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| REVIEW

Subgingival microbiota and immune response modulation of osseointegrable implants

Modulação da microbiota subgengival e resposta imune dos implantes osseointegráveis

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ABSTRACT

Osseointegrable dental implants are biomaterials made of titanium or other alloys mixed with titanium, which have high biocompatibility and allow osseointegration. However, this process can be modulated by changes in the complex mechanisms between microbiota, immune response and host. The present study aims to present how the immune system-microbiota-host interaction influences the osseointegration process of titanium dental implants and its alloys. A literature review was performed through electronic and manual searches in several databases, including PubMed, LILACS, Google Scholar, SciELO and Web of Science for articles published in the last 20 years in English and Portuguese. The formation of a temporary fibrin matrix on the implants surface after implantation implies the recruitment, adhesion and activity of immune cells at this site, with the release of pro-inflammatory molecules and recruitment of neutrophils. In the second moment, monocytes and macrophages (M1) are recruited, producing, in this step, reactive oxygen species. In the later stage of inflammation, macrophages (M2) help in tissue regeneration with expression of anti-inflammatory cytokines. In addition, the implants surface provides a site for microbial colonization mediated by salivary pellicle and topographical features. Thus, in symbiosis the modulation of the immune response will be favorable to osseointegration. However, the dysbiotic process exacerbates the inflammatory progression modulating the immune response influencing abnormal tissue healing or scar and fibrosis formation, compromising osseointegration. Different conditions of the subgingival microbiota will influence different immunological cascades, generating different cellular responses and positive or negative modulation of the osseointegration process.

Indexing terms: Dental implants. Microbiota. Immunity.

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RESUMO

Os implantes dentários osseointegráveis são biomateriais constituídos de titânio ou outras ligas misturadas com titânio, as quais possuem alta biocompatibilidade e permitem a osseointegração. Esse processo pode ser modulado por alterações nos mecanismos complexos entre microbiota, resposta-imune e hospedeiro. O presente estudo busca apresentar como a interação sistema imune-microbiota-hospedeiro influenciam no processo de osseointegração proveniente de implantes dentários de titânio. Foi realizada uma revisão de literatura através de busca eletrônica e manual em diversas bases de dados, incluindo PubMed, LILACS, Google Acadêmico, SciELO e Web of Science para artigos publicados nos últimos 20 anos em inglês e português. A formação de uma matriz provisória de fibrina na superfície dos implantes após a implantação implica no recrutamento, adesão e atividade das células imunes, com a liberação de moléculas pró-inflamatórias e recrutamento de neutrófilos. No segundo momento, monócitos e macrófagos (M1) são recrutados, produzindo espécies reativas a oxigênio. Já no estágio posterior da inflamação, macrófagos (M2) ajudam na regeneração do tecido com expressão de citocinas anti-inflamatórias. Além disso, a superfície dos implantes oferece um local para colonização microbiana mediada pela película salivar e características topográficas. Assim, em simbiose a modulação da resposta imune vai ser favorável à osseointegração. Contudo, em estado de doença periodontal, o processo disbiótico exacerba a progressão inflamatória modulando a resposta imune influindo em um processo cicatricial comprometendo a osseointegração. Diferentes condições da microbiota subgengival vão influenciar em cascatas imunológicas diferentes gerando respostas celulares diferentes e modulação positiva ou negativa do processo de osseointegração.

Termos de indexação: *Implantes dentários. Microbiota. Imunidade.*

INTRODUCTION

Titanium (Ti) osseointegrable dental implants developed by Brånemark et al. (1969) more than 50 years ago ensure direct structural and functional contact of the bone with the implant [1,2]. This biomaterial has been used with high success rates of 90.9% to 97.7% after 15 years of implantation [3]. Moreover, it has good biocompatibility, corrosion resistance, and excellent mechanical properties [4]. Additionally, the implant surface is constituted by a passive layer of titanium oxide that is formed as soon as it comes into contact with the surroundings, and has the capacity of self-repairing by re-oxidation when damaged [3,5].

Three forms of Ti are used for endosseous dental implants, these being commercially pure titanium grade IV (Ticp IV - ASTM F67), commercially pure titanium grade II (Ticp II - ASTM F67) and a titanium alloy composed of titanium-aluminum-vanadium (Ti-6AI-4V - ASTM F136) [5]. The surface properties of implants are significant in hard and soft tissue integration, so there is a need for surface modifications to increase these interactions between proteins, cells and even mediate antimicrobial properties to promote tissue regeneration and decrease the duration of treatment [4,5].

In general, long-term biocompatibility rates are excellent and implant failures occur in a small number of patients. Primary implant failure due to insufficient osseointegration occurs in 1-2% of patients in the first few months. Secondary failure can develop several years after successful osseointegration in about 5% of patients and is commonly caused by peri-implantitis [2].

With regard to the subgingival microbiota, it consists of approximately 400 species present in the periodontal pocket [6]. The composition of the subgingival biofilm associated with peri-implantitis indicates high levels of certain microbial species associated with periodontitis [1]. However, other non-oral microorganisms have also been detected in the composition of this subgingival biofilm [7].

Peri-implantitis is characterized by a polymicrobial infection with an inflammatory character around the implant, involving soft tissues and a possible progressive loss of the supporting bone and potential implant compromise [8,9]. Although dental implants have good biocompatibility, peri-implant infections have been widely reported. Peri-implant diseases are presented in two forms: peri-implant mucositis (PM) and peri-implantitis (PI) [8].

Microorganisms are often introduced on implant surfaces during surgery. This colonization can trigger the inflammatory process, activation of osteoclasts, leading to implant failure in both early and later stages. Therefore, antimicrobial activity is an important property for Ti implants [4]

Successful implantation depends on a balance between microbiome, host and immune system. However, this homeostasis can be disturbed by external impacting factors leading to secondary implant problems and possibly failure due to strong immune response and inflammatory reactivation [9].

Based on response kinetics and function, the immune system is classified into two different types, innate and adaptive immunity [10]. Neutrophils and macrophages perform phagocytic and signaling functions, especially, at the beginning of the inflammatory phase of biomaterial implantation. Ultimately, these cell types determine the outcome of implants such as foreign body response, fibrointegration or osseointegration. Other cell types, such as dendritic cells, mast cells, natural killer cells, and innate lymphoid cells, may also play an immunomodulatory role in the context of biomaterials [11].

Increasing evidence shows that the immune system plays an important role in achieving successful tissue regeneration, either directly or indirectly. Hence, strategies have been dedicated to prevent immune overreaction in order to achieve the desired tissue regeneration [10]. The present study aims to present how the immune-microbiotic-host system interaction influences the osseointegration process from titanium dental implants and their alloys.

