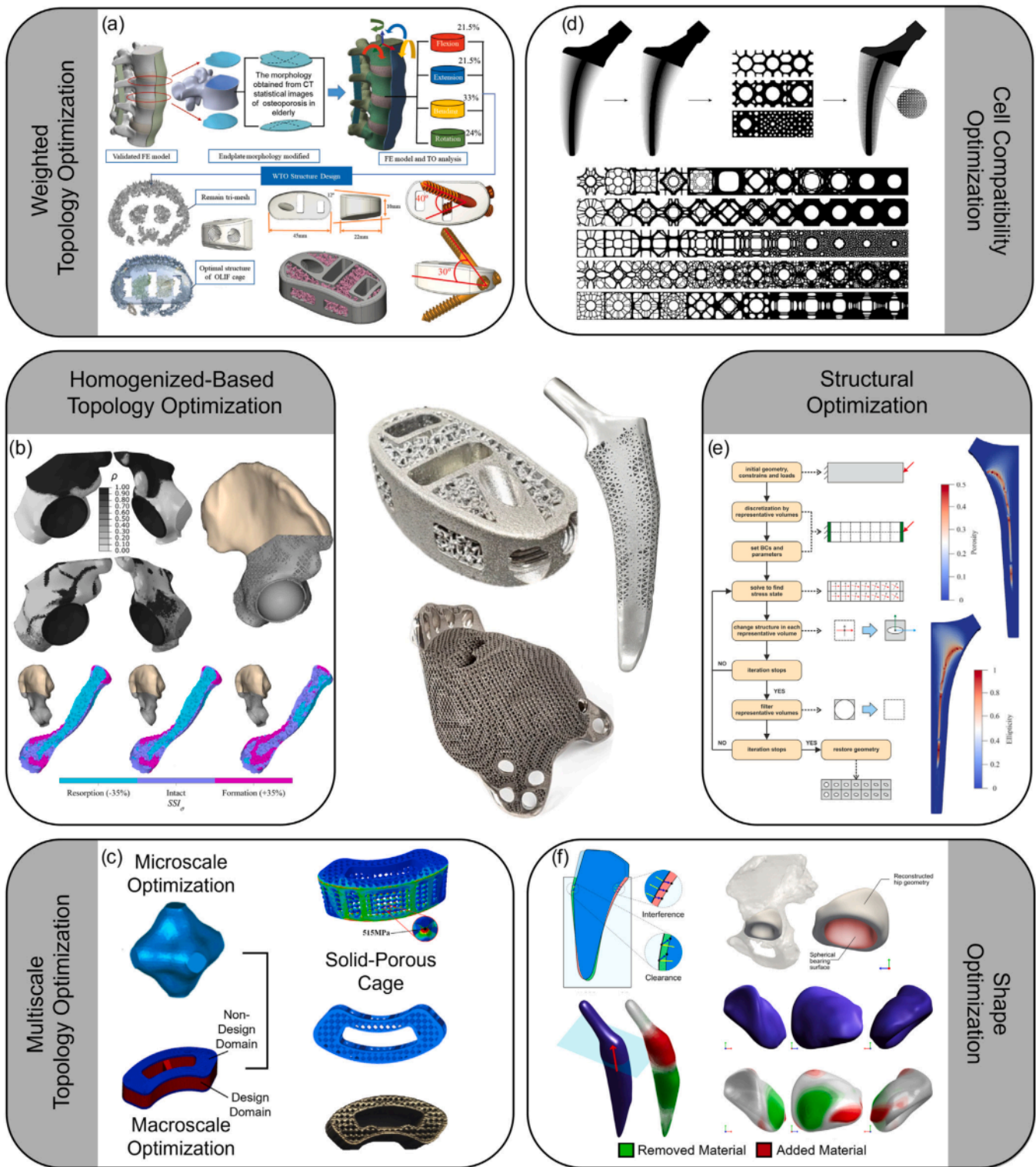


Fig. 14. (a) Workflow of weighted topology optimization for designing a Ti-6Al-4V oblique lumbar interbody fusion cage, infilled with Yang-Ming lattice unit cells. The final structure is achieved by addressing four weights corresponding to biomechanical loads at the L3-L4 lumbar segment of a 70-year-old female osteoporotic patient. Adapted from [2]. (b) Example of a homogenization-based topology-optimized custom pelvic lattice-based implant. This includes the lattice density distribution from the TO, the final lattice-based implant, and stress-shielding improvements based on the Stress Shielding Index (SSI). Adapted from [4]. (c) Multi-scale topology optimization scheme for an L-PBF Ti-6Al-4V transforaminal lumbar interbody fusion cage. The process includes microscale optimization for defining the optimal lattice unit cell and macroscale optimization for the framework structure, starting from a bulk solid cage. Adapted from [567]. (d) Cell compatibility TO strategy for optimizing transitions in cell topologies and bulk modulus within the structure, applied to a stem hip implant. Adapted from [568]. (e) Structural optimization algorithm based on the basic-cell concept. The SMO is applied to a stem hip implant to reduce stress concentrations, ensure uniform load distribution, and minimize total implant volume by eliminating low-stiffness cells. Adapted from [495]. (f) Level-set-based shape optimization algorithm for tailoring implant insertability into host bone. Examples include optimized material addition and removal for proper insertion of stem hip and acetabular cup implants. Adapted from [569]. Examples of lattice-based prosthetic devices in the center of the figure are taken from: Spinal [2], Acetabular [570], Hip [571].

Table 8

Overview of Topology Optimization and Structural Optimization methods and their applications in the design of lattice-based MAM orthopedic implants. The table categorizes optimization approaches based on the method employed, the target of the optimization, the algorithm type, as well as the cost and constraint functions. It also highlights the specific medical applications, lattice unit cell types, materials, and AM processes utilized (Abbreviations: ND, not defined).

Optimization Method	Target	Type	Application	Cost Function	Constraint Functions	Unit Cell Type	AM Process & Material	Main Findings	Ref.
Standard TO	Compliance	SIMP	Spinal	(Min.) Energy of structural compliance	Volume (20%)	Gyroid, Schwarz, Body-centered cubic	ND, Ti-6Al-4V	TO design allowed to achieve a stress distribution closer to the natural bone loading conditions, reducing bone density loss and facilitating bone remodeling. // The Facet Contact Force (FCF) in the segments affected by fusion (C3/C4 and C5/C6) is smaller than for the high density cages, showing a possible protection of the facet joints of adjacent segments.	Xu et al. 2023 [572]
Weighted TO	Compliance	SIMP	Spinal	(Min.) Strain Energy Density	Volume fraction, Yield Strength Factor	Rhombic Dodecahedron	L-PBF, Ti-6Al-4V	41.5% reduction in maximum Mises stress compared to a traditional trussed implant.// The optimized implant achieved double the maximum compression load and stiffness per unit mass compared to the trussed implant.// Clinical application yielded positive short-term outcomes, with no subsidence or shifting.	Kang et al. 2021 [573]
Weighted TO	Compliance	SIMP*	Spinal	(Min.) Compliance	Volume, Multidirectional load conditions	Gyroid	L-PBF, Ti-6Al-4V	Design of a curved-surface TO cage with higher contact surface area and better stress distribution on the endplate (lower risk of subsidence).// Yield load and stiffness of the curved-surface TO cage are compliant with ISO 23089.	Huang et al. 2023 [566]
Weighted TO	Compliance	SIMP*	Spinal	(Min.) Compliance	Volume, Multidirectional load conditions	Yang-Ming	L-PBF, Ti-6Al-4V	ROM decreased on an average of 75% with respect to the intact model, leading to a better implant stability.// Reduced endplate damage and risk of cage subsidence due to large contact area.// Mechanically and Fatigue tested according to FDA recommendations.	Lai et al. 2023 [2]

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worth mentioning that, in most of the HBTO applications, a geometrical parameter of the lattice, i.e., the unit-cell length, must be assumed fixed, to guarantee the unit-cell continuity within the lattice domain.

In contrast to HBTO, multiscale TO, depicted in Fig. 14c, incorporates two distinct optimization schemes at the two different length scale. According to Wang et al. [500,567], an initial local optimization problem is set to define the optimal unit-cell that maximizes stiffness, subjected to predefined volume constraints. Subsequently, a homogenization-based TO is applied on a global scale, aiming to optimally distribute the TO-designed unit-cell within the design domain of the spinal fusion cage. Unlike HBTO, which requires lattice unit topologies defined *a priori*, multiscale TO allows the determination of the unit-cell topology as a result of the local optimization process itself. However, multiscale TO also faces two major challenges and limitations: it is bounded to regular microstructural patterns, and it may yield sub-optimal solutions, thus solutions not representing the real optimum

for that given problem. Recent advancements have introduced a variety of more sophisticated strategies to tackle these limitations. Notably, within the context of bone implant design, Smit et al. [583] have developed a Full-Scale TO (FSTO) methodology to design compliant porous bone scaffolds. FSTO operates as a mono-scale, high-resolution approach capable of producing structures with multi-scale features and a customizable porous microstructure. This method surpasses multi-scale TO by eliminating the assumption of distinct length scales, which is particularly crucial in lattice-based prosthetic designs where the scale separation is often insufficient. Implants range from a few centimeters in cervical fusion cages to ten or twenty centimeters for hip stems, with microstructures typically consisting of unit-cells a few millimeters in size and pores and struts ranging from 200-900 μm . FSTO addresses these scale discrepancies and potential connectivity issues between cell units or units with varying strut sizes, presenting a more effective alternative for designing architected cellular materials for implants.

Table 8 (continued).

