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Review on titanium and titanium alloy usage in biomedical implantation applications

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Abstract

Titanium and titanium alloys possess various properties which contribute to their superior osseointegration and durability in implant fixture applications. This review discusses the current state of titanium use in biomedical research, development, and clinical application structures. The microstructural and mechanical properties of commercially pure titanium and titanium alloys are outlined, as well as the effects of their mechanical properties on biocompatibility and stress shielding. Processing methods of titanium alloys which improve these properties are discussed including thermomechanical processing, selective laser melting, electron beam melting, laser shock peening, and sol-gel processing. Also, multiple bioactive glass coatings on titanium implant pieces are currently being explored to improve bone-implant interactions. The high average tensile strength of titanium and its effective biocompatibility can be observed in the clinical application of various structural implants containing titanium alloys. The benefits and drawbacks of commercially pure titanium and titanium alloys, resulting from the current state of research and applications, are outlined and compared.

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1. Introduction

Biomedical implants first utilized gold and silver materials, yet they proved to be too expensive and provide inadequate mechanical properties [1]. After metallic materials and alloys were introduced for implants, they displayed better mechanical properties, yet lacked in providing lasting biocompatibility [1]. Biocompatibility can be defined as the behavior of any given material with living tissue and cells including toxic, harmful, or irritative effects [1]. In the early 1900s steel fracture plates were developed and primarily implemented in surgeries. In the 1960s titanium and cobalt alloys began to be regularly implemented in medical surgeries due to their better biocompatibility [2]. However, for a given medical implant application such as a hip implant, specific properties must be considered for both mechanical and biocompatible capabilities.

The material chosen for most of a hip implant must maintain a high average tensile strength, toughness, and fatigue life to withstand long-term wear in a human body. Regarding behavior with living tissues, the material must also have minimum corrosivity and allow proper implant fixation [3]. Comparing metals for bone repair implants to polymers and conventional ceramics, their higher average tensile strength, high toughness, reasonable fatigue life, and moderate Young's modulus values make them a superior candidate [2]. However, titanium offers properties and features which surpass those of other metals when considering most joint implants. The popularity of titanium use is primarily due to its high tensile and yield strength, yet relatively low Young's modulus [2]. **Table 1** displays this superiority through its high tensile strength and low Young's modulus, which when combined with its light weight provide the best material candidate for a hip joint replacement [2].

Table 1. Comparison on tensile strength, yield strength, and elastic modulus of various implants with bone [4] [5] [6]

Material	Tensile strength (MPa)	Yield strength (MPa)	Elastic modulus (GPa)
Bone (cortical)	*70-150*	*30-70*	*15-30*
Stainless steel	490-1350	190-690	200-210
Cobalt based alloys	655-1793	310-1586	210-253
Titanium based alloys	690-1100	585-1060	55-110
Dense HA ceramics	40-100	-	70-120
Bioglass 45S5	42	-	35

The relative similarity in Young's modulus between bone and titanium results in a decrease in stress shielding. The two most common titanium materials used in both dentistry and orthopedic implants are commercially pure titanium and the titanium alloy Ti6Al4V. Other titanium biomaterials which are more expensive or used for more niche biomedical applications include TiNbZr alloys, Ni-Ti, Ti-(Ta,Nb)-Fe alloys, Ti25Ta, Ti12Mo6Zr2Fe, and Ti6Al7Nb [2, 7, 9] [1,3].

The bone interaction, tissue interaction, and cell interaction with any introduced medical device are determined by the implant material and its correlating properties. These properties include general material properties, mechanical properties, microstructural properties, and surface properties [2]. Osseointegration (bone ingrowth into the implant) must also be considered when designing, testing, and implementing metallic implants to improve biocompatibility. Further processing techniques and surface treatments can also enhance these interactions for clinical applications. This review will first analyze the critical microstructural properties of titanium biomaterials that allow for allotropic transformations of phases which can be tailored via thermomechanical processing. The mechanical properties of titanium materials will then be discussed, including those which affect bone-implant interactions through stress shielding. Processing methods that enhance these properties to improve biocompatibility will be outlined, including surface modification mechanisms and bioactive glass coatings. Lastly, clinical implant systems using the two most commonly used titanium materials, Ti6Al4V and commercially pure titanium will be analyzed [3, 5].

