Oral Microbiome Associated with Peri-Implant Infections – A Review

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Abstract: Dental treatments using dental implants have been well documented over the past 40 years and with great success. The dental implant installed in the place of missing teeth should always involve proper forecasting by the dentist. Namely, it is important to know the microbiome surrounding the implant, from its planning till final rehabilitation. The exact time of microbiome formation, as well as microorganisms involved, are essential for the proper implementation and success of the implant. However, internal contaminations of the rehabilitated implants, the extracellular components of microorganisms, such as endotoxins, have a huge influence on implant success. In addition, it is also very important the knowledge concerning implants surfaces and associated microorganisms. This study conducted a literature review on the oral microbiome and its relationship with the peri-implant infection, with the discussion of several classical and current studies. Although it can be concluded that the peri-implant microbiome is characterized by the microbiome present before dental implant placing, more studies are required to better elucidate the planning and the longevity of dental implant treatment.

Keywords: dental implant; peri-implant microbiome; oral microbiome; periodontal disease

1. Introduction

Dental implants have been largely used for the last 40 years. They are artificial structures, made up of titanium, that are installed in the place of a missing tooth. Implants are anchored in the bone, through the concept of osseointegration [1].

The implant-abutment connection represents the weakest point of the dental implant, due to a micro-gap between the implant-abutment interface, which may cause microbial leakage [2]. The occurrence of microleakage through this interface is not surprising since the diameter of the smallest oral bacterial species may range from 0.2 to 0.7 μm [3] and the micro-gaps resulting from implant-abutment attachment vary from 1 to 70 μm [4], depending on the type of platform connection [5]. These hollow spaces may act as reservoir for commensal and/or pathogenic bacteria, especially anaerobic or micro-aerophilic species, representing a potential source of tissue inflammation, which may lead to bone resorption [6]. In consequence of that bacterial leakage, two types of diseases, peri-implant mucositis and peri-implantitis, that, being like gingivitis and periodontitis, can affect implants.

Mucositis is characterized by inflammation restricted to the peri-implant mucosa, without bone loss, while peri-implantitis is a deep inflammatory lesion, characterized by bleeding, peri-implant pocket and progressive loss of bone support around implants [7,8]. Peri-implantitis, like periodontitis, is an endogenous infection, poly-microbial and opportunistic, that occurs by the conjunction action of local microbiota [7].

This study involves a bibliographic review concerning oral microbiome formation that occurs around implants and its characterization, as well as the analysis of peri-implant infections that can evolve to the undesirable implant loss.

The theme is of great importance in nowadays rehabilitation scenery since it is commonly performed in dental practices and is well accepted by patients. Therefore, clinicians, in general, must possess knowledge to perform an adequate and safe procedure and ensure long lasting dental implants treatments.

2. Materials and Methods

A bibliographic search was performed using PubMed and B-On databases. Keywords used were: “dental implants AND microbiology”, “loss of dental implants AND microbiology”, “microbiology AND microleakage”, “oral microbiome”.

Oral Microbiome

The oral cavity is a dynamic system continuously colonized by microorganisms being called the oral microbiome. This recent concept assumes the involvement of these microorganisms with the host, including the survival capacity against the immune system defence [9].

In the oral cavity, the microbiome is inserted in different anatomic structures, in the form of biofilm, forming an ecosystem that, in equilibrium, allows the maintenance of health. However, ecological changes in the microbiome allow the development of pathogenic agents that can cause disease [10].

Biofilm development occurs in teeth and mucosa, as well as in artificial surfaces like prosthesis and implants. Therefore, oral biofilm acts as a pathogenic community, where microorganisms become less vulnerable to immune cells, like neutrophils and antibodies as well as anti-microbial agents [11]. Nowadays, the idea of how oral biofilm causes disease, like caries, periodontitis or peri-implantitis disease is explained by the ecological hypothesis of plaque, that

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determines that it is the interaction between microorganisms and the host that defines the state of health or disease [12].