Homogenization-Subsidence-based TO		SIMP	Spinal	(Max.) Strain Energy Density	Volume, Manufacturing constraints (on homogenization)	Tetrahedron-based	L-PBF, Ti-6Al-4V	Reduced risk of subsidence due to a 14% and a 21.7% improvement in von Mises and normal strain distribution under physiological loading conditions.	Moussa et al. 2018 [574]
Homogenization-Lightweighting-based TO		SIMP*	Spinal	(Min.) Volume*	Density and porosity limitations on the cell	Octet-truss	L-PBF, ZK60 and Ti-6Al-4V	Stress at the endplate-cage interface reduced by 40% for the optimized ZK60 cage.// Improved bone ingrowth potential.// ZK60 optimized cage outperformed Ti-6Al-4V.	Sun et al. 2021 [575]
Multiscale TO	Compliance (Local), Lightweighting (Global)	SIMP	Spinal	(Min.) Strain energy density (Local), Min. Volume (Global)	Volume Fraction (Local), Stiffness/Displacement (Global)	Variable (TO-designed)	L-PBF, Ti-6Al-4V	The optimized cage reduced the solid volume by 9%, increasing space for bone grafts while matching the stiffness of conventional porous cages.// Peak stress on the cage was significantly decreased, enhancing long-term integrity.// Stress on bone endplates was reduced, lowering the risk of cage subsidence.// The fabricated cage demonstrated a porosity of 70%, with a pore diameter favorable for bone ingrowth.	Wang et al. 2020 [567]
Multiscale TO	Lightweighting (Local), Lightweighting (Global)	SIMP	Spinal	(Min.) Unit cell volume (Local), (Min.) Volume (Global)	Elastic Modulus 80% Bone Endplate, Displacement under physiological loading conditions (Global)	Variable (TO-designed)	L-PBF, Ti-6Al-4V	Lower risk of subsidence due to the lower peak stress on bone endplate for the TO cage.// A 72.2% porosity in the structure shows a favorable bone ingrowth.// The AM-printed device shows discrepancies from the as-designed TO model that might alter the overall mechanical properties.	Wang et al. 2022 [500]

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Additionally, the combination of SMO and TO within a unified framework has been proposed by Bolshakov et al. [495]. They introduced a novel, efficient computational technique based on the concept of a basic cell and its adaptable application to intricate design spaces. This method significantly enhances design flexibility by enabling the creation of inhomogeneous porous structures. Within these different frameworks proposed for an advanced design of lattice-based implants, the optimization problem often relies on the compliance minimization, which essentially means maximizing the implant stiffness. This cost function is often quantified through the implant's strain energy density, as shown in Eq. (12):

$$\min_{\rho} : C(\rho) = \frac{1}{2} F^T U(\rho) = \sum_{e=1}^N \frac{1}{2} u_e^T K_e(\rho) u_e \quad (12)$$

Here, the implant compliance, $C(\rho)$, determined by the global load vector F and nodal displacement vector $U(\rho)$ of the implant, is computed as the sum of the half-products of the transposed displacement vector for each element, u_e^T , the elemental stiffness matrix, $K_e(\rho)$, and the elemental displacement vector, u_e . Constraints on volume fractions are required to ensure a decrease in the total volume of the design space. This allows to mitigate the risk of stress-shielding, while keeping sufficient load-bearing capacity of the prosthesis. An alternative approach focuses on optimizing the implant's energy stiffness both at the bone-implant interface (boundary conditions) and under external forces. This optimization considers constraints on pre-operative

stresses, stiffness, and von Mises stresses at the bone-implant interface [4,571,574,577]. Unlike the classical compliance optimization, minimizing the disparity between post-operative and pre-operative physiological stress states does not necessarily impose a volume constraint, crucial to prevent the optimal solution from being a completely solid implant [577]. Still in the context of cost function based on implant compliance, the work of Moussa et al. [574] is noteworthy for its approach which focuses on the maximization of the compliance, achievable by the minimization of the inverse of the strain energy density. The authors claimed its effectiveness in reducing the risk of subsidence of a cervical fusion cage. Also in this case, volume constraints are needed to define optimal solutions with material removal.

Another commonly employed target of TO in the orthopedic field is the lightweighting of implants, as defined in Table 8. The advantage of lightweighted devices is multiple. Reducing the material not only lowers the implant's equivalent stiffness, which in turn minimizes stress-shielding effects but also makes production more cost-effective and environmentally sustainable. Typically, the goal of lightweighting is to reduce the implant's volume, as shown in Eq. (13):

$$\min_{\rho} : V = \sum_{e=1}^N \rho_e V_e \quad (13)$$

This objective function is mainly associated with constraint functions that ensure the fulfillment of specific design and structural requirements of the implant, thus typically based on stresses or strain/

Table 8 (continued).

Homogenization-Compliance-based TO		SIMP	Hip (Acetabular Cup)	(Min.) Strain Energy Density	Volume, Manufacturing constraints (on homogenization)	Tetrahedron-based	L-PBF, Ti-6Al-4V	The maximum contact stress and the micromotions were reduced of 21.4% and 26%.	Moussa et al. 2020 [576]
Homogenization-Physiological Stress State		SIMP	Hip	(Min.) Energy Stiffness	Preoperative stress	Body-Centered Cubic (BCC)	L-PBF, Stainless Steel	Reduction of the RMSE stress deviation between the physiological model and TO and non-TO implants up to 81% and 66% in GZ6 and GZ7.// Micro-FE model validation for accurate stress prediction, including the lattice and bone microstructure	Muller et al. 2024 [577]
Homogenization-Physiological Stress State		SIMP	Hip (Acetabular Cup)	(Min.) Stress Difference between pre-and post-surgery	Stiffness, Volume, Critical pre-operative stress	Octet-truss	ND, Ti-6Al-4V	Significant reduction in peri-prosthetic bone resorption (from 44% to 18%).// Improved stress distribution without compromising structural integrity.// Development of a novel approach for lattice-based stress-shielding resistant TO.	Babazadeh-Naseri et al. 2023 [4]
Multiscale TO	Lightweighting (Local), Compliance (Global)	ND	Hip	(Min.) Volume (Local), (Min.) Compliance (Global)	Fatigue threshold on von Mises stress of 600 MPa (Local), Volume Fraction restrictions at 10-20%-30% (Global), Regional Compliance Area of 5% of the intact femur (Global), Manufacturing	Face and Body Centered Cubic with vertical Struts (FBCCZ)	L-PBF, Ti-6Al-4V	Stress-shielding has been evaluated according to the SSI metrics.// A reduction by over 50% with respect to a traditional implant.// Implant should meets the ISO 7206-4 Fatigue Standards.	He et al. 2018 [578]

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displacement thresholds. For example, Wang et al. [500,567] introduced a displacement constraint to keep the stiffness of the outer framework of the TO-porous implants aligned with the bony endplate's stiffness in the spine's lumbar section under prescribed physiological loads. Kaymaz et al. [581] applied constraints to manage the maximum Von Mises stress of the humerus bone fixation plate, ensuring the implant structural integrity while keeping bone-like properties and reducing stress-shielding criticalities. The concept of lightweighting is often applied in multiscale TO, particularly at the local scale for the design of customized lattice units, where the volume minimization is crucial for a maximization of the bone in-growth in the porous lattice channels as shown in [4]. In this work, the authors employ a stiffness constraint function determined as the difference between the single entries of the elasticity tensor of reference with respect to the obtained effective elasticity tensor.

On the other hand, He et al. [578] explored a TO strategy aimed at material savings and quicker printing times by keeping the lattice

topology consistent, focusing on variations of the strut sizes rather than of classical lattice density, thus without keeping fixed the cell length. They included constraints on beam end sizes to ensure nodal connectivity and continuity within the lattice domain. Moreover, to address the structural durability of the designed material, they considered fatigue strength requirements as per ISO 7206-4 [234], setting a constraint to keep the von Mises stress below a 600 MPa safety threshold for an L-PBF Ti-6Al-4V lattice-based implant.

Aside from cost functions based on the compliance and volume minimizations, the recent advancements of TO approaches in the orthopedic field is also shown by the development of ad-hoc TO and SMO cost functions for specific functionalities of the prostheses. It is worth mentioning, for instance, the bone remodeling TO strategies, such as the ones proposed by [495], inspired by Cowin's model of bone adaptation to mechanical loads, and by Garner et al. [579], who proposed a modified versions of Huiskes's models for bone resorption and

Table 8 (continued).

Multi-Objective TO	Bone re-modeling, Load-induced interface fracture	SIMP*	Hip	Min-Max problem: 1) Interface stress (Min. max value of Hoffman's failure criterion), 2) Bone remodeling (strain energy density)	Critical bone remodeling value, Critical interface stress value	Cubic Anti-Chiral	ND, Ti-6Al-4V	The optimized titanium hip implant outperforms traditional solid implant designs by 64.0% in bone remodeling and 13.2% in interface fracture risk.// The Developed method better optimize load transfer and reduce the risks of bone loss and interface fracture.	Garner et al. 2022 [579]
Structural and Standard TO	Bone adaptation to loads	Basic-cell method	Hip	(Min.) Stress concentration and uniform load distribution (SMO), (Min.) Volume/Stiffness (TO)	Porosity threshold, Ellipticity threshold, Functional surfaces, Yield stress threshold	Basic Cell	ND	Volume reduction by 9%–11%, keeping the load bearing capacity and achieving an optimal internal porous structure.// Optimal porous structure is expected to facilitate specific functional loads.	Bolshakov et al. 2024 [495]
Compatibility Optimization	Cell Compatibility	Three-field SIMP	Hip	(Max.) Bulk modulus	Unit cell volume limitations, Cubic-symmetric isotropy conditions	Multiple	L-PBF, Ti-6Al-4V	The proposed approach can successfully generate functionally graded orthopedic implants with different cells spatially varying within the design domain and guaranteeing bone ingrowth and structural integrity.// The fabrication of a 2D Hip stent validated the method's feasibility for practical biomedical applications.	Garner et al. 2019 [568]
Shape Optimization	Insertability	Level-set	Hip (Acetabular Cup)	(Min.) Total shape changes, (Min.) Risk of implant loosening (Hoffman Risk Reduction)	Insertability	None	ND	Custom SO provides insight for the design of implants with both ease of fit and insertion keeping their structural integrity.// Fitting constraint as a path-planning problem reduces the complexity of Insertability models.// Reduction of the Hoffman Insertability Risk index by 94% for a SO implant.	Garner et al. 2023 [569]

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apposition. The first [495] strives to reduce stress concentrations, ensure uniform load distribution, and minimize the hip endoprosthesis's total volume by eliminating cells lacking sufficient stiffness in a combined SMO and TO approach. This optimization is constrained by the implant's boundary conditions, by designating non-optimizable functional surfaces at the bone-implant interface which preserve essential biological and mechanical functionalities of the implant. Additionally, constraints on basic cell properties such as porosity and ellipticity aim to maintain prosthetic structural integrity are integrated. The adopted workflow of Bolshakov et al. [495] is summarized in Fig. 14e. Conversely, Garner et al. [579] presented a multi-objective optimization (WTO) framework to minimize both bone apposition and resorption through a strain energy density approach while concurrently reducing the risk of interface fracture failure by minimizing the Hoffman multi-axial failure criterion's maximal value at the implant interface. This framework is bound by thresholds for critical bone remodeling and interface values to prevent surpassing physiological limits. Furthermore, in separate work, Garner et al. [569] expanded optimization solutions for hip endoprostheses, addressing other critical design considerations. They devised a shape optimization (SO) algorithm to improve the

implant's insertability into the host bone by employing a level-set method that minimizes an insertability metric, indicative of total shape alterations. This metric assists in assessing the complete insertability or extractability of the implant, based on its ability to move infinitesimally outward from its inserted configuration without interference, as illustrated in Fig. 14f. Although this method does not conform to TO strategies, it possesses the inherent capability to be effortlessly integrated into a TO framework due to its unique formulation and the cost function's differentiability. This potential for integration into TO, as highlighted by the authors, underscores the algorithm's versatility and its contribution to the future development of more comprehensive, multi-steps, strategies for orthopedic implant design.

