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Titanium Alloys for Biomedical Applications: A Review on Additive Manufacturing Process and Surface Modification Technology

Bin Luo1, Liang Miu[1,2], Yiwa Luo[1]* and Xuecheng Peng[3]

[1]*State Key Laboratory of Advanced Metallurgy, University of Science and Technology, China*

[2]*CITIC Pacific Special Steel Group Jiangsu, China*

[3]*School of Metallurgical and Ecological Engineering, University of Science and Technology Beijing (USTB), China*

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***Corresponding author:** Yiwa Luo, State Key Laboratory of Advanced Metallurgy, University of Science and Technology, China

Abstarct

Titanium and its alloys are favored as substrates for orthopedic implants due to their exceptional mechanical properties, robust corrosion resistance, and favorable biocompatibility. Nonetheless, the relatively high modulus of elasticity and intrinsic biological inertness of titanium impede effective osseointegration and compromise the long-term stability of these implants in human body. To address these limitations, this review examines the synergistic application of additive manufacturing processes and surface modification techniques. The paper outlines the production of porous titanium alloys for orthopedic applications through additive manufacturing and evaluates current surface modification methods aimed at enhancing the implants' biocompatibility and mechanical congruence with bone tissue.

Keywords: Additive manufacturing; Titanium implants; Porous titanium alloy; Surface modification; Alkali heat treatment

Introduction

In recent years, the demand for orthopedic implants has increased as the number of skeletal patients has grown. Bone replacement is an effective method to address bone diseases by replacing damaged and necrotic bone with replaceable orthopedic implants to promote bone tissue regeneration and achieve long-term stability in the body. Orthopedic implant materials used to repair, replace, or enhance the function of bone tissue include metallic materials, polymeric materials, and bio ceramics [1,2].

Metallic materials are commonly used for bone repair due to their excellent mechanical properties and good biocompatibility, especially in areas that require mechanical support, such as humerus, femur, tibia and other long bones. Among them, titanium and its alloys, due to their good mechanical properties, biocompatibility and corrosion resistance [3], are widely used in different parts of the repair and replacement surgery, such as oral and maxillofacial, spine, hip [2,4]. The titanium-based materials most frequently utilized in the medical field are commercially pure titanium (cp-Ti) and the TC4 (Ti6Al4V) [5]. However, the modulus of elasticity for dense Ti6Al4V alloys is 110 GPa, much higher than human bone. (0.02~20Gpa,) This discrepancy can result in the stress shielding phenomenon, where the implant bears a disproportionate amount of load, potentially leading to bone resorption, osteoporosis, and implant loosening over time. In contrast, porous structures, celebrated for their low bulk density, expansive specific surface area, and superior energy absorption, have been demonstrated through numerous studies to significantly lower the elastic modulus. This reduction facilitates bone ingrowth and enhances the stability of the implant [6]. A porous titanium alloy, which integrates the superior physical and chemical attributes of titanium with the beneficial properties of porosity, exemplifies functional-structural integration [7].

Traditional manufacturing techniques often struggle to precisely control the pore diameter, porosity, and shape when fabricating titanium alloy scaffolds, leading to unpredictable pore connectivity and uncontrollable microstructures. In recent years, additive manufacturing (AM/3D printing technology) has made great progress to prepare implant, which offers a high degree of design freedom, rapid prototyping capabilities, and the production of components with excellent mechanical properties as shown in Figure 1. It allows for the creation of parts with intricate designs based on digital models, enabling tailored and precise manipulation of the geometric parameters and morphology of porous titanium alloys. The resulting structures exhibit a fine, uniform organization and surpass the strength of those produced by conventional casting and forging methods.

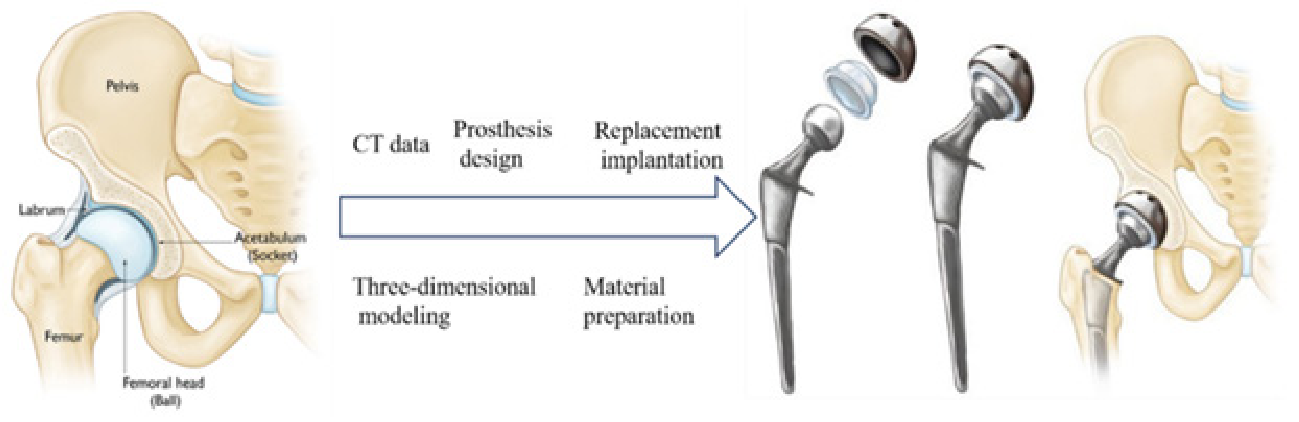

Figure 1: Process of joint prosthesis replacement.

Preparation Technology of Complex Structured Porous Implants

Natural bone is composed of dense and porous cancellous bone, the latter having a microstructure of interwoven trabeculae with multi-scale surface features. Biomimetic implants that mimic these structures can help address stress shielding issues. There is ongoing development of such implants with specific porous designs to improve the mechanical properties of metallic implants. However, traditional methods like powder metallurgy and fiber sintering for creating porous titanium alloys often produce materials with limited pore sizes and uneven distributions, affecting their long-term stability in the body. In contrast, 3D printing technology offers a superior alternative by enabling the design and production of complex porous structures with greater precision and control. The technology facilitates the creation of implants with regular and finely-tuned architectures that closely mimic the natural bone's intricate geometry. As depicted in Figure 2, which illustrates various methods for preparing porous materials, 3D-printed implants demonstrate a distinct advantage in terms of structural regularity and controllability. The following 3D printing techniques are commonly used to prepare complex porous structures of titanium.

