metals

MDPI

Review

Review of the Use of Metals in Biomedical Applications: Biocompatibility, Additive Manufacturing Technologies, and Standards and Regulations

Leila Ladani * and Michael Palmieri

Mechanical and Aerospace Engineering, Arizona State University, Tempe, AZ 85283, USA; mpalmie1@asu.edu
* Correspondence: ladani@asu.edu

Abstract: Advanced manufacturing techniques such as Additive Manufacturing (AM) have grown rapidly in major industries such as aerospace, automotive, and biomedical device manufacturing. Biomedical industry has benefitted immensely from AM because of its flexibility in design and its rapid production cycle. Powder bed processes are the major production technique for metal-based AM implants. This paper serves as a comprehensive review on the research efforts being made using AM to develop new patient centered medical devices. This review focuses on AM of the most common metals for biomedical applications, Magnesium alloys, Cobalt-Chromium alloys, pure Titanium, Titanium alloys. Several different aspects are discussed including biocompatibility and osseointegration, application of specific metals in different types of implants, their advantages and disadvantages, mechanical properties in comparison to bone, and their production technologies. Regulatory and quality assurance hurdles that are facing new innovations made using AM are discussed.

Keywords: additive manufacturing; biocompatibility; biomedical; implants; metals

Citation: Ladani, L.; Palmieri, M. Review of the Use of Metals in Biomedical Applications: Biocompatibility, Additive Manufacturing Technologies, and Standards and Regulations. *Metals* **2024**, *14*, 1039. https://doi.org/10.3390/met14091039

Academic Editor: Giovanni Meneghetti

Received: 4 July 2024
Revised: 30 August 2024
Accepted: 31 August 2024
Published: 12 September 2024

1. Introduction

Additive manufacturing (AM) is a general term that refers to a process in which a part is built using 3D model data by joining a material layer by layer. This contrasts with traditional subtractive or formative manufacturing [1–5]. AM has been around since the late 1980s and early 1990s, with one of the original patents being issued in 1989 to Carl Deckard for Selective Laser Sintering (SLS) [1]. AM, often referred to as 3D printing [1,2] utilizes computer generated designs, typically created through modern CAD programs (SolidWorks 3D CAD, AutoCAD, Fusion360, etc.) as the data source to build the part. The 3D model must then be digitally sliced into printing layers and saved as a stereolithography (.stl) file [1,2]. There are multiple types of printing methods used today, such as DMLS (Direct Metal Laser Sintering), Selective Laser Melting (SLM), Directed Energy Deposition (DED), Fused Deposition Modeling (FDM), all with their own advantages and disadvantages [1–7]. As print techniques continue to advance, the role of AM in all industries will only continue to increase.

The medical industry has particularly benefited from the development of AM technologies. The customization and geometric complexity of parts built using AM has allowed health care providers to design devices and implants customized to each patient [1–3]. Additionally, the digital framework on which AM is built, and modern medical imaging methods (CT, MRI, X-Ray) both utilize layered digital data, allowing for a relative smooth transition from image to model [1]. Furthermore, AM can utilize many of the same materials used for modern medical devices. These include materials such as metals (e.g., Ti6Al4V, NiTi, Mg, Steel etc.), ceramics, and polymers (e.g., combination of PEEK (Polyether-ether-ketone) [8] with many different materials such as HA (Hydroxyapatite), TCP (TriCalcium Phosphate), $BaSO_4$ (Barium sulfate) etc.), and more recently composite

materials. This paper will specifically focus on metals and metal-based composites, and their role in manufacturing biomedical devices using AM.

Historically the use of metals has had a prominent role in medical devices, with successful implants dating back to 2500 BC [9]. Dental metal implants have a long history dating back to 2500 BC where ancient Egyptians used ligature wires made out of gold to stabilize teeth [9]. Metals have numerous advantages that make them ideal for use in the body, including their inertness and ability to take structural loads [10]. In situations where implants are subject to static, dynamic or cyclic load, metals perform better than polymers and ceramics [11].

Working with metals can significantly reduce the number of components required for assembly, their weight, and the throughput required during production, directly lowering the risk of contamination for medical applications [10,12–15]. The modern merger between highly customizable AM techniques and the mechanical and physical properties of metals has researchers and industry alike excited about the vast potential to provide rapid patient specific care at a fraction of the cost. This synchronization can be seen in Figure 1, which illustrates the process flow from start to finish of an AM medical device. Medical imaging captures the specific needs of the patient. The image is then translated into a 3D model design. The model passes through the various stage gates until it is ready to be manufactured for use in patients. It is critical that healthcare professionals and AM engineers are in constant communication throughout the entire process, most importantly during the image acquisition and modeling steps [3,16]. In practice, healthcare professionals, such as the doctors performing the surgery will meet with AM design engineers to carefully design and tweak the implant to ensure the intraoperative fit is smooth. It is important to include medical professionals during the design process so that they can make sure the implant is being designed with the real-world human element being considered rather than trusting the geometry will line up purely based on computer modeling. This process ensures tailoring to patient sizes, needs and specification.

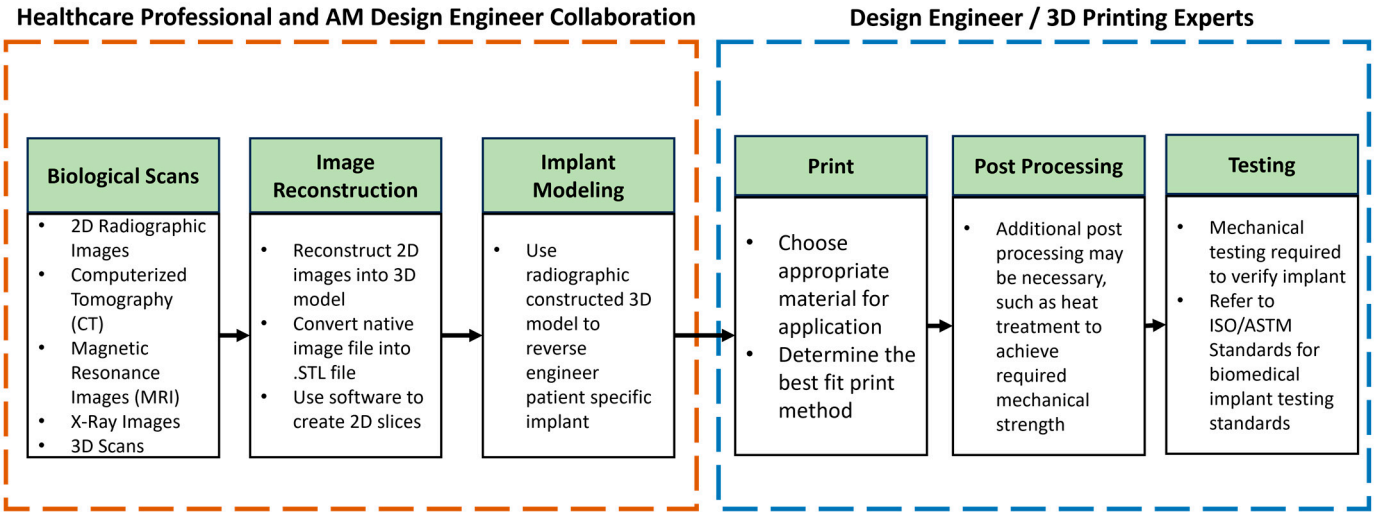

Figure 1. Image of implant process diagram highlighting the most crucial steps for biomedical devices using AM.

Although metal-based AM has made great strides since its conception in the 20th century, there are certain limitations researchers and manufacturers are working to resolve. One of these major limitations is the number of biocompatible metals that can also be formed into devices or implants using AM. Currently there is a limited selection of metals that meet both the mechanical and biological criteria [1]. Titanium (Ti) and Ti-based alloys have been used extensively for biomedical implant applications given their high mechanical strength to weight ratio and excellent biocompatibility. There has been a push

to investigate the potential for metal-based composites which can provide the mechanical strength benefits of metallics while increasing the biocompatibility through the inclusion of a ceramic material [17–20]. An example of this are Mg-based composites, which can be used for temporary fixation implants, such as screws or plates [21]. The second limitation facing biomedical AM is the ability to produce devices with adequate mechanical performance [22]. The mechanical performance of implants made by AM is dependent on the microstructure formed during the print process. There are several adjustable process parameters that all influence the final microstructure, and properly controlling these is key to reliably printing quality implants [23].

This paper is organized as follows: Section 2 introduces the metals used in biomedical applications. Section 3 details production methodologies in metal AM. Section 4 outlines the regulatory pathway for medical implants made using AM. Finally, Section 5 concludes the paper with suggestions for future research in this field.

2. Metals Used in Biomedical Applications

Materials used for biomedical applications are categorized as: metals, metal composites, polymers, and ceramics with metal being the most widely used due to their advantageous properties like inertness and structural functions [24,25]. Metals are currently being used in a wide range of biomedical applications such as dentistry and orthopedic implants. The use of AM for metal implants has become increasingly popular over conventional manufacturing due to the ability to create highly customizable, intricate, and lightweight components. Commonly used metals for AM include magnesium, titanium, and its alloys such as TiNi, Cobalt Chromium, Inconel, Nickel, Silver [26]. Depending on the specific application, the appropriate metal is selected based on wear resistance, corrosion resistance, and mechanical properties. In this section we will focus on pure metals and metallic alloys.

2.1. Factors That Determine Biocompatibility

One of the issues with implants is what is called Foreign Body Reaction (FBR). FBR or Foreign Body Response is defined by the William Dictionary of Biomaterials as the "Overall response of the host to the presence of a foreign body," [27]. The initial response of the body to implanted materials is how it heals wounds naturally. Foreign materials in the body can sometimes cause long-lasting inflammation, which is a key feature of the body's response to foreign objects. When a blood vessel is injured, it becomes permeable, and platelets gather at the site of injury. These platelets release certain chemicals that attract white blood cells called neutrophils, which help with early inflammation. Later, other types of white blood cells called mononuclear cells move in and stick around where the material meets the body tissue. Over time, because of the persistent presence of the implanted material, these cells can merge into giant cells. This process can lead to the formation of scar tissue around the implant, which can cause problems and sometimes make the implanted device fail [28].

Therefore, the key factors related to the success of a metallic implant is its biocompatibility. The definition of biocompatibility can often take many forms, but it is generally defined as "the ability of a material to perform with an appropriate host response in a specific application" [29–31]. A broader term, Osseointegration has been used to address implants biocompatibility and long-term behavior in the body. Osseointegration was originally defined first by Richard Brånemark as "continuing structural and functional coexistence, possibly in a symbiotic manner, between differentiated, adequately remodeled, biologic tissues and strictly defined and controlled synthetic components, providing lasting, specific clinical functions without initiating rejection mechanisms." [32]. An implant's ability to successfully integrate with the surrounding tissue is vital for long-term implant viability [33].

The evaluation of the osseointegration and biocompatibility of a metallic implant must be comprehensive and there are numerous properties that can predict a metals potential biocompatibility [31,33,34]. For a medical device to be approved to the U.S. market, the manufacturer must provide the FDA with sufficient data showing the biocompatibility

of the medical device [35]. Bandyopadhyay et al. further expands on the definition of biocompatibility as it pertains to orthopedic implants and categorizes an implants biocompatibility into three groups: mechanical, biological, and histocompatibility [34]. Mechanical biocompatibility refers to the placement of the implant at the surgery site and how well it performs its intended role, typically for metallic implants, this is loadbearing in nature [34]. The interface between implant and the surrounding tissue encompasses biological compatibility, while histocompatibility describes the inflammatory response, and blood compatibility of the implant [34].

Determining the degree of biocompatibility of a material is not simple, and often it is necessary to piece together the larger picture from many individual properties that can help predict success. Some of the most important factors that have been determined to be important markers on biocompatibility success are Young's Modulus mismatch between the implant and most typically the bone, porosity, corrosion resistance, surface roughness/topography, surface charge, free surface energy, cytotoxicity, and wettability [31,33,34,36].

Young's Modulus mismatch is one of the most critical when evaluating a metallic materials viability as an implant material. The average Young's modulus of a metallic material is typically much larger than that of cortical bone, which over time will lead to a phenomenon known as "stress-shielding" [31,33,34,36]. Stress shielding is described as the loss of bone density due to the redistribution of load that occurs when an implant (bone-implant interface) takes over the load on the bones [37]. The bone resorption and remodeling are governed by Wolff's Law, which describes how a bone maintains its shape and radiodensity (material's relative resistance to X-rays and radio waves) [37,38]. The bone responds to normal continuous physiological loads by remodeling itself which is a reaction to constant micro-fractures. When an implant, typically a metallic based one is interfaced with bone, the stiffness mismatch leads to the implant absorbing much of the continuous load the bone used to feel. This could lead to bone resorption, resulting in a less dense bone which commonly leads to implant loosening and eventual failure [33,34,37,38]. Stress Shielding can be explained in simple mechanical terms as follows (refer to Figure 2 below).

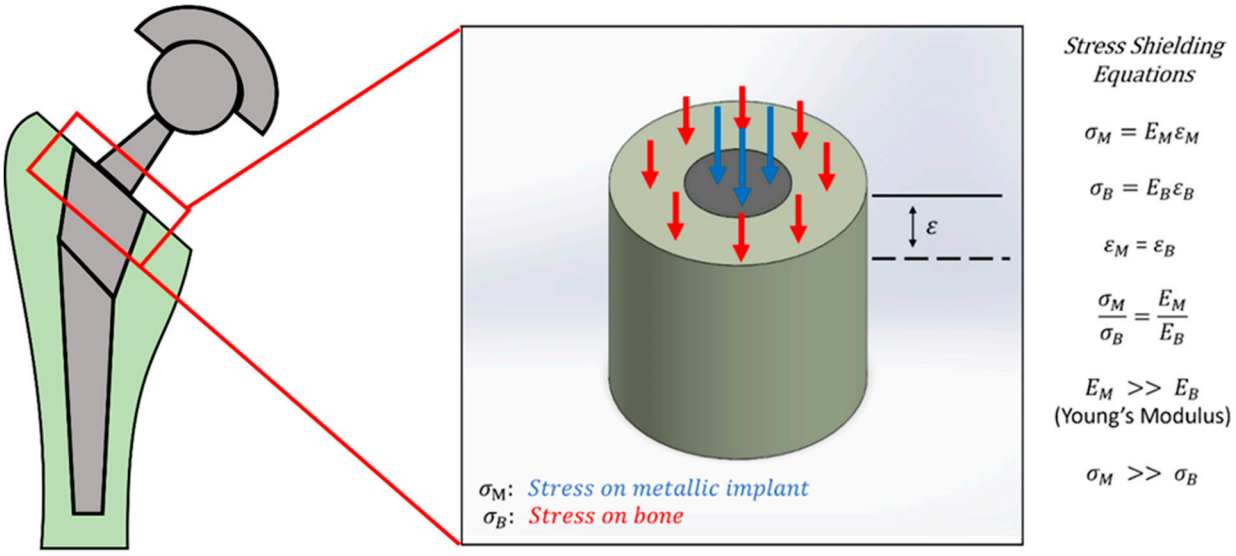

Figure 2. Simple mechanical representation for the concept of stress shielding when related to an implant with a larger elastic modulus (E) than the surrounding bone.

As the implant receives a physiological load, the strain (ε) is the same for both the implant and bone since they are interfaced with each other. Typically, the elastic modulus (E) of the metallic implant is much greater than that of bone, $E_M >> E_B$. This leads to the stress induced in the implant to be much higher than that of the stress experienced by the surrounding bone ($\sigma_M >> \sigma_B$) .

There has been a great deal of research into how to manufacture implants which exhibit a lower Young's Modulus and reduce the effect of "stress-shielding" [34]. One of the techniques that are used to reduce Young's modulus of the implant, hence reducing the stiffness mismatch, is designing porous materials for implants [39,40]. Porosity not only helps reduce the stiffness mismatch, it helps cell integration with and into the material [41]; inward dispersion of oxygen, nutrients, analytes, and outward diffusion of pharmaceutical agents, angiogenesis (formation of new blood cells) [42–44] and pro-healing responses from immune cells [45–47] that can affect FBR.

Literature has shown that that pore size, volume fraction porosity, pore-pore interconnectivity, and pore shape strongly influence an implant's mechanical properties and its ability to successfully integrate with the surrounding tissue [34]. The main role of porosity modification for metallic implants is to improve tissue adhesion, growth, and vascularization [40]. A study done by Li. et al., where Ti6Al4V bone scaffolds were manufactured with varying pore size and porosity concluded that an increase of porosity and pore size had a positive effect on the amount of new bone growth [48]. The "optimal pore size" was reported to be between 150–600 microns. Li. et al. mentions that these studies were conducted with porous-coated metallic and porous-coated calcium-phosphate implants and did not have well controlled architecture [49–53]. The effects of pore size and shape may vary depending on the type of implant used [48,54].

The "optimal pore size" for metallic scaffolds has not yet been determined [48]. One study by Holister et al. used well controlled Hydroxyapatite scaffolds to test the effects of pore size and geometry and found that bone ingrowth was not dependent on the pore size between 400 and 1200 microns [55]. This is in contrast with several studies that found changes in pore size and shape can have a significant effect on the osteoconductive properties of implants [34,48]. Osteoconduction is the bone growth on a surface of the implants [56]. Osteoconduction is an essential element of osseointegration as osseointegration necessitates a stable anchorage of an implant achieved by direct bone-to-implant contact [56].

Corrosion resistance is another major component of metallic biocompatibility [31,33,34]. Corrosion resistance describes the ability of the metallic implant to withstand the electrolyte rich environment inside the body. These implants undergo electrochemical corrosion from the bodily fluid-implant surface interaction which reduces the structural integrity of the implant over time [31]. Eliaz describes that dissolved salts are the most influential components for implant corrosion in the body, specifically, chloride ions and other halides enhance corrosion of almost all metals [57]. The most important characteristics of the bodily fluid environment that contribute to the corrosion of metallic implants are the chloride, dissolved oxygen, and pH levels. Low pH levels around the implant surface can also contribute to significant localized corrosion [57]. Types of corrosion that are commonly found in metallic implants are pitting, crevice, galvanic, intergranular, stress-corrosion cracking, corrosion fatigue and fretting corrosion [58]. When an implant is first introduced into the body the new implant and act of implantation can disturb the blood supply and subsequent ionic equilibrium which can initiate corrosion events such as pitting and crevice corrosion at implant interfaces [58]. Titanium (Ti) and Ti-based alloys are typically used for load-bearing implants largely in part due to Ti's excellent corrosion resistance [31,33].

The surface roughness is a parameter to describe the overall surface quality of an implant and provides an insight into the morphology of the outermost layer of an implant surface [59]. The surface roughness of load-bearing implants has been shown to play a major role in bone growth promotion and bone/tissue adhesion to the implant surface [31,33]. Alla et al. explains that tissue response to bio implants is significantly impacted by the surface features and texture of the implant [60]. Textured surfaces provide more surface area for integrating the implant surface with bone through the osseointegration process [60]. Dental implant research has shown that bone tissue can adapt to surface irregularities between the 1–100-micron range and adjusting surface topography can be used to increase the dental implant's stability [60].

Although it is known that surface topography plays a role in biocompatibility, the optimal surface conditions are still being investigated and optimized [33]. There is research being focused on micro topographical and nano topographical surface roughness and its connection to osseointegration [61]. Kane et al. asserts that nanoscale roughness may replicate the intrinsic surface roughness of bone further aiding in implant compatibility [62]. Surface modification techniques such as sandblasting, acid etching, electrical discharge machining, anodic oxidation can all play a role in affecting the biocompatibility of an implant [59,63,64].

Another factor that determines biocompatibility is surface free energy. "Surface energy may therefore be defined as the excess energy at the surface of a material compared to the bulk, or it is the work required to build an area of a particular surface" [31,65]. It has been used as a predictive factor for implant biocompatibility with research showing that implants that can retain a high free surface energy could promote osteoblast differentiation in vitro [31,66]. Quinn et.al describes the role that surface charge and surface free energy play in predicting the success of an implant. Their research explains that during implant implementation the surface charge has an impact on the "initial plasma binding" on the implant which has a role in the adherence of bacterial or mammalian cells [31].

