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Chapter 5

Peri-implantitis Microbiota

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Abstract

Dental implant surgery has been a successful therapeutic option for the rehabilitation of partially or completely edentulous jaws for many years. However, evidence regarding the causative factors of peri-implant disease is still lacking. Peri-implantitis is an inflammatory disease affecting the soft and hard tissues surrounding osseointegrated implant associated with the formation of a bacterial biofilm on the implant surface close to the marginal tissues. The aim of this chapter is to summarize the knowledge regarding the microbiota associated with peri-implant infection and to review the different microbial diagnostic tests to understand the peri-implant microbiota, as well as summarize the present knowledge regarding management of peri-implantitis and propose further recommendations for future studies. This chapter shows that the scientific data regarding the microbiota responsible for peri-implantitis initiation and progression are still inconclusive. A microbiological test may thus be one diagnostic method to be used to understand the complexity of microbiota associated with the peri-implant sulcus. However, in order to resolve inflammation and arrest disease progression, the understanding of the biofilm development is essential.

Keywords: dental implant, peri-implant infection, peri-implantitis, peri-implant microbiota, peri-implant microbial test

1. Introduction

Dental implants have become a successful therapeutic option to replace missing tooth. It has been estimated that approximately 12 million implants are placed every year, worldwide [1]. With the global increase of dental implant placement, there is a continued need for investigation regarding the etiology, risk factors and treatment for dental implant complications. Moreover, the widespread use of dental implants has led to an increase in biofilm-mediated

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peri-implant disease. There is an undisputed effect between the formation of an oral biofilm on the implant surface and the initiation of the inflammatory process around osseointegrated dental implants [2].

Initially, clinical measures such as probing were not recommended since it was believed that this could harm the mucosal seal. Therefore, diagnostic measures were limited to the radiographic examination. Thus, disease remained undiagnosed for many years. Therefore, failing dental implants were not diagnosed, and only failed implants were detected where the implant needed to be removed [3]. First, the term peri-implantoclasia was used to describe the disease condition, that is, catabolic condition with/without sepsis or suppuration, around the dental implant [4, 5]. However, this term was replaced shortly after with *peri-implantitis*, which became the accepted terminology for the infectious nature of the pathologic condition surrounding peri-implant tissue [6, 7].

Peri-implantitis has been described as a "site specific" condition or as an "inflammatory bacterial driven destruction of the implant supporting apparatus," which means that microorganisms play an important role in peri-implantitis [8, 9]. The prevalence of peri-implantitis shows a wide range (10-25%) in different study populations primarily due to the definition of peri-implantitis, i.e. the chosen cut-off level for registering marginal bone loss and the duration of the patient's follow-up [10, 11]. However, one of the major challenges in the treatment of peri-implantitis is the lack of effective treatments.

2. Periodontitis versus peri-implantitis

Peri-implantitis is defined as an inflammatory disease affecting the soft and hard tissues surrounding osseointegrated functioning implants, while periodontitis is defined as inflammation affecting the tissues around the teeth [12, 13]. Despite the similarities between peri-implantitis and periodontitis, they seem to differ in extent, composition and progression of lesions [14, 15]. Peri-implant disease is known to be multifactorial with risk factors identical to periodontitis, including poor oral hygiene, smoking, diabetes, and genetic factors [2, 16]. History, or current periodontitis status, increases the risk of peri-implantitis [2, 16–19]. However, there is a complex interaction between the development of periodontitis and peri-implantitis and the formation of bacterial biofilm [2, 16].

