Biomaterials Advances 183 (2026) 214755

Contents lists available at ScienceDirect

Biomaterials Advances

journal homepage: www.journals.elsevier.com/materials-science-and-engineering-c

Review

Advances in β-titanium alloys for safer and greener biomedical implants

Dulexy Solano-Orrala [a,b,1], Eliana Díaz-Cruces [c,1], Jorge Troconis [d],
Ezequiel Zamora-Ledezma [e,j], Joan Manuel Rodríguez-Díaz [f], Madalina Simona Baltatu [g],
Andrei Victor Sandu [g,h], Javier Hermoso-Gil [a], Frank Alexis [i], Petrica Vizureanu [g,h,*],
Camilo Zamora-Ledezma [a,b,**]

[a] *Bioengineering & Regenerative Medicine Research Group (Bio-ReM), Escuela de Ingeniería, Arquitectura y Diseño (EIAD), Universidad Alfonso X el Sabio (UAX), Avenida de la Universidad 1, 28691, Villanueva de la Cañada, Madrid, Spain*

[b] *Biomedical Research Unit (UIB-UAX), Universidad Alfonso X el Sabio (UAX), Avenida de la Universidad 1, 28691 Villanueva de la Cañada, Madrid, Spain*

[c] *Grupo de Investigación Derecho, Equidad, Gobernanza y Sostenibilidad Para la Justicia Social (LEGOS), Facultad de Ciencias Jurídicas, Universidad a Distancia de Madrid (UDIMA), 28400 Collado Villalba, Madrid, Spain*

[d] *Centro de Física, Instituto Venezolano de Investigaciones Científicas, IVIC, Apartado Postal 20632, Caracas, 1020-A, Venezuela*

[e] *Laboratorio Funcionamiento de Agroecosistemas y Cambio Climático - FAGROCLIM, Departamento de Ciencias Agrícolas, Facultad de Ingeniería Agrícola, Universidad Técnica de Manabí, 13132, Lodana, Ecuador*

[f] *Departamento de Procesos Químicos, Biotecnología y Alimentos, Facultad de Ingenierías y Ciencias Aplicadas, Universidad Técnica de Manabí, Portoviejo, 130105, Ecuador*

[g] *Department of Technologies and Equipments for Materials Processing, Faculty of Materials Science and Engineering, Gheorghe Asachi Technical University of Iasi, Iasi, 700050, Romania*

[h] *Academy of Romanian Scientists, 54 Splaiul Independentei St., Sect.5, 050094, Bucharest, Romania*

[i] *Departamento de Ingeniería Química, Colegio de Ciencias e Ingeniería, Instituto de Energía y Materiales, Instituto de Microbiología, Universidad San Francisco de Quito (USFQ), 170901, Quito, Ecuador*

[j] *Centro de Investigación en Recursos Naturales y Sustentabilidad. Universidad Bernardo OHiggins, Santiago 8370993, Chile*

ARTICLE INFO

Keywords:
Fabrication
Characterization
Biocompatibility
Cytotoxicity
Elastic modulus
β-Ti alloy
Machine learning
Intellectual property
Regulatory

ABSTRACT

In the biomedical field, titanium alloys have long been preferred for orthopedic and dental devices due to their excellent biocompatibility and mechanical strength, making them suitable for long-term implantation. However, recent findings indicate that certain alloying elements, such as vanadium, cobalt, and copper, may pose cytotoxic risks when present at higher concentrations or under specific conditions. As a response to these concerns, current research is focused on developing titanium alloys that feature a lower elastic modulus and improved compatibility with bone elasticity. It also aims to exclude potentially cytotoxic elements and incorporate advanced surface modifications, thereby providing effective solutions to these challenges. Based on these identified needs this review highlights the latest advancements in the design of β-Ti alloys through safer and greener methods. It places particular emphasis on pre-clinical in vitro and in vivo studies that evaluate the safety and performance of implants. Additionally, discusses the potential of artificial intelligence and computational methods for predicting and optimizing alloy properties. Unlike previous reviews that focus mainly on microstructure, mechanical behavior or specific clinical niches, this review includes alloy design and processing with pre-clinical evidence, regulatory and intellectual-property dimensions, and life-cycle and sustainability assessments. By linking β-Ti alloy development to circular-economy strategies, biodegradable metallic alternatives and emerging machine-learning tools for alloy prediction, the review provides a framework for the clinical translation of safer and

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* Correspondence to: P. Vizureanu, Department of Technologies and Equipments for Materials Processing, Faculty of Materials Science and Engineering, Gheorghe Asachi Technical University of Iasi, Iasi, 700050, Romania.

** Correspondence to: C. Zamora-Ledezma, Bioengineering & Regenerative Medicine Research Group (Bio-ReM), Escuela de Ingeniería, Arquitectura y Diseño (EIAD), Universidad Alfonso X el Sabio (UAX), Avenida de la Universidad 1, 28691, Villanueva de la Cañada, Madrid, Spain.

E-mail addresses: dsolacor@uax.es (D. Solano-Orrala), floreliana.diaz@udima.es (E. Díaz-Cruces), jorge.troconis@gmail.com (J. Troconis), ezequiel.zamora@utm.edu.ec (E. Zamora-Ledezma), joan.rodriguez@utm.edu.ec (J.M. Rodríguez-Díaz), madalina-simona.baltatu@academic.tuiasi.ro (M.S. Baltatu), andrei-victor.sandu@academic.tuiasi.ro (A.V. Sandu), jhermgil@uax.es (J. Hermoso-Gil), falexis@usfq.edu.ec (F. Alexis), petrica.vizureanu@academic.tuiasi.ro (P. Vizureanu), camilza@uax.es (C. Zamora-Ledezma).

[1] Dulexy Solano-Orrala & Eliana Díaz-Cruces contributed equally to this work and are listed as joint first authors.

https://doi.org/10.1016/j.bioadv.2026.214755
Received 13 October 2025; Received in revised form 20 January 2026; Accepted 30 January 2026

greener titanium implants, offering a complete overview of the critical factors influencing the future development of titanium alloy implants for biomedical applications.

1. Introduction

Commercially pure titanium (CP–Ti) has been a leading biomaterial for prostheses and dental implants [1]. However, it faces mechanical and biological challenges that can affect the longevity of implants [2]. This has led to the preference for titanium alloys, which offer enhanced properties tailored to clinical needs. These advantageous characteristics support the viability of titanium alloys as alternatives to CP–Ti in the fabrication of prostheses and dental implants [3]. These alloys, including Ti-6Al-4V, are valued in various industries due to their excellent mechanical strength, corrosion resistance, and biocompatibility [4–6]. While Ti-6Al-4V is known for its superior performance, it has an elastic modulus of about 112 GPa, compared to the 30 GPa of human cortical bone [7]. This significant difference can lead to stress shielding, which compromises surrounding bone tissue and may cause bone resorption, looseness, and implant failure.

Further, the difference in stiffness between metal and bone can cause stress shielding, which undermines the surrounding bone tissue and heightens the likelihood of bone resorption, loosening, and implant failure (see Fig. 1a) [8,9]. On a cellular level, inflexible materials can also affect the differentiation of cells into osteoblasts, the cells responsible to create new bone. Indeed, recent studies have demonstrated that mechanical strain can regulate and promote the proliferation of osteoblasts and their later transformation into mature bone cells osteocytes (see Fig. 1b) [10,11]. Additionally, long-term performance of these alloys has raised some concerns due to the release of aluminum and vanadium ions from Ti-6Al-4 V. The release of Al and V metal ions from this alloy however, had a negative effect on cell viability and severely reduced implant biocompatibility [12]. Indeed, the long-term performance of conventional alloys such as Ti–6Al–4V has raised concerns regarding the release of aluminum and vanadium ions into the surrounding tissues [13–15]. Current studies have suggested that, at sufficiently high doses, aluminum exposure may be associated with adverse neurological effects, alterations in bone metabolism and local inflammatory responses. As example, depending on the dose, Al ions have in fact been associated with serious neurotoxic consequences, particularly in light of research linking it to bone brittleness, Alzheimer's disease and possible local inflammatory triggers [16]. However, the clinical relevance of these findings for contemporary implant materials remains uncertain, and some clinical reports have explicitly noted that the small amounts of aluminum released from dental or orthopedic devices may not necessarily lead to severe systemic neurological or metabolic bone disease. In this context, aluminum is best regarded as a potentially critical element that warrants careful monitoring and dose control, rather than as a fully proven systemic toxicant in the setting of modern Ti-based implants. This uncertainty has nevertheless stimulated the development of newer β-type titanium alloys that aim to minimize or eliminate elements such as Al and V while preserving mechanical performance and long-term biocompatibility.

β-Titanium alloys have been developed to address several challenges in materials science [18]. Recent studies on β-titanium alloys, including Ti—Nb, Ti—Ta, Ti—Zr, Ti–Sn–Nb–Ta–Sb, and Ti–Nb–Ta–Mo systems,

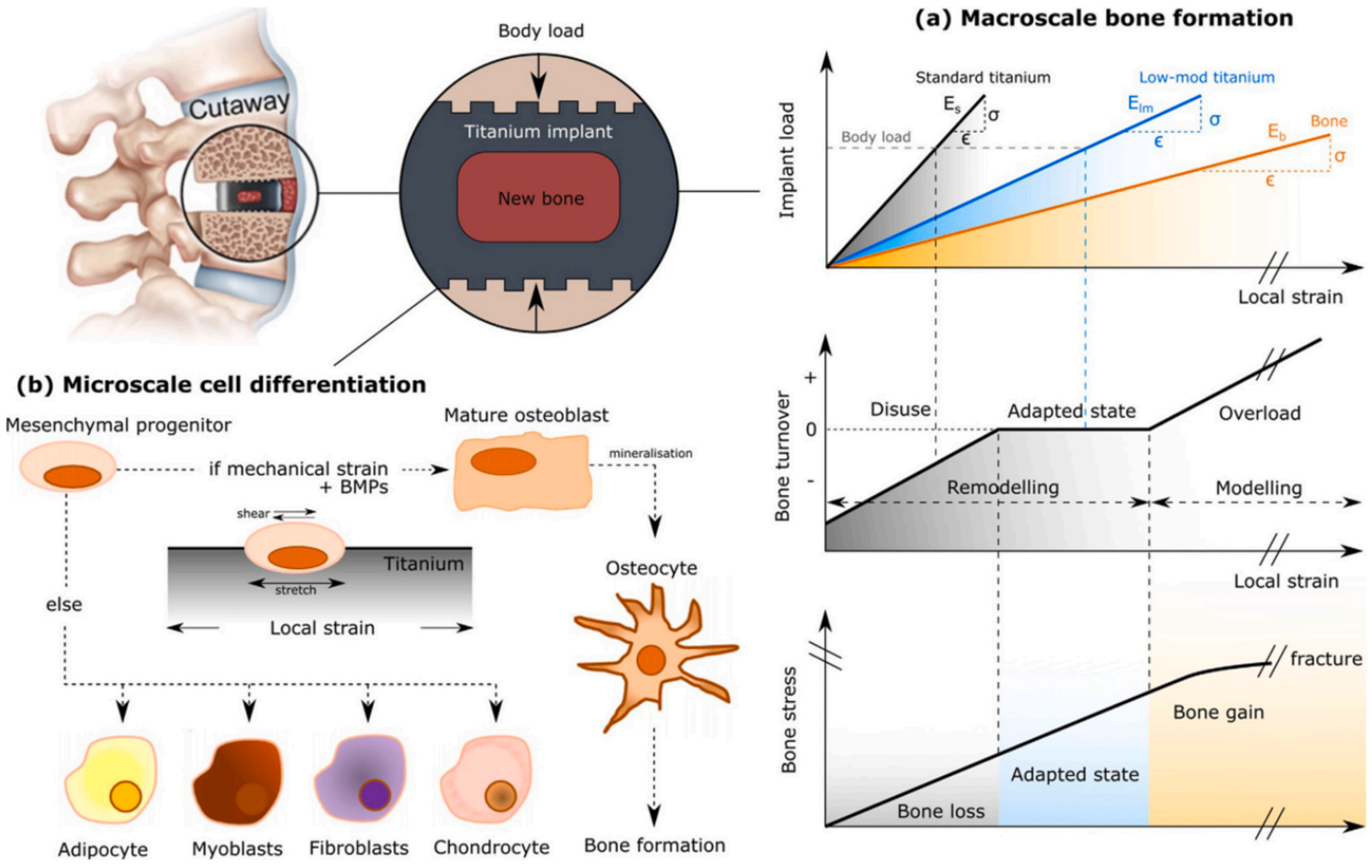

Fig. 1. Diagram showing the effect of implant material stiffness in: (a) bone formation at the macro scale, and (b) cell differentiation and osteocyte formation at the micro-scale (Adapted from [17]).

indicate that these alloys have reduced elastic moduli and enhanced tensile strengths compared to traditional metals and alloys [8]. Notably, β-Ti alloys show a significantly lower elastic modulus (approximately 80 GPa) than other titanium alloys, while still maintaining comparable strength-to-weight ratios and improved fatigue resistance. This makes them particularly advantageous for reducing stress shielding in biomedical implants. Using low-modulus materials can accelerate and enhance bone regeneration around metallic implants. It is also important to highlight that these β-Ti alloys, which contain a higher concentration of β-stabilizers such as molybdenum, tantalum, and zirconium, possess a microstructure where the β phase predominates [9]. Due to the non-toxic nature of these β-stabilizers, β-type titanium alloys not only exhibit lower elastic moduli but also offer improved biocompatibility compared to other types of titanium alloys.

Although several alloys are designed for biomedical applications, many studies reported in literature are inconclusive concerning the possibility of using these new materials as substitutes to CP–Ti [8]. Thus, current research aims to develop titanium alloys that combine a lower elastic modulus, improved compatibility with bone elasticity, the exclusion of potentially cytotoxic elements, and advanced surface modifications, providing an effective and comprehensive solution to these challenges.