Recent advances from metagenomic studies have developed a new model of periodontal disease pathogenesis. Chronic periodontitis does not result from individual pathogens but rather from polymicrobial synergy and dysbiosis associated with a dysregulated immune response inducing inflammation-mediated tissue damage [13]. Namely, changes in microflora environment, due to pH, diet and hygiene alterations, the use of broad range antibiotics, the commitment of the immune system, among others, can lead to changes in biofilm composition. Because of those changes, certain microbial species can exhibit higher virulence, allowing opportunistic microorganisms to cause disease [12,13,14].

The way tissues are formed around implants, when compared with teeth, is different, however similarities exist in the microbial colonization during biofilm formation [15]. Despite this similarity, fundamental differences exist between periodontal and peri-implant tissues, like absence of Sharpey fibres in peri-implant tissues [9]. In this case, collagen fibres of the submucous connective tissue are aligned in parallel to implant surfaces, resulting in a deeper gap than the gingival sulcus, allowing easier penetration of microorganisms.

The lack of periodontal ligament gives certain disadvantages to the implant when compared with teeth, like:
- Reduction of physical barriers that allows entrance of microorganisms in submucous tissues; consequently, the conformation of peri-implant tissues makes them more susceptible to endogenous infections, when compared with periodontal tissues;
- Lack of adequate blood flow that decreases supply of nutrients and immune system cells, required for early stages of infection;
- Reduction of implants response to masticatory forces [8].

In face of this scenario, immediate postoperative failures can occur, resulting from contamination during surgery, that show up as microbial infections and healing problems [9]. Late failure usually occurs as a result of chronic infections in peri-implant tissues. It is therefore of great importance the study of the oral microbiome that is present in dental implants and the way it sets up.

3. Development of peri-implant microbiome

The use of osseointegration has shown to be an excellent method in the replacement of lost teeth [16-21]. Osseointegrated dental implants (Figure 1) are metal structures, mainly made up of titanium, that are surgically installed in the alveolar bone, in the place where one or more teeth were lost. They are used due to their characteristics like biocompatibility, stability and resistance to corrosion.

After dental implant installation, and according to the circumstances and planning of the case, a prosthetic rehabilitation is installed, with the help of prosthetic components that are linked to implants and will support the prosthesis, giving the required function and aesthetics [9].

Prosthetic components (Figure 2) are mostly made up of metal, however, and for aesthetic reasons, other materials have been introduced in the prosthetic components of dental rehabilitations like zirconia oxide [22]. Differences in microbial colonization between ceramic and metal surfaces are still a controversial issue, as some in vitro studies point out that microbial colonization in zirconia oxide surfaces is lower when compared with titanium surfaces [23,24] and others verified that the predominant factor for adhesion depends more on the bacterial species itself [25].

With the increase in the use of dental implants rehabilitation, it becomes necessary the study on biofilm formation, composition and action on implant surface. The formation of dental biofilm on implants surface can lead to the development of local infections capable of causing implant loss [9]. In this way, it is very important the study of dental biofilm formation on implants and understand when it occurs.
Several studies demonstrate biofilm formation on dental implants. Koka et al. [26], in a study with partially edentulous patients, suggested that colonization of marginal implant plaque occurred within 14 days, whereas subgingival colonization took longer and occurred within 28 days (Figure 3) [26].

In the meantime, patients with history of aggressive properly controlled periodontitis, that were rehabilitated with dental implants, did not have changes or inflammations after osseointegration [36]. On the other hand, Botero et al. [17] verified that partially edentulous patients with periodontal involvement, that were rehabilitated with dental implants, showed around implants, pocket and bone loss, with high levels of periodontopathogens (facultative anaerobes after 6 months of implant exposition to oral environment) in subgingival microbiome. This indicates that teeth might serve as a microbial reservoir, suggesting that patients with history of periodontal disease would have increased risk of peri-implant disease [17].

In this way, teeth and implants can serve as niches for dental biofilm formation and induce gingivitis and mucositis, that can develop to periodontitis and peri-implantitis respectively [19].

4. Dental implant surfaces

Artificial surfaces of implants and rehabilitation structures allow the formation of dental biofilm [9]. Therefore, it is required to know surfaces of different types of implants for an adequate choice for lowest possible biofilm accumulation.

