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Peri-implant infections

de Waal, Yvonne Catharina Maria

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SUMMARY

Peri-implant infections jeopardize long-term survival and success of dental implants. Infection limited to the peri-implant mucosa is called peri-implant mucositis. Peri-implantitis is characterized by the additional loss of supporting bone. **Chapter 1** briefly provides an overview of the epidemiology, pathophysiology, etiology, diagnosis and treatment of peri-implant infections.

Because the number of implants placed in everyday clinical practice is continuously increasing, it is reasonable to anticipate an increasing prevalence of peri-implant infections. This underlines the necessity for scientifically based clinical guidelines for prevention and treatment. The general aim of this thesis was to investigate epidemiological and microbiological aspects of peri-implant infections and to evaluate the effects of various protocols for treatment of peri-implantitis.

The systematic review described in **chapter 2** aimed to evaluate whether fully edentulous and partially edentulous subjects should be regarded similar when evaluating long-term implant treatment. The peri-implant conditions between fully edentulous and partially edentulous subjects were compared and the prevalence of peri-implant diseases in both groups was investigated. In total, 55 publications describing 46 studies were included.

Fully edentulous subjects harbored more plaque at their implants than partially edentulous subjects. Modified bleeding index scores were significantly higher in fully edentulous subjects, but no differences in bleeding on probing, implant loss and probing pocket depth were observed between both groups. No meta-analysis could be performed on prevalence of peri-implant mucositis and peri-implantitis. In general, prevalence of peri-implantitis was 0-3.4% after 5 years and 5.8-16.9% after 10 years of implant evaluation. A higher prevalence was reported in smokers and patients with a history of periodontitis. Overall, no definitive conclusions could be drawn regarding the association between edentulism and prevalence of peri-implant infection.

Whether or not the composition of the plaque, in addition to the quantity of the plaque, would also differ between fully and partially edentulous implant patients, was investigated by means of the systematic review described in **chapter 3**. In total, eleven publications describing ten studies were selected. Due to numerous differences among the selected studies no meta-analysis could be performed. Six out of ten studies showed a significant difference in the composition of the submucosal peri-implant microflora in healthy and peri-implant mucositis conditions between fully edentulous and partially edentulous subjects. Partially edentulous subjects showed a potentially more pathogenic composition, which means that they harbored higher proportions of bacteria that have been associated with periodontal and peri-implant infection. However, microbiological results were not unanimous among the studies. The existing data were insufficient for a clear conclusion regarding peri-implantitis cases. Overall, due to lack of a meta-analysis, the variability in microbiological outcomes and the limited number of studies available, it was concluded that the current evidence for an association between dental status and peri-implant microflora seems not to be robust.

In **chapter 4** we aimed to evaluate the effect of full-mouth tooth extraction on the oral microflora, with emphasis on the presence and load of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*. Adult patients (n=30), with moderate to advanced periodontitis and scheduled for full-mouth tooth extraction, were consecutively selected. Prior to and 1 and 3 months after full-mouth tooth extraction saliva, tongue, buccal and gingival mucosa and subgingival plaque/prosthesis samples were obtained. Aerobic and anaerobic culture techniques and quantitative real-time polymerase chain reaction (qPCR) were employed for the detection of oral pathogens. Full-mouth tooth extraction resulted in reduction below detection level of *A. actinomycetemcomitans* and *P. gingivalis* in 15 of 16 and 8 of 16 previously positive patients using culture techniques and qPCR, respectively. Those patients remaining qPCR positive showed a significant reduction in load of these bacteria. It was concluded that full-mouth tooth extraction significantly changes the oral microflora. Although significantly reduced in numbers, putative periodontal pathogens can persist in the edentulous oral cavity up to three months after full-mouth tooth extraction. Factors that enable these bacterial species to persist in the edentulous oral cavity are currently unknown. Furthermore, it remains unknown if low levels of these residual periodontal pathogens comprise a risk for future peri-implant infectious complications.

The aim of the case-control study presented in **chapter 5** was to compare oral microbiological characteristics of subjects with healthy peri-implant conditions and subjects with peri-implantitis while controlling for the influence of various patient-related and implant-related factors. Peri-implant submucosal microbial samples were collected from 89 patients with peri-implantitis (cases) and from 71 patients with only implants with healthy peri-implant conditions (controls). Samples were analyzed using culturing techniques for presence and bacterial counts of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, *Parvimonas micra*, *Fusobacterium nucleatum* and *Campylobacter rectus*. Multivariable logistic regression was used to explore the association of disease status with the microbiological characteristics. The variables gender, patient age, smoking, dental status, implant function time and presence of plaque were included as potential confounders. Peri-implant disease status was significantly associated with the submucosal presence of *P. gingivalis*, *P. intermedia*, *T. forsythia* and *F. nucleatum*. The association with disease status was most obvious for *P. intermedia* (OR 15.0, 95% CI [5.0, 44.6]) and *T. forsythia* (OR 8.6, 95% CI [3.6, 20.5]). Prevalence of *A. actinomycetemcomitans* was very low in both health (1%) and disease (3%). It was concluded that the periodontal pathogens *P. gingivalis*, *P. intermedia*, *T. forsythia* and *F. nucleatum* are associated with peri-implantitis.