Zhao et al. explains that it is thought that surface energy modulates bone cell maturation and differentiation. Surface energy is directly related to wettability of the surface. Wettability is defined as "the interaction of a liquid droplet with a surface" [31]. This is a metric for implant biocompatibility because it looks at the hydrophilic or hydrophobic properties of the implant, which relates to the potential ability to resist bacterial adhesion, according to Quinn et al. bacteria typically adhere to hydrophobic surfaces [31].Higher surface energy means the surface is more wettable. It is also thought that a higher surface energy is ideal for biomedical implants because the associated increased wettability will enhance the interaction between the implant surface and the surrounding bodily environment [66] There are various experimental methods to extract the surface energy of a material based on the contact angle from the process of wetting a solid surface [67]. The contact angle (CA) can be measured using various experimental approaches such as the sessile drop test, tilting plate method, and densiometric Wilhelmy method [67]. There are three common methods to extract the surface free energy from the contact angle data, Zisman method, Equation of state, and the Geometric mean approach [67]. The contact angle (θ) for an ideal surface was described by Thomas Young using the solid-liquid (γ_{sl}), solid-air (γ_s), and liquid-air (γ_l) interfacial energy interactions [67]. Equation (1) describes this relationship.

Figure 3 illustrates how these quantities are related visually. A small θ is indictive of a liquid that spreads out on a surface with a uniform thickness. This means that wettability can be enhanced either through increasing the solid surface free energy or decreasing the liquid surface energy (surface tension). Higher solid surface energy results in better wettability.

$$cos\theta = \frac{\gamma_s - \gamma_{sl}}{\gamma_l} \quad (1)$$

Wettability depends on both the chemical composition of the implant and the surface roughness of the outermost implant layer. A wettable surface is hydrophilic and results in a contact angle < 90°, whereas a hydrophobic (non-wettable) surface will have a contact angle > 90° [31]. Bacterial adhesion to the surface is impacted by wettability. Bacteria prefer to adhere to hydrophobic surfaces rather than hydrophilic surfaces [68]. Lin et al. states that depending on the wettability of the surface (hydrophilic or hydrophobic) different types of bacteria are attracted to the implant surface [69]. Surfaces which were hydrophilic were shown to attract bacteria such as Staphylococcus aureus and Escherichia coli. Whereas hydrophobic surfaces attracted bacterial strands Psx. Taiwanensis and Staph. Epidermidis [69]. It is worth noting that the hydrophobic surfaces reduced the adhesion of M. Silvanus, Staphylococcus aureus, D. geothermalis, and Streptococcus mutans [69]. The wettability has also been shown to be related to cell adhesion, proliferation, differentiation,

and bone mineralization, with most studies finding that hydrophilic surfaces enhance these processes [70].

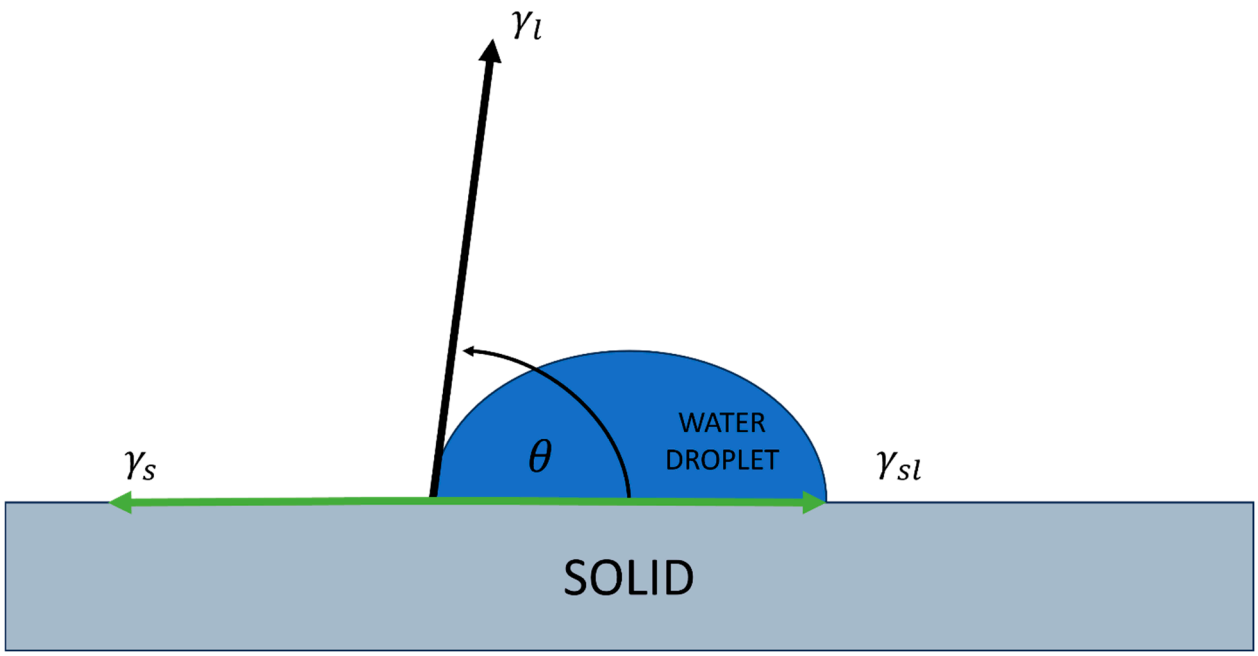

Figure 3. Visual representation of how the contact angle is measured for a water droplet.

Cytotoxicity is related to the chemical composition of the metals being used for an implant. It is important to choose an implant material that is not composed of or degrades into chemical compounds that are known to be cytotoxic or genotoxic [31]. Cytotoxins refer to chemical compounds which cause cell damage, inflammation, and sometimes cell death [71], while genotoxic compounds specifically cause DNA or chromosomal damage [72].

Quinn et al. outlines some examples of this occurring in chromium implants [31]. Chromium has been linked to cytotoxic or genotoxic effects. Co-Cr implants have been extensively used in load-bearing applications but there is a risk of wear processes that could release cytotoxic chromium elements [31]. Various health complications have been reported in the literature for cobalt, chromium, stainless steels, aluminum, and vanadium [31]. It is important to consider not only the initial material composition of the implant but the potential byproducts of wear and corrosion that can occur for many of these long-term implant solutions.

Another important piece of an implant's biocompatibility profile is fatigue resistance, or fatigue strength. Fatigue describes the failure of a material under repeated stresses and mechanical loads, which will result in a material fracture under a load weaker than a load under single application [73,74]. Understanding a materials fatigue resistance, or ability to resist fracture under repeated loading is especially important for permanent medical fixations, such dental, hip, and knee replacements. Evaluating the fatigue resistance of a material for biomedical applications is multi-faceted and requires a broader understanding of how fatigue can lead to complications. One of the main fatigue related complications that can arise is from negative host-tissue responses [75]. This occurs when debris, from implant wear, causes an inflammatory and immunological response and leads to further implant loosening and physiological complications [75].

Predicting biocompatibility involves a complex matrix of various mechanical, biological, chemical properties of a desired implant material. Using a combination of all these properties researchers and healthcare professionals can effectively evaluate the potential of a metallic material for biomedical applications. Research into new materials for biomedical

implants will have to carefully consider all the mentioned factors for the material to be considered safe and effective for long term use.

2.2. Metals Used in Biomedical Implants Applications

Several metallic elements are found in the human body, making them candidates for biomedical implant applications. Calcium is the most abundant metallic element in the human body and is primarily found in bones and teeth. It plays a crucial role in bone formation, muscle contraction, nerve function, and blood clotting. Magnesium is involved in over 300 biochemical reactions in the body, including energy production, muscle and nerve function, and protein synthesis. It is found in bones, muscles, and cells. Potassium is a vital electrolyte that helps regulate fluid balance, muscle contractions, and nerve signals. It is found predominantly inside cells and is crucial for maintaining proper heart function. Sodium is another essential electrolyte involved in regulating fluid balance and nerve function. It is found primarily in extracellular fluids. Iron is necessary to produce hemoglobin, the protein in red blood cells that carries oxygen from the lungs to the rest of the body. It is also involved in energy production and cell growth. Iron is primarily found in red blood cells and stored in the liver. Zinc is a trace element that plays a role in immune function, wound healing, DNA synthesis, and cell division. It is found in cells throughout the body and is particularly abundant in the skin, eyes, and prostate gland. Copper is involved in various enzymatic reactions, including those related to energy production, connective tissue formation, and iron metabolism. It is found in organs, bones, muscles, and the brain. Manganese is a cofactor for several enzymes involved in metabolism, bone formation, and antioxidant defense. It is found in bones, liver, kidneys, and pancreas. Chromium plays a role in insulin function, glucose metabolism, and the regulation of blood sugar levels. It is found in small amounts in the body, primarily in the liver. Out of these naturally occurring elements in the body, only a limited number can provide structural integrity and loadbearing capacity to be a candidate for implants. For example, Magnesium is a material that is one of the prime candidates in load bearing biomedical implants.

In addition to these metals that naturally exist in the body, another group of metals are biomedically inert. Biomedically inert metals are those that exhibit minimal or no reactivity when in contact with biological tissues or fluids. These metals are often used in biomedical applications where corrosion resistance and biocompatibility are crucial. Gold is highly corrosion-resistant and biocompatible, making it suitable for various biomedical applications such as dental implants, prosthetic devices, and drug delivery systems. Platinum is another noble metal known for its inertness and biocompatibility. It is used in medical implants, electrodes, and catheters. Titanium and its alloys are widely used in biomedical implants due to their excellent corrosion resistance and biocompatibility. Titanium is inert in biological environments and forms a stable oxide layer (titanium dioxide) on its surface, which enhances its biocompatibility. Tantalum is highly corrosion-resistant and biocompatible, making it suitable for orthopedic implants, dental implants, and surgical instruments. Zirconium and its alloys exhibit excellent corrosion resistance and biocompatibility, making them suitable for dental implants and other medical devices. Silver is known for its antimicrobial properties and is used in wound dressings, catheters, and other medical devices. While silver can react with some biological substances, it is generally considered biocompatible. Certain stainless-steel alloys, such as 316L stainless steel, are considered biomedically inert due to their corrosion resistance and biocompatibility. However, some individuals may have allergic reactions to certain components in stainless steel, such as nickel. Scientists have utilized these two groups of metals (naturally occurring in the body and biomedically inert metals) to come up with new alloys and compositions that satisfy all the requirements for biomedical implant applications.

Historically, metals such as gold, silver, and bronze were used in ancient civilizations for various medical purposes, including wound closure and dental work. Egyptians, Greeks, and Romans used gold and silver for prosthetic limbs and dental implants. With advancements in metallurgy during the 18th and 19th century, more durable metals like

steel and iron became available. However, their use in implants was limited due to issues like corrosion and biocompatibility. The discovery and development of new alloys like stainless steel and cobalt-chromium alloys during the 20th century revolutionized the field of orthopedic implants. Stainless steel was first used for orthopedic screws and plates in the 1920s, followed by cobalt-chromium alloys in the 1930s. These materials provided better strength and corrosion resistance. Titanium and its alloys emerged as promising materials for biomedical implants in the 1950s and due to their excellent biocompatibility and corrosion resistance became the prime candidate for biomedical implants. Titanium implants were initially used in dentistry and then expanded to orthopedic applications. Ti-6Al-4V became widespread in various biomedical implants, including dental implants, joint replacements, and bone fixation devices. The development of surface treatments and coatings further enhanced the performance of titanium implants. In recent years, there's been a focus on improving the mechanical properties and biocompatibility of implant materials. Materials such as tantalum, zirconium, magnesium, Co-Cr alloys and various biodegradable metals are being explored for specific applications. This section summarizes different materials used in biomedical applications, their specific properties that make them suitable for these applications and their drawbacks and limitations are discussed.

2.2.1. Magnesium Alloys

Over the course of the 20th century, researchers have dedicated substantial efforts to harnessing the unique advantages of Mg-based materials for medical applications [76–78]. Specifically, Mg and its alloys have gained significant research interest in bone repair [79].

Mg-based bone fixation devices, such as screws, pins, and plates, have been engineered to provide crucial support during bone repair procedures [80]. They offer early-stage mechanical support and uniquely undergo gradual degradation, resulting in a reduction of their load-bearing capacity [81,82]. This controlled degradation process facilitates a more natural transition of stress on the surrounding bone tissue, ultimately fostering the healing and reshaping of new bone [82–84]. Mg is commonly alloyed with zinc (Zn), manganese (Mn), calcium (Ca), and zirconium (Zr), which have been identified as non-toxic alloying metals because they are commonly absorbed from one's diet [85,86].

In addition to their use in bone fixation devices, Mg and Mg alloys are being explored as promising scaffold materials for bone tissue engineering applications [87,88]. Bone tissue engineering involves the transplantation of cells into an artificial scaffold [84]. These scaffolds provide a three-dimensional environment conducive to cell adhesion and growth, enabling the directed growth of new tissue [82]. An ideal bone tissue engineering scaffold should ideally feature pore sizes akin to those found in natural bone, typically ranging from tens to hundreds of microns [77,82]. Additionally, a high level of porosity and an interconnected pore structure is essential to support nutrient transfer and metabolite removal [89].

The current research of AM biodegradable metals, including Mg alloys is still limited, but it has been determined that laser powder bed fusion (LBF) is the most promising AM method for this fabrication [90–93]. Mg is highly flammable, especially in powder form and it has created significant research hesitation due to this safety concern [92]. Additionally, much of the research on AM of Mg alloys is focused on the WE43 composition, as it has the most readily available powder compared to the other Mg alloy compositions [90,92,93]. Using AM for the fabrication of porous Mg alloy scaffolds has been a primary focus for research [92,94–96].Current understanding of the biodegradation behavior of this LPBF scaffolds is not well understood and continued effort to fully understand how AM process parameters affect the biodegradability of these implants will be crucial. Mg alloys remain an interesting material for biomedical applications and have the potential to serve a large role in future orthopedic implants [90–96].

Mechanical Properties of Mg Alloys

The primary advantage with Mg alloys is its close alignment with the mechanical properties of natural bone which can be seen in Table 1 [82]. With an elastic modulus of around 45 GPa, which closely matches that of cortical human bone (7–20 GPa), Mg materials can effectively mitigate the stress shielding phenomenon [97]. This places magnesium alloys in a favorable position, surpassing biopolymers like poly-ether-ether ketone (PEEK), poly (l-lactic acid) (PLLA), and polyglycolic acid (PGA) due to their low mechanical strength [98–100]. Mg based alloys exhibit superior strength, well-defined decomposition behavior, and superior resistance to impact [101]. Additionally, their density, ranging from 1.74 to 1.84 g/cm^3 depending on the alloy, closely approximates that of bone (1.8–2.1 g/cm^3) [97].

Table 1. Mechanical properties of natural cortical bone from a human femur and Mg alloy properties of the WE43 composition.

Material	Density (g/cm^3)	Modulus (GPa)	Compressive Yield Strength (MPa)	Fracture Toughness (MPa·m$^{\frac{1}{2}}$)	% Elongation
Cortical bone (Longitudinal Direction)	1.8–2.1 [82]	17.90 ± 3.90 [102] 18.20 ± 1.88 [103]	115.06 ± 16.36 [103,104]	2–6 [104]	1.07–2.10 [82]
Cortical bone (Transverse Direction)	1.8–2.1 [82]	10.10 ± 2.40 [102] 5.65 ± 1.61 [105] [1] 6.49 ± 3.22 [105] [2]	41.8 ± 19.4 [105] [1] 44.1 ± 21.1 [105] [2]	2–6 [104]	1.07–2.10 [82]
Mg alloys	1.84 [106]	44.2 [106]	172 [94]	15.9 [107]	2 [106]

1: Circumferential direction. 2: Radial direction.

Biocompatibility of Mg and Mg Alloys

Pure Mg and Mg alloys exhibit remarkable biocompatibility with the human body, reducing the probability of adverse tissue responses [83]. This remarkable feature arises from the natural occurrence of Mg in the human body. Typically, Mg naturally occurs in the human body, with organisms containing approximately 25g of elemental Mg, with 50-60%, residing within the bone [108]. This inherent presence of Mg alloys in the human body reinforces their biocompatibility, effectively minimizing the risk of implant rejection [109]. Additionally, Mg alloys are biodegradable, and their degradation by-products, Mg ions, are non-toxic to the human body [110].

However, it is important to note that the gradual degradation of Mg alloys is related to their corrosion resistance, which compared to other commonly used biomedical metallics is relatively low [111]. Accelerated degradation because of corrosion may cause premature weakening of the implant. Additionally, hydrogen evolution, which is the principal cathodic reaction and concurrent with the corrosion of magnesium alloys [112–115], can significantly interfere with the healing process [112–114]. Additionally, hydrogen gas (H2) evolution during magnesium corrosion can create subcutaneous gas bubbles [115] and gas bubbles adjacent to the implants, which can cause the separation of tissues and/or tissue layers [116]. This is why Mg based implants are often used for temporary fixation devices that do not require long term load bearing applications [117].

Another important characteristic of Mg is its unique osteopromotive properties [80]. The release of Mg ions stimulates the rise of osterix levels through Mg transporter proteins, promoting bone regeneration at the periosteal region [79,109]. Osterix (Osx) aids in the process of bone formation because it is "an osteoblast-specific transcription factor essential for osteoblast differentiation and bone formation [118]". Osteoblasts are known for three functions regarding bone formation, growing new bones, reshaping bones and healing damaged bones [119].

The combination of magnesium's mechanical similarity with cortical bone and excellent biodegradability, biocompatibility, and osteopromotive properties makes pure Mg and Mg alloys excel as biomaterials. Mg based implants offer the potential to be significant materials in orthopedic applications. [50,88].

2.2.2. Cobalt Chromium Alloys

Cobalt-Chromium (Co-Cr) alloys have gained widespread recognition for their exceptional mechanical characteristics, rendering them highly valuable in various applications, including dental implants, and orthopedic implants [120,121]. According to ASTM F75-23 "Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants (UNS R30075)" [121], the allowed chemical composition of Co-Cr alloys is given by a maximum mass percentage of 27-30% Chromium, 5-7% Molybdenum, and $\leq$ 1% of various other elements such as nickel, iron, carbon, and silicon [121]. Most Co–Cr alloys typically contain 25 to 30 wt% of Cr to impart sufficient corrosion resistance making them more suitable for biomedical applications [122]. Co–Cr alloys exhibit the highest wear resistance in between all metals used for biomedical implants. Consequently, Co–Cr alloys are the biomaterial of choice for applications that undergo friction and wear during the performance of the device [122]. This includes joints that experience movements and contacts that experience friction; e.g., hip, knee and shoulder arthroplasty [123] and dental implants [124].

Mechanical Properties of Co-Cr Alloys

Mechanical properties of alloys are a function of their phases and microstructures. This is particularly important in cases where a high percentage of both materials is used in making the alloy. Co goes through an allotropic transformation at 690K changing from γ with FCC crystal structure to ε hcp crystal structure. This transformation temperature increases as the percentage of Cr increases. In biomedically suited applications the percentage of Cr is typically in the range of 20% to 30% with 1100 and 1200 K transformation temperature respectively. This impacts the ratio of the phases existing in the material at room temperature. γ phase is more ductile while ε phase has higher hardness that helps with wear resistivity [125]. The ratio of these phases determines the properties of the Co-Cr material and its suitability to specific applications.

Co-Cr alloys have hardness in the range of 33 HRC for cast samples and 39 HRC for samples printed using SLM [125] making them harder than many other metals. Heat treatment of Co-Cr-Mo alloys can improve the mechanical properties by affecting the grain size, orientation texture and second phase precipitation [126]. The significant influence on wear and mechanical properties is due to the transition from the γ-FCC phase to the ε-HCP phase [126].

Co-Cr alloys implants could experience ductility issues, which can lead to increased deformation over time [127]. Ductility, primarily assessed through properties like elongation and reduction in area during tensile testing, should be a point of consideration for long-term applications like joint replacements [128]. To enhance their mechanical properties, Co-Cr alloys may contain trace amounts of nickel, carbon, and nitrogen [129].

Different compositions have been used in biomedical applications for both permanent and temporary fixtures as shown in Table 2. The various alloy compositions of Co-Cr have their own ASTM standard outlining the material chemical composition and production status [130].

Table 2. Various Co-Cr alloys and orthopedic fixation type each is used for.