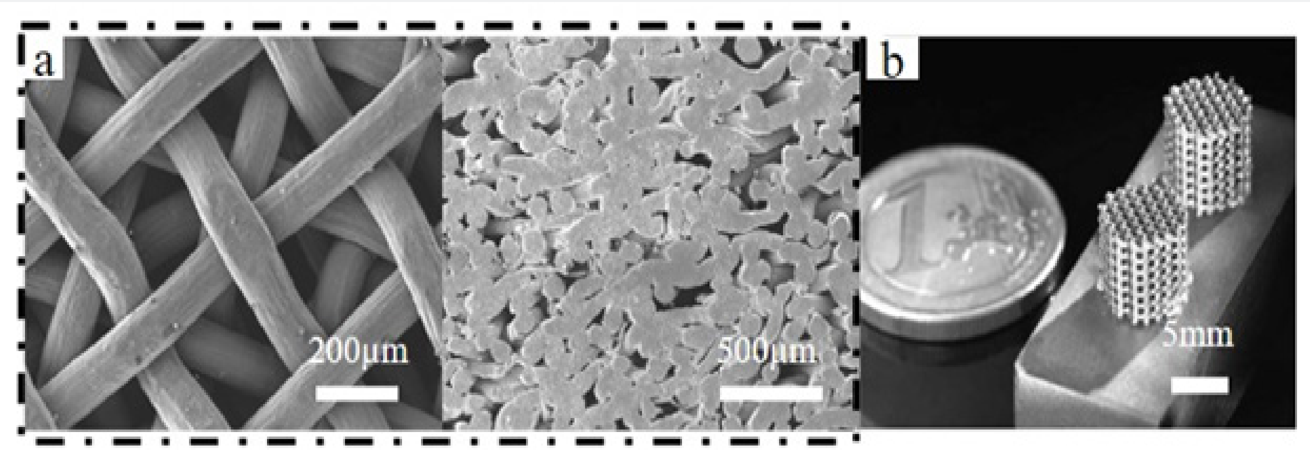

Figure 2: Different processing of porous titanium making: (a) SEM micrographs of sintered titanium mash [70], (b) 3D printed titanium mesh structures [71].

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Powder bed fusion technology

Powder bed fusion (PBF) represents a highly advanced technique within the realm of additive manufacturing, particularly for titanium alloys. As depicted in Figure 3, the essence of this method involves the sequential deposition of a metal powder layer followed by the targeted melting or sintering of specific areas through the application of a laser or electron beam. Subsequently, the build platform is lowered to allow for the deposition of another powder layer, and the sintering process is repeated in a layer-wise manner until the fabrication of the desired component is complete. To prevent oxidation of the metal, it is imperative that this procedure is conducted within an inert atmosphere. This method is particularly well-suited for the production of small, intricate parts that demand high dimensional precision.

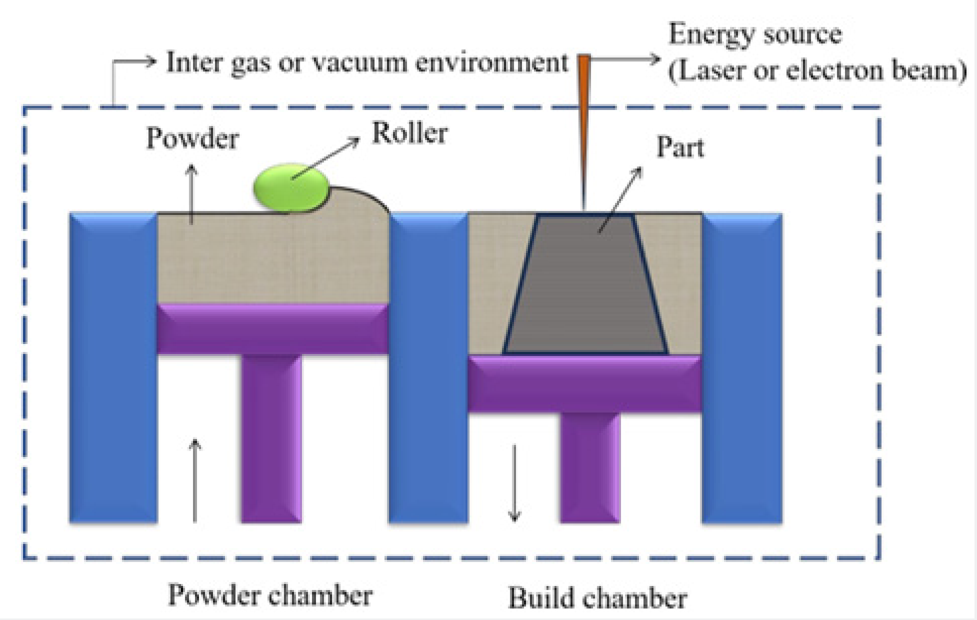

Figure 3: Schematic diagram of powder melting process.

Depending on the heat source, PBF can be categorized into laser powder bed fusion (L-PBF) and electron beam powder bed fusion (EB-PBF). L-PBF includes selective laser sintering (SLS) and selective laser melting (SLM). SLS involves a binder with metal powder for part formation, contrasting with SLM's use of pure metal powder, eliminating the need for binders. SLS parts may have reduced strength and integrity due to the binder's lower melting point and tendency to create voids, impacting mechanical properties and accuracy, unlike the stronger, more precise SLM parts.

SLM technology can successfully produce porous structured scaffolds that mechanical and biological properties similar to those of human bones, which cannot be produced by traditional methods [8,9]. These scaffolds have pore connectivity and high porosity closer to the elastic modulus of bone trabeculae. The sensitivity of SLM to printing parameters, such as laser power, scanning speed, and scanning spacing, allows for precise control over the microstructure and resultant properties of the final product [10]. This sensitivity confers a significant advantage when fabricating porous implants. During the SLM process, the material undergoes rapid melting followed by quick cooling, which leads to the formation of a fine and uniform microstructure. This microstructure significantly enhances the mechanical properties of the scaffold. Furthermore, the precision of SLM enables the creation of scaffolds with a controlled degree of porosity that can be less than 0.1mm, facilitating the production of scaffolds with increased porosity and high-precision complex structures. Pei et al. [11] prepared Ti6Al4V porous specimen orthopedic implants by SLM technique, and the results showed that the porous structure significantly reduced the stress shielding effect while promoting the proliferation and differentiation of osteoblasts on the implant, and successfully induced the inward growth of bone tissue. Zheng et al. [12] successfully prepared titanium scaffolds with higher connectivity porosity (>70%) using SLM technique to investigate the optimal pore size for the strongest osseointegration of titanium implants.