Concerning implant surface, there is no consensus among scientific community on if microbial composition is affected by different geometry implants’ surfaces. Some studies report relevant results but are constantly changing due to new technologies in dental implants manufacture. Several changes in implant design have been done in the last years, in an attempt to decrease the space between the implant and the prosthetic component, to reduce bacterial proliferation. However, only limited success was obtained so far [37].

Rougher implants can favour biofilm development and consequently peri-implantitis [38]. In a more recent study it was also shown that peri-implantitis can lead to bigger bone loss, due to the presence of periodontal pathogens in implants of internal connexion, when compared to implants with “morse cone” type connexions [37].

Besides different implant surfaces that suffer microbial colonization, implants are also subjected to local exudates, pH, toxins and components of microbial release. In this way, some authors study titanium corrosion and its consequences, namely, the tribocorrosion which is a material degradation process due to the combined effect of corrosion and wear and that has been identified as the major degradation mechanism that results in dental implants failure [39]. Biological consequences of titanium corrosion and its accumulation in tissues are significative, and there may be changes in peri-implant tissues and chronic inflammation that can lead to implant loss [40]. Titanium corrosion has been detected at considerable levels in tissues and fluids adjacent to implants [41].

In fact, physiology of the environment where the implant is inserted varies with the place and its installation mode, being composed by a complex system with organic and inorganic...
components, like ions, aminoacids, proteins and fatty acids, as well as living cells [42].

The composition of that environment can be altered according with patient’s health and, consequently, can lead to implant loss [43]. Therefore, inflammation and/or conditions associated with corrosion can create an acidic environment [44]. Measurements done in titanium alloys of orthopaedic implants showed that implant’s place is acid, with pH around 2.5. For dental implants, this can be associated to the presence of biofilm or acidogenic bacteria, capable of reducing local pH below 4.5 [45].

So, debris released from the degradation of dental implants has cytotoxic and genotoxic potential for peri-implant tissues. Thus, the amount and physicochemical properties of the degradation products determine the magnitude of the detrimental effect on peri-implant tissues [46].

5. Oral microbiome associated with dental implants

Subgingival microbiome associated with dental implants has shown to be similar to dental microbiome [47,48]. However, microbiological studies have suggested the transmission of subgingival microorganisms, from dental locations to peri-implant spots [49].

Initial colonization of the oral microbiome occurs by adhesion of earlier colonizers (earlier microorganisms), including Streptococcus oralis, S. gordonii and Actinomyces naeslundii. This initial colonization favours adhesion of secondary invaders where biofilm formation occurs by the interaction and multiplication of available microorganisms [50]. With biofilm establishment, synergic and antagonist microbial interactions occur enriching the biofilm in the spot and in prosthetic components, making clear the relationship between the biofilm and host response [50].

Biofilm in healthy peri-implant spots has been characterized with high proportion of Gram positive cocci. In the meantime, in peri-implantitis cases, biofilm has high amounts of Gram negative bacteria, as well as Gram positive coccus (Parvimonas sp. and Peptostreptococcus sp.) [51]. However, other studies reported that Aggregatibacter actinomycetemcomitans and P. gingivalis were found in big quantity in peri-implant lesions [52,53]. These two pathogens can be considered the predominant microorganisms, being responsible for destructive infection in peri-implantitis [17]. Also, Van de Velde et al. [54] demonstrated the presence of A. actinomycetemcomitans, Fusobacterium sp., P. gingivalis, Pseudomonas aeruginosa and T. forsythia, in implants diagnosed with peri-implantitis. Symbiosis between Bacteroides sp. and P. aeruginosa seems to favour the persistence of P. aeruginosa in inflamed regions around implants [54].

Researchers did not observe considerable differences in subgingival flora around teeth or dental implants [30]. Other studies also analysed the frequency of A. actinomycetemcomitans and A. viscosus in supragingival biofilm, observing 92% vs 57% in teeth and 90% vs 73% in implants, suggesting that subgingival microbiome is similar in teeth and implants [55]. In 2006, Quirynen et al. [19], using molecular biology techniques like PCR, observed small differences in microflora of teeth and implants [19].

