GENERAL INTRODUCTION

During the past decades, dental implant therapy has developed into a successful treatment option, both for partial and complete edentulism. The concept of osseointegration was developed in the 1960s by P.I. Brånemark (1929-2014) and co-workers at the University of Göteborg. They were also the first to describe the use of osseointegrated dental implants for anchorage of dental prostheses (Brånemark et al. 1969). In the years thereafter, many different implant systems have been developed and the indications for their application have been gradually extended. Nowadays, the implant retained overdenture has even become the first choice of treatment for the edentulous mandible (Feine et al. 2002). In 2007 it was calculated by Statistics Netherlands that 8% of the Dutch population of fully edentulous patients have dental implants to support a full prosthesis. Overall, there were 800 thousand adults in the Netherlands (6.6% of the total adult population) with one or more dental implants and it is expected that this number will continuously increase.
High survival rates of dental implants are generally reported (5-years survival rate 95.7%-97.1%; 10-years survival rate 89.8%-92.8%) (Pjetursson et al. 2012, Jung et al. 2012, Pjetursson et al. 2014). Yet, these survival rates do not surpass the longevity of natural teeth (Holm-Pedersen et al. 2007). Teeth surrounded by healthy periodontal tissues yield longevity of up to 99.5% over 50 years. Periodontally compromised teeth, that are treated and maintained regularly, or endodontically treated non-vital teeth still yield high survival and success rates: 10-year survival rate of 92-93% for periodontally compromised teeth, 10-year survival rate of > 90% for primary endodontically treated teeth as well as retreated teeth, 5-year survival rate < 80% for teeth with existing periapical pathology (Holm-Pedersen et al. 2007). It has therefore been stated that teeth should be given priority over dental implants whenever possible, unless multiple risks jeopardize their long-term prognosis (Lang et al. 2007).

Implant failure and success

In evaluating implant treatment, survival rate is often used as primary outcome. However, reporting on the clinical condition of surviving implants, *i.e.* implant success, is also important. To be considered successful, an implant-supported restoration has to meet certain criteria in terms of function (ability to chew), tissue physiology (absence of pain and other pathological processes) and user satisfaction (esthetics and absence of discomfort) (Esposito et al. 1998b). If the performance of an implant-supported restoration, measured in some quantitative way, falls below an acceptable level it is regarded a failure.
Failures can be due to technical and biological complications. Technical complications are caused by mechanical damage of the implant, implant components or suprastructures. Biological complications refer to disturbances in the function of the implant characterized by biological processes affecting the tissues supporting the implant (Berglundh et al. 2002). According to occurrence in time biological complications can further be divided into early failures and late failures. In early failures osseointegration has not been sufficiently established and it represents an interference with the healing process. Late failures are characterized by a failure to maintain osseointegration and are caused by a process of loss of osseointegration (Esposito et al. 1998b). The main etiological factors for early dental implant failure are surgical trauma, impaired healing

ability, infection and insufficient bone volume and quality (Esposito et al. 1998a). In late dental implant failures peri-implant infections are considered to play the predominant role (Esposito et al. 1998a).

Epidemiology of peri-implant infections

Peri-implant infection results from a disturbance of the balance between the microbiological challenge and host response. Infection limited to the peri-implant mucosa is called peri-implant mucositis. Peri-implantitis is characterized by the additional loss of supporting bone (Zitzmann & Berglundh 2008). If peri-implant infection is left untreated it may ultimately lead to implant loss.

The 10-years prevalence of peri-implant mucositis is estimated to be 63% on patient level (range 39.4-76.6, 95%CI 58.9-67.1) and 30% on implant level (range 8.9-48.1, 95%CI 28.6-32.8) (Atieh et al. 2013). The 10-years prevalence of peri-implantitis ranges from 6% to 47% on patient level (mean 18.8%, 95%CI 16.8-20.8) and from 2% to 37% on implant level (mean 9.6%, 95%CI 8.8-10.4) (Atieh et al. 2013). Based on these prevalence figures it can be concluded that peri-implant infection following dental implant placement is a frequently occurring complication.