METHODS

The literature search consisted of articles in Portuguese and English in the platforms: PubMed, LILACS, Google Scholar, SciELO and Web of Science in the last 20 years. The following search terms were used in the virtual databases: "dental implants", "titanium implants", "osseointegration", "biocompatibility", "bioactivity", "surface roughness", "surface modification", "implant surface", "microbial colonization", "oral biofilm", "oral microbiota", "subgingival microbiota", "peri-implantitis", "immune response", "innate response", and "macrophages". Inclusion criteria were articles that addressed dental implants made of titanium and its alloys, composition characteristics, biocompatibility, implant stability, roughness, wettability, osseointegration potential, inflammatory response, immune response, and subgingival microbiota colonization. The exclusion criteria were articles that addressed the use of non-titanium implants, non-dental implants, non-ossointegrable implants, duplicate articles, and those that were not related to the main topic of this review. A total of 20 articles (table 1) were selected for the composition of this study according to the inclusion and exclusion criteria. We also used data extracted from textbooks relevant to the theme of the work.

Table 1. Summary of research on the Interaction between Immune Response and Subgingival Microbiota.

	Features	Reference
Bone Tissue Interaction with Ti Implant	After dental implants are anchored, a sequence of immune-inflammatory responses, followed by angiogenesis and osteogenesis, occur to achieve osseointegration. These events play a key role in the initial homeostasis as they release cytokines and growth factors that stimulate deposition of the collagenous matrix around the titanium oxide layer, leading to newly formed bone tissue (usually occurs 5 days later). Osteoclasts drive the process of bone resorption and remodeling and replacement by lamellar bone with a higher degree of mineralization. Titanium induces bioactivity favoring bone remodeling over resorption. The osteoblasts attach themselves to the mineralized collagenous matrix, forming a sealing zone, depositing bone directly on the implant surface (micro scale). In 8 to 12 weeks, the lamellar bone begins biological stability, meaning osseointegration.	Lee & Bance [12] Insua et al. [13] Terheyden et al. [14]
Surface Topography	The topography of the dental implant can be classified into macro-, micro- and nanoscale. It is crucial for adhesion and differentiation of osteoblasts during the initial phase of osseointegration, as well as in long-term bone remodeling. It can be modified at various levels, from the macroscopic design or shape of the implant to the introduction of microscopic, or nanoscopic topographies superimposed on each other, in order to alter growth, metabolism and migration, as well as cytokine and osteogenic cell growth factor production.	Smeets et al. [2]

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Roughness	Surface roughness is a parameter that affects the osteoconduction rate, mainly influencing the establishment of primary stability. Rougher surfaces are directly proportional with a higher microbial colonization while smoother surfaces tend to aggregate a lower colonization. In addition, immune system cells such as neutrophils, monocytes, dendritic cells, and macrophages are affected and modulate their response depending on the surface roughness.	Elias et al. [15] Rohr et al. [16] Leite et al. [17] Brito et al. [18]
Wettability	Wettability is expressed by the water contact angle that ranges from 0° to 90° on hydrophilic surfaces to greater than 90° on hydrophobic surfaces. Perhaps the most influential surface property in modulating the activation of anti-inflammatory macrophages is surface energy (usually calculated, indirectly, by means of wettability). Increasing surface energy greatly elevates the anti-inflammatory macrophage polarization in various applications. Hydrophilic surfaces significantly decrease pro-inflammatory leukocyte activation compared to hydrophobic, cationic, or anionic surfaces.	Zhou et al. [4]
Primary Stability	Primary implant stability is an indirect indication of osseointegration and can be assessed, clinically, by: clinical mobility testing, radiological imaging, resonance frequency analysis. With implant insertion, a dental implant gains primary stability. The implant is passively stabilized in the surgical wound by mechanical friction with the primary bone contacts. The denser the host bone, the more primary bone contacts are available and the greater the primary stability. Primary stability implies that the friction holding the implant in place is greater than the higher dynamic loading forces applied.	Khan et al. [5]
Microbiota-Inmune System-Host Interaction	The microorganisms indigenous to the oral microbiome live in a symbiotic state with the host, adhering to any biotic or abiotic surfaces present in this ecosystem. Microbial accumulation and biofilm formation on implanted materials can trigger various biological and chemical processes, such as polymicrobial infections and biomaterial deterioration. The Ti particles released by microbial corrosion, increase the release of pro-inflammatory cytokines, infiltration of immune-inflammatory cells and activation of osteoclastic activity, generating unfavorable results. Therefore, the presence of Ti products around dental implants may contribute to peri-implant bone resorption, microbial dysbiosis, and consequently increase the risk of developing peri-implantitis of osseointegration failure. The different conditions that the subgingival microbiota may find itself in, whether in symbiosis or dysbiosis, together with the surface characteristics of Ti implants, will influence the polarization of different immune cell profiles, generating immune cascades with different cellular responses, ultimately causing a positive or negative modulation of the osseointegration process.	Costa et al. [3] Albrektsson et al. [9] Belibasakis & Manoil [19] Albrektsson et al. [20]
Peri-implantitis	It is a polymicrobial infection around dental implants in prosthetic function, causing inflammation of the peri-implant tissue (release of inflammatory mediators of periodontal disease), which may lead to progressive damage to the supporting bone tissue and occasionally to implant loss. In other words, biofilm formation on the surfaces of dental implants is one of the main causes of the etiopathogenesis of peri-implantitis, and the main reason for implant failure. The resulting changes in the implant microenvironment cause dysbiotic changes that exacerbate inflammatory progression, and it has been shown that the peri-implant microbiota gradually gains complexity as the infection progresses.	Charalampakis & Belibasakis [1] Faveri et al. [7] Zheng et al. [8] Pérez-Chaparro et al. [21]
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	Features	Reference
Innate Immune Response	It is the first response to harmful stimuli. It counts on the action of neutrophils, monocytes, and macrophages. Neutrophils and macrophages have phagocytic and signaling functions, especially at the beginning of the inflammatory phase of biomaterial implantation. Ultimately, these cell types determine the outcome of implants as inflammation, foreign body response, fibrointegration or osseointegration. Neutrophils exhibit distinct phenotypes along a pro-anti-inflammatory spectrum, although these phenotypes are not as well characterized as those of macrophages. M1 macrophages are considered harmful to tissue repair. In contrast, M2 macrophages have pro-regenerative capabilities.	Zhang et al. [10]
Adaptive Immune Response	When innate immune cells fail to defeat the threat of invasion, mobilization of adaptive immunity occurs from B and T cells, which can specifically eliminate the threat encountered. There are several subsets of T cells with distinct functionalities triggered by different chemokines and cytokines. Dendritic cells play roles similar to macrophages, promoting early inflammation and resolving late inflammation. B cells have as their main role during the immune response to present antigens and produce antibodies.	Abaricia et al. [11]
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RESULTS

Titanium osseointegrable implants

The success of osseointegrable dental implants is determined by the biological response (inflammatory and immune) and by the behavior of adjacent tissues at the tissue-implant interface [22]. In this sense, the process of osseointegration, first coined by Per-Ingvar Brånemark [2], is linked to the incorporation of steps in the initial tissue response to implantation, such as osteogenesis and peri-implant bone remodeling, which ultimately leads to bone formation on the implant surface (at the micrometer scale) [12]. At the nanometer scale, there is a protein interface between the bone and biomaterial surface [23].