EB-PBF technology is mainly an electron beam melting technology, or EBM, which utilizes an electron beam as a heat source to melt the powder into a liquid. The process is very similar to SLM except that the electron beam utilizes a vacuum

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environment. The direction of the electron beam is controlled by an electromagnetic deflection coil, which realizes the selective melting of the metal powders, and then the process is carried out step by step. This technology is capable of producing both dense and porous titanium implants with tailored mechanical properties. A distinguishing advantage of EBM over SLM is its higher energy density, which can potentially expedite production timelines and diminish manufacturing costs. However, it also presents challenges such as the need for mold preheating, risk of false sintering, and the necessity for support structures that can complicate post-processing. Despite these, EBM is a valuable technique for creating complex, porous titanium implants, as demonstrated by the fabrication of acetabular cups shown in Figure 4 [13]. SLM and EBM are the most commonly used technologies and scaffolds they made offer superior wear resistance [10], microhardness, compressive strength, and tensile strength compared to conventional casting materials [14,15], with a minimal release of titanium (Ti), aluminum (Al), and vanadium (V) ions. Despite these advantages, these techniques face challenges including elevated production costs, energy use, and issues such as anisotropy and residual stresses in the metal parts.

Figure 4: Porous titanium alloy acetabulum cup prepared by EBM [13].

Targeted energy deposition technology

Directed energy deposition technology uses a laser or electron beam as an energy source to simultaneously deposit, melt and solidify materials such as powders or wires. Laser directed energy deposition includes: laser cladding, laser melt injection and laser engineered net shaping (LENSTM). Surface modification technology and 3D part manufacturing technology can be divided into two categories by their roles. They can be used to develop diverse types of coatings by melting and solidifying the material on the substrate by means of a high-power laser. LENSTM is applicable for both targeted surface modification and the fabrication of complete three-dimensional constructs. The LENSTM process operates by directing metal powders with a high-power laser towards argon-pressurized nozzles, focusing them at a convergence point to form a micro-molten pool. This molten material then solidifies upon contact with a substrate that moves along the X and Y axes, forming a layer as the melt pool is deposited. After each layer is completed, the system elevates in the Z direction to build the part progressively. The entire process takes place within a sealed glove box to prevent material oxidation.

Design of Pore Structure for Complex Structured Porous Implants

Designing a porous structure can realize two advantages. On the one hand, reasonable porosity can promote the growth of bone tissue and cell aggregation, provide a place for the differentiation of osteoblasts and bone marrow stem cells as well as the migration of blood vessels, and improve the bonding strength of the interface between the implant and bone; on the other hand, porosity can reduce the modulus of elasticity and the density of the material, so as to make it have a low elastic modulus that is more similar to that of bone, and thus reduce the stress shielding to increase the lifetime of the implant. It was concluded that the type of unit structure of porous scaffolds [16], pore size [17] and porosity [18] will determine the mechanical properties, permeability and biological properties of porous scaffolds. Therefore, the

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design of reasonable pore parameters is essential to optimize the performance of the implant.

Pore structure

Depending on the selected biomaterials, manufacturing methods and usage scenarios, the geometry of pores can be rectangular, spherical, hexagonal. Additive manufacturing technology, particularly, enables the production of complex geometrical shapes [19]. The common structural unit model is shown in Figure 5.

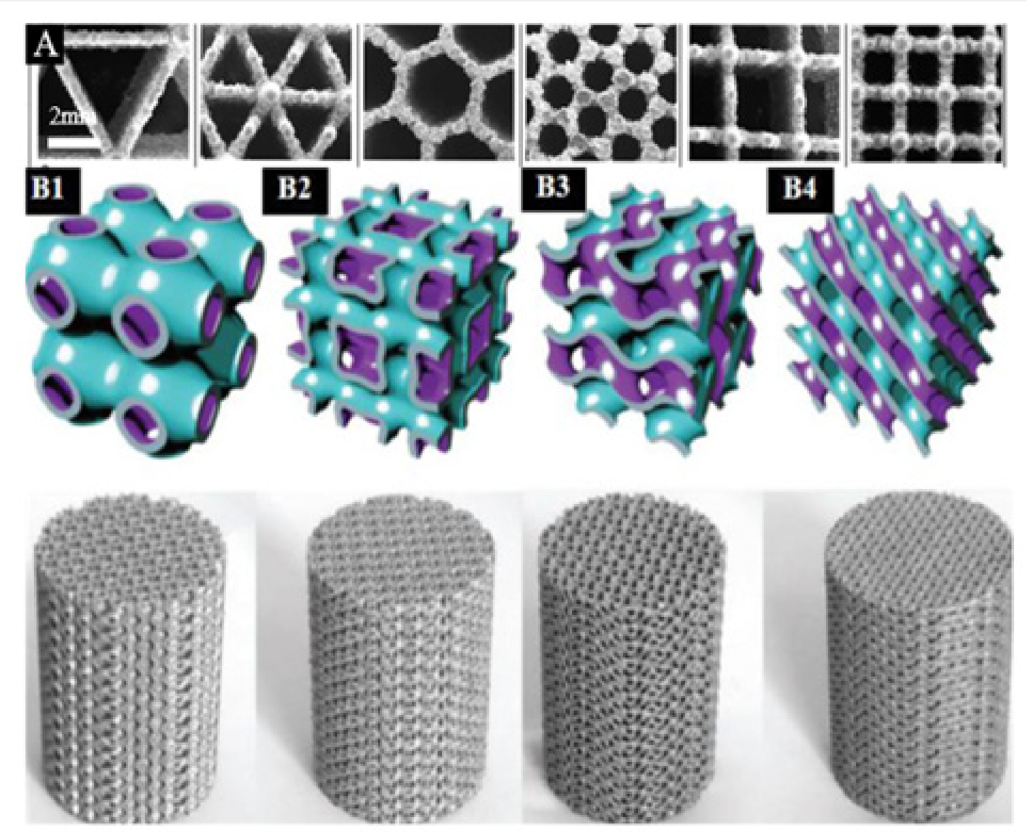

Figure 5: Common structural models: (A) different pore size and shapes (B) Topological structure of Ti6Al4V porous biomaterial as bone regeneration based on the minimum surface of the triple period: (B1) primitive, (B2) I-WP, (B3) gyroid, and (B4) diamond [72].