This is in line with observations on other 'permanent' permucosal/percutaneous osseointegrated medical implants, for example implants for limb prosthesis fixation (Campoccia et al. 2013). Infection rates for this relatively new type of percutaneous devices range from 18% to 55% up to 5 years (Tillander et al. 2010, Tsikandylakis et al. 2014, Brånemark et al. 2014). Infection rates for totally internal osseointegrated implant devices, such as knee or hip prostheses are much lower, being approximately 2% within 2 years of functioning and about 0.5% between 2 and 10 years (Ong et al. 2009, Kurtz et al. 2010). The reason for this lower infection rate is that totally internal implants are placed in a sterile environment and are protected from exposure to external contaminations. Infections of these types of implants are usually caused by contamination of the implant surface before or during surgery or haematogenous seeding from a distant infected site (Campoccia et al. 2013). Permucosal/percutaneous implants on the other hand penetrate the protective body barriers, *i.e.* mucosal membranes and skin, and create conditions even for limited-aggressive opportunistic pathogens to gain access to and invade internal tissues (Campoccia et al. 2013).

Pathophysiology and etiology of peri-implant infections

Plaque accumulation at dental implant-supported restorations induces an inflammatory response in the peri-implant mucosa (peri-implant mucositis), which is characterized by increased proportions of T- and B-cells in the infiltrated connective tissue area (Zitzmann et al. 2001). This host response to the bacterial challenge is similar to the development of gingivitis at teeth (Pontoriero et al. 1994, Zitzmann et al. 2001). Because it is expected that peri-implant mucositis proceeds peri-implantitis as gingivitis proceeds periodontitis, treatment of peri-implant mucositis has to be the pre-requisite for the prevention of peri-implantitis (Lang et al. 2011b). Failure to do so may result in gradual enlargement of the inflammatory cell infiltrate and increase in numbers of plasma cells, lymphocytes, neutrophil granulocytes and macrophages (Berglundh et al. 2011). The apical extension of the inflammatory cell infiltrate in peri-implantitis is

often more pronounced than in periodontitis and is in most cases located apical of the pocket epithelium and close to the alveolar bone (Berglundh et al. 2011).

Microbiology of peri-implant infections

The microbiota associated with peri-implant infection varies from person to person and is in most cases dominated by a variety of Gram-negative anaerobic bacteria (Mombelli & Décaillet 2011, Kumar et al. 2012). The use of new molecular techniques such as polymerase chain reaction and pyrosequencing has revealed that the periodontal and peri-implant microflora is far more diverse than previously thought and harbors 'uncultivable' species of which the potential pathogenic role in periodontal and peri-implant diseases is unknown (Kumar et al. 2003, Kumar et al. 2012). Nevertheless, several periodontal bacteria have been associated with peri-implant disease, such as *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia*, *Fusobacterium nucleatum* and *Prevotella intermedia* (Mombelli et al. 1987, Leonhardt et al. 1999, Shibli et al. 2008, Kumar et al. 2012). However, there are also some marked differences between the periodontal and peri-implant microbiota. The diversity of peri-implant biofilms, in both health and disease, seems significantly lower than the diversity of subgingival biofilms (Kumar et al. 2012). Furthermore, several species, including previously unsuspected and unknown organisms, seem unique to the peri-implant niche, for example species belonging to the genera *Anaerococcus, Anaerovorax, Exiguobacterium* and *Burkholderia* (Kumar et al. 2012). Despite the fact that it has convincingly been demonstrated that micro-organisms are involved in the peri-implant disease process there is no proof that they are always the primary cause of the condition (Mombelli & Décaillet 2011). A suitable ecological environment is necessary to facilitate bacterial colonization and maturation of biofilms. Changes in local ecological conditions that favor the outgrowth of bacterial pathogens may be viewed as the true origin of peri-implant disease (Mombelli & Décaillet 2011).