Co-Cr Alloy	Type of Fixation	Reference
Co–28Cr–6Mo	Permanent	[121,122,130–137]
Co–20Cr–15W–10Ni	Permanent or Short-term	[122,130–132,138–142]
Co–35Ni–20Cr–10Mo	Permanent	[122,130–132,143]
Co–Cr–Ni–Mo–Fe	Permanent	[122,130–132,144,145]

Biocompatibility of Co-Cr Alloys

Cobalt was discovered in 1735 by Georg Brandt. It is one of the essential trace elements in the human body [146] and is very widespread in the natural environment [147]. Co is a

component of vitamin B12, which supports the production of red blood cells. Very small amounts are needed for animals and humans to stay healthy [148]. However, in excess quantities and in its inorganic form, cobalt can result in significant toxicity [149].

Cr is also a naturally occurring element that is found in the environment. However, depending on the oxidation number (II to VI), it may be beneficial or toxic to the body. Trivalent chromium (chromium III) is the most chemically stable form of Cr, and it is the most common natural form found in the earth's crust. It is also an essential nutrient for normal function of the human body as it helps regulate how your body processes fats and sugars [150]. On the other hand Cr VI oxide or hexavalent chromium can cause significant health issues such as skin ulcers, allergenic reactions or even cancer [150].

One of the main concerns of Co-Cr implants which is found more significantly in Metal on Metal (MOM) type implants is the possibility of release of these metals in the body. In (MoM) hip implants, the movement between the metal ball and cup during activities like walking or running can lead to the release of metal particles. Additionally, metal particles may be released in other jointed areas. As these metal surfaces slide against each other, tiny particles can wear away and enter the surrounding tissue [151]. This could cause adverse health effects such as inflammatory reactions, discoloration, and tissue hyperplasia (an increase in cell count of a tissue or organ [152] in nearby regions [153,154]. Despite these issues, Co-Cr implants are still considered one of the main materials used for implants requiring wear and corrosion resistivity. Co-Cr alloys possess excellent corrosion resistance (The corrosion resistance of CoCr alloys is more than an order of magnitude greater than that of stainless steels) [131] due to the formation of a protective film on their surface, minimizing the potential for adverse immune and tissue reactions and emphasizing their role in various medical applications [126,155]. The development of a passive film, primarily composed of Chromium oxide, Cr_2O_3 with traces of Co and other metal oxides on the surface, provides robust protection against corrosion [155].

Additionally, in many cases Ni, Mo, W and Fe elements are added in small percentages to the alloy composition to create certain phases and enhance properties. Each of these metals could have a significant impact on health. For example excessive exposure to Ni could cause cardiovascular, respiratory, or kidney disease [156]. In small percentages used in Co-Cr implants these concerns are minimized [157].

The biocompatibility of Co-Cr alloys underscores their safe usage within the human body, especially in the manufacturing of medical devices and long-term implants [158]. While the likelihood of allergic reactions in patients using Co-Cr alloys is minimal, it's essential to be aware of the potential release of tiny metal particles during joint movement, which can occasionally trigger reactions in the human body, particularly in patients with known metal allergies such as nickel [159], which is used in both short term and permanent chemical compositions of Co-Cr alloys (Table 2).

2.2.3. Ti and Ti-Alloys

Titanium is not found in the human body and does not play any known biological role human body [160]. However, it is biomedically inert material and is non-toxic even in large doses [130]. Titanium and various Ti-based alloys have continued to be one of the most widely used metals for biomedical applications [31,161–168]. Table 3 gives a list of the common types of Ti alloy compositions and unalloyed Ti that are used for biomedical applications. The use of Ti for medical applications has been around as early as the 1940s, where early animal testing showed little adverse reactions to bone metal interface [165]. As manufacturing processes improved titanium became increasingly studied and clinical trial after clinical trial showed it to be a safe non-cytotoxic metal [165].

Table 3. Various applications of pure titanium and titanium alloys.

Material	Application	References
Commercially Pure-Ti.	- Dental Implants - Tooth roots - Mandibular reinforcement plates - Internal fixation plates- Spinal Implants	[31,165,169,170]
Ti-6Al-4V	- Joint Replacement - Spinal spacer - Dental Implants	[31,165,169–171]
Ti-6Al-7Nb	- Joint Replacement - Spinal spacer - Dental Implants	[165,169,170]
Ti-15Mo-5Zr-3Al	Joint replacement	[165]
Ti-6Al-2Nb-1Ta-0.8Mo	Joint replacement	[165,170]

Compared to stainless steel and cobalt alloys, titanium alloys are superior in biocompatibility due to their excellent corrosion resistance [172,173]. In vitro mutation assays have shown that mutagenicity is not significant, suggesting that titanium alloys are safe for both humans and animals [172]. Most of the Ti alloys used in the medical field today are either alpha-beta or metastable-beta alloys, as they possess many of the necessary mechanical and biological properties for implantation [31]. Ti is typically mixed with other elements such as V, Al, Nb, Zr, Mo, Fe and Ta to make alloys such as Ti6Al4V and other alloys [130].

Titanium is seen in numerous biomedical applications, ranging from medical instruments to joint replacements [31,165]. Table 3 shows the various applications of different titanium alloys and CP-Ti. From Table 3 it is clear the current role of titanium in biomedical applications is critical for long-term, load-bearing environments [31,165]. Ti-6Al-4V is the alloy that sees most of its use in joint replacement, with hip and knee being as the most common replacements being done [165]. Titanium is generally used for the femoral stem part of the hip replacement [31]. Titanium has also been used to manufacture bone fixators such as plates, pins, screws, and rods [174]. Applications of Titanium extend to outside of the body with external prostheses, surgical instruments, and healthcare products [165]. The great corrosion resistance of titanium makes it a good material to be used for surgical equipment, such as scissors, forceps, and needle holders [175].

Mechanical and Physical Properties of Ti and Ti Alloys

There are two main mechanical properties that make titanium-based implants so effective. The first being is its elastic modulus which is a measure of a materials stiffness. Although there is a mismatch of the elastic modulus between that of Ti (103–120 GPa) and cortical bone (~10–30 GPa), titanium's elastic modulus is still considerably lower than that of stainless steel (~200 GPa) and Co-Cr alloy (~210 GPa) implants [31,165]. This mismatch of elastic modulus can lead to the effect of stress shielding, which can cause the surrounding bone to atrophy, cause implant loosening, and an increase in osteoclast activity [31]. Wolff's law describes how a bone adapts to the amount of mechanical load imparted on the bone. Bone strengthening occurs when mechanical loading is increased and vice versa, decreasing with strength as loading is reduced [176]. If the implant "shields" the surrounding bone from stress the bone will negatively respond by atrophying, often leading to implant loosening [31]. Research has shown that titanium has the highest inherent specific strength (strength-to-weight ratio) of any pure metal, which allows it to support sustained implant articulation over a long period of time [31,177]. The alloyed titanium compositions (see Table 4) have a much higher tensile strength than pure titanium (Grades 1-4) making them even more suited for load bearing implants. New Ti alloy compositions such as Ti-29Nb-13Ta-4.6Zr (TNTZ) offer an alternative to Ti-6Al-4V, providing a better mechanical match (Elastic modulus of ~60 GPa which is closer to the elastic modulus of cortical bone) and eliminating the use of Vanadium which has been found to be toxic [166].

Table 4. Mechanical properties of various grades of CP-Ti, Ti-6Al-4V, and Ti-6Al-7Nb.

Property	ASTM Grade 1 [178]	ASTM Grade 2 [178]	ASTM Grade 3 [178]	ASTM Grade 4 [178]	Ti-6Al-4V [165,178,179]	Ti-6Al-7Nb [165,178]
Chemical Composition	0.20% Iron 0.18% Oxygen	0.30% Iron 0.25%Oxygen	0.30% Iron 0.35% Oxygen	0.50% Iron 0.40% Oxygen		
Elastic Modulus (GPa)	103–107	103–107	103–107	103–107	114–120	105–120
Yield Strength (MPa)	170	275	380	483	795	817
Ultimate Tensile Strength (MPa)	240	345	450	550	860	933

Biocompatibility of Ti and Ti Alloys

The biocompatibility of pure Titanium and Titanium alloys is one of the major advantages of using titanium for long-term orthopedic implants. The great biocompatibility can be credited to its corrosion resistance, bio-inertness, and its remarkable ability to osseointegrate [31,165,180].

The corrosion resistance of titanium-based implants is due to the ability for Ti to passively produce a thin protective titanium dioxide layer on the implant surface, even in environments with small amounts of oxygen [165]. It exhibits the highest corrosion resistance between the two other commonly used metals, stainless steel, and Co-Cr alloys [31]. This passive dioxide film helps to protect against chemical reactions between the implant surface and surrounding tissue [165]. Quinn et al. notes that although the passive dioxide film protects against corrosion, it is not thick enough to prevent the release of titanium wear particles in the surrounding tissue [31]. Titanium debris has been found to be distributed throughout the body, being found in the liver, spleen, and lymphatic system [31,181]. Ti-6Al-4V releases vanadium oxide due to passivation which is thermodynamically unstable and ends up in solution within the body [182]. This can be toxic to patients and can pose a problem for permanent fixtures. Additionally, Ti-6Al-4V implants release Al ions which have been shown to enter cells and migrate throughout the body. High levels of exposure to Al ions have been shown to cause cytotoxic, genotoxic, and immunological effects which can appear locally at the implant site or throughout the body [183]. Semlitsch et.al developed their own Ti alloy using Niobium instead of Vanadium to try and combat this toxic release of vanadium oxide [182]. Instead during passivation this alloy releases niobium pentoxide which is much less toxic than the vanadium ions released with Ti-6Al-4V.

Other factors that have been shown to affect the biocompatibility of titanium implants are the surface topography, wettability, and free surface energy. As mentioned in Section 2.1 Biocompatibility the surface topography commonly has a profound effect on the osseointegration between the bone implant interfaces. Rupp et al. explained that for titanium used in dental implants a surface roughness with S_a between 1 and 2 microns showed better osseointegration than implants with smoother (<1 um) and rougher (>2 um) surface roughness [161]. Wettability deals with the hydrophilic or hydrophobic nature of a material and it has been shown that titanium treated with anodization and perfluorooctyl-triethoxysilane resulted in the formation of TiO_2 nanotubes on the surface which reduced the adhesion of bacteria [69]. Pure Ti has a high free surface energy due to the oxide layer it forms at room temperature [66]. This oxide layer is hydrophilic causing binding with surrounding structural water and creating oxide surfaces, which can spontaneously nucleate apatite layers, ultimately enhancing osseointegration with the bone-implant interface [66]. If the implant is hydrated through surface modification it can retain an even higher free surface energy [31].

One important area of investigation for Ti and Ti-based alloyed orthopedic implants is porosity. As stated previously one of the drawbacks of Ti is its high elastic modulus relative to the cortical bone that implants interface with. The elastic modulus of Ti can be as high as six times greater than cortical bone, which leads to numerous implant failure modes [184]. A porous structure can both reduce the elastic modulus of an implant and allow better tissue growth between the bone and implant [184,185]. The ability to control

the level of porosity and maintain optimal mechanical performance is key in designing new porous implants. This balance is being continually improved upon with the use of additive manufacturing techniques. AM allows for complex porous structures to be fabricated and research has shown that using AM does not reduce the biocompatibility of the Ti implant. One study looked at human cell response to both solid and porous Ti6Al4V structures made using EBM. It was found that these structures had no more cytotoxic profiles than that of commercial Ti6Al4V and proliferation of cells seeded on the porous structure showed both cell outgrowth and ingrowth capabilities [186].

Due to titanium's excellent strength to weight ratio, corrosion resistance, and biocompatibility it has positioned itself as one of the most versatile metals for the biomedical industry [165]. Able to be used on internal load-bearing implants, external healthcare products such as wheelchairs, and surgical equipment, Ti is well-established as one of the most important metals we have for biomedical applications [31,165,175].

3. Production Methods

Prior to widespread use of Additive Manufacturing (3D printing), metal implants were fabricated using casting, machining, forging and powder metallurgy. Electroforming was used for creating implants with intricate geometries or for producing implants with specific surface properties. These techniques were effective but often resulted in implants that were relatively bulky and lacked the advanced surface modifications and biomaterial combinations seen in more modern manufacturing methods used today. After the advent of 3D printing in the 1980s, manufacturers started using 3D laser and electron beam melting and sintering to build implants. These new technologies offer numerous advantages that make them suitable for biomedical applications including the ability to rapidly fabricate free form and custom-built implants within a few days, and possibility to create the porosity and surface properties that promote osseointegration. Additionally, these techniques are particularly suitable for the main category of metals used for biomedical applications such as Ti, Co-Cr, stainless steel materials. The number of research publications related to AM fabrication of biomedical implants increased drastically in the past two decades, making AM the preferred method for fabrication of these implants.

This chapter focuses on the characteristics of metallic components produced by various AM powder-bed processes [6,7]. Specifically, it details production methods falling under powder-based AM. These include SLM (Selective Laser Melting), EBM (Electron Beam Melting), and BJ (Binder Jetting). These are characterized by their use of either a laser source or an electron beam to melt or sinter metallic powders to produce functional components [187]. This section highlights the distinctive features, advantages, and disadvantages of each production method, with a primary focus on their use for biomedical devices.

3.1. Direct Metal Laser Sintering (DMLS)

The process of laser Sintering is an advanced AM technique first conceptualized in the mid-1980s at the University of Texas at Austin [188,189]. This process has become widely recognized for its ability to construct three-dimensional objects with precision [190]. DMLS mainly relies on the utilization of high-powered lasers to fuse particles of powdered metals in a layer-by-layer progression [191].

The process of DMLS starts with a powder bed feed ensuring the first layer of powder is evenly distributed on the build plate. During this process, an automated material supply mechanism ensures a consistent reservoir of powdered material is raked over the build surface as each layer is being sintered [192]. A laser is subsequently deployed to selectively irradiate the material, causing partial fusion, and shaping the object according to design specifications [193]. This can be seen in Figure 4, which illustrates the process of DMLS. Supports are required when printing metal parts, unlike SLS which does not require conventional supports [191,194].

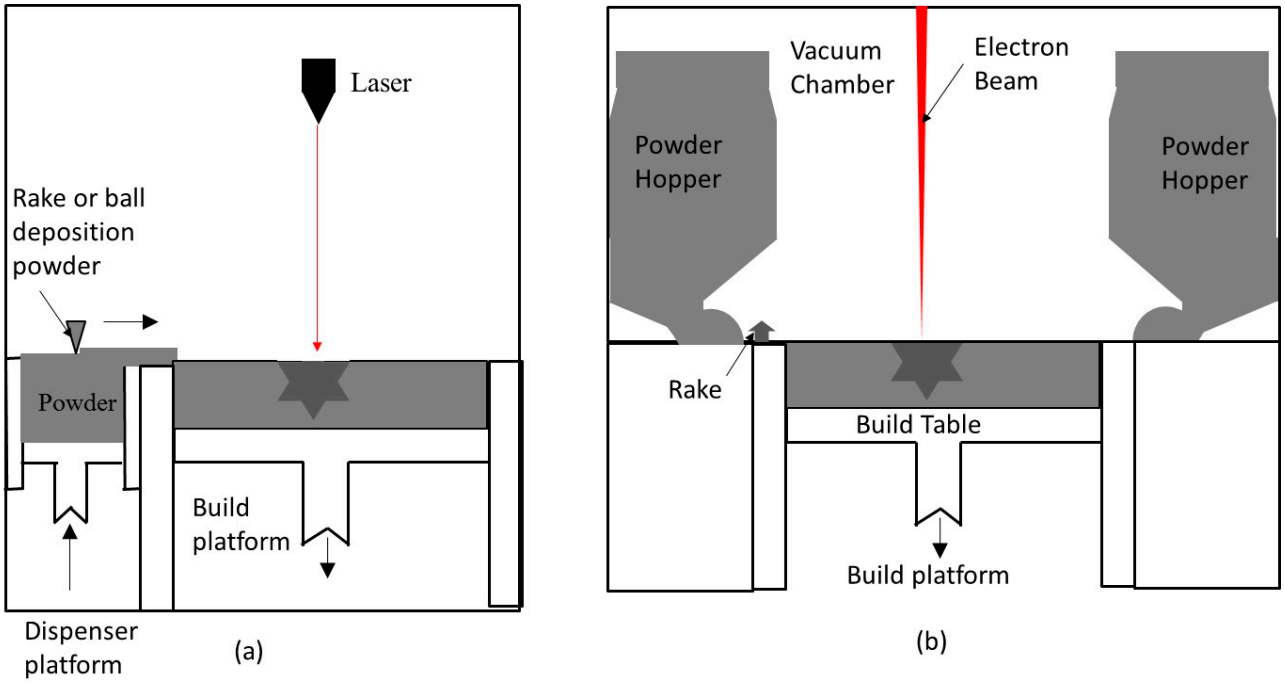

Figure 4. (**a**) Schematic of typical laser melting system, (**b**) Schematic of electron beam melting system. Reprinted with permission from ref. [6]. Copyright 2021. DEStech Publications, Inc. Lancaster, PA, USA.

The precision offered by DMLS makes it a preferred choice for fabricating components characterized by intricate and demanding geometries [195].

However, DMLS can be cost-intensive, primarily due to the substantial upfront capital required for laser equipment and procurement of materials [196]. Additionally, DMLS-manufactured objects may exhibit undesirable porosity, necessitating post-processing to rectify structural imperfections and remove unfused powder [197,198]. It may also require intricate adjustments in bonding and sintering mechanisms due to variations in material characteristics, potentially complicating the manufacturing process [199].

In the context of medical applications, DMLS has carved out a significant presence. It particularly excels in the creation of personalized implants and prosthetic devices [191,200]. The precision and material versatility inherent to metal sintering has enabled the fabrication of many types of customized medical devices [201,202].

3.2. Selective Laser Melting (SLM)

DMLS and SLM are two distinct powder-based additive manufacturing processes, each utilizing lasers and powdered materials to construct three-dimensional objects [203,204]. While they share fundamental principles, they exhibit unique characteristics that set them apart.

In both DMLS and SLM, the process starts with a reservoir of powdered material [205,206]. The distinguishing factor lies in the powder fusion method [207]. DMLS utilizes lasers to selectively sinter the powder layer by layer, without fully melting the particles [193,208]. In contrast, SLM uses a laser to fully melt and fuse the powdered material. [209]. This key difference in material treatment leads to variations in the density, strength, and structural properties of the produced components [210].

One of SLM's notable strengths is its compatibility with a wide range of metallic materials, including titanium, iron alloys, cobalt-chromium, and stainless steel [16,211]. It excels in creating high-density, high-strength components, even with complex geometries, reducing material waste [212]. SLM's unique capability to produce intricate structures without the need for a separate binder or melting phase is a significant advantage [211,213].

SLM presents its own set of challenges. Effective operation often demands specialized knowledge due to the use of various materials and precision laser technology. The cost im-

plications associated with materials and equipment can act as a deterrent to its widespread adoption [211]. Furthermore, SLM may not be suitable for materials requiring precise composite properties, and it necessitates high laser power and good beam quality, which can result in longer build times and potential issues like melt pool instabilities and higher residual stresses [88,209,210,214]. Additional complexity arises through this manufacturing technique that builds the material layer by layer. 3D printing methods commonly are known to produce anisotropic material [215,216] and columnar grain structures in the build orientation [217]. Thermal gradients throughout the build [218–220] can also result in microstructural variations that could cause the local and global mechanical behavior to be different [217].

SLM excels in creating customized medical implants and prosthetic devices. It does so by leveraging its precision and versatility with diverse materials to meet the unique anatomical and physiological requirements of individual patients [221,222]. SLM predominantly employs metal powders such as steel, titanium, and aluminum alloys. Since SLM can choose from a wide range of metallic materials, it can be used for many different medical applications. [88,223].

3.3. Electron Beam Melting (EBM)

EBM is a form of powder bed fusion (PBF), which is an AM technique which utilizes a high energy source to selectively melt metallic powders [203,224–228]. EBM differs from SLM by utilizing an electron beam in a vacuum chamber to melt the powder rather than a high-powered laser [208,229–233]. EBM was pioneered by the Swiss company Arcam AB in 1997 [203,224–226]. It has since been acquired by General Electric (GE) where GE is continuing to develop EBM capabilities [225].

Tamayo et al. describes the four distinct processing steps for EBM production. Step 1 starts with spreading the metallic powder evenly across the build plate which should be preheated to maintain part stability. Typically for part building, a layer thickness of 100 microns is raked onto the build plate [203]. The powder then gets preheated to around 700 degrees Celsius which partially sinters the powder and increases electroconductivity. This pre-heat temperature can change depending on the metal used [224]. Once the powder is properly heated, the electron beam quickly scans the build area (~10^2 mm/s) and selectively melts the powder. The build plate then resets its position, and the process repeats back to step 1 [224–227].