In partially edentulous patients, morphological types found did not show significative differences between teeth and implants. Kohavi et al. [55] identified similar microbiome in healthy teeth of partially and totally edentulous patients, being mainly composed of Gram-positive coccus with low count of spirochetes and mobile bacilli.

However, in 2011, Quirynen & Van Assche [56] detected high levels of bacteria related with periodontitis and peri-implantitis, in totally edentulous patients, agreeing with other similar studies [30,57,58].

Periodontal bacteria, like P. gingivalis, T. forsythia and T. denticola, were found with the same prevalence, in teeth and implants, being P. gingivalis the most prevalent [29]. It was also observed high prevalence of Fusobacterium sp. in implants spots after their installation, agreeing with data from van Winkelhoff & Winkel [28].

In 2008, Shibl et al. [59] evaluated the supra and subgingival microflora, in healthy implants and implants with peri-implant disease. Supragingival microflora was similar in both groups [59]. Veilonella parvula and F. periodonticum were the dominant species [59]. Besides these, four bacterial species were found in high significance levels in the group of implants with peri-implantitis: 3 periodontal pathogens of the red complex (P. gingivalis, T. forsythia and T. denticola) and P. nigrescens (P<0,05) [59].

In subgingival region, the complex profiles that shelter most beneficial species (purple, yellow and green) were similar between healthy implants and implants with peri-implantitis. Most pathogens of the red and orange complexes were found in high levels in the group of implants having peri-implantitis [60,61], P. gingivalis, T. forsythia, T. denticola, F. nucleatum, F. nucleatum ss vicentii and P. intermedia were found in significantly higher levels in subgingival biofilm of implants with peri-implantitis (p<0,05) [60,61]. Three bacterial species (A. naeslundii, S. intermedius and S. mitis) and a facultative periodontal pathogen (F. periodonticum) were found in high levels in supragingival biofilm when compared with subgingival samples of healthy implants (p<0,05) [59].

Levels of 3 microorganisms, V. parvula, S. gordonii and S. intermedius, as well as F. periodonticum, were significantly higher in the supragingival biofilm when compared with subgingival biofilm of implants with peri-implantitis. A higher medium count was observed for certain pathogens like F. nucleatum nucleatum, P. intermedia, P. nigrescens, T. denticola, Selenomonas noxia (p<0,05) and T. forsythia (p<0,05) in subgingival biofilm of implants with peri-implantitis [59].

In 1991, Slots et al. [62] also reported that in implants with peri-implantitis it is possible to detect big quantities of Gram-negative anaerobic bacteria, including Fusobacteria, spirochetes, B. forsythus, P. intermedia, P. nigrescens and P.
gingivalis. A. actinomyctemcomitans was also isolated in this type of lesion. In this way, microflora in peri-implantitis lesions resemble adult refractory periodontitis [62].

Recently, Zhuang et al. [63] demonstrated that periodontal pathogens are common in both places, periodontal and peri-implant, independently of health or disease. It was also evident that there was difference in the involvement of some pathogens in disease conditions. Prevalence and level of P. gingivalis and F. nucleatum were significantly associated with periodontitis, but not associated with peri-implantitis. However, A. actinomyctemcomitans was associated with periodontitis as well as with peri-implantitis [63].

It is important to note that differences observed in these studies can be explained by the use of different methodologies in microbial identification, since half of the oral biofilm is composed of non-cultivable microflora [64].

As a conclusion, differences seem to exist between microbial profile of healthy implants and implants with peri-implant disease, in supra and subgingival biofilm. The main differences were high levels of certain periodontal pathogens and low proportions of microbial complexes (compatible with the host) in the group of implants with peri-implantitis. The striking presence of species of the red complex in supragingival biofilm of implants with peri-implantitis suggests a propitious environment for reservoir of pathogenic species, being able to contribute to re-infection in treated subgingival spots [59].

6. Association of peri-implant disease with periodontal disease

Studies have shown that the microbiome around implants that failed is similar to the microbiome of teeth with periodontitis, in composition as well as proportion of microorganisms. Hence, the association of peri-implant disease with periodontal disease have been reported for several studies [37,49].