Risk factors of peri-implant infections

Patients with a history of treated periodontitis have a significantly greater risk of developing peri-implantitis than patients without such a history (odds ratios 3.1-4.7) (Heitz-Mayfield & Huynh-Ba 2009). This could be due to the fact that periodontitis patients generally harbor more putative periodontal pathogens in their oral cavity than non-periodontitis patients (Van Winkelhoff et al. 2002, Kumar et al. 2003, Boutaga et al. 2006) and/or these patients may have a potentially higher genetic susceptibility to develop periodontal/peri-implant disease (Gruica et al. 2004, Laine et al. 2006). Smokers have a significantly higher risk for developing peri-implantitis than non-smokers (odds ratios 3.6-4.6) and this association seems to be dose-related (Heitz-Mayfield 2008, Heitz-Mayfield & Huynh-Ba 2009). Furthermore there seems to be a synergistic effect between smoking and specific interleukin (IL-1) gene polymorphisms and a higher risk for peri-implantitis (Gruica et al. 2004, Laine et al. 2006). The third major risk factor for peri-implantitis is poor oral hygiene (Heitz-Mayfield 2008). Presence of plaque at > 30% of the sites is associated with increased risk for peri-implant mucositis and peri-implantitis (Ferreira et al. 2006). This association between full-mouth plaque score and peri-implant infection seems to be dose dependent. Ferreira et al. (2006)

found an odds ratio for very poor oral hygiene and peri-implantitis of 14.3 (95%CI 9.1-28.7). Lack of accessibility for oral hygiene at implant sites, for example due to improper prosthetic reconstructions, has been related to presence of peri-implantitis (Serino & Ström 2009). Furthermore, progression from peri-implant mucositis to peri-implantitis is significantly associated with lack of preventive maintenance (Costa et al. 2012). Attendance in a structured maintenance program seems to be strongly related to implant survival (Anner et al. 2010) and a lower prevalence of peri-implantitis (Atieh et al. 2013). Other factors that have been suggested as potential risk factors for development of peri-implant infection include absence of keratinized mucosa (Brito et al. 2014), alcohol consumption (Galindo-Moreno et al. 2005), diabetes (Ferreira et al. 2006), rough implant surface (Astrand et al. 2004) and implant brand (Derks et al. 2015). However, the evidence on these factors is limited and sometimes conflicting.

Loose components, caused by fracture of the implant or abutment, or iatrogenic factors such as submucosal remnants of dental cement, implant malpositioning or ill-fitting suprastructures might also initiate peri-implant inflammation, by provoking a foreign body reaction and/or by creating local ecological conditions which facilitate undisturbed biofilm-formation (Wilson 2009).
The role of implant overload on peri-implant bone loss and peri-implant infections is controversial and, due to limited available evidence, not clear. However, it has been suggested that the effect depends on the health status of the peri-implant mucosa (Naert et al. 2012). Supra-occlusal contacts acting in a non-inflamed peri-implant environment do not seem to negatively affect osseointegration, whereas supra-occlusal contacts in the presence of inflammation seem to increase the plaque-induced bone resorption (Naert et al. 2012).
Titanium allergy and intolerance have also been suggested as possible initiating factors for peri-implant disease and causes for implant failure (Siddiqi et al. 2011). The prevalence of true titanium allergy seems to be low in dental implant patients (Sicilia et al. 2008), but debris-mediated titanium intolerance could play a more significant role in dental implant failure (Jacobi-Gresser et al. 2013). In fact, wear, or debris-mediated implant loosening, is the most common cause of failure in hip and knee arthroplasties (Landgraeber et al. 2014). Corrosion products of titanium implants may initiate macrophages, through phagocytosis of titanium particles, to produce inflammatory cytokines, leading to osteolysis and loosening of the implant. It has been shown that host factors, or the immune response to titanium particles, plays a significant role in this process. Particularly patients with risk genotypes of *IL1A*, *IL1B*, *IL1RN* and/or *TNFA* may be more susceptible to this type of dental implant failure than others (Taira et al. 2009, Jacobi-Gresser et al. 2013).

Diagnosis of peri-implant infections

Essential in the diagnosis of peri-implant disease is probing of the peri-implant sulcus. An increase in probing pocket depth over time is associated with attachment loss and bone loss (Lang et al. 1993, Schou et al. 1993a, Schou et al. 1993b). Probing with a light force does not seem to damage the peri-implant tissues and is recommended for regular evaluation of peri-implant tissues (Heitz-Mayfield 2008). It has been shown