Moreover, Garner et al. [568] also explored the possible integration of different cell unit topologies within a single design domain. They devised a cell compatibility TO strategy using a three-field SIMP model to optimize the bulk modulus of individual cells while ensuring smooth transitions in cell topology and mechanical properties by incorporating adjacent cell pairs into the optimization process, as schematized in Fig. 14d. This approach is subject to volume constraints on individual cells and symmetry conditions (cubic-symmetric conditions for cell isotropy)

Table 8 (continued).

Standard TO	Compliance	SIMP*	Tibial	(Min.) Compliance	Volume (20%)	Deformed Yang-Ming	L-PBF, Ti-6Al-4V	To suggested to have a structural volume in the posterior end near the cortical bone.// Reduction in total displacement, maximum implant stress and maximum 1st principal stress in the screw with respect to a commercial T-plate spacer.// Manufacturing errors are below 1%.// Fatigue biomechanical evaluation of the TO lattice-based cage revealed a higher number of cycles before failure compared to the commercial T-plate spacer.	Wang et al. 2023 [580]
Probabilistic TO Approach	Lightweighting	SIMP*	Humerus Bone Fixation Plate	(Min.) Volume	Maximum von Mises Stress	Gyroid	L-PBF, Ti-6Al-4V	Mitigation of stress shielding and enhancement bone ingrowth (due to the reduced stiffness and volume).// Development of a failure probabilistic assessment validating the design's reliability amidst uncertainties.	Kaymaz et al. 2023 [581]
Standard TO	Elastic modulus	SIMP	General	(Min.) inverse of the bulk modulus and an isotropy penalty factor	Volume	TO-designed	L-PBF, Ti-6Al-4V	TO-designed lattice with a bone-like properties (target value of $E=20$ GPa and porosity of 50%).// AM wall thickness variations and porosity increase impact the mechanical properties.	Vilardell et al. 2019 [582]
Full-Scale TO	Compliance	SIMP	Bone scaffolds for critical size defects	(Min.) Strain energy	Local volume at voxel scale, Compression strain energy similar to the adjacent tissue stiffness	Undefined*	L-PBF, Ti-6Al-4V, PEEK	Approach that addresses the entire scaffold structure's optimization, without separating the design into distinct microscale and macroscale components.// 81% improvement in design efficacy with respect to a multi-objective TO	Smit et al. 2023 [583]

to prevent improper cell transitions, underlining the sophisticated balance between structural optimization and functional integration in orthopedic implant design.

5.3.2.1. Spinal implants: MAM and TO-based design strategies have shown relevant improvements in the design and efficacy of cervical and lumbar spinal implants [2,500,566,567,572–575]. In cervical applications, Xu et al. [572] recently investigated TO implants designed specifically for anterior cervical discectomy and fusion (ACDF), embedding Gyroid, Schwarz, and Body-Centered Cubic (BCC) lattice structures. These TO designs offer a more uniform stress distribution on the C5 cortical bone surface, potentially reducing the risk of bone damage. For instance, during flexion, lattice-TO cages have shown an increase in the cortical bone average stress of 125.8%, 216.3% and 194.4%, respectively for the Gyroid, Shwartz and BCC lattices. Additionally, the authors revealed that the contact forces at facet joints were lower for TO-cages when compared to bulk implants, suggesting a better protection of the adjacent segment's facet joints from overloading conditions. Despite these improvements, TO did not significantly reduce intradiscal pressure at adjacent segments, suggesting a limitation in fully mitigating adjacent segment degeneration. Similarly, Moussa et al. [574] investigated the risk of cage subsidence of a C6/C7 ACDF implant, employing the von Mises stress distributions and the strains in the normal direction of the upper C7 vertebral body surface, as evaluation metrics. The authors reported a 10%–14% reduction in average von Mises stress and about 20% in normal strains on the posterior, left, and right lateral regions of the C7 superior surface under severe combined loading conditions, suggesting a notable biomechanical improvement over non-TO designs. Sun et al. [575] evaluated the performances of a ZK60 cervical interbody fusion cage with a TO optimized octet truss lattice infill, in comparison with a Ti-6Al-4V

fusion cage. The authors obtained an increase of about 83% in the bone graft stress, indicating a promising mechanical stimulation of the bone graft while ensuring enough stability. Additionally, a stress reduction of about 96% was achieved at the endplate-cage interface without compromising the desired range of motions (ROMs) of the device and thus suggesting a lower tendency to induce bone microfractures on the vertebral endplates as well as a reduced risk of cage subsidence.

Concerning lumbar spinal implants, Kang et al. [573] designed a topology optimized artificial vertebral implant (AVI) for the reconstruction of multi-segment spinal defects, in the frame of patients suffering of significant bone loss due to tumors or trauma. The evaluation of the TO AVI was performed numerically and experimentally. The maximum von Mises stress, which was registered for the axial rotation, is reduced of about 30% from the 80.64 MPa of the non-TO-implant to the 56.74 MPa of the TO implant. This decrease underscores the potential of topology optimization to diminish the risk of cage subsidence and stress-related bone complications, a conclusion further supported by promising short-term *in vivo* results. Moreover, experimental compression tests demonstrated a more favorable stress distribution and superior mechanical properties in the TO AVI, including a maximum compression load of 72.72 ± 0.55 kN and a response stiffness of 60.93 ± 0.81 kN/mm—values that are four times higher than those of non-optimized implants. These findings suggest enhanced structural integrity of the implant. However, limitations related to the embedding of the full spectrum of complex physiological loads and *in vivo* interactions into the FE model are shown, restricting a complete understanding of the prosthesis behavior. Additionally, the authors highlight the absence of long-term *in vivo* data, which is necessary to fully validate the proposed implant. Similarly, Huang et al. [566] showed that TO design of a L3/L4 posterior lumbar interbody fusion cage reduced the maximum stresses on the vertebral endplates

and experimentally reported higher yield load and stiffness than the standard requirements, notably improving the cage performance with respect to commercially available cages, thus granting for a long-term viability and integration of the implant. Lai et al. [2] also investigated the manufacturing errors associated with the printing of a TO oblique lumbar interbody fusion (OLIF) cages and experimentally verified the dynamic properties of the cage, according to FDA suggestions, proving a good printing accuracy as well as an endurance limit of 5 million cycles at 6000 N. Fatigue tests revealed no global failure of the cage but micro-cracks nucleation at the anterior/posterior cage edges. Wang et al. [500,567] developed a thorough analysis of multiple sequential TO-optimized Transforaminal lumbar interbody fusion (TLIF) cages, with and without external reinforcement structures (RPF). The authors revealed a reduction of the peak stresses on the vertebral endplates of about 17% in the RPF model, an increase in the bone graft SED, which suggests a higher bone stimulus and bone ingrowth, and an overall reduction of the flexion peak von Mises stress of about 50% with respect to the previous stages of optimization. Nonetheless, a reduction in the ROMs indicates an important limitation in the full restoration of the physiological motion capabilities of the spinal segment.

5.3.2.2. Hip implants: Similarly to spinal implants, the main advantages driven by topology optimization strategies in the hip prosthetic design focuses on improvements of the stress distribution at the bone-implant interface without compromising the implant structural integrity. Moussa et al. [576] achieved a decrease in the maximum contact stresses of 21.4% in a TO-optimized design of an acetabular cup for THA. Additionally, the authors focused on the micromotion detection, calculated as the relative sliding distance at the bone-implant interface. Micromotions are either the cause of an enhanced bone ingrowth ($< 28 \mu\text{m}$) or the cause of fibrotic tissue growth which inhibits a correct biological fixation ($> 150 \mu\text{m}$). Despite the solid cage has already shown micromotion values well below this threshold ($9.04 \mu\text{m}$), the proposed TO led to a further reduction of about 26% ($6.69 \mu\text{m}$) in the optimized acetabular cup. In another study on acetabular cups [4], TO allowed to reduce the volume of the peri-prosthetic bone which is predicted to undergo bone resorption after surgery. This decrease can beneficially reduce the stress-shielding phenomenon, numerically calculated through stress-shielding indices (SSI), based on the von Mises stresses and SED values of bone elements in the FE model. A reduction from 44% to 18% is achieved due to the introduction of lattice structures with an optimized porosity in the acetabular cup. Furthermore, the implant in this study [4] was also verified against a yielding failure criterion, revealing that 99% of the prosthetic elements had a safety factor greater than 11 and a minimum safety factor of 2, which indicated that the lattice porous design is not compromising the overall structural integrity of the device. To guarantee a long-term stability and avoid revision surgery, it is also necessary to guarantee a proper implantability, minimizing the risk of aseptic loosening of the prostheses. Garner et al. [569] focused on this issue and reported an optimized patient-specific acetabular cup with a 94% reduction of the modified Hoffman instability risk index.

Stem hip implants are often referenced as the main case study for optimization strategies to be applied in THA. Also, within these prosthetic typologies, TO guarantees a decrease of the post-operative stresses to the physiological loads as shown in Muller et al. study [577], where 81% and 66% reduction of the RMSE stress deviation for TO stem implants are achieved at Gruber Zones GZ6 and GZ7. A validation by means of μCT s and μFE models proved the feasibility of the printed prosthesis and suitability of the homogenized models for the evaluation of the surrounding bone model. SSI metrics are also employed by He et al. [578] in the design of a TO hip stem with FBBCZ variable size lattices. The authors claimed that their implant could reduce more than 50% the risk of stress-shielding, by simultaneously guaranteeing a survival of 10^7 cycles.

5.3.3. Limitations of topology optimization

Despite the clear advantages that the synergistic action of TO techniques and MAM can bring to the design of next-generation implants, TO presents several important limitations worth noting. As stated in Section 4.1.1, the structural integrity of architected cellular materials remains a significant concern for the widespread adoption of MAM lattice-based implants. TO strategies, and particularly HBTO strategies, overlook the complex geometry of metamaterials due to their intrinsic formulation of a homogenized fictitious medium. While this approach reduces the computational cost of numerical simulations, it neglects local phenomena, such as fatigue, which are crucial for the longevity of implants [157,585].

In most TO formulations, it is challenging to incorporate objective functions focused on the fatigue assessment of implants, being fatigue a localized effect acting at struts and junctions. To address this issue, fatigue criteria are often embedded in the TO scheme by defining passive constraint functions based on the bulk material properties [571,578]. However, it is well known that fatigue properties in AM lattices are inferior to those in bulk materials, potentially leading to unsafe implant designs.