The size and the shape of the pores determines the size and orientation of the trabecular structure, which in turn determines the stress distribution inside these structural elements, thus affecting the mechanical properties of porous biomaterials. Studies have examined the mechanical properties of Ti6Al4V scaffolds, revealing that scaffolds with similar porosity but distinct unit cell geometries, such as diamond, tetrahedral, and cubic octahedron exhibit variations in fatigue strength and overall mechanical behavior. For example, Zadpoor et al. [20] constructed porous titanium specimens based on diamond structural units by SLM method for mechanical testing, and their yield stresses and modulus of elasticity were 99.64±8.91 MPa~8.20±0.44 MPa and 4.24±0.07 GPa~0.37±0.03 GPa. Xiong et al. [21] prepared porous scaffolds with diamond and honeycomb shaped unit structures by SLM technique and found that honeycomb shaped porous scaffolds with supporting structures in the outer layer exhibited the highest yield strength, toughness, and stable mechanical properties, which are more suitable for load-bearing applications. According to previous studies, cubic shaped cellular structures have similar stiffness and strength to cortical and cancellous bone [22,23]. Although cubic and octahedral unit structures have been found to mimic the stiffness of natural bone [24], the optimal cellular architecture for bone implantation is still under investigation.

Porosity

Porosity, defined as the ratio of pore volume to the total volume within a material, is a critical parameter that influences the load-bearing capacity of an implant. Proper porosity and connectivity facilitate osteoblast adhesion, proliferation and differentiation, and can direct the growth of bone tissue into the pore space. The introduction of dense material into the pore space will have an effect on the strength and modulus of material, and as the porosity increases, the modulus of elasticity decreases but the mechanical properties decrease. Consequently, selecting

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an appropriate porosity is crucial for the stability of the implant. The porosity of porous metal scaffolds can be adjusted according to the elastic modulus and other mechanical properties of the target bone. It is generally believed that the porosity of porous titanium should be within the range of natural human bone porosity (50%~90%). High porosity structures are often more conducive to bone ingrowth compared to those with low porosity [25]. Elevated porosity levels have also been shown to elicit varied cellular responses and enhance the osteogenic potential of cells, as demonstrated by in vivo studies [26]. In addition, pore connectivity is important for the diffusion of nutrients, oxygen and body fluids [27]. An increase in porosity often correlates with enhanced pore connectivity, facilitating the efficient transport of cellular nutrients and the removal of metabolic waste products.

Pore size

Pore size in titanium implants is crucial for balancing mechanical integrity with bone growth integration. While larger pores facilitate osseointegration and stability by increasing cellular surface area, they must not compromise the scaffold's strength or hinder cell functions. The optimal pore size is critical, a general consensus suggests a minimum of 100μm to accommodate osteoblast dimensions and support cell migration and function, yet sizes larger than 300μm may promote capillary ingrowth for improved nutrient and waste exchange [28].

Patrick H. Warnke et al. utilized SLM technology to fabricate Ti6Al4V scaffolds with pore sizes between 0.45-1.2mm and assessed their cellular compatibility. The study found the scaffolds to be biocompatible, with osteoblasts proliferating most actively in 0.5mm pores and showing optimal spreading in the 0.5-0.6mm range. However, a decrease in osteoblast population was noted for pores over 0.9mm. The research also suggested that the scaffold's compressive strength could be tailored by altering pore sizes [8]. Naoya et al. [17] employed SLM to create diamond-shaped scaffolds with 65% porosity and varying pore sizes (0.3mm, 0.6mm, and 0.9mm). These were implanted in rabbit femoral cancellous bone to evaluate bone ingrowth. The study, which evaluated bone ingrowth, compressive strength, and implant stability, determined that the 0.6mm pore-sized scaffold was optimal for bone integration. Yuhao Zheng et al. [12] used SLM 3D printing to produce titanium alloy scaffolds with pore sizes ranging from 0.1 to 0.5mm and over 70% porosity. *In vivo* experiments revealed that scaffolds with cubic monoliths had superior osseointegration, especially when pore sizes were around 200μm. This size was shown to improve cell infiltration, bone growth, and the stability of the scaffold-host bone interface.

Surface Modification to Improve Biocompatibility of Porous Implants

As an orthopedic implant, it is important to be concerned not only with its mechanical properties, but also with its biocompatibility in the human body, whether it is non-toxic in the human body, promotes osteogenesis and osseointegration, and ensures long-term stability [29]. In addition to the structure of the implant, the surface properties of the implant (chemical composition, surface morphology, surface roughness, etc.) have an important influence on the effect of osseointegration [30]. For 3D printed titanium alloy porous scaffolds, although they have a certain roughness and porosity, which reduces the stress shielding phenomenon and provides space for osteoblasts to adhere and grow, the bioinertness of their surfaces and the release of cytotoxic alloying elements [31,32] are still unavoidable. The biologically inert artificial joint prosthesis will be surrounded by a layer of encapsulated fibrous membrane after implantation, making it difficult to form a solid bond with the matrix, leading to slow bone growth at the bone-implant interface, or even the occurrence of fibrous encapsulation and inflammation, increasing the incidence of postoperative loosening of the prosthesis, which ultimately leads to implantation surgery failure.

To enhance the biocompatibility of titanium and its alloys for medical implants, various modification techniques are employed. These include physical methods like vapor deposition and thermal spraying, as well as chemical treatments such as alkali heat treatment and anodic oxidation. The goal of these modifications is to either apply bioactive coatings for improved surface reactivity or alter the surface morphology to better integrate with biological tissues.

Spray different coatings

Due to its biologically inert surface and lack of bioactivity, titanium and its alloys have a limited ability to induce new bone formation and prevent further osseointegration. To augment their bioactivity, a common strategy involves the application of surface coatings designed to enhance the osseointegration potential of the implants, consequently accelerating the healing process. Surface coating in this context denotes the procedure of adhering a layer of bioactive material onto the titanium implant surface. This process commonly incorporates materials such as apatite coatings, oxidized surface layers, and metallic coatings to elevate the implant's bioactivity and promote a more integrated biological response.