Given these considerations, this review highlights the latest progress in β-Ti alloy design and processing for biomedical implants by the incorporation of suitable amounts of β-stabilizing elements, such as Ta, Mo, Nb, Mg, Fe, Cr. A particular emphasis is paid on safer alloying strategies, pre-clinical in vitro and in vivo performance, advanced surface modifications, and the incorporation of computational and machine-learning approaches, together with regulatory, intellectual property and sustainability dimensions. In this context, recent reviews, such as that by Calazans et al. on β-type Ti alloys for dental implants, have provided detailed analyses of microstructure, mechanical behavior and biological performance in specific clinical contexts. Building on these contributions, the present work adopts a broader perspective including but not limited to both dental and orthopedic load-bearing applications and explicitly links alloy design and fabrication routes to clinical translation pathways and life-cycle and circular-economy considerations, thereby aiming to provide a complete framework for the development of safer and greener titanium alloy implants.

2. Classification of Ti alloys

Titanium alloys can be classified into three categories based on their microstructure at room temperature: α-alloys, β-alloys, and α + β alloys [19]. These alloys are created using three categories of elements: (1) α-stabilizers: Elements such as nitrogen (N), aluminum (Al), oxygen (O), and carbon (C) stabilize the α-phase by raising the transition temperature. (2) β-stabilizers: Elements like iron (Fe), molybdenum (Mo), nickel (Ni), vanadium (V), chromium (Cr), niobium (Nb), and cobalt (Co) favor the β structure by lowering the transition temperature. (3) Neutral elements: Zirconium (Zr) and tin (Sn) are considered neutral because they do not affect the stability of either the α or β structures [20]. An overview of the primary titanium alloys currently employed in biomedical applications, along with their typical compositions and key properties, is presented in Table 1.

Table 1
List of the main titanium alloys that found application in the biomedical field in the past 5 years.

Alloy name	Phase type	Area of Application	Key Results	Reference
Ti-10Fe-10Ta-4Z	α-β	Joint replacement	Optimal combinations of strength and ductility can be achieved.	[29]
Ti-Mg (BTiMg) hybrid system	near α	Orthopedic and dental surgeries	This new material can significantly improve osseointegration and reduce the risk of stress shielding.	[30]
Ti-13Nb-13Zr	β-type	Production of advanced dental implant systems	Nanostructured microstructures to minimize bacterial colonization and promote osteoblast growth.	[31]
Ti-12Mo-6Zr-2Fe	β-type	Total hip replacements.	The interaction between the surfaces of Ti64 and TMZF with simulated body fluid is very similar	[32]
Ti–6Al–7Nb	(α + β)-type	Dental prostheses	Alloy castings can be used to produce dental prostheses of improved wear resistance and mechanical strength.	[33]
Ti–3Al–2.5 V	(α + β)-type	Medical devices	Higher hardness and ultimate tensile strength can easily be obtained whereas care must be taken to keep high ductility.	[34]
Ti–15Mo	β-type	Dental implant applications.	Alloy exhibit passivity at anodic potentials at all concentrations of the fluoride ions studied.	[35]
Ti-29Nb-13Ta-4.6Zr	[34]β-type	Biomedical application.	Potential enough as a coating layer to improve the bioactivity implant.	[36]
Ti-35Nb-7Zr-5Ta	β-type	Orthopedic implant	Superior mechanical properties and anti-corrosion potential	[37]
Ti–6Al–4V ELI	β-type	Dental implant	The fatigue resistance of alloy is greatest when the electron beam orientation is perpendicular to the direction of crack propagation	[38]

First, α-type titanium alloys are exclusively composed of the α-phase and include various grades, such as commercially pure titanium (CP–Ti) [10]. Initially, CP–Ti was developed to replace stainless steels and Co—Cr alloys for implants since stainless steels and Co–Cr-based alloys contain cytotoxic elements, including Ni, Co, and Cr. However, some hard tissues or load-bearing connective tissues have higher requirements of mechanical properties; where CP–Ti may not satisfy this requirement due to its moderate strength [17]. Also, near-α titanium alloys (a subclass of α-Ti alloys), known as super-α-alloys, mainly consist of the α-phase with only a minor presence of the β phase (typically <5 vol%). These alloys differ from α-type titanium alloys by incorporating a small quantity of β-stabilizers that typically ranges from 1 to 2 wt% [4]. Both α-type and near-α titanium alloys share similar characteristics, including exceptional corrosion resistance, good weldability, and high creep resistance, making them suitable for high-temperature applications.

The second classification of titanium alloys is β-titanium alloys. These alloys offer higher specific strength, thermal stability, hardenability, fracture toughness, and good workability compared to α-titanium alloys [21]. Additionally, they can be enhanced through aging heat treatment. β-Ti alloy systems are the most preferred materials for biomedical applications [22]. The β phase is characterized by a decrease in elastic modulus, which helps prevent stress shielding at interfaces due to the significant difference in elastic modulus between artificial and natural bone [23]. This property makes β-titanium alloys more suitable for use within the human body. As a result, recent research has focused on developing novel, cost-effective β-titanium alloys with advantageous mechanical properties for biomedical use, utilizing inexpensive alloying elements such as Fe, Mn, Sn, and Cr [1]. Some important β-titanium alloys include Ti12Mo6Zr2Fe, Ti-13Nb-13Zr, Ti—15Mo, Ti-29Nb-13Ta-4.6Z, Ti-35Nb-7Zr-5Ta, and Ti–6Al–4V ELI. Table 1 outlines the key results and applications of these β-titanium alloys. Furthermore, β-Ti alloys are categorized into stable β-type, metastable β-type, and near β-type alloy systems based on the percentage of β stabilizer [24]. Metastable β-titanium alloys are extremely versatile materials with significant applications in medicine and other engineering fields. Their low density and high strength, achievable through precipitation hardening, make them excellent structural materials for use in aircraft. Moreover, because they can be produced with non-toxic elements and exhibit high strength, low modulus, and low porosity, β-Ti alloys are highly desirable as biomedical materials [25].

Finally, (α + β) titanium alloys are known for their good formability, high strength at room temperature, and moderate strength at elevated temperatures [26]. These alloys exhibit a variety of microstructural behaviors, such as the presence of both β and α phases (lamellar and equiaxed), which depend on the thermomechanical processing conditions [27]. (α + β) titanium alloys offer improved fabrication capabilities and moderate strength at high temperatures. Unlike α-titanium alloys, (α + β) titanium alloys can be heat-treated to optimize their mechanical properties. The volume fractions and characteristics of the α and β phases can vary based on alloy composition, heat treatment temperature, and cooling rate. In addition to commercially pure titanium (CP-Ti), Ti6Al4V (Ti64) is the most widely used (α + β) titanium alloy in the biomedical field, accounting for 50% of total titanium production [1,28].

3. The impact of alloying elements on the mechanical properties of biomedical titanium alloys

The primary design factors influencing a new alloy includes its mechanical properties and biocompatibility. Thus, implants require first strong mechanical properties to withstand the stresses and cycles of fatigue they face during use. Thus, in the fabrication of implants, it is essential to achieve a moderate level of hardness to ensure optimal machinability but ensuring sufficient stiffness to protect the bone from mechanical stresses [39]. Also, the elastic modulus is a vital property for the biomechanical interface between the bone and the implant. Indeed, reducing the elastic modulus can alleviate bone atrophy and enhance the distribution of stress at the interface between the implant and the bone. As a matter of fact, it is imperative for the elastic modulus to be as comparable to that of the bone as possible, as "stress shielding" has been associated with conditions such as osteoporosis and localized bone resorption near the implant site [40]. In metals and alloys, it is often challenging to optimize both hardness and elastic modulus at the same time. Notably, the literature indicates that the addition of elements such as Mo, Nb, Ta, and Zr can generally enhance the strength and elastic modulus of titanium alloys. However, achieving the right balance between these properties remains a significant challenge for biomedical implants, especially when compared to commercially pure titanium (CP-Ti). For this reason, a thorough understanding of the mechanical properties of biomaterials and the ability to predict their behavior when anchored to bone are essential for advancing implant performance, as illustrated in Fig. 2.

Typically, alloys that contain lower concentrations of β-stabilizers tend to result in α + β phases, which are characterized by higher elastic modulus values due to the inclusion of the α phase. Conversely, an increase in the concentration of β stabilizers can lead to a reduction in the α structure within the alloy, resulting in decreased hardness and, subsequently, a lower elastic modulus. The modulation of such features are of paramount importance as implants should have an elastic modulus close to that of human bone to minimize stress shielding and bone resorption [1]. As summarized in Fig. 3, the elastic modulus of conventional metallic biomaterials such as stainless steels and CoCr alloys remains far above that of cortical bone, typically exceeding 190–200 GPa, which strongly predisposes them to stress-shielding effects. In contrast, α + β Ti–6Al–4V shows an intermediate modulus around 110–120 GPa, whereas many β-type Ti alloys fall in the 60–90 GPa range, substantially narrowing the mismatch with cortical bone and thus offering a more favorable stress distribution at the bone–implant interface. This graphical comparison highlights why reducing modulus through appropriate β-stabilizer selection and microstructural control is central to the design of safer, next-generation Ti alloys for load-bearing implants [5]. Nonetheless, the challenges associated with currently used surgical implants are closely linked to poor β stability and the inappropriate selection of alloying elements when designing titanium (Ti) alloys with improved mechanical properties. Notably, enhanced β-stability is crucial for Ti alloys to address the stress shielding phenomenon because the β-phase exhibits a lower elastic modulus compared to other Ti alloy phases [41]. In this context, the percentage of β-stabilizer elements (i.e., Ta, Mo, Nb, Mn, Fe, and Cr) impacts the fraction of the β-phase in Ti alloys. Besides, it has been reported that β-titanium alloys with several specific β-stabilizer elements exhibit lower cytotoxicity and improved cell viability when compared to Ti-6Al-4V [40–43]. Some examples of these alloys includes but is not limited to Ti-29Nb-13Ta-4.6Zr, Ti-35Nb-5Ta-7Zr, Ti-35Nb-2Ta-3Zr, Ti-24Nb-4Zr-8Sn, and Gum Metals (Ti-Nb-Ta-Zr-O alloys).

A high elastic modulus in implant materials can lead to stress shielding, which is a significant concern in developing effective surgical implants [44]. If the elastic modulus is insufficient, metallic implants

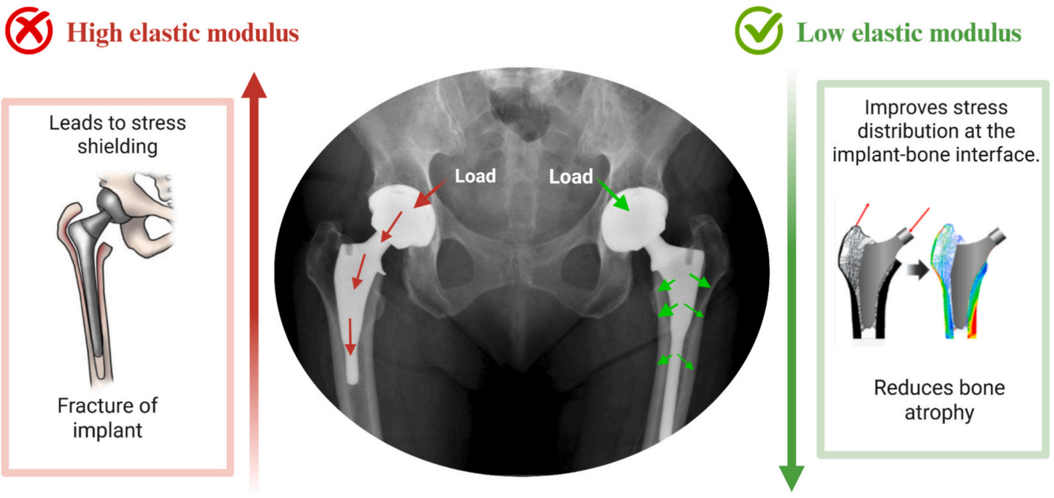

Fig. 2. Diagram illustrating the behavior of hip implants with both high and low elastic modulus.

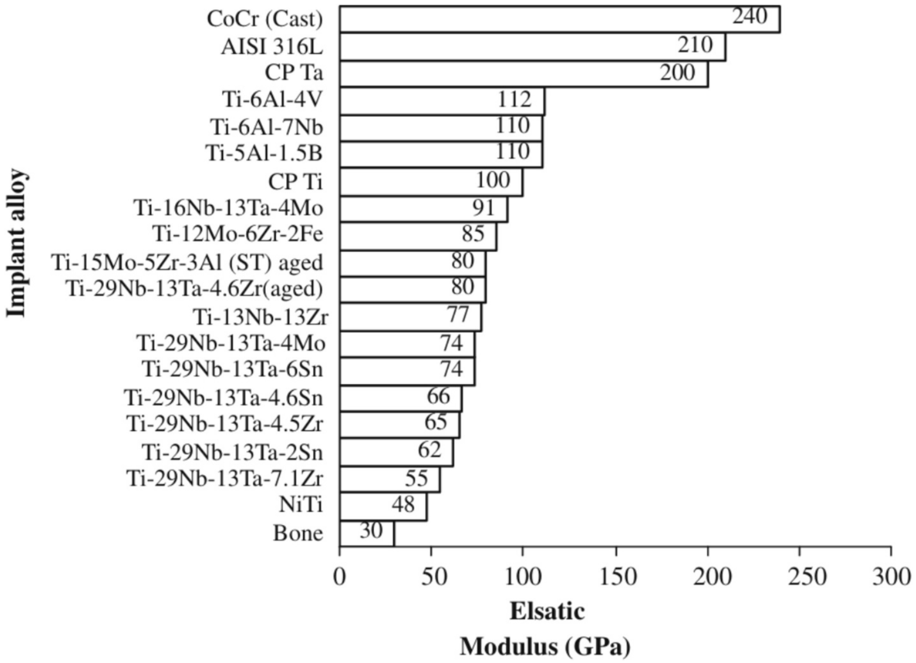

Fig. 3. Comparison of elastic modulus values of different biomaterials with that of human bone. (adapted From [42]).

may experience slight movements. Therefore, it is crucial to avoid this situation, as it can result in prosthesis failure and implant loosening [45]. For instance, several studies have shown that single β-phase titanium alloys with relatively low β-phase stability tend to exhibit lower elastic modulus values than conventional α + β titanium alloys such as Ti–6Al–4V, while still maintaining adequate strength for load-bearing applications. This behavior is attributed to the predominance of the β phase and the suppression or reduction of the stiffer α phase, which together lead to a closer match with the elastic modulus of cortical bone [18,46,47]. Additionally, the incorporation of zirconium (Zr) and small amounts of oxygen has been found to enhance the elastic properties of titanium (Ti) alloys, indicating that both Zr and O act as β-stabilizers in β-type Ti alloys [45].