Another inherent limitation of HTO and multi-scale TO strategies is the generation of theoretically optimal designs with intricate multi-scale features that are difficult to manufacture with current technologies. Transitioning from a multi-scale design, which embeds different microstructures at various length scales, to a single-scale design practical for manufacturing—a process known as de-homogenization—can result in sub-optimal performance due to intrinsic limitations of this technique. The major challenge indeed lies in preserving the intricate details and performance advantages of the lattice design. During the homogenization process, lattice structures are simplified into an averaged, continuum model that fails to capture all the intricate details of the microstructural geometry. When transitioning back to the detailed lattice structure in the de-homogenization process, this mismatch can result in geometrical inaccuracies [586,587]. Geometric distortions of the lattice units often arise due to the necessity of stretching or modifying the base cells to align with the optimized macro-scale layout, leading to inconsistencies in the final lattice structure. These inconsistencies can create stress concentrations and weak points within the material, compromising its structural integrity and durability. Furthermore, smoothing boundaries from coarse-scale homogenization to fine-scale lattice structures introduces additional errors, complicating both manufacturing and functional performance [526].

5.4. Fatigue modeling and optimization strategies

The translation of these sophisticated designs from computational models to clinically viable products often encounters significant challenges, primarily due to the lack of experimental validation and comprehensive mechanical characterization. Optimized implants are predominantly validated at a computational level [588], with real-world experimental testing being sporadically conducted, if at all. This gap is due in part to the complexity and cost associated with manufacturing and testing prototypes. As a result, most implants are assessed only through simulations that predict their behavior under idealized conditions. This lack of thorough mechanical characterization can obscure critical failures that might occur in actual medical scenarios, particularly under dynamic physiological conditions. To bridge this gap, this section presents strategies for incorporating fatigue considerations in a separate subsequent stage of the design process:

- **1. Direct Fatigue Testing:** The most straightforward approach involves fatigue testing on 3D printed prototypes that have been topologically optimized. This method allows for direct observation of fatigue failure mechanisms under controlled testing conditions [180,235]. For instance, Fig. 15a shows the fatigue test carried out on a porous hip joint prosthesis [235]. Similarly,

fatigue tests are carried out on laboratory coupons and the resulting fatigue strength expressed in global stresses is transferred to the fatigue verification of the implant wherein the global stress distribution is computed via homogenized FE models [589,590].

- **2. Stress Analysis on de-homogenized RVE:** A local stress analysis for fatigue calculation requires reconstructing the actual topology of the metamaterial. This process begins by assuming that strains in the homogenized macroscopic optimized model can be decoupled from stresses at the micro/meso scale [500,591, 592], by means of de-homogenization of single-cell RVEs [592–594]. The critical RVE cell is identified using an index derived from the homogenized strains or stresses [593]. The theoretical framework of this approach is depicted in the flowchart reported in Fig. 15b [591]. For the analysis, the stress field within the RVE is examined using FE analysis, considering either the nominal CAD geometry or an imperfect geometry of the lattice to reflect more realistic conditions [547]. Fatigue calculations are then performed, utilizing a Haigh diagram, as in Fig. 4, [591,595] to account for mean stress effects or applying a suitable multiaxial fatigue [596] criterion to address the complexities of the stress states. In instances where the nominal CAD geometry is used, a modifying factor is introduced to account for surface roughness effects [596], enhancing the model's accuracy in predicting fatigue life under actual operating conditions.
- **3. Incorporating Printing Imperfections:** In the aforementioned approach, it is implicitly assumed that printing inaccuracies are uniformly distributed across the entire component, making the RVE representative of typical manufacturing imperfections found in lattice structures [157]. However, if this uniformity assumption does not hold true, advanced imaging techniques such as μ CT scans are employed to capture the geometry of the entire imperfect lattice [597,598]. This includes detailing strut waviness and cross-sectional irregularities. These imperfections are then integrated into FE models to evaluate their impact on the fatigue life of the implant. This process, although resource-intensive as discussed in Section 5.2.4, is crucial for understanding the comprehensive fatigue performance of the implant. By capturing and modeling the actual imperfections, engineers can more accurately predict how these variables influence the implant's durability under normal use conditions. In some instances, a local stress or strain energy approach is also employed to account for the material's fatigue notch sensitivity. This method focuses on the high-stress regions that are most susceptible to crack initiation and propagation, providing a more nuanced insight into the structural integrity of the implant.
- **4. Beam Element Models and Sub-Modeling:** A more computationally efficient approach employs modified beam elements able to reflect imperfections in the beam section, often identified by μ CT scans or stereoscopic inspections image analyses [538, 599,600]. This method establishes boundary conditions for sub-models at critical locations within the lattice structure. These locations are sometimes selected randomly and subsequently analyzed using extreme value statistics and notch fatigue calculation methods [538]. This technique not only enhances the accuracy of the model by incorporating real-world imperfections but also optimizes computational resources by focusing on the most critical areas where fatigue failure is most likely to initiate. The modus operandi of this approach is schematically illustrated in Fig. 15c [538]. Beam element modeling can be also employed for SMO within the design stage of a lattice component to define its optimal printing orientation for improved fatigue life [601].
- **5. Finite Cells Method (FCM):** The FCM has been proposed as a method to simplify the pre-processing steps required for analyzing implants directly from μ CT images. By employing high-order finite elements, FCM allows for the direct simulation on the μ CT images, avoiding the need to create an external mesh, thus simplifying and accelerating the analysis [602,603].

- **6. Digital Twin Technology:** An emerging innovative approach that has recently gained traction is the use of digital twins, which involves creating synthetic CT scans of implants through advanced machine learning algorithms [604]. This method evades the costly and time-consuming process of physically printing and scanning prototypes. Instead, a digital twin – a comprehensive virtual model – accurately represents the physical object. It is developed based on the predicted characteristics of the implant, including potential manufacturing imperfections and detailed surface morphology [605]. To achieve this, machine learning algorithms are trained on a large database of CT scans from actual printed components. This training enables the algorithms to accurately recognize and replicate complex morphological patterns, ensuring that the digital twin mirrors real-world physical conditions as closely as possible. Fig. 15d shows the application of this concept to the prediction of buckling [606], but the same idea can be applied in the future to fatigue strength assessments [606].

To conclude, the optimization and validation of orthopedic implants require a nuanced understanding of both global optimization techniques and localized phenomena like fatigue. By integrating both computational and experimental methodologies and addressing the specific challenges posed by additive manufacturing imperfections, the field can enhance the reliability and efficacy of implants, ensuring they meet the rigorous demands of medical use.

5.5. New trends in the design of orthopedic lattice-based implants

5.5.1. Machine learning-based design

Machine learning (ML) is revolutionizing the design and optimization process of the orthopedic implants, significantly accelerating their development and enhancing their performances. Traditional trial-and-error and heuristic methods are more often being replaced by data-driven approaches, either as stand-alone networks or as embedded into TO frameworks [607]. These approaches leverage supervised or un-supervised learning algorithms such as random forests, support vector machines (SVM), neural networks (NN), variational autoencoders (VAE) and generative adversarial networks (GAN) to predict and optimize the mechanical properties of implants, ensuring they meet specific load distribution or stress reduction requirements. Additionally, ML algorithms combined with experimental dataset on lattice metamaterials, can efficiently enable the rapid evaluation of numerous material compositions and structural configurations, identifying the most effective designs [607]. This not only accelerates the discovery process for novel designs but also allows for more accurate implant customization suit individual patient needs, thereby enhancing their effectiveness and potentially reducing the risk of implant complications.

In the frame of ML approaches embedded into TO strategies, Zeng et al. [608] introduced a multi-network deep learning method for the inverse design of gradient metamaterials grounded on TO scheme. This method incorporates a Generative Adversarial Network (GAN), a Property Prediction Network (PPN), and a Structure Generation Network (SGN) into a TO framework, leveraging on an analogy between color space and mechanical parameter space, converting parametric design into a pixel-matching problem, as shown in Fig. 16b. In their case study, the authors applied this method to design a hip joint prosthesis with a gradient modulus and Poisson's ratio inspired by the biomechanical load state of the femur. This design promotes effective load distribution and minimizes the risk of interface failure between the prosthesis and bone by means of gradient auxetic structure with multiple unit-cells. Negative Poisson's ratio unit-cells are placed on one side of the implant, aimed at enhancing bonding under a tension stress state with the surrounding bone. A middle zone with a zero Poisson's ratio for a smooth transition is then designed. The authors also emphasize the model's efficiency, noting that it ensures a design flow with geometric connectivity between base cells in just 2 s.

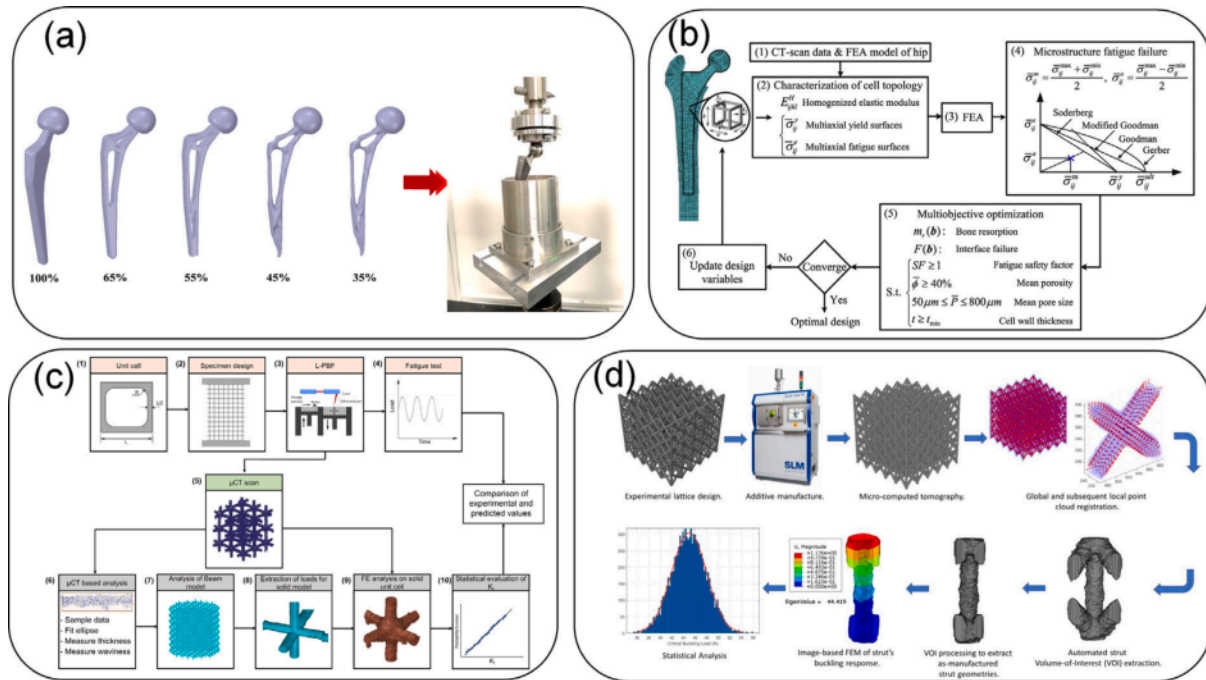


Fig. 15. Different approaches to fatigue design of prosthetic devices. (a) direct fatigue testing of a porous hip joint prosthesis. Adapted from [235]. (b) Stress analysis on a de-homogenized Representative Volume Element (RVE) conducted using finite element (FE) analysis. The flowchart of this approach is illustrated by the image adapted from [591]. (c) Beam model of the entire lattice components and submodeling of critical parts done combining CT scans and FE models with solid elements. Adapted from [538]. (d) Digital twin of the actual geometry of the printed component involving the creation of a synthetic CT scans through advanced machine learning algorithms. This method is illustrated in the figure adapted from [606] where buckling behavior is anticipated but future developments will include also the fatigue assessment.

