Prevention and treatment of peri-implant diseases

Cleaning of titanium dental implant surfaces

Louropoulou, A.

Publication date
2017

Document Version
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PREVENTION AND TREATMENT OF PERI-IMPLANT DISEASES

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Anna Louropoulou

PERIODONTOLOGY

Prevention And Treatment of Peri-implant Diseases

- Cleaning of titanium dental implant surfaces -

Anna Louropoulou

The studies in this thesis were conducted at the department of Periodontology of the Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam and Vrije Universiteit Amsterdam, The Netherlands.
The author declares no conflicts of interest. Work for this paper is partly funded by a regular academic appointment at the ACTA.

The thesis was supported by

Kliniek voor Parodontologie Rotterdam

paro·praktijk·utrecht

Cover design and lay-out by Wouter Rijnen
Printed by Gildeprint, Enschede, The Netherlands
ISBN: 978-90-826057-1-6, published by DIDES

Prevention And Treatment of Peri-implant Diseases

- Cleaning of titanium dental implant surfaces -

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof.dr.ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties
ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit
op woensdag 26 april 2017, te 13:00 uur

door

Anna Louropoulou
geboren te Agrinio, Griekenland

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Faculteit der Tandheelkunde

To Nikolas

"We cannot solve our problems
with the same thinking we used
when we created them."
Albert Einstein

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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 Brånemark (Brånemark 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).

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 & Décaillet 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). Immunological 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

and future challenge for patients and dental professionals (Derks et al. 2016).

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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Chapter 2

Titanium surface alterations following the use of different mechanical instruments: a systematic review

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D.E. Slot
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Clinical Oral Implants Research 2012; 23: 643-658.

Introduction

The inflammatory lesions that develop in the tissues around implants are collectively recognized as peri-implant diseases. Peri-implant diseases include two entities: peri-implant mucositis and peri-implantitis (Zitzmann & Berglundh 2008). According to the consensus report of the 6th European Workshop on Periodontology, peri-implant mucositis is defined as an inflammatory reaction in the mucosa surrounding a functioning implant while peri-implantitis describes an inflammatory process that affects the soft tissues around an osseointegrated implant in function and results in the loss of supporting bone (Lindhe & Meyle 2008).

Peri-implant disease is the result of an imbalance between the bacterial load and host defense (Tonetti & Schmid 1994). Peri-implant diseases have been associated with predominantly Gram-negative anaerobic flora (Mombelli & Lang 1998). Bacterial colonization on oral implant surfaces starts immediately after contact with the oral environment and occurs rapidly (Fürst et al. 2007). Within weeks after the placement of implants in the oral cavity, a sub-gingival flora associated with periodontitis is established (van Winkelhoff et al. 2000; Quirynen et al. 2006). This colonization seems to be influenced by the surface roughness, surface-free energy and chemical composition (Quirynen et al. 1993; Rimondini et al. 1997). A surface roughness value (Ra) of $\approx$0.2 μm has been suggested as a threshold roughness value below which no further significant changes in the total amount of adhering bacteria can be observed due to the larger size of most bacteria (Quirynen et al. 1993; Bollen et al. 1996). Because of their physical characteristics (i.e., screw-shaped design together with the various degrees of surface modifications), implants and implant components seem to accumulate more plaque than natural teeth (Quirynen et al. 1993; Quirynen et al. 1995). Currently, various types of implant surfaces, ranging from smooth machined to rough surfaces, are used in different implant components (Esposito et al. 2007). It has been reported that even on relatively smooth implant surfaces (e.g., abutments), plaque accumulates faster when compared to natural teeth, with up to 25 times more bacteria adhering to rough implant surfaces than smooth ones (Quirynen et al. 1995). Hence, the removal of bacterial biofilm from an implant surface constitutes a basic element for the prevention and treatment of peri-implant diseases (Klinge et al. 2002; Renvert et al. 2008). The instruments used for surface decontamination should not make the surface more biofilm-retentive but they should aim to minimize the *de novo* formation of biofilm. To our knowledge, there is no direct evidence for the effect of roughness induced by instruments on plaque accumulation. However, in one study (Duarte et al. 2009) it has been observed that the levels of *S. sanguinis* adhesion were lower on rough

surfaces treated with metal curette. The same study, failed to show a significance difference in the levels of *S. sanguinis* adhesion among smooth surfaces treated with metal curettes and untreated controls, although a trend for higher adhesion on the smooth surfaces treated with the metal curette was observed. The authors commented that these results should be interpreted with caution.

The therapies and instruments proposed for the prevention and management of peri-implant diseases appear to be based, to a large extent, on the available evidence regarding treatment of periodontitis. The main problem associated with the removal of plaque from implant surfaces is the possible damage to the implant surfaces. Any damage to the surface induces changes in the chemical oxide layer that may result in increased corrosion. This process impairs the adhesion of fibroblasts and thus the biocompatibility of the implant (Dmytryk et al. 1990; Fox et al. 1990). These results have led to a demand for plaque and calculus removal only using instruments that cause little to no surface damage.

Different treatment modalities and instruments have been suggested for the decontamination of implant surfaces, as part of the surgical treatment of peri-implantitis both in animals and in humans, either as stand-alone treatments or in various combinations including mechanical instruments, chemical agents and lasers (Schou et al. 2004). All of these methods have been associated with advantages and disadvantages, with no definitive gold standard. In a recent review (Claffey et al. 2008) regarding the surgical treatment of peri-implantitis, the authors concluded that based on evidence from human and animal studies, no single method of surface decontamination is superior. It should be noted, however, that surface decontamination was not the primary parameter evaluated in the abovementioned studies.

The effect of different mechanical instruments on titanium surfaces with respect to surface changes, cleaning efficacy and cell adherence (biocompatibility) has been evaluated in several *in vitro* studies (Fox et al. 1990; Homiak et al. 1992; Rühling et al. 1994; Meschenmoser et al. 1996; Mengel et al. 2004). Some of these instruments, such as metal curettes and conventional sonic and ultrasonic scalers, have shown to damage the implant surface severely. Other instruments such as non-metal instruments and air abrasives, although less damaging, have been associated with incomplete removal of plaque and potentially damaging products or possible surgical complications, such as emphysema (Schou et al. 2003).

All of these treatment modalities can potentially modify the implant surface. The surface profile and roughness produced by the different instruments may significantly impact the newly formed biofilm, thus playing an important role in peri-implant health maintenance.

In addition, residues from soft scalers and air abrasives may influence bacterial adhesion, healing events and re-osseointegration. So far, there is little consensus regarding instruments that are more appropriate for use on implant surfaces. At present, systematic reviews are considered to be the strongest form of medical evidence. They are considered to be the primary tool for summarizing the existing evidence in a reproducible and systematic way, and they are crucial for evidence-based dentistry. To date, no systematic review has evaluated the existing information regarding the influence of mechanical instruments on implant surfaces.

Therefore, the aim of this review is to systematically examine, based on the existing literature, the effects of different mechanical instruments on the characteristics and roughness of implant surfaces.

Materials and Methods

This systematic review was conducted in accordance with the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA-statement) (Moher et al. 2009).

Focused question

What are the effects of the different mechanical instruments used on implant surfaces compared to untreated (pristine) surfaces?

Search strategy

Three internet sources were used to identify publications that met the inclusion criteria: the National Library of Medicine, Washington, D.C. (MEDLINE-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). The search was conducted up to March 2010. The search was designed to include any published study that evaluated the effects of mechanical instruments on titanium surface characteristics. To achieve this goal, a comprehensive search was performed. All possible treatment modalities for the cleaning of titanium surfaces were included, which ensured the inclusion of papers that used mechanical means as an alternative to other treatment modalities. All reference lists of the selected studies were hand-searched by the two reviewers (A.L & G.A.W) for additional papers that could meet this review's eligibility criteria. The terms used in the search strategy are presented in Box 1. The search strategy was customized according to the database been searched.

Box 1. Search terms used for PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE. The search strategy was customized according to the database been searched.