The randomized controlled trials presented in **chapters 6 and 7** aimed to evaluate the effect of implant surface decontamination with chlorhexidine solutions during surgical peri-implantitis treatment on clinical and microbiological parameters. Respectively, thirty patients with 79 implants (chapter 6) and forty-four patients with 108

implants (chapter 7) with peri-implantitis were treated with resective surgical treatment consisting of bone re-contouring, surface debridement and chemical decontamination and apically repositioned flap. In chapter 6 patients were randomly allocated to decontamination with 0.12% chlorhexidine (CHX) + 0.05% cetylpyridinium chloride (CPC) (test group) or a placebo solution (without CHX/CPC, placebo group). In chapter 7 patients were randomly allocated to decontamination with a 2% CHX solution (test group) or 0.12% CHX + 0.05% CPC (control group). Microbiological parameters were recorded during surgery, clinical and radiographic parameters were recorded before treatment (baseline), and at 3, 6 and 12 months after treatment. Implant surface decontamination with 0.12% CHX + 0.05% cetylpyridinium chloride (CPC) in addition to mechanical debridement of the implant surface during the resective surgical treatment procedure led to a greater immediate suppression of anaerobic bacteria on the implant surface than the placebo-solution (chapter 6). Increasing the CHX concentration to 2% did not significantly increase the immediate antimicrobial effect of the debridement and decontamination procedure (chapter 7). No differences were observed in bleeding, suppuration, probing pocket depth and radiographic bone loss between the placebo group, the 0.12 CHX group and the 2% CHX group. It was concluded that, despite the immediate microbiological effect, chlorhexidine rinsing of the implant surface, in addition to mechanical implant surface debridement, does not enhance clinical outcomes of resective peri-implantitis treatment.

In **chapter 8** it was aimed to identify prognostic indicators for the outcome of resective peri-implantitis treatment, by an analysis of the pooled data of the two randomized controlled trials described in **chapters 6 and 7**. Primary outcome variable was failure of peri-implantitis treatment after 12 months. Multilevel univariable and multiple logistic regression analyses were performed to evaluate the effect of various potentially prognostic indicators on the primary outcome. Peri-implantitis treatment was unsuccessful in 106 implants (57%) and 48 patients (67%) after 12 months. The variables 'order of inclusion' and mean bone loss at baseline were significant prognostic indicators for treatment failure. Post-hoc analyses were carried out in a subgroup of patients to eliminate the effect of 'order of inclusion'. The univariable post-hoc analysis showed a significant association for smoking, maximum pocket depth at baseline, mean bone loss at baseline and presence of plaque. In the multiple regression post-hoc analysis only the variables smoking and mean bone loss remained statistically significant. It was concluded that the outcome of surgical peri-implantitis treatment is influenced by the experience of the surgical team with the surgical procedure. The observed learning effect has consequences for clinical practice and for conducting and interpreting clinical trials on peri-implantitis treatment. Other prognostic indicators are amount of peri-implant bone loss at baseline and smoking, and to a lesser extent, probing pocket depth at baseline and presence of plaque during follow-up.

The main research outcomes are discussed and general conclusions are drawn in **chapter 9**. Peri-implantitis is not very likely to occur within the first five years of implant functioning, but is frequently observed after this period. This, combined with

the notion that peri-implantitis seem difficult to treat successfully, even by a surgical treatment approach, stresses the importance of disease prevention.

A careful individual risk assessment should be made prior to dental implant placement. The use of a pre-implantological checklist, including all known risk factors for implant failure, is necessary. Potential risk factors should be eliminated whenever possible and (periodontal) infection should be properly controlled before implant placement. Extraction of teeth with a poor prognosis assists in reducing putative periodontal pathogens and total oral bacterial load and might limit the colonization of newly-placed dental implants with potentially virulent pathogens such as *P. gingivalis*. However, more (longitudinal) research is necessary for clarifying the specific role of microbial factors in the development of peri-implant infections and for establishing a better understanding of the preventive and therapeutic implications.

Decontamination of the implant surface with chlorhexidine, in addition to mechanical implant surface debridement, does not enhance clinical outcomes of resective peri-implantitis treatment. Therefore, it is recommended that future research focuses on other methods of implant surface debridement and decontamination. In addition, research should focus on the added value of systemic antibiotics in conjunction with a non-surgical and/or surgical treatment approach for peri-implantitis and on the indication for and added value of regenerative procedures. Peri-implantitis treatment outcomes may not only be influenced by the chosen treatment strategy, but are also influenced by other factors such as experience of the surgical team, severity of the disease (bone loss and pocket depth) and behavioral factors (smoking, presence of plaque). Therefore, early diagnosis of peri-implantitis and control of behavioral factors are crucial in achieving peri-implantitis treatment success.