Jia et al. [609] developed a generative-TO integrated framework of which effectiveness was demonstrated through the design of a femur support structure. This application aimed to achieve precise stress modulation to prevent aseptic loosening and peri-prosthetic fracture while stimulating bone regeneration. The optimized design ensured that the support structure provided the right amount of shear stress to promote bone healing. The architecture consists of two main components: a material property optimizer and a virtual growth simulator. The first is the topology optimization network. It determines whether sub-regions of the material should be solid or void and identifies optimal frequency combinations of building blocks.

The virtual growth simulator, depicted in Fig. 16a, incorporates the ML aspect, by means of a fully connected NN with two hidden layers. It allows to map and integrate disordered microstructures with varying properties based on frequency combinations of building blocks. This information is then fed back into the optimizer to enhance the accuracy and efficiency of the design process.

Wu et al. [611] proposed an innovative multiscale TO framework enhanced by derivative-aware neural network (DANN) to design non-uniform iso-truss lattice structures with tailored mechanical responses. The DANN enables accurate prediction of the elastic behavior of unit cells while providing the sensitivity information required for optimization. This approach greatly reduces the computational cost compared to conventional iterative FE²-based methods. The resulting ML-TO optimized lattices achieve more uniform strain distributions, offering a promising strategy to mitigate stress shielding and enhance bone regeneration, demonstrated by the authors through case studies on L-PBF Ti-6Al-4V mandibular and femoral reconstruction implants.

ML approaches can also be employed as stand-alone architectures able to entirely substitute TO schemes for the design of lattice-based orthopedic implants. In this scenario, Peng et al. [610] provide an exhaustive example of the integration of ML in orthopedic implant design by the Generative Architecture Design (GAD) and Multi-objective

Active Learning Loop (MALL) method, shown in Fig. 16c. This innovative approach combines an autoencoder NN with FEM simulations to efficiently explore and optimize high-dimensional design spaces. The GAD component learns effective representations of architectural designs, reducing the complexity of the design space. The MALL component enhances the design process through an iterative loop of sampling, reconstruction, scaffold selection, and FEM simulation. This loop employs an epsilon-greedy search method to select data points that meet target properties and integrates the results into the dataset for further refinement. This architecture ensures that the scaffolds are optimized for mechanical properties of the bone tissue such as elastic modulus and yield strength, as shown for the design of bone grafting implants. The GAD-MALL method successfully designed gyroid scaffolds with elastic moduli of 2500 MPa and 5000 MPa, mimicking the mechanical behavior of trabecular and compact bones, while providing high interconnectivity ideal for bone osteointegration. Furthermore, the authors claim that GAD-MALL approach is highly efficient and robust, requiring only a small initial dataset and quickly discovering optimal designs.

Beyond ML frameworks aimed at structurally optimizing the implant architecture, recent developments have increasingly focused on inverse design strategies capable of generating unit-cell geometries tailored to specific mechanical requirements. For example, in [612], the authors proposed a deep learning framework that integrates point cloud representations with an autoencoder and a multi-layer perceptron (MLP) to capture the nonlinear relationships between geometry and mechanical properties. This approach enables the rapid generation of unit cells that replicate bone-like characteristics, including target elastic moduli, Poisson's ratios, and porosity.

Wang et al. [613] presented a data-driven method employing a dual 3D convolutional neural network (CNN) architecture to design spinodal structures with anisotropic elastic properties that closely mimic those of human bone. The first CNN replaces computationally expensive

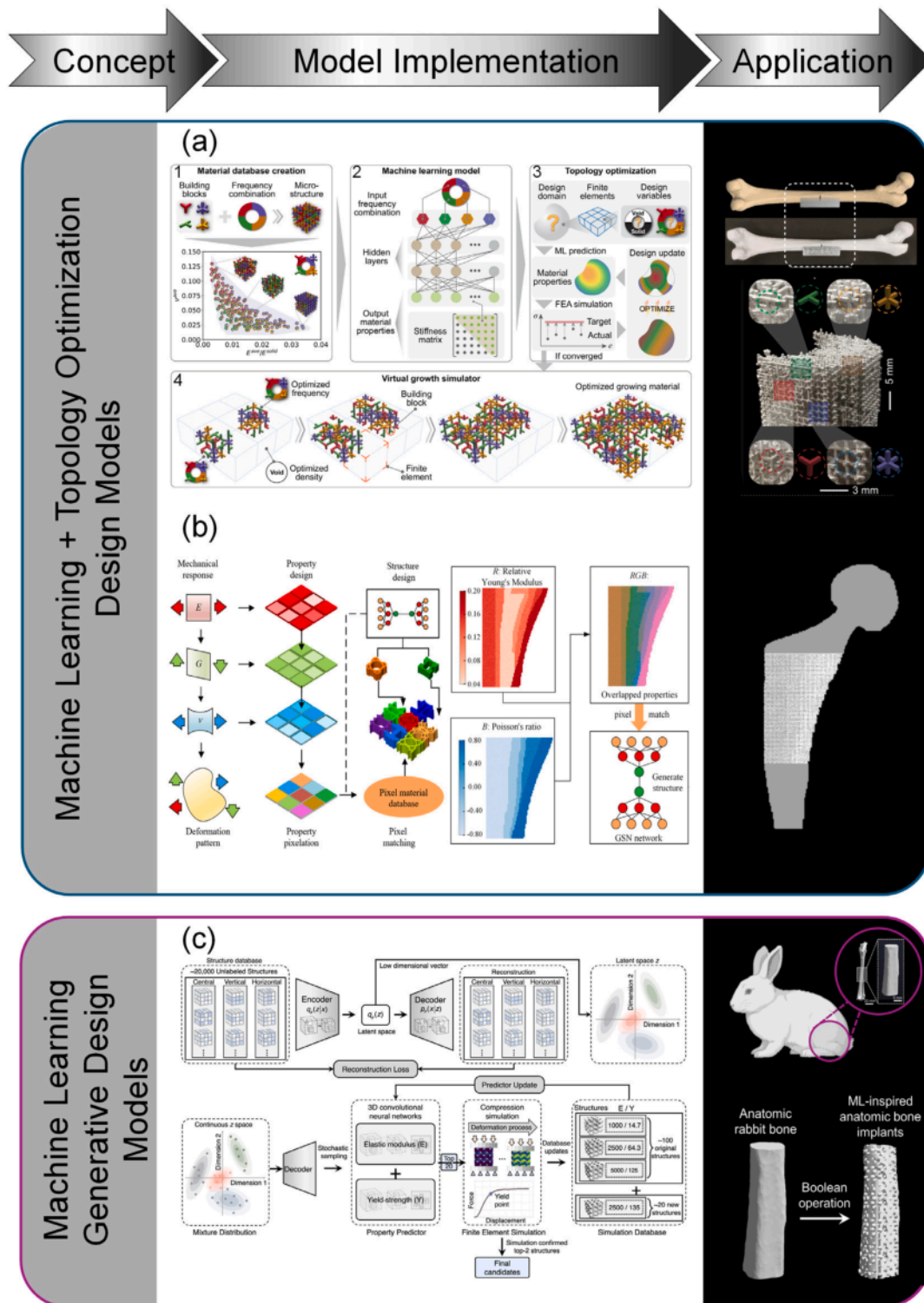


Fig. 16. (a) Example of a ML workflow integrated into a TO scheme. The process begins with creating a material database, defining building blocks, their frequency, and associated material properties. A fully connected NN predicts material properties, which are then used as design variables in the TO scheme to modulate stress distribution in the target FE domain. Once convergence is achieved, a virtual growth simulator fills the optimized domain with irregular lattices. The black section illustrates a lattice-optimized femur support structure. Adapted from [609]. (b) Integration of a GAN, PPN, and SGN into a TO framework. The approach uses a pixel-matching problem, where the R-G-B channels correspond to material properties such as Young's modulus (E), shear modulus (G), and Poisson's ratio (ν). The black section shows the results of the proposed scheme for a stem hip implant. Adapted from [608]. (c) Stand-alone ML architecture example, employing a generative architecture design and active learning loop (GAD-MALL). The workflow begins with scaffold designs generated from porosity matrices using an encoder-decoder architecture. These designs are iteratively optimized through the MALL framework via sampling, property prediction, candidate selection, and FEM validation for mechanical performance. The black section illustrates an optimized lattice bone implant designed for rabbit models.

Source: Adapted from [610].

phase-field simulations by learning the evolution of spinodal decomposition, while the second CNN predicts the stiffness tensor of the generated structures. By tuning input parameters to direct morphological anisotropy and screening a large number of candidates, the system successfully identifies spinodal architectures with mechanical performance comparable to natural bone, while maintaining the continuous, smooth pore networks essential for nutrient transport and vascularization.

However, a persistent challenge in many ML-based design frameworks is their reliance on large, high-quality training datasets, which often limits their practical applicability in the design of market-ready implants. Addressing this issue, Raßloff et al. [614] recently proposed a Bayesian optimization framework for the inverse design of spinodoid structures, which leverages Gaussian process regression and active learning to operate effectively in data-scarce environments. This strategy enables efficient exploration of the design space with minimal initial data, making it a promising tool for accelerating the design of bioinspired architected materials under practical constraints.

While this section has primarily emphasized the role of ML in the structural design and optimization of orthopedic lattice-based implants, it is increasingly evident that ML plays a broader role throughout the entire implant development process, from early prototyping and structural optimization to post-implantation monitoring [615,616]. As a matter of fact, ML techniques are often employed to optimize AM process parameters [617,618], tailor the microstructure of base materials [619,620], and predict or improve the component's mechanical properties [621–623].