{‹Subject› AND ‹Adjective› AND ‹Intervention›}

{‹*Subject*: (<dental OR dent$ OR oral> AND <implant$>) OR (dental implant [MesH] OR dental implant OR dental implant OR dental implants OR dental implant$ OR dental implantation [textword]) ›
AND
‹*Adjective*: (smooth OR structure OR texture OR roughness OR surface OR biofilm OR plaque index OR dental plaque OR plaque OR dental deposit* [textword]) ›
AND
‹*Intervention*: (ultrasonic OR curette OR scaling OR acid OR laser OR polishing OR debridement OR curettage OR chlorhexidine OR air abrasion OR cleaning OR cleaning agents OR instrumentation OR ardoz-X OR decontamination OR citric acid OR phosphoric acid OR CPC OR cetylpridinium chloride OR SLS OR sodium lauryl sulphate OR EDTA OR ethylenediaminetetraacetic acid OR chlortetracycline OR demeclocycline OR doxycycline OR lymecycline OR methacycline OR minocycline OR oxytetracycline OR rolitetetracycline OR tetracycline OR tetracyclines OR hydrogen peroxide OR H2O2 OR sodium perborate OR peroxyborate OR peroxycarbonate [textword])›}

Screening and selection

Only papers written in English were accepted. Letters and narrative/historical reviews were not included in the search. The papers' titles and abstracts were first screened independently by two reviewers (A.L & G.A.W) for eligibility. Following selection, full-text papers were carefully read by the two reviewers. Those papers that fulfilled all selection criteria were processed for data extraction. Disagreements were resolved by discussion. If disagreements persisted, the judgment of a third reviewer (D.E.S) was decisive. The following eligibility criteria were used:

- Controlled studies: presence of an untreated control or presence of a pre-treatment control
- Titanium surfaces of dental implants or implant components or discs, strips or cylinders simulating such surfaces

- Treatment with mechanical instruments including curettes and/or scalers, (ultra)sonic instruments, air abrasives/air polishers, rubber cups/points with and without paste and burs/polishers
- Outcome parameters such as surface characteristics, surface texture, surface roughness, surface alteration evaluated with scanning electron microscopy (SEM) and/or profilometry

Assessment of heterogeneity

Factors that were recorded to evaluate the heterogeneity of the primary outcomes across the studies were as follows:

- Study outline characteristics
- Implant component/brand
- Treatment performed
- Number of treated surfaces
- Funding

Quality assessment

Two reviewers scored the methodological quality of the studies selected for analysis. This assessment of methodological quality combined several proposed criteria as described by Ntrouka et al. (2011). Criteria were described for each of the three domains: external validity, internal validity and statistical methods. The three quality criteria used to assess external validity were: clinical representation of the surface; validation of the evaluation method; and information regarding reproducibility data. Internal validity was assessed based on the following four criteria: random treatment allocation; blinding of the examiner; blinding during statistical analysis; and appropriate comparison conditions, i.e. preparation, manipulation and treatment of the surface identical, except of the intervention. The assessment of the statistical validity was based on the following four criteria: sample size and power of calculation; presentation of point estimates for primary outcome measurements; presentation of measures of variability for the primary treatment outcome; and statistical analysis. Regarding statistical analysis, not only the presence or absence of statistics but also the validity of the statistical method used was assessed. Each item was scored with either a '+' for an informative description of the issue and a study design that met the quality standards, '-' for an informative description but a study design that failed to meet the quality standards or '?' for lacking or insufficient information. A study was classified as having a low risk of bias when

the surface was clinically representative; the examiner was blinded; preparation, manipulation and treatment of the surface were identical except for the intervention; point estimates were presented for the primary outcome measurements; and valid statistical analyses were described. Studies that lacked one of these five criteria were classified as having a moderate potential risk of bias, while those that lacked two or more such criteria were classified as having a high potential risk of bias (van der Weijden et al. 2009).

Data extraction and analysis

Data were extracted from the selected papers by two reviewers (A.L & D.E.S). Titanium surfaces were divided into smooth and rough surfaces. In addition, two different surface evaluation methods were used: scanning electron microscopy (SEM) and profilometry. Further data analysis was performed separately for the smooth and rough surfaces and for the two evaluation methods. Disagreements were resolved via discussion. If the disagreement persisted, the judgment of a third reviewer (G.A.W) was considered to be decisive. After a preliminary evaluation of the selected papers, considerable heterogeneity was found in the study design, treatment modalities, outcome variables and results. In some studies, only a descriptive or graphic representation of the results was given. Only few studies performed a statistical analysis of the data. Consequently, it was impossible to perform valid quantitative analyses of the data or a subsequent meta-analysis. Therefore, a descriptive presentation of the data had to be adopted.

Grading the 'body of evidence'

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system proposed by the GRADE working group was used to grade evidence emerging from this review and to rate the quality of evidence and strength of the recommendations (Guyatt et al. 2008).

Results

Search and selection

The PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE searches identified 2,685, 187 and 959 papers, respectively (Figure 1). In total, 3,592 unique papers were found. The initial screening of titles and abstracts identified 38 full-text papers. After the full-text reading, four papers were excluded, of which three (Dmytryk et al. 1990; Speelman et al. 1992; Dennison

et al. 1994) were excluded because no data were provided regarding surface alterations after instrumentation. One paper (Baumhammers et al. 1975) was excluded because it referred to the contamination of implants prior to insertion. Additional hand-searching of the reference lists of selected studies yielded no additional papers. Finally, 34 papers were processed for data extraction.

Assessment of heterogeneity

After a preliminary evaluation of the selected papers, considerable heterogeneity was observed. Information regarding the study characteristics is provided in Table 1, which presents a summary of the study outline characteristics and the authors' conclusions. Most studies included in the review were *in vitro* studies; three studies (Matsuyama et al. 2003; Kawashima et al. 2007; Schwarz et al. 2008) were *in situ* studies, while another evaluated the effect of different mechanical instruments on failed implants (Mouhyi et al. 1998). Different mechanical instruments were used, and a great degree of heterogeneity was observed regarding the treatment parameters (i.e., number of strokes, treatment time, force applied, angulation of the instrument, distance from the treated surface and number of treated surfaces).

Twelve studies were supported by grants, of which nine were national and three were industrial. In three studies, the authors declared no conflict of interest. In ten studies, the materials used were donated from companies.

Study outcomes

In all of the studies, surface alterations following instrumentation were evaluated with scanning electron microscopy (SEM). In 10 studies, surface roughness was also quantified using a profilometer. Most of the studies investigated the effects of instrumentation on smooth implant surfaces (especially implant abutments), while 11 studies evaluated rough surfaces. Only two types of rough surfaces were examined: titanium plasma sprayed (TPS) and sandblasted and acid-etched (SLA).

SEM

All selected studies evaluated the effects of instrumentation on titanium surfaces using SEM. Photomicrographs taken after instrumentation were compared either to pre-treatment photomicrographs or to an untreated control. In some studies the 'new' surface, which was produced after instrumentation, was ranked using a 4-point roughness scale, as 'smoother', 'comparable to' or 'rougher' compared to the untreated, pristine, surface (Cross-Poline et al.

1997; Bain et al. 1998). Finally, some of the studies evaluated the presence of work traces after instrumentation, i.e. deposits of the instrument materials on the instrumented surface. Tables 2a and 2b present the changes of smooth and rough implant surfaces compared to untreated surfaces based on evaluations with a SEM.

Smooth surfaces

Almost all studies in this section evaluated the effects of instrumentation on abutments, implant necks or discs simulating smooth abutment surfaces. Only four studies (Barnes et al. 1991; Augthun et al. 1998; Bailey et al. 1998; Mouhyi et al. 1998) investigated smooth implant bodies.

Different non-metal curettes were evaluated: plastic, carbon, resin-reinforced and resin-unreinforced curettes. Regarding the effects of these instruments on smooth surfaces, most studies showed that the resulting surfaces were comparable to the untreated control. In two studies, the use of a non-metal curette resulted in a rougher surface (Hallmon et al. 1996; Bain et al. 1998). In a study by Hallmon et al. (1996), surface alterations associated with instrumentation appeared to be cumulative with respect to time (or strokes), while in a study by Bain et al. (1998) that tested four non-metal scalers, only the Advanced Implant Technologies scaler was found to create significantly rougher surfaces than all other instruments. Finally, in a study by Homiak et al. (1992), the plastic curette slightly smoothed the surface after several treatments.