2. Microstructural Properties of Titanium and Titanium Alloys

The allotropic transformations of pure titanium provide varying crystallographic forms. At room temperature, titanium has a hexagonal close-packed (HCP) structure, designated as α phase [2]. At 880°C, the crystallographic form is transformed to β phase with a body centered-cubic structure (BCC). Due to this allotropic transformation, the five categories which describe the phases of titanium, and its alloys include: α, β, near α, near β, and α+β. The ω phase is often present in the β phase as well; the ω phase is less commonly seen in biomedical titanium alloys yet can increase microhardness [7]. Elements such as Zr, O, Al, N, V, and C have been used to stabilize these various crystalline phases [2].

Alloying the elemental composition of titanium can vary its structural properties, which can prove useful in biological applications. Titanium products are fabricated using die forging, extrusion, hot and cold forming, machining, chemical milling, and joining [2]. The allotropic transitions of titanium in these processes affect its microstructure, and as a result, heating rates and temperature conditions must be precisely maintained. Due to the stress shielding and higher Young's modulus of α+β alloys, focus has recently shifted to researching β phase dominant titanium alloys. These alloys have proven to exhibit better biocompatibility, due to non-toxic elements, and lower Young's modulus values, two valuable characteristics in combatting stress shielding and implant failures [2, 7]. Considering the universal effects of thermomechanical processing of titanium alloys, flash thermal treatments have produced ultra-fine β grains, cold rolling has formed a uniform single β phase, hot forging and solid solution treatment has created recrystallized grains, and cold swaging has decreased Young's modulus values significantly [2]. Ultra-fine grains can increase strength of titanium implants; this property's effect on bone-implant interaction will be described further when considering mechanical properties.

Of the titanium alloys which provide sufficient biocompatibility, two samples of commercially pure titanium (CP Ti) and Ti6Al4V were analyzed by Ryniewicz et. al to determine the variations in their microstructures [8]. The CP Ti samples were cut off from factory-made pieces and made from milling before heat and plastic treatment and the Ti6A14V samples had Direct Metal Laser Sintering (DMLS). All the samples were polished and etched in a similar manner [8]. The results displayed that the CP Ti samples possess an α phase granular microstructure while the Ti6A14V alloy contains an α+β phase fine-grained microstructure. Scanning electron microscopy (SEM) displayed that the CP Ti's grain size was uniform at about 20 μm, which displays reasonably suggested adhesive properties, likely improving bone-implant interaction. Further analysis of the results revealed that the CP Ti contained martensitic structure and only titanium via elemental composition analysis. The Ti6Al4V two-phase composition displayed a lamellar form of a β phase matrix with α phase needle structures [8]. Aluminum stabilizes the α phase and strengthens Ti6Al4V while also reducing density. The two-phase and fine-grained structure of Ti6Al4V samples produced by Ryniewicz provides better strength, durability, and density compared to CP Ti [8]. The reusability in production due to DMLS is also an advantage when considering production cycles [8]. Biesiekierski's investigation found the microstructure to also vary significantly between the alloys in the Ti-(Ta,Nb)-Fe system, including: near pure β phase in Ti12Nb5Fe, β with some ω phase in Ti10Ta4Fe, and a combined α+β phase in Ti7Ta5Fe [7].

The various phases present and stabilizing elements in these alloys and other titanium materials must be considered in design for prosthetic implants. One area of current research lies in stabilizing the β phase to reduce stress shielding; this often decreases the titanium material's Young's modulus, allowing the material's stiffness to closer match that of cortical bone as introduced in **Table 1**. Titanium-tantalum alloys possess better β phase stabilization and focus, which could provide higher strength values and lower elastic modulus values as compared to other titanium alloys. TiNbZr alloys often possess superior elasticity due to the presence of the ω phase within the β phase [2]. However, further research is necessary for titanium-tantalum alloys regarding other biocompatibility properties such as corrosive behavior and wear resistance [9]. These specific properties of strength and stiffness will be further discussed in the next section.