Ti and its alloys, for example, Ticp grade IV (F67) and Ti-6Al-4V (F136) are the most common materials employed for the manufacture of dental implants due to their good biocompatibility, mechanical strength and resistance to corrosion (electrolytic reaction between the material and the environment) at a rate of less than 0.00025 mm/year [22]. The success of these Ti-based implants is mainly due to the combination of suitable biomaterial properties and the ability to spontaneously form a passive oxide layer when in contact with O2 from the atmosphere, the main and most important one being referred to as TiO2 (Rutilo) [3].

In addition, commercialized Ti implants are currently classified as bioactive, which means that they have the capacity to induce bone formation on the surface, allowing bone formation and remodeling (osseointegration), and

differ from bioinert implants (usually in ceramic materials) that are not able to provoke an active osseointegration response [12].

In this respect, the surface properties of these implants will be crucial for the modulation of the biological response and the success of osseointegration. Thus, these properties of topography and composition will determine the success of implant stabilities [2]. However, these same properties that influence osseointegration also interfere in biofilm formation and immune response [3].

Influence of the subgingival microbiota on the osseointegration process

Immediately after the Ti implant is inserted into the gnatic bones, the biomaterial is quickly exposed to protein-rich fluids, such as plasma and saliva, forming a protein layer on the Ti surface (formation of a temporary granulation tissue matrix) [23]. Thus, protein adsorption represents the first biological interaction of the human body to implanted biomaterials [3]. From this event, a salivary film is rapidly adsorbed onto the orally exposed surfaces, which promotes adhesion of the first colonizing species, in turn providing the surface receptors for the incremental coadhesion of late colonizers (figure 1) [19].

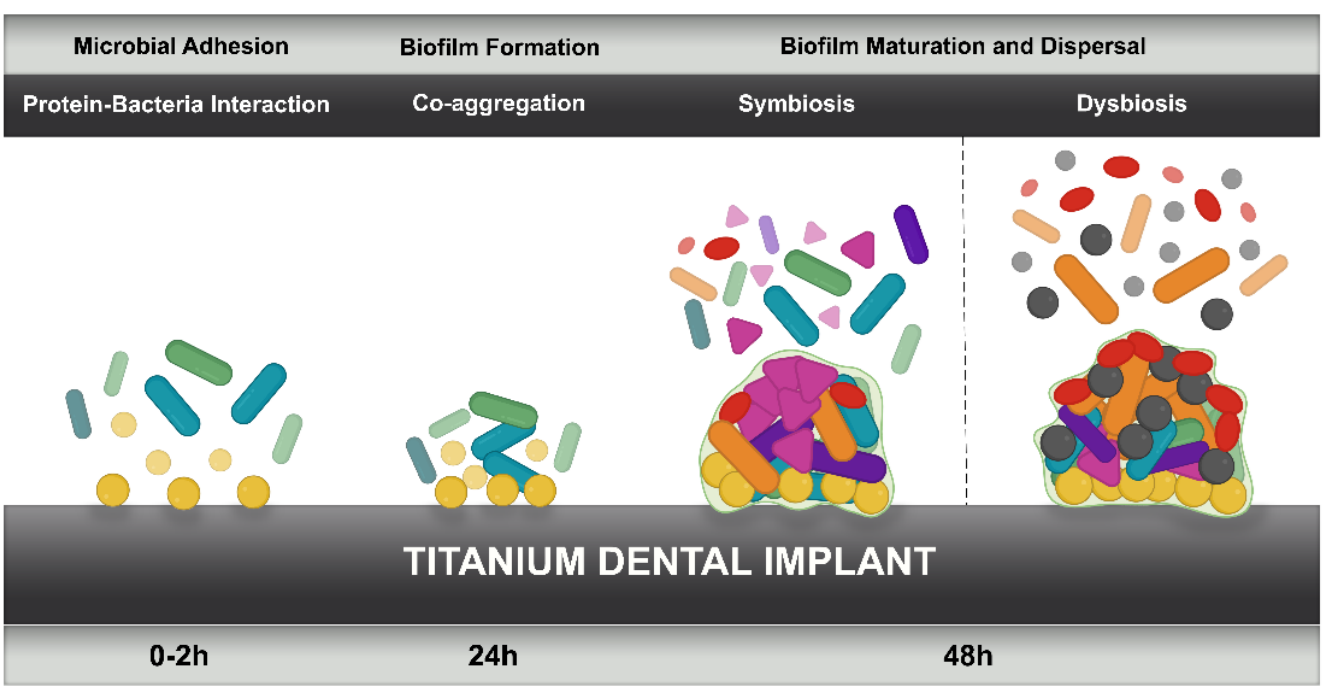

Figure 1. Subgingival biofilm formation.
Note: Representation of the Socransky Microbial Complex adapted with concepts from Colombo & Tanner [24]. Biofilm formation on the surface of a titanium implant over 48h. In 0-2h occurs microbial adhesion (interaction between proteins and bacteria); in 24h occurs biofilm formation (coaggregation of biofilm); in 48h occurs the maturation and dispersion of this biofilm (in a state of symbiosis or dysbiosis). Adapted from Costa et al. [3].

In the oral environment, the indigenous microorganisms of the oral microbiota live in a state of amphibiosis with the host, adhering to any biotic or abiotic surfaces present in the oral ecosystem [3].

Therefore, the formation of biofilm on the surface of implanted biomaterials can trigger biological and chemical processes, such as polymicrobial infections of inflammatory character, up to the deterioration of the biomaterial, since they attenuate the electrochemical stability, leading to corrosion processes (metallic biomaterials) [19]. Thus, the formation

of subgingival biofilm on the Ti surface is the main factor in the etiopathogenesis of infections related to dental implants [9].

In the early stages of colonization, the microbial composition of the peri-implant biofilm resembles that of healthy periodontal sites, with less diversity [19]. In the first months after implant insertion, these bacterial microbial communities can reach a symbiotic homeostasis equilibrium with the host and be compatible with peri-implant health.

However, when tissue inflammation is favored and the microenvironment of the peri-implant sulcus is altered, these modifications can cause dysbiotic changes in the subgingival microbiota that exacerbate inflammatory progression and ultimately peri-implant health and implant functionality [19]. The changes from health to disease include an increase in diversity and a gradual exhaustion of commensals, along with an enrichment of classical and emerging periodontal pathogens (figure 2) [8].

