Romanian Journal of Oral Rehabilitation

Vol. 17, No.2 April-June 2025

BIOCOMPATIBILITY OF TITANIUM DENTAL IMPLANTS: INFLUENCES ON OSSEOINTEGRATION AND LOCAL IMMUNITY

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Abstract

Titanium dental implants are a durable therapeutic solution with a high clinical success rate due to their mechanical properties, corrosion resistance, and exceptional biocompatibility. This review analyzes the relationship between titanium, osseointegration, and local immune response, highlighting the decisive role of biological interactions in the long-term success of implants. The osseointegration process involves well-defined stages of inflammation, proliferation, and remodeling in which the implant surface plays a central role in the recruitment and differentiation of osteogenic cells. Simultaneously, the local immune response must be controlled and transient, being mediated mainly by macrophages, whose polarization towards the M2 phenotype supports bone regeneration. Although titanium is recognized for its favorable behavior in the biological environment, certain challenges persist: chronic inflammatory reactions, surface contamination, and the influence of the microbiome on integration. Current research explores functionalized, nanostructured surfaces and implant customization strategies to improve biological integration. An in-depth understanding of immunological and tissue mechanisms is essential for the development of predictable and personalized implant-prosthetic solutions.

Keywords: Titanium, dental implants, biocompatibility, osseointegration, immunity

Introduction

Dental implants are the current standard in edentulous rehabilitation, offering a durable, functional, and aesthetic alternative to traditional prostheses. The success of this treatment depends essentially on the ability of the implant to integrate stably and in the long term into the bone structure, a process known as osseointegration. The choice of implant material is therefore a critical factor, influencing not only the mechanical strength of the device but also its biological behavior in contact with living tissues [1-3].

Titanium is the most widely used material in the manufacture of dental implants due to its exceptional physicochemical properties and outstanding biocompatibility. Discovered in 1791, but medically applied only in the second half of the twentieth century, titanium has established itself through its unique ability to spontaneously form a passive oxide layer (TiO_2), which protects it against corrosion and reduces the aggressive immune response from the body. Biocompatibility, in this context, refers to the ability of a material to interact with the biological environment without generating significant side effects, while facilitating tissue regeneration [1-4].

In dental implantology, biocompatibility is not limited only to the

DOI: 10.62610/RJOR.2025.2.17.30

absence of toxicity, but also involves the ability of the material to support cell adhesion, osteoblast proliferation, angiogenesis, and functional integration into the alveolar bone. At the same time, the material must avoid triggering a chronic immune reaction that could lead to implant failure. Therefore, the study of the interaction between the implant surface and the local biological microenvironment, consisting of inflammatory cells, immune mediators, serum proteins, and the microbiome, is essential for understanding the mechanisms of success or failure of the dental implant [1-3,5].

Osseointegration, a term introduced by Brånemark in the 1960s, describes the direct structural and functional connection between living bone and the surface of an implant. This process involves a succession of biological events starting with the postoperative acute inflammatory response, followed by cell proliferation and the formation of a new bone matrix. All these steps can be positively or negatively influenced by the physicochemical characteristics of titanium and the surface treatments applied [2-5].

However, in addition to its undeniable benefits, titanium can induce, under certain conditions, a chronic inflammatory response or a local hypersensitivity reaction, especially in the presence of contaminants, metal particles resulting from wear, or bacterial biofilm. Therefore, a deeper analysis of how titanium influences the delicate balance between healing and inflammation in the peri-implant environment is required [3-5].

The purpose of this review is to critically analyze the biocompatibility of titanium dental implants, focusing on their influences on osseointegration and local immune response. The cellular and molecular mechanisms involved in the interaction between the implant surface and the host tissues will be explored, with a focus on the role of cytokines, inflammatory cells, and factors that can modulate the peri-implant immune response.

Properties of titanium relevant to dental implantology

Titanium is the reference material in dental implantology due to its unique combination of mechanical, chemical, and biological properties. Its ability to support osseointegration without causing a severe immune response places it at the top of clinical preferences. Titanium's excellent biocompatibility derives from both its chemical composition and its electrochemical behavior in the biological environment [3-6].