EBM has been shown to be one of the most complete methods for producing metallic medical parts. It can create complex, patient specific geometries, with the potential to keep costs lower than traditional manufacturing techniques [203,224,225]. EBM has specific advantages when considering it to be used for orthopedic implants, specifically those using Ti and Ti-based alloys. Like other powder-bed printing methods it can be used to create porous scaffold structures that help better match the mechanical properties of bone to that of the metallic implant [203,225,227]. It has also been shown to produce metallic implants with surface conditions that can help promote bone growth [224]. Generally, EBM produces a higher surface roughness due to two reasons. One the beam diameter is larger in E-beam versus laser [229]. Secondly the powder size distribution is larger in B-beam versus laser. The surface roughness of EBM compared to SLM was found to be Ra = 25–35 μm and Ra = 11 μm respectively in one study [224]

Although there is no definitive conclusion as to what surface characteristics are optimal for bone growth, research has shown increased improved bone-implant contact with rougher implant surfaces which could promote osteointegration [230] When comparing it to SLM, it can offer advantages such as high beam scanning speed and beam deflection [211,225,231].

Metal selection for EBM is based on many factors. One critical factor to consider is the electro conductivity of the metal [225]. Since this method uses an electron beam to heat up the surface, the surface must be conductive in order to allow proper flow of electrons through the powder [203,224,225]. This conductivity is enhanced through initial sintering. This sintering step and heated base plate is unique to EBM.

Many metallic materials have been fabricated using e-beam including Ti and Titanium alloys, Co-Cr alloys, stainless steel (316L), and Titanium-Ni alloys [208,229–233]. EBM has been used to produce knee implants, jaw implants, bone scaffolds, and cellular lattice structures [203,225].

One limitation of EBM is limited material selection. The need to find not only biocompatible, sufficiently strong metals, but also metals that are sufficiently electro conductive significantly reduce the number of materials usable for biomedical EBM [225]. Due to large powder size and the larger beam size compared to laser, EBM method could have dimensional precision issues of the cellular structures and there is a possibility that un-melted powder can be trapped within the part structure [225]. A drawback of EBM compared to that of SLM is the need for vacuum conditions in the build chamber. This creates a risk of electrostatic discharge of the powder, which could lead to process instability [224].

Further research into biomedical EBM should focus on material research and process control. With the restrictive nature of EBM's material selection, there should be an emphasis on finding new alloys or ways to process existing metallic powders to increase the application range of EBM [203]. Process optimization is very important to control porosity which is a necessary structure property that can either aid or harm the success of an implant. EBM offers the ability to design and control porosity, even controlling the shape of the cell structure [203,225]. But undesirable pore development from non-optimized process parameters could lead to defective devices [203].

3.4. Binder Jetting (BJ)

Binder Jetting (BJ) is one of the seven defined AM techniques described by ISO/ASTM 52900:2021 [232]. It is a powder bed process that also incorporates techniques from inkjet printing technology [228]. The original concept was invented at Massachusetts Institute of Technology (MIT) by Saches et al. [228,233,234]. The patent was published in 1993 and only two years later the company Z Corporation obtained a license for the binder jetting process [233,234]. Since the invention of this AM method there have been numerous companies that have developed technologies based off the technique, such as ExOne, ZCorp, Voxeljet, Desktop Metal and HP [233].

As stated previously, BJ is a powder bed-based AM technique [228,233,235–238]. There are two distinct differences between BJ and other common powder-based methods such as SLM, DMLS, and EBM. These being the use of a liquid binding agent, typically glycerol-based, to temporarily bind the powder as the part is being built and the mandatory reliance on post-processing techniques to sinter and debind the part [228,233,235–238].

The BJ system setup is described by Zhang et.al as being comprised of two main components, a powder bed, and a powder tank [228]. The process begins with a counter rotating roller spreading a thin initial layer of powder on the build plate [236]. This is followed by the deposition of the liquid binding agent from the machine's nozzles. The nozzles move in the X and Y planes, depositing the agent in specific locations which have been determined from the CAD model input [228,233,235–238]. It is this binding agent where BJ draws its similarities to inkjet printing. Once the binding agent has been applied to the first layer of powder, the build plate will lower in the Z-axis and the process repeats, building the part layer by layer [228,233,235–238]. The completed part prior to post-processing is referred to as the "green body" [228,235]. This process differs from other common PBF and DED methods, as the powder is not sintered or fused thermally throughout the build process. The final sintering is achieved in the crucial post-processing step.

Typically the process of sintering and debinding the part is done in one single heat treatment process [235]. Li et.al breaks this process down into three main steps; first the green body undergoes several hours of low temperature (175–450 °C) heating to burn away the binding agent [235]. This process can take anywhere from 6–12 h to complete [228]. The debound part (brown part) is sintered at an elevated temperature, around 1000 °C for 24–36 h [228,235] and then the sintered part is cooled down, ending the BJ process. This entire post processing is typically done in vacuum conditions or some protected environ-

ment to avoid oxidation [235]. Optimizing the sintering and debinding process is key to achieving high density, mechanically strong parts [228,233,235,236,238–240]. In addition to sintering the part, some research has explored the use of low-melting point metals to "infiltrate" the voids left behind by burning away the binding agent, with improves the final part's density, and ductility [228].

There are many important factors to consider when trying to achieve high-quality parts from BJ. Two of the most important metrics for determining the quality of an AM fabrication are the density of the part, and the final geometric accuracy. Li et.al states, "The density of additively manufactured parts is one of the essential properties driving the quality of functional parts. Pores in the parts concentrate the local stresses, thus deteriorating the mechanical performance" [235,241]. Due to BJ being unique in that it involves two distinct process steps, printing, and sintering/de-binding it is worth describing the factors that affect each step.

Within the printing step, powder properties and powder bed density are critical factors. The particle size, and morphology of the powders used plays an important role in the final density and homogeneity of the part [235]. It has been shown that a finer powder will lead to a higher density part [228,235], but it is important to know that the finer the powder the more difficult it is for the roller to effectively spread the powder on the build plate [228].

Like other metal AM processes, BJ is affected by many process parameters and optimizing these parameters is key to achieving parts comparable to traditionally manufactured parts. Fabrication is dependent on printing orientation, print speed, binder agent saturation, layer thickness, drying power level, spreading speed, powder size distribution [228,233,235,242,243]. Three of the most important parameters being powder size, layer thickness and heat treatment conditions, all of which have a significant impact on the part density [228].

Post processing parameters play just as a vital role in fabrication quality as do printing parameters. Sintering temperature and melting temperature is a key factor for BJ [236]. Due to the nature of "cooking" off the binder agent and the sintering process there is unavoidable part shrinkage that occurs during the post processing step [235]. This has proven to be a significant problem with the dimensional accuracy of BJ parts, which would be unacceptable for large scale manufacturing tolerances.

To achieve higher densities, there has been considerable investigations into using various materials at different stages of the printing process to "infiltrate" or modify the properties of the pure material powder. This includes adding nanoparticles into the binder jet agent to fill spaces between the powder particles [236]. The use of low melting point metals, such as bronze are used to "infiltrate" the fabricated part to remove residual porosity and achieve higher densities [236]. Research into adding materials such as silicon nitride (Si_3N_4) to 420 Stainless Steel has shown to increase the density, improve mechanical properties, and increase the dimensional accuracy of the final part [236,244].

Binder jetting is compatible with a variety of different types of materials (polymers, ceramics, metals, metal matrix materials, and composite materials) [235,236]. This review will focus on the research surrounding BJ metal printing. Li et.al reviewed the literature involving metallic BJ research and found that the most investigated materials were pure iron and ferrous alloys [235].

The industrial use of BJ produced parts focuses on metals specifically stainless steels, and bronze-infiltrated stainless steels [233]. Industrial applications demand high density parts, which has been achieved for stainless steel powders, ranging from 92% to 95% for gas atmosphere sintering [233]. This density can be further increased if Hot Isostatic Pressing is used, allowing for components to reach over 99% density [233,245]. Inconel and Cobalt-Chromium have also been used with BJ, which can be a desirable manufacturing technique for those alloys due to their inherent machining difficulties [233,246,247].

Binder Jetting offers numerous advantages over other power bed processes, such as relatively low upfront equipment costs, complex geometries, and typically faster print times [228,233,235]. Certain binder jetting machines have achieved per layer printing

speeds of only a few seconds, due to the ability to equip multiple binder agent nozzles, and the process operates at a significantly lower temperature than PBF or DED [228,233]. Additionally, the part volume capable with BJ is quite large, some as large as 780 mm × 400 mm × 400 mm for metal parts [233]. BJ has a broad selection of compatible materials because it does not require the use of high energy lasers, or electron beams to sinter and melt the powdered materials. This opens up the possibility to use metals with high optical reflectivity, high thermal conductivity, and low thermal stability [228,235,236]. Fayazfar et al. notes that the main advantage of BJ is due to the low operating temperature at which the part is built. There is no rapid heating or cooling of a melt pool which prevents the addition of residual stresses in the final part [236]. The build chamber does not have to be environmentally controlled or be under vacuum conditions in order for BJ to operate, opening up more material opportunities, and reducing the manufacturing safety risk [236].

Although BJ offers numerous advantages, it is not without its flaws. The most prominent disadvantage to BJ is the post processing sintering phase that is mandatory. This phase often leads to lower final density than other powder bed processes and final part shrinkage is unavoidable leading to geometric accuracy problems. The mechanical properties are directly related to the density of an AM manufactured part and BJ struggles to compete with traditional metallurgy and metal AM process to achieve the highest densities [235,236,248,249]. Defects can arise in the "green body" part when using ultra fine powders to manufacture a part. The ultra fine powders are more difficult to spread with the powder roller and powder clumping can occur due to humidity [236]. When using BJ on a large scale, it can actually be more expensive than traditional metallurgy and although the print speed is faster than PBF and DED, the intricate post processing step is lengthy and actually makes the overall lifecycle of a BJ fabrication slower than PBF or DED [228,233].

As with all current AM techniques the future research for BJ will need to focus on process parameter optimization to continue to approach the mechanical and physical properties that are commonly achieved through traditional manufacturing methods. For BJ specifically the two main areas of focus, outlined by Ziaee et.al should be split into both steps of the build, the powder laying and the post process sintering/de-binding. There is a knowledge gap in the understanding of powder and binder droplet interactions and best practices to use finer powders [233]. The sintering post-processing step is the key to achieving the necessary density for adequate mechanical strength, but most material systems are struggling to achieve full density [233], which will need to be a main focus on BJ research moving forward. Research conducted on the mechanical properties of BJ parts is scarce compared to PBF and DED methods, which is a critical space for future work [235]. If the use of BJ is to be extended to an increased manufacturing role rather than appearance prototyping, more work must be done to increase the geometric accuracy, density, and mechanical property variation of the printed parts [233].

A unique material challenge with BJ related to use for biomedical applications is the biocompatibility of not just the powder but the liquid binder agent. There can be binder residue left in the final part, and if that binder is not biocompatible it can cause complications within the body. This typically restricts the binder agents to pure water, chloroform, or some water-polymer solutions and acid-based binders if the printed part will be used within the human body. [233,250]. The use of BJ for the manufacture of biomedical devices is limited and as of now strictly for research. Research has been done using BJ to print pure Ti bone implants [251] and porous cellular Ti structures [252]. Although BJ is theoretically promising for AM of biomedical devices, this has not been proven through commercial manufacturing. As stated earlier, continued research on the mechanical properties of metallic parts made from BJ and finding more biocompatible binder agents to avoid toxicity concerns will be needed to compete with the dominant PBF methods.

4. Standards and Regulations

4.1. FDA Technical Guidance on Additive Manufacturing

The use of AM for medical devices has dated back to the early 1990s with the creation of custom dental implants and prosthetics [3]. The patent for SLS was granted in 1989 to Carl Deckard and had an immediate impact on the innovation of medical devices [189]. This was largely in part because both AM and medical imaging techniques such as CT and MRI utilize layered computer data. There was a natural connection between the two technologies, and it has continued to enable the rapid design and production of quality custom implants [189].

Although this technology has been around since the late 1980s and early 1990s, it has only been recently (the past 10 years) that it has been officially recognized by the main medical governing body of The United States, the Food and Drug Administration (FDA). The FDA is the regulatory agency in the United States responsible for the enforcement and approval of all medical devices produced in the US. Medical devices produced using AM fall under their jurisdiction and recently the FDA have taken steps to establish a guidance framework specific to AM [253].

The FDA's technical guidance, "United States Food and Drug Administration's (FDA), "Technical Considerations for Additive Manufactured Medical Devices" was drafted in 2016 and issued in 2017 [253]. The purpose of this technical guidance, "is to outline technical considerations associated with AM processes, and recommendations for testing and characterization for devices that include at least one additively manufactured component or additively fabricated step" [253].

This FDA guidance is a compilation of initial considerations that the FDA believe are critical for safe and effective manufacturing of medical devices using AM [2,253]. The FDA asserts that these guidelines are not legally enforceable and rather are the agency's initial work on conceptualizing the regulations surrounding 3D printed medical devices. Rust et al. [2] explains that the pre-market approval process is the same for both traditionally manufactured and additively manufactured devices. The guidance outlines that 3D printed devices are classified into one of three classifications, Class I, Class II, or Class III. The different classifications determine the risk profile (refer to Figure 5), Class 1 being the lowest risk to patient and user. These include devices such as enema kits, and elastic bandages [254]. The highest risk devices then being Class III, which typically are devices such as implants [2,253,255].

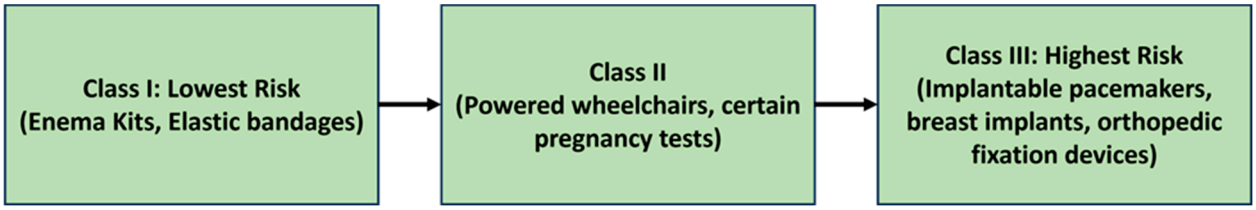

Figure 5. Graphical representation of FDA medical device classification based on risk profile. Reprinted with permission from ref. [15]. Copyright 2010. Woodhead Publishing. Sawston, UK.

The FDA determines the classification level of all medical devices based on "the level of control necessary to assure the safety and effectiveness of the device" [256]. When making the determination the FDA will evaluate both the device's "intended use" and "indications of use". The classification will determine which regulatory controls the FDA will apply to the market clearance process. The FDA have evaluated approximately 1700 generic medical device types and grouped them into 16 specialties they refer to as panels [256]. Rust et.al [2] also explains that the FDA is principally concerned with the final medical device design and how it safely demonstrates its design purpose. The FDA does not regulate the individual material or process being used to manufacture the device, but rather how those parameters were used to create a safe and effective device [2,253].

Morrison et.al [255] provides a case study outlining the Pre-Market Approval (PMA) process for their specific AM medical device. The author's device is an implant which falls under the FDA's Class III medical device classification. This puts the device in the highest risk to patient and user category which has the most stringent premarket approval process. For Class III devices the FDA can grant an Investigational Device Exemption (IDE). This IDE grants the device manufacturer the ability to carry out a clinical trial to gather safety and effectiveness data [257]. This IDE is primarily given to support a device through the PMA. Additionally, the IDE can be granted to devices already market approved but have undergone design modifications or are looking for approval for different use indications [257].

Morrison et.al walks through the parameters that the FDA requires be controlled and accounted for during the device's manufacturing process (refer to Table 5) [253,255]:

Table 5. Summary of design parameters that need to be controlled for AM FDA device approval.

Process Parameter	Description of FDA Requirements for Approval
Design control	Necessary to incorporate verification and design validation steps to control design variants that arise due to inherit customization of print process [255]
Raw materials	Follow FDA Quality System (QS) Regulation/Medical Device Good Manufacturing Practices [258] Recycling of raw material poses a unique challenge for 3D printed devices; need to consider how to verify material is still safe and effective after recycling.
Technical considerations	Print Parameters (scan speed, laser beam energy density, etc.) significantly impact final device characteristics. FDA requires documentation outlining the print process parameters used to make final device
Post processing	Standard guidance for post processing quality assurance has not yet been published. Need to provide sufficient data to FDA that post processing has not altered the safety and efficacy profile of the final device design
Cleaning and finishing	FDA has not explicitly outlined the requirements for validating that cleaning and finishing of the print has not altered the mechanical or structure properties. It is expected that the FDA will still require some form of documentation verifying cleaning/finishing did not alter device properties; manufacturer discretion on how that is shown
Sterilization	FDA applies the sterilization criteria (ISO 22441:2022) [259]
Biocompatibility	FDA enforces ISO10993 standards for evaluating biocompatibility for Class III 3D printed devices

Not all these items listed in the table have specific standards or specifications that need to be followed to provide sufficient data for FDA approval. In some cases, the FDA has adopted specific ISO standards, such as in the case of sterilization control [255]. There are regulatory gaps that the FDA should highly consider defining to better control AM device approval. This would also provide manufacturers with clear directions for what documentation to provide throughout the pre-market approval process.

A device approved by the FDA is approved for the specific use case set by the manufacturer during the pre-market approval. Once a device is approved for a specific use case it will have to undergo the approval process again if the manufacturer decides to change or

add an additional use case [2]. This is the case for both 3D printed devices and traditionally manufactured devices.

The current regulatory landscape surrounding AM medical devices are still very much in their infancy. Approval of devices using AM follows the same approval process being used for traditionally manufactured devices. The assigned classification of the device is the biggest determining factor for the level of regulatory scrutiny.

4.2. Insufficient Guidance for AM Medical Devices

With the rapidly expanding AM market for medical devices, the guidance issued by the FDA [253] is not sufficient to keep up with the industry demands for regulation. Research done by Pew Charitable Trusts along with 17 expert interviews concluded that the 2017 FDA Guidance on Additive Manufacturing had several key issues that required attention. The three key issues that were identified in the research were enforceability of guidelines, resource-to-demand, and innovation pacing compared to regulations [260].

The researchers at Pew stressed the need for the FDA to begin creating legally enforceable rules surrounding additive manufacturing. An example provided discussed the possibility of the FDA requiring health care facilities with 3D printing capabilities to register their facility to the FDA. This would allow the FDA to compile a list of facilities across the country that they could monitor and audit if necessary [260]. The investigation also identified areas of ambiguity in the technical guidance that will raise issues with enforcement. The FDA does not explicitly define what regulations will apply to health care facilities with AM capabilities or device manufacturers [260]. Additionally, there needs to be a clear distinction between medical products and medical services. The researchers at Pew highlighted a common example that falls into a "gray area". The use of 3D printed patient specific cutting guides can be seen by some as a device and by others as a medical service necessary for surgery [260]. The FDA has authority over medical products but typically does not regulate medical services, as that is handled by state legislation [260]. The research by Pew expresses the need for the FDA to be more specific and clearer with their definitions and classifications if they intend to effectively enforce AM guidelines. Medical devices, both traditionally manufactured and 3D printed, are given risk-based classifications, Class I–III [2,253,260]. These classifications are the most critical determination on how the FDA regulates and approve the device. Therefore, it is crucial that the definitions used to assign these classifications are clearly defined. This was one of the major concerns the Pew researchers found with the current FDA technical guidelines. The terms, "very-low-risk", "minimal risk", and "lowest risk" are examples of vague terms used to classify devices. Precise definitions will limit the possibility of loopholes manufacturers could exploit for preferential classifications of their devices [260].

Resource allocation for the rapidly growing industry of medical 3D printing was stressed as a concern needing attention from the FDA. There is a concern that the FDA is stretched thin with their ability to manage all point of care facilities and device companies using AM for medical devices [260]. Some suggestions from the experts interviewed in the study include, "outsourcing some oversight to other organizations-such as a hospital accreditor, professional medical association, or engineering society" [260]. To date there has been no determination as to which of these agencies would take on this role. The FDA should consider whether one or a combination of all these organizations will be most effective at taking some of the oversight burden off the FDA.