Apatite coatings

Apatite, the primary inorganic constituent of human bone, is represented by hydroxyapatite (HA) and tricalcium phosphate (TCP), both of which closely resemble the natural bone's calcium-phosphorus ratio of 1.71. These calcium phosphate salts are biocompatible and have been extensively used as bioprosthetic materials. Despite their widespread use, their brittleness and low strength restrict their application in load-bearing regions. However, the application of apatite coatings on titanium alloys addresses this issue by providing mechanical support and leveraging apatite's bioactivity [32-34]. When used as an implant coating, the coating's calcium and phosphate ions are released,

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enhancing osteoblast adhesion and aggregation. This process stimulates the growth of new bone tissue in conjunction with the coating and the existing bone, while the coating's unique porous surface facilitates implant-bone tissue integration [35].

Li et al. [36] prepared a hydroxyapatite coating on the surface of 3D printed porous titanium alloy by polydopamine-assisted hydroxyapatite deposition, which was shown to enhance osteoblast adhesion, proliferation, and differentiation *in vitro*, and to promote osseointegration and osteogenesis *in vivo*. Mangal Roy et al. [37] utilized LENS technology to fabricate TCP coatings on titanium alloy. This method offers the benefit of a compositional gradient at the metal-ceramic interface, potentially enhancing implant longevity and reducing interfacial complications. In Figure 6, SEM analysis showed increased cell attachment on the TCP coating, with cells exhibiting a spread morphology and pseudopod extension. After 11 days, a cell layer had formed, and the presence of spherical ECM indicated mineralization, confirming the coating's biocompatibility with OPC1 cells. The coating's hardness was significantly enhanced by the presence of fine isometric crystals and a high TCP volume fraction [38].

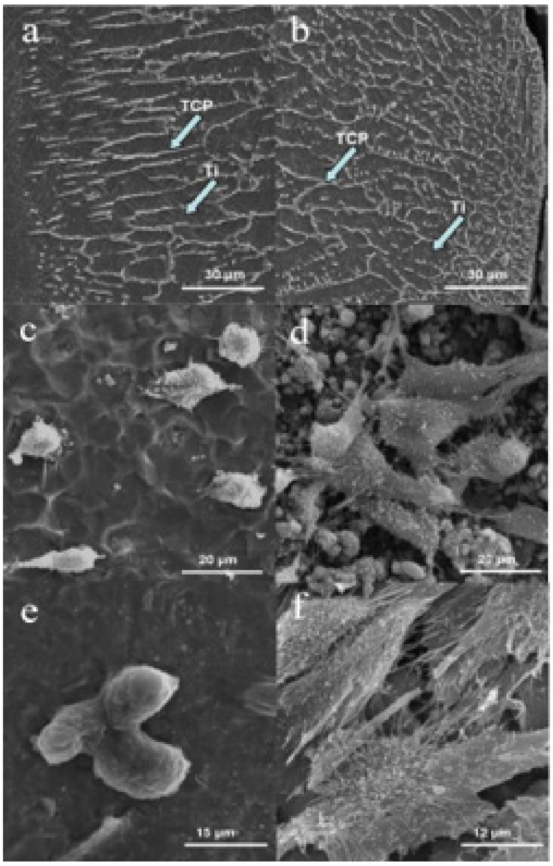

Figure 6: SEM image of the TCP coating [37]: (a) near the substrate and (b) the outer surface of the coating. SEM images of OPC1 cells adhering to the surface after 5 days of cell culture:(c) uncoated Ti; (d)TCP coated Ti; After 11 days of cell culture: (e) uncoated Ti; (f) TCP coated Ti

Metal coatings

Recent attention has focused on new metal biomaterials like niobium (Nb) and tantalum (Ta) for their wear resistance and bioactivity [39]. Both in vitro apatite formation tests and in vivo histomorphometric studies confirm these materials' bioactivity and bone compatibility [40,41]. However, the high production costs and the high melting points of Nb and Ta, along with their strong affinity for oxygen, have hindered the creation of pure Nb or Ta implants using conventional methods. SLM has been identified as a viable technique for Nb implant fabrication [42,43]. Sheng Zhang et al. used SLM to create porous Nb coatings of varying thicknesses on pure Ti substrates. SEM analysis characterized the coatings' morphology and microstructure, while *in vitro* studies assessed cell adhesion, morphology, and proliferation. The Nb coatings exhibited higher average hardness than Ti. SEM, immunofluorescence, and CCK-8 cell counting in vitro tests demonstrated the Nb coatings' superior performance, with cells showing extended pseudopods that strongly adhered to the surfaces [44]. The protruding pseudopods and cell connections were found to facilitate nutrient transport

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and information exchange [45]. Consequently, Nb coatings have enhanced biocompatibility, promoting cell attachment, growth, and potentially improving early bone tissue biofixation.

The biological properties of Tantalum (Ta) are deemed superior to those of Ti both in vivo and in vitro contexts [46]. Notably, porous Ta coatings exhibit biological responses comparable to those of pure Ta, offer reduced manufacturing costs, and demonstrate enhanced durability, positioning them as promising candidates for applications in spinal, hip, and knee implant technologies. Vamsi Krishna Ballaet al. [47] successfully deposited Ta coatings on Ti surfaces using LENSTM and investigated their biocompatibility in vitro using human osteoblast cell line hFOB. The study found that Ta-coated surfaces markedly surpassed Ti in cell adhesion, growth, and extracellular matrix production, with a sixfold higher cell density on Ta compared to pure Ti, as measured by MMT. The increased surface energy and wettability of Ta surfaces significantly enhance cell-material interactions. Moreover, the dense Ta coatings, which are free from pores and abrupt interfaces with the substrate, do not share the low fatigue resistance typical of porous coatings, a key advantage for their application in early biofixation. Some research investigated and evaluated the in vitro frictional properties of Ta coatings on laser-machined Ti surfaces in loadbearing implant applications. Experiments showed that Ta coatings had an order of magnitude lower wear rate than Ti, with higher wear resistance and toughness. Tang Junrong et al. [48] prepared rough porous Ta coatings and their Ta/HA composite coatings on Ti6Al4V substrates by cold spraying technique and showed that they have good bioactivity and are beneficial to apatite nucleation and SBF mineralization. Upregulation of cell spreading and bone-related gene expression was also observed in in vitro culture experiments for the coatings obtained with different pore sizes.

Preparation of micro and nano structures

In addition to the preparation of coatings to increase the biocompatibility of titanium alloy implants, the biocompatibility can also be improved by altering the surface morphology and increasing the surface bioactivity, etc. The main method of altering the surface morphology is to construct micrometer, nano, or micro-nano bi-level structures on the surface of the implant, which promotes cell proliferation and differentiation on the surface of the implant, as well as improves the rate of osseointegration.