Pure titanium (Ti cp - commercially pure) is available in several grades (1–4), differentiated by oxygen content and other residual alloying elements. Grade 4 is the most commonly used in implantology due to the optimal ratio between mechanical strength and malleability. For applications requiring higher mechanical strength, titanium alloys are used, the most common being Ti-6Al-4V (grade 5), which contains 6% aluminum and 4% vanadium. These additions improve mechanical properties, but raise questions about potential ion release and long-term biocompatibility [4-6].

From a mechanical point of view, titanium stands out for its excellent strength-to-weight ratio, having a low density (~4.5 g/cm^3) and a tensile strength between 550–900 MPa, depending on the grade. Its modulus of elasticity (about 100–

110 GPa) is closer to that of cortical bone (10–30 GPa) compared to other metals (e.g., stainless steel or cobalt-chromium), which reduces the risk of "stress shielding," a phenomenon in which the difference in stiffness leads to the resorption of the peri-implant bone. This mechanical compatibility contributes to the physiological distribution of occlusal forces and the maintenance of long-term bone stability [3-6].

Chemically, titanium is a reactive metal, which spontaneously forms, in contact with oxygen, a passive layer of titanium oxide (TiO_2) with a thickness of 2–10 nm. This layer is extremely stable, self-healing (recovers quickly if damaged), biologically inert, and resistant to corrosion, including in acidic or biofluid-laden environments. The natural passivation of titanium prevents the release of metal ions and reduces the direct interaction of the material with immune cells, thus explaining its biocompatible behavior [4-6].

The surface of the implant plays an essential role in the biological response. Roughness, surface energy, and hydrophobicity influence protein adhesion and osteogenic cell behavior. Titanium can be treated by sandblasting, anodizing, acid etching, or applying bioactive layers (e.g., hydroxyapatite) to improve cell response and stimulate the formation of new bone. Moderately rough surfaces ($Ra = 1–2\ \mu m$) are the most effective in promoting osseointegration, compared to smooth or excessively rough surfaces [4-7].

Another significant property is electromagnetic compatibility. Titanium is not ferromagnetic and does not interfere with imaging investigations such as MRI, which is a major clinical advantage compared to other metallic materials. Additionally, titanium has a low electrical conductivity, making it less susceptible to electrochemical processes that could lead to galvanic corrosion in the presence of other metals [5-8].

Despite the obvious advantages, it should be noted that titanium oxide is not completely biologically inert. Its interactions with plasma proteins and inflammatory cells may vary depending on surface condition, the presence of contaminants, and local clinical conditions. Also, in some cases, hypersensitivity reactions or chronic inflammation may occur, associated with metal particles resulting from wear, micro-movements, or incorrect surgical manipulation [4-7].

Table 1 summarizes titanium's key physicochemical and biological properties that make it suitable for dental implantology. Properties such as high mechanical strength, corrosion resistance, and biocompatibility contribute to the material’s long-term clinical success. Additionally, its favorable elastic modulus reduces bone resorption, while modifiable surface characteristics enhance cellular interactions and osseointegration. These features, combined with compatibility in medical imaging, establish titanium as the gold standard in the field of dental implants [4-10].

DOI: 10.62610/RJOR.2025.2.17.30

Table 1. Relevant properties of titanium for dental implantology

Property	**Description**	**Biological/clinical significance**	**Examples/notes**
Mechanical strength	High tensile strength, fatigue resistance	Withstands masticatory forces	Grade 4 titanium, Ti-6Al-4V alloy
Elastic modulus	Closer to bone than other metals	Reduces stress shielding and bone resorption	100–110 GPa vs. 10–30 GPa for cortical bone
Corrosion resistance	Stable oxide layer (TiO_2)	Prevents ion release and inflammatory reactions	Forms instantly upon air exposure
Surface modifiability	Can be sandblasted, acid-etched, and anodized	Improves cell adhesion and osteoblast activity	SLA surfaces, nanostructuring
Biocompatibility	Low cytotoxicity, minimal immune response	Supports tissue integration	Widely accepted in long-term clinical use
Radiolucency	Compatible with imaging diagnostics	Allows postoperative monitoring	Non-ferromagnetic, safe for MRI

The properties of titanium – mechanical strength, modulus of elasticity close to that of bone, chemical stability, and favorable biological behavior – justify its widespread use in dental implantology. However, to optimize biological integration and reduce immunological risks, a thorough understanding of the interactions between the titanium surface and the peri-implant biological environment is essential, as well as the adaptation of processing technologies to the biological requirements of each clinical case [5-8].