Treatment of a smooth implant surface with an (ultra)sonic device with a non-metal tip caused no visible changes to the surface in most studies, although a slight change was observed in two studies (Kwan et al. 1990; Mengel et al. 1998). However, in a study by Schwarz et al. (2003), the Vector system with a carbon tip resulted in conspicuous surface damage (scratches), while in a study by Hallmon et al. (1996), a cumulative alteration of the abutment surface was observed after instrumentation with a sonic scaler with a plastic tip (Dynatip, PRO-DEX Inc., Santa Ana, CA, USA). The authors commented that 'the surface alteration appeared to be cumulative with respect to time of treatment and resulted in a moguled appearance accompanied by discrete grooves peripherally that appeared to correspond to the whipping action of the tip.' This was interpreted as an increase in surface roughness by the evaluators when compared to the non-instrumented control.

All studies evaluating the effect of metal curettes on smooth implant surfaces showed a damaging effect of the instrument on the surfaces. In most cases, instrumentation resulted in a severe roughening of the original surface. Nevertheless, in a study by Augthun et al.

(1998), only the thread edges presented evidence of instrumentation after a steel curette was used to instrument the smooth titanium fixture for 60 s. The severity of surface damage appears to be dependent on strokes, pressure used and the number of treatments.

A roughening of the smooth surface was also observed in all studies evaluating treatment with (ultra)sonic devices with metal tips. Similarly, titanium curettes caused a roughening of the implant surface in all studies. However, it should be noted that titanium curettes resulted in less pronounced surface damage than did the metal curettes or (ultra)sonic devices with metal tips.

The use of rubber cups/points, both with or without paste, appears to leave the surfaces unaltered. In some studies, rubber cups resulted in a progressively slight decrease in the roughness. Only in one study (Brookshire et al. 1997) did the use of a rubber cup with tin oxide slurry for 20 sec on commercially pure titanium abutments result in minor surface scratches. These results disagree with the conclusion by Homiak et al. (1992) that significant smoothening of the surface seemed to have occurred after the use of rubber cups with tin oxide slurry for 50 sec on similar abutments.

Fifteen studies evaluated the effect of air abrasives on smooth titanium surfaces. Five of these studies showed no visible effects of air abrasives on surface roughness, while in six studies the air abrasive system caused a slight increase in surface roughness with small irregular crater-like defects. Results from four studies (Homiak et al. 1992; Koka et al. 1992; McCollum et al. 1992; Razzoog & Koka 1994) indicated that air powder abrasive produces a surface that is smoother than the original surface of the machined titanium. Koka et al. (1992) commented that this decrease in surface roughness may be because the average dimension of the particles of the abrasive system is greater than the surface roughness dimension of the machined titanium surface. This results in abrasions of the titanium until the surface roughness equals the dimension of the abrasive particles.

In two studies, diamond burs and polishing devices were found (Augthun et al. 1998; Barbour et al. 2007) to cause severe damage to the smooth titanium surfaces, resulting in an increase in surface roughness.

Aside from the surface alterations, some studies looked at the presence of work traces after instrumentation. Metal instruments were found to leave pronounced work traces. Post-treatment deposits on the titanium surfaces were also observed with titanium curettes and air abrasive systems.

Rough surfaces

The surface alterations after instrumentation with different mechanical means were evaluated for two different rough surfaces: titanium plasma-sprayed (TPS) and sand-blasted and acid-etched (SLA).

In two studies (Rühling et al. 1994; Mengel et al. 1998), scanning electron microscopy observations of TPS surfaces did not reveal surface damage after treatment with non-metal curettes and (ultra)sonic devices with non-metal tips. In contrast, Augthun et al. (1996) demonstrated small defects on the implant surface after treatment with a plastic curette, while Bailey et al. (1998) showed surface disruptions with particle dislodgement and smoothening of the surface. Furthermore, instrumentation with plastic instruments was found to produce deposits of curette materials on the implant surface (Ramaglia et al. 2006). Regarding the SLA surfaces, plastic curettes and (ultra)sonic scalers with plastic tips did not seem to damage the implant surface (Rühling et al. 1994; Duarte et al. 2009). In one study (Schwarz et al. 2003), the use of the Vector system with a carbon tip resulted in surface damage (scratches) and deposition of the used carbon fibers in both SLA and TPS surfaces.

Metal curettes and (ultra)sonic devices with metal tips seem to cause considerable changes to both TPS and SLA surfaces. The irregularities on the rough surfaces appear to smoothen out with parts of the TPS coating either torn or scraped off, in a way that is similar to etched and sandblasted surfaces (Rühling et al. 1994).

One study (Mengel et al. 1998) examined the effect of a titanium curette and a rubber cup with paste on TPS surfaces. The results showed that the titanium curette left slight work traces and removed very little substance. It was concluded that these instruments should be used with caution. On the contrary, rubber cups were found to leave implant surfaces unchanged.

No study was identified that evaluated the effect of titanium curettes and rubber cups on sandblasted and acid-etched surfaces.

Four studies evaluated the effect of air abrasives on TPS surfaces. In two studies (Barnes et al. 1991; Mengel et al. 1998), no differences were observed compared to the untreated surfaces. In a study by Augthun et al. (1998), the implant surface demonstrated small defects after treatment, while a study by Ramaglia et al. (2006) found considerable amounts of spray powder deposits on the TPS surface. Regarding the sandblasted and acid-etched surfaces, air powder abrasives with sodium bicarbonate powder resulted in changes in the morphology of the titanium surfaces. They appeared smoother, as the edges

of elevations on the surfaces were leveled down (Kreisler et al. 2005; Schwarz et al. 2009; Duarte et al. 2009). In contrast, the application of amino acid glycine abrasive powders did not result in specific alterations of SLA surfaces, as shown in the study by Schwarz et al. (2009)

Finally, two studies (Augthun et al. 1998; Rimondini et al. 2000) evaluated the effects of diamond burs and diamond polishing devices on TPS surfaces; the diamond burs produced smoother surfaces with removal of the plasma sprayed coating. Similarly, carbide burs were shown to smoothen the TPS surfaces (Rimondini et al. 2001). Debris was produced after the use of both diamond and carbide burs (Rimondini et al. 2001).

Profilometry

The quantitative (objective) evaluations of the instrumented surfaces were performed with a profilometer, i.e., a surface-measuring instrument, which expressed the roughness levels in Ra and Rz values in most studies. The mean roughness, Ra, is defined as the arithmetic mean of the absolute values of real profile deviations related to the mean profile. The mean roughness profile depth, Rz, is defined as the arithmetic mean of the positive predominant crest and the analog absolute value of the negative crests. In two studies (Mengel et al. 1998; Mengel et al. 2004), the Pt, i.e., the profile height, was also evaluated. The profile height served as a basis for determining the amount of titanium substance removed by the treatment. In one study (Fox et al. 1990) a HeNe laser instrument was used to measure roughness and the results were reported as relative specular reflectance. This aspect of the study was not included for further analysis, since no Ra, Rz or Pt values were provided. Two studies (Meschenmoser et al. 1996; Mengel et al. 1998) were also excluded from the further profilometric analysis because profilometric data were not given or were unclear.

Tables 3a and 3b present the alterations of smooth and rough implant surfaces compared to untreated surfaces based on evaluations with a profilometer.

Smooth surfaces

Four studies evaluated the effect of non-metal instruments on smooth surfaces. All four evaluated the effects of non-metal curettes/scalers, while two (Matarasso et al. 1996; Sato et al. 2004) also evaluated the effects of (ultra)sonic instruments with non-metal tips. All of the studies concluded that non-metal instruments did not produce any change to the treated surfaces.

The treatment of smooth surfaces with metal instruments increased the surface roughness. A roughening of the smooth titanium surfaces was observed in all studies evaluating the effect of metal curettes, titanium curettes and (ultra)sonic instruments.