3D printing innovation is outpacing the creation of new standards and regulations specifically targeting products made with 3D printing. The FDA guidance on additive manufacturing was released in 2017 and there has not been a comprehensive update to that review. Between then and now there has been substantial research and implementation of 3D printing in the medical device field. Pew raised concerns that the FDA is being outpaced by the innovation of this technology and will need to work hard to establish a process in which they can create necessary regulations in a timeline that coincides with research and industry. Pew suggested that it could be beneficial if the FDA leans on third

party engineering agencies to help establish and maintain the regulatory framework for additive manufacturing [260]. The FDA has made it clear in their technical guidance that they will utilize ISO/ASTM standards to help establish their market approval process [253]. Leveraging ISO/ASTM standards will help the FDA keep up to date with the latest technical considerations surrounding AM and can simply mandate health care facilities and device manufacturers follow specific ISO/ASTM standards deemed appropriate. Using the ISO standards website, a search containing the term "additive manufacturing" and specifying dates from 2018 to 2023 yielded 81 standards both published and under development. A sample of these can be found in Table 6. With there being 81 standards within a 5-year period it is apparent that there is a demand and effort being made to keep up with the rapid development of AM technology.

Table 6. Recent published and under development ISO/ASTM standards for additive manufacturing.

Standard Code	Standard	Status/Date	References
ISO/ASTM 52900:2021	Additive manufacturing: General Principals: Fundamentals and vocabulary	Published/2021	[35]
ISO/ASTM 52904:2019	Additive manufacturing: Process characteristics and performance Practice for metal powder bed fusion process to meet critical applications	Published (to be revised)/2019	[261]
ISO/ASTM 52909:2022	Additive manufacturing of metals: Finished part properties Orientation and location dependence of mechanical properties for metal powder bed fusion	Published (to be revised)/2022	[262]
ISO/ASTM DIS 52948	Additive manufacturing for metals: Non-destructive testing and evaluation imperfections classification in PBF parts	Under Development	[263]
ISO/ASTM DIS 52938-1	Additive manufacturing of metals: Environment, health and safety, Part 1: Safety requirements for PBF-LB machines	Under Development	[264]
ISO/ASTM TR 52905:2023	Additive manufacturing of metals: Non-destructive testing and evaluation, Defect detection in parts	Published/2023	[265]
ISO/ASTM DIS 52927	Additive manufacturing: General principles, Main characteristics and corresponding test methods	Under Development	[266]
ISO/CD 5092	Additive manufacturing for medical: General principles, Additive manufacturing of non-active implants	Under Development	[267]
ISO/ASTM 52911-3:2023	Additive manufacturing: Design, Part 3: PBF-EB of metallic materials	Published/2023	[268]

4.3. Ensuring Standardization and Quality Control of AM Devices

The inherent nature of 3D printing allows for extreme customization of product design and materials, leading to an infinite number of design possibilities [255]. This strength is also one of the greatest challenges that faces standardizing and controlling the quality of products. Marinez-Marquez et.al performed qualitative research looking at best practices to ensure product quality for 3D printed devices [269]. The current best practice for manufacturers to control product design, production and testing is using ISO/ASTM standards. As stated in the previous section, ISO/ASTM are the gold standard when it comes to best manufacturing practices, and they are used by the FDA to approve devices to market.

To increase production quality of 3D printed medical devices Marinez-Marquez et.al asserts that there are several key technologies that need to be carefully considered. The first being a robust communication network between the clinical and engineering personnel. This will reduce the risk of miscommunications and potential design flaws during the product development stage [269]. The quality of the product will also critically depend on the ability for a manufacturer to both monitor the print process in real time and have a robust system in place to evaluate device components postproduction [269].

The FDA also outlined challenges posed by AM medical devices, which include optimal process validation, characterization, and assessment methods for final devices [253,255,269]. These broad terms refer to the whole AM process from start to finish and try to encapsulate the main challenge of AM, which is the sheer number of design inputs possible to produce a medical device. The FDA held a workshop in 2014 for device manufacturers, AM companies, and academia to discuss all major considerations for AM [253]. The group conclude that there were five broad themes to understand for medical AM [253].

1. Materials
2. Design, printing, and post-printing validation
3. Printing characteristics and parameters
4. Physical and Mechanical assessment of final devices
5. Biological considerations of final devices (cleaning, sterility, and biocompatibility)

Each of the above criteria is constantly evolving, with new material research, improved print technology, and the publication of better-defined testing methods. There is a continual need for revision and the creation of regulations and standards to keep up with the demand for AM technology. For the eventual end user (patients) to receive maximum benefit from the emergence of custom device implants, the agencies working to ensure safety and quality need to work hard to keep up with this new wave of biomedical manufacturing. This will ensure innovation is not stifled and the patients will receive safe and effective devices.

5. Conclusions and Future Remarks

This review investigated the biocompatibility and mechanical performance for the most common metals used in medical device manufacturing. Selecting an implant material is a complex problem that requires several different considerations including, biocompatibility, osseointegration integration, conduction and induction, mechanical compatibility, toxicity of elements and long-term performance and impact. The four most widely used AM methods for biomedical applications were reviewed DMLS, SLM, EBM, and BJ and their advantages and disadvantages in fabricating metal implants is discussed. Additionally, it is important to review the current regulatory framework in place for maintaining safe and effective production of medical devices using AM. This review chose to focus on the current regulations in the United States.

Creation of novel materials that meet the biocompatibility criteria as well as provide the mechanical performance necessary for short term or long-term application is and will need to continue to be a main research focus. An exciting area of this research is surrounding the idea of using metallic composites, specifically using Mg and Ti along with bio ceramic reinforcement material. The use of composite materials for biomedical applications has seen increased research interest due to their potential to solve many of the key limitations facing conventional metallics. Metals are a great material to start a composite interface because naturally metals are light-weight materials relative to their mechanical strength, and they have high temperature and corrosion resistance. These metal composites have been shown to have improved mechanical strength, thermal properties and increased lightweight capabilities [197]. The most common types of metal composites applicable to biomedical devices are metal matrix composites (MMCs) reinforced with ceramics or other metals. Currently, MMCs are typically produced using one of two methods, Liquid state fabrication or Solid-state fabrication [270]. Liquid state fabrication refers to the method in which the reinforcement material is added to the metal matrix that has been fully or partially put in a molten state [270]. Solid-state fabrication can refer to either diffusion bonding or powder metallurgy [270]. Research into PBF for Mg-based and Ti-based MMCs is currently limited and requires additional support to fully understand the best processes for manufacturing these materials. Zhang et al. concludes that there are six major areas to focus on, Matrix-Reinforcement composition design, sourcing high quality powders, process parameter optimization, mechanics of the unique solidification process, careful reinforcement selection, and post-processing research [271]. Although the research is limited in this field, there is great potential to combine the advantageous

material properties of Mg-based and Ti-based MMCs with the highly customizable nature of AM.

Refining the printing process to create devices with comparable or better mechanical performances to that of traditional manufacturing is needed to take advantage of the complex geometries that can be achieved with AM. The regulatory section of this paper also makes clear that concrete regulations are important for future widespread adoption of this technique and will be a major driving force for continued safe and effective clinical use. Metal AM has already proven itself as a great option for creating new and innovative medical devices and it is clear from this review there is even more room for this technology to develop and become the dominant form of patient centered device manufacturing.

Author Contributions: L.L.: Conceptualization, investigation, methodology, supervision, writing-original draft, writing-review and editing. M.P.: Investigation, methodology, writing-original draft, writing-review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: We thank the National Science Foundation and the Division of Graduate Education for their support of this research. This work is part of the NSF Research Traineeship program supported under Grant 2152254.

Data Availability Statement: No new data were created or analyzed in this study.

Acknowledgments: We thank Eric Prosser, Unit Head and Associate Librarian for Arizona State Universities library STEM Division for early consultation about research methodology. We also thank Reggie Angell for reviewing and providing feedback for our manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Chua, K.; Khan, I.; Malhotra, R.; Zhu, D. Additive Manufacturing and 3D Printing of Metallic Biomaterials. *Eng. Regen.* **2021**, *2*, 288–299. [CrossRef]
2. Rust, B.; Tsaponina, O.; Maniruzzaman, M. Recent Innovations in Additive Manufacturing Across Industries: 3D Printed Products and FDA's Perspectives. In *3D and 4D Printing in Biomedical Applications*; John Wiley & Sons, Ltd: Hoboken, NJ, USA, 2019; pp. 443–462. ISBN 978-3-527-81370-4.
3. Kumar, R.; Kumar, M.; Chohan, J.S. The Role of Additive Manufacturing for Biomedical Applications: A Critical Review. *J. Manuf. Process.* **2021**, *64*, 828–850. [CrossRef]
4. Velásquez-García, L.F.; Kornbluth, Y. Biomedical Applications of Metal 3D Printing. *Annu. Rev. Biomed. Eng.* **2021**, *23*, 307–338. [CrossRef] [PubMed]
5. Bandyopadhyay, A.; Bose, S.; Das, S. 3D Printing of Biomaterials. *MRS Bull.* **2015**, *40*, 108–114. [CrossRef]
6. Ladani, L. *Additive Manufacturing of Metals: Materials, Processes, Tests, and Standards*; DEStech Publications, Incorporated: Lancaster, PA, USA, 2021; ISBN 978-1-60595-600-8.
7. Ladani, L.; Sadeghilaridjani, M. Review of Powder Bed Fusion Additive Manufacturing for Metals. *Metals* **2021**, *11*, 1391. [CrossRef]
8. Ma, H.; Suonan, A.; Zhou, J.; Yuan, Q.; Liu, L.; Zhao, X.; Lou, X.; Yang, C.; Li, D.; Zhang, Y. PEEK (Polyether-Ether-Ketone) and Its Composite Materials in Orthopedic Implantation. *Arab. J. Chem.* **2021**, *14*, 102977. [CrossRef]
9. Abraham, C.M. A Brief Historical Perspective on Dental Implants, Their Surface Coatings and Treatments. *Open Dent. J.* **2014**, *8*, 50–55. [CrossRef]
10. Zaman, H.A.; Sharif, S.; Idris, M.H.; Kamarudin, A. Metallic Biomaterials for Medical Implant Applications: A Review. *Appl. Mech. Mater.* **2015**, *735*, 19–25. [CrossRef]
11. Mahapatro, A. Metals for Biomedical Applications and Devices. *J. Biomater. Tissue Eng.* **2012**, *2*, 259–268. [CrossRef]
12. Cooke, S.; Ahmadi, K.; Willerth, S.; Herring, R. Metal Additive Manufacturing: Technology, Metallurgy and Modelling. *J. Manuf. Process.* **2020**, *57*, 978–1003. [CrossRef]
13. Sames, W.J.; List, F.A.; Pannala, S.; Dehoff, R.R.; Babu, S.S. The Metallurgy and Processing Science of Metal Additive Manufacturing. *Int. Mater. Rev.* **2016**, *61*, 315–360. [CrossRef]
14. Davoodi, E.; Montazerian, H.; Mirhakimi, A.S.; Zhianmanesh, M.; Ibhadode, O.; Shahabad, S.I.; Esmaeilizadeh, R.; Sarikhani, E.; Toorandaz, S.; Sarabi, S.A. Additively Manufactured Metallic Biomaterials. *Bioact. Mater.* **2022**, *15*, 214–249. [CrossRef] [PubMed]
15. Matsushita, T. 14—Orthopaedic Applications of Metallic Biomaterials. In *Metals for Biomedical Devices*; Niinomi, M., Ed.; Woodhead Publishing Series in Biomaterials; Woodhead Publishing: Sawston, UK, 2010; pp. 329–354. ISBN 978-1-84569-434-0.
16. Ni, J.; Ling, H.; Zhang, S.; Wang, Z.; Peng, Z.; Benyshek, C.; Zan, R.; Miri, A.K.; Li, Z.; Zhang, X.; et al. Three-Dimensional Printing of Metals for Biomedical Applications. *Mater. Today Bio* **2019**, *3*, 100024. [CrossRef] [PubMed]

17. Ali, M.; Hussein, M.A.; Al-Aqeeli, N. Magnesium-Based Composites and Alloys for Medical Applications: A Review of Mechanical and Corrosion Properties. *J. Alloys Compd.* **2019**, *792*, 1162–1190. [CrossRef]
18. Haghshenas, M. Mechanical Characteristics of Biodegradable Magnesium Matrix Composites: A Review. *J. Magnes. Alloys* **2017**, *5*, 189–201. [CrossRef]
19. Harun, W.S.W.; Asri, R.I.M.; Alias, J.; Zulkifli, F.H.; Kadirgama, K.; Ghani, S.A.C.; Shariffuddin, J.H.M. A Comprehensive Review of Hydroxyapatite-Based Coatings Adhesion on Metallic Biomaterials. *Ceram. Int.* **2018**, *44*, 1250–1268. [CrossRef]
20. Haider, A.; Haider, S.; Han, S.S.; Kang, I.-K. Recent Advances in the Synthesis, Functionalization and Biomedical Applications of Hydroxyapatite: A Review. *RSC Adv.* **2017**, *7*, 7442–7458. [CrossRef]
21. Li, N.; Liu, W.; Wang, Y.; Zhao, Z.; Yan, T.; Zhang, G.; Xiong, H. Laser Additive Manufacturing on Metal Matrix Composites: A Review. *Chin. J. Mech. Eng.* **2021**, *34*, 38. [CrossRef]
22. Harun, W.S.W.; Manam, N.S.; Kamariah, M.S.I.N.; Sharif, S.; Zulkifly, A.H.; Ahmad, I.; Miura, H. A Review of Powdered Additive Manufacturing Techniques for Ti-6al-4v Biomedical Applications. *Powder Technol.* **2018**, *331*, 74–97. [CrossRef]
23. Ahmed, N.; Barsoum, I.; Haidemenopoulos, G.; Al-Rub, R.K.A. Process Parameter Selection and Optimization of Laser Powder Bed Fusion for 316L Stainless Steel: A Review. *J. Manuf. Process.* **2022**, *75*, 415–434. [CrossRef]
24. Amirtharaj Mosas, K.K.; Chandrasekar, A.R.; Dasan, A.; Pakseresht, A.; Galusek, D. Recent Advancements in Materials and Coatings for Biomedical Implants. *Gels* **2022**, *8*, 323. [CrossRef] [PubMed]
25. Vaiani, L.; Boccaccio, A.; Uva, A.E.; Palumbo, G.; Piccininni, A.; Guglielmi, P.; Cantore, S.; Santacroce, L.; Charitos, I.A.; Ballini, A. Ceramic Materials for Biomedical Applications: An Overview on Properties and Fabrication Processes. *J. Funct. Biomater.* **2023**, *14*, 146. [CrossRef] [PubMed]
26. Balazic, M.; Kopac, J. Improvements of Medical Implants Based on Modern Materials and New Technologies. *J. Achiev. Mater. Manuf. Eng.* **2007**, *25*, 31–34.
27. Grainger, D. The Williams Dictionary of Biomaterials David F. Williams, Liverpool University Press, Liverpool, Great Britain, 1999. *Mater. Today* **1999**, *2*, 29. [CrossRef]
28. Crawford, L.; Wyatt, M.; Bryers, J.; Ratner, B. Biocompatibility Evolves: Phenomenology to Toxicology to Regeneration. *Adv. Healthc. Mater.* **2021**, *10*, 2002153. [CrossRef]
29. Williams, D.F. *The Williams Dictionary of Biomaterials*; Liverpool University Press: Liverpool, UK, 1999; ISBN 978-0-85323-734-1.
30. Nair, L.S.; Laurencin, C.T. Biodegradable Polymers as Biomaterials. *Prog. Polym. Sci.* **2007**, *32*, 762–798. [CrossRef]
31. Quinn, J.; McFadden, R.; Chan, C.-W.; Carson, L. Titanium for Orthopedic Applications: An Overview of Surface Modification to Improve Biocompatibility and Prevent Bacterial Biofilm Formation. *iScience* **2020**, *23*, 101745. [CrossRef]
32. Brånemark, R.; Branemark, P.I.; Rydevik, B.; Myers, R.R. Osseointegration in Skeletal Reconstruction and Rehabilitation: A Review. *J. Rehabil. Res. Dev.* **2001**, *38*, 175–182.
33. Donaghy, C.L.; McFadden, R.; Smith, G.C.; Kelaini, S.; Carson, L.; Malinov, S.; Margariti, A.; Chan, C.-W. Fibre Laser Treatment of Beta TNZT Titanium Alloys for Load-Bearing Implant Applications: Effects of Surface Physical and Chemical Features on Mesenchymal Stem Cell Response and Staphylococcus Aureus Bacterial Attachment. *Coatings* **2019**, *9*, 186. [CrossRef]
34. Bandyopadhyay, A.; Mitra, I.; Goodman, S.B.; Kumar, M.; Bose, S. Improving Biocompatibility for next Generation of Metallic Implants. *Prog. Mater. Sci.* **2023**, *133*, 101053. [CrossRef]
35. International Organization for Standardization. *Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a Risk Management Process*; International Standard Organization: Geneva, Switzerland, 2018.
36. Mitra, I.; Bose, S.; Dernell, W.S.; Dasgupta, N.; Eckstrand, C.; Herrick, J.; Yaszemski, M.J.; Goodman, S.B.; Bandyopadhyay, A. 3D Printing in Alloy Design to Improve Biocompatibility in Metallic Implants. *Mater. Today* **2021**, *45*, 20–34. [CrossRef] [PubMed]
37. Chmielewska, A.; Dean, D. The Role of Stiffness-Matching in Avoiding Stress Shielding-Induced Bone Loss and Stress Concentration-Induced Skeletal Reconstruction Device Failure. *Acta Biomater.* **2023**, *173*, 51–65. [CrossRef] [PubMed]
38. Ridzwan, M.; Shuib, S.; Hassan, A.Y.; Ahmed Shokri, A.; Ibrahim, M. Problem of Stress Shielding and Improvement to the Hip Implant Designs: A Review. *J. Med. Sci.* **2007**, *7*, 460–467. [CrossRef]
39. yadav, P.; Beniwal, G.; Saxena, K.K. A Review on Pore and Porosity in Tissue Engineering. *Mater. Today Proc.* **2021**, *44*, 2623–2628. [CrossRef]
40. Bandyopadhyay, A.; Espana, F.; Balla, V.K.; Bose, S.; Ohgami, Y.; Davies, N.M. Influence of Porosity on Mechanical Properties and in Vivo Response of Ti6Al4V Implants. *Acta Biomater.* **2010**, *6*, 1640–1648. [CrossRef]
41. Haugen, H.J.; Bertoldi, S. Characterization of Morphology—3D and Porous Structure. In *Characterization of Polymeric Biomaterials*; Elsevier: Amsterdam, The Netherlands, 2017; pp. 21–53. ISBN 978-0-08-100737-2.
42. Annabi, N.; Nichol, J.W.; Zhong, X.; Ji, C.; Koshy, S.; Khademhosseini, A.; Dehghani, F. Controlling the Porosity and Microarchitecture of Hydrogels for Tissue Engineering. *Tissue Eng. Part B Rev.* **2010**, *16*, 371–383. [CrossRef]
43. Sharkawy, A.A.; Klitzman, B.; Truskey, G.A.; Reichert, W.M. Engineering the Tissue Which Encapsulates Subcutaneous Implants. I. Diffusion Properties. *J. Biomed. Mater. Res.* **1997**, *37*, 401–412. [CrossRef]
44. Sharkawy, A.A.; Klitzman, B.; Truskey, G.A.; Reichert, W.M. Engineering the Tissue Which Encapsulates Subcutaneous Implants. III. Effective Tissue Response Times. *J. Biomed. Mater. Res.* **1998**, *40*, 598–605. [CrossRef]
45. Hernandez, J.L.; Woodrow, K.A. Medical Applications of Porous Biomaterials: Features of Porosity and Tissue-Specific Implications for Biocompatibility. *Adv. Healthc. Mater.* **2022**, *11*, e2102087. [CrossRef]

