Oral Microbiota in Patients with Peri-Implant Disease

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Peri-implant infections are the most common complications related to the placement of dental implants. There are many microbial similarities between peri-implantitis and periodontitis but due to current laboratory techniques there are just as many differences. The peri-implant microbiota presents a lower microbial quality than the periodontal microbiota, becoming increasingly complex as it progresses from peri-implant mucositis to peri-implantitis. The microbial difference detected between the peri-implant and periodontal microbiota is primarily related to whole bacterial populations, rather than specific bacterial taxa. The use of probiotics could support the reduction of peri-implant pockets, in association with mechanical debridement, due to their mechanism of action of competitive inhibition for adhesion sites. The peri-implant microbiota represents a qualitatively inferior but quantitatively superior bacterial ecosystem for some bacterial genera compared to the periodontal microbiota, showing that a progression from healthy state to peri-implantitis causes changes in microbiota composition in the absence of specific disease-causing bacteria.

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1. Introduction

Dental implants are medical–surgical devices placed in the jaw bones in order to replace one or more missing teeth by prosthetics [1]. The process that leads to integration of dental implants into the bone was described by Branemark in the 1960s and is called osseointegration, which is a direct connection, both structural and functional, between the vital bone and the surface of a loaded (i.e., prosthetic) implant [2].

Peri-implant infections are the most common complications related to the placement of dental implants: they are classified into peri-implant mucositis and peri-implantitis [3]. According to the most recent guidelines, the diagnosis of peri-implant mucositis can be made if bleeding on probing (BOP) or suppuration is present in the absence of radiographic crestal bone loss (beyond initial remodeling); peri-implantitis also involves bone resorption (beyond initial remodeling) and, consequently, an increase in probing pocket depth (PPD) [4].

The prevalence of peri-implant mucositis and peri-implantitis can be as high as 80% and 56%, respectively [5].

Risk factors related to the development of peri-implant disease reported in the literature are: smoking [6], genetic factors such as a combined IL-1 genotype positivity [7], history of periodontitis [8], poor oral hygiene [9], systemic diseases (uncontrolled diabetes mellitus, cardiovascular and immunodepressive diseases) [10], iatrogenic causes (such as extra cement) [11], poor peri-implant soft tissue quality (keratinized gingiva thickness < 2 mm) [12], history of one or more implant losses [13], excessive occlusal loading [14], and titanium particles [15].

The primary etiological factor in the development of peri-implant diseases is the biofilm, which is a complex microbial community consisting of numerous micro-organisms that can communicate with each other through fine molecular processes (known as “quorum sensing”) [16]. The oral microbiota consists of more than 700 different species, which rarely live in planktonic form but aggregate in communities to form the biofilm; it can grow both on mineralized tooth surfaces, leading to periodontitis, and on titanium implant surfaces, leading to peri-implant mucositis and, in the long term, peri-implantitis [17].

Salivary film, termed “acquired pellicle”, is a bacteria-free biofilm that covers dental and implant surfaces exposed to the oral cavity due to the presence of saliva; different surface receptors are expressed in order to set up molecular links with late bacterial colonizers [18].

Salivary film on titanium surfaces does not include low molecular weight cystatins and mucins, in contrast to biofilms adherent to enamel surfaces [19]. However, the underlying differences in the composition of films formed on titanium does not appear to represent a risk factor that can increase initial bacterial adhesion to implant surfaces [20].

2. Current Studies

Implant health will be achieved if a symbiosis is established between the host and the peri-implant biofilm; however, in the presence of peri-implantitis risk factors, dysbiotic changes can occur to the microbiota constituting the peri-implant biofilm, setting off peri-implant soft tissue inflammatory processes, leading to peri-implant mucositis and peri-implantitis [21]. The implant material has gained interest in recent years because it may participate in peri-implant biofilm dysbiosis [22]. As a result of the process of corrosion and attrition of the implant, caused by both the exposure of titanium for long periods to oral environment and the frictional forces developing physiologically at the implant-abutment interface, ions and nano- or microparticles of this metal may be released at the peri-implant soft tissue level [23]. To date, it is unclear whether such release of metallic material can establish a tissue inflammatory response and, in association with the presence of the microbial component, play an important role in the progression of peri-implant disease [24].

Regarding the implant material, the addition of niobium and zirconium to the titanium implant alloy has been shown to have a similar bacterial adhesion pattern compared to implants composed of titanium and vanadium, with a slight increase in adhesion of *A. naeslundii* and *S. sanguinis* [25].

In the presence of poor oral hygiene for a period longer than three weeks, it has been found that dysbiosis of the peri-implant biofilm occurs, with bacterial proliferation of *Tannerella forsythia, Prevotella intermedia, Fretibacterium Fastidiosum* and *Treponema denticola* [26].

Few systematic reviews have shown that the peri-implant microbiota is similar to the periodontal microbiota in health or disease [27][28]. However, with the use of more recent molecular techniques, capable of analyzing and detecting with more precision a considerably higher number of microorganisms, the first microbial differences between submucosal biofilms, in implants, and subgingival biofilms, in teeth, have been highlighted [29]. Although logic might suggest that implants and adjacent teeth have a similar microbiota because they share a similar ecological niche, i.e., the interdental space, more recent studies suggest the presence of important differences in diagnosis and therapy, probably due to different anatomy, histology, and peri-implant immunological characteristics [30].