Micrometer structures (e.g., microgrooves, micropits, microbarbs, etc.) can increase the surface area of the implant, enhance the mechanical embedding of the implant with osteoblasts, improve the mechanical properties of the implant, and improve the rate of bone-implant bonding by promoting cell adhesion and osseointegration [49]. Nanostructures (e.g., nanotubes, nanowires, nanopores, nanoparticles, etc.) can regulate the behavior of cells by regulating the information transfer between cells, providing a better growth environment for osteoblasts, and promoting osteoblast proliferation and differentiation [50].

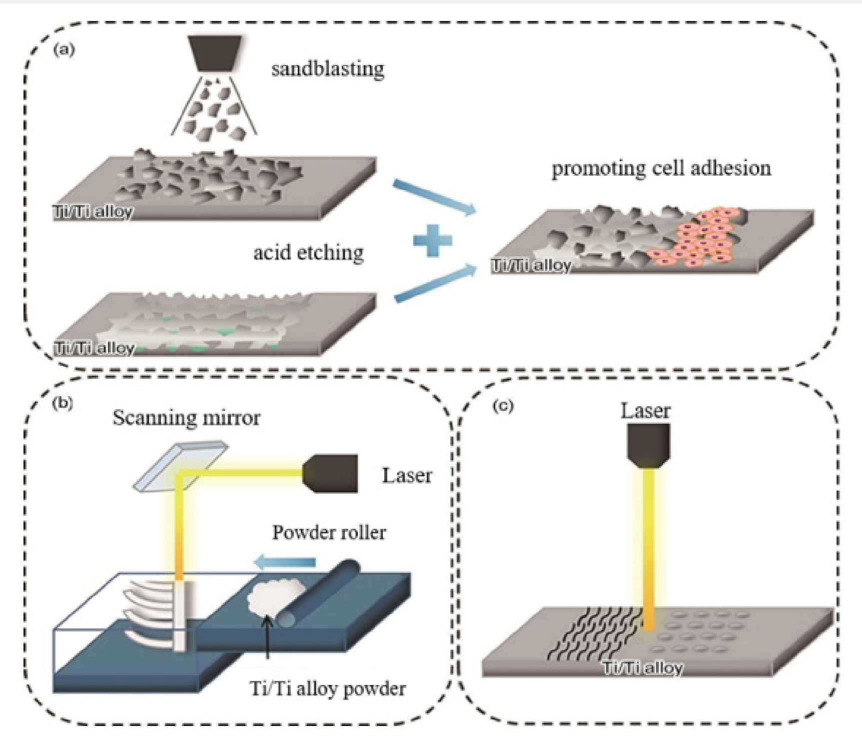

Figure 7: Sand blasting, acid etching and their combination technology diagram.

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Sandblasting, acid etching

Sandblasting and acid etching are proven methods for enhancing implant surface roughness through micro-features, which have shown clinical success in commercial products. The process starts with selecting appropriate sand particle sizes for sandblasting (Figure 7), where particles are propelled onto the implant surface under regulated air pressure. Following this, acid etching is applied for a set time to remove residual sand and create a micro-topography. The larger concavities from sandblasting are refined by the finer depressions formed during etching, which promote cell adhesion and an enhanced surface profile. This results in a homogeneous, disordered microstructure that increases overall surface roughness, benefiting protein adhesion and material bioactivity. The choice of etching reagents and treatment duration are crucial; for Ti6Al4V alloys, high-temperature, concentrated hydrochloric (HCl) and sulfuric (H_2SO_4) acids are often used to achieve a continuous secondary micrometer pore structure [51].

Gao Han et al. [52] observed the surface morphology of Ti6Al4V alloy following a treatment process that involved sandblasting, a subsequent 1:1 mixture of 20% hydrochloric acid (HCl) and 30% sulfuric acid (H2SO4) for pickling, and ultrasonication, as depicted in Figure 8. The treated surface exhibited a gradient structure. Park et al. [53] showed that this structure increases fibronectin and osteoblast attachment on the Ti surface. Zinger [54] prepared titanium alloys with different surface morphologies by sandblasting + acid etching, photo-etching with different patterns and polishing, and were subjected to osteoblast cell culture experiments to study the regulation of specific microstructural features on the proliferation and differentiation of osteoblasts. The results showed that the micrometer-scale morphology was favorable for cell attachment and growth, and the level of PGE-2, which played an important role in cell growth, varied with the microstructure.

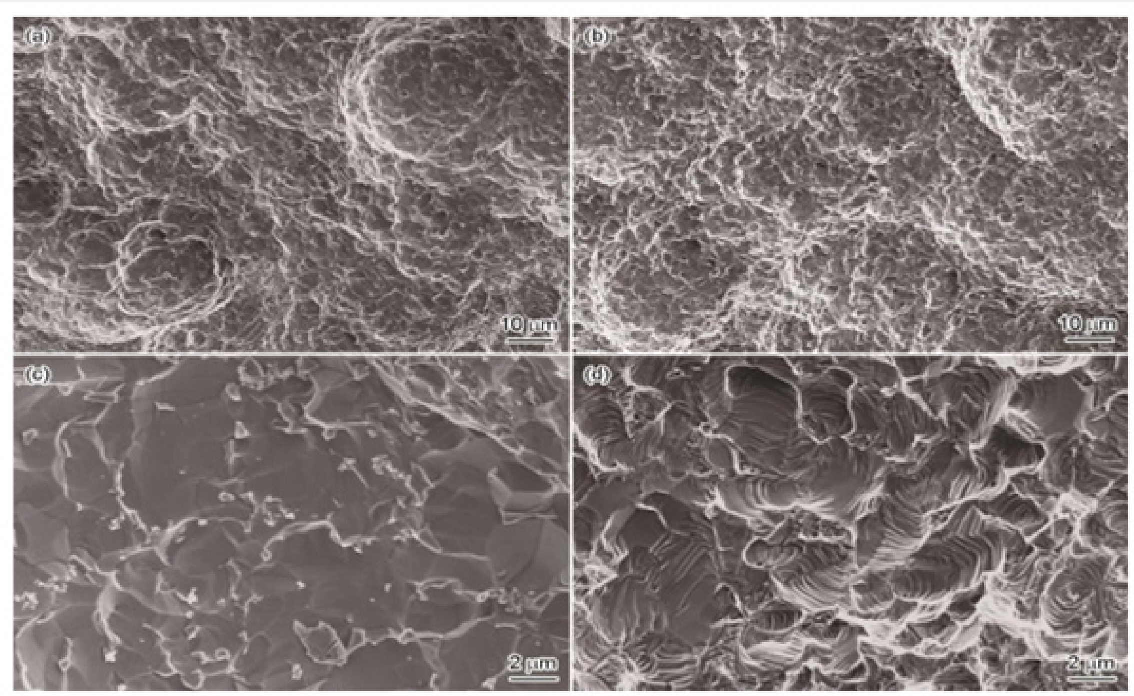

Figure 8: SEM image of Ti6Al4V after sand blasting +20%HCl: 30%H2SO4= 1:1 (volume ratio) mixed pickling for 60min [55].