46. Sussman, E.M.; Halpin, M.C.; Muster, J.; Moon, R.T.; Ratner, B.D. Porous Implants Modulate Healing and Induce Shifts in Local Macrophage Polarization in the Foreign Body Reaction. *Ann. Biomed. Eng.* **2014**, *42*, 1508–1516. [CrossRef]
47. Brown, B.N.; Ratner, B.D.; Goodman, S.B.; Amar, S.; Badylak, S.F. Macrophage Polarization: An Opportunity for Improved Outcomes in Biomaterials and Regenerative Medicine. *Biomaterials* **2012**, *33*, 3792–3802. [CrossRef] [PubMed]
48. Li, J.P.; Habibovic, P.; van den Doel, M.; Wilson, C.E.; de Wijn, J.R.; van Blitterswijk, C.A.; de Groot, K. Bone Ingrowth in Porous Titanium Implants Produced by 3D Fiber Deposition. *Biomaterials* **2007**, *28*, 2810–2820. [CrossRef] [PubMed]
49. Bobyn, J.D.; Pilliar, R.M.; Cameron, H.U.; Weatherly, G.C. The Optimum Pore Size for the Fixation of Porous-Surfaced Metal Implants by the Ingrowth of Bone. *Clin. Orthop. Relat. Res.* **1980**, *150*, 263–270. [CrossRef]
50. Bobyn, J.D.; Stackpool, G.J.; Hacking, S.A.; Tanzer, M.; Krygier, J.J. Characteristics of Bone Ingrowth and Interface Mechanics of a New Porous Tantalum Biomaterial. *J. Bone Jt. Surg. Br.* **1999**, *81*, 907–914. [CrossRef]
51. Bobyn, J.D.; Wilson, G.J.; MacGregor, D.C.; Pilliar, R.M.; Weatherly, G.C. Effect of Pore Size on the Peel Strength of Attachment of Fibrous Tissue to Porous-Surfaced Implants. *J. Biomed. Mater. Res.* **1982**, *16*, 571–584. [CrossRef]
52. Boyde, A.; Corsi, A.; Quarto, R.; Cancedda, R.; Bianco, P. Osteoconduction in Large Macroporous Hydroxyapatite Ceramic Implants: Evidence for a Complementary Integration and Disintegration Mechanism. *Bone* **1999**, *24*, 579–589. [CrossRef]
53. Chang, B.S.; Lee, C.K.; Hong, K.S.; Youn, H.J.; Ryu, H.S.; Chung, S.S.; Park, K.W. Osteoconduction at Porous Hydroxyapatite with Various Pore Configurations. *Biomaterials* **2000**, *21*, 1291–1298. [CrossRef]
54. Augustin, J.; Feichtner, F.; Waselau, A.-C.; Julmi, S.; Klose, C.; Wriggers, P.; Maier, H.J.; Meyer-Lindenberg, A. Effect of Pore Size on Tissue Ingrowth and Osteoconductivity in Biodegradable Mg Alloy Scaffolds. *J. Appl. Biomater. Funct. Mater.* **2022**, *20*, 22808000221078168. [CrossRef]
55. Hollister, S.; Lin, C.; Saito, E.; Lin, C.; Schek, R.; Taboas, J.; Williams, J.; Partee, B.; Flanagan, C.; Diggs, A.; et al. Engineering Craniofacial Scaffolds. *Orthod. Craniofacial Res.* **2005**, *8*, 162–173. [CrossRef]
56. Albrektsson, T.; Johansson, C. Osteoinduction, Osteoconduction and Osseointegration. *Eur. Spine J.* **2001**, *10*, S96–S101. [CrossRef]
57. Eliaz, N. Corrosion of Metallic Biomaterials: A Review. *Materials* **2019**, *12*, 407. [CrossRef] [PubMed]
58. Hansen, D.C. Metal Corrosion in the Human Body: The Ultimate Bio-Corrosion Scenario. *Electrochem. Soc. Interface* **2008**, *17*, 31–34. [CrossRef]
59. bin Anwar Fadzil, A.F.; Pramanik, A.; Basak, A.K.; Prakash, C.; Shankar, S. Role of Surface Quality on Biocompatibility of Implants—A Review. *Ann. 3D Print. Med.* **2022**, *8*, 100082. [CrossRef]
60. Alla, R.K.; Ginjupalli, K.; Upadhya, N.; Mohammed, S.; sekar, R.; Ravi, R. Surface Roughness of Implants: A Review. *Trends Biomater. Artif. Organs* **2011**, *25*, 112–118.
61. Li, B.E.; Li, Y.; Min, Y.; Hao, J.Z.; Liang, C.Y.; Li, H.P.; Wang, G.C.; Liu, S.M.; Wang, H.S. Synergistic Effects of Hierarchical Hybrid Micro/Nanostructures on the Biological Properties of Titanium Orthopaedic Implants. *RSC Adv.* **2015**, *5*, 49552–49558. [CrossRef]
62. Kane, R.; Ma, P.X. Mimicking the Nanostructure of Bone Matrix to Regenerate Bone. *Mater. Today* **2013**, *16*, 418–423. [CrossRef]
63. Wong, M.; Eulenberger, J.; Schenk, R.; Hunziker, E. Effect of Surface Topology on the Osseointegration of Implant Materials in Trabecular Bone. *J. Biomed. Mater. Res.* **1995**, *29*, 1567–1575. [CrossRef]
64. Barfeie, A.; Wilson, J.; Rees, J. Implant Surface Characteristics and Their Effect on Osseointegration. *Br. Dent. J.* **2015**, *218*, E9. [CrossRef]
65. Surface Energy. Wikipedia 2024. Available online: https://en.wikipedia.org/wiki/Surface_energy (accessed on 30 August 2024).
66. Zhao, G.; Schwartz, Z.; Wieland, M.; Rupp, F.; Geis-Gerstorfer, J.; Cochran, D.L.; Boyan, B.D. High Surface Energy Enhances Cell Response to Titanium Substrate Microstructure. *J. Biomed. Mater. Res. Part A* **2005**, *74A*, 49–58. [CrossRef]
67. Barbosa, T.P.; Naves, M.M.; Menezes, H.H.; Pinto, P.H.; de Mello, J.D.; Costa, H.L. Topography and Surface Energy of Dental Implants: A Methodological Approach. *J. Braz. Soc. Mech. Sci. Eng.* **2017**, *39*, 1895–1907. [CrossRef]
68. Chan, C.-W.; Carson, L.; Smith, G.C.; Morelli, A.; Lee, S. Enhancing the Antibacterial Performance of Orthopaedic Implant Materials by Fibre Laser Surface Engineering. *Appl. Surf. Sci.* **2017**, *404*, 67–81. [CrossRef]
69. Tang, P.; Zhang, W.; Wang, Y.; Zhang, B.; Wang, H.; Lin, C.; Zhang, L. Effect of Superhydrophobic Surface of Titanium on *Staphylococcus Aureus* Adhesion. *J. Nanomater.* **2011**, *2011*, e178921. [CrossRef]
70. Gittens, R.A.; Scheideler, L.; Rupp, F.; Hyzy, S.L.; Geis-Gerstorfer, J.; Schwartz, Z.; Boyan, B.D. A Review on the Wettability of Dental Implant Surfaces II: Biological and Clinical Aspects. *Acta Biomater.* **2014**, *10*, 2907–2918. [CrossRef] [PubMed]
71. Giannella, R.A. Chapter 107—Infectious Enteritis and Proctocolitis and Bacterial Food Poisoning. In *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 9th ed.; Feldman, M., Friedman, L.S., Brandt, L.J., Eds.; W.B. Saunders: Philadelphia, PA, USA, 2010; pp. 1843–1887.e7. ISBN 978-1-4160-6189-2.
72. Phillips, D.H.; Arlt, V.M. Genotoxicity: Damage to DNA and Its Consequences. *EXS* **2009**, *99*, 87–110. [CrossRef]
73. Amin Yavari, S.; Wauthle, R.; van der Stok, J.; Riemslag, A.C.; Janssen, M.; Mulier, M.; Kruth, J.P.; Schrooten, J.; Weinans, H.; Zadpoor, A.A. Fatigue Behavior of Porous Biomaterials Manufactured Using Selective Laser Melting. *Mater. Sci. Eng. C* **2013**, *33*, 4849–4858. [CrossRef]
74. Fatigue | Fatigue Cracking, Stress Corrosion, Fracture Mechanics | Britannica. Available online: https://www.britannica.com/science/fatigue-materials-failure (accessed on 24 May 2024).
75. Teoh, S.H. Fatigue of Biomaterials: A Review. *Int. J. Fatigue* **2000**, *22*, 825–837. [CrossRef]
76. Allavikutty, R.; Gupta, P.; Santra, T.S.; Rengaswamy, J. Additive Manufacturing of Mg Alloys for Biomedical Applications: Current Status and Challenges. *Curr. Opin. Biomed. Eng.* **2021**, *18*, 100276. [CrossRef]

77. Zhang, T.; Wang, W.; Liu, J.; Wang, L.; Tang, Y.; Wang, K. A Review on Magnesium Alloys for Biomedical Applications. *Front. Bioeng. Biotechnol.* **2022**, *10*, 953344. [CrossRef]
78. Dutta, S.; Gupta, S.; Roy, M. Recent Developments in Magnesium Metal-Matrix Composites for Biomedical Applications: A Review. *ACS Biomater. Sci. Eng.* **2020**, *6*, 4748–4773. [CrossRef]
79. Yang, Y.; He, C.; Dianyu, E.; Yang, W.; Qi, F.; Xie, D.; Shen, L.; Peng, S.; Shuai, C. Mg Bone Implant: Features, Developments and Perspectives. *Mater. Des.* **2020**, *185*, 108259. [CrossRef]
80. Laires, M.; Monteiro, C.; Biosci, M.B.-F. Role of Cellular Magnesium in Health and Human Disease. *Front. Biosci.* **2004**, *9*, 262–276. [CrossRef] [PubMed]
81. Dong, J.; Lin, T.; Shao, H.; Wang, H.; Wang, X.; Song, K.; Li, Q. Advances in Degradation Behavior of Biomedical Magnesium Alloys: A Review. *J. Alloys Compd.* **2022**, *908*, 164600. [CrossRef]
82. Lu, Y.; Deshmukh, S.; Jones, I.; Chiu, Y.L. Biodegradable Magnesium Alloys for Orthopaedic Applications. *Biomater. Transl.* **2021**, *2*, 214. [CrossRef]
83. Amukarimi, S.; Mozafari, M. Biodegradable Magnesium-based Biomaterials: An Overview of Challenges and Opportunities. *MedComm* **2021**, *2*, 123–144. [CrossRef]
84. Agarwal, S.; Curtin, J.; Duffy, B.; Jaiswal, S. Biodegradable Magnesium Alloys for Orthopaedic Applications: A Review on Corrosion, Biocompatibility and Surface Modifications. *Mater. Sci. Eng. C* **2016**, *68*, 948–963. [CrossRef]
85. Campos Becerra, L.H.; Hernández Rodríguez, M.A.L.; Esquivel Solís, H.; Lesso Arroyo, R.; Torres Castro, A. Bio-Inspired Biomaterial Mg–Zn–Ca: A Review of the Main Mechanical and Biological Properties of Mg-Based Alloys. *Biomed. Phys. Eng. Express* **2020**, *6*, 042001. [CrossRef]
86. H, I.; Ns, M.; M, E. Mechanical and In Vitro Corrosion Properties of a Heat-Treated Mg-Zn-Ca-Mn Alloy as a Potential Bioresorbable Material. *Adv. Metall. Mater. Eng.* **2017**, *1*, 1–17.
87. Mohamed, A.; El-Aziz, A.M.; Breitinger, H.G. Study of the Degradation Behavior and the Biocompatibility of Mg–0.8Ca Alloy for Orthopedic Implant Applications. *J. Magnes. Alloys* **2019**, *7*, 249–257. [CrossRef]
88. Ahmadi, M.; Tabary, S.A.A.B.; Rahmatabadi, D.; Ebrahimi, M.S.; Abrinia, K.; Hashemi, R. Review of Selective Laser Melting of Magnesium Alloys: Advantages, Microstructure and Mechanical Characterizations, Defects, Challenges, and Applications. *J. Mater. Res. Technol.* **2022**, *19*, 1537–1562. [CrossRef]
89. Al-Maharma, A.Y.; Patil, S.P.; Markert, B. Effects of Porosity on the Mechanical Properties of Additively Manufactured Components: A Critical Review. *Mater. Res. Express* **2020**, *7*, 122001. [CrossRef]
90. Li, K.; Ji, C.; Bai, S.; Jiang, B.; Pan, F. Selective Laser Melting of Magnesium Alloys: Necessity, Formability, Performance, Optimization and Applications. *J. Mater. Sci. Technol.* **2023**, *154*, 65–93. [CrossRef]
91. Kopp, A.; Derra, T.; Müther, M.; Jauer, L.; Schleifenbaum, J.H.; Voshage, M.; Jung, O.; Smeets, R.; Kröger, N. Influence of Design and Postprocessing Parameters on the Degradation Behavior and Mechanical Properties of Additively Manufactured Magnesium Scaffolds. *Acta Biomater.* **2019**, *98*, 23–35. [CrossRef] [PubMed]
92. Li, Y.; Zhou, J.; Pavanram, P.; Leeflang, M.A.; Fockaert, L.I.; Pouran, B.; Tümer, N.; Schröder, K.-U.; Mol, J.M.C.; Weinans, H.; et al. Additively Manufactured Biodegradable Porous Magnesium. *Acta Biomater.* **2018**, *67*, 378–392. [CrossRef] [PubMed]
93. Qin, Y.; Wen, P.; Guo, H.; Xia, D.; Zheng, Y.; Jauer, L.; Poprawe, R.; Voshage, M.; Schleifenbaum, J.H. Additive Manufacturing of Biodegradable Metals: Current Research Status and Future Perspectives. *Acta Biomater.* **2019**, *98*, 3–22. [CrossRef]
94. Hyer, H.; Zhou, L.; Liu, Q.; Wu, D.; Song, S.; Bai, Y.; McWilliams, B.; Cho, K.; Sohn, Y. High Strength WE43 Microlattice Structures Additively Manufactured by Laser Powder Bed Fusion. *Materialia* **2021**, *16*, 101067. [CrossRef]
95. Xie, K.; Wang, N.; Guo, Y.; Zhao, S.; Tan, J.; Wang, L.; Li, G.; Wu, J.; Yang, Y.; Xu, W.; et al. Additively Manufactured Biodegradable Porous Magnesium Implants for Elimination of Implant-Related Infections: An in Vitro and in Vivo Study. *Bioact. Mater.* **2022**, *8*, 140–152. [CrossRef]
96. Li, Y.; Jahr, H.; Zhang, X.-Y.; Leeflang, M.A.; Li, W.; Pouran, B.; Tichelaar, F.D.; Weinans, H.; Zhou, J.; Zadpoor, A.A. Biodegradation-Affected Fatigue Behavior of Additively Manufactured Porous Magnesium. *Addit. Manuf.* **2019**, *28*, 299–311. [CrossRef]
97. Antoniac, I.; Miculescu, M.; Mănescu, V.; Stere, A.; Quan, P.H.; Păltânea, G.; Robu, A.; Earar, K. Magnesium-Based Alloys Used in Orthopedic Surgery. *Materials* **2022**, *15*, 1148. [CrossRef]
98. Zhang, J.; Yang, S.; Yang, X.; Xi, Z.; Zhao, L.; Cen, L.; Lu, E.; Yang, Y. Novel Fabricating Process for Porous Polyglycolic Acid Scaffolds by Melt-Foaming Using Supercritical Carbon Dioxide. *ACS Biomater. Sci. Eng.* **2018**, *4*, 694–706. [CrossRef]
99. Shuai, C.; Li, Y.; Wang, G.; Yang, W.; Peng, S.; Feng, P. Surface Modification of Nanodiamond: Toward the Dispersion of Reinforced Phase in Poly-l-Lactic Acid Scaffolds. *Int. J. Biol. Macromol.* **2019**, *126*, 1116–1124. [CrossRef]
100. Panayotov, I.V.; Orti, V.; Cuisinier, F.; Yachouh, J. Polyetheretherketone (PEEK) for Medical Applications. *J. Mater. Sci. Mater. Med.* **2016**, *27*, 118. [CrossRef] [PubMed]
101. Song, J.; Chen, J.; Xiong, X.; Peng, X.; Chen, D.; Pan, F. Research Advances of Magnesium and Magnesium Alloys Worldwide in 2021. *J. Magnes. Alloys* **2022**, *10*, 863–898. [CrossRef]
102. Reilly, D.T.; Burstein, A.H. The Elastic and Ultimate Properties of Compact Bone Tissue. *Journal of Biomechanics* **1975**, *8*, 393–405. [CrossRef] [PubMed]
103. Mirzaali, M.J.; Schwiedrzik, J.J.; Thaiwichai, S.; Best, J.P.; Michler, J.; Zysset, P.K.; Wolfram, U. Mechanical Properties of Cortical Bone and Their Relationships with Age, Gender, Composition and Microindentation Properties in the Elderly. *Bone* **2016**, *93*, 196–211. [CrossRef]

