Prevention and treatment of peri-implant diseases

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Chapter 1

Introduction
**Serendipity**

Dental implants provide a successful treatment modality for replacing missing teeth. It is a treatment option widely used nowadays for fully and partially edentulous patients, which yields excellent long-term results, with 10-year success and survival rates above 95% (Buser et al. 2017). This breakthrough in oral rehabilitation was initiated 65 years ago by the work of Professor Per-Ingvar Brånemark from the University of Gothenburg in Sweden, whom is considered to be the “father” of modern implantology. In 1952, he serendipitously discovered the bone bonding properties of titanium, when he was studying blood flow in rabbit femurs by placing titanium chambers in their bone. Over time the chamber became firmly affixed to the bone and could not be removed (Brånemark, 1983). He named this phenomenon osseointegration, from the Latin word *os*, which means bone, and *integrate*, which means to make a whole. His ongoing research and experimentation led finally to the development of screw-type titanium implants, which he named *fixtures*. In 1965, for the first time Brånemark himself placed four of these implants in the edentulous mandible of a patient (Brånemark et al. 1977). They integrated within six months and remained in place for over 40 years, until the patient passed away.

A second pioneer of modern implantology was Professor André Schroeder from the University of Bern, in Switzerland. His entré to the dental implant arena began when he became acquainted with the Institute Straumann, a company with experience in metallurgy and metal products used in orthopaedic surgery. With the support and consultation of the founder Dr. Straumann, Schroeder began experimenting with metals used in orthopaedic surgery with the goal of developing a dental implant system for clinical use (Laney, 1993). His group was the first to document direct bone-to-implant contact utilizing a histologic technique incorporating nondecalcified sections with titanium implants in situ (Schroeder et al. 1976). Schroeder was also interested in the soft tissue reactions to titanium implants. His group was again the first one publishing on this topic, a few years later (Schroeder et al. 1981).

Over the past six decades, since the pioneering work of the two research groups in Sweden and Switzerland up until now, significant progress has been achieved in the field of implantology. The goal was, on one hand, to improve treatment outcomes from both a functional and an aesthetic point of view and to increase predictability and long-term stability, and, on the other hand, to reduce the number of required surgical interventions, treatment time, risk of complications, pain and morbidity for the patients. These developments included among others the introduction of new implant surfaces to reduce healing time and
improve osseointegration, the development of bone and soft tissue regenerative procedures to overcome soft and hard tissue deficiencies in potential implant sites and the possibility to use cone-beam computer tomography as part of the surgical and/or prosthetic planning (Buser et al. 2017).

**Osseointegration**

One definition of osseointegration, a term initially introduced by Bränemark (Bränemark et al. 1969), was proposed by Albrektsson and colleagues (1981), who suggested that this is “a direct structural and functional connection between ordered, living bone, and the surface of a load-bearing implant”. Recently, the definition of osseointegration has been refined to “a time-dependent healing process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved and maintained in bone during functional loading” (Zarb & Koka 2012). Osseointegration is a dynamic process during which primary stability, which is mechanical in nature, becomes substituted by secondary stability, the nature of which is biological (Bosshardt et al. 2017). The series of events leading to osseointegration can be summarized as follows: formation of a coagulum, formation of granulation tissue, formation of bone and bone remodelling; the latter continues for the rest of life (Bosshardt et al. 2017).

For many years, osseointegration has been considered merely as a woundhealing phenomenon. However, over the last decades, there was a paradigm shift, whereby the notion of body implants as inert biomaterials was replaced for that of immune-modulating interactions with the host. According to some researchers, osseointegration must also be perceived as an immune-modulated inflammatory process, with the immune system largely influencing the healing process (Trindade et al. 2016). Recently, the concept of foreign body equilibrium has been introduced. Osseointegration is considered as a balanced foreign body reaction, characterized by a steady state situation in the bone and a mild chronic inflammation (Albrektsson et al. 2014).

**Marginal Bone Level Changes**

For successful treatment outcomes with dental implants osseointegration should not only be achieved but also be maintained. Yet, some changes in the marginal bone level over time are mostly accepted. In general, marginal bone loss during the first year after prosthetic loading is accepted as an inevitable phenomenon and is considered as an adaptive remodelling of the
bone to surgical trauma and functional loading (Adell et al. 1981). The amount of this initial bone loss seems to be related to the implant design and/or surface properties and the location of the implant-abutment interface (Hermann et al. 2000; Laurell & Lundgren 2011). After this initial bone remodelling, a steady state condition should be expected, with most of the implants showing comparable and minimal annual bone loss thereafter (Laurell & Lundgren 2011; Jimbo & Albrektsson 2015). Still, if making a frequency distribution of the bone loss in a patient population, some implants will show more bone loss than others and a few implants will even show ongoing loss of bone over time (Buser et al. 2017). Continuous marginal bone loss might constitute a threat to implant survival or might result in unfavourable aesthetic outcomes and patient’s discomfort (Coli et al. 2017).