Although sandblasted and acid-etched titanium implants promote osteoblast differentiation, the microscale surface tends to inhibit osteoblast proliferation, resulting in less bone accumulation [54]. Thus, researchers often combine it with other surface modification techniques to enable micro-nanostructural incorporation, such as anodizing and alkali heat treatment [55].

Anodizing

Anodic oxidation modification involves using titanium or its alloy as an anode in an acidic electrolyte to create micro- and nano-scale surface features, including nanotubes and nanopores, under the influence of an electric current (Figure 9). These enhanced surface structures promote osteoblast proliferation and differentiation, addressing the challenge of poor osteointegration associated with traditional titanium alloy implants. The process also improves the corrosion resistance and biocompatibility of the implants, reducing the risk of rejection [56]. Studies have demonstrated that anodic oxidation leads to the formation of

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ordered nanotube arrays on titanium and its alloys. Specifically, TiO_2 nanotubes form on pure titanium, while the composition of nanotubes on different titanium alloys may vary, generally mirroring the alloy substrate's composition. For instance, nanotubes from Ti-Al alloys consist of TiO_2 and Al_2O_3 [57]. In the case of the Ti6Al4V alloy, the addition of Al and V results in a mixed $\alpha + \beta$ crystalline structure. Post-anodic oxidation, ordered nanotube arrays are observed in the α-phase, whereas the $\alpha+\beta$ phase exhibits a hybrid structure of nanotube arrays and nanopores [58]. Ding et al. [59] combined sandblast etching and anodic oxidation techniques to modify the surface of titanium to obtain layered micro- and nanocomposite structures. Lee et al. [60] prepared TiO_2 nanotube arrays by two-step anodic oxidation, which can be used as a carrier for recombinant human bone morphogenetic proteins while promoting osseointegration. S. Amin Yavari et al. [61] investigated the effects of anodic oxidation parameters and heat treatment on the surface morphology and apatite deposition ability of porous titanium, and the results showed that different anodic oxidation parameters produced nanotube arrays with different sizes, and nanotube arrays with appropriate sizes could significantly increase cellular activity [62,63]. For example, after interaction with MSCs, TiO_2 nanotube arrays around 15 nm can effectively promote cell adhesion, proliferation and differentiation, but when the diameter of the nanotubes is larger than 50 nm, the cell activity decreases and even programmed cell death occurs [64]. However, it has also been pointed out that osteoblasts also have good activity on the surface of TiO_2 nanotube arrays with a diameter of more than 100 nm. The optimal size of the nanotubes for cell adhesion and proliferation varies with different cells.

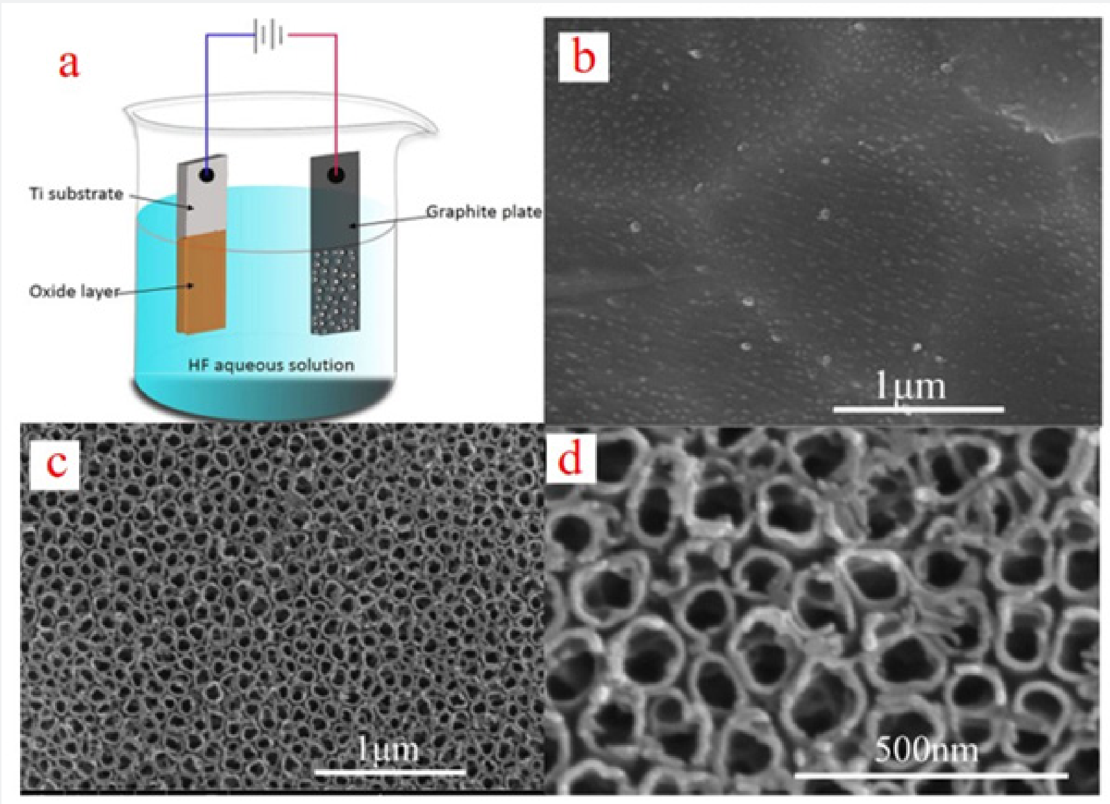

Figure 9a: Schematic diagram of anodizing; b: nanotube arrays before anodizing; c,d: nanotube arrays afteranodizing [73].