One of the major anatomical differences between periodontal and peri-implant tissue is the presence of a periodontal ligament around the tooth, while the implant is in an ankylosed state. Although there is extensive information regarding the histopathological characteristics of human periodontal lesions, only a few studies have evaluated peri-implantitis lesions in humans. Berglundh et al. concluded in a systematic review that critical histopathological differences exist between the two lesions [20]. For example, the apical extension of the inflammatory cell infiltrate was more pronounced in peri-implantitis lesions compared to that in periodontal lesions. In peri-implantitis, the inflammatory cell infiltrate was, in most cases, located apical of the pocket epithelium. In both types of lesions, the infiltrate was dominated by plasma cells and lymphocytes, but in peri-implantitis, the neutrophil granulocytes and macrophages occurred in larger proportions [20]. In a recent animal study on mice, where

periodontitis and peri-implantitis lesions were experimentally induced by ligatures, a striking difference was observed on comparing the spontaneous healing after ligature removal. More bone was regained after ligature removal around teeth compared with that around implants in the peri-implantitis lesions. The intrinsic ability of the periodontal ligament to repair bone around teeth may thus be one of several key factors influencing treatment outcomes of peri-implantitis [21]. Moreover, soft tissues around teeth and implants are of similar dimensions [3]. The outer surface of the gingiva and peri-implant mucosa is covered by keratinized oral epithelium, but the peri-implant mucosa continues marginally with a thin nonkeratinized barrier epithelium, which is similar to the junctional epithelium around teeth [3]. However, the reaction of the soft and hard tissue after microbial colonization is similar in many aspects [3].

It was previously believed that there are similarities between peri-implantitis and periodontitis microbiota, and that periodontal pathogens translocate into peri-implant tissue. These similarities were once considered a critical factor in disease causation [19]. Recently, it has been reported that peri-implantitis and periodontitis microbial environments are distinct, with differences in core microbiota between the two conditions [20, 22–24].

3. Peri-implant microbiology

Implant insertion appears to stimulate the mechanism of mature biofilm development. However, this initially formed biofilm is in a commensal state [25, 26]. The biofilm that surrounds healthy implants is confined supramucosally, regardless of the fact that it can be found in massive amounts [27]. Bacterial colonization starts approximately 30 min after the implant is inserted into the oral environment [28, 29]. Recently, studies identified more than 700 bacterial species and 25,000 phylotypes in the oral cavity [22, 30–32].

The bacterial composition of the peri-implant biofilm harbors a similar microbiota to that of the neighboring teeth [33], which means that teeth serve as reservoirs for bacterial colonization in the biofilm surrounding implants [6, 34–36]. Similarities between peri-implant and periodontal microflora have been shown in several studies [37–39]. The subgingival microbiota of diseased implants has generally been considered to share some common characteristics [33].

The peri-implant microbiota of healthy sites has been shown in some studies to be more diverse and complex than in peri-implantitis, which indicates that healthy sites have a more stable and healthy ecosystem [40, 41]. On the other hand, other studies have shown higher microbiota diversity in diseased subjects [42]. These observations demonstrate that the microbial communities in both healthy and diseased tissue are quite different; however, generally, most taxa are present in both conditions [42, 43].

The subgingival microbiota of healthy implants and peri-implantitis are colonized by periodontopathic microorganisms [44, 45]. For example, the peri-implantitis microbiota showed up to a 40% higher frequency of red complex and orange complex compared to healthy implants [8, 44, 46–51]. The most frequent periodontal pathogens presented in a peri-implantitis lesions are from genera such as Bacteroides, Prevotella, Porphyromonas, Treponema, and Tannerella [46, 52–54]. Moreover, there is an increase in the diversity of species in the more advanced

stages of disease [51]. Previous studies suggest that periodontopathic bacteria are not the only periodontal pathogens active in peri-implantitis, and that noncultivable microorganisms such as asaccharolytic anaerobic Gram-positive rods **(AAGPRs)** and oxidized graphene nanoribbons **(OGNRs)** may also play an important role in peri-implantitis lesions [41, 44, 54–57]. In addition, Gram-negative microorganisms such as *Aggregatibacter actinomycetemcomitans* (Aa), *Parvimonas micra* (Pm), and *Campylobacter rectus* (Cr) were identified in 52% of the studies [46, 48, 58–65] presented in a systematic review by Lafaurie [44]. Few studies have shown the presence of *Pseudomonas aeruginosa*, *Candida albicans*, *Staphylococcus aureus*, and *Staphylococcus Warneri* in peri-implantitis lesions [46, 47, 66]. In addition, the Epstein-Barr virus has been considered an enhanced risk factor in peri-implantitis lesions [67, 68]. However, it is not yet considered a microbiologic marker for peri-implantitis [67, 68]. The role of phylum Synergistetes in peri-implantitis lesions is still debated. Some recent studies have shown a strong association between this phylum and the occurrence of peri-implantitis [69, 70], while others conclude there is no relationship [71]. Therefore, peri-implantitis lesions represent a heterogeneous infection [44].