The incidence of peri-implantitis has increased continuously over the last years, being related with the loss of implants. Many factors play a fundamental role in complications and implant failures like implant and prosthetic components design [37] as well as bacterial colonization in implants.

Bacterial colonization around dental implants can lead to some local diseases, being the most common, mucositis and peri-implantitis. Mucositis (Figure 4) is an inflammation restricted to peri-implant mucosa in the implant, without bone loss. Peri-implantitis (Figure 5) is a deep inflammatory lesion, characterized by bleeding, peri-implant pocket and progressive loss of bone support around implants. These two forms of infection resemble respectively gingivitis and periodontitis in teeth [7,8].

![Figure 4: Mucositis spots.](image4)

![Figure 5: Periapical X-ray of implant affected by peri-implantitis.](image5)

Peri-implantitis, like periodontitis, is an endogenous polymicrobial and opportunist infection, that appears by the combined action of local microbiome [7], resulting from the disequilibrium between bacteria and host response, that can lead to local inflammation or bone loss, and sometimes to implant loss [8].

Several studies that indicate dental implant failure after osseointegration, show the presence of high levels of periodontopathogenic bacteria (P. gingivalis, P. intermedia and A. actinomyctemcomitans) in peri-implant lesions [17,26,65,66]. In patients with a history of periodontitis, putative periodontal pathogens prevailed in the microbiome of diseased implants. Diseased implants and corresponding healthy sites appear to have distinct microbiological ecosystems [67].

Bacterial colonization by periodontopathogens has been considered a risk factor for peri-implantitis. Other studies indicate that teeth can be a source of bacteria in partially edentulous patients that were rehabilitated with dental implants [35,68,69].

In the meantime, the presence of microorganisms related with periodontitis and peri-implantitis found in gingival and peri-implant grooves, respectively, did not mean implant failure, and did not result in disease [31].

Work of Renvert & Persson [49] showed that patients with periodontitis history can have increased risk of peri-implant
infections. Moreover, Heitz-Mayfield & Lang [8] stated that patients susceptible to periodontal disease, have higher susceptibility to peri-implant disease when compared with patients without history of periodontal disease [8].

To decrease the chance of implant loss due to periodontopathogenic bacteria, several researchers propose elimination of these pathogens before dental implant installation [28,70,71].

In individuals with history of periodontal disease, local decontamination prior to implant setting should be done, but also in patients without history of periodontal disease. Besides, scientific data are limited in relation to periodontopathogen colonization in patients without history of periodontal disease and little is known about the efficacy of reduction of these microorganisms, especially in long term [72,73]. Nowadays, it is believed that treated sites are subject to recolonization with a microbiota similar to that present before therapy. The degree and speed of recolonization depends on the treatment protocol, the distribution patterns of periodontal microorganisms elsewhere in the oral cavity and the quality of the patient’s oral hygiene [74].

Plus, in classic bacterial infections, the diversity of the microbiota decreases as the disease develops. However, in most cases of periodontitis, the diversity of the flora increases. Given the large diversity and the complex interactions among the members of the microbiota, a therapeutic concept that targets one responsible bacterial species or strain with a highly specific agent appears to be an unrealistic approach. Therefore, little evidence supports microbiological testing as an approach to obtain better clinical outcomes. In fact, at present, no protocol exists with proven superiority, in terms of efficiency or effectiveness over scaling and root planning plus systemic amoxicillin and metronidazole for the therapy of any form of periodontal disease [74].

7. Dental Implant Connexions and Internal Contamination

Infiltration of microorganisms and their sub-products in implants makes relevant the study of implant and its prosthetic components surfaces. Penetration of bacteria and bacterial fluids can occur to the internal portion of dental implants and can be the cause of the inflammatory process that occurs in peri-implant tissues [68,75,76].

One of the major changes in the use of two steps implants has been the use of implants type “morse cone”, to try avoiding internal contamination of implants, through the decrease of spaces between the implant and corresponding prosthetic components. However, microorganisms can grow and serve as bacterial stores in those places, being able to induce inflamed areas and bone loss around implants, through prosthetic components (in prosthetic pillar/implant junction) [27].