Biocompatibility of titanium: tissue interactions

The biocompatibility of titanium is determined by the direct interactions between the implant surface and the peri-implant biological environment immediately after insertion. These interactions condition the initial immune response, the activation of healing processes, and the initiation of osseointegration. Although titanium is considered an inert material, its biological behavior is active, being influenced by chemical composition, structure, and surface treatments [5-10].

Shortly after the implant is inserted into the bone, its surface comes into contact with blood and tissue fluids, which causes the formation of an adsorbed film of serum proteins (albumin, fibrinogen, fibronectin, vitronectin). This protein film is critical for the subsequent determination of cellular behavior. The cells do not interact directly with the metal, but with this biological film, and its composition is influenced by the surface energy, roughness, and degree of hydrophobicity of the implant [6-10].

Subsequently, macrophages and neutrophils migrate to the implant site, initiating the inflammatory response. In the case of a biocompatible material such as titanium, the inflammatory response is moderate, controlled, and transient. Macrophages play a dual role – they

DOI: 10.62610/RJOR.2025.2.17.30

phagocytose any contaminants and coordinate the transition to the healing phase by releasing growth factors and cytokines such as IL-10, TGF-β, and VEGF. Also, the polarization of macrophages towards the M2 phenotype (anti-inflammatory, pro-regenerative) is a positive indicator of biocompatibility. In contrast, prolonged polarization towards the M1 (pro-inflammatory) phenotype is associated with poor integration and risk of bone resorption [5,7-10].

The surface of titanium directly influences cellular behavior. Surfaces treated with sandblasting and acid etching favor adhesion and differentiation of osteoblasts, while smooth surfaces are less effective in stimulating bone formation. Osteoblasts recognize binding sequences from adsorbed proteins and attach through integrins, initiating the formation of extracellular matrix and its mineralization. At the same time, endothelial cells are recruited via VEGF to initiate local angiogenesis, which is necessary to support the new bone mass. Another relevant aspect is the interaction with epithelial cells and gingival fibroblasts, essential for the formation of an effective biological barrier in the transmucosal area. Titanium facilitates epithelial attachment, forming a sealing area that prevents bacterial invasion and the development of peri-implantitis.[5-10].

Metal contaminants or industrial oil residues resulting from the manufacturing process can significantly affect biocompatibility. Also, the formation of an early bacterial biofilm, especially with species such as *Porphyromonas gingivalis*, can alter the local immune response, favoring chronic inflammation. For this reason, strict control of the sterilization and handling of the implant is essential for maintaining its biological properties [6-9].

Although rare, cases of titanium hypersensitivity reactions have been documented, characterized by persistent inflammation, non-infectious peri-implantitis, and early implant failure. These reactions are considered immune-mediated (type IV) and may be associated with the release of titanium ions or particles following friction, corrosion, or traumatic insertion. Prior assessment of allergic risk, although controversial, may be justified in cases with a complex allergic history. The biocompatibility of titanium is the result of a delicate balance between stimulating tissue regeneration and avoiding excessive activation of the immune system. Its interactions with proteins, inflammatory cells, and osteogenic cells determine the quality of implant integration and long-term stability. Optimization of the implant surface and control of contaminants are essential to support a favorable biological response in the complex context of the oral environment [6,8-11].

Osseointegration of titanium implants

Osseointegration is the fundamental biological process that determines the long-term success of dental implants. Defined as a direct structural and functional link between the living bone and the implant surface, osseointegration involves a complex succession of cellular and molecular events, significantly influenced by the properties of the implant material, especially in the case of titanium [6,8-11].

The osseointegration process begins immediately after the insertion of the implant, with the activation of the inflammatory cascade. The local inflammatory response, although transient, is essential for triggering regeneration. Neutrophils and macrophages are the first cells recruited at the site of surgical injury. They release cytokines and growth factors (IL-1β, TNF-α, TGF-β, VEGF) that regulate the recruitment of mesenchymal cells and initiate the bone healing process. Macrophages, depending on their polarization (proinflammatory M1 or pro-regenerative M2), can decisively influence the transition from inflammation to bone formation [4,9-11].