Moreover, the strength of the alloy must be adequate to withstand the various mechanical loads encountered by an implant, including bending, torsion, compression, and tension. A summary of the mechanical properties associated with the most used and recent types of titanium alloys, including key parameters such as tensile strength, elastic modulus, and elongation, is provided in Table 2 for convenient comparison and reference within the context of biomedical applications. Research indicates that materials chosen as replacements for hard tissue should possess specific characteristics, such as tensile strength and fracture toughness, to ensure the integrity of the implant and prevent plastic deformation during the implantation process [48]. This stability is vital for maintaining the relationship between prosthetic components and the implant. Consequently, it has been reported that the strength of the alloy increases proportionally with higher contents of Zr and tin (Sn).

Recent studies suggest that Sn is more effective than Zr in enhancing the mechanical properties of titanium alloys, while other elements such as niobium (Nb), tantalum (Ta), and palladium (Pd) show lower effectiveness [55]. For example, the Ti–15Sn–4Nb–2Ta–0.2Pd alloy exhibits a tensile strength that exceeds that of the benchmark Ti–6Al–4V alloy used in medical applications. Therefore, elements such as molybdenum

Table 2
Mechanical properties for different types of Ti alloys.

Material	Ultimate tensile strength (MPa)	Yield strength (MPa)	Elastic modulus (GPa)	Elongation (%)	Main Result	Reference
Ti–27Nb–7Fe–8Cr	2000	940 ± 23	72 ± 5	–	Young's modulus decreases from 116 GPa to 72 GPa as the β stability improves.	[49]
Ti-7Mn-10Nb	1842	842	87	34	Phase and microstructural evolution induced by Nb addition is elucidated.	[50]
Ti-16Nb-10Hf	740–850	730–740	81	10	The alloys possessed good biocompatibility obtained through cell live and dead staining experiments	[10]
Ti-25Zr-25Nb	1588	1025	60	32.9	The alloys were composed of β main phase and β minor phase, therefore the alloys exhibited a very low Young's modulus of 60–61 GPa, which can effectively reduce the stress shielding effect.	[51]
Ti–11Nb–7Fe	2006	985	86	42	β-type Ti-11Nb-7Fe exhibits a better combination of properties than CP-Ti and Ti-6Al-4V for orthopedic application.	[52]
Ti–33Zr–5Fe–4Cr	1711	1210	–	–	Ti-35Zr-5Fe demonstrates enhanced mechanical properties, including superior ultimate compressive strength (~1.7 GPa), high yield strength (1138 MPa), high hardness (2.29 GPa) and large plastic strain (23.2%)	[53]
Ti–24Nb–4Zr–8Sn	665	563	53	14	Low-modulus biomedical beta titanium components were produced by selective laser melting	[54]
Ti–12Mo–6Zr–2Fe	927	911	82	–	Ti alloy does not exhibit any strain hardening to help resist the abrasion from the ceramic particles	[32]

(Mo), Zr, Ta, Sn, and Nb are currently considered the safest alloying metals to modify the properties of biomaterials and ensure their suitability for implantation. Additionally, β-phase stabilizing elements like Mo and vanadium (V) enhance the resistance to stress corrosion cracking in titanium due to improved heat treatment capabilities. Furthermore, ductility is also an essential property as it facilitates numerous manufacturing processes, which is particularly important given the complex geometries often associated with implants. The alloy's microstructure and grain size can be modified to enhance both strength and ductility. Notably, the strength parameters of titanium grains are improved by the addition of niobium, resulting in yield strength and tensile strength enhancements ranging from 1.5 to 1.6 times compared to CP-Ti. Moreover, as reported recently, incorporating tantalum into titanium-niobium-zirconium alloys, improves the ultimate tensile strength and elongation of the alloy. However, increasing the concentration of Sn within the β-phase of titanium-niobium alloy tends to reduce both ductility and tensile strength. Recently, Datta et al. demonstrated that a higher concentration of β-stabilizers may compromise the material's resistance [48]. These findings, derived from a predictive model, was subsequently validated through the production of Ti–Al-Zr-Mo-Nb–Ta-Sn-Cr alloy that exhibited inferior strength compared to the titanium alloy Ti-6Al-4V. In contrast, other alloy variants with reduced concentrations of β-stabilizers, such as Ti–6Al–7Nb, Ti–15Zr–4Nb–4Ta, and Ti–13Nb–13Zr, have demonstrated elevated resistance levels compared to conventional β-rich alloys. To achieve such properties, it is required to fabricate a microstructure characterized, a thermomechanical alloy processing technique. With this aim, a recent reported study compared alloys with varying concentrations of CuNi, and revealed that reducing these elements enhances the ductility and elevates the tensile strength to 1050 MPa [56]. Likewise, Niobium (Nb) also offers excellent performance attributes, including low modulus, superior corrosion resistance, biocompatibility, non-allergenic properties, non-toxicity, non-cytotoxic effects, and good superelastic and shape memory characteristics, all of which are vital for improving surgical implant materials [57]. Additionally, Nb has a lower melting point compared to Mo and Ta. Furthermore, it has been reported that a high Nb content would enhance the β-phase stability of Ti alloys. By the same token, the addition of iron (Fe), which is widely recognized as a low-cost and strong β-stabilizing element, further improves tensile and bending strength in Ti alloys [58]. Moreover, iron (Fe) helps to reduce the precipitation of the α-phase, lowers the starting temperature, and supports the retention of the β-phase at room temperature. Additionally, the incorporation of chromium (Cr) in titanium (Ti) alloys offers advantages such as cost-effectiveness, enhanced β-stabilization, and improved corrosion resistance.

It is important to note that the apparent discrepancies in 'optimal' concentrations reported for elements such as Fe and Cr largely reflect differences in processing routes, microstructural states and testing protocols rather than purely compositional effects. For example, similar nominal Fe additions can lead to significantly different elastic modulus and strength values depending on whether the alloy is processed by casting, thermomechanical treatment or powder-based routes, and on the presence of retained α or ω phases. Likewise, variations in solution and aging treatments, cooling rates and sample geometry can strongly influence phase distribution, grain size and residual stress, thereby modifying the mechanical response and corrosion behavior attributed to a given alloy composition. Consequently, reported composition–property relationships must be interpreted in the light of these methodological variables, and there is a clear need for more systematic studies that decouple composition from processing history to define truly comparable windows of Fe, Cr and other β-stabilizer contents for biomedical β-Ti alloys [59,60]. As a result, recent research has focused on designing titanium alloys that utilize abundant and inexpensive elements like Fe, manganese (Mn), chromium (Cr), and tin (Sn), while ensuring that the performance requirements for surgical implant materials are maintained.

Nowadays, the development of β-type titanium alloys tailored for biomedical applications continues to be a highly dynamic research area. The data presented in Table 2 clearly demonstrate that alloying with both costly (e.g., Nb, Mo, Ta, Zr) and more economical elements (e.g., Fe, Cr, Mn, Sn) can significantly influence the mechanical behavior of titanium alloys, particularly the reduction of the elastic modulus to values closer to that of human bone. This adjustment is vital in minimizing the stress shielding effect and enhancing the longevity and integration of implants [61]. Despite the promising results, no single alloy has yet met all ideal criteria, low modulus, high strength, excellent corrosion resistance, biocompatibility, and low production cost. Further, the addition of specific β-stabilizing alloying elements such as niobium (Nb), tantalum (Ta), molybdenum (Mo), zirconium (Zr), iron (Fe), manganese (Mn), chromium (Cr), and tin (Sn) has proven highly beneficial for the design of next-generation titanium alloys for biomedical implants. These elements enhance the stability of the β-phase at room temperature, which is associated with a lower elastic modulus, which in turns is a key requirement for reducing stress shielding and ensuring biomechanical compatibility with bone [62]. Moreover, these elements contribute to the refinement of microstructure, improve mechanical strength (both tensile and compressive), and in many cases enhance corrosion resistance and biocompatibility.

3.1. *Stability of Ti-based implants*

From a long-term clinical perspective, the stability of Ti-based devices depends on the combined mechanical, microstructural and chemical performance of the alloy under physiological loading and environmental conditions. As a matter of fact, the β-type titanium alloys are very attractive because their lower elastic modulus can reduce stress shielding; however, their metastable β microstructure must remain sufficiently stable under cyclic loading and body temperature to prevent excessive phase transformation, loss of mechanical strength or detrimental changes in fatigue behavior over time. Based on these facts, it is expected that inadequate microstructural stability, particularly in alloys with marginal β-phase stability, may lead to premature fatigue damage or crack initiation at weak interfaces [63,64]. Furthermore, for biomedical applications corrosion and biological stability are critical to maintaining the integrity of the bone–implant interface. For instance, as reported in literature, the native TiO_2 passive layer generally confers excellent corrosion resistance in physiological fluids, yet local pH variations, fretting at modular junctions or the presence of inflammatory mediators can promote localized degradation and increased metal ion release. For β-Ti alloys designed to exclude elements with known or suspected cytotoxicity, sustained passivation and controlled ion release are essential to avoid adverse tissue reactions and to ensure stable osseointegration throughout the implant's service life. Consequently, the design of β-type Ti alloys for safer and greener implants must simultaneously optimize mechanical and microstructural stability, fatigue performance, and corrosion resistance to achieve durable biomedical applications [65,66].

4. Preparation methods for β-type Ti alloys

In biomedical applications, there are several methods for preparing Ti-alloys materials with controlled morphology and microstructure, including sintering, investment casting, and rapid prototyping [67]. In such materials, the porous structure not only reduces the elastic moduli but also improves tissue adhesion and encourages the ingrowth of bone-like cells [68,69]. At present, it has been widely demonstrated that different preparation methods can result in varying properties of titanium and its alloys. Indeed, powder metallurgy and additive manufacturing are the two predominant techniques for fabricating porous β-type titanium alloys [63]. Worth mentioning that both conventional sintering and additive manufacturing, are based on the principles of powder metallurgy, using metal powders as a raw material. In the case of sintering, the powders are pressed into a preliminary shape, followed by a heat treatment that allows the particles to coalesce through solid-state diffusion. This approach allows for control of porosity by adjusting the particle size, compaction pressure or by adding pore-forming agents. On the other hand, modern additive manufacturing technologies, such as Selective Laser Melting (SLM) or Electron Beam Melting (EBM), use fine spherical powders, selectively melted, layer by layer, according to a three-dimensional digital model. These methods allow the production of porous structures with complex geometries and a controlled pore distribution, essential aspects in the design of personalized biomedical implants [70]. Therefore, although both methods involve powder metallurgy, they differ significantly in terms of geometric precision, control of the porous architecture and practical applicability, each having specific advantages depending on the requirements of the targeted biomedical application.

Metal powders are the essential raw material in the powder metallurgy process, and their characteristics significantly influence the behavior during processing and the final properties of the parts obtained. There are several methods for obtaining powders, chosen depending on the nature of the metal, the required degree of purity and the field of application [71]. One of the most widely used methods is atomization, which consists of spraying a molten metal through a jet of inert gas (e.g. nitrogen or argon) or water, resulting in metal particles in powder form. Gas atomization allows the production of powders with a nearly spherical shape, which gives them good compressibility and flowability, making them preferred in applications such as 3D printing or the manufacture of parts with complex geometries. In contrast, water atomization produces more angular particles at lower costs, being used in standard industrial applications [72].

Chemical reduction is a commonly used method for obtaining metal powder precursors. In this process, metal oxides are converted into pure metals through a reaction with a reducing agent, such as hydrogen or carbon. This technique is often employed to produce powders of metals like iron, nickel, or tungsten, and it has the advantage of yielding porous powders that are beneficial for the sintering process. Another method for producing metallic powder precursors is electrolysis. This involves depositing metal in powder form onto a cathode within an electrolytic cell. Electrolysis is particularly suitable for high-purity metals, such as copper, nickel, or silver. However, the main drawback of this method is its high production costs.

Additionally, there are physical methods, such as mechanical grinding, which are simple and can be scaled for industrial use. This technique is especially applicable to brittle metals or composites, as it involves fragmenting materials in ball mills or using air jets. However, one of the main disadvantages of mechanical grinding is that the resulting powders tend to have irregular shapes and may be contaminated. Therefore, these powders are typically used in less critical applications or for the development of new experimental compositions [71]. For biomedical, other modern and high-tech methods can be used. For instance, plasma spraying or electron beam spraying deserve special attention as they allow obtaining powders with perfect sphericity, precise control of composition and high purity [73]. Thus the key factors affecting the essential characteristics of powders include the shape of the particles (spherical or irregular), size and particle size distribution, chemical purity and reactivity toward the atmosphere. Thus, the choice of the method of obtaining metal powder precursors must be made according to the specific requirements of the final application, especially when precise functional properties are sought, as is the case with porous biomedical implants.