3. Mechanical Properties of Titanium and Titanium Alloys

Regarding the mechanical properties of CP Ti and other titanium alloys, there are several alloys which stand out due to their characteristic features. The Ti-Nb-Ta-Zr-O alloy has been called the "gum metal" due to its high strength, reasonably low Young's modulus, super elasticity, and super plasticity, mainly due to the dislocation free plastic deformation of this alloy [2]. Biesiekierski's study also compared the alloys in the Ti-(Ta,Nb)-Fe system to determine their mechanical properties with minimal processing [7]. The tensile strengths of Ti12Nb5Fe, Ti7Ta5Fe, and Ti10Ta4Fe alloys were found respectively as 740, 1250, and 1360 MPa, which is relatively high compared to other metals [7]. A high tensile strength with low density is attractive for biomedical implants such as total joint replacements. The elastic moduli of these alloys were found to be more than twice that of human bone, and their corrosion resistance was noted to be equal to that of CP Ti [7]. Therefore, the balance between maintaining high tensile strength and low elastic modulus to reduce stress shielding must be considered along with corrosion resistance.

Although Ti6A14V's microstructural properties, microhardness, and basic mechanical properties prove to be superior, it poses difficulties due to low corrosion resistance and stress shielding behavior [2]. In other words, it offers high strength yet too high of Young's modulus; consider that CP Ti has an even higher Young's modulus, further enabling stress shielding [2]. The varying elements and phases present in Ti6Al4V also result in its increased hardness (4.49 GPa) and a Young's modulus of 130 GPa, measured via nanoindentation [8]. However, CP Ti has an average microhardness value of 2.28 GPa and Young's modulus of 136 GPa [8]. To lessen stress shielding, the admissible strain, which is the ratio of yield strength to Young's modulus, should be maintained between 0.43% and 0.55% [7]. Alloys such as Ti6Al4V and Ti6Al7Nb display admissible strain values of 0.78% and 0.55% respectively, exceeding the target range for bone implantation applications [7]. One possible alloying element which could produce a favorable admissible strain value is iron, as it is inexpensive, plentiful, and an effective β phase stabilizer. Iron has been utilized in Ti12Mo6Zr2Fe; yet, this alloy was established many years ago and there currently lacks sufficient testing of the biocompatibility of iron [7]. β-phase Ti25Ta should also be considered as an alternative to Ti6Al4V due to its lower elastic modulus value, however, it also maintains lower yield and tensile strength with an admissible strain value of 0.75% [9, 10]. As previously mentioned when discussing the superior β phase stabilization of titanium-tantalum alloys, their implant fixation behavior including corrosive activity and wear resistance should be investigated further [9].

4. Processing to Enhance Biocompatibility of Titanium and Titanium Alloys

Stress shielding can be avoided not only by pairing similar Young's moduli, but also through surface modifications. The effects of stress shielding include bone resorption, notches, and crack propagation which cause implant failures [2, 9]. Selective laser melting (SLM) is an additive manufacturing technique utilized to melt regions of powder layers with laser beams, which ultimately increases microhardness, fatigue resistance, and compressive tensile strength in titanium alloys [2]. Laser engineered net shaping is used to also enhance the surface of titanium biomaterials, mainly α+β titanium alloys. Yet, SLM has proven to be more effective in benefiting Ti6A14V specifically [2].

Post-shaping processes can also aid in improving surfaces of titanium biomaterials. Shen et al. used laser shock peening to improve Ti6Al7Nb's resistance against cracks through compressive surface stress via surface modification [11]. Sol-gel processing is also an effective method for surface modification wherein the annealing stage controls the crystallography of the sol-gel coating, which in turn affects the titanium ion release and surface texture [12]. Greer et al. concluded that sol-gel annealing aids in controlling toxicity and forming superior nanotexture of CP Ti without compromising its hardness or bending strength [12]. The uniformity of nanotexture can directly affect adhesion in osseointegration.

Research and production of titanium scaffolds that best imitate the properties of human bone have improved recently. The gradient porous form of biomaterials must be considered, as they can be optimized for their location of implantation. Bone porosity is non-uniform with variation in different areas on both the microscopic and macroscopic level [13]. Electron beam melting (EBM) and SLM have played a crucial role in this process, helping to develop Ti6Al4V and Ti6Al7Nb alloys with proper porosity gradients, biocompatible Young's moduli, and superior porosity [2].

SLM has been proven to help with many mechanical properties including fatigue resistance and tensile strength, while also tailoring the porosity of titanium biomaterials [2]. Furthermore, post-shaping processes such as laser shock peening and sol-gel annealing provide improved compressive surface stresses and toxicity/nanotexture control, respectively [11, 12].