5.5.2. Bio-inspired designs

Bio-mimetic and bio-inspired design approaches are increasingly gaining interest within the scientific and industrial communities, to tailor ad-hoc properties, leveraging microstructural features and constitutive laws from natural sources. Biomimetic designs can be obtained either by a direct replication of natural structures, by reverse engineering or through bio-inspiration approaches which use nature as a general guideline to inspire the design of new materials [624]. The manufacturing freedom given by MAM allows to design novel lattice units, mimicking the behavior of different natural materials, such as bamboo, trees, leaves and flowers as well as specific features of animal parts, like the turtle shell or the woodpecker's beak, to cite any. It is worth noting that architected cellular materials can be defined *per-se* as bio-inspired structures, mimicking the hierarchical complex porous structures as the cancellous bone. Hence, employing architected cellular material for orthopedic implant design can be already defined as a bio-inspired design approach. Nonetheless, specific bio-design tuning of the cells or new unit-cell design formulations can further boost their biomechanical efficiency, optimizing their use as bone scaffolds for orthopedic purposes. For instance, drawing inspiration from the trabecular bone 3D networks, Alsheghri et al. [625] exploit a heuristic structural network algorithm to mimic the natural process of constructive development and regression of natural bone tissue, as shown in Fig. 17b. This process involves the incremental removal of redundant least-loaded elements in a network based on simulated loaded conditions. Through an iterative TO scheme, scaffolds with optimal connectivity and functionality with minimal material use can be designed at different scale levels. In a preliminary work of Chen et al. [626], the authors instead propose an innovative approach to designing orthopedic implants by drawing inspiration from the vascular bundle structure of bamboo (Fig. 17a). The bamboo-inspired porous Ti-6Al-4V scaffolds (BISs) were developed using a 3D interconnected model that replicates the natural microstructure of bamboo, known for its exceptional strength-to-weight ratio. BIS structures reported enhanced mechanical and permeability properties, comparable to or better than those of natural human bone, making them promising candidates for load-bearing orthopedic implants. To tackle the same requirements, viz. enhanced permeability and bone-like mechanical

properties, Tan et al. [627] proposes a novel hollow BCC Ti-6Al-4V lattice inspired by cross-sectional geometry of the horsetail plant, shown in Fig. 17c. FE and experimental results show a fine-tuning of the mechanical properties, matching the ones of natural bone, particularly in terms of yield strength and elastic modulus. Furthermore, the authors discovered that isotropic characteristics of the unit-cells are decoupled from the outer strut radius, thus tremendously simplifying the design process, avoiding convoluted effects. A novel bio-inspired EBM Ti-6Al-4V lattice structure, the Triply Arranged Octagonal Rings (TAOR), has also been proposed as a suitable candidate bone orthopedic application [628]. The authors took a general bio-inspiration from octagonal geometries found in several natural rock formations. The TAOR design, reported in Fig. 17d, aims to achieve a balance between low stiffness and high mechanical strength. In comparison with the Kelvin and rhombic dodecahedron (RD) cells, experimental tests revealed that the TAOR cells exhibited superior elastic modulus, compressive strength, crush strength, and a bending-dominated failure mode. Despite most of the works focuses on preliminary scaffold designs, bio-inspiration can also be directly applied to the design of a implant, as shown in [629]. The proposed method involves creating porosities in the implant that mimic the natural distribution, size, shape, and orientation of trabecular bone structures. FE analysis is then employed to identify the stress distribution within the implant and guide the material removal process. This approach ensures that the implant maintains its mechanical integrity while reducing stiffness and mass. Experimental validation demonstrated that the bio-inspired prosthesis achieved a 25% reduction in stiffness compared to the initial prosthesis and a 29% reduction in material. This design significantly narrows the stiffness gap between the implant and the bone, potentially reducing stress-shielding and improving implant longevity. Additionally, another bio-inspired design is proposed, aiming to boost the osteointegration process by optimizing porosity sizes, albeit with a slight compromise on stiffness reduction.

Bio-inspiration can be incorporated into the optimization process through the application of techniques like genetic algorithms (GAs), as shown in Fig. 17e. These algorithms are capable of effectively solving both constrained and unconstrained optimization problems. They operate by mimicking natural selection to generate high-quality solutions, employing biologically inspired mechanisms such as mutation, crossover, and selection. To mitigate stress-shielding and bone resorption, Xu et al. [630] employed GA and TO to design a functionally graded Burch-Schneider (BS) cage for hip arthroplasty. The GA replicates the natural evolution of biological structures, such as human bone tissue. In this process, each unit-cell is treated as a chromosome that, through crossover (with a 0.3 factor) and mutation (with a 0.2 factor), generates new generations, evolving lattice material densities and thereby optimizing the cage's mechanical performance. The optimized design showed substantial improvements, reducing maximum Von-Mises stress by 18% compared to a uniform porosity lattice cage and by 75% compared to a fully solid cage. This approach significantly enhances the structural integrity and fatigue resistance of the implant. Saviour et al. [498] also employs GA for the design of a functionally graded porous uncemented acetabular component. A non-dominated sorting genetic algorithm (NSGA-II) is employed to strike an optimal balance between minimizing polyethylene (PE) liner wear and peri-prosthetic bone resorption. The design optimization involved varying porosity levels at the acetabular rim and dome, as well as adjusting radial and polar functional gradation exponents to enhance implant performance. Five optimal functionally graded porous designs (OFGPs) were identified, exhibiting reduced strain shielding in cancellous bone and comparable bone-implant interfacial micromotions to solid metal-backing designs.

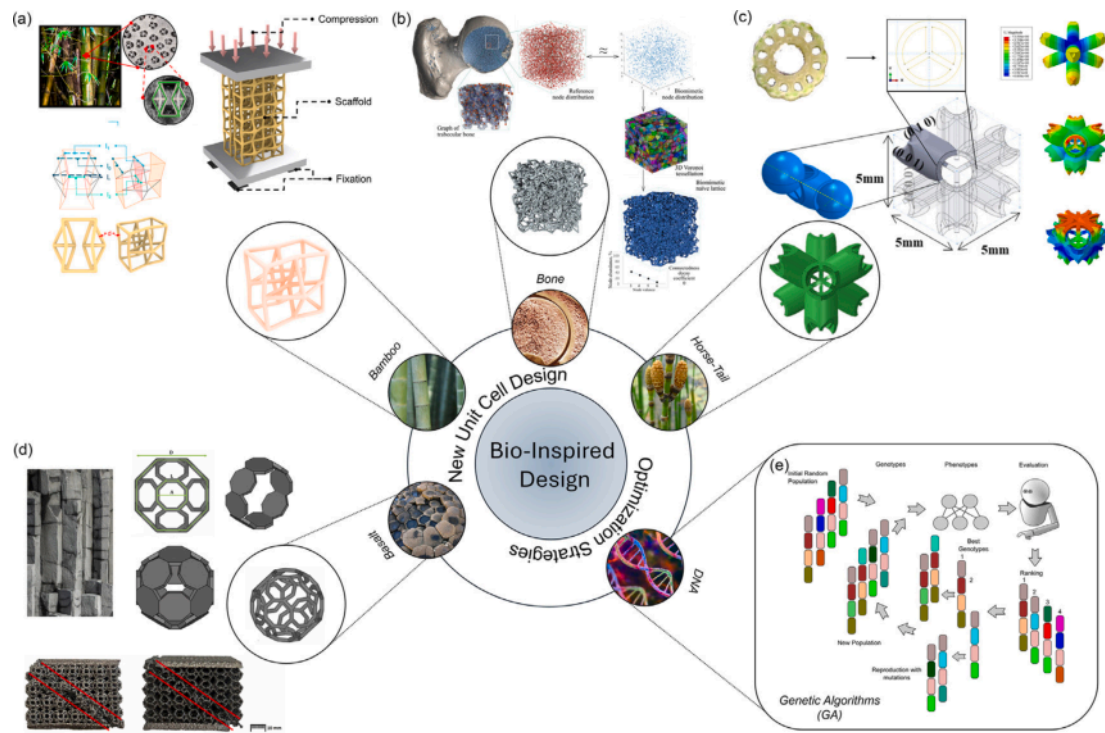


Fig. 17. (a) Unit cell and scaffold inspired by the macro- and micro-morphological features of the vascular bundle structure of bamboo. Adapted from [626] with the bamboo image sourced from [631]. (b) Bone-inspired lattice structure developed using a structural network algorithm that emulates the natural processes of bone tissue growth and regression. Adapted from [625] with the bone tissue image sourced from [632]. (c) Horse-tail-inspired hollow BBC lattice unit cell. Adapted from [627], with the horse-tail plant image sourced from [633]. (d) Triply Arranged Octagonal Rings (TAOR) unit cell, inspired by octagonal patterns found in natural rock formations like basalt. Adapted from [628] with basalt rock images sourced from [634,635]. (e) Bio-inspired optimization strategies using genetic algorithms based on mechanisms such as mutation, crossover, and selection. Adapted from [636].

6. Pathway to regulatory approval of medical implants

Building on the insights from Section 4 regarding implant requirements and Section 5 on design strategies, this section transitions to a more practical approach, bridging the gap between conceptualization and industrial application. Taking L-PBF Ti-6Al-4V lattice-based spinal cage implant as an example, Fig. 18 shows a comprehensive framework for its development and commercialization, ensuring regulatory compliance throughout the product lifecycle. While specifically designed for intervertebral body fusion devices, this framework is adaptable to various implant types, with appropriate modifications to meet specific regulatory requirements. This workflow takes inspiration from the FDA's Quality System Regulation (21 CFR Part 820 [637]) and ISO 13485:2016 [638] standards. It begins with implant design through CT-based anatomical data acquisition, enabling both patient-specific and standardized designs. CAD modeling and FE analysis optimize implant geometry under physiological loading conditions, as discussed in Sections 5.1 and 5.2. TO further enhances the design by minimizing stress-shielding and reducing mass while maintaining structural integrity. Lattice structures are subsequently integrated within TO regions to enhance biomechanical properties (see Section 5.3).

Given the intricate geometry of lattice-based components, it is crucial to incorporate specific design guidelines early in the process to ensure a reliable outcome that adequately addresses manufacturing challenges, such as effective powder removal, as outlined in ASTM F3530-22 [639]. Concurrent with design, ISO 14971:2019 [640] defines compliant risk management protocols that must be established to systematically identify hazards, assess risks, and develop mitigation strategies. The risk management protocol remains active throughout

the device lifecycle and is a fundamental requisite for regulatory submission prior to commercialization. A guidance on the application of ISO 14971 [640] is provided by ISO/TR 24971:2020 [641]. For L-PBF Ti-6Al-4V intervertebral body fusion device, manufacturing-related risks can include porosity control, anisotropic behavior, surface roughness variations, residual stress, and powder removal. Moreover, in the context of medical devices, powder reuse introduces additional risks due to its potential impact on the mechanical and physical properties of lattice-based components. Therefore, well-defined reuse protocols should be established and validated in accordance with ASTM F3456-22 [642] to ensure material consistency and device reliability. Biological-related risks can cover inflammatory responses, osseointegration variability, bulk material cytotoxicity and implant toxicity. Following risk assessment, comprehensive validation protocols ensure product safety and reliability through interconnected testing phases.