After the inflammatory phase, the proliferative phase occurs, in which mesenchymal stem cells migrate around the implant, differentiate into osteoblasts, and begin to synthesize the bone extracellular matrix. The surface of the titanium implant plays an essential role here. The treated surfaces (e.g., sandblasting-etching, SLA, anodizing) present a micro- and nano-structured topography that favors the attachment, proliferation, and differentiation of osteoblasts. Studies have shown that moderately rough surfaces (Ra ≈ 1–2 μm) stimulate bone formation more effectively than smooth surfaces, directly influencing the expression of osteogenic markers such as alkaline phosphatase, osteocalcin, and type I collagen [9-11].

Another essential element at this stage is angiogenesis. Effective vascularization of the peri-implant area is necessary for the delivery of nutrients, oxygen, and cells responsible for bone remodeling. Titanium, in combination with a balanced immune response, stimulates the release of VEGF and supports the formation of new blood vessels. Thus, a microenvironment favorable to osteogenesis is created [9-12].

The bone maturation and remodeling phase completes osseointegration. At this stage, the initial trabecular bone is gradually replaced by mature lamellar bone, with organized collagen orientation and increased mineral density. Remodeling is a continuous process, governed by the balance between the activity of osteoblasts and osteoclasts. A well-osseointegrated implant has a bone-implant contact area without fibrous interposition and with tight adaptation to the metal surface [9-13].

A determining factor in the success of osseointegration is the primary stability of the implant, defined as immediate mechanical anchoring in the host bone. This depends on bone density, implant geometry, and surgical technique. Secondary stability, acquired through the formation of new bone, is closely related to osseointegration. If a loss of stability occurs between the two phases (e.g., due to excessive micro-movements), the process may fail, leading to the formation of fibrous tissue instead of bone [10-13].

Modulation of the local immune response

The success of titanium dental implants depends not only on the properties of the material or mechanical integration into the bone, but also on how the host organism responds immunologically to the presence of the implant. The local immune response, triggered immediately after insertion, is an essential step in the osseointegration process. If this response is well controlled and transient, it facilitates tissue regeneration; If it becomes chronic or excessive, it can lead to implant failure by interfering with bone formation or initiating destructive inflammatory processes [6,10-14].

In the first postoperative phase, the titanium implant is recognized as a "sterile

DOI: 10.62610/RJOR.2025.2.17.30

foreign body". Although titanium does not trigger a classic immune response of rejection, it does generate an acute inflammatory reaction mediated by macrophages, neutrophils, and other cells of the innate immune system. They release several proinflammatory cytokines (IL-1β, TNF-α, IL-6) and growth factors (TGF-β, VEGF), which subsequently regulate mesenchymal cell recruitment, angiogenesis, and bone formation [11-14].

Macrophages play a key role in modulating this response. Depending on local stimuli, they can polarize into two functional phenotypes: M1 (pro-inflammatory, bactericidal) and M2 (anti-inflammatory, pro-regenerative). An effective transition from the M1 to M2 phenotype is essential for promoting bone healing and avoiding chronic inflammation. Titanium surfaces, especially those treated to increase roughness and controlled hydrophobicity, can favor this M2 polarization, positively influencing implant integration [6,11-14].

In Figure 1, macrophages polarize into M1 or M2 phenotypes in response to specific signals. M1 macrophages are pro-inflammatory, microbicidal, and involved in Th1 responses, while M2 macrophages exhibit anti-inflammatory properties, support tissue regeneration, angiogenesis, and matrix remodeling. This polarization balance is crucial in the context of titanium dental implants, influencing healing, osseointegration, and long-term clinical success [14].