Only one study (Matarasso et al. 1996) evaluated the effect of plain rubber cups on smooth titanium surfaces, where no changes in roughness were observed. The treatment of smooth surfaces with rubber cups and paste resulted in a smoothening of the surfaces in three studies evaluating these instruments (Matarasso et al. 1996; Mengel et al. 2004; Barbour et al. 2007).

Treatment with air abrasives resulted in no change (Duarte et al. 2009) or in a slight increase of the surface roughness (Matarasso et al. 1996) One study (Barbour et al. 2007) evaluated the debridement of smooth abutment surfaces with diamond burs as part of a polishing protocol, which observed large increases in surface roughness.

From the aforementioned evidence, it is obvious that metal instruments, including metal curettes/scalers, (ultra)sonic scalers with metal tips and diamond burs all generate increases in surface roughness values. Titanium curettes also increase the surface roughness, although this change is less pronounced. All other treatment modalities produced little to no change in surface roughness.

Rough surfaces

The effect of non-metal curettes on rough surfaces was evaluated in three studies. Rühling et al. (1994) looked at TPS and SLA surfaces, Ramaglia et al. (2006) treated TPS surfaces and Duarte et al. (2009) investigated SLA surfaces. Treatments of SLA surfaces with non-metal curettes resulted in surfaces that were comparable to the untreated control, while treatments of TPS surfaces with the same instruments resulted in no surface changes in a study by Rühling et al. (1994) and in a small surface roughness decrease in a study by Ramaglia et al. (2006). Treatment of both surfaces with (ultra)sonic instruments with no metal tips produced no significant changes in the surface roughness parameters (Rühling et al. 1994).

Two studies (Rühling et al. 1994; Ramaglia et al. 2006) looked at the effects of metal curettes on TPS surfaces. In both studies, a decrease in surface roughness parameters was observed after treatment. Two studies (Rühling et al, 1994; Duarte et al. 2009) also evaluated the effects of metal curettes on SLA surfaces. One study (Rühling et al. 1994) showed a decrease in surface roughness, while the other (Duarte et al. 2009) showed no relevant changes. It should be noted that in a study by Rühling et al. (1994), implant surfaces were treated with

360 strokes, whereas in a study by Duarte et al. (2009), the surface was treated with approximately 30 strokes. This difference may explain the observed discrepancies in post-treatment surface characteristics.

The treatment of TPS and SLA surfaces with (ultra)sonic instruments with metal tips resulted in a decrease in the post-treatment roughness parameters.

One study (Ramaglia et al. 2006) investigated the effects of air abrasives on TPS surfaces and found a decrease in roughness parameters after treatment. No significant changes in Ra values were registered after treatment of SLA surfaces with an air-powder abrasive system (Duarte et al. 2009).

Two studies (Rimondini et al. 2000; Rühling et al. 2001) evaluated the effects of carbide and diamond burs used alone or in sequence with another on the characteristics of TPS and SLA surfaces. For both surfaces, all of the procedures resulted in a significant reduction of the surface roughness parameters.

No studies using profilometry were found that evaluated the effect of titanium curettes and rubber cups with or without paste on rough implant surfaces.

Quality assessment

The quality assessment of the various studies is presented in Table 4. The estimated risk of bias is considered to be high for 25 studies, moderate for six studies and low for only three studies (Fox et al. 1990; Bain et al. 1998; Mengel et al. 2004). From the 13 studies that used a profilometer to evaluate the surface alterations, two are considered to have a low, five a moderate and five a high risk of bias. Reproducibility data were not reported in any of the included studies.

Grading the 'body of evidence'

Table 5 shows a summary of the various aspects that were used to rate the quality of evidence and strength of recommendations according to GRADE (Guyatt et al. 2008, GRADE working group). As the data for the air abrasives are inconsistent with a high risk of bias, the strength of recommendation is considered to be weak for both smooth and rough (SLA and TPS) surfaces. For the metal instruments and rubber cups, although the data have a high risk of bias, they are consistent. Therefore, the strength of recommendation is considered to be moderate. For the non-metal instruments the data have a high risk of bias and are fairly consistent for the smooth and consistent for the rough surfaces. Therefore, the strength of recommendation is considered to be weak for the smooth and moderate for the rough surfaces.

Discussion

Maintaining healthy tissues around implants is considered to a critical factor for their long-term success (Grusovin et al. 2010). Although there are only a few available studies to date that evaluate the long-term effects of supportive programs for implant patients, periodic control and maintenance of dental implants are considered to be effective in the prevention of disease occurrence (Hultin et al. 2007). Professionally administered maintenance consists of the removal of dental plaque and calculus from implant parts exposed to the oral environment. Various methods have been advocated, with no definitive gold standard (e.g., plastic instruments, air abrasives, polishing rubber cups) (Schou et al. 2003; Claffey et al. 2008; Grusovin et al. 2010).

Implant components exposed to the oral environment are smooth. Thus, the prevention of peri-implant diseases requires that the smooth surfaces are kept clean. At the same time, special care is required to prevent damage to implant surfaces. The presence of grooves, scratches and adverse surface alterations associated with instrumentation may facilitate the accumulation of plaque and calculus. This phenomenon is associated with peri-implant soft tissue inflammation in both animal and human models (Berglundh et al. 1992; Pontoriero et al. 1994). Based on this review, rubber cups, both with or without paste, and non-metal instruments seem to be 'implant-safe' as they cause almost no damage to smooth implant surfaces. In some studies, these instruments were found to actually slightly smoothen the surfaces (Homiak et al. 1992; McCollum et al. 1992). In one study (Hallmon et al. 1996), a cumulative roughening of an abutment surface accompanied the use of a sonic instrument with a non-metal tip (Sonic Dynatip). The short-term use of non-metal instruments does not seem likely to produce a considerable level of surface roughening, though a roughening of the surface can be seen in the long run. This damage can vary depending on the instrument used. Different non-metal instruments have been used (e.g., plastic, unreinforced resin, reinforced resin, and Teflon-coated instruments), and it is clear that different instruments may have different effects on the surfaces of commercially pure titanium (Bain et al. 1998). It seems possible to remove minor scratches and to restore the integrity of surfaces that have been slightly altered as a result of professional instrumentation with polishing procedures using rubber cups with flours of pumice or polishing agents (Kwan et al. 1990; Rapley et al. 1990; McCollum et al. 1992).

Although they were found to cause little to no damage to the smooth surfaces, air abrasives leave powder deposits on the surface. Whether such residues influence healing events

is still unknown. It should be noted that different variables such as water flow, exposure time, size and hardness of the particles, air pressure and nozzle-target distance may affect the abrasive capacity of these systems and thus their effects on the titanium surfaces. Metal instruments are not recommended for the instrumentation of smooth titanium surfaces, as they can cause severe surface damage. Three studies included in this review (Barnes et al 1991; Augthun et al. 1998; Mouhyi et al. 1998) evaluated the effects of instrumentation on smooth (machined) titanium fixtures. Again, both plastic instruments and air abrasives were found to cause almost no damage to the surfaces.

To improve the resistance to mechanical load, almost all implants today have a roughened surface in the area where osseointegration is designed to occur. When peri-implantitis occurs, alveolar bone loss, apical shift of the soft tissues and exposure of the rough implant surface is observed, resulting in the bacterial colonization of the rough surfaces. The decontamination of the exposed rough surface is considered mandatory for the successful treatment of peri-implantitis. The goal of such decontamination is to eliminate bacteria and render the surface conducive to bone regeneration and re-osseointegration (Mombelli, 2002). In contrast, the removal of the macroscopic and microscopic retentions to reduce microbial adherence and colonization is suggested for those implant surfaces that remain exposed to the oral environment (Lozada et al. 1990; Jovanovic et al. 1993). The effects of different mechanical instruments have been evaluated only for two types of rough surfaces: a moderately rough surface (SLA) and a rough surface (TPS).