104. Morgan, E.F.; Unnikrisnan, G.U.; Hussein, A.I. Bone Mechanical Properties in Healthy and Diseased States. *Annu. Rev. Biomed. Eng.* **2018**, *20*, 119–143. [CrossRef]
105. Dong, X.N.; Acuna, R.L.; Luo, Q.; Wang, X. Orientation Dependence of Progressive Post-Yield Behavior of Human Cortical Bone in Compression. *J Biomech* **2012**, *45*, 2829–2834. [CrossRef]
106. American Institute of Chemical Engineers. *Properties and Selection: Nonferrous Alloys and Special-Purpose Materials*; ASM International: Detroit, MI, USA, 1990; ISBN 978-1-62708-162-7.
107. Elektron® WE43B 2018. Available online: https://www.luxfermeltechnologies.com/wp-content/uploads/2019/01/113909-Luxfer-MEL-Technologies-DS-467-Elektron-WE43B-ST1.pdf (accessed on 30 August 2024).
108. Charyeva, O.; Dakischew, O.; Sommer, U.; Heiss, C.; Schnettler, R.; Lips, K.S. Biocompatibility of Magnesium Implants in Primary Human Reaming Debris-Derived Cells Stem Cells in Vitro. *J. Orthop. Traumatol.* **2016**, *17*, 63. [CrossRef]
109. de Baaij, J.H.F.; Hoenderop, J.G.J.; Bindels, R.J.M. Magnesium in Man: Implications for Health and Disease. *Physiol. Rev.* **2015**, *95*, 1–46. [CrossRef]
110. Sanchez, A.H.M.; Luthringer, B.J.C.; Feyerabend, F.; Willumeit, R. Mg and Mg Alloys: How Comparable Are in Vitro and in Vivo Corrosion Rates? A Review. *Acta Biomater.* **2015**, *13*, 16–31. [CrossRef]
111. Xu, L.; Liu, X.; Sun, K.; Fu, R.; Wang, G. Corrosion Behavior in Magnesium-Based Alloys for Biomedical Applications. *Materials* **2022**, *15*, 2613. [CrossRef]
112. Williams, D. New Interests in Magnesium. *Med. Device Technol.* **2006**, *17*, 9–10. [PubMed]
113. Chakraborty Banerjee, P.; Al-Saadi, S.; Choudhary, L.; Harandi, S.E.; Singh, R. Magnesium Implants: Prospects and Challenges. *Materials* **2019**, *12*, 136. [CrossRef] [PubMed]
114. Zeng, R.; Dietzel, W.; Witte, F.; Hort, N.; Blawert, C. Progress and Challenge for Magnesium Alloys as Biomaterials. *Adv. Eng. Mater.* **2008**, *10*, B3–B14. [CrossRef]
115. Poinern, G.E.J.; Brundavanam, S.; Fawcett, D. Biomedical Magnesium Alloys: A Review of Material Properties, Surface Modifications and Potential as a Biodegradable Orthopaedic Implant. *Am. J. Biomed. Eng.* **2012**, *2*, 218–240. [CrossRef]
116. Song, G. Control of Biodegradation of Biocompatable Magnesium Alloys. *Corros. Sci.* **2007**, *49*, 1696–1701. [CrossRef]
117. Liu, Y.; Cheng, W.-l.; Gu, X.-j.; Liu, Y.-h.; Cui, Z.-q.; Wang, L.-f.; Wang, H.-x. Tailoring the Microstructural Characteristic and Improving the Corrosion Resistance of Extruded Dilute Mg–0.5Bi–0.5Sn Alloy by Microalloying with Mn. *J. Magnes. Alloys* **2021**, *9*, 1656–1668. [CrossRef]
118. Tang, W.; Li, Y.; Osimiri, L.; Zhang, C. Osteoblast-Specific Transcription Factor Osterix (Osx) Is an Upstream Regulator of Satb2 during Bone Formation. *J. Biol. Chem.* **2011**, *286*, 32995–33002. [CrossRef]
119. Osteoblasts & Osteoclasts: Function, Purpose & Anatomy. Available online: https://my.clevelandclinic.org/health/body/24871-osteoblasts-and-osteoclasts (accessed on 30 August 2024).
120. Tuna, S.H.; Karaca, E.; Aslan, I.; Pekkan, G.; Pekmez, N.Ö. Evaluation of Corrosion Resistance of Co-Cr Alloys Fabricated with Different Metal Laser Sintering Systems. *J. Adv. Prosthodont.* **2020**, *12*, 114. [CrossRef]
121. *ASTM F75-18*; Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants (UNS R30075). F75-23. ASTM International: West Conshohocken, PA, USA, 2023.
122. Acharya, S.; Soni, R.; Suwas, S.; Chatterjee, K. Additive Manufacturing of Co–Cr Alloys for Biomedical Applications: A Concise Review. *J. Mater. Res.* **2021**, *36*, 3746–3760. [CrossRef]
123. Liao, Y.; Hoffman, E.; Wimmer, M.; Fischer, A.; Jacobs, J.; Marks, L. CoCrMo Metal-on-Metal Hip Replacements. *Phys. Chem. Chem. Phys.* **2013**, *15*, 746–756. [CrossRef]
124. Sahoo, P.; Das, S.K.; Paulo Davim, J. Tribology of Materials for Biomedical Applications. *Mech. Behav. Biomater.* **2019**, *1*, 1–45. [CrossRef]
125. Dolgov, N.; Dikova, T.; Dzhendov, D.; Pavlova, D.; Simov, M. Mechanical Properties of Dental Co-Cr Alloys Fabricated via Casting and Selective Laser Melting. *Mater. Science. Non-Equilib. Phase Transform.* **2016**, *2*, 3–7.
126. Li, H.; Wang, M.; Lou, D.; Xia, W.; Fang, X. Microstructural Features of Biomedical Cobalt–Chromium–Molybdenum (CoCrMo) Alloy from Powder Bed Fusion to Aging Heat Treatment. *J. Mater. Sci. Technol.* **2020**, *45*, 146–156. [CrossRef]
127. Konieczny, B.; Szczesio-Wlodarczyk, A.; Sokolowski, J.; Bociong, K. Challenges of Co–Cr Alloy Additive Manufacturing Methods in Dentistry—The Current State of Knowledge (Systematic Review). *Materials* **2020**, *13*, 3524. [CrossRef] [PubMed]
128. Li, H.; Fu, M.W.; Lu, J.; Yang, H. Ductile Fracture: Experiments and Computations. *Int. J. Plast.* **2011**, *27*, 147–180. [CrossRef]
129. Lee, S.H.; Nomura, N.; Chiba, A. Significant Improvement in Mechanical Properties of Biomedical Co-Cr-Mo Alloys with Combination of N Addition and Cr-Enrichment. *Mater. Trans.* **2008**, *49*, 260–264. [CrossRef]
130. Chen, Q.; Thouas, G.A. Metallic Implant Biomaterials. *Mater. Sci. Eng. R Rep.* **2015**, *87*, 1–57. [CrossRef]
131. Davis, J.R. *Handbook of Materials for Medical Devices*; ASM International: Materials Park, OH, USA, 2003.
132. Bandyopadhyay, A.; Avila, J.D.; Mitra, I.; Bose, S. *Additive Manufacturing of Cobalt-Chromium Alloy Biomedical Devices*; ASM International: Detroit, MI, USA, 2022. [CrossRef]
133. Acharya, S.; Gopal, V.; Gupta, S.K.; Nilawar, S.; Manivasagam, G.; Suwas, S.; Chatterjee, K. Anisotropy of Additively Manufactured Co–28Cr–6Mo Influences Mechanical Properties and Biomedical Performance. *ACS Appl. Mater. Interfaces* **2022**, *14*, 21906–21915. [CrossRef]
134. Ren, F.; Zhu, W.; Chu, K. Fabrication, Tribological and Corrosion Behaviors of Ultra-Fine Grained Co–28Cr–6Mo Alloy for Biomedical Applications. *J. Mech. Behav. Biomed. Mater.* **2016**, *60*, 139–147. [CrossRef]

135. Sánchez-De Jesús, F.; Bolarín-Miró, A.M.; Torres-Villaseñor, G.; Cortés-Escobedo, C.A.; Betancourt-Cantera, J.A. Mechanical Alloying of Biocompatible Co–28Cr–6Mo Alloy. *J. Mater. Sci. Mater. Med.* **2010**, *21*, 2021–2026. [CrossRef]
136. Efremenko, B.; Zurnadzhy, V.; Chabak, Y.; Lekatou, A.; Horňak, P.; Vojtko, M.; Efremenko, V. Microstructure-Properties Characterization of Selective Laser Melted Biomedical Co-28Cr-6Mo Alloy. *Mater. Sci. Forum* **2023**, *1081*, 143–148. [CrossRef]
137. Iatecola, A.; Longhitano, G.A.; Antunes, L.H.M.; Jardini, A.L.; Miguel, E.d.C.; Béreš, M.; Lambert, C.S.; Andrade, T.N.; Buchaim, R.L.; Buchaim, D.V.; et al. Osseointegration Improvement of Co-Cr-Mo Alloy Produced by Additive Manufacturing. *Pharmaceutics* **2021**, *13*, 724. [CrossRef] [PubMed]
138. Li, C.-L.; Choi, S.-W.; Oh, J.M.; Hong, J.-K.; Yeom, J.-T.; Kang, J.-H.; Mei, Q.-S.; Park, C.H. Bimodal Grain Structures and Tensile Properties of a Biomedical Co–20Cr–15W–10Ni Alloy with Different Pre-Strains. *Rare Met.* **2021**, *40*, 20–30. [CrossRef]
139. Ueki, K.; Ueda, K.; Nakai, M.; Nakano, T.; Narushima, T. Microstructural Changes During Plastic Deformation and Corrosion Properties of Biomedical Co-20Cr-15W-10Ni Alloy Heat-Treated at 873 K. *Met. Mater. Trans. A* **2018**, *49*, 2393–2404. [CrossRef]
140. Ueki, K.; Ueda, K.; Narushima, T. Microstructure and Mechanical Properties of Heat-Treated Co-20Cr-15W-10Ni Alloy for Biomedical Application. *Met. Mater. Trans. A* **2016**, *47*, 2773–2782. [CrossRef]
141. Li, C.-L.; Oh, J.M.; Choi, S.-W.; Hong, J.-K.; Yeom, J.-T.; Mei, X.-M.; Mei, Q.; Yu, Z.; Park, C.H. Study on Microstructure and Mechanical Property of a Biomedical Co-20Cr-15W-10Ni Alloy during Multi-Pass Thermomechanical Processing. *Mater. Sci. Eng. A* **2020**, *785*, 139388. [CrossRef]
142. *ASTM F1091-20*; Standard Specification for Wrought Cobalt-20Chromium-15Tungsten-10Nickel Alloy Surgical Fixation Wire (UNS R30605). ASTM International: West Conshohocken, PA, USA, 2020.
143. Narushima, T. 19—New-Generation Metallic Biomaterials. In *Metals for Biomedical Devices*, 2nd ed.; Niinomi, M., Ed.; Woodhead Publishing Series in Biomaterials; Woodhead Publishing: Sawsto, UK, 2019; pp. 495–521. ISBN 978-0-08-102666-3.
144. Hiyama, K.; Ueki, K.; Ueda, K.; Narushima, T. Probing Plastic Deformation-Related Properties in Static Recrystallized Co–Cr–Fe–Ni–Mo Alloy for Biomedical Applications. *Mater. Sci. Eng. A* **2024**, *899*, 146458. [CrossRef]
145. *ASTM F1058-16*; Standard Specification for Wrought 40Cobalt-20Chromium-16Iron-15Nickel-7Molybdenum Alloy Wire and Strip for Surgical Implant Applications (UNS R30003 and UNS R30008). ASTM International: West Conshohocken, PA, USA, 2017.
146. Czarnek, K.; Terpiłowska, S.; Siwicki, A.K. Review Paper Selected Aspects of the Action of Cobalt Ions in the Human Body. *cejoi* **2015**, *2*, 236–242. [CrossRef]
147. Ortega, R.; Bresson, C.; Fraysse, A.; Sandre, C.; Devès, G.; Gombert, C.; Tabarant, M.; Bleuet, P.; Seznec, H.; Simionovici, A.; et al. Cobalt Distribution in Keratinocyte Cells Indicates Nuclear and Perinuclear Accumulation and Interaction with Magnesium and Zinc Homeostasis. *Toxicol. Lett.* **2009**, *188*, 26–32. [CrossRef]
148. Cobalt Poisoning: MedlinePlus Medical Encyclopedia. Available online: https://medlineplus.gov/ency/article/002495.htm (accessed on 18 June 2024).
149. Chen, R.J.; Lee, V.R. Cobalt Toxicity. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
150. SA Health Chromium: Health Effects. Available online: https://www.sahealth.sa.gov.au/wps/wcm/connect/Public+Content/SA+Health+Internet/Conditions/Chemicals+and+contaminants/Chromium+health+effects (accessed on 30 August 2024).
151. *Concerns about Metal-on-Metal Hip Implants*; FDA: Silver Spring, MD, USA, 2023. Available online: https://www.fda.gov/medical-devices/metal-metal-hip-implants/concerns-about-metal-metal-hip-implants (accessed on 30 August 2024).
152. Definition of Hyperplasia—NCI Dictionary of Cancer Terms—NCI. Available online: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hyperplasia (accessed on 24 May 2024).
153. Karimi, S.; Alfantazi, A.M. Ion Release and Surface Oxide Composition of AISI 316L, Co-28Cr-6Mo, and Ti-6Al-4V Alloys Immersed in Human Serum Albumin Solutions. *Mater. Sci. Eng. C* **2014**, *40*, 435–444. [CrossRef]
154. Ammarullah, M.I.; Afif, I.Y.; Maula, M.I.; Winarni, T.I.; Tauviqirrahman, M.; Akbar, I.; Basri, H.; van der Heide, E.; Jamari, J. Tresca Stress Simulation of Metal-on-Metal Total Hip Arthroplasty during Normal Walking Activity. *Materials* **2021**, *14*, 7554. [CrossRef] [PubMed]
155. Gotman, I. Characteristics of Metals Used in Implants. *J. Endourol.* **1997**, *11*, 383–389. [CrossRef] [PubMed]
156. Suárez, J.V.; Gómez, J.F.; García, M.P.; Pérez, J.R. Poisoning by Metals Used in Prosthetic Materials in Orthopedics and Its Current Management. *Rev. Cuba. Ortop. Traumatol.* **2021**, *35*, 1–10.
157. Argentieri, M.; Kommala, D.; Schabowsky, C.N. Cobalt Chromium (Co-Cr) Safety Profile. Available online: https://www.fda.gov/media/165145/download (accessed on 30 August 2024).
158. Fu, W.; Liu, S.; Jiao, J.; Xie, Z.; Huang, X.; Lu, Y.; Liu, H.; Hu, S.; Zuo, E.; Kou, N. Wear Resistance and Biocompatibility of Co-Cr Dental Alloys Fabricated with CAST and SLM Techniques. *Materials* **2022**, *15*, 3263. [CrossRef]
159. Duarte, I.; Mendonça, R.F.; Korkes, K.L.; Lazzarini, R.; Hafner, M.d.F.S. Nickel, Chromium and Cobalt: The Relevant Allergens in Allergic Contact Dermatitis. Comparative Study between Two Periods: 1995–2002 and 2003–2015. *An. Bras. Dermatol.* **2018**, *93*, 59. [CrossRef]
160. Pais, I.; Fehér, M.; Farkas, E.; Szabó, Z.; Cornides, I. Titanium as a New Trace Element. *Commun. Soil Sci. Plant Anal.* **1977**, *8*, 407–410. [CrossRef]
161. Rupp, F.; Gittens, R.A.; Scheideler, L.; Marmur, A.; Boyan, B.D.; Schwartz, Z.; Geis-Gerstorfer, J. A Review on the Wettability of Dental Implant Surfaces I: Theoretical and Experimental Aspects. *Acta Biomater.* **2014**, *10*, 2894–2906. [CrossRef]
162. Niinomi, M.; Liu, Y.; Nakai, M.; Liu, H.; Li, H. Biomedical Titanium Alloys with Young's Moduli Close to That of Cortical Bone. *Regen. Biomater.* **2016**, *3*, 173–185. [CrossRef]

163. Aufa, A.N.; Hassan, M.Z.; Ismail, Z. Recent Advances in Ti-6Al-4V Additively Manufactured by Selective Laser Melting for Biomedical Implants: Prospect Development. *J. Alloys Compd.* **2022**, *896*, 163072. [CrossRef]
164. Nicholson, J.W. Titanium Alloys for Dental Implants: A Review. *Prosthesis* **2020**, *2*, 100–116. [CrossRef]
165. Sarraf, M.; Rezvani Ghomi, E.; Alipour, S.; Ramakrishna, S.; Liana Sukiman, N. A State-of-the-Art Review of the Fabrication and Characteristics of Titanium and Its Alloys for Biomedical Applications. *Bio-Des. Manuf.* **2022**, *5*, 371–395. [CrossRef] [PubMed]
166. Niinomi, M.; Nakai, M. Titanium-Based Biomaterials for Preventing Stress Shielding between Implant Devices and Bone. *Int. J. Biomater.* **2011**, *2011*, 836587. [CrossRef] [PubMed]
167. Menezes, P.; Misra, M.; Kumar, P. *Tribology of Additively Manufactured Materials: Fundamentals, Modeling, and Applications*; Elsevier: Amsterdam, The Netherlands, 2022.
168. Bocchetta, P.; Chen, L.-Y.; Tardelli, J.D.C.; dos Reis, A.C.; Almeraya-Calderón, F.; Leo, P. Passive Layers and Corrosion Resistance of Biomedical Ti-6Al-4V and β-Ti Alloys. *Coatings* **2021**, *11*, 487. [CrossRef]
169. Rack, H.J.; Qazi, J.I. Titanium Alloys for Biomedical Applications. *Mater. Sci. Eng. C* **2006**, *26*, 1269–1277. [CrossRef]
170. Marin, E.; Lanzutti, A. Biomedical Applications of Titanium Alloys: A Comprehensive Review. *Materials* **2023**, *17*, 114. [CrossRef]
171. Chen, L.-Y.; Cui, Y.-W.; Zhang, L.-C. Recent Development in Beta Titanium Alloys for Biomedical Applications. *Metals* **2020**, *10*, 1139. [CrossRef]
172. Kodama, T. Study on biocompatibility of titanium alloys. *Kokubyo Gakkai Zasshi* **1989**, *56*, 263–288. [CrossRef]
173. Lemons, J.E.; Niemann, K.M.W.; Weiss, A.B. Biocompatibility Studies on Surgical-Grade Titanium-, Cobalt-, and Iron-Base Alloys. *J. Biomed. Mater. Res.* **1976**, *10*, 549–553. [CrossRef]
174. Vijayavenkataraman, S.; Gopinath, A.; Lu, W.F. A New Design of 3D-Printed Orthopedic Bone Plates with Auxetic Structures to Mitigate Stress Shielding and Improve Intra-Operative Bending. *Bio-Des. Manuf.* **2020**, *3*, 98–108. [CrossRef]
175. Froes, F.; Qian, M. *Titanium in Medical and Dental Applications*; Woodhead Publishing: Sawston, UK, 2018; ISBN 978-0-12-812457-4.
176. Rowe, P.; Koller, A.; Sharma, S. Physiology, Bone Remodeling. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
177. Lewallen, E.A.; Riester, S.M.; Bonin, C.A.; Kremers, H.M.; Dudakovic, A.; Kakar, S.; Cohen, R.C.; Westendorf, J.J.; Lewallen, D.G.; van Wijnen, A.J. Biological Strategies for Improved Osseointegration and Osteoinduction of Porous Metal Orthopedic Implants. *Tissue Eng. Part B Rev.* **2015**, *21*, 218–230. [CrossRef]
178. *ASTM B265-20a*; Standard Specification for Titanium and Titanium Alloy Strip, Sheet, and Plate. ASTM International: West Conshohocken, PA, USA, 2010.
179. Elias, C.N.; Lima, J.H.C.; Valiev, R.; Meyers, M.A. Biomedical Applications of Titanium and Its Alloys. *JOM* **2008**, *60*, 46–49. [CrossRef]
180. Khodaei, M.; Hossein Kelishadi, S. The Effect of Different Oxidizing Ions on Hydrogen Peroxide Treatment of Titanium Dental Implant. *Surf. Coat. Technol.* **2018**, *353*, 158–162. [CrossRef]
181. Dissemination of Wear Particles to the Liver, Spleen, and Ab...: JBJS. Available online: https://journals-lww-com.ezproxy1.lib.asu.edu/jbjsjournal/abstract/2000/04000/dissemination_of_wear_particles_to_the_liver,.2.aspx (accessed on 2 November 2023).
182. Semlitsch, M.F.; Weber, H.; Streicher, R.M.; Schön, R. Joint Replacement Components Made of Hot-Forged and Surface-Treated Ti-6Al-7Nb Alloy. *Biomaterials* **1992**, *13*, 781–788. [CrossRef] [PubMed]
183. Sansone, V.; Pagani, D.; Melato, M. The Effects on Bone Cells of Metal Ions Released from Orthopaedic Implants. A Review. *Clin. Cases Min. Bone Metab.* **2013**, *10*, 34–40. [CrossRef] [PubMed]
184. El-Hajje, A.; Kolos, E.C.; Wang, J.K.; Maleksaeedi, S.; He, Z.; Wiria, F.E.; Choong, C.; Ruys, A.J. Physical and Mechanical Characterisation of 3D-Printed Porous Titanium for Biomedical Applications. *J. Mater. Sci. Mater. Med.* **2014**, *25*, 2471–2480. [CrossRef]
185. Soro, N.; Brassart, L.; Chen, Y.; Veidt, M.; Attar, H.; Dargusch, M.S. Finite Element Analysis of Porous Commercially Pure Titanium for Biomedical Implant Application. *Mater. Sci. Eng. A* **2018**, *725*, 43–50. [CrossRef]
186. Haslauer, C.M.; Springer, J.C.; Harrysson, O.L.A.; Loboa, E.G.; Monteiro-Riviere, N.A.; Marcellin-Little, D.J. In Vitro Biocompatibility of Titanium Alloy Discs Made Using Direct Metal Fabrication. *Med. Eng. Phys.* **2010**, *32*, 645–652. [CrossRef]
187. Oliveira, J.P.; LaLonde, A.D.; Ma, J. Processing Parameters in Laser Powder Bed Fusion Metal Additive Manufacturing. *Mater. Des.* **2020**, *193*, 108762. [CrossRef]
188. Beaman, J.J. Historical Background. *Fundam. Laser Powder Bed Fusion Met.* **2021**, *1*, 1–14. [CrossRef]
189. Mazzoli, A. Selective Laser Sintering in Biomedical Engineering. *Med. Biol. Eng. Comput.* **2012**, *51*, 245–256. [CrossRef]
190. Gokuldoss, P.K.; Kolla, S.; Eckert, J. Additive Manufacturing Processes: Selective Laser Melting, Electron Beam Melting and Binder Jetting—Selection Guidelines. *Materials* **2017**, *10*, 672. [CrossRef] [PubMed]
191. Saptarshi, S.M.; Zhou, C. Chapter 2—Basics of 3D Printing: Engineering Aspects. In *3D Printing in Orthopaedic Surgery*; Dipaola, M., Wodajo, F.M., Eds.; Elsevier: Amsterdam, The Netherlands, 2019; pp. 17–30. ISBN 978-0-323-58118-9.
192. Kantaros, A.; Ganetsos, T.; Petrescu, F.I.T. Three-Dimensional Printing and 3D Scanning: Emerging Technologies Exhibiting High Potential in the Field of Cultural Heritage. *Appl. Sci.* **2023**, *13*, 4777. [CrossRef]
193. Kumar, S. Selective Laser Sintering: A Qualitative and Objective Approach. *JOM* **2003**, *55*, 43–47. [CrossRef]
194. Garcia, J.; Yang, Z.L.; Mongrain, R.; Leask, R.L.; Lachapelle, K. 3D Printing Materials and Their Use in Medical Education: A Review of Current Technology and Trends for the Future. *BMJ Simul. Technol. Enhanc. Learn.* **2018**, *4*, 27. [CrossRef]
195. Yusuf, S.M.; Cutler, S.; Gao, N. Review: The Impact of Metal Additive Manufacturing on the Aerospace Industry. *Metals* **2019**, *9*, 1286. [CrossRef]