Overall, the choice of preparation methodology for β-Ti alloys involves a balance between microstructural control, mechanical performance, cost and scalability. Thus, conventional wrought and casting routes remain attractive for their maturity, standardization and relatively low cost, but they offer limited control over complex porosity and patient-specific geometries and can involve significant material waste. For its part, powder metallurgy techniques provide improved tailoring of composition and porosity at moderate cost, yet they may suffer from residual porosity, heterogeneous densification and the need for careful control of powder handling and contamination. On the contrary, additive manufacturing enables unprecedented design freedom, near-net-shape production and integration of lattice structures that reduce stiffness and promote osseointegration, although it still faces challenges related to process-induced defects, surface roughness, anisotropy, high equipment cost and energy consumption. Based on these findings, from a clinical and industrial standpoint, future optimal strategies are therefore likely to rely on hybrid approaches that combine the robustness of established processes with the design flexibility of advanced powder-based and additive techniques, while progressively integrating sustainability and life-cycle criteria into process selection.

Finally, as far as the cost are concerned, in the adoption of β-Ti alloy structures for clinical use, it is worth mentioning that conventional wrought and cast processes remain comparatively cost-effective due to established industrial infrastructure and lower capital investment. For its part, comparatively, powder metallurgy and additive manufacturing typically involve higher raw-powder prices, stricter quality control requirements and significant equipment and energy costs, which can increase the overall cost per implant despite reductions in material waste. Furthermore, alloy design strategies that rely on abundant and relatively inexpensive elements such as Fe, Mn or Sn may offer economic advantages over compositions rich in high-cost refractory metals like Nb or Ta. Consequently, the practical current and future deployment of safer and greener β-Ti alloys must balance performance and sustainability targets with manufacturing and material costs to ensure that the resulting devices remain viable for large-scale biomadical applications.

4.1. *Powder metallurgy (PM)*

PM is one of the most widely used methods for the manufacture of porous titanium alloys, including β-type alloys, used in biomedical applications. The process involves several essential steps such as the preparation and mixing of powders, compaction in molds under high pressure, and sintering at high temperatures in a controlled atmosphere. This technique allows for the control of porosity by adjusting the particle size, pressing pressure, and sintering parameters. In addition, pore-forming agents such as NaCl or urea can also be introduced, which are subsequently removed to create an interconnected porous structure [70]. In this way, this method offers the advantage of using customized compositions and allows for the production of homogeneous structures with relatively low production costs, especially for large batches which are of paramount importance for industrial scalability and applications. Moreover, the resulting porosity contributes to the reduction of the elastic modulus of the alloy, which helps to reduce the transmission of mechanical load to the surrounding bone and improve osseointegration. Thus, this method remains a viable and effective choice for the development of orthopedic and dental implants with optimized porous structure. In the biomedical area, a concrete example of the application of powder metallurgy for porous titanium alloys is the manufacture of dental and orthopedic implants. These implants are typically made of porous titanium alloys, which through their structure allow good osseointegration and reduce the “stress shielding” effect due to their low elastic modulus, close to that of natural bone. For example, companies such as Stryker or Nexxt Spine produce implants for intervertebral fusion from porous titanium alloy, used in spinal treatments. These implants have a porous structure that facilitates the growth of bone tissue inside the pores, ensuring a durable biological fixation [73].

At the same time, in dentistry, porous titanium alloys are used for dental implants due to their ability to integrate well with the jawbone, providing long-term stability and reducing the risk of rejection. Thus, powder metallurgy allows obtaining these porous structures with optimized mechanical and biological properties for advanced biomedical applications [74]. PM is particularly interesting when working with high-melting-point materials like titanium or cobalt-based alloys.

However, despite its benefits in material usage and the capacity to design microstructures using controlled processing settings, the technology is intrinsically limited in terms of geometric complexity. PM's standard compaction and sintering stages limit the ability to fabricate components with complicated characteristics like internal channels, lattice structures, or micro-scale surface textures. Achieving such dimensions frequently needs additional machining operations or hybrid approaches, such as integrating PM with additive manufacturing technologies, to enable the fabrication of advanced implant designs that meet mechanical and biological requirements. In this context, the sintering environment is an important parameter in powder metallurgy because it affects the chemical composition, microstructural integrity, and performance characteristics of the final alloy. Hence, inert or reducing atmospheres, such as high-purity argon, hydrogen, or high vacuum, are commonly used to reduce oxidation and unwanted chemical interactions during heat treatment. This is especially important in the processing of reactive metals such as titanium and its alloys, where their attraction for oxygen and nitrogen at high temperatures can cause interstitial contamination. These elements can negatively affect the ductility and mechanical behavior of the material, by producing brittle phases, as well as a significant drop fatigue resistance, which are important features in biomedical applications [73].

4.2. Additive manufacturing (AM)

AM is a very common and cutting-edge materials processing method that allows for the layer-by-layer manufacturing of complicated metal components directly from digital designs and 3D rendering. This method involves the selective deposition and subsequent fusion of metal powders using high-energy sources such as lasers (in Selective Laser Melting, SLM) or electron beams (in Electron Beam Melting, EBM). AM has substantial advantages over traditional manufacturing methods, especially in biomedical applications where design flexibility, material efficiency, and the capacity to make patient-specific implants are crucial. The process enables the fabrication of complicated geometries such as lattice structures, internal channels, and graded porosity, which are very desirable in orthopedic implants for promoting osseointegration and reducing stiffness mismatch with natural bone.

To the best of present knowledge, SLM and EBM are the most used AM techniques for creating porous β-type titanium alloys. These technologies allow the achievement of extremely complex geometries, including trabecular structures or graded porosity, which are difficult to achieve using conventional methods. In this context, in SLM, a high-power laser selectively melts layers of fine titanium powder in an inert gas atmosphere (usually argon), whereas EBM achieves identical melting and consolidation with a concentrated electron beam in a high-vacuum environment. Each approach provides significant advantages. For instance, SLM offers better resolution and surface finish, whereas EBM often produces lower residual stresses and faster build rates for bigger parts. On the contrary, both technologies allow for fine control of porosity and microstructure, which can be tuned to meet the mechanical and biological needs of load-bearing implants. Therefore, it is evident that by controlling the processing parameters (laser power, scanning speed, layer thickness), it is possible to adjust the degree of fusion and the microstructure, thus influencing the mechanical and biological properties of the part [61]. It is significant to point out, that a major advantage of additive manufacturing is the ability to produce personalized implants, perfectly adapted to the patient's morphology, using 3D models obtained by computed tomography or 3D scanning. This technology also significantly reduces material loss and the time required for prototyping [75].

In the case of implants, the porosity generated by additive manufacturing not only reduces the elastic modulus, bringing it closer to that of bone, but also favors biological fixation through cell migration and proliferation within the structure. Indeed, the ideal biomaterial implant or scaffold must also have an open and interconnected porosity. At the same time, the integration of porosity into a precise internal design allows for the optimization of the strength-to-weight ratio and the distribution of stresses in contact with bone tissue [76].

Although additive manufacturing offers exceptional control over the geometry and porous architecture, the technology also presents a series of limitations that must be considered in biomedical applications. One of the main disadvantages is the high cost of equipment and spherical metal powders, which must have a strictly controlled quality (uniform size, sphericity, purity) [77]. In addition, the layer-by-layer construction process is relatively slow, which may limit the economic applicability for large-scale production. Furthermore, residual stresses generated during rapid solidification can lead to deformations or cracks, often requiring post-processing heat treatments such as annealing or HIP (hot isostatic pressing) to stabilize the fabricated material. Additionally, the surface roughness can be high, requiring additional machining or finishing, especially in areas of contact with living tissue or other mechanical components. Another significant aspect is reproducibility, as very small variations in process parameters can lead to important differences in the mechanical or microstructural properties of the fabricated material, which requires rigorous quality control. Fig. 4 shows an example of the development of a personalized hip implant through additive manufacturing, through a detailed CT scan of the patient's pelvis, with very fine resolution, which allows the exact capture of the shape and dimensions of the affected area. Based on this data, a 3D model of the bone and defect is built using specialized computer-aided design software. In this model, the implant is designed to perfectly match the patient's morphology, with a compact outer part for strength and an internal trabecular structure with variable porosity to mimic the mechanical properties of natural bone [57].

Furthermore, the implant design is optimized through topological algorithms that adjust the pore distribution to obtain an elastic modulus adapted to the contact areas with cortical and cancellous bone. To make the implant, a Ti-6Al-4V ELI (Extra Low Interstitials) titanium powder is selected, which is recognized for its biocompatibility and excellent mechanical properties. In the present example, the additive manufacturing process is performed using Selective Laser Melting, followed by a thermal annealing treatment and a surface treatment with hydroxyapatite to stimulate biological fixation [77]. Finally, the implant undergoes rigorous quality control, including micro-CT scans to verify porosity and mechanical tests to ensure resistance to repeated stress. The implant thus produced allows for rapid and safe bone integration,

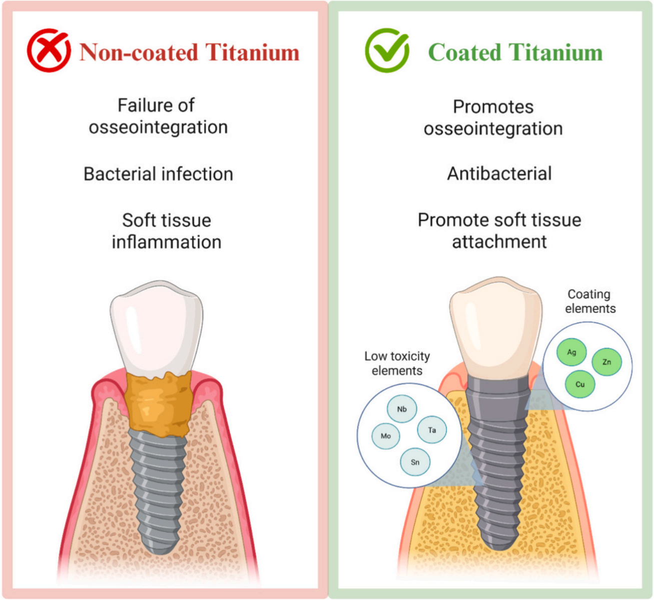

Fig. 4. Illustration comparing uncoated titanium and coated titanium.

adapting perfectly to the patient's anatomy and reducing the risks associated with standard implants. This additive manufacturing method significantly shortens production time and increases the chances of successful surgery. As exemplified, additive manufacturing presents significant potential to transform medical production, offering personalized, efficient, and functional solutions that open new horizons in the fields of implants and tissue engineering.

4.3. Surface engineering and tribological performance of Ti-based implants

Despite their favorable mechanical and corrosion behavior, Ti-based materials are intrinsically disadvantaged in tribological terms because of their relatively low hardness, high chemical reactivity and tendency to gall under sliding contact, which can result in increased wear and debris formation in articulating or micro-motion-prone interfaces [78,79]. Aiming to mitigate these limitations, several surface-engineering strategies have been developed, including the deposition of hard ceramic (such as Alumina, Zirconia) or nitride coatings (such as TiN, TiCN, TiAlN), thermochemical treatments, ion implantation, and laser-based surface modification, which increase surface hardness and reduce friction without compromising bulk mechanical properties. In addition, micro- and nano-texturing, as well as the design of graded or composite surface layers incorporating lubricious phases or bioactive ceramics, can further improve wear resistance and control debris generation. All these abovementioned approaches allow β-Ti alloys to retain their advantageous bulk properties but at the same time achieving tribological performance compatible with demanding biomedical applications [80].

5. Biocompatibility & citotoxicity

Biocompatibility and corrosion resistance represent the two most critical attributes of biomaterials [81]. Upon implantation, the devices provoke numerous reactions within the biological environment, interacting with bodily fluids, proteins, and cells, which ultimately determine the success of the implantation [82–84]. Consequently, biocompatibility testing is an essential requirement for biomedical titanium and titanium alloy implants [54]. To evaluate the safety and efficacy of titanium, it is routinely subjected to in vitro cytotoxicity assessments utilizing specific cell types, including but not limited to MSCs, L929 and MC3T3-E1 cells. These evaluations consistently affirm the viability and reliability of titanium as a material for implants [85]. Recently, Anene et al. highlighted the mechanical characteristics of various titanium and titanium-based alloys [81]. Furthermore, authors claimed that when titanium and its alloys were in contact with bone, the formation of a fibrous tissue barrier was absent, confirming the biocompatibility of the material.

On the contrary, for applications requiring high mechanical strength, such as hip joint implants, titanium alloys are preferred due to their superior mechanical properties compared to pure titanium [86,87]. Among all titanium alloys, Ti-6Al-4V is the most prevalent implanted material, attributed to its strength of 1000 MN/m^2 (19%) and a 40% increase in corrosion resistance relative to pure titanium [88]. However, the ions release from Ti-alloys such as aluminum (Al) and vanadium (V) can induce toxicity in surrounding tissues upon wear in the biological environment. Also, Mo in titanium is not suitable for biomaterial application in high amounts due to the increased possibility of ion releasing to the surrounding tissue, resulting in totally diminished cytoplasm content and reduced cell spreading. Therefore, this element must be used in small quantities, just as in the case of Ni, V, and Al. With this scenario in mind, nowadays, extensive research efforts are being directed toward the development of an alloy without aluminum (Al) and vanadium (V) elements. Furthermore, Wang et al. [89] claim that the toxicity levels of Al, V, and iron (Fe) surpass those of other elements, including nickel (Ni), niobium (Nb), and tin (Sn).

In this way, the incorporation of tin (Sn) into the titanium matrix enhances hardness, corrosion, resistance, contributing to a reduction in the modulus of elasticity, with a low toxicity level. It is noteworthy that that aluminum, in particular, may cause both neurological and non-neurological damage, leading to various health issues such as brain damage, digestive disorders, neurotoxicity, contact dermatitis, breast cancer, osteomalacia, anemia, and encephalopathy [90]. As a result, the biocompatibility of alloying elements in titanium alloys used as implant materials has become an important area of research [91]. Currently, many researchers are actively investigating the toxicity and biocompatibility of various components in these alloys. Indeed, orthopedic implants can fail when wear debris is released into surrounding tissues, leading to inflammation, tissue damage, and reduced functionality of the implant. This usually necessitates a replacement, which often entails costly revision surgery that has a lower success rate than the initial procedure. Additionally, the presence of foreign substances such as cement particles, metal beads, or hydroxyapatite from coatings worsens the creation of wear debris at the junction between the orthopedic implant and the human body.