The reasons for marginal bone loss, taking place after the first year of function, are controversial and highly debated (Buser et al. 2017). According to some researchers, bone loss occurring after the initial remodelling is mainly due to bacterial infection (Lang & Berglundh 2011). Others consider a change in the immunological balance of the foreign body equilibrium as the primary cause for marginal bone loss around implants (Trindade et al. 2016). This change may be elicited by combined factors such as implant hardware, clinical handling and patients’ characteristics. It is assumed that, the mechanism behind the action of these combined factors is bone microfractures or other types of bone injury that leads to inflammation, which in turn triggers bone resorption (Qian et al. 2012).

The 2012 Estepona Consensus reported that crestal bone loss may occur due to many other reasons than infection. Implant-, clinician-, and patient-related factors, as well as foreign body reactions, may contribute to crestal bone loss (Albrektsson et al. 2012). Implant factors include: material, surface properties and design (e.g. ease of plaque removal), unsuitable types of implants, broken components, and loose or ill-fitting components. Clinician factors include: surgical and prosthodontic experience skills and ethics. Patient factors include: systemic disease and medication, oral disease (e.g. untreated or refractory periodontal disease, local infections), behaviour (e.g. patient compliance with oral hygiene and maintenance, smoking) and site-related factors (e.g. bone volume and density, soft tissue quality). Foreign body reactions include: corrosion by-products or excess cement in soft tissues (De Bruyn et al. 2017). In case of an aseptical loosening of an implant, microbial colonization can possibly be a later event and hence, been seen as a further clinical complication (Trindade et al. 2016).
Chapter 1

Introduction

Peri-implant diseases

The term “peri-implantitis” was introduced almost 50 years ago, to describe pathological conditions of infectious nature around implants (Levignac 1965; Mombelli et al. 1987). In one of the first animal studies describing the histologic characteristics of ligature induced peri-implantitis lesions in dogs, the authors wrote: “It is possible that the inability of the peri-implant tissue to heal following “subgingival” infection may in rare situations result in a process of progressing osteomyelitis” (Lindhe et al. 1992). At the First European Workshop on Periodontology in 1993 it was agreed that peri-implant disease is a collective term for inflammatory processes in the tissues surrounding an osseointegrated implant in function. Peri-implant mucositis was defined as a reversible inflammatory process in the soft tissues surrounding a functioning implant, while peri-implantitis was defined as a destructive inflammatory process around osseointegrated implants in function, leading to peri-implant pocket formation and loss of supporting bone (Albrektsson & Isidor 1994).

The threshold levels of probing pocket depth or attachment loss and/or marginal bone loss required to distinguish between reversible and irreversible conditions around implants have been a matter of debate between scientists since the 1990s (Coli et al. 2017). These discussions within the scientific community led to the recognition that clinical and radiographic baseline measurements are necessary in order to be able to follow implants over time and to distinguish between health and disease. This has also resulted in a modification of the definition of peri-implantitis. At the Seventh European Workshop on Periodontology in 2011 it was agreed that peri-implantitis is characterized by changes in the level of crestal bone over time beyond the physiologic remodelling in conjunction with bleeding on probing with or without concomitant deepening of the peri-implant pockets (Lang & Berglundh 2011). But, baseline recordings are not always available. Therefore, a year later, at the Eighth European Workshop on Periodontology, a more pragmatic case definition was recommended. In the absence of previous radiographic records, a vertical distance of 2 mm from the expected marginal bone level following remodelling was suggested as an appropriate threshold level, provided peri-implant inflammation was evident (Sanz & Chapple 2012).

Histologically, comparative analyses of human gingival and mucosal biopsies revealed that peri-implantitis lesions are larger and more aggressive than periodontitis lesions around teeth. Peri-implantitis lesions extended to a position that was apical to the pocket epithelium.
and were not surrounded by noninfiltrated connective tissue (Carcuac & Berglundh 2014). Thus, from a clinical point of view peri-implantitis may display a more aggressive character and may be expected to progress more rapidly when compared to periodontitis lesions (Salvi et al. 2017). A study assessing the pattern of progression of peri-implantitis in a large cohort of randomly selected implant-carrying individuals concluded that peri-implantitis progresses in a non-linear accelerating pattern (Derks et al. 2016).