5. Bioactive Glass Coating of Titanium and Titanium Alloys

Direct skeletal attachment is a developing technological method in prosthetic surgeries, which provides superior force and moment interaction due to permanent connections between the implant and body [14]. However, it tends to provide more issues with infection, skin irritation, and implant failure than conventional socket attachment technologies [14]. As these infections pose issues in implantation surgeries, utilizing bioactive films can be considered an effective treatment in modifying the implant's surface to improve patients' experiences with direct skeletal attachment. Bioactive glass coatings on titanium prosthetics stimulate tissue regeneration by supporting better overall osseointegration, as well as enabling relatively easy handling and application during implantation [14].

Marques et al. found that F18 Bioactive Glass maintains increased bioactivity and bactericidal properties in its applied metallic surfaces [15]. F18 Bioactive Glass is a recently developed glass composition deriving from the SiO_2–Na_2O–K_2O–CaO–MgO–P_2O_5 system with a large workability range of applications compared to other bioactive glass coatings [15]. A hydroxyapatite layer is formed when F18 Bioactive Glass is exposed to aqueous solution, including that which occurs in the body. This layer helps inorganic materials acclimate in bone-implant connection during bone replacement, orthopedic implants, and bone tissue repair. The study displayed that the bioactive glass improved osseointegration and bone density in the application process within two weeks after treatment. There was also an increase in surface roughness for the coated surface, which was speculated to support adhesion due to the increased surface area on titanium's surface [15].

There are multiple studies supporting the improvement of osseointegration with usage of other bioactive glass coatings. Chitosan-bioactive glass coating includes chitosan, which has valuable antibacterial and antimicrobial properties, and bioactive glass, which has been known to improve osseointegration and bioactivity [2]. One study found that no bacteria survived on chitosan-bioactive glass coatings applied to titanium implant materials, proving their resistance against infection. Another study utilized a nano-porous silica coating combined with bioactive glass on a titanium surface and found increased apatite formation, which assists with the formation of bone tissue near the implant several weeks after implantation [2].

Bioactive glass coatings containing titanium oxide on titanium biomaterials have also been analyzed to determine their osseointegrative capability [14]. Silica-based and borate-based bioactive glasses infused with TiO_2 as metallic coatings for prosthetics both ease the bone-implant connection; however, the thermal behavior of the borate-based series allowed greater processing windows than the silica-based series [14]. To combat irritative issues with direct skeletal attachment, bioactive glass coatings which increase bactericidal properties of surfaces provide potential for improving osseointegration. F18 Bioactive Glass allows increased bioactivity and increased adhesion for titanium biomaterial's surfaces, while chitosan-bioactive glass coatings and coatings infused with TiO_2 also have proven to aid in osseointegration.

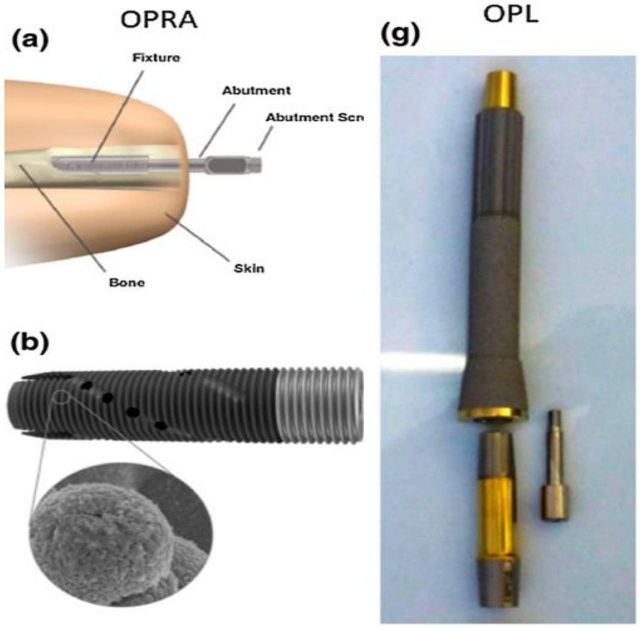

Figure 1. OPRA implant system in an amputated limb (a) and the exterior surface (b) which is formed with Ti6A14V to best assist and improve osseointegration [16]. OPL implant system (g) which utilizes Ti6A14V [16].