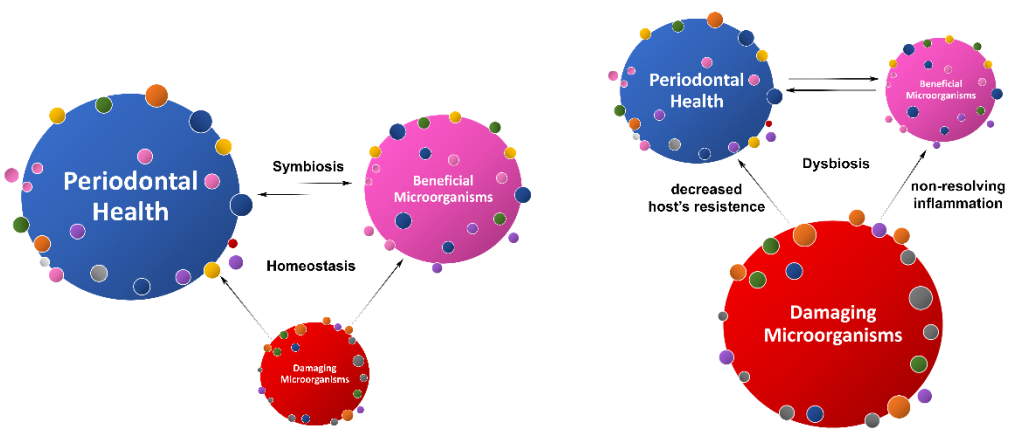

Figure 2. Peri-Implant Microbiota in a State of Symbiosis and Dysbiosis.
Note: Representation of the Socransky Microbial Complex adapted with concepts from Colombo & Tanner [24]. Microbial communities that resemble those of healthy periodontal sites. They can achieve a symbiotic equilibrium with the host and be compatible with peri-implant health. However, site modifications cause dysbiotic changes in the microbiota exacerbating inflammatory progression and ultimately compromising peri-implant health and implant functionality. Adapted from Belibasakis & Manoil [19] and Eggert & Levin [25].

Traditionally, investigations into the etiopathogenesis of classical infections were based on individual bacterial species in complex microbial communities, following the one-pathogen-one-disease perspective. However, this paradigm has changed, establishing the perspective of the oral biofilm with dysbiotic potential in the breakdown of microbial homeostasis. This implies saying that changing microbial entities can alter the pathogenicity of microbial communities and from that lead to a process of dysbiosis thus causing infections [8,24].

As such, investigations of the complexity of microbial communities in peri-implant sites suggest that in a state of symbiosis (periodontal/peri-implant health) the composition of the peri-implant microbiota is different from the periodontal microbiota. However, in a state of dysbiosis (periodontal/peri-implant disease) the composition of this microbiota is the same in both situations, both in the tooth and in the implant [7,8].

Under a structural biomechanical point of view, however, biofilm formation depends on surface properties such as roughness, wettability, surface energy, oral microbiota, as well as environmental conditions such as pH, salivary flow rate, oxygen level, nutrition (macronutrient and micronutrient consumption ratio) and oral hygiene condition [3,26]. In other words, the surface topography of the implant directly affects microbial colonization and, depending on the other factors, the progression of an inflammatory infection such as peri-implantitis [27], while modifications with surface treatments of its characteristics can decrease the susceptibility of adherence and colonization of this subgingival biofilm [19].

Although the success rates of dental implants are high, it has been reported that 5 to 10% [22,28] of them fail due to mechanical problems, lack of osseointegration, infection, or rejection, and must be removed [22,23]. Among these causes, the development of peri-implantitis remains the main reason for failure of these implants [9].

The survival of pathogenic species in the subgingival microbiota depends on their ability to develop into biofilms, which protects them from environmental challenges and increases their growth (quorum sensing). Therefore, biofilm formation on dental implant surfaces is a major cause of the etiopathogenesis of peri-implantitis [22].

Besides, because peri-implantitis is a polymicrobial infection of inflammatory character, there is a production of pro-inflammatory mediators that trigger the activity of osteclasts (bone resorption) and interfere in the process of tissue regeneration, which directly implies a reverse effect on osseointegration [14].

Added to this process, microbiologically induced corrosion - as this deleterious phenomenon is called - promotes deterioration of the implant surface (associated with the oxidation mechanism), including discoloration, corrosion, cracking, scratching, and an increase in surface roughness. Microbial corrosion results in the release of metal ions or even particles (when associated with the attrition process) into the surrounding tissues that can stimulate an exacerbated inflammatory response, peri-implant bone resorption, and microbiological dysbiosis [3,19].

These corroded Ti surfaces may promote increased adhesion of microbial species and a higher biofilm density due to deterioration of the biomaterial and increased roughness. Therefore, corroded implant surfaces may compromise tissue regeneration processes and reduce the active capacity of osteoblasts (proliferation, differentiation and bone formation) [3].

The presence of Ti products around dental implants may contribute to peri-implant bone resorption, microbial dysbiosis, and consequently increase the risk of developing/aggravating peri-implantitis [3].

Innate and adaptive immune response in osseointegrable implants

The response to implanted biomaterials occurs in four phases: hemostatic, inflammatory, proliferative and remodeling [11]. Thus, the immune response to the foreign body initiates a complex host defense cascade that often leads to the scarring process, fibrosis, and results in repair of damaged tissue compatible with the failure of function.

As a result, tissue engineering strategies in the sense of composition and surface treatments have been dedicated to prevent immune overreaction in order to achieve the desired tissue regeneration [10] by inducing polarization of the inflammatory response into pathways that promote bone formation as part of the host response to bioactive implants and reducing negative tissue responses that could lead to rejection and thus the foreign body response [12].

Furthermore, there are still strategies to make dental implant surfaces antimicrobial in nature in order to prevent the development of infections such as peri-implantitis [22]. Thus considering the feasible variety of chemical and physical modifications of biomaterials for tissue regeneration [10].

Implantation of a biomaterial results in tissue injury during the surgical procedure. After injury and initiation of the hemostasis phase [11], necrotic cells or fragments of the damaged extracellular matrix may release some pro-inflammatory molecules, which are called damage-associated molecular patterns (DAMPs). Similarly, molecular signals released by bacteria, fungi, and viruses are called pathogen-associated molecular patterns (PAMPs). Both DAMPs and PAMPs can induce local inflammation [29] and, together with proteins adsorbed on the implant surface, have important impacts on recruitment, adhesion and activity of immune cells at the implant site [10].

The innate immune system is considered the first to respond to tissue injury, which includes the actions of neutrophils, mast cells, monocytes, and macrophages. When these innate immune cells fail to resolve this event, they can mobilize the adaptive immunity of B and T cells, which can specifically eliminate the threat encountered (figure 3) [29].