Based on the abovementioned drawbacks, the development of new β-Ti alloys that incorporate non-toxic elements such as tantalum (Ta), niobium (Nb), and zirconium (Zr) has been accelerated in response to growing concerns regarding metal toxicity. Notably, the introduction of Ta has been shown to significantly reduce metal release concentrations [92,93]. For instance, Okazaki et al. [94] has demonstrated that cell growth rates for β-Ti alloys, including Ti-15Zr-4Nb-4Ta, exceed those observed with Titanium alloy Ti-6Al-4V Furthermore, Kopova et al. identified the β-Ti alloy Ti–35Nb–7Zr–6Ta–2Fe–0.5S as a viable material for orthopedic implants, owing to its exceptional biocompatibility, strength, and compatibility with the elastic modulus of bone [95]. As claimed by authors, this particular alloy displayed enhanced cell population density and collagen I production in human osteoblasts cultured over a 21-day period, compared to the standard Ti–6Al–4V alloy. The latter highlights its potential application in load-bearing implants. Additionally, according to their findings, the cell viability indicated that Ti–xTa alloys also exhibit superior biocompatibility compared to the Ti-6Al-4V (ELI) alloy [4]. Similarly, osteoblast were cultured on Ti–5Nb–xFe alloys, and showed that the rate of cell proliferation is associated with the concentration of iron (Fe) ions released from the Ti-alloy to the medium and the chemical interactions occurring between Fe ions and the cells. These findings indicate that Fe ions, at a specific ratio, exhibit commendable biocompatibility.

To date, many approaches can be used to overcome the cytotoxicity drawbacks of such materials. Hence, two principal methods for enhancing the biocompatibility deserve special attention. The first approach involves the reduction of toxic elements, leading to the development of β-type Ti alloys that manifest improved cell viability and growth rates compared to conventional Ti–6Al–4V alloys. The second approach involves surface modification techniques [41,96–98]. Titanium and its alloys are generally regarded as biocompatible, however, they exhibit bioinert properties due to the passivation oxide layer, which demonstrates a lack of reactivity at both cellular and tissue levels (see Fig. 4). Further, the smooth surface of titanium hinders osseointegration with bone, resulting in an intervening fibrous or connective tissue layer that can lead to implantation failure and considerable discomfort for patients [99–101].

In the field of orthopedic surgery, a higher level of osseointegration is associated with improved mechanical stability and an extended useful lifespan of implants. Achieving this outcome necessitates a focus on specific biomolecular adsorption and the regulation of osteogenesis-related cells, while also preventing fibroblast adhesion and micromotions during the initial stages. It is widely recognized that the primary interface established between the titanium surface and the surrounding tissue determines the success or failure of the implants [102]. The development of this critical interface is influenced by both the characteristics of the implant surfaces and the biological response of the host, with the former being considerably more amenable to regulation. Accordingly, to enhance the interaction at the interface, surface modification represents the most effective approach to improving biocompatibility. As a result, even though β-type Ti alloys do not incorporate toxic alloying elements, it is essential to further enhance their osseointegration capabilities. Surface modifications aimed at increasing the bioactivity of Ti alloys have garnered significant attention within the scientific community [103]. In this regard, Takematsu et al. [104] conducted treatments with alkali solutions on Ti–29Nb–13Ta–4.6Zr using electrochemical, hydrothermal, or combined methods for different durations. Their findings revealed that, regardless of the specific methods or parameters employed, the surface of Ti–29Nb–13Ta–4.6Zr exhibited a mesh-like structure with a pronounced capacity to induce apatite formation. Additionally, Dikici et al. [105] synthesized calcium phosphate/TiO_2 composite coatings on Ti–29Nb–13Ta–4.6Zr through the sol–gel process, discovering that the resulting coating significantly enhanced bioactivity, as both calcium phosphate and TiO_2 demonstrate high bioactivity toward bone cells. Recently, there has been substantial interest in specific metallic elements owing to their biological significance, particularly their antibacterial properties. For instance, it has been reported that silver (Ag), copper (Cu), and zinc (Zn) exhibit intrinsically antibacterial activity against a broad spectrum of microorganisms, including those that exhibit resistance to conventional antibiotics [106]. Furthermore, it has been demonstrated that surfaces treated with Ag exhibit superior antibacterial performance compared to those treated with Cu and Zn [60]. As well, organic coatings (or layers) have attracted considerable attention. In recent decades, the immobilization of extracellular matrix (ECM) proteins on the surfaces of Ti implants has been increasingly explored, particularly with CP–Ti and Ti–6Al–4V alloys [107,108]. For instance, CP–Ti coated with collagen has shown enhanced bioactivity for human mesenchymal cells. Similar results have been observed with other types of organics coatings such as chitosan-based films, polymer composites, and antibiotic-loaded hybrid layers. However, there remains a scarcity of literature regarding organic coatings on β-type Ti alloys. Nevertheless, given the substantial success of organic coatings on other Ti alloy types, β-type Ti alloys enhanced with bioactive coatings are anticipated to represent a future trend in the domain of biomedical Ti alloys.

6. Applications

The development of metastable β-Ti alloys for biomedical applications represents the other significant effort in this class of alloys. Table 3 outlines the latest research findings on titanium alloys utilized in biomedical applications, along with their corresponding in vivo studies. The study conducted by Liu et al. [109] highlights the superior performance of the Ti10Mo6Zr4Sn3Nb (referred to asTi-B12) alloy over conventional Ti6Al4V. In vitro assays showed that Ti—B12 did not negatively impact the morphology, proliferation, or apoptosis of MC3T3-E1 cells, indicating low cytotoxicity. In vivo tests revealed no acute systemic toxicity, skin irritation, or allergic reactions in animal models. Ti—B12 significantly improved osteoblast adhesion, alkaline phosphatase (ALP) secretion, and mineralization, with higher ALP gene expression and calcium deposition compared to controls ($p < 0.05$). Although OCN and Runx2 gene expression differences were not statistically significant, Ti—B12 showed consistently higher levels. After three months of rabbit implantation, Ti—B12 achieved superior osseointegration, fusing directly with bone tissue without fibrous encapsulation. These results support Ti—B12 excellent biocompatibility and potential for use in orthopedic implants.

In the paper titled "Research Progress of Titanium-Based Alloys for Medical Devices" by Baltatu et al. [73], the in vivo biological assays demonstrated promising osseointegration and biocompatibility of the newly developed Ti25Mo7Zr15TaxSi alloys. After implantation into rabbit tibial bone, histological and CT analyses revealed active periosteal regeneration, with mesenchymal stem cells differentiating into osteoblasts and osteocytes. The formation of both trabecular and compact

Table 3
Summary of β-Type Ti Alloys Evaluated in in vivo studies.

Composition	Application	In vivo studies	Follow up period	Results	Reference
Ti-6Al-4V	Dental implant	rabbit femoral condylar defect	4 or 8 weeks	Femtosecond laser serves as a promising technique for surface modification in orthopedic applications.	[111]
Ti-35Nb-2Ta-3Z	Bone regeneration and integration	White male rabbits with 48 implants per group	12 weeks	The system effectively accelerates bone regeneration and improves osseointegration.	[112]
Ti10Mo6Zr4Sn3Nb (Ti—B12)	Orthopedic and maxillofacial implants	White rabbits, weighing 2.5–3 kg	12 weeks	Alloys were perfectly embedded in the lateral epicondyle of femur, and no peeling or displacement was found	[109]
Ti25Mo7Zr15TaxSi (x = 0.05, 0.75, 1 wt%)	Surgical implants	Mature rabbits (*Oryctolagus cuniculus*) aged 8–10 months.	8 weeks	The proliferation of mesenchymal stem cells was observed in the periosteum and peri-implant area, differentiating into osteoblasts and then into osteocytes.	[73]
TiAlV containing AgNPs	Veterinary Application. Tibial plateau leveling osteotomy surgery.	Six dogs with clinical signs of the damaged cranial cruciate ligament.	12 weeks	Implant provided good biocompatibility in vivo and facilitated the bone healing process.	[113]
Ti6Al4V	Bone defects	A rabbit model of a lateral femoral condyle defect	6 and 12 weeks	Slow-release of VEGF and BMP-9 could continuously act on local bone defects and enhance osseointegration at	[114]
TiNbSn	Fracture treatment devices.	Rabbits	8 weeks	The TiNbSn alloy plate with a low Young modulus improves the early formation of new bone and stiff callus at the osteotomy site	[115]
TiO2-modified Ti-24 Nb-4 Zr-7.9	Dental or orthopedic implants	White rabbits	4 and 12 weeks	The results indicate that the cytocompatibility and early osseointegration were enhanced by the nanoTiO2 coating.	[30]
Ti–29Nb–13Ta-4.6Zr (TNTZ)	Orthopedic implant	White male Rattus nor vegicus Wistar rats weighing 300 g.	12 weeks	The HA coating on the surface of the implant can reduce excessive inflammation, enhance the osteogenesis process, and then improve osseointegration	[110]
Ti6Al4V-6.5wt%Cu	Orthopedic internal fixation operations	Rats with an age of 3 months and a weight of 400–450 g	6 weeks	Alloy shows a great potential as a bone implant material due to its positive effects against bacterial infection and on bone formation	[116]
Ti-6Al-4V	Dental implant	Rabbit	6 weeks	Good incorporation of bone into the porous scaffolds	[117]
Ni-Ti	Scaphoid bone nonunion	18 patients with scaphoid nonunion	14 weeks, 16 weeks, 18 weeks	All 18 patients achieved satisfactory reduction and fixation with a mean union time of 4.2 months	[118]

bone tissue was observed adjacent to the implants, accompanied by cartilage islands and mineralized zones. Immunohistochemical staining showed strong expression of osteopontin (OPN), MMP-2, and MMP-9, indicating active bone remodeling and extracellular matrix production. These markers confirmed enhanced osteogenesis and integration of the alloy into the host bone tissue, with no signs of adverse reactions or rejection, thus supporting the alloy's potential for orthopedic applications.

In Addition, the study "Hydroxyapatite Coating on Titanium Alloy TNTZ for Increasing Osseointegration and Reducing Inflammatory Response In Vivo on *Rattus norvegicus* Wistar Rats" by Nuswantoro et al. [110] shows that hydroxyapatite (HA) coating enhances Ti–29Nb–13Ta–4.6Zr (TNTZ) implants. After two weeks in rat tibiae, HA-coated implants had a removal torque of 8.1 Ncm, significantly higher than the 1.7 Ncm of non-coated implants, indicating better osseointegration. ELISA analysis also revealed lower levels of the inflammatory marker TNF-α in the HA-coated group (29.44 ng/L compared to 36.16 ng/L), indicating less inflammation. Histological analysis showed more osteoblasts, chondroblasts, and bone trabeculae around HA-coated implants, while non-coated ones were mostly surrounded by granulation tissue and active osteoclasts. Overall, the HA coating promotes bone healing and integration while reducing inflammation, making it a promising option for orthopedic implants.

The history of Ti alloys used in biomedical applications is more recent compared to use in aircraft structures and can be divided into development for orthopedic implants and orthodontics. Alloys for orthodontics can be further categorized into those for devices (appliances) or wires and those for dental implants. Orthodontic alloys for devices and wires have the same requirement as orthopedic alloys for low toxicity, biocompatibility, good corrosion resistance, good formability, and good weldability. However, orthodontic alloys also require high spring back and low stiffness to apply lighter and more constant forces to move teeth. In consideration of the aforementioned criteria, titanium alloys represent the most appropriate choice for application in medical implants when compared to stainless steel and cobalt-chromium alloys. This preference is due to the superior characteristics exhibited by titanium alloys, including a higher strength to weight ratio, reduced stiffness, enhanced biocompatibility, and improved corrosion resistance. Furthermore, Fig. 5 illustrates examples of titanium implants utilized within the human body.

7. Application of computational techniques in Ti alloys

In recent years, machine learning has gained great relevance in materials science, enabling the design and development of innovative alloys with specific properties. In the case of titanium (Ti) alloys, which are fundamental for biomedical applications such as orthopedic and dental implants, various computational techniques have been employed to optimize their composition and improve their biomechanical compatibility [119]. Traditional empirical methods, such as molybdenum equivalence (Moeq), the electron-to-atom ratio (e/a), d-electron theory, and high-throughput approaches, have been widely used to predict and adjust their properties. However, most of these models are often computationally expensive and inefficient. In this context, machine learning has emerged as a powerful alternative to accelerate the design of these alloys, reducing computational demands without compromising accuracy in predicting their mechanical and structural characteristics [58,120].

Indeed, traditional methods are simplified computational approaches that use relationships derived from experimental data or approximate theoretical models. Unlike first-principles atomistic calculations or explicit numerical simulations such as molecular dynamics or continuum mechanics, these methods rely on mathematical correlations obtained from the physical and chemical properties of materials.