Therefore, implants are not protected against bacterial installation, becoming necessary changes in the connexion area of prosthetic pillar with the implant [77]. In a recent meta-analysis study, Tallarico et al. [78] concluded that bacteria could easily be colonized at the implant-abutment interface and also affirmed that it is evident from a clinical point of view that inner portions of implant-abutment interfaces should always be considered contaminated, even in clinically healthy conditions.

Existing spaces between the retention screw and the prosthetic pillar are the main pathway of bacterial access in crowns on implants [79]. Through those spaces it is possible that fluids with bacterial sub-products and nutrients required for bacterial growth slip away by the interface prosthetic pillar/implant, contributing for the bad breath and the development of peri-implantitis [34].

Dental implant design in the connexion area of the implant with prosthetic pillar, might have strong impact on bacterial penetration [80].

Quirynen & van Steenberghe [81] showed bacterial penetration in the interface prosthetic pillar/implant, with implants of the external hexagon type.

Another work studied bacterial penetration through the interface prosthetic pillar/implant, in 13 different combinations of prosthetic pillar/implant [77]. Among diverse combinations used, the internal connexion and the use of silicone rings demonstrated to have lower bacterial infiltration [77].

The existence of spaces smaller than 4 µm between crowns and implants of the Ha-Ti system is not an effective barrier against infiltration by S. aureus [82]. Work of Orsini et al. [85] was in accordance with that, mentioning spaces of 1 to 5 µm between implant and the retention screw that could be filled by bacteria. Therefore, bacteria can be found in the most apical portion of the implant cylinder.

According with Piattelli et al. [84], prosthesis retained by screws or by cement can suffer penetration by bacteria or bacterial fluids to the inside of implants. However, there was less penetration in prosthesis retained by cement, being these ones more effective against penetration of bacteria and bacterial fluids [84].

Some implant systems possess sealing by a silicone ring that might reduce bacterial infiltration [85]. In this study, contamination of internal portions of prosthetic pillars of implants retained by screws was analysed. These researchers observed an amorphous and crystalline contamination suggesting calcium and phosphate, in all surfaces [85].

Microbial contamination was seen with higher intensity in the group without sealing [85]. No differences in bacterial morphology was observed between the group of sealed implants and the group without sealing. Most abundant microorganisms were coccius while bacilli were very rarely found. In clinical cases, microbial infiltration occurred in the interface prosthetic pillar/implant, although this contamination had been limited to patients having high standard of oral hygiene. In this way, authors concluded that contamination can be reduced with the use of silicone ring [85].
In the in vitro study of Steinebrunner et al. [80], bacterial infiltration was analysed along the interface prosthetic pillar/implant. Implants with internal connexions of the type tri-channels showed the higher amount of bacterial infiltration relative to implants of external hexagon connexion, internal hexagon and implants with silicone ring and implants with internal connexion by friction, respectively [80].

In other in vitro studies, without charges and charge dynamics, it was demonstrated that implants with “morse cone” connexion had minimal infiltration. These studies looked for contamination by A. actinomycetemcomitans, P. gingivalis and E. coli [86,87].

Microorganism penetration occurs in the different types of existing connexions. For this, it is required the development of new technologies for the improvement and decrease of internal contamination of implants [88].

8. Conclusion

From this review performed on oral microbiome and its relationship with peri-implant infections, it is possible to conclude that:
- Peri-implant microbiome is composed of microbiome present before installation of dental implants;
- The moment when microbiome develops on dental implant is still under discussion and there is no consensus among researchers;
- Microbiome established around dental implants is similar to the microbiome of periodontitis, in health, and also in cases of periodontal disease;
- There are several prosthetic components for rehabilitation of masticatory and aesthetic functions of the patient, however no totally efficient component is still available against micro-infiltrations to the inside of the implant;
- Deeper studies are still required to find an implant with the correct surface that decreases microbial colonization and ensures bigger success in dental implant treatments.

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