Based on this review, it can be concluded that non-metal instruments seem to cause no damage either to TPS or sandblasted and acid-etched surfaces. On the contrary, metal instruments and burs seem to smoothen rough surfaces by removing the surface coating. Finally, the air abrasives seem to cause little to no damage to the surface. From the abovementioned evidence, non-metal instruments and air abrasives seem to be appropriate options if the treatment goal includes the preservation of the rough surface. Metal instruments and burs may be more appropriate if the removal of the coating and establishment of a smooth surface are required. No studies so far have evaluated the effects of rubber cups on rough titanium surfaces.

Aside from the degree of damage, there are some other clinically significant factors that must be considered. The flexibility and size of non-metal curettes may prevent their secure and exact placement and application, which may result in inefficient plaque removal. This is more evident with screw-type implants. Surface alteration may be of secondary interest

if the means of instrumentation prove to be ineffective in removing accretions. In addition, although they provide easier access to the contaminated surfaces, air abrasives can cause epithelial desquamation and significant gingival irritation, while the danger of emphysema has also been reported in some studies (Newman et al. 1985; Bergendal et al. 1990). Furthermore, deposits of instrumentation materials or residues of the air-abrasive cleaning powders may interfere with tissue healing. It becomes thus evident that in clinical situations the effectiveness of the instruments may be influenced by other factors. The effectiveness of instruments, the response of the tissues to the 'new' surfaces produced after instrumentation and the effect of instrument deposits on tissue healing should be evaluated in clinical settings.

The estimated risk of bias was assessed as proposed by Ntrouka et al. (2011), although it was modified to suit the particular type of research as included in this review. As additional items 'point estimates for the primary outcome variable' and 'blinding to the examiner' were added. These items are important with respect to the focused question. 'Validation of the model' was not considered to be an appropriate criterion, since the focused question only allowed 'treatment' of titanium surfaces. Furthermore, since all treated surfaces were titanium surfaces prepared by the manufacturer in a standardized way or discs or strips simulating such surfaces, random allocation of the treatment was not considered to be a critical issue. Reproducibility data were not reported in any of the included studies or were not applicable, since only visual description was given in a SEM observation. Considering this as an item for the assessment of risk of bias would therefore result in overestimation. It was subsequently not taken as a decisive factor. The authors of this review however recognize that reproducibility data would improve the quality of the reported results and urge those that perform studies in the future to include this as part of the publication.

Limitations

One important limitation of this review is the lack of validation of the outcome assessment. In terms of overall strength of the evidence, the lack of validation and repeatability for the evaluation method is a major limiting factor for the interpretation of the data. In the literature, very different roughness values are reported when seemingly similar surfaces have been evaluated. This difference in values is a result of using different measuring instruments and techniques. It becomes, thus, obvious that without a standard procedure, it is generally impossible to compare values from one study with another (Wennerberg & Albrektsson

2000). In this study, the authors suggested some standards for topographic evaluation of oral implants in terms of measuring equipment, filtering process, and selection of parameters, in order to make the comparison of values reported in different studies possible. Furthermore, they report that a major limitation of SEM observations is that they are prone to subjective interpretations. If strict criteria should be applied then none of the studies included in this review would meet these criteria, which is a major limitation of the review. The reader could, therefore, consider the absence of validation of the outcome parameter as an item for downgrading the GRADE assessment and consider the strength of recommendation as weak.

Another limitation is the small sample size of the included studies. The n was 5 of less in 16 out of the 29 included studies, while in the rest 5 studies the n was unclear. This has an impact on the interpretation of the results especially when combined with the potential lack of standardization of the outcome assessment methods.

Another potential limitation may be the restriction to the English language. It is difficult to predict in which cases the exclusion of studies published in languages other than English may bias a systematic review (Higgins & Green 2008).

Conclusion

Non-metal instruments and rubber cups seem to be the instruments of choice for the treatment of a smooth implant surface, especially if the preservation of surface integrity is the primary goal. Similarly, for rough implant surfaces, non-metal instruments and air abrasives are the instruments of choice, especially if surface integrity needs to be maintained. Metal instruments and burs are recommended only in cases where the removal of the coating is required. However, one limitation of this study should be indicated, which is that only limited types of implant surfaces were evaluated. As such, these recommendations are applicable for machined, TPS and SLA surfaces and may only be extrapolated to other types of surfaces. It should also be noted that these recommendations are based mostly on *in vitro* studies. The clinical impact of these findings requires clarification.

Acknowledgements

Declaration of interest

The authors declare that they have no conflict of interest.

The research was self-funded by the authors and their institution

Authors' contributions:

A. Louropoulou contributed to the conception, design, acquisition, analysis, interpretation of data, drafted the manuscript.

D.E. Slot contributed to the design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

G.A. van der Weijden contributed to the conception, design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

All authors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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* Studies included in the review