196. Wahlström, T.; Sahlström, J. Additive Manufacturing in Production. Master's Thesis, Lund University, Lund, Sweden, 2016.
197. Rajendran, S.; Palani, G.; Kanakaraj, A.; Shanmugam, V.; Veerasimman, A.; Gądek, S.; Korniejenko, K.; Marimuthu, U. Metal and Polymer Based Composites Manufactured Using Additive Manufacturing—A Brief Review. *Polymers* **2023**, *15*, 2564. [CrossRef]
198. Flodberg, G.; Pettersson, H.; Yang, L. Pore Analysis and Mechanical Performance of Selective Laser Sintered Objects. *Addit. Manuf.* **2018**, *24*, 307–315. [CrossRef]
199. Riza, S.H.; Masood, S.H.; Rashid, R.A.R.; Chandra, S. Selective Laser Sintering in Biomedical Manufacturing. *Met. Biomater. Process. Med. Device Manuf.* **2020**, 193–233. [CrossRef]
200. Mangano, F.; Bazzoli, M.; Tettamanti, L.; Farronato, D.; Maineri, M.; Macchi, A.; Mangano, C. Custom-Made, Selective Laser Sintering (SLS) Blade Implants as a Non-Conventional Solution for the Prosthetic Rehabilitation of Extremely Atrophied Posterior Mandible. *Lasers Med. Sci.* **2013**, *28*, 1241–1247. [CrossRef]
201. Lee Ventola, C. Medical Applications for 3D Printing: Current and Projected Uses. *Pharm. Ther.* **2014**, *39*, 704.
202. Aimar, A.; Palermo, A.; Innocenti, B. The Role of 3D Printing in Medical Applications: A State of the Art. *J. Healthc. Eng.* **2019**, *2019*, 5340616. [CrossRef] [PubMed]
203. Sing, S.L.; An, J.; Yeong, W.Y.; Wiria, F.E. Laser and Electron-Beam Powder-Bed Additive Manufacturing of Metallic Implants: A Review on Processes, Materials and Designs. *J. Orthop. Res.* **2016**, *34*, 369–385. [CrossRef]
204. Wei, S.; Zhang, J.; Zhang, L.; Zhang, Y.; Song, B.; Wang, X.; Fan, J.; Liu, Q.; Shi, Y. Laser Powder Bed Fusion Additive Manufacturing of NiTi Shape Memory Alloys: A Review. *Int. J. Extrem. Manuf.* **2023**, *5*, 032001. [CrossRef]
205. Olakanmi, E.O.; Cochrane, R.F.; Dalgarno, K.W. A Review on Selective Laser Sintering/Melting (SLS/SLM) of Aluminium Alloy Powders: Processing, Microstructure, and Properties. *Prog. Mater. Sci.* **2015**, *74*, 401–477. [CrossRef]
206. Kruth, J.P.; Vandenbroucke, B.; Vaerenbergh, J.V.; Mercelis, P. Benchmarking of Different SLS/SLM Processes as Rapid Manufacturing Techniques. In Proceedings of the International Conference Polymers & Moulds Innovations (PMI), Gent, Belgium, 20–23 April 2005.
207. Klocke, F.; Arntz, K.; Teli, M.; Winands, K.; Wegener, M.; Oliari, S. State-of-the-Art Laser Additive Manufacturing for Hot-Work Tool Steels. *Procedia CIRP* **2017**, *63*, 58–63. [CrossRef]
208. Hassan, M.S.; Billah, K.M.M.; Hall, S.E.; Sepulveda, S.; Regis, J.E.; Marquez, C.; Cordova, S.; Whitaker, J.; Robison, T.; Keating, J.; et al. Selective Laser Sintering of High-Temperature Thermoset Polymer. *J. Compos. Sci.* **2022**, *6*, 41. [CrossRef]
209. Fang, Z.C.; Wu, Z.L.; Huang, C.G.; Wu, C.W. Review on Residual Stress in Selective Laser Melting Additive Manufacturing of Alloy Parts. *Opt. Laser Technol.* **2020**, *129*, 106283. [CrossRef]
210. Zhang, W.-N.; Wang, L.-Z.; Feng, Z.-X.; Chen, Y.-M. Research Progress on Selective Laser Melting (SLM) of Magnesium Alloys: A Review. *Optik* **2020**, *207*, 163842. [CrossRef]
211. Bartolo, P.; Kruth, J.P.; Silva, J.; Levy, G.; Malshe, A.; Rajurkar, K.; Mitsuishi, M.; Ciurana, J.; Leu, M. Biomedical Production of Implants by Additive Electro-Chemical and Physical Processes. *CIRP Ann. Manuf. Technol.* **2012**, *61*, 635–655. [CrossRef]
212. Praneeth, J.; Venkatesh, S.; Krishn, L.S. Process Parameters Influence on Mechanical Properties of AlSi10Mg by SLM. *Mater. Today Proc.* **2023**. [CrossRef]
213. Mohanty, S.; Gokuldoss Prashanth, K. Metallic Coatings through Additive Manufacturing: A Review. *Materials* **2023**, *16*, 2325. [CrossRef] [PubMed]
214. Nagarajan, B.; Hu, Z.; Song, X.; Zhai, W.; Wei, J. Development of Micro Selective Laser Melting: The State of the Art and Future Perspectives. *Engineering* **2019**, *5*, 702–720. [CrossRef]
215. Keshavarzkermani, A.; Sadowski, M.; Ladani, L. Direct Metal Laser Melting of Inconel 718: Process Impact on Grain Formation and Orientation. *J. Alloys Compd.* **2018**, *736*, 297–305. [CrossRef]
216. Aravind Shanmugasundaram, S.; Razmi, J.; Mian, M.J.; Ladani, L. Mechanical Anisotropy and Surface Roughness in Additively Manufactured Parts Fabricated by Stereolithography (SLA) Using Statistical Analysis. *Materials* **2020**, *13*, 2496. [CrossRef]
217. Ladani, L. Local and Global Mechanical Behavior and Microstructure of Ti6Al4V Parts Built Using Electron Beam Melting Technology. *Met. Mater. Trans. A* **2015**, *46*, 3835–3841. [CrossRef]
218. Romano, J.; Ladani, L.; Razmi, J.; Sadowski, M. Temperature Distribution and Melt Geometry in Laser and Electron-Beam Melting Processes—A Comparison among Common Materials. *Addit. Manuf.* **2015**, *8*, 1–11. [CrossRef]
219. Andreotta, R.; Ladani, L.; Brindley, W. Finite Element Simulation of Laser Additive Melting and Solidification of Inconel 718 with Experimentally Tested Thermal Properties. *Finite Elem. Anal. Des.* **2017**, *135*, 36–43. [CrossRef]
220. Ahsan, F.; Ladani, L. Temperature Profile, Bead Geometry, and Elemental Evaporation in Laser Powder Bed Fusion Additive Manufacturing Process. *JOM* **2020**, *72*, 429–439. [CrossRef]
221. Mullen, L.; Stamp, R.C.; Brooks, W.K.; Jones, E.; Sutcliffe, C.J. Selective Laser Melting: A Regular Unit Cell Approach for the Manufacture of Porous, Titanium, Bone in-Growth Constructs, Suitable for Orthopedic Applications. *J. Biomed. Mater. Res. B Appl. Biomater.* **2009**, *89*, 325–334. [CrossRef]
222. Pimenov, D.Y.; Berti, L.F.; Pintaude, G.; Peres, G.X.; Chaurasia, Y.; Khanna, N.; Giasin, K. Influence of Selective Laser Melting Process Parameters on the Surface Integrity of Difficult-to-Cut Alloys: Comprehensive Review and Future Prospects. *Int. J. Adv. Manuf. Technol.* **2023**, *127*, 1071–1102. [CrossRef]
223. Aboulkhair, N.T.; Simonelli, M.; Parry, L.; Ashcroft, I.; Tuck, C.; Hague, R. 3D Printing of Aluminium Alloys: Additive Manufacturing of Aluminium Alloys Using Selective Laser Melting. *Prog. Mater. Sci.* **2019**, *106*, 100578. [CrossRef]

224. Körner, C. Additive Manufacturing of Metallic Components by Selective Electron Beam Melting—A Review. *Int. Mater. Rev.* **2016**, *61*, 361–377. [CrossRef]
225. Tamayo, J.A.; Riascos, M.; Vargas, C.A.; Baena, L.M. Additive Manufacturing of Ti6Al4V Alloy via Electron Beam Melting for the Development of Implants for the Biomedical Industry. *Heliyon* **2021**, *7*, e06892. [CrossRef] [PubMed]
226. Murr, L.E. Metallurgy of Additive Manufacturing: Examples from Electron Beam Melting. *Addit. Manuf.* **2015**, *5*, 40–53. [CrossRef]
227. Zhang, L.-C.; Liu, Y.; Li, S.; Hao, Y. Additive Manufacturing of Titanium Alloys by Electron Beam Melting: A Review. *Adv. Eng. Mater.* **2018**, *20*, 1700842. [CrossRef]
228. Zhang, Y.; Wu, L.; Guo, X.; Kane, S.; Deng, Y.; Jung, Y.-G.; Lee, J.-H.; Zhang, J. Additive Manufacturing of Metallic Materials: A Review. *J. Mater. Eng Perform* **2018**, *27*, 1–13. [CrossRef]
229. Alkhatib, S.E.; Sercombe, T.B. High Strain-Rate Response of Additively Manufactured Light Metal Alloys. *Mater. Des.* **2022**, *217*, 110664. [CrossRef]
230. Matos, G.R.M. Surface Roughness of Dental Implant and Osseointegration. *J. Maxillofac. Oral Surg.* **2021**, *20*, 1–4. [CrossRef]
231. Hao, L.; Harris, R. Customised Implants for Bone Replacement and Growth. In *Bio-Materials and Prototyping Applications in Medicine*; Bártolo, P., Bidanda, B., Eds.; Springer: Boston, MA, USA, 2008; pp. 79–107. ISBN 978-0-387-47683-4.
232. *ISO/ASTM 52900:2021(en)*; Additive Manufacturing—General Principles—Fundamentals and Vocabulary. International Organization for Standardization: Geneva, Switzerland, 2021. Available online: https://www.iso.org/obp/ui/#iso:std:iso-astm:52900:ed-2:v1:en (accessed on 22 April 2024).
233. Ziaee, M.; Crane, N.B. Binder Jetting: A Review of Process, Materials, and Methods. *Addit. Manuf.* **2019**, *28*, 781–801. [CrossRef]
234. Sachs, E.M.; Haggerty, J.S.; Cima, M.J.; Williams, P.A. Three-Dimensional Printing Techniques. US5204055A, 20 April 1993.
235. Li, M.; Du, W.; Elwany, A.; Pei, Z.; Ma, C. Metal Binder Jetting Additive Manufacturing: A Literature Review. *J. Manuf. Sci. Eng.* **2020**, *142*, 090801. [CrossRef]
236. Fayazfar, H.; Salarian, M.; Rogalsky, A.; Sarker, D.; Russo, P.; Paserin, V.; Toyserkani, E. A Critical Review of Powder-Based Additive Manufacturing of Ferrous Alloys: Process Parameters, Microstructure and Mechanical Properties. *Mater. Des.* **2018**, *144*, 98–128. [CrossRef]
237. Mostafaei, A.; Elliott, A.M.; Barnes, J.E.; Li, F.; Tan, W.; Cramer, C.L.; Nandwana, P.; Chmielus, M. Binder Jet 3D Printing—Process Parameters, Materials, Properties, Modeling, and Challenges. *Prog. Mater. Sci.* **2021**, *119*, 100707. [CrossRef]
238. Chin, S.Y.; Dikshit, V.; Meera Priyadarshini, B.; Zhang, Y. Powder-Based 3D Printing for the Fabrication of Device with Micro and Mesoscale Features. *Micromachines* **2020**, *11*, 658. [CrossRef] [PubMed]
239. Bai, Y.; Wagner, G.; Williams, C.B. *Effect of Bimodal Powder Mixture on Powder Packing Density and Sintered Density in Binder Jetting of Metals*; University of Texas at Austin: Austin, TX, USA, 2015; Available online: https://hdl.handle.net/2152/89376 (accessed on 30 August 2024).
240. Inaekyan, K.; Paserin, V.; Bailon-Poujol, I.; Brailovski, V. Binder-jetting additive manufacturing with water atomized iron powders. In Proceedings of the AMPM 2016, Boston, MA, USA, 5–7 June 2016.
241. Ghoussoub, J.N.; Tang, Y.T.; Panwisawas, C.; Németh, A.; Reed, R.C. On the Influence of Alloy Chemistry and Processing Conditions on Additive Manufacturability of Ni-Based Superalloys. In *Superalloys 2020*; Tin, S., Hardy, M., Clews, J., Cormier, J., Feng, Q., Marcin, J., O'Brien, C., Suzuki, A., Eds.; Springer International Publishing: Cham, Switzerland, 2020; pp. 153–162.
242. Miyanaji, H.; Zhang, S.; Lassell, A.; Zandinejad, A.; Yang, L. Optimal Process Parameters for 3D Printing of Porcelain Structures. *Procedia Manuf.* **2016**, *5*, 870–887. [CrossRef]
243. Do, T.; Bauder, T.J.; Suen, H.; Rego, K.; Yeom, J.; Kwon, P. Additively Manufactured Full-Density Stainless Steel 316L with Binder Jet Printing. In Proceedings of the ASME 2018 13th International Manufacturing Science and Engineering Conference, College Station, TX, USA, 18–22 June 2018; American Society of Mechanical Engineers Digital Collection: New York, NY, USA, 2018.
244. Sun, L.; Kim, Y.H.; Kim, D.; Kwon, P. Densification and Properties of 420 Stainless Steel Produced by Three-Dimensional Printing With Addition of Si3N4 Powder. *J. Manuf. Sci. Eng.* **2009**, *131*, 061001. [CrossRef]
245. Kumar, A.; Bai, Y.; Eklund, A.; Williams, C.B. Effects of Hot Isostatic Pressing on Copper Parts Fabricated via Binder Jetting. *Procedia Manuf.* **2017**, *10*, 935–944. [CrossRef]
246. Sa'ude, N.; Ibrahim, M.; Ismail, N.A.; Ibrahim, R. Freeform Fabrication of Titanium Based Powder by Inkjet 3D Printer. In Proceedings of the International Conference on Leading Edge Manufacturing in 21st Century, Fukuoka, Japan, 8 September 2011.
247. Nandwana, P.; Elliott, A.; Siddel, D.; Merriman, A.; Peter, W.; Babu, S. Powder Bed Binder Jet 3D Printing of Inconel 718: Densification, Microstructural Evolution and Challenges. *Curr. Opin. Solid State Mater. Sci.* **2017**, *21*, 207–218. [CrossRef]
248. Allen, S.M.; Sachs, E.M. Three-Dimensional Printing of Metal Parts for Tooling and Other Applications. *Met. Mater.* **2000**, *6*, 589–594. [CrossRef]
249. Bailey, A.C.; Merriman, A.; Elliot, A.; Basti, M.M. Preliminary Testing of Nanoparticle Effectiveness in Binder Jetting Applications. In Proceedings of the International Solid Freeform Fabrication Symposium, Austin, TX, USA, 8 August 2016.
250. Zhou, Z.; Buchanan, F.; Mitchell, C.; Dunne, N. Printability of Calcium Phosphate: Calcium Sulfate Powders for the Application of Tissue Engineered Bone Scaffolds Using the 3D Printing Technique. *Mater. Sci. Eng. C* **2014**, *38*, 1–10. [CrossRef]
251. Xiong, Y.; Qian, C.; Sun, J. Fabrication of Porous Titanium Implants by Three-Dimensional Printing and Sintering at Different Temperatures. *Dent. Mater. J.* **2012**, *31*, 815–820. [CrossRef]
252. Sheydaeian, E.; Fishman, Z.; Vlasea, M.; Toyserkani, E. On the Effect of throughout Layer Thickness Variation on Properties of Additively Manufactured Cellular Titanium Structures. *Addit. Manuf.* **2017**, *18*, 40–47. [CrossRef]

253. Center for Devices and Radiological Health. *Technical Considerations for Additive Manufactured Medical Devices Guidance*; FDA: Silver Spring, MD, USA, 2018.
254. Learn if a Medical Device Has Been Cleared by FDA for Marketing. Available online: https://www.fda.gov/medical-devices/consumers-medical-devices/learn-if-medical-device-has-been-cleared-fda-marketing (accessed on 30 August 2024).
255. Morrison, R.J.; Kashlan, K.N.; Flanangan, C.L.; Wright, J.K.; Green, G.E.; Hollister, S.J.; Weatherwax, K.J. Regulatory Considerations in the Design and Manufacturing of Implantable 3D-Printed Medical Devices. *Clin. Transl. Sci.* **2015**, *8*, 594–600. [CrossRef] [PubMed]
256. Classify Your Medical Device. Available online: https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device (accessed on 19 October 2023).
257. Investigational Device Exemption (IDE). Available online: https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/investigational-device-exemption-ide (accessed on 19 October 2023).
258. 21 CFR Part 820—Quality System Regulation. Available online: https://www.ecfr.gov/current/title-21/part-820 (accessed on 19 October 2023).
259. Lambert, B.; Martin, J. Chapter III.1.2—Sterilization of Implants and Devices. In *Biomaterials Science*, 3rd ed.; Ratner, B.D., Hoffman, A.S., Schoen, F.J., Lemons, J.E., Eds.; Academic Press: Cambridge, MA, USA, 2013; pp. 1339–1353. ISBN 978-0-12-374626-9.
260. Talkington, K. FDA's Regulatory Framework for 3D Printing of Medical Devices at the Point of Care Needs More Clarity. Available online: https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2022/07/fdas-regulatory-framework-for-3d-printing-of-medical-devices-needs-more-clarity (accessed on 30 August 2024).
261. International Organization for Standardization. *Additive Manufacturing—Process Characteristics and Performance Practice for Metal Powder Bed Fusion Process to Meet Critical Applications*; International Organization for Standardization: Geneva, Switzerland, 2019.
262. International Organization for Standardization. *Additive Manufacturing of Metals: Finished Part Properties Orientation and Location Dependence of Mechanical Properties for Metal Powder Bed Fusion*; International Organization for Standardization: Geneva, Switzerland, 2022.
263. International Organization for Standardization. *Additive Manufacturing for Metals—Non-Destructive Testing and Evaluation Imperfections Classification in PBF Parts*, International Organization for Standardization: Geneva, Switzerland, 2023.
264. International Organization for Standardization. *Additive Manufacturing of Metals—Environment, Health and Safety, Part 1—Safety Requirements for PBF-LB Machines*; International Organization for Standardization: Geneva, Switzerland, 2023.
265. International Organization for Standardization. *Additive Manufacturing of Metals: Non-Destructive Testing and Evaluation, Defect Detection in Parts*; International Organization for Standardization: Geneva, Switzerland, 2023.
266. International Organization for Standardization. *Additive Manufacturing: General Principles, Main Characteristics and Corresponding Test Methods*; International Organization for Standardization: Geneva, Switzerland, 2024.
267. International Organization for Standardization. *Additive Manufacturing for Medical: General Principles, Additive Manufacturing of Non-Active Implants*; International Organization for Standardization: Geneva, Switzerland, 2024.
268. International Organization for Standardization. *Additive Manufacturing: Design, Part 3: PBF-EB of Metallic Materials*; International Organization for Standardization: Geneva, Switzerland, 2023.
269. Martinez-Marquez, D.; Jokymaityte, M.; Mirnajafizadeh, A.; Carty, C.P.; Lloyd, D.; Stewart, R.A. Development of 18 Quality Control Gates for Additive Manufacturing of Error Free Patient-Specific Implants. *Materials* **2019**, *12*, 3110. [CrossRef] [PubMed]
270. Sharma, A.K.; Bhandari, R.; Pinca-Bretotean, C. A Systematic Overview on Fabrication Aspects and Methods of Aluminum Metal Matrix Composites. *Mater. Today Proc.* **2021**, *45*, 4133–4138. [CrossRef]
271. Zhang, C.; Li, Z.; Zhang, J.; Tang, H.; Wang, H. Additive Manufacturing of Magnesium Matrix Composites: Comprehensive Review of Recent Progress and Research Perspectives. *J. Magnes. Alloys* **2023**, *11*, 425–461. [CrossRef]