There are many factors that determine the variation in peri-implant microbiota and also the degree of its shift from the healthy microbiota found in the peri-implant sulcus. These factors include differences in the microbiological detection methods used in various studies [45, 72]. Moreover, inter-individual variations in oral microbiota (such as the presence of pathologic conditions in the oral environment, for example, untreated periodontal disease, smokers, or the status of edentulous), study design (longitudinal or cross-sectional, number of participants), and how the samples are handled all influence variations between studies [14, 72, 73]. To date, there is still limited data on which bacteria are involved in the initiation and progression of peri-implantitis disease [15]. Therefore, we should emphasize the fact that regardless of the statistically significant changes in peri-implant microbiota, microbiome composition shows a high tendency for changes that lead to a shift from a healthy status to a diseased status [72].

4. Microbial diagnostic tests

To date, clinical and radiographic data are the main diagnostic methods for the diagnosis of peri-implant disease. However, these methods are limited because they only detect the disease after a certain level of destruction [45]. Therefore, the use of microbiological tests is important to be able to determine the microbiota associated with the peri-implant sulcus [45]. There are different ways of testing the bacterial composition at the peri-implant sites. First, the sample is collected using sterile paper points, a sterile periodontal probe or a curette. These samples are then analyzed either by culture-based methods, molecular methods, sequencing methods, or other advanced new methods (i.e., metagenomics).

Culture-based methods were the first approach in helping understanding the human microbiomes. However, 20–60% of the microbiome is known to be uncultivable [74]. The limitation of this technique is that it is both time-consuming, and the results underestimate the diversity of the human microbiota.

The molecular methods, such as PCR or DNA-DNA hybridization, help to increase the number of bacterial species known to be oral commensals, which leads to increased understanding of

the disease process. These methods are faster and more sensitive than the culture-based ones, but are also limited because of the need to pre-select DNA probes for the specific bacterial taxa to be investigated [39]. Therefore, one has to be cautious when interpreting these results, as finding "unexpected" microbiota is impossible with these techniques, thus creating a risk of bias. However, these techniques have overcome the limitations of culturing techniques.

During the last few years, sequencing methods such as 16S rRNA have allowed the evaluation of an entire community's microbiome [39, 57]. These methods use a universal primer system to detect a broad range of bacterial taxa [75, 76] and discover previously new undetected and uncultivable bacteria [41, 57, 70]. Sequencing methods are able to overcome the limitations of the above-mentioned methods. On the other hand, this technique also has limitations. For example, in determining differences at the strain level, some taxa may escape detection due to less effective primer binding or differential amplification [39, 72].

Recently, some studies have used metagenomic methods for investigating microbiomes. This method is based on extracting DNA directly from the sample without "looking for" a specific organism and can be randomly sequenced or functionally screened for activities of interest [77]. These methods have recently provided valuable insights into the pathogenesis of periodontitis and may allow a paradigm shift in the understanding of peri-implantitis disease. However, studies using this technique are still ongoing.

5. Management of peri-implantitis

To date, there is no clear evidence to indicate what the initiating factors for peri-implant disease are. However, microbial infections with bacteria and possibly yeasts and viruses play an important role in the disease process [16, 46, 78, 79]. Peri-implantitis is always considered an infectious disease with the need for antimicrobial treatment to empirically target specific putative bacteria [78, 80–87]. The primary treatment goals of peri-implantitis are to resolve inflammation and arrest disease progression. Surface decontamination is important to consider during treatment. There is no gold standard in the treatment of peri-implantitis. However, surgical access with the adjunctive use of different chemical detergents, air powder abrasive devises or lasers have been previously presented to achieve surface decontamination [88].