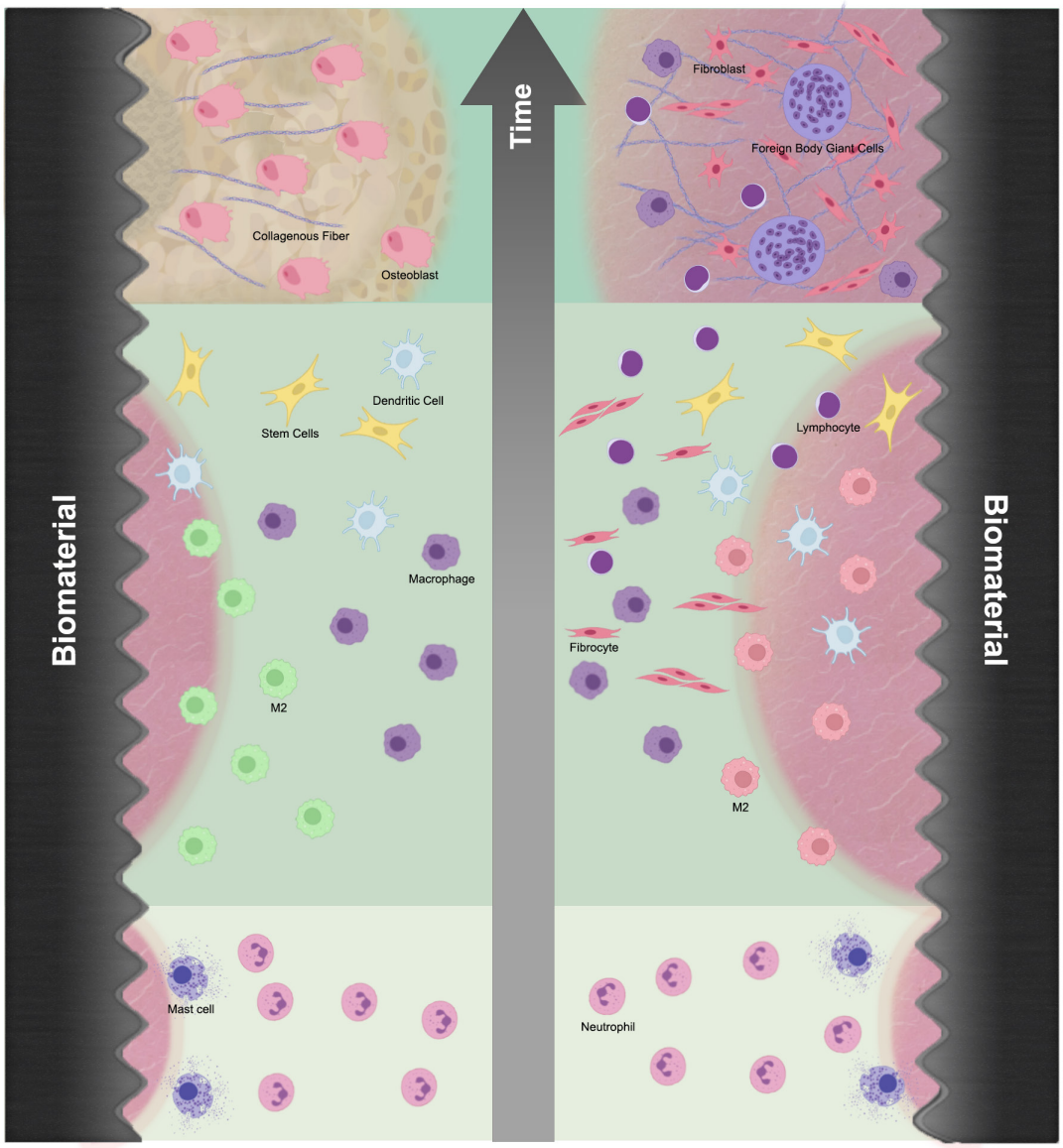

Figure 3. Innate and adaptive immunity cells in the process of integration with biomaterials.
Note: Sequence of events occurring on the surface of dental implants after implantation. Interaction of innate immunity cells with the implant surface in response to the presence of the biomaterial and evolution to an adaptive response over time. Adapted from Abaricia et al. [11].

Neutrophils are mobilized during hemorrhage, after implantation, and are abundant during hemostasis and the early inflammatory stage [14], and are one of the first innate immune cells to migrate toward the site of injury in response to external injury or invasion [30].

Neutrophils exhibit distinct phenotypes along a pro-anti-inflammatory spectrum. There is evidence that early neutrophils are of pro-inflammatory phenotypes and are short-lived, while later neutrophils are of anti-inflammatory phenotypes and persist for up to 3 days [11].

These neutrophils play complex and multifaceted roles in classical inflammation through the production of cytokines and chemokines, phagocytic activity, secretion of myeloperoxidase (MPO) and elastase and generation of reactive oxygen species (ROS) [14].

The prolonged activation of neutrophils results in chronic inflammation and a delay in tissue regeneration [10,14], due to their pro-inflammatory profile. On the other hand, neutrophils can also contribute to tissue regeneration by

means of growth factor secretion, helping in the remodeling of mesenchymal stem cells (MSCs) and in the resolution of inflammation by means of apoptosis [30], with these activities being promoted by the anti-inflammatory profile of these cells.

Thus, neutrophils respond differentially to changes in the roughness and wettability (hydrophilicity) of Ti implant surfaces; on smooth or rough hydrophobic surfaces, neutrophils secrete higher levels of cytokines and proinflammatory enzymes while also undergoing increased formation of neutrophil extracellular networks (NETs) compared to those on rough hydrophilic surfaces [11]. In addition to surface topography, roughness and wettability have also been shown to modulate neutrophil activation [11].

Following injury, a large number of circulating monocytes are recruited to the site of injury (surgical wound) by sensing chemokine and cytokine signals. Together with resident macrophages, these immune cells undergo phenotypic and functional changes as they participate in inflammation and the subsequent tissue regeneration process [29]. Hence, inflammatory monocytes promote inflammation and reach peak concentration within 48 hours. In contrast, anti-inflammatory monocytes contribute to mediating inflammation [10] by promoting matrix shaping, angiogenesis, and fibrosis prevention [14].

In the case of macrophages, the pro-inflammatory phenotype, called M1 macrophages, can be triggered in an inflammatory environment by cytokines and are well known as necrotic for secreting reactive chemicals and phagocytizing apoptotic neutrophils, necrotic tissue fragments, and pathogens. Excessive activation or constant mobilization of M1 can impair tissue regeneration and cause damage. Unlike M1 macrophages, M2 (anti-inflammatory) macrophages are considered to assist tissue homeostasis. These are involved in matrix remodeling, expressing relevant cytokines to promote collagen fiber formation and unshaped dense connective tissue, leading to wound contraction and closure [30].

As a result, M1 macrophages, at an early stage, produce a number of toxic materials, such as ROS, degradative enzymes, and acids, which are considered harmful for tissue regeneration. However, at a later stage of inflammation, macrophages polarize to the M2 type phenotype, which aids in tissue regeneration through the expression of anti-inflammatory cytokines (figure 4) [10].

Macrophage phenotypes can be induced by mass and surface physicochemical properties of the biomaterial to be implanted, such as material composition, roughness, surface topography, and hydrophilicity, which affect the inflammatory response and the consequent integrative fate of biomaterials [11].

The most influential surface property in modulating anti-inflammatory macrophage activation is surface energy. It is usually measured, indirectly, by means of hydrophilicity, increased surface energy increases the anti-inflammatory macrophage polarization in various applications [11].