Figure 1. Data base search and literature selection

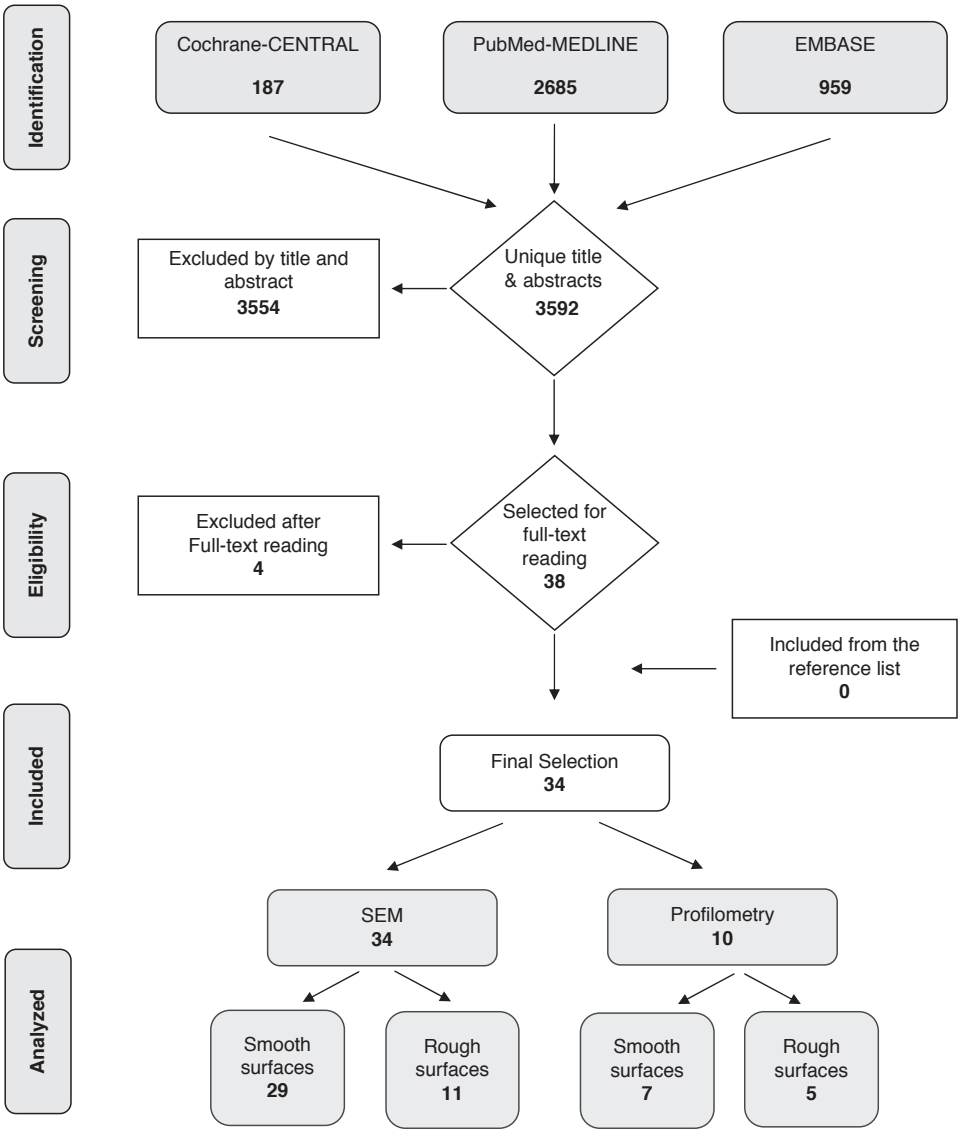

Table 1. Summary of the included studies sorted by year of publication

Study #	Authors	Implant component / Brand	Treatment (n= # of surfaces/components treated with each instrument)	Control	Outcome parameter	Authors' conclusion
1	Thomson-Neal et al. (1989)	Neck / - Startanius - Ultimatics	- titanium scaler (n=2) - ultrasonic scaler with metal tip (n=2) - sonic scaler with metal tip (n=2) - rubber cup with paste (n=2) - air polisher (n=2)	Untreated section of the surface	SEM	Various procedures may have a deleterious effect on the surface. The rubber cup polishing with paste was the least abrasive professional modality.
2	Rapley et al. (1990)	Abutment / Brånemark	- stainless-steel scaler (n=1) - plastic scaler (n=1) - ultrasonic scaler with metal tip (n=1) - rubber cup (n=1) - rubber cup with paste (n=1) - air abrasive (n= 1) - Eva yellow plastic tip (n=1)	Untreated abutment	SEM	The metal scaler and the ultrasonic scaler with metal tip created a severely roughened surface. The rubber cup with paste created a smoother surface than the control, while the rest instruments left the surface comparable to the control.
3	Fox et al. (1990)	Neck / IMZ	- stainless-steel curette (n=10) - titanium curette (n=10) - plastic curette (n=10)	Untreated section of the surface	SEM Profilometry	Plastic instruments produced an insignificant alteration of the titanium implant surface after instrumentation while metal instruments significantly altered the titanium surface.
4	Kwan et al. (1990)	Titanium strip similar to available implant abutments / ?	- ultrasonic scaler with metal tip (n=1) - ultrasonic scaler with plastic tip (n=1)	Untreated section of the surface	SEM	An ultrasonic scaler with plastic tip may be a promising device for in-office maintenance of dental implants. The plastic may only produce microscratches or smearing of plastic which can be polished out.

Study #	Authors	Implant component / Brand	Treatment (n= # of surfaces/components treated with each instrument)	Control	Outcome parameter	Authors' conclusion
5	Barnes et al. (1991)	Body and neck / - Strykers DB -Denar Steri-Oss - IMZ	- air abrasive polisher (n=16)	Pre-treatment control	SEM	No perceptible difference was noted between pre-treatment and post-treatment photomicrographs regarding the surface integrity of the implant material.
6	Gantes et al. (1991)	Titanium cylinders resembling implant neck / ?	- plastic scaler (n=1) - sonic scaler with plastic tip (n=1) - rubber cup (n=1) - rubber cup with paste (n=1) - air polisher with baking soda (n=1)	Untreated section of the surface	SEM	Air powder devices using baking soda should be avoided for maintenance of titanium implants.
7	Koka et al. (1992)	Abutment / Brånemark	- air abrasive A (n=1) - air abrasive B (n=1)	Untreated abutment	SEM	Both surfaces appeared to be smoother than controls and thus be more resistant to plaque formation. A non crystallic deposit was observed to abutments exposed to air abrasive B.
8	Homiak et al. (1992)	Abutment / Nobelpharma	- stainless-steel scaler (n=1) - plastic scaler (n=1) - rubber cup (n=1) - rubber cup with paste (n=1) - air abrasive (n=1)	Untreated section of the surface	SEM	The metal scaler was seen to roughen the titanium surface. All other modalities tested appeared to smooth the titanium surface by removing surface debris and rounding off the sharp machined grooves present on the untreated abutment surface.

Study #	Authors	Implant component / Brand	Treatment (n= # of surfaces/components treated with each instrument)	Control	Outcome parameter	Authors' conclusion
9	McCollum et al. (1992)	Abutment / Brånemark	- plastic scaler (n=48) - rubber cup with paste (n=48) - air abrasive (n=48)	Untreated section of the surface	SEM	For maintenance and prophylaxis any of these may be used without damaging the surface.
10	Ruhling et al. (1994)	Neck/abutment and body / - Bonefit - IMZ - Frialit-2 - NLS	- stainless-steel curette (n=?) - gold-coated curette (n=?) - plastic curette A (n=?) - plastic curette B (n=?) - ultrasonic scaler with metal tip (n=?) - sonic scaler with metal tip (n=?) - ultrasonic scaler with non metal tip (n=?) - sonic scaler with non metal tip (n=?)	Untreated section of the surface	SEM Profilometry	No discernible damage was caused by sonic and ultrasonic scalers with non metal tips or plastic curettes on smooth titanium surfaces. Instrument material residues were found on rough implant surfaces.
11	Razzoog et al. (1994)	Abutment / Brånemark	- air abrasive A (n=2) - air abrasive B (n=2)	Untreated surface	SEM	Under the experimental conditions tested, neither of the two systems tested seemed to cause significant abrasion of the surface of titanium abutments.
12	Kuempel et al. (1995)	Titanium discs simulating an implant abutment / Alfa –Johnson Mathey	- stainless-steel curette (n=10) - gold-coated curette (n=10) - plastic scaler (n=10)	Untreated disc	SEM	The stainless-steel curette and the gold-coated curette resulted in dramatic alterations in surface characteristics.

Study #	Authors	Implant component / Brand	Treatment (n= # of surfaces/components treated with each instrument)	Control	Outcome parameter	Authors' conclusion
13	Hallmon et al. (1996)	Abutment Brånemark	- stainless-steel curette A (n=1) - stainless-steel curette B (n=1) - plastic scaler A (n=1) - plastic scaler B (n=1) - plastic curette (n=1) - sonic scaler with metal tip (n=1) - sonic scaler with non metal tip (n=1)	Untreated abutment	SEM	The plastic scalers appear to be instruments of choice for debridement of titanium abutment surfaces if preservation of surface integrity is the primary objective.
14	Matarasso et al. (1996)	Neck ITI Bonefit	- stainless steel curette (n=4) - titanium curette (n=4) - plastic curette A (n=4) - plastic curette B (n=4) - ultrasonic scaler with metal tip (n=4) - ultrasonic scaler with non metal tip (n=4) - rubber cups (n=4) - polishing brushes (n=4) - abrasive rubber cups (n=4) - air polisher (n=4)	Untreated neck	SEM Profilometry	The stainless steel curette, the ultrasonic scaler, the titanium curette and the air polisher, that increase surface roughness, should be avoided. Preference should be given to systems that do not alter the implant surface or that smoothen the titanium implants and are hence more suitable to maintain plaque control and to promote epithelial attachment.
15	Meschenmoser et al. (1996)	Abutment Friatec	- stainless-steel curette (n=1) - titanium curette (n=1) - plastic curette (n=1) - ultrasonic scaler with metal tip (n=1) - air abrasive (n=1)	Untreated section of the surface	SEM Profilometry	The steel curette and the ultrasonic system are totally unsuitable for cleaning titanium implants.

Study #	Authors	Implant component / Brand	Treatment (n= # of surfaces/components treated with each instrument)	Control	Outcome parameter	Authors' conclusion
16	Cross-Poline et al. (1997)	Abutment / Straumann	- gold-coated curette (n=6) - plastic curette A (n=6) - plastic curette B (n=6)	Untreated section of the surface	SEM	The gold-coated curette created the roughest surface.
17	Brookshire et al. (1997)	Abutment / Nobel Biocare Spectra System Implants	- metal curette (n=2) - gold-coated curette (n=2) - plastic curette (n=2) - rubber cup and paste (n=2) - air-abrasive (n=2)	Pre-treatment control	SEM	No significant surface alteration was produced by the air abrasive system. All other oral hygiene methods either created significant surface alterations, left residual particles on the abutment surfaces, or both.
18	Mengel et al. (1998)	Body and abutment / - Screw- Vent implant with abutment - ITI full –screw implant - Standard Brånemark implant with standard abutment	- stainless-steel curette (n=12) - titanium curette (n=12) - plastic curette (n=12) - ultrasonic scaler with metal tip (n=12) - sonic scaler with metal tip (n=12) - sonic scaler with non metal tip (n=12) - rubber cup with paste (n=12) - air polisher (n=12)*	Untreated implant and abutment surface	SEM Profilometry	The air polisher, the rubber cup and the plastic curette can be used for supragingival removal of calculus and plaque on implant surfaces without the risk of damage.
19	Mouhyi et al. (1998)	Implant body / Brånemark	- air-abrasive (n=6) *	Untreated implant	SEM	The air-abrasive treatment of implants resulted to topographical and elemental changes.
20	Bain et al. (1998)	Abutment / Brånemark	- non metal scaler A (n=1) - non metal scaler B (n=1) - non metal scaler C (n=1) - non metal scaler D (n=1)	Untreated abutment	SEM	Non-metal scaler A caused the less damage to the abutments.