Data regarding the effect of systematic antibiotics on peri-implantitis lesions are lacking long-term outcomes. Although the effect of systemic antimicrobials agents in the surgical treatment of peri-implantitis is still limited [38], time and dosage have made the risk of antibiotic resistance development a reality [78, 89]. Using antimicrobial agents may risk developing bacterial resistance and the overgrowth of superinfecting microorganisms that are difficult to eradicate [78]. The development of opportunistic pathogens, such as *S. aureus* or EBV, may lead to a change in the normal symbiotic ecosystem to a dysbiotic ecosystem by affecting the local innate immune response. This, in turn, leads to overgrowth of superinfecting bacteria and yeast [90–93]. The development of antimicrobial resistance will escalate peri-implant disease in the coming years. Therefore, the need for microbial sampling and testing is mandatory in order to prevent the risk of superinfection. These tests will identify the presence of ongoing specific microbial challenges that are difficult to eliminate and allow disease to progress.

Moreover, strict supportive maintenance therapy should be considered to prevent disease recurrence and to keep ecological balance in the oral microbiota [94]. Therefore, the presence of antimicrobial agents that do not alter colonization resistance will lead to a decrease in the risk of development, spread and dissemination of resistant strains among patients [91].

6. Conclusion and future perspectives

Peri-implantitis is heterogeneous, polymicrobial infection where certain core microbiota may pose a significant role. Scientific evidence identifying the specific microbiota responsible for the development and progression of peri-implant infection is still inconclusive. A review of the literature points to an enrichment of well-recognized pathogens in addition to newly proposed pathogenic microorganisms, several of which have not yet been cultivated. Therefore, understanding the peri-implantitis microbiota will improve strategies for prevention, supportive therapy, risk assessment, early diagnosis of peri-implantitis, and timely intervention—all key aspects of long-term survival of dental implants [95]. Based on the available knowledge presented in the literature, **Figure 1** summarizes important tips to the clinician. Future studies designed to understand the peri-implantitis microbiota should include careful selection of cases and controls, and the incorporation of state-of-the-art approaches, such as metagenomics [95].

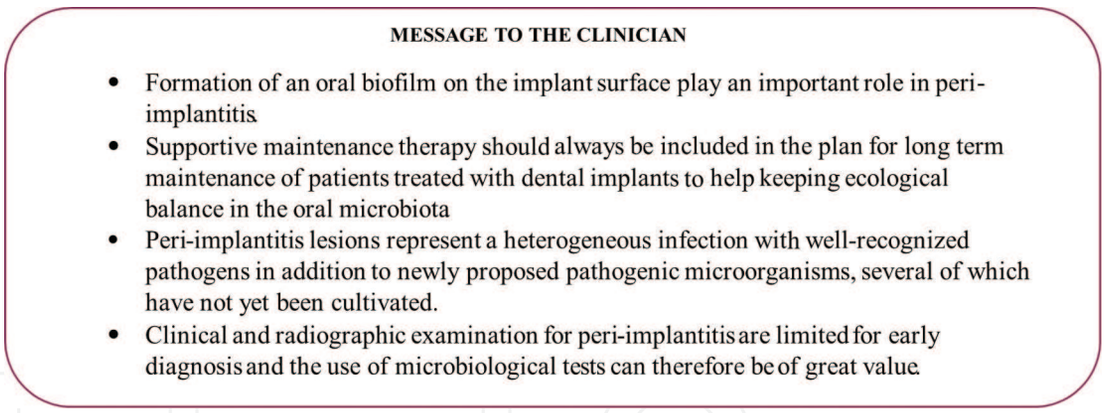

Figure 1. Tips for the clinician regarding peri-implantitis.

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