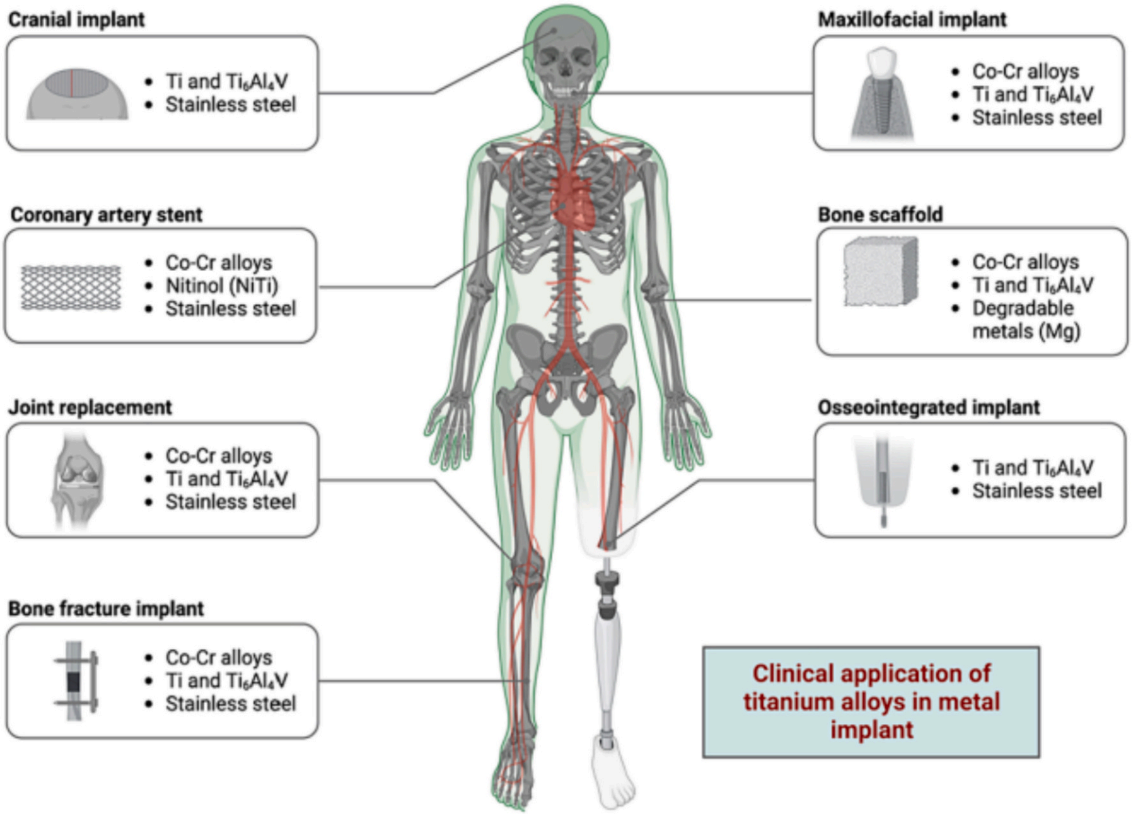

Fig. 5. Metal implant in the human body, highlighting the biomedical applications of Ti alloys in cranial, maxillofacial, orthopedic, and cardiovascular devices. Adapted from ref. [83].

The molybdenum equivalence method (Moeq), for example, is an empirical approach based on alloy design rules that quantifies the contribution of each element to the stability of the β-phase in titanium alloys compared to molybdenum, a common stabilizer of this phase. This method allows predicting the structural stability of alloys and guiding their design [121]. On the other hand, the electron-to-atom ratio (e/a) is based on electronic properties, using the number of valence electrons per atom to estimate phase stability and mechanical properties in titanium alloys. This approach establishes that a higher e/a ratio usually indicates greater β-phase stability, allowing structural behavior prediction and guiding alloy design [122]. For its part, D-electron theory is a semi-empirical model based on electronic structure that considers d-electron occupancy and behavior to explain phase stability and elastic modulus in titanium alloys. Proposed by Morinaga [123], this theory is based on d-electron energy and bond number to predict mechanical properties and phase stability, making it useful in designing alloys with low elasticity modulus and good mechanical properties [124]. Likewise, high-throughput methods combine computational techniques with automation that use databases and empirical or first-principles models to quickly evaluate multiple alloy compositions [121].

On the other hand, machine learning (ML) has become a key tool in designing low-modulus Ti alloys. These techniques enable efficient prediction of material properties and alloy composition optimization. For example, the Extreme Gradient Boosting (XGBoost) algorithm has been widely used to predict the elastic modulus of β-Ti alloys, achieving an R-squared value of 0.962 and an RMSE of 3.16 GPa, demonstrating its effectiveness in predicting the elastic modulus of Ti alloys [125]. Another study combined XGBoost with Moeq and e/a to design β-Ti alloys for medical applications with low modulus [126]. Further, Extra Tree Regression (ETR) has also been used to predict the Young's modulus of Ti alloys by analyzing a database of 246 alloys, identifying specific heat as the most influential parameter in reducing Young's modulus [127]. Additionally, Artificial Neural Networks (ANN) with the Rule of Mixtures (ROM) have been used to generate objective functions in multi-objective optimization Genetic Algorithms (GA), to design of a three-layer dental implant with optimal composition and processing parameters [128]. Very recently, Random Forest and Neural Network techniques have also been applied to predict the bulk modulus (K) and shear modulus (G) of Ti-Nb-Zr ternary alloys. In this study, authors used models to predict Young's modulus throughout the Ti-Nb-Zr system, with Random Forest proving to be the most accurate [129].

Also, worth mentioning that first-principles calculations based on Density Functional Theory (DFT) have been employed to investigate the structural, electronic, and mechanical properties of Ti alloys. Bahloul et al. (2023) [130] used first-principles methods to investigate low-modulus Ti alloys, including DFT with the generalized gradient approximation (GGA), the virtual crystal approximation (VCA), the special quasi-random structure (SQS), and the coherent potential approximation (CPA). These approaches were used to study the mechanical properties of β-Ti–15Nb–xSi alloys, finding that increasing Si concentration reduces Young's modulus, making these alloys suitable for biomedical applications. Fig. 6, and Table 4, show a conceptual map including the most powerful computational techniques used to study Ti alloys.

In the context of biomedical applications, where mechanical compatibility between the implant and bone tissue is crucial, machine learning techniques such as XGBoost, Random Forest, and neural networks have proven particularly promising due to their high accuracy in predicting elastic modulus, shear modulus, and other key mechanical properties. Among them, the XGBoost algorithm stands out as one of the most effective tools, achieving predictions with minimal errors (RMSE of 3.16 GPa) and high correlation with experimental data ($R^2 = 0.962$) [125]. Moreover, its ability to integrate with traditional metallurgical models such as Moeq and e/a provides an additional advantage by incorporating physicochemical fundamentals into the learning process [126]. This combination of accuracy, computational efficiency, and versatility makes XGBoost an ideal technique for accelerating the design of low-modulus Ti alloys, specifically aimed at orthopedic and dental implants, where adequate mechanical strength is required without compromising biocompatibility or inducing stress shielding. Complementary techniques such as Extra Tree Regression [127], artificial neural networks in multi-objective optimization schemes [129], and Random Forest [128] have also shown valuable results, reinforcing the utility of machine learning in the rational design of titanium alloys for medical applications.

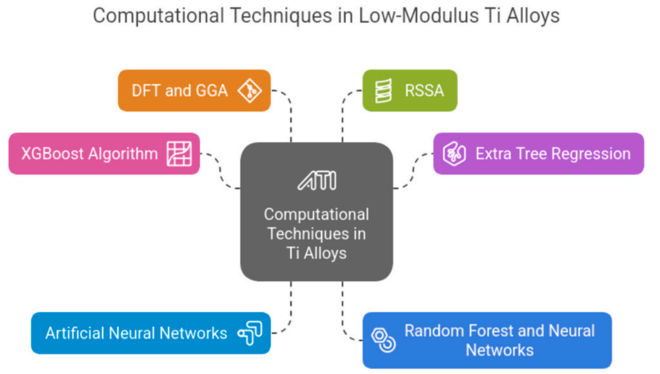

Fig. 6. Computational techniques used for the prediction and optimization of mechanical properties in β-Ti alloys, including machine learning methods and first-principles simulations.

Table 4
Computational techniques used for the prediction and optimization of mechanical properties in β-Ti alloys, including machine learning methods and first-principles simulations.

Technique	Description	Reference
XGBoost Algorithm	Predicts the elastic modulus of β-Ti alloys with high accuracy.	[125,126]
Extra Tree Regression	Predicts Young's modulus based on specific heat.	[127]
Artificial Neural Networks (ANN)	Generates objective functions for multi-objective optimization.	[128]
Random Forest and Neural Networks	Predicts bulk and shear moduli in Ti-Nb-Zr alloys.	[129]
DFT and GGA	Investigates the mechanical properties of β-Ti–15Nb–xSi.	[130]
RSSA	Optimizes Ti alloys for prosthetic applications.	[48]

8. Regulation of patents and intellectual property in the development of titanium alloys for biomedical applications

The development of titanium alloys for biomedical applications is a field at the interconnection of advanced materials science, regulatory compliance, and intellectual property management. As these alloys become increasingly vital for surgical implants and medical devices, understanding the legal and ethical frameworks that govern their innovation and commercialization is essential. This section explores the key regulatory standards, strategies for intellectual property protection, and the challenges and opportunities associated with managing patents and proprietary technologies in the biomedical sector. Additionally, it directs the ethical considerations and the importance of balancing innovation with equitable access to life-saving medical technologies. Thus, this section is aimed to provide a clear understanding of the complex environment that shapes the development and deployment of titanium alloys in modern medicine.

8.1. Regulatory and normative landscape

Titanium and its alloys have become fundamental materials in the field of surgical implants and medical devices. However, the safety and effectiveness of devices made from titanium depend not only on the intrinsic properties of the material, but also on strict compliance with international standards. Organizations such as ISO (International Organization for Standardization) and ASTM (American Society for Testing and Materials) have established a regulatory framework that defines the chemical composition, mechanical performance, and quality control requirements for titanium alloys used in medical applications.

8.1.1. ISO standards

The International Organization for Standardization (ISO) has established a comprehensive set of standards to regulate the use of titanium and its alloys in medical devices and surgical implants [131]. These standards address critical aspects such as chemical composition, mechanical performance, and biocompatibility, ensuring that titanium-based materials consistently meet the stringent requirements necessary for safe and effective clinical use. Therefore, by adhering to ISO guidelines, alongside complementary ASTM standards, manufacturers can guarantee the reliability and quality of implants designed for demanding healthcare applications [132]. Among the most relevant ISO standards in the biomedical field, specifically in the area of development of prostheses and dental implants, the ISO 5832 series stands out as the definitive reference for metallic materials used in surgical implants. Within this series [132], ISO 5832-2 specifies the requirements for unalloyed titanium, detailing acceptable chemical compositions, mechanical properties such as tensile strength and elongation, and standardized testing protocols [133,134]. This ensures that only titanium of sufficient purity and mechanical integrity can be used in applications like bone screws, plates, and dental implants, minimizing the risk of adverse biological reactions. Similarly, ISO 5832-3 focuses on the Ti-6Al-4V ELI (Extra Low Interstitial) alloy, which is the most commonly used titanium alloy in orthopedic and dental implants [135,136]. This standard imposes strict limits on impurities and interstitial elements and mandates comprehensive mechanical testing to guarantee the alloy's biocompatibility, fracture toughness, and fatigue resistance. Other parts of the ISO 5832 [137] series, such as ISO 5832-11 for Ti-6Al-7Nb, address additional titanium alloys and product forms, ensuring consistency and traceability throughout the supply chain [138]. Beyond material specifications, ISO 10993 plays a critical role by outlining the biological evaluation of medical devices. This standard provides a risk-based framework for assessing potential biological hazards through a series of tests, including cytotoxicity [8,139], sensitization, irritation, systemic toxicity, genotoxicity, and implantation studies. Thus, ISO 10993 stands as essential for demonstrating that titanium-based devices will not provoke harmful biological responses when in contact with tissues or bodily fluids.

Meanwhile, quality management is another backbone of medical device regulation, which is addressed in detail by ISO 13485 [140]. This standard defines the requirements for a quality management system (QMS) tailored to the medical device industry, covering every aspect from design and development to production and post-market activities. For manufacturers of titanium implants, ISO 13485 certification is often a prerequisite for market access, assuring regulators and customers that products are consistently manufactured to the highest standards of safety and quality [140]. Risk management is equally vital and is governed by ISO 14971, which provides a structured methodology for identifying, evaluating, and controlling risks associated with medical devices throughout their lifecycle [141]. For titanium alloys, this involves systematic assessment of potential hazards such as material defects, corrosion, mechanical failure, and biocompatibility issues. The standard emphasizes continuous risk monitoring and mitigation, which is essential for ensuring patient safety and maintaining regulatory compliance.

8.1.2. ASTM standards

ASTM standards are a set of voluntary, internationally recognized technical documents developed by ASTM International (formerly the American Society for Testing and Materials). These standards define explicit requirements for materials, products, systems, and services to ensure quality, safety, performance, and consistency across industries. Thus, in the biomedical area, ASTM standards play a pivotal role in defining the quality and performance benchmarks for titanium alloys used in surgical implants and other medical devices. Among the most relevant to the Ti-alloys related biomaterials are ASTM F1472, ASTM F136 (which aligns with ISO 5832-3), and ASTM F620, each addressing different forms and compositions of titanium alloys to ensure their suitability for biomedical applications [142]. For instance, ASTM F1472 establishes the chemical, mechanical, and metallurgical requirements for wrought titanium-6aluminum-4vanadium alloy or Grade 5 titanium (UNS R56400), which is widely used in the manufacture of surgical implants. This standard specifies the acceptable limits for alloying elements and impurities, as well as the mechanical properties such as tensile strength, yield strength, and elongation. It also outlines procedures for testing and inspection, ensuring that the material possesses the necessary purity, structural integrity, and consistency required for medical use [143]. Similarly, ASTM F136, harmonized with ISO 5832-3, specifically addresses the requirements for the Ti-6Al-4V ELI alloy. This alloy is preferred for critical implant applications due to its enhanced ductility, fracture toughness, and biocompatibility. Further, ASTM F136 details the allowable chemical composition, mechanical properties, and microstructural characteristics, along with the testing protocols that manufacturers must follow. The standard ensures that implants made from Ti-6Al-4V ELI meet the highest standards for safety and performance, particularly in load-bearing orthopedic and dental devices [137]. Likewise, ASTM F620 focuses on titanium alloy forgings intended for surgical implants. This standard covers not only the chemical and mechanical requirements but also the specific processes involved in forging, such as annealing treatments and the evaluation of mechanical properties post-processing. By regulating these aspects, ASTM F620 ensures that forged titanium components exhibit the necessary strength, toughness, and fatigue resistance for long-term implantation [144]. A detailed overview of the legal and normative requirements that govern the use of titanium alloys in medical devices is presented in Table 5.