Study #	Authors	Implant component / Brand	Treatment (n= # of surfaces/components treated with each instrument)	Control	Outcome parameter	Authors' conclusion
21	Augthun et al. (1998)	Implant body - IMZ Friatec - Brånemark	- stainless-steel curette (n=2) - plastic curette (n=2) - ultrasonic scaler with metal tip (n=2) - air abrasive (n=2) - diamond polishing device (n=2)	Untreated implant	SEM	The air abrasive and the plastic curette caused little or no surface damage in all implants.
22	Bailey et al. (1998)	Abutment Implant body ?	- ultrasonic scaler with metal tip (n=?) - ultrasonic scaler with non-metal tip (n=?)	Untreated section of the surface	SEM	The plasma-sprayed surfaces showed significant surface alterations after the use of both ultrasonic tips.
23	Rimondini et al. (2000)	Implant body IMZ	- carbide burs and diamond burs (n=?)	Untreated implants and untreated abutment	SEM Profilometry	The most effective titanium plasma sprayed removal obtained by 30μm and 15 μm mean-particle-size diamond burs and carbide 12 plus 16 bladed burs used in sequence.
24	Ruhling et al. (2001)	Flat titanium specimens and prefabricated implant cylinders IMZ	- diamond–coated files of different roughness depths (n=?)	Untreated section of the surface	SEM Profilometry	The results of this experimental study show that it is possible to remove the TPS coating from implants and to polish the exposed implant surfaces using the instruments described here. During the instrumentation of the implant surfaces, contamination with the material of the instrument can be expected.
25	Matsuyama et al. (2003)	Abutment ?	- ultrasonic scaler with metal tip (n=3)	Pre-treatment control	SEM	The surface of abutment was damaged by mechanical injuries during the instrumentation with the hard tip of the ultrasonic scaler.

Study #	Authors	Implant component / Brand	Treatment (n= # of surfaces/components treated with each instrument)	Control	Outcome parameter	Authors' conclusion
26	Schwarz et al. (2003)	Titanium discs - IMZ-Twin Plus - ITI	- ultrasonic scaler with non metal tip (n=48)	Untreated control	SEM	All surfaces treated with this ultrasonic scaler showed conspicuous surface damage and debris of the used carbon fibres.
27	Mengel et al. (2004)	Abutment 3i	- stainless-steel curette (n=?) - titanium curette (n=?) - plastic curette (n=?) - ultrasonic scaler with metal tip (n= ?) - rubber cup with paste (n=?) - air abrasive (n=?)	Untreated section of the surface	SEM Profilometry	The ultrasonic scaler and the steel and titanium curettes left pronounced traces on the mechanically smoothened abutments and increased the Rz. Substantial substance removal was recorded following the use of the ultrasonic scaler and the steel curettes.
28	Sato et al. (2004)	Abutment Steri-Oss	- plastic scaler (n=5) - ultrasonic scaler with non metal tip A (n=5) - ultrasonic scaler with non metal tip B (n=5)	Untreated abutment	SEM Profilometry	Ultrasonic scalers with non-metal tip produced no significant damage to titanium surfaces compared to plastic scalers These scalers would be suitable for implant maintenance.
29	Kreisler et al. (2005)	Titanium discs Friadent	- air abrasive (n=12)	Untreated discs	SEM	Air abrasive resulted in a change of surface morphology of the titanium surface.
30	Ramaglia et al. (2006)	Implant body 3i	- stainless-steel curette (n=3) - plastic curette (n=3) - ultrasonic scaler with metal tip (n=3) - air abrasive (n=3)	Untreated implant	SEM Profilometry	Although plastic curette and air-abrasive induced less implant surface alterations, they left deposits on the surface that may affect, in vivo, the tissue healing process.

Study #	Authors	Implant component / Brand	Treatment (n= # of surfaces/components treated with each instrument)	Control	Outcome parameter	Authors' conclusion
31	Barbour et al. (2007)	Abutment / Nobelbiocare	Two polishing protocols - A: diamond bur 15s, green carborundum stone rotary point, brown silicon rubber point, green impregnated silicon rubber point, cloth mop+polishing compound (n=?) - B: brown silicon rubber point, green impregnated silicon rubber point, cloth mop+polishing compound (n=?)	Pre-treatment control	SEM Profilometry	Polishing protocol B may be preferable to polishing protocol A since less material is removed and there is less chance of rough areas remaining.
32	Kawashima et al. (2007)	Abutment / Steri-Oss	- ultrasonic scaler with metal tip (n=7) - ultrasonic scaler with non-metal tip A (n=7) - ultrasonic scaler with non-metal tip B (n=7)	Untreated abutment	SEM Profilometry	The scalers with non-metal tip produced smooth abutment surfaces. These scalers are suitable for use in dental implant maintenance.
33	Schwarz et al. (2009)	Titanium discs / Straumann	- air abrasive with powder A (n=6) - air abrasive with powder B (n=6) - air abrasive with powder C (n=6) - air abrasive with powder (n=6) *	Untreated discs	SEM	The sodium carbonate powder resulted after repeated surface treatment in an obvious alteration of the surface morphology.
34	Duarte et al. (2009)	Titanium discs with smooth and rough surfaces / AS Technology	- stainless-steel curette (n=20) - plastic curette (n=20) - air abrasive (n=20)	Pre-treatment control	SEM Profilometry	Metal curettes are not recommended for smooth titanium surface debridement due to severe texture alteration. Rough surfaces treated with a metal curette and the air-powder abrasive system were less susceptible to bacterial adhesion due to surface modification and the presence of abrasive deposits.

? Data not given * n was calculated by the authors of this review

Table 2a. Summary of studies using scanning electron microscopy (SEM) to evaluate the changes on a smooth implant surface (abutment/implant neck/implant body) after instrumentation compared to an untreated control.

Instrument	Study number (#)	Surface roughness score[1]		Summary of the surface changes compared to control[2]
		tx	c	
Non-metal curettes/scalers	#2	?	?	0
	#3	◊	◊	0
	#6	◊	◊	0
	#8	◊	◊	-
	#9	◊	◊	-
	#10	◊	◊	0
	#12	◊	◊	0
	#13	?	0	+
	#14	◊	◊	0
	#15	◊	◊	0
	#16	2.5-3.2	1.5	0
	#17	◊	◊	0
	#18	?	?	0
	#20	2.45-3.91	2	+
	#21	?	?	0
	#27	?	?	0
	#28	?	0	0
	#34	◊	◊	0
(Ultra)sonic scalers with non-metal tip	#4	◊	◊	+
	#6	◊	◊	0
	#10	◊	◊	0
	#13	?	0	+
	#14	◊	◊	0
	#18	?	?	+
	#22	◊	◊	0
	#26	◊	◊	+
	#28	?	0	0
	#32	?	?	0
Metal curettes/ scalers	#2	?	?	+
	#3	◊	◊	+
	#8	◊	◊	+
	#10	◊	◊	+
	#12	◊	◊	+
	#13	?	0	+
	#14	◊	◊	+
	#15	◊	◊	+
	#16	4.0	1.5	+
	#17	◊	◊	+
	#18	?	?	+
	#21	?	?	+
	#27	?	?	+
	#34	◊	◊	+