In order to enhance the biocompatibility of implants, many studies have also been conducted to improve chemical modification or functionalization on the surface of TiO_2 nanotube arrays, such as the use of mineral coatings, grafting of bioactive molecules, and so on. Addition of Ca/P coating (especially hydroxyapatite, HA) improves the osseointegration properties of implants, Ogaw et al. [64] investigated that modification of HA nanocoatings on titanium implants with micro-nanostructured surfaces improved the integration of the bone-implant interface.

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Alkali heat treatment

The alkali heat treatment is a widely used method to enhance the surface roughness and biological activity of titanium implants. It involves treating titanium and its alloys with an alkali solution, such as NaOH or KOH, at high temperatures to form a sodium titanate gel layer. This layer, upon further heating to around 600°C, converts into amorphous sodium titanate and rutile TiO_2. When these treated implants are placed in simulated body fluid, sodium ions are exchanged for hydrogen ions, raising the local pH and promoting the formation of bone-like apatite. This exchange also increases surface roughness and energy, which aids in osteoapatite nucleation and accelerates hydroxyapatite deposition [65]. It stimulates osteoblast proliferation and differentiation, thereby significantly enhancing the osteoconductive properties of the titanium matrix. The overall enhancement in biological activity is due to these combined effects.

KIM et al. [66] treated titanium in a 50 mol/L NaOH solution at 60°C for 24 hours, followed by heat treatment at various temperatures. The results showed that a dense sodium titanate layer formed at 600°C, while crystalline sodium titanate and rutile were produced at 700°C. Xu et al. [67] created porous titanium implants with a simple cubic structure, mimicking the rabbit bone model (Figure10). These implants were sandblasted and treated in a 5 M NaOH solution at 80°C for 8 hours, yielding a nano-web structure resembling the natural extracellular matrix. This structure increased cell-substrate contact, enhancing cellular functions, proliferation, and protein content. Dalby et al. [68] noted that disordered nanopit features, like the nano-web, were more effective in cellular differentiation and osteoinductivity than ordered nanopits. The nano-web topography also induced tighter cell junctions and increased osteoblast differentiation, accelerating bone maturation around the implant and improving biomechanical stability [69]. *In vivo* experiments confirmed the nano-web structure's positive impact on bone growth into the scaffold, with significant bone volume observed after eight weeks. (Figure10g & Figure10h) Clinically, this method was used in 70 HA-coated porous titanium hip implantations with a 4.8-year follow-up, resulting in only one case requiring prosthesis revision [70-73].

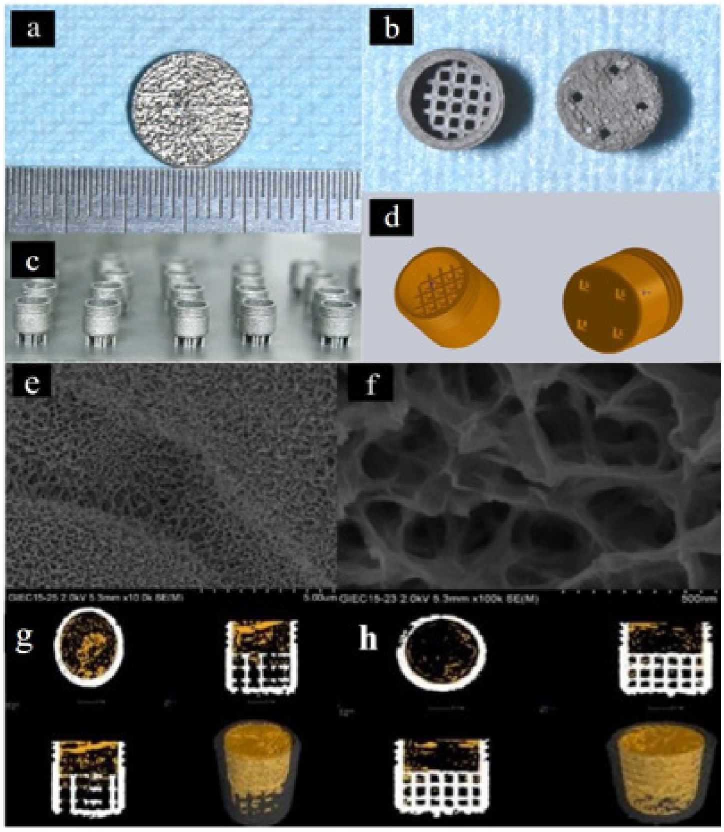

Figure 10: Macroscopic morphology of components and SEM images after alkali heat treatment.
(a)original SLM titanium disk samples; (b) design scaffold shape; (c, d) actual samples, inner diameter 5mm; outer diameter 6mm; vertical height 5mm, internal porous support (pillar size: 0.2mm; Aperture 0.6mm); (e) SAH micro-rough surface; (f) SEM images of ECM-like three-dimensional nanonetwork structure; (g, h) 3D reconstruction images of regenerated bone tissue structure after 4 and 8 weeks in some representative specimens.

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Challenges and Prospects of Porous Titanium Alloy Implant Preparation Technology

In summary, the ongoing advancement of 3D printing technology is leading to wider acceptance of 3D-printed titanium alloy medical devices by both medical professionals and patients. Research focuses on using 3D printing to develop titanium alloy scaffolds that are both mechanically strong and biocompatible. However, the field still faces several challenges that require further improvement and innovation.

a) The current 3D printing material landscape is primarily limited to porous pure titanium and Ti6Al4V alloy, with a narrow range of powders and low yields. There's a scarcity in the exploration of new titanium alloys for 3D printing. Thus, there's a critical need to develop titanium alloys with a low modulus that include biocompatible elements like Ta, Nb, Mo, Zn. This should be accompanied by:

i. deeper research into the structural properties of lower modulus titanium alloys that mimic human bone's mechanical characteristics.

ii. the development of innovative surface coatings for porous titanium alloys to improve bioactivity and biocompatibility.

iii. a more integrated medical experimental approach to align with new titanium alloy development.

Currently, the majority of porous scaffolds are fabricated using repetitive unit structures, resulting in a uniform and symmetrical porosity that contrasts with the irregular and heterogeneous porosity observed in natural human bone. Human bone exhibits a gradient architectural pattern, being denser on the exterior and progressively more porous towards the interior. To enhance biomimicry, the design of scaffolds should evolve to incorporate this gradient structure. This approach aims to harmonize the mechanical integrity and biological performance necessary for effective implant integration and function.

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