ISO/ASTM 52920:2023 [643] is recommended as a foundational reference standard at this stage, providing general qualification principles that ensure consistency and reproducibility of industrial additive manufacturing processes, covering aspects such as data preparation, feedstock handling, build-cycle execution, ancillary equipment, and overall manufacturing infrastructure. Additionally, for L-PBF manufactured medical devices, rigorous validation is required in adherence to ASTM F3604-23 [644]. This standard provides detailed guidelines for Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ), explicitly addressing software workflow validation, requalification protocols after significant process changes, and thorough integration of risk management practices aligned with regulatory expectations reported in ISO 13485 [638] and ISO 14971 [640].

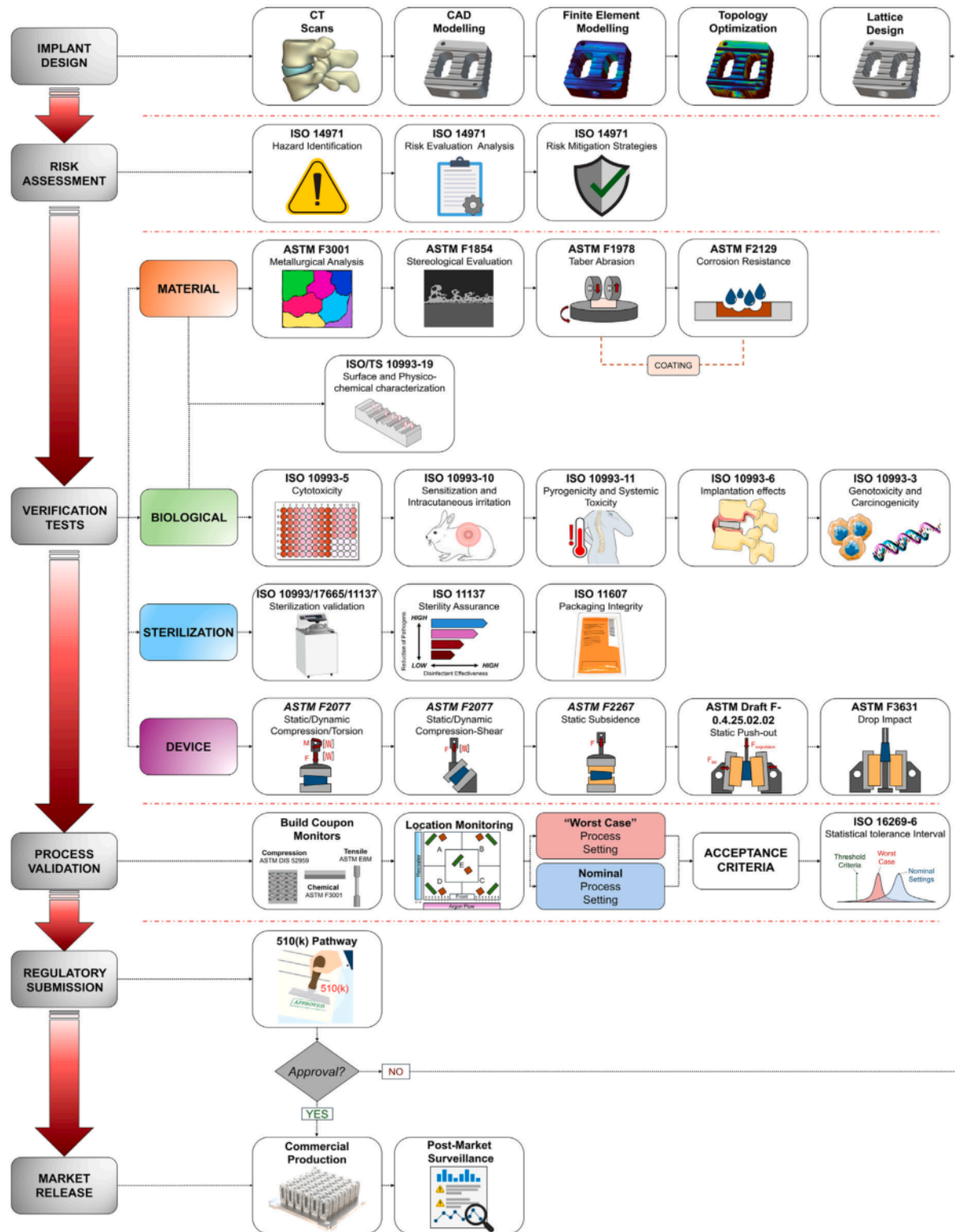


Fig. 18. Exemplificative workflow from design to commercialization of an L-PBF Ti-6Al-4V intervertebral lattice spinal implant, in compliance with regulatory standards throughout the entire product lifecycle. The process begins with implant design, incorporating steps such as CT scans, CAD and FE modeling, TO strategies for lattice design. Risk assessment addresses hazard identification, risk evaluation, and mitigation strategies, following ISO 14971:2019 [640] standards. Verification tests are categorized into four main areas: material characterization, biological assessment, sterilization procedures, and device mechanical testing. Material characterization involves metallurgical analysis, stereological evaluation, and coating testing in line with ASTM standards. Biological evaluation ensures compliance with ISO 10993 [645–653] for cytotoxicity, sensitization, and implantation effects. Sterilization procedures include validation, sterility assurance levels, and packaging integrity verification. Mechanical testing covers compression, shear, push-out, drop impact, and dynamic loading. Process validation follows the “worst case” principle as per FDA recommendations. Regulatory submission is carried out via FDA 510(k) pathways, culminating in commercial production and post-market surveillance.

The validation phase includes four critical testing categories: material characterization, biological assessment, sterilization validation, and device performance evaluation. Material characterization should start with metallurgical analysis of Ti-6Al-4V ELI powder and manufactured components, establishing chemical composition limits, powder morphology requirements, and microstructural and mechanical properties in accordance with ASTM F3001-14(2021) [654] and ASTM F2924-14(2021) [655]. Corrosion susceptibility assessment through potentiostatic testing (ASTM F746-4(2021) [656]) evaluates resistance to pitting and crevice corrosion under simulated physiological conditions, specifically for large size implants. This method provides critical potentials and insights into the material's ability to re-passivate, ensuring long-term performance and structural integrity *in vivo* (see Section 4.1.4). For coated implants, surface characterization following ASTM F1854-15 [657] quantifies coating thickness, void content, and mean intercept length—parameters essential for coating integrity assessment and biological response prediction. The wear resistance of a thermal spray coating is evaluated via the Taber Abraser method (ASTM F1978-22 [658]), quantifying the surface degradation resistance, particularly critical for articulating surfaces and insertion interfaces. Although not schematized in Fig. 18, additional tests such as shear and tensile testing of metallic or calcium phosphate coatings, as specified by ASTM F1044-05(2017)e1 [659] and ASTM F1147-24 [660], are commonly required in regulatory evaluations to ensure sufficient adhesion strength and coating reliability for clinical applications.

Material characterization is not only necessary for the implant's mechanical assessments but it also serves as a foundational step for biological testing. ISO 10993-18:2020 [652] indeed highlights the importance of chemical characterization to identify potential toxicological risks from leachable and degradation products, while ISO 10993-19:2020 [653] emphasizes the critical role of surface topography and morphological characteristics in determining biological responses. As a matter of fact, as discussed in Section 4.2, surface topography, porosity, and chemical uniformity can influence cellular adhesion, osseointegration, and inflammatory responses, underscoring the need for comprehensive material characterization before proceeding to biological evaluation. Biological evaluation adheres to a systematic approach under ISO 10993-1:2018 [645]. For spinal cage implants, classified as permanent/long-term devices with direct bone contact (type C), the assessment mainly focuses on long-term exposure and bone-specific interactions. The evaluation sequence begins with cytotoxicity testing (ISO 10993-5:2009 [648]), examining cellular death, growth inhibition, and cell viability reduction. Sequential assessments include sensitization and intracutaneous reactivity testing (ISO 10993-10:2021 [650]), the latter by means of standardized extract injections in rabbit models. Material-mediated pyrogenicity testing aims to verify the fever-inducing potential of the implant. Systematic toxicity studies (ISO 10993-11:2017 [651]) progress from acute to chronic exposure effects, encompassing immediate responses, subacute and subchronic effects over weeks to months, and long-term exposure impacts. Implantation analyses (ISO 10993-6:2016 [649]) evaluate local pathological effects at both macroscopic and microscopic levels over clinically relevant periods to assess tissue integration. Genotoxicity testing (ISO 10993-3:2014 [647]) employs *in vitro* assays for DNA damage detection, while carcinogenicity assessments typically rely on risk evaluation rather than direct testing (transgenic models if needed). Notably, biological tests may be waived given sufficient safety evidence from scientific literature, clinical history, comprehensive toxicological data, and/or chemical characterization, adhering to the 3Rs principle (Reduction, Refinement, Replacement) of animal testing outlined in ISO 10993-2:2022 [646]. Implant safety and effectiveness also critically depend on maintaining sterility until surgical deployment. Sterilization methods, as detailed in Section 4.3.2, are selected based on implant material and geometry, primarily including ethylene oxide (EtO), moist heat sterilization, and gamma radiation. These processes are ruled by

ISO 10993-7:2008 [459] and ISO 11135:2014 [458] (establishing EtO residual limits and byproducts), ISO 17665:2024 [456] (controlling microbial lethality through temperature, time, and moisture parameters), and ISO 11137-3:2017 [457] (specifying radiation dose measurements and sterility assurance level (SAL) validation).

Package integrity validation follows ISO 11607:2019 [661] protocols, ensuring sterile barrier maintenance during handling, transport, and storage until clinical use. Mechanical device testing evaluates spinal cage structural integrity under simulated clinical conditions.