Concerning dendritic cells (DCs), these can detect biomaterials through toll-like receptors upon activation by ligands on the adsorbed protein layer deposited on implants [10]. They play similar roles in the immune response as macrophages, promoting early inflammation and resolving late inflammation [29]. In addition, DCs also respond to changes in surface roughness and hydrophilicity. Hydrophobic Ti with smooth or rough topography induced mature or pro-inflammatory DC phenotypes, while hydrophilic Ti induces an immature or anti-inflammatory phenotype, similar to the phenotypic changes seen in macrophages [11].

Mast cells (MC) actively participate in inflammation, proliferation and regeneration/remodeling after biomaterial implantation and have a well-documented role in the unfolding of a foreign body response [31].

The degranulation of this cell type after biomaterial implantation, especially the release of histamine and interleukin 4 (IL-4), leads to the recruitment and adhesion of other inflammatory cells at the implantation site. In addition, the long-term presence of mast cells at the implantation site is related to the degree of fibrosis around the implant [11].

Finally, T cells (T lymphocytes) are part of the adaptive immune system and play a critical role in the specific immune response [29]. Like macrophages, there are several subsets of T cells with distinct functionalities triggered by different chemokines and cytokines, such as Th2 cells (T helper lymphocytes) that help resolve inflammation by regulating anti-inflammatory M2 macrophages [10].

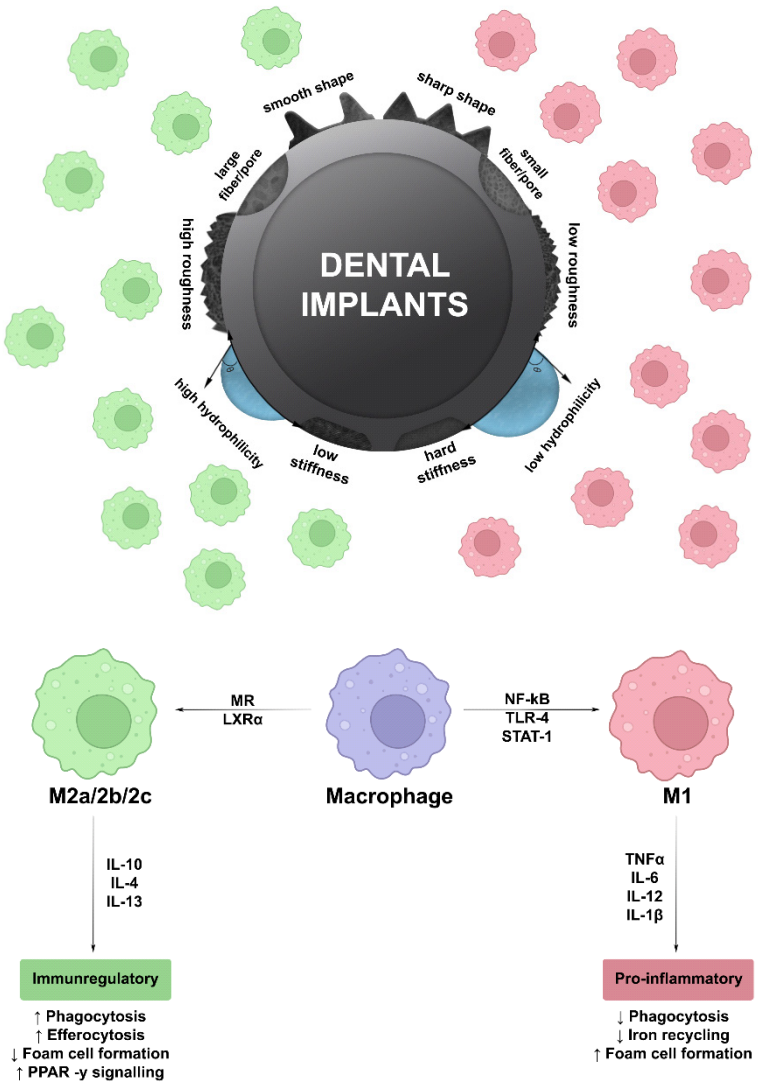

Figure 4. Macrophage polarization dependent surface properties.
Note: Physical cues from titanium dental implants, including shape, substrate stiffness, and the different surface properties, can cause varied macrophage responses, and may trigger a strong inflammatory response (M1 macrophage subtype), or may be associated with anti-inflammatory response (M2 macrophage subtype). Adapted from Zhang et al. [10].

The immune system plays a vital role in the response to tissue damage and its subsequent regeneration. Therefore, several efforts have been made to explore a means of regulating the behavior of immune system cells through factors including physical, chemical, and biological stimuli, all primarily focused on limiting the inflammatory reaction and promoting a regeneration phase [10].

DISCUSSION

The osseointegration process of a Ti implant is influenced by several modulating factors that contribute to its success or failure, and consequently, implant loss. Among the main factors that modulate osseointegration of dental implants, the immune response of the host and the symbiotic or dysbiotic relationship of the microbiota with the peri-

implant sites are of particular importance. Thus, as mentioned earlier, the biocompatibility of the material is of great importance and a predictor of osseointegration, as it is essential to establish a stable fixation with direct bone-implant contact and without the presence of fibrous tissue at the interface.

Ti is widely used as an implant biomaterial because it is highly biocompatible, bioactive, and has excellent mechanical properties. However, this biomaterial is also susceptible to microbial adhesion and accumulation. Therefore, polymicrobial infections induced by biofilms are the main reason for failure of dental implants, as oral biofilms can reduce the electrochemical stability of the implanted material, leading to faster corrosion and deterioration processes [3,9]. In other words, one can look at the success of implantation as a delicate immunological balance that, when influenced by external factors, can generate secondary problems of the implant resulting in failure due to the immune response and strong inflammatory activation.

That said, Albrektsson et al. [9] state in their study that there is evidence that Ticp is not biologically inert, but instead activates the body's innate immune system.

Increasing evidence shows that the immune system plays an important role in achieving successful tissue regeneration, either directly or indirectly, in which the immune response to the foreign body initiates a complex host defense cascade and often leads to scarring and fibrosis, and results in impaired tissue repair and organ function failure [10].

In the initial inflammatory and regeneration phase (up to hours), both the coagulation cascade and the complement system interact intimately or adjacent to the biomaterial surface and modulate each other's activities, thereby affecting inflammation, cell recruitment, and attachment to surfaces [9].

Immune cells can promote or resolve inflammation to impair or assist stem cell/tissue proliferation and differentiation, leading to scarring or tissue restoration. Therefore, in order to achieve the desired tissue regeneration, it is very important to understand the underlying mechanism of the response of different immune cells.

The immune system reaction and inflammation require well-engaged and active biochemical processes to restore homeostasis, which consequently leads to implant osseointegration. Therefore, immune cell infiltration as an important part of host responses significantly affects the biocompatibility and function of dental implants and can lead to failure [11].