The presence of a biofilm containing pathogens plays an important role in the initiation and progression of peri-implant diseases (Heitz-Mayfield & Lang 2010). Microorganisms may be present but they are not always the origin of the problem (Mombelli & Décaillot 2011). Inflammatory reactions in the peri-implant tissues can be initiated or maintained by several iatrogenic factors e.g. excess cement remnants, inadequate restoration-abutments seating, over-contouring of restorations, implant mal-positioning, technical complications such as loosening of a screw or fracture of implant components (Lang & Berglundh 2011). Immuno-logical reactions with foreign body provocation may present an alternative theory for peri-implantitis. Nevertheless, bacteria can be present in the implant interface during marginal bone resorption (Albrektsson et al. 2017). In a study discussing different triggering factors for peri-implantitis, it was concluded: “If only one of these factors would start a chain reaction leading to lesions, then the other factors may combine to worsen the condition. With other words, peri-implantitis is a general term dependent on a synergy of several factors, irrespective of the precise reason for first triggering off symptoms” (Mouhyi et al. 2012).

The prevalence of peri-implant diseases represents another controversial issue (Tarnow, 2016). Estimates of patient-based weighted mean prevalences and ranges for peri-implant mucositis and peri-implantitis were reported in a recent systematic review. The prevalence for peri-implant mucositis was reported at 43% (range, 19% to 65%), whereas for peri-implantitis it amounted to 22% (range, 1% to 47%). There was a positive relationship between prevalence and time in function of the implants (Derks & Tomasi 2015). In this review, seven different definitions of peri-implantitis, based on the amount of bone loss over time, were recognized. Because of these differences in case definition, with varying thresholds for the assessment of bone loss and reference time points from which the bone loss occurred, a wide range in the prevalence of peri-implant diseases has been reported in the literature, making it difficult to globally estimate the true magnitude of the disease (Salvi et al. 2017). Considering the large number of implants placed worldwide, peri-implantitis is considered a current

Although there are many clinical studies showing long-term success for dental implants, patients and dental care professionals should expect to see both biological and technical complications in their daily practice (Heitz-Mayfield et al. 2014). It is generally accepted that peri-implantitis is not an easy and predictable disease to treat. The key is prevention (Tarnow, 2016). As it is assumed that peri-implant mucositis is the precursor to peri-implantitis and that a continuum exists from healthy peri-implant mucosa to peri-implant mucositis and to peri-implantitis, prevention of peri-implant diseases involves the prevention of peri-implant mucositis and the prevention of the conversion from peri-implant mucositis into peri-implantitis, by timely treatment of existing peri-implant mucositis (Jepsen et al. 2015). Prevention is based on proper case selection, proper treatment planning, proper implant placement and properly designed restorations, but also, on regular monitoring of the implants and meticulous maintenance by both the dental care professionals and the patients (Tarnow, 2016).

Aims of this thesis

The removal of biofilm from the surface of an implant-supported restoration, professionally administered and/or self-performed, constitutes a basic element for the prevention and treatment of peri-implant diseases. Various instruments have been proposed for implant surface cleaning. Mechanical instruments and chemical agents are the instruments most commonly used for this purpose.

The first aim of the thesis was to assess the effect of the abovementioned instruments on different titanium dental implant surfaces. The efficacy of various patient-administered, mechanical modalities for plaque removal from implant-supported restorations was also evaluated.

A second aim of the thesis was to develop a clinical guideline to aid in decision-making regarding the diagnosis, prevention and treatment of peri-implant diseases. Recommendations regarding the best available instruments to use on dental implant surfaces were also incorporated.
More specifically, the objectives of the research presented in the following chapters were:

In **chapter 2**, the aim was to systematically examine, based on the existing literature, the effect of different mechanical instruments on the characteristics and roughness of titanium dental implant surfaces.

In **chapter 3**, the aim was to systematically evaluate, based on the existing literature, the ability of different mechanical instruments to clean contaminated titanium dental implant surfaces.

In **chapter 4**, the aim was to systematically evaluate, based on the available evidence, the effect of different mechanical instruments on the biocompatibility of titanium dental implant surfaces.

In **chapter 5**, the aim was to investigate *in vitro* the possible effect of five commercially available air-abrasive powders, on the viability and cell density of three types of cells: epithelial cells, gingival fibroblasts and periodontal ligament fibroblasts.

In **chapter 6**, the study aim was to systematically collect the available evidence, and, based on the existing literature, evaluate the ability of different chemotherapeutic agents to decontaminate biofilm-contaminated titanium surfaces.

In **chapter 7**, the aim was to systematically evaluate the efficacy of various patient-administered, mechanical modalities for plaque removal from implant-supported restorations.

In **chapter 8**, an epitome of the clinical guideline on the diagnosis, prevention and management of peri-implant diseases is presented.

**Disclaimer:** The majority of the chapters in this thesis have already been published in scientific dental journals. The study design is comparable in various aspects and some text duplications were inevitable. Because most chapters are based on separate scientific publications, but often concern similar topics, there is inevitably considerable overlap between chapters. Different journal requirements have also created some variations in terminology from one chapter to the next and different reference style. For expository reasons, the chapters in this thesis are not arranged chronologically.
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