Static and dynamic testing (ASTM F2077-24 [229]) requires five specimens per configuration, assessing compression, compression-shear (45° or 27°), and torsional properties at physiological temperature (37°C). Dynamic fatigue tests simulate prolonged stress through 5 million cycles at 25%, 50%, and 75% of the static yield load. Subsidence resistance testing (ASTM F2267-24 [250]) employs Grade 15 polyurethane foam blocks simulating vertebral endplates, with region-specific intradiscal heights (lumbar: 10 mm, thoracic: 6 mm, cervical: 4 mm). Intra-operative durability assessment (ASTM F3631-24 [662]) simulates surgical impacts using a 1 kg drop weight in progressive stair-step loading schemes, employing either foam block insertion or rigid block impact methods. Push-out testing (ASTM F04.25.02.02) evaluates implant migration resistance under simulated post-operative conditions to ensure adequate vertebral fixation stability. Process validation ensures manufacturing reproducibility through build coupon monitors, including lattice compression specimens (ASTM DIS 52959 [663]), tensile bars (ASTM E8-E8M-22 [664]), and chemical analysis coupons (ASTM F3001-14(2021) [654]). Location-specific monitoring across the build chamber addresses variations in thermal gradients and powder distribution (ISO/ASTM 52904:2024 [665]).

Process validation must take into account both nominal conditions and worst-case scenarios according to FDA recommendations. The worst-case evaluation principle represents a core element of FDA's regulatory framework, spanning multiple aspects of manufacturing workflows. This consideration is especially necessary for metallic AM technologies, where unique challenges emerge from build location variability, part orientation, and material reuse. Systematic assessment of variations in build parameters, environmental conditions, and material properties is essential to determine their impact on final parts, ensuring devices meet quality, safety, and reliability standards, even under the most challenging manufacturing conditions. The quality of L-PBF finished part as well as the possible post-processing operations, including surface finishing and HIP, should comply with ASTM/ISO 52908:2023 [666]. Furthermore, to validate these requirements for both nominal and worst-case conditions, acceptance criteria with thresholds for mechanical properties, dimensional accuracy, and material consistency are established using ISO 16269-6:2014 [667] statistical tolerance intervals. FDA additionally recommends non-destructive evaluation (NDE) methods, including CT scanning and ultrasound, for device integrity verification. Useful guidelines for appropriate NDE testing are reported in ISO/ASTM TR 52905:2023 [668] and ASTM F3704/F3704M-24 [669]. Before a medical device can be commercialized, the FDA requires regulatory clearance through the submission of classification-specific documentation. Intervertebral body fusion devices are generally classified as Class II devices when they include bone grafting material. As such, they typically follow the 510(k) pathway, which involves demonstrating substantial equivalence to predicate devices through safety, efficacy, and technological validation. For novel devices without predicates, the De Novo classification may be pursued based on preclinical data, while high-risk devices require Premarket Approval (PMA), supported by extensive clinical evidence. This applies to Class III devices, which, in the context of intervertebral body fusion, are those that incorporate therapeutic biologics, as specified in FDA 21 CFR 888.3080 [670]. Post-approval, commercial production initiates with scaled manufacturing processes under validated protocols. Continuous post-market surveillance monitors clinical performance through adverse event tracking, follow-up studies, and

clinical feedback, facilitating device refinement and long-term safety assurance.

Recent regulatory approvals have demonstrated the efficacy of translating metal additive manufacturing (MAM) lattice-based implants from theoretical design to clinical implementation. Continuing with the spinal implant case study, several devices have obtained FDA 510(k) clearance and CE certification between 2022 and present, with representative examples cataloged in Table 9. These regulatory achievements validate the development workflow illustrated in Fig. 18. Ulrich Medical's uCerv Flux-C cervical cage [671] (premarket 510(k) notification number K241396 in 2024) obtained clearance through quantitative demonstration of mechanical equivalence and comprehensive materials characterization. Osseus Fusion's Pisces-SA ALIF cage [672] (premarket 510(k) notification number K213935 in 2022) established a precedent as the first ALIF 3D printed device approved for standalone implementation with anchor-based fixation and diamond lattice architecture. NanoHive Medical's Hive™ Standalone Cervical System [673] (premarket 510(k) notification number K223190 in 2022) implements a biomimetic "soft titanium" rhombic dodecahedron lattice architecture with calibrated elastic modulus properties to approximate vertebral bone mechanical characteristics. More recently, Camber Spine's SPIRA-Anterior Lumbar Spacers [674] (premarket 510(k) notification number K234077 in 2024) introduce a patented spiral lattice structure with integrated screw or blade fixation, providing enhanced biomechanical properties.

It is worth noting that, despite their significant potential for advancing implant technology, most lattice-based orthopedic systems currently proceed through the Substantial Equivalence (SE) pathway, citing previously approved predicate devices in their 510(k) submissions. While this regulatory approach streamlines market access and meets established requirements, it simultaneously limits the scope of innovation that manufacturers can implement without triggering more comprehensive review procedures. On top of this, publicly accessible FDA documentation predominantly covers devices that have completed the authorization process [675], generating an incomplete picture of orthopedic innovative implants. Moreover, devices with potential to establish new benchmarks in the field (breakthrough designation) typically remain under confidentiality agreements until formal approval. This creates a temporal disconnection between cutting-edge developments and officially recognized advancements in the regulatory domain.

7. Concluding remarks

This paper provides a comprehensive review on the design and development of metallic lattice-based orthopedic implants. Special focus has been placed on the pivotal role that additive manufacturing (AM) techniques play in reshaping the landscape of orthopedic implant design and fabrication. Our investigation revealed a significant shift toward the integration of bio-inspired and data-driven design approaches, notably through the adoption of inverse design methodologies. These approaches have shown remarkable potential in enhancing the customization and multifunctionality of implants, thereby aligning implant properties more closely with the physiological and biomechanical requirements of individual patients.

The exploration of new material selections and the innovative application of AM technologies have facilitated the development of implants with complex geometries and tailored mechanical properties that mimic natural bone structure. This not only aids in achieving better osseointegration but also addresses the critical challenge of reducing stress shielding, a common issue with traditional implants that can lead to premature failure. Moreover, the capacity of AM to produce porous structures, which support vascularization and cell growth, heralds a new era in implant design that could significantly improve recovery times and outcomes for patients.

Regulatory standards and clinical translation remain substantial hurdles. Our review underscores the necessity for ongoing revisions of

regulatory frameworks to keep pace with technological innovations. The establishment of clear, robust guidelines that can accommodate the unique aspects of AM implants is crucial for ensuring their safety, efficacy, and quality. This regulatory evolution should be informed by continuous clinical feedback and emerging research findings to facilitate the seamless integration of these advanced technologies into routine clinical practice.

Future research should focus on several key areas to further the development of lattice-based orthopedic implants. First, there is a need for long-term clinical studies to evaluate the performance and safety of these implants in a broader patient demographic. Such studies will provide invaluable data that can refine design parameters and improve predictive models used in implant design. Additionally, the potential for integrating smart technologies, such as sensors or drug-delivery systems, into lattice-based orthopedic implants represents an exciting frontier that could transform post-operative care and monitoring.

In conclusion, the field of metallic lattice-based orthopedic implants is poised at the brink of a transformative shift, driven by advances in additive manufacturing and design methodology. As we continue to harness these technologies, collaboration across disciplines – combining insights from material science, biomedical engineering, and clinical practice – will be essential. By fostering a synergistic approach to innovation, research, and regulatory policy, we can unlock the full potential of next-generation implants to significantly enhance patient care and treatment outcomes in orthopedics.

CRedit authorship contribution statement

Melika Babaei: Writing – original draft, Writing – review & editing, Conceptualization. **Simone Murchio:** Writing – review & editing, Conceptualization, Writing – original draft. **Lorena Emanuelli:** Writing – review & editing, Writing – original draft. **Raffaele De Biasi:** Writing – review & editing, Writing – original draft. **Luigi Branca Vergano:** Writing – review & editing, Writing – original draft. **Roberto Giuliani:** Writing – original draft, Writing – review & editing, Data curation. **Shuya Tian:** Writing – original draft, Writing – review & editing. **Marie-Luise Wille:** Writing – review & editing, Supervision, Writing – original draft. **Filippo Berto:** Writing – original draft, Writing – review & editing, Supervision. **Massimo Pellizzari:** Writing – review & editing, Supervision, Conceptualization, Writing – original draft, Project administration. **Matteo Benedetti:** Writing – original draft, Project administration, Writing – review & editing, Supervision, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used the ChatGPT (OpenAI's GPT-4-turbo model) tool in order to improve readability and decrease English grammar mistakes. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 9

Examples of metal AM lattice-based spinal devices which received FDA's clearance.

Device	Manufacturer	Type of Implant	Manufacturing Method	Material	Lattice Type	Regulatory Status	Approval Year
uCerv Flux-C	Ulrich Medical	Cervical fusion	L-PBF	Ti-6Al-4V ELI	Randomized porous network	510(k) K241396 [671]	2024
Pisces-SA	Osseus Fusion Systems	Standalone ALIF	Not Specified	Ti-6Al-4V ELI	Diamond	510(k) K213935 [672]	2021
Hive Cervical	NanoHive Medical	Cervical fusion (standalone or with plate)	Not Specified	Soft Titanium®	Rhombic dodecahedron (proprietary)	510(k) K223190 [673]	2022
SPIRA® Anterior Lumbar Spacers	Camber Spine	ALIF, LLIF and OLIF	Not Specified (Spira® technology)	Ti-6Al-4V	Open Matrix Spiral Lattice (proprietary)	510(k) K234077 [674]	2024
Wave-Form C	Orthofix (SeaSpine)	Cervical fusion	Laser Powder Bed Fusion (L-PBF)	Ti-6Al-4V ELI	Waveform technology (proprietary)	510(k) K212904 [676]	2021
Cervical Spine Truss System (CSTS)	4WEB Medical	Cervical fusion	Not specified	Ti-6Al-4V	Open Truss Architecture (proprietary)	510(k) K231739 [677]	2023

Data availability

Data will be made available on request.

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Massimo Pellizzari was born in 1970, in Bolzano, Italy and got his masters degree in Materials Engineering in 1996 at the University of Trento (Italy). In 2000 he got a PhD in Metallurgical Engineering at the University of Padova. Since 2023 Prof. Pellizzari is full professor of Metallurgy at the University of Trento. His research activity is focused on production, heat treatment and surface engineering of steels, development of powder metallurgical tool steel by ball milling and Spark Plasma Sintering and additive manufacturing. In the last years his research group has spent many efforts in the development of additively manufactured Ti alloys for orthopedic prostheses. Hes the author of more than 100 papers in peer reviewed international journals and 2 chapters in books. Since 2015, hes member of the executive committee of the International Federation for Heat Treatment and Surface Engineering (IFHTSE), and since January 2024 president. Prof. Massimo Pellizzari is member of the scientific committee of "La Metallurgia Italiana", of the editorial boards of "International Journal of Microstructure and Materials Properties", "Metals" (MDPI) "High-Temperature Materials" (SCIEngine) and has recently joined the Scientific Program Committee of the conference Additive Manufacturing Meets Medicine.



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