8.2. Intellectual property protection strategies

The commercialization and protection of innovations in biomedical materials, particularly titanium and its alloys, are governed by a rigorous regulatory and normative landscape designed to ensure patient safety, product efficacy, and market integrity [145]. Titanium's exceptional performance have made it a material of choice for surgical implants and medical devices. However, the safe and effective use of titanium-based innovations hinges not only on their inherent properties but also on strict adherence to international standards and regulatory requirements [146]. In a similar way, the protection of intellectual property in the field of β-titanium alloys is a key factor in ensuring competitiveness and technology transfer in sectors such as biomedical. In recent years, there has been a steady increase in the number of patents related to these alloys, reflecting the interest in protecting innovative chemical compositions, improvements in mechanical properties, and new manufacturing methods [121]. Relevant patent examples include those that claim specific β-alloy compositions, detailing the proportion of stabilizing elements such as molybdenum, vanadium, niobium, or chromium, which enable superior microstructures and mechanical properties, such as high strength, low density, and excellent biocompatibility [43]. In addition, many inventions focus on advanced manufacturing methods, such as additive manufacturing and powder metallurgy. The protection of these processes often includes claims on specific processing parameters that improve the homogeneity and performance of the alloys. On the other hand, surface treatments also

Table 5
Legal and normative framework governing titanium alloys in medical devices.

Legal/ Normative Instrument	Scope and Application	Juridical Relevance	Obligations for Manufacturers/Users	International Harmonization	Legal Consequences of Non-Compliance	Strategic Importance
ASTM F136 / ASTM F1472	Technical standards for Ti-6Al-4V (Gr 5) alloys in medical devices (composition, mechanical properties, testing)	Serve as technical references required by regulators (FDA, MDR, etc.) for market approval; compliance is often a prerequisite for commercialization	Ensure compliance with chemical, mechanical, and quality requirements; maintain documentation and traceability; periodic testing	Referenced by FDA (USA), MDR (EU), and other authorities; harmonized with ISO 5832-3	Denial of market access, product recalls, legal liability, regulatory sanctions	Foundation for product safety, facilitates global market entry, supports legal defensibility
ISO 5832-3	International standard for Ti-6Al-4V alloys in surgical implants (material purity, mechanical integrity)	Recognized globally; required for CE marking and international trade	Demonstrate conformity through testing and certification; subject to regulatory audits	Harmonized with ASTM standards; referenced in global regulations	Loss of certification, export/import restrictions, regulatory penalties	Enables international commercialization, ensures high safety and quality standards
ISO 13485	Quality management systems for medical device manufacturing and supply	Legal requirement in many jurisdictions; essential for regulatory approval and ongoing compliance	Implement and maintain QMS; undergo regular audits; ensure traceability and record-keeping	Required for CE mark (EU), MDSAP (Canada, Australia, etc.), recognized by FDA	Fines, withdrawal of products, suspension of operations, exclusion from markets	Guarantees process reliability, underpins regulatory submissions, enhances reputation
ISO 10993	Biological evaluation and biocompatibility testing of medical devices	Legal basis for safety assessment; referenced by authorities for market approval	Conduct and document biocompatibility tests; provide evidence in regulatory submissions	Referenced by FDA, MDR, and other agencies worldwide	Regulatory rejection, product recalls, liability for patient harm	Ensures patient safety, reduces litigation risk, critical for regulatory acceptance
FDA (USA) / MDR (EU)	Regulatory frameworks for medical devices (market authorization, safety, surveillance)	Legally binding; establish requirements for market entry and post-market oversight	Submit technical files, clinical data, and compliance documentation; mandatory adverse event reporting	Reference ASTM, ISO standards; some mutual recognition agreements	Criminal/civil penalties, product bans, mandatory recalls, loss of market authorization	Determines access to major markets, ensures ongoing compliance, protects public health
WIPO Treaties (PCT, Madrid, Hague)	Intellectual property protection (patents, trademarks, designs)	Provide legal mechanisms for protecting and enforcing innovations in titanium implant technology	File for patents, trademarks, or designs; manage international registrations	Facilitate protection in multiple countries through single application	Loss of exclusive rights, risk of infringement, loss of competitive advantage	Secures innovation, enables technology transfer, incentivizes R&D investment
National Standards/ NOM (e.g., NOM-153-SSA1–1996, Mexico)	Local regulatory requirements for medical devices (technical, sanitary, professional standards)	Define mandatory minimum requirements; supplement international standards	Ensure compliance with local laws and standards; adapt to specific national requirements	May reference or align with international standards	Administrative sanctions, inability to market products locally, reputational damage	Ensures local market access, addresses country-specific risks, complements global compliance

represent a field of innovation and protection, as they improve biocompatibility and tissue integration through techniques such as abrasive particle blasting, acid solution treatments, or functional coatings [147].

Table 5 provides key elements for the legal analysis of medical devices made from titanium alloys, as it synthesizes the main normative and legal instruments that regulate their production, commercialization, and intellectual property protection at both international and national levels. Firstly, it includes the technical standards ASTM F136 and F1472, as well as ISO 5832-3, which establish the requirements for chemical composition, mechanical properties, and testing methods for the Ti-6Al-4V alloy, widely used in surgical implants for its biocompatibility and mechanical strength. Generally, compliance with these standards is a mandatory requirement for accessing regulated markets, such as the United States and the European Union, where authorities like the FDA (Food and Drug Administration) and the MDR (Medical Device Regulation) require conformity with these standards for product approval and surveillance.

The table also highlights the importance of ISO 13485, which obliges manufacturers to implement quality management systems specific to medical devices, and ISO 10993, which regulates biocompatibility testing, both essential aspects to ensure patient safety and product traceability. In addition, it includes the regulatory frameworks of the FDA and MDR, which not only require compliance with international technical standards but also establish binding legal obligations such as the submission of technical files, clinical data, and mandatory reporting of adverse events. In the field of innovation protection, and intellectual property, the table incorporates international treaties administered by WIPO (World Intellectual Property Organization), PCT (Patent Cooperation Treaty), Madrid System (Madrid Agreement and Madrid Protocol), and Hague System (Hague Agreement) which facilitate the protection of patents, trademarks, and industrial designs in multiple countries through unified procedures, thus ensuring commercial exclusivity and return on R&D investment. Finally, national/regional standards examples such as NOM-153-SSA1-1996 in Mexico are considered, which complement international standards and adapt requirements to local needs and risks, being mandatory for commercialization in specific markets.

8.2.1. *Recent cases of intellectual property protection in beta titanium alloys*

To provide a clearer understanding of the legal and normative framework governing titanium alloys in medical devices, the following section presents two specific examples that illustrate how intellectual property protection has been key in the development and application of advanced titanium alloys. Both cases reflect the patent strategies, covering not only innovative chemical compositions but also manufacturing methods and microstructure control [148]. The first case corresponds to patent ES2426313T3, which describes a high-strength quasi-β titanium alloy and the methods for its manufacture, designed for critical applications in the aerospace industry such as landing gear. This invention focuses on a specific composition that includes aluminum, vanadium, iron, molybdenum, chromium, and oxygen in precise proportions, achieving a combination of high strength, hardenability, and ductility.

The protection granted by this patent covers not only the innovative chemical composition but also the processing methods, such as subtransus heat treatments and specific proportions of isomorphic and eutectoid β-stabilizers. This protection strategy prevents third parties from reproducing the alloy or its processes without authorization, ensuring that the holders retain control over its commercial exploitation and enabling technology transfer on an international scale [149]. Another interesting example is the patent ES2322082T3, which focuses on a titanium aluminide-based alloy with a fine and homogeneous morphology, suitable for lightweight structural applications. This invention addresses the problem of variability in composition and temperature fluctuations during industrial production, ensuring the homogeneity of the alloy without the need to fundamentally modify manufacturing procedures. The patent protects both the chemical composition, which includes defined percentages of aluminum, niobium, molybdenum, boron, and carbon, in addition to the titanium base, and the manufacturing method, which can be carried out using melting techniques or powder metallurgy. It also claims the controlled presence of the beta phase up to specific temperatures, improving structural stability and process safety. This protection allows the holders to exploit the invention in different sectors where lightweight and high-strength materials are strategic [150,151]. Table 6 presents the most relevant information about the two examples of patent protection in Ti-alloy, serving as a concise reference for understanding the current landscape of intellectual property in this field.

The table provides a comparative legal analysis of two selected Spanish patents (ES2426313T3 and ES2322082T3) focused on advanced titanium alloys for strategic industrial applications. The table outlines the legal consequences of infringement, which include civil actions (such as injunctions and damages), administrative remedies, and, in some cases, criminal sanctions for willful violations. These enforcement mechanisms are essential for maintaining the value and integrity of the patented technology.

9. Sustainability dimensions of metallic biomaterials in global healthcare

The global implementation of metallic biomaterials in healthcare applications, particularly for bone prostheses and orthopedic implants, represents a critical point of technological advancement and environmental stewardship that demands urgent attention to sustainability principles. The metallic biomaterials sector includes a diverse range of materials including titanium alloys, stainless steel, cobalt-chromium alloys, and emerging biodegradable metals such as magnesium, iron, and zinc, which collectively support millions of patients worldwide through joint replacements, dental implants, and cardiovascular devices [152]. However, the production of metals currently accounts for 40% of all industrial greenhouse gas emissions and 10% of global energy consumption, processing 3.2 billion tons of minerals annually while generating several billion tons of by-products [153]. This substantial environmental footprint necessitates a fundamental transformation toward sustainable practices that can reconcile the growing demand for metallic biomaterials with planetary health objectives and circular economy principles.

The sustainability challenges inherent in metallic biomaterials extend beyond manufacturing to include the entire product lifecycle, from raw material extraction through end-of-life management. Indeed, contemporary metallic implants, while offering superior mechanical properties and biocompatibility, present significant environmental concerns due to their reliance on energy-intensive primary production processes and their permanent residence in the body, which precludes traditional recycling pathways [152–154]. The current linear "take-make-dispose" model predominates in the sector, where approximately two-thirds of metallurgical production relies on primary sources rather than recycled materials [155]. Furthermore, the complexity of modern implants, often incorporating multiple metal components with different compositions, creates additional challenges for material recovery and circular management. These sustainability concerns are amplified by the demographic trends driving increased demand for orthopedic implants, with hip replacement surgeries alone projected to increase from 1.8 million procedures in developed countries in 2015 to 2.8 million by 2050 [155].

In view of this current landscape, to address the sustainability challenges of metallic biomaterials in healthcare, it is crucial to adopt a life cycle perspective that incorporates environmental, technological, regulatory, and global factors. Fig. 7 synthesizes the main sustainability dimensions of metallic biomaterials across their life cycle, integrating environmental, technological, regulatory and socio-economic factors into a single conceptual framework. The diagram illustrates how upstream impacts from ore extraction and energy-intensive primary metal production propagate through manufacturing, clinical use and end-of-

Table 6
Examples of patent protection in titanium alloy innovations.

Case / Patent	Protected Subject Matter	Scope of Protection	Legal Rights Conferred	Strategic Sectors/Uses	Territorial Coverage	Licensing and Exploitation	Legal Consequences of Infringement
ES2426313T3	- Quasi-beta titanium alloy composition - Manufacturing methods (including sub-transus heat treatments, beta stabilizer ratios)	- Exclusive rights over the specific chemical composition and the described production processes - Covers any unauthorized manufacturing, use, sale, or importation of the alloy or its methods	- Right to exclude third parties from commercial exploitation - Right to license, assign, or enforce the patent - Enables control over technology transfer	Aerospace (critical components, e. g., landing gear)	Spain (and possibly other countries through priority claims and patent family)	The holder may license or transfer rights; negotiate royalties or technology transfer agreements	Civil actions for infringement: injunctions, damages, prohibition of use or sale, customs seizure
ES2322082T3	- Titanium aluminide-based alloy with defined elemental composition - Manufacturing methods (melting, powder metallurgy) - Control of the beta phase up to specific temperatures	- Exclusive rights over the alloy composition and production techniques - Claims cover both product and process, including phase control for greater stability	- Right to exclude others from manufacturing, using, or selling the alloy or its process - Right to license or assign - Control over commercial exploitation in strategic sectors	Aerospace, automotive (lightweight, high-strength structures)	Spain (and other jurisdictions through patent family: EP, JP, US, etc.)	The holder may grant licenses, establish partnerships, or enforce rights against infringers	Civil and administrative remedies: injunctions, damages, possible criminal sanctions for willful infringement

Fig. 7. Sustainability dimensions in the life cycle of metallic biomaterials.

life phases, while also showing leverage points where circular-economy strategies (such as recycling, secondary production and biodegradable alternatives) and digital tools can reduce the overall footprint. By mapping these interconnected pressures and opportunities, Fig. 7 underlines that the development of β-Ti alloys for greener healthcare cannot be guided solely by mechanical or biological performance, but must also align with decarbonization targets, regulatory constraints and realistic recycling and recovery pathways (Table 7).

9.1. *European leadership in circular economy initiatives*

During the last decades Europe demonstrated their commitment to develop sustainable approaches to metallic biomaterials through a set of policy frameworks and innovative industry initiatives that prioritize circular economy principles. As a matter of fact, the European Union's commitment to achieving climate neutrality by 2050 has catalyzed significant investments in sustainable metallurgy and biomaterials innovation, positioning the region at the forefront of the global transition toward environmentally responsible healthcare technologies [161]. In this context, the European Recycling Industries' Confederation (EuRIC) has published recently the Circular Economy Action Plan for Recycled Metals that addresses critical barriers to sustainable metal use, including stagnating domestic demand for recycled metals, biased methodologies for defining green products, and insufficient focus on recyclers in key policies such as the Clean Industrial Deal [162]. This strategic framework recognizes that recycling already provides between 40% and 55% of Europe's aluminum, copper, and zinc supply, demonstrating the continent's existing capacity for circular metal management [163].