The first studies aimed to identify bacteria around healthy implants and, in the presence of peri-implant pathologies, used anaerobic cultures and phase-contrast microscopy, detecting Gram-positive cocci and non-motile bacilli at the level of healthy implants; in the presence of peri-implant mucositis, a greater presence of cocci, motile bacilli and spirochetes was observed, while other Gram-negative, motile and anaerobic species emerged in peri-implantitis [17].

Subsequently, with the advent of newer techniques such as polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), or checkerboard DNA-DNA hybridization (CKB), a more precise inventory of micro-organisms involved in peri-implant infections has been provided, often assessing the presence of periodontopathogenic bacteria: this includes members of the “red complex” bacterial cluster, including *Porphyromonas gingivalis, Tannerella forsythia, Treponema denticola, but also Treponema I-III* and *Synergistetes cluster A* [31].

From these early studies, the main differences in the peri-implant oral microbiota compared to the periodontal microbiota indicated the presence of pathogens such as *Peptostreptococcus* spp. or *Staphylococcus epidermidis* and *Staphylococcus aureus* [32].

Through the advent of next-generation sequencing (NGS), which is a sequencing technology used to rapidly determine the order of nucleotides in whole genomes or targeted regions of DNA or RNA, it has been possible to provide quantitatively and qualitatively enhanced classification of the oral microbiota [33].

The first study which used NGS to compare the peri-implant and periodontal microbiota was by Kumar [34]; it was concluded that 85% of the individuals analyzed shared <8% bacteria between peri-implant and periodontal sites. It was shown that the peri-implant microbiota appears to be, both in health and disease, quantitatively and qualitatively lower than the periodontal microbiota. In addition, the researchers highlighted the presence, at the peri-implant site, of bacterial genera that are not present at the periodontal site: for example, the *genera Burkholderia*, *Anaerovorax*, *Anaerococcus*, *Aerofilium* and *Exiguobacterium*. The predominant genera in the peri-implant microbiota were *Butyrivibrio, Campylobacter, Eubacterium, Prevotella, Selenomonas, Streptococcus,*

Actinomyces, Leptotrichia, Propionibacterium, Peptococcus, Lactococcus, and *Treponema*. Implant sites with peri-implantitis had lower concentrations of *Prevotella* and *Leptotrichia* and higher concentrations of *Actinomyces, Peptococcus, Campylobacter, Streptococcus nonmutans, Butyrivibrio, Pseudoramibacter alactolyticus,* and *Streptococcus mutans*than *healthy peri-implant sites* [29].

In a later study, also based on the use of NGS, an increased concentration of *Prevotella nigrescens* was shown in sites with peri-implantitis, while bacteria such as *Peptostreptococcaceae* spp. and *Desulfomicrobium orale* were significantly higher in periodontitis. In addition, the greater the severity of peri-implantitis, the higher the concentration of *Treponema* sp. *HMT-257*, which is correlated with radiographic bone resorption, subsequent increase in peri-implant pocket, and suppuration [35].

Another study showed a gradual differentiation of the microbial community from peri-implant health to peri-implant mucositis and finally to peri-implantitis. An increased concentration of periodontal bacteria such as *Porphyromonas gingivalis*, *Tannerella forsythia,* and *Prevotella intermedia* was detected at sites with peri-implant mucositis, whereas in the presence of peri-implantitis, the study observed the presence of quantitatively rich microbial communities, with an increased concentration of bacteria from the genus *Eubacterium* spp. [36]. Moreover, if the subject is a smoker, in healthy peri-implant sites the peri-implant microbiota is qualitatively less diversified, but there are more bacteria typical of peri-implant disease; instead, in sites with peri-implant mucositis, there is a quantitative reduction of bacterial species typically present in a healthy peri-implant site, also reducing its bacterial diversification; finally, it has been demonstrated that there are no qualitatively and quantitatively significant changes in the progression from peri-implant mucositis to peri-implantitis [37].

Bacteria from the classes Gammaproteobacteria (genus Vibrio), Epsilonproteobacteria (genus Campylobacter), and Bacilli (genus Granulicatella) were identified in greater amounts in the peri-implant crevicular fluid of healthy sites, whereas the classes Gammaproteobacteria (genus Acinetobacter and Moraxella) and Actinobacteria (genus Micrococcus) mainly in sites with peri-implantitis [38].

Bacteria belonging to the genus Filifactor, typically found at sites with chronic periodontitis, Dialister, Mogibacterium, Propionibacterium, Acinetobacter, Staphylococcus, Paludibacter, and Bradyrhizobium were identified only at healthy peri-implant sites [39].

The introduction of a new sequencing system, called MiSeq Illumina, has the advantage of reducing the procedural error and increasing the ability to detect more bacterial species. It has been shown that, at healthy peri-implant sites, there is a predominance of bacteria belonging to the class Actinomycetia and bacterial species such as *Veillonella dispar*, *Rothia dentocariosa* and *Streptococcus sanguinis*, while in the presence of peri-implantitis, the microbiota is characterized by the quantitative increase of bacteria belonging to the classes Bacteroidia, Spirochaetes, Synergistia (species *Synergistetes* spp. *HOT-360*), Clostridia (species *Clostridiales* spp. *HOT-093* and *Catonella morbi*), Deltaproteobacteria, of periodontopathogenic bacteria belonging to the “red complex” and finally of bacterial species such as *Porphyromonas* spp. *HOT-395*, *Porphyromonas nigrescens, Porphyromonas*

oris, Treponema maltophilum, *Dialister invisus, Eubacterium saphenum, Filifactor alocis, Freitbacterium fastidiosum, Mitsuokella* spp. *HOT 131, Chloroflexi* spp., *Tenericutes* spp. and *Fretibacterium HMT 360* [40].

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