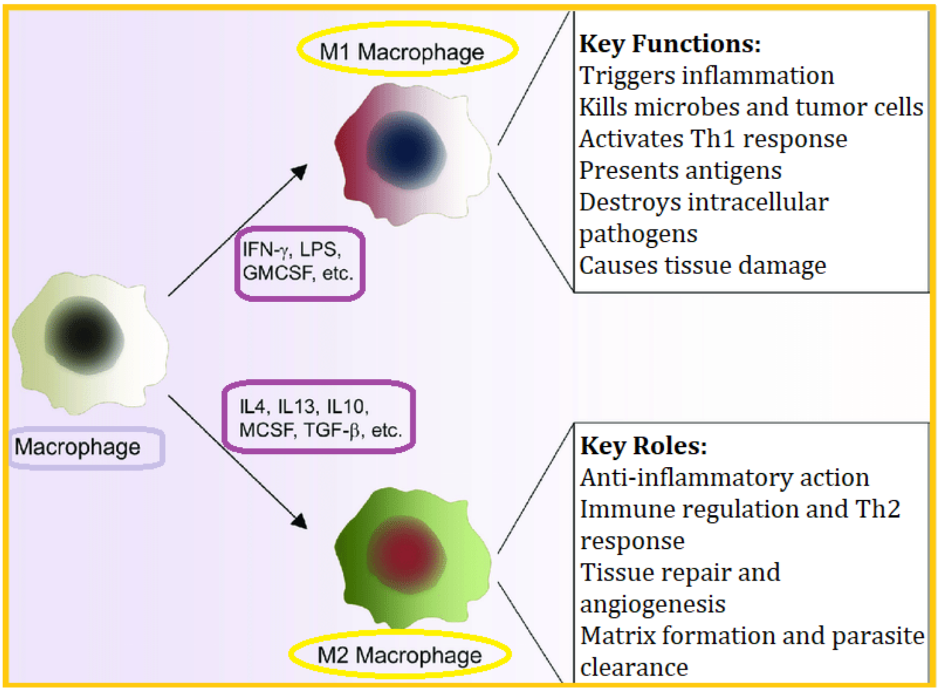

Figure 1. Macrophage polarization into M1 or M2 subtypes depends on local signals. M1 cells promote inflammation and defense, while M2 cells support tissue repair, angiogenesis, and immune regulation, key processes influencing implant osseointegration outcomes [14].

Another important aspect in the context of the local immune response is the activation of dendritic cells and T lymphocytes. Although to a lesser extent than in the case of allogenes, these cells can be activated by the presence of metal particles or surface contaminants, resulting in the release of proinflammatory cytokines. In rare cases, this response may take the form of a type IV hypersensitivity reaction, with the appearance of non-infectious peri-implantitis or early bone loss [12-14].

In addition, bacterial biofilm plays an indirect but crucial role in modulating the immune response. Early colonization of the implant surface by pathogenic bacteria (e.g., *Porphyromonas gingivalis*, *Fusobacterium nucleatum*) can amplify the inflammatory response and keep the M1 phenotype of macrophages active. This persistent state of immune activation contributes to the destruction of peri-implant tissues and increases the risk of osseointegration failure. Therefore, the prevention of bacterial colonization, through rigorous oral hygiene and aseptic manipulation of the implant, is essential [13,14].

Table 1 highlights the main cell types involved in the local immune response to titanium dental implants, their biological roles, influence on osseointegration, and current modulation strategies. Macrophages, neutrophils, and lymphocytes directly influence implant integration or rejection, while the presence of bacterial biofilm can induce chronic inflammation. By modifying the implant surface and using bioactive coatings, immune responses favorable to bone regeneration and long-term success can be stimulated [6-14].

Table 1. Immune response modulation at titanium dental implants

Cell type	**Role in immune response**	**Effect on osseointegration**	**Modulation strategies**
Macrophages (M1)	Initiate acute inflammation, release IL-1β, TNF-α	Prolonged activation impairs bone formation	Surface treatments to reduce M1 polarization
Macrophages (M2)	Promote tissue regeneration and resolution of inflammation	Enhance bone healing and vascularization	Use of bioactive coatings (e.g., IL-4)
Neutrophils	Early responders phagocytose debris, release ROS	Transient role; excessive activity may damage tissue	Minimize surgical trauma
T lymphocytes	Mediate adaptive immune responses	Possible role in chronic inflammation and rejection	Prevent contamination and systemic sensitization
Dendritic cells	Antigen presentation, immune activation	May enhance or suppress local immunity	Surface purity and controlled topography
Bacteria (biofilm)	Trigger chronic inflammation	Disrupt osseointegration via immune activation	Aseptic protocol, antimicrobial coatings

On the other hand, titanium surfaces can be modified to promote a favorable immune response. Modern technologies allow the functionalization of the surface with bioactive molecules (e.g., anti-inflammatory peptides, heparin, IL-4) that can stimulate the polarization of macrophages towards M2, reducing inflammation and accelerating healing. These "immuno-modulative" surfaces represent a promising direction in the

DOI: 10.62610/RJOR.2025.2.17.30

development of next-generation implants [10-15].