that the mucosal attachment around implants after probing with a light force (0.25 N) is completely recovered within five days (Etter et al. 2002). Bleeding after gentle probing is a second valuable parameter for diagnosis of peri-implant infections (Heitz-Mayfield 2008). Bleeding on probing shows a high negative predictive value, *i.e.* absence of bleeding on probing is indicative for healthy peri-implant conditions (Jepsen et al. 1996, Luterbacher et al. 2000). Presence of bleeding on probing at more than half of the recall visits over a 2-year period is associated with progression of peri-implant disease (increase in probing pocket depth and/or bone loss) (Luterbacher et al. 2000). The presence of suppuration indicates presence of an inflammatory lesion and is most often related to a bacterial infection (Heitz-Mayfield 2008). Suppuration is associated with progressive bone loss (Roos-Jansåker et al. 2006, Fransson et al. 2008) and peri-implantitis (Roos-Jansåker et al. 2006, Lang et al. 2011b) and is a frequent observation at implants with peri-implantitis (Lang et al. 2011a). Radiographs are required for evaluation of peri-implant bone levels and for distinguishing peri-implant mucositis from peri-implantitis (Heitz-Mayfield 2008). Progressive bone loss, as observed by comparing two consecutive radiographs, is indicative for presence of peri-implantitis. In the differential diagnosis of peri-implant disease it is important to include identification of possible underlying problems, even if suppuration or presence of a biofilm point to a bacterial infection (Mombelli & Décaillet 2011). In addition, peri-implant bone loss as a result of peri-implant infection should be distinguished from bone loss as a result of remodeling or overload. Physiological remodeling of peri-implant bone takes place during the first few months after implant placement when the biological width is created (Berglundh & Lindhe 1996, Sculean et al. 2014). The amount of physiological bone loss differs between implant systems and depends, amongst other factors, on implant positioning (Tatarakis et al. 2012). Initial bone loss might be more pronounced at implants that are placed too deep (Hämmerle et al. 1996) or to close to other structures (Tarnow et al. 2000). Implants that are placed too deep generally also have deeper initial peri-implant pockets. This by its self might also be considered an initiating factor for peri-implant disease because pockets of 5 mm or more can be viewed as protected habitats for putative pathogens (Mombelli & Décaillet 2011).

Treatment of peri-implant infections

Once peri-implant infection has been diagnosed it is essential to initiate a prompt curative intervention in order to resolve the inflammatory lesion and prevent (further) bone loss. Mechanical non-surgical therapy can be effective for the treatment of peri-implant mucositis, but non-surgical approaches for the treatment of peri-implantitis have shown to be unpredictable and, in most cases, not effective (Renvert et al. 2008, Esposito et al. 2012, Heitz-Mayfield & Mombelli 2014). If non-surgical therapy does not resolve the inflammatory lesion, it is recommended to perform access surgery (Lindhe et al. 2008), thus facilitating proper granulation tissue removal and debridement and decontamination of the implant surface. The removal of the biofilm on the implant surface may be compromised by the screw-shaped design of the implant and a rough implant surface. Because mechanical debridement alone may not be adequate to achieve sufficient biofilm removal, additional measures such as laser therapy, the use of antibiotics and/or the use of antiseptics such as hydrogen peroxide or chlorhexi-

dine are currently used. As of yet, a validated protocol for treatment of peri-implantitis is not available (for review see: Esposito et al. 2012, Heitz-Mayfield & Mombelli 2014). Currently used interventions may be effective, but it is unknown which interventions are most effective, and for the interventions having similar degrees of effectiveness it is unknown which one has less side effects, is easier and cheaper to use (Esposito et al. 2012, Heitz-Mayfield & Mombelli 2014).

Objectives of this thesis

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 of peri-implant infections.
The general aim of this thesis was to investigate epidemiological and microbiological aspects of peri-implant infections and to evaluate the effect of various protocols for treatment of peri-implantitis.

Specific aims were:

- to compare peri-implant conditions between fully and partially edentulous implant patients and to investigate the prevalence of peri-implant diseases;
- to evaluate the peri-implant microflora in fully and partially edentulous subjects;
- to evaluate the effect of full-mouth tooth extraction on the composition of the oral microflora;
- to investigate the microflora associated with peri-implant health and peri-implantitis;
- to investigate the effect of implant surface decontamination using chlorhexidine solutions during surgical peri-implantitis treatment;
- to identify prognostic indicators for the outcome of surgical peri-implantitis treatment.

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