Thus, the initial injury to the peri-implant tissue triggers an inflammatory response mediated by cells of innate immunity, such as macrophages, dendritic cells, mast cells and neutrophils (table 2). Throughout this work, it was noticed that the cells of innate immunity are those that are indeed decisive in determining the success of osseointegration. Among the cells of this distinct group, neutrophils and especially macrophages stand out.

Table 2. Main immune cells and their characteristics.

1 of 2

Immune Cells	Features
Neutrophils	Innate immune cells that have the function of secreting bactericidal content and proteases that exhibit the ability to destroy pathogens or produce neutrophil extracellular traps (NETs) with bacterial phagocytic ability. In addition, the surface properties of biomaterials can modulate neutrophil activation.
Macrophages	Cells that are related to the process of tissue regeneration and repair. Pro-inflammatory macrophages (M1) secrete reactive chemicals, phagocytize apoptotic neutrophils, necrotic tissue fragments, and pathogens. Anti-inflammatory macrophages (M2) help in tissue homeostasis, being involved in matrix remodeling and collagen and connective tissue formation. Regarding biomaterials, macrophage activation and phenotype can be altered by their physicochemical characteristics, such as surface topography, wettability and hardness.
Dendritic Cells	Phagocytic mononuclear cells that act as guardians of the inflammatory response, performing more tolerogenic functions during homeostasis, promoting early inflammation and resolving late inflammation. They may also be related to osteoclastogenesis and bone renewal. In addition, dendritic cells can detect biomaterials through toll-like receptors.

Table 2. Main immune cells and their characteristics.

Immune Cells	Features
Monocytes	They participate in inflammation and the subsequent tissue repair process by providing matrix shaping, angiogenesis, and prevention of fibrosis, through the secretion of cytokines such as TGF-B and IL-10.
Mast cells	Granulocytic cells play an important role in allergic reactions, wound repair through cell recruitment, angiogenesis, and extracellular matrix deposition, as well as in fibrosis and foreign body response to implanted biomaterials.
Lymphocytes	These cells are related to the body's adaptive immune responses. Pro- or anti-inflammatory effects, usually associated with other innate or adaptive immune cells in response to physical or chemical properties in biomaterials, such as increases in pro-inflammatory cytokines IL-1β, IL-17 and TNF-α or release of anti-inflammatory cytokines, may in part be the result of activation of lymphoid cells.

Source: Adapted from Zhang et al. [10] and Abaricia et al. [11].

These cells are directly related to the process of regeneration and tissue repair. Neutrophils are predominant and early cells in peri-implant tissues [31] and secrete bactericidal content and proteases that exhibit the ability to destroy pathogens or produce extracellular neutrophil traps (NETs) with bacterial phagocytic ability. Since neutrophils also exhibit distinct phenotypes along a pro-anti-inflammatory spectrum, as do macrophages, they may act either with a pro-inflammatory profile delaying the tissue repair process, or with an anti-inflammatory profile, of later response, which, by stimulating tissue regeneration, favors the osseointegration process.

The findings of Zhang et al. [10] showed that in recent studies also indicated that neutrophils are involved in macrophage polarization and contribute to tissue regeneration. That is, the reduction of pro-inflammatory macrophage accumulation in response to NETs secreted by neutrophils resulted in successful osseointegration [31].

This contradicts the traditional concept that neutrophils are considered detrimental to tissue repair, as they have shown a protective role in helping to resolve inflammation. However, this mechanism still needs to be further elucidated.

Macrophages, on the other hand, are the main cells in the innate immune responses to implants. They play an indispensable role in the osseointegration of implants and outline their fate [33]. They can present two subtypes within the pro-anti-inflammatory spectrum.

Fretwurst et al. [32] concluded that M1 macrophages are dominant cells in patients with peri-implantitis. Furthermore, Wang et al. [33] showed that peri-implant bone loss in a murine model had a positive correlation with the presence of M1 macrophages. Several studies have revealed that the presence of M2 macrophages in the peri-implant tissue is related to reduced inflammation, improved wound regeneration, and ultimately successful implant osseointegration [31].

Thus, while M1-type macrophages secrete reactive chemicals, phagocytize apoptotic neutrophils, necrotic tissue fragments, and pathogens, M2-type macrophages assist in tissue homeostasis, being involved in matrix remodeling and collagen and connective tissue formation.

However, according to the study by Zhang et al. [10] persistent activation of M2a, a subtype within the group of macrophages with anti-inflammatory action, can lead to pathological fibrosis formation.

This characteristic is atypical within the concepts that have traditionally been determined for this cell type and its function, which leads us to conclude that further studies need to be developed to determine the pro- and anti-inflammatory properties of the cells and mechanisms involved in the immune response.

In any case, macrophages may have a binary role in directing the implant to failure or success, modulating the osseointegration process and therefore being the main cells of the innate immunity involved in this process.

There is no doubt that the other cells of the innate response, and to a lesser extent, the adaptive response, are fundamental in the complex cascade of host defense that is launched after the initial installation of the implant and establishment of the inflammatory phase, contributing with the emission of stimuli and cytokines that will help dictate

the destiny of the implants. However, in the face of what has been found so far, cells such as mast cells, dendritic cells, lymphocytes, and monocytes do not play as significant a role in this process as macrophages and neutrophils.

Given the importance of the behavior of the cells that act in the immunoinflammatory processes triggered after implantation of Ti implants, strategies have been explored to avoid an exaggerated immune reaction in order to achieve the desired tissue regeneration. Thus, the immune-inflammatory balance should obviously be modulated by factors such as implant design, material chemistry, mechanical stress, implant location, and surgery [9].

Thus, from the findings of this study, we know that neutrophils respond differentially to changes in the roughness and wettability (hydrophilicity) of Ti implant surfaces. That is, on smooth or rough hydrophobic surfaces neutrophils are induced to assume a more pro-inflammatory profile, secreting cytokines and enzymes with these functions, a profile that contrasts in comparison with those on rough hydrophilic surfaces.

Regarding macrophages, their phenotypes can also be induced by mass and surface physicochemical properties of the biomaterial to be implanted, such as material composition, substrate stiffness, surface topography, and wettability, the latter being the most influential property in modulating anti-inflammatory macrophage activation.

These characteristics and properties of Ti implant surfaces are valuable tools, since they have the ability to affect the inflammatory response by modulating the profile of cells that act against this process, and the consequent integrative fate of biomaterials. Therefore, several studies have been dedicated to this area, aiming to favor osseointegration and provide promising potentials for tissue regeneration.

In a condition of oral health, a symbiotic relationship exists between oral microorganisms and the host [34]. However, when the immune system exhibits continuous imbalance, its function of serving as a defense against surrounding microorganisms automatically decreases, and a secondary microbial action can be seen [20].