6. Clinical Applicability of Titanium and Titanium Alloys

When using titanium, infection and toxicity must be considered to provide patients the most positive experience during and after an implantation surgery. Vanadium has been considered toxic when released in the body, and therefore other stabilizing elements such as those in Ti6Al7Nb have been considered [2]. Aluminum and nickel have also been noted to cause harmful effects on the human body in their alloys and implantation applications [7]. One study found that wear resistance of Ti6Al7Nb in hip implant surgeries was less than that of Ti6Al4V under the same testing conditions [2].

As a foundational basis for other implant structures, the OPRA treatment protocol was introduced in 1998 to standardize implant designs for amputations [16]. In this system the load is transferred from the prosthetic to the abutment, the fixture, and then the bone. Years after being introduced this implant system has transitioned from primary use of CP Ti to Ti6A14V. Other implant systems such as OPL and AEAHBMA have been established more recently, also using Ti6A14V. Although the ITAP and POP implant systems are currently under development, they have been tested and begun utilizing only Ti6A14V rather than CP Ti. Of the three clinically available and widely approved implant systems, OPL and OPRA utilize mainly Ti6A14V (as seen in **Figure 1**), which proves the usefulness of the Ti6A14V titanium alloy in current implant systems and surgeries [16].

Regarding other clinical applications of titanium biomaterials, CP Ti is often used in dental implantations [2]. As mentioned, titanium-tantalum alloys are not currently used in market due to the lack of research on biocompatibility-related issues [9]. Although aluminum is known to cause negative effects on the body considering Ti6A14V and Ti6Al7Nb (two commonly used alloys for joint implantations), iron is also toxic to the human body when considering Ti12Mo6Zr2Fe for biomedical implantations [7, 9].

7. Conclusion

Regarding the properties of titanium, it possesses superior biocompatibility, high tensile and yield strength, low Young's modulus values which are nearer to that of bone, and it undergoes allotropic transformations. These transformations can be tailored via thermomechanical processing to enhance materials with phases present for specific applications [2]. The two most used titanium biomaterials are CP Ti and Ti6Al4V [2]. Ti6Al4V possesses a two-phase microstructure, which allows for the lower density aluminum to stabilize the α phase while vanadium stabilizes the β phase [8]. β phase stabilization is a recent microstructural property that current research is focused on to possibly decrease stress shielding effects. The mismatch in stiffnesses between the implant material and bone can ultimately cause crack propagation and implant failures; β–stabilizing elements such as Ta, Nb, and Fe have been further explored in titanium alloys to maintain strength yet effectively decrease Young's moduli [7, 11].

Regarding mechanical properties, maintaining the balance between tensile strength and Young's moduli is vital when reducing stress shielding and can be seen in analyzing admissible strain values. Other properties involved in biocompatibility and osseointegration also must be considered such as toxicity, porosity, and corrosion resistance. SLM can maintain the porosity of titanium biomaterials used in bone scaffolds, while also improving the fatigue resistance of commonly used materials such as CP Ti and Ti6Al4V [2]. Post-shaping processes such as laser shock peening and sol-gel annealing have proven to negate these biocompatibility issues through controlling nanotexture and surfaces of titanium biomaterials [11, 12]. Bioactive glass coatings of titanium biomaterials are also being explored to improve osseointegration via enhanced increased bioactivity and adhesion at bone-implant surfaces [2, 14, 15].

Clinical applications of titanium alloys have been utilized in successful systems such as the OPRA and OPL. Both of these systems utilize the Ti6Al4V alloy, demonstrating its effective use in clinical applications [16]. However, the possible harmful effects to the human body of both vanadium and aluminum have been noted, and as a result, current research is focused on using titanium alloys with β-stabilizing elements (such as Ta, Nb, and Fe) to combat stress shielding by decreasing Young's moduli [7, 11]. However, other elements and processing mechanisms should be further researched to reach an admissible strain value best suited for bone-implant connections [7]. The effectiveness of titanium-tantalum alloys, bioactive glass coatings, and toxicity/corrosion control must be further understood to decrease implant failures associated with the use of Ti6Al4V, Ti6Al7Nb, and CP Ti in current-day prosthetics [2, 7, 9].

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Conflict of Interest

The author declares no conflict of interest.

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