Challenges and perspectives in research

Although titanium dental implants have demonstrated outstanding performance in clinical practice, current research highlights numerous challenges related to optimizing the interactions between the material and the biological environment. At the heart of contemporary concerns is the desire to improve osseointegration and long-term stability, while reducing immunological and infectious risks. Thus, research is increasingly oriented towards the deep understanding of the molecular and cellular mechanisms involved, but also towards the development of new generations of implants with active biological functions [11-15].

Recent studies by Cocos et al. and Earar eta al. offer valuable insights relevant to future research directions in implantology, highlighting the interplay between surgical challenges, prosthetic materials, and oral-systemic health. Their investigations address the link between impacted third molars and TMJ dysfunction, the use of A-PRF+ in smokers, the behavioral management of pediatric dental anxiety, and the application of ceramic-filled composite resins for temporary restorations. Additionally, research on dental guards and parafunctions reinforces the importance of preventive strategies. These multidisciplinary contributions support the need for personalized, evidence-based approaches in optimizing implant integration and long-term clinical outcomes [16-22].

Recent literature on biomaterials highlights important advances relevant to modern implantology, offering new research directions regarding compatibility, functionality, and the personalization of therapeutic solutions. Studies on traumatic irritation fibroma, hydrogels used for nervous system regeneration, the performance of gold in dental prosthetics, and biodegradable polymers applied in cardiac repair suggest valuable cross-disciplinary applications and technological transfer. Additionally, artificial intelligence in orthodontic diagnostics and 3D bioprinting for tissue regeneration open innovative perspectives that may be adapted to peri-implant contexts. These contributions support the development of bioactive, personalized implants integrated within a clinical framework focused on advanced biocompatibility and controlled tissue regeneration [23-28].

One of the main challenges is the lack of a standardized and predictive model that accurately reflects the biological behavior of implants in the oral cavity. Most in vitro or animal model studies provide valuable information, but are often difficult to translate directly into the clinic, due to biological, microbial, and functional differences. From an immunological point of view, an important direction is represented by the investigation of the patient's individualized response. The influence of genetic and epigenetic profiling on local immune behavior in the context of implantation is increasingly being studied. Genetic polymorphisms of genes encoding cytokines (e.g., IL-1, TNF-α), TLR-type receptors, or bone remodeling factors could explain the variations in the success rate of implants, gradually allowing the implementation of a personalized medicine model in implantology [29-31].

In addition to the biological aspects, future challenges also include the integration of digital technologies with the biological design of implants. CAD/CAM technologies, 3D printing, and biomechanical simulations can enable customized implants tailored to individual bone morphology and specific functional loads to reduce mechanical stress and increase implant longevity. Porous titanium printed implants with controlled porosity are already being tested, offering high potential for three-dimensional bone integration [31-34].

Research in the field of titanium biocompatibility is advancing rapidly, to move from passive, structural implants to biofunctional devices, which actively participate in the processes of regeneration and local defense. Progress in the fields of molecular biology, nanotechnology, tissue engineering, and medical informatics will allow, shortly, the development of customized solutions with superior clinical performance and minimal biological risks [35-38].

Conclusions

Titanium dental implants continue to be the gold standard in oral rehabilitation, due to their unique combination of mechanical properties, corrosion resistance, and excellent biocompatibility. The effective osseointegration and long-term stability of these devices depend on a complex interaction between the implant surface, the local immune response, and the peri-implant cellular behavior. The treated surfaces of titanium can favorably modulate osteoblast activity and macrophage polarization, supporting bone regeneration and inflammation control.

However, challenges remain significant in terms of the variability of the biological response between patients, the influence of contaminants, the risk of chronic inflammation, and the occurrence of peri-implantitis. Future research needs to integrate knowledge from cell biology, surface engineering, and personalized medicine to optimize implant performance.

The clinical success of titanium implants does not depend solely on mechanical integration, but on a fine harmonization between material properties, tissue microenvironment, and local immunity. This understanding opens up real prospects for the development of biologically active implants, adapted to the patient's profile.

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