What happens is that when the immune system stops favoring the osseointegration process, we can also see secondary bone resorption caused by microorganisms. However, Albrektsson et al. [9] state that the primary response is actually the imbalance of the immune system that removes the defense against microorganisms

Whereas, if granulocytes encounter a large number of microorganisms, they recruit more neutrophils by releasing pro-inflammatory cytokines, meaning that the abundance of microorganisms prolongs and amplifies the cellular immune response [14].

So, it can be suggested that the chronic inflammation observed at the implant site may be partly a defense against microbial invasion and the other part of this defense against inflammation itself, the immune response to implants being given by the action of macrophages or macrophage-derived cells [9].

Ata-Ali J et al. [35] developed a study involving 34 patients with 77 dental implants (comprising 23 mucositis and 54 healthy peri-implant sites) and concluded that bacterial biofilm induces an inflammatory response that can lead to the development of peri-implant mucositis. Bacterial products from periodontal pathogens stimulate the production of secreted inflammatory mediators, which cause destruction of peri-implant tissues.

In any case, the microbiological factor, whether generating a secondary inflammation response or not, remains a factor of importance concerning the future of osseointegration. Macromolecular and bacterial adhesion and the subsequent formation of biofilm on the anchoring part of an implant are pointed out as one of the main causes of its failure [9].

The oral microbiome consists of several hundred different microbial species, which are able to form complex biofilms on oral surfaces. This makes the peri-implant mucosa and the commensal biofilm play important roles in maintaining homeostasis between microbe and host [34].

In the early stages of colonization, the microbial composition of the peri-implant biofilm resembles that of healthy periodontal sites, with less diversity [19]. In the first months after implant insertion, these bacterial communities can reach a symbiotic homeostasis equilibrium with the host and be compatible with peri-implant health.

However, several factors are capable of inducing homeostasis dysregulation between the microbiota-host relationship. This dysbiosis is accompanied by an increased inflammatory reaction and a change in the microbiome, which can lead to oral infections, such as peri-implantitis [34].

These changes, in turn, cause dysbiotic changes in the subgingival microbiota that exacerbate inflammatory progression and ultimately peri-implant health and implant functionality [19]. In this sense, these changes from a health state to a disease state include an increase in diversity and a gradual depletion of commensals, along with an enrichment of classical and emerging periodontal pathogens.

The results of Zheng et al. [8] confirm these data, as they indicate that peri-implant diseases are associated with changes in microbial enrichment. Their studies also state that implants and teeth share histopathological and ecological similarities, and therefore it was proposed that the microbial communities around these structures should be similar.

The finding that periodontal pathogens can also trigger peri-implantitis is expected, since the periodontal and the peri-implant subgingival pocket are similar microenvironments located in the same ecosystem, the oral cavity. So, in theory, they would offer similar nutritional and redox conditions to colonizing species [21].

Therefore, it is assumed that the same colonization pattern that occurs in healthy periodontal tissues or in periodontal disease may also occur around the subgingival surface of dental implants.

Traditionally, studies on the pathogenesis of the peri-implant microbiota have analyzed individual bacterial species in complex microbial communities. More recent work has shown that peri-implant diseases may be polymicrobial in etiology, caused by a change in the microbial community rather than a single pathogen [8].

As the complexity of microbial communities in peri-implant sites is described, we found that peri-implant diseases were associated with subgingival dysbiotic microbial communities.

Furthermore, there is evidence that the peri-implant microbiome may be distinct from the periodontal microbiome [1].

It may seem logical that implants and adjacent teeth share similar microbiota as they share a similar ecological niche, that is, interdental space. However, the distinct surface topography and immunological characteristics of peri-implant tissues may explain why biofilms associated with teeth or implants can harbor diverse bacterial species.

In this manner, the overall results of studies using culture and targeted molecular diagnostic techniques suggest that peri-implantitis is associated with a specific mixed microbiota that shows several similarities with the microbial profile associated with periodontal infections, as well as some other microorganisms not commonly associated with the etiology of periodontitis [7]. Another relevant point is the corrosive biodegradation of biomaterials, in which corroded Ti surfaces, or ions such as Al and V, can promote increased adhesion of microbial species and a higher density of biofilm.

Some studies have hypothesized that the implant surface covered by biofilm undergoes accelerated corrosion due to an acidic environment generated by bacterial cell metabolism and released products [3]. The presence of Ti products around dental implants may contribute to peri-implant bone resorption, microbial dysbiosis, and consequently increase the risk of developing/aggravating peri-implantitis [3].

Therefore, titanium ions and released micro- or nanoparticles may affect the surrounding tissues [36] and enhance the macrophage inflammatory response [37]. Whether this is clinically significant for the progression of peri-implantitis remains to be proven, although Ti may act as an initiating agent for the immune response, with the microbial component being required to instigate inflammation.

We can therefore state that corroded implant surfaces may promote microbial recolonization, impair regeneration procedures, and reduce the ability of host cells to reconnect and proliferate.

Topographic patterns with different shapes and sizes inhibit biofilm formation compared to flat surfaces. In addition to the surfaces already mentioned, antimicrobial, anticorrosive and biocompatible coatings have also been indicated as strategies to improve implant survival and consequently decrease the harmful effect of microbial corrosion.

It is understood that surface topography and roughness exhibit enormous effects on the response of cells and bacteria to materials. Although rough surfaces are proven to improve osseointegration of Ti implants, they may increase the possibility of infection due to microbial accumulation and adhesion [4]. Being so, it is important to balance the dilemma between osseointegration and antibacterial properties in surface design.

In other words, the different conditions that the subgingival microbiota can find itself, whether in symbiosis or dysbiosis, combined with the surface characteristics of Ti implants, will influence the polarization of different immune cell profiles, generating alternative immune cascades with different cellular responses, ultimately causing a positive or negative modulation of the osseointegration process.

CONCLUSION

The present study concluded that different conditions of the subgingival microbiota will influence different immune cascades generating different cellular responses and positive or negative modulation of the osseointegration process. Therefore, we can state that implants survive in the body due to balanced defense reactions in the form of inflammation and activation of the innate immune system. However, in certain cases, implant failure will occur characterized by bacterial attacks and/or reactivation of the immune system that will now act against microbiological stimuli.

What is observed in current studies is the focus on only the host-immune-response or host-microbiotic interaction in the osseointegration process of Ti implants. It is important to highlight that more studies should be developed with the focus of research correlating both the host immune response and the microbiological relationship concomitantly. Moreover, the various mechanisms that govern the profiles and polarization of immune cells still need to be better elucidated, as well as their response to microbial challenge.

Thus, a thorough understanding of the host-microbiome interaction at the peri-implant site may provide the basis for improving peri-implant disease prevention and therapy strategies and for developing future strategies focusing on immune cell immunomodulation in a target-driven, sequential and dynamic manner induced by Ti implants.

Collaborators

NS Silva and ACR Almeida performed effective and intellectual participation, data interpretation and manuscript preparation. M Nascimento, BM Souza and, TGB Lourenço and AT Posch were responsible for guidance and supervision, critical review and final approval.

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