Table 7
Comparative carbon footprint of metallic biomaterial production.

Material	Production Method	Carbon Footprint (kg CO_2e/kg)	Energy Consumption (MJ/kg)	References
Titanium	Kroll Process	17–53.7	314.52	[75]
Titanium	Additive Manufacturing	14.9–38.8	143.22	[156]
Magnesium	Pidgeon Process (China)	17.1–28	150–200	[157]
Magnesium	Electrolytic Process	5.3–17.8	80–120	[158]
Zinc	Special High Grade	3.89	15–25	[158]
Iron	Blast Furnace	1.76	20–30	[159]
Recycled Titanium	Advanced Recycling	7.8	45–75	[160]

For its part, the medical technology sector includes diverse circularity approaches that address the complex challenge of integrating sustainable practices with stringent regulatory requirements. Furthermore, the academic research has demonstrated that successful circular economy implementation in healthcare requires overcoming significant barriers, including regulatory constraints, high upfront investment costs, and limited consumer awareness, with studies identifying cultural and market barriers as primary impediments to transition. Also, at EU level, the Chemical recycling technologies promoted through EU for medical device circularity, has achieved up to 30% substitution of virgin materials in polyurethane-based medical applications without compromising safety standards [164]. It is worth noting that EU promoted digital technologies combined with a circular economy would enable dematerialization and optimized resource utilization. However, implementation faces challenges due to company culture resistance and the persistence of linear supply chain systems [165]. Last but not least, a crucial issue lies in the life cycle assessment, as highlighted by recent studies revealing that healthcare systems generate substantial environmental impacts. Indeed, recently Mckenzie et al. reported a very detailed work on the environmental impact of health care for musculoskeletal procedures, claiming that such interventions alone are responsible for producing significant carbon footprints that necessitate systematic approaches to waste reduction and material recovery [156]. Finally authors urged to incorporate recycling strategies which require segregation by material type, composition, and contamination risk, to maintain biocompatibility standards [166].

9.2. Environmental impact assessment and life cycle considerations

A very important issue in metallic biomaterials and specifically Ti-alloys based biomaterials deals thus with the life cycle assessment (LCA). As demonstrated, recent studies reveal significant environmental impacts that necessitate systematic approaches to sustainability optimization across the entire value chain. For instance, titanium hip prosthesis manufacturing demonstrates that additive manufacturing processes can reduce environmental burden while maintaining material performance standards, with the production phase accounting for 69.3% of total environmental impact at 38.8 kg CO_2 equivalent per femoral stem [156]. In this context, the notion of 'green' processing must be understood in a strict life-cycle sense rather than being equated solely with reduced scrap or near-net-shape capabilities. Although powder-based and additive manufacturing routes can substantially decrease material waste and enable lighter, lattice-type structures, they are also associated with higher electricity demand, complex powder production chains and, in some cases, more energy-intensive post-processing than conventional wrought or subtractive methods. As several LCA studies on metallic implants have shown, the net environmental benefit of these technologies depends on the balance between reduced material use, improved functional performance and the additional energy and resource inputs they require, so that a process can only be considered genuinely 'greener' when its full life-cycle impact (including powder production, manufacturing, use phase and end-of-life) is demonstrably lower than that of established routes [156].

Similarly, titanium knee implant manufacturing showed that additive manufacturing techniques using electron beam melting can reduce carbon dioxide emissions to 14.88 kg per part compared to conventional manufacturing approaches, while consuming only 143.22 MJ of primary energy versus 314.52 MJ for traditional milling processes [167]. All these works indicate substantial opportunities for reducing the environmental footprint of metallic biomaterials through advanced manufacturing technologies and process optimization. Furthermore, the environmental assessment of medical procedures themselves reveals additional dimensions of sustainability concern, with carbon emissions per surgical procedure ranging from 7.8 to 28.8 kg CO_2 equivalent for hand surgery procedures, highlighting the broader ecosystem impact of metallic biomaterial applications. As reported in the literature through recent comparative studies of different surgical techniques, such as anterior cruciate ligament reconstruction methods, demonstrate that material selection and surgical approach can significantly influence environmental outcomes, with some techniques showing 300% higher carbon footprints than alternatives [154]. A very representative example is that the use of disposable versus reusable surgical instruments for lumbar spine fusion procedures demonstrated that environmental optimization requires careful consideration of sterilization energy requirements, as the steam sterilization is to date by far a major contributor to greenhouse gas emissions [167].

9.3. Biodegradable metals and emerging sustainable alternatives

Based on the abovementioned environmental issue around the development of novel metallic biomaterials and tailored medical grade β-Ti-alloys, the development of biodegradable metallic biomaterials has emerged as a paradigmatic shift toward sustainability that addresses fundamental limitations of permanent implants while supporting regenerative medicine approaches. These biodegradable metals such as magnesium, iron, and zinc alloys would offer superior mechanical behavior compared to biodegradable polymers while providing controlled degradation profiles that match tissue regeneration timeline [152]. For instance, magnesium alloys demonstrate particularly promising characteristics with specific strength values, relatively low elastic modulus of 41 GPa, and density of 1.74 g/cm^3 that closely approximate bone properties, thereby minimizing stress shielding effects while supporting gradual load transfer to regenerating tissue [168]. Further, the controlled degradation of magnesium alloys materials eliminates the need for secondary surgical procedures for implant removal, reducing patient morbidity and healthcare system burden while addressing long-term biocompatibility concerns associated with permanent metal implants. Also, another strategy based on the integration of bio-based and sustainable metal alternatives represents another important research line that flourished recently that takes advantage of using renewable resources and biological processes to create environmentally friendly materials with unique performance characteristics [169]. This route utilizes materials derived from biological sources or employ sustainable production methods that significantly reduce carbon footprints and resource depletion compared to conventional metallurgical processes [168]. As highlighted, all seem to point to the future trends the development of sustainable secondary production pathways that maximize scrap utilization and minimize primary resource extraction would represent a critical transition toward circular metallurgy, with projections indicating that recycled materials could provide up to two-thirds of the metal supply by 2050–2060.

It is worth mentioning that when considering partially bio-based or biodegradable devices, Ti alloys occupy a complementary rather than directly interchangeable position. β-Ti alloys are designed to provide long-term structural support with high fatigue resistance, a stable passive oxide layer and minimal dimensional change over time, making them suitable for permanent or long-lasting biomedical devices and specially for orthopedic and dental implants. In contrast, biodegradable metals such as Mg, Fe and Zn alloys, as well as partially bio-based composite systems in which metallic phases are combined with bio-derived polymers or ceramics, aim to deliver temporary mechanical support that gradually decreases as the surrounding tissue regenerates, thereby reducing or eliminating the need for implant removal and potentially improving overall life-cycle performance. Although these bio-based and biodegradable solutions may offer clear advantages in selected indications and from a circular-economy perspective, their current mechanical reliability, control over degradation and clinical evidence are still more limited than for Ti alloys; therefore, at present, β-Ti implants are better viewed as robust benchmarks against which emerging partially bio-based devices are compared, rather than direct replacements in most load-bearing applications.

9.4. Future prospects and global implementation gaps

The global transition toward sustainable metallic biomaterials faces significant implementation drawbacks that require coordinated international action and substantial technological advancement to achieve meaningful environmental impact reduction. To date, current recycling capabilities for biomedical metals remain severely limited due to contamination concerns, regulatory restrictions, and the complex multi-material composition of modern implants, creating a critical need for innovative recycling technologies and regulatory frameworks that can safely process medical-grade materials [170]. Thus, the development of device-specific recycling protocols and the establishment of harmonized international (global) standards for secondary medical materials represent essential steps toward global sustainability in the biomaterials sector. Furthermore, the disparity between developed and developing countries in access to sustainable biomaterial technologies creates additional challenges for equitable global implementation of environmentally responsible healthcare solutions. Further, the estimated growth in demand for orthopedic implants, driven by aging populations and increased life expectancy, will necessitate proactive measures to prevent unsustainable resource consumption and environmental degradation. According to these claims, all seem to point that it will be compulsory that the future research priorities must focus on developing impurity-tolerant alloys that can accommodate recycled content without compromising biocompatibility or mechanical performance [171]. A crucial tool that would help in the future will probably be based on the combination of artificial intelligence and machine learning in materials design that offers unprecedented opportunities for optimizing sustainability parameters while maintaining clinical efficacy. Additionally, the development of modular implant systems that facilitate component replacement and material recovery would also be a promising route for extending product life cycles and reducing overall environmental impact [156]. International collaboration through organizations such as the OECD (Organization for Economic Cooperation and Development) will be crucial for establishing global standards, sharing best practices, and ensuring that sustainability advances in metallic biomaterials contribute equitably to improved health outcomes worldwide while supporting the achievement of Sustainable Development Goal 9 through resilient infrastructure and sustainable industrialization.

10. Future trends of metastable beta titanium alloys

Titanium (Ti) and its alloys have been widely used as orthopedic implants for several decades. Applications such as artificial joints, dental implants, and bone fixtures have been realized; however, there are still many opportunities for further development to meet clinical needs. The most crucial factor for any implant is its ability to remain in the human body for an extended period without causing adverse side effects, particularly for metallic implants made of Ti alloys. Therefore, porous Ti-based alloys are considered a promising innovation for the future, as they have been shown to promote tissue regeneration and securely anchor implants by regulating the degree of sintering. Furthermore, the traditional powder metallurgy process can be enhanced by using the self-propagating higher temperature synthesis (SHS) method for sintering. However, surface treatment aimed at stimulating a bond between the implant and the surrounding tissue presents significant challenges in the development of titanium alloy implants.

Future research on titanium alloys for orthopedic and dental applications can be improved in several key areas: (1) Future strategies should focus on the design of cost-effective β-Ti alloys that incorporate abundant elements without compromising essential mechanical or biological properties. Alloys such as Ti–27Nb–7Fe–8Cr and Ti–11Nb–7Fe may serve as successful candidates for balancing cost-effectiveness with superior mechanical performance. (2) The development of advanced computational methods, such as phase field modeling, can be beneficial in simulating how microstructures evolve during processing and their impact on mechanical properties. For example, phase field modeling could predict the formation of precipitates during the anti-aging treatment process. A critical initial step involves estimating mechanical properties based on the evolving microstructure. Additionally, innovative compositions of β-Ti alloys could significantly benefit from first-principles calculations. (3) Promoting thermomechanical processes that yield alloys with enhanced fatigue and wear resistance is essential. The establishment of high-throughput methods for evaluating potential microstructures could greatly facilitate this effort. However, the limited availability of performance parameter information on these alloys hampers their application in therapeutic contexts. Therefore, it is imperative to explore additive manufacturing to develop innovative materials and custom-designed implants. (4) To leverage the translational medicine aspect of these materials, it is crucial to utilize large animal models for long-term biocompatibility evaluation. Key areas of investigation should include analyzing leached metal ion concentrations and their cytotoxic effects, rates of corrosion, debris formation due to wear, associated inflammatory responses, osseointegration rates, and the effects of stress shielding. In addition to in vivo testing, the efficacy of these materials should also be assessed using commercially available medical device simulators.

11. Conclusions

Titanium and its alloys have become the backbone of modern biomedical implants, offering an unmatched combination of mechanical strength, corrosion resistance, and biocompatibility. However, the drive toward safer, greener, more effective, and sustainable healthcare solutions have catalyzed the evolution of β-type titanium alloys, which address the limitations of traditional materials by offering lower elastic moduli and eliminating cytotoxic elements such as aluminum and vanadium. Further, recent advances in alloy design (enabled by the strategic incorporation of β-stabilizing elements like niobium, tantalum, and iron) have produced materials that better mimic bone properties and enhance osseointegration, as demonstrated by promising in vitro & in vivo studies. As illustrated through the present work, one of the major issues in current and future development of tailored Ti-alloys will lie on the inclusion of computational methods and artificial intelligence which has accelerated the discovery and optimization of new alloys, enabling rapid prediction of properties and the tailoring of compositions for specific clinical needs. The incorporation of these cutting-edge tools will allow the development of recyclable, biodegradable, and impurity-tolerant alloys, as well as the adoption of circular economy principles and digital design tools. Nevertheless, a lot of challenges remain ahead, particularly regarding the sustainability of titanium production and the global harmonization of regulatory standards. Beyond summarizing recent advances in β-type Ti alloy composition and processing, this review integrates sustainability metrics, regulatory and intellectual property issues, and clinical translation challenges, thereby providing a complete framework that complements previous reviews focused primarily on microstructural and mechanical aspects. Looking ahead, successful clinical translation of these β-Ti systems will depend on generating robust long-term clinical evidence and aligning alloy design and processing with regulatory, manufacturing and cost constraints to enable their routine adoption in orthopedic and dental practice.

CRediT authorship contribution statement

Dulexy Solano-Orrala: Writing – original draft, Formal analysis, Data curation. **Eliana Díaz-Cruces:** Writing – original draft, Resources, Investigation, Formal analysis. **Jorge Troconis:** Writing – original draft, Validation, Software. **Ezequiel Zamora-Ledezma:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Joan Manuel Rodríguez-Díaz:** Writing – original draft, Investigation, Formal analysis, Data curation. **Madalina Simona Baltatu:** Writing – original draft, Visualization, Validation, Formal analysis. **Andrei Victor Sandu:** Writing – original draft, Visualization, Resources, Methodology, Conceptualization. **Javier Hermoso-Gil:** Writing – original draft, Visualization, Software, Resources, Conceptualization. **Frank Alexis:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Petrica Vizureanu:** Validation, Supervision, Funding acquisition. **Camilo Zamora-Ledezma:** Writing – review & editing, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Funding

Authors acknowledge funding received from the Era-Min Cofund 2023 action COOL&SMARTTIT, supported by MCIU/AEI/10.13039/501,100,011,033/UE.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Camilo Zamora Ledezma reports was provided by State Agency of Research. Camilo Zamora Ledezma reports a relationship with State Agency of Research that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data is included in the main text on the manuscript

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