Instrument	Study number (#)	Surface roughness score[1]		Summary of the surface changes compared to control[2]
		tx	c	
Titanium curettes	#1	◊	◊	+
	#3	◊	◊	+
	#14	◊	◊	+
	#15	◊	◊	+
	#18	?	?	+
	#27	?	?	+
(Ultra)sonic scaler with metal tip	#1	◊	◊	+
	#2	?	?	+
	#4	◊	◊	+
	#10	◊	◊	+
	#13	?	0	+
	#14	◊	◊	+
	#15	◊	◊	+
	#18	?	?	+
	#21	?	?	+
	#22	◊	◊	+
	#25	◊	◊	+
	#27	?	?	+
	#32	?	?	+
Diamond burs	#21	?	?	+
	#31	◊	◊	+
Abrasive rubber cups	#14	?	?	-
Rubber cups/points without paste	#2	?	?	0
	#6	◊	◊	0
	#8	◊	◊	-
	#14	◊	◊	0
	#31	◊	◊	0
Rubber cups/points with paste	#1	◊	◊	?
	#2	?	?	-
	#6	◊	◊	0
	#8	◊	◊	-
	#9	◊	◊	-
	#14	◊	◊	0
	#17	◊	◊	+
	#18	?	?	0
	#27	?	?	-
Eva yellow plastic tip	#2	?	?	0

Instrument	Study number (#)	Surface roughness score[1]		Summary of the surface changes compared to control[2]
		tx	c	
Air abrasive/air polisher	#1	◊	◊	+
	#2	?	?	0
	#5	?	?	0
	#6	◊	◊	+
	#7	◊	◊	-
	#8	◊	◊	-
	#9	◊	◊	-
	#11	◊	◊	-
Air abrasive/air polisher	#14	◊	◊	+
	#15	◊	◊	+
	#17	◊	◊	0
	#18	?	?	0
	#19	◊	◊	+
	#21	?	?	0
	#34	◊	◊	+

4-point roughness scale (1-4 from smooth to severely roughened); the score of the untreated control is given in each study; for the treated surface the mean roughness was calculated by the authors based on information given in the studies

[1] ◊: no scale, no data; ?: scale used but no data given/data unclear

[2] +: surface rougher than the control; -: surface smoother than the control; 0: surface comparable to the control

* estimated by the authors based on information given in the article

tx: treated surface; c: control surface

Table 2b. Summary of studies using scanning electron microscopy (SEM) to evaluate the changes on a rough implant surface after instrumentation compared to an untreated control.

Instrument	Study number (#)	Surface	Surface roughness score[1]		Summary of the surface changes compared to control[2]
			tx	c	
Non-metal curettes/scalers	#10	TPS	◊	◊	0
	#21	TPS	?	?	?
	#30	TPS	◊	◊	?
	#10	SLA	◊	◊	0
	#34	SLA	◊	◊	0
(Ultra)sonic scalers with non-metal tip	#10	TPS	◊	◊	0
	#18	TPS	?	?	0
	#22	TPS	◊	◊	-
	#26	TPS	◊	◊	?
	#10	SLA	◊	◊	0
	#26	SLA	◊	◊	?
Metal curettes/ scalers	#10	TPS	◊	◊	-
	#18	TPS	?	?	-
	#21	TPS	?	?	?
	#30	TPS	◊	◊	-
	#10	SLA	◊	◊	-
	#34	SLA	◊	◊	-
Titanium curettes	#18	TPS	?	?	?
(Ultra)sonic scaler with metal tip	#10	TPS	◊	◊	-
	#18	TPS	?	?	-
	#21	TPS	?	?	?
	#22	TPS	◊	◊	-
	#30	TPS	◊	◊	-
	#10	SLA	◊	◊	-
Diamond burs	#21	TPS	?	?	?
	#23	TPS	◊	◊	-
Carbide burs	#23	TPS	◊	◊	-

Instrument	Study number (#)	Surface	Surface roughness score[1]		Summary of the surface changes compared to control[2]
			tx	c	
Rubber cups/points with paste	#18	TPS	?	?	0
Air abrasive/air polisher	#5	TPS	?	?	0
	#18	TPS	?	?	0
	#21	TPS	?	?	?
	#30	TPS	◊	◊	?
	#29	SLA	◊	◊	-
	#33	SLA	◊	◊	-
	#34	SLA	◊	◊	-

1 ◊: no scale, no data; ?: scale used but no data given/data unclear

2 +: surface rougher than the control; -: surface smoother than the control; 0: surface comparable to the control

tx: treated surface; c: control surface

TPS: titanium plasma sprayed

SLA: sand-blasted and acid etched

Table 3a. Summary of studies using profilometry to evaluate the changes on a smooth implant surface after instrumentation compared to an untreated surface.

Instrument	Study number (#)	Ra[1] (μm)		Rz[2] (μm)		Pt[3]	Summary of the surface changes compared to control[4]
		tx	c	tx	c		
Non-metal curettes/ scalers	#14	0.49	0.5	3.47	3.98	☐	0
	#27	☐	☐	0.30	0.35	0.00	0
	#28	?	?	?	?	☐	0
	#34	0.24	0.19	☐	☐	☐	0
(Ultra)sonics with non-metal tip	#14	0.52-0.44	0.5	3.46-3.05	3.98	☐	0
	#28	?	?	?	?	☐	0
	#32	?	?	?	?	?	?
Metal curettes/ scalers	#14	1.32	0.5	8.50	3.98	☐	+
	#27	☐	☐	0.86	0.38	8.48	+
	#34	0.38	0.20	☐	☐	☐	+
Titanium curettes	#14	0.80	0.5	6.0	3.98	☐	+
	#27	☐	☐	0.61	0.29	0.00	+
(Ultra)sonics with metal tip	#14	2.08	0.5	11.92	3.98	☐	+
	#27	☐	☐	1.45	0.33	17.57	+
	#32	?	?	?	?	?	?
Diamond burs	#31	1.77	0.25	☐	☐	☐	+
Diamond polishers	#24	☐	☐	4.7	8.7	☐	-
Rubber cups/points without paste	#14	0.57-0.48	0.5	4.48-3.72	3.98	☐	0
Rubber cups/points with paste	#14	0.36-0.22	0.5	2.15- 1.54	3.98	☐	-
	#27	☐	☐	0.40	0.37	0.00	-
	#31	0.25	0.42	☐	☐	☐	-
Air abrasive/air polisher	#14	0.80-0.68	0.5	5.38-4.78	3.98	☐	+
	#34	0.20	0.18	☐	☐	☐	0

[1] Ra: mean roughness defined as the arithmetic mean of the departure of the profile from the mean line

[2] Rz: predominant crest mean index defined as the average of all peal-to-valley heights in the assessment length

[3] Pt: all profile deviations from the linear compensations

[4] +: surface rougher than the control; -: surface smoother than the control; 0: surface comparable to the control

tx: treated surface; c: control surface

? data not given; ☐ not applicable

Table 3b. Summary of studies using profilometry to evaluate the changes on a rough implant surface after instrumentation compared to an untreated surface.

Instrument	Study number (#)	Surface	Ra[1] (μm)		Rz[2] (μm)		Pt[3]	Summary of the surface changes compared to control[4]
			tx	c	tx	c		
Non-metal curettes/ scalers	#10	TPS	☐	☐	24.6-26.6*	26.5	☐	0
	#30	TPS	7.7	10.2	38.2	64.8	☐	-
	#10	SLA	☐	☐	19.2-18.9*	21.3	☐	0
	#34	SLA	0.70	0.70	☐	☐	☐	0
(Ultra)sonics with non-metal tip	#10	TPS	☐	☐	24.7-26.0*	26.5	☐	0
	#10	SLA	☐	☐	21.0-22.0*	21.3	☐	0
Metal curettes/ scalers	#10	TPS	☐	☐	19.9-23.2*	26.5	☐	-
	#30	TPS	6.5	10.2	39.8	64.8	☐	-
	#10	SLA	☐	☐	15.9-16.2*	21.3	☐	-
	#34	SLA	0.73	0.71	☐	☐	☐	0
(Ultra)sonics with metal tip	#10	TPS	☐	☐	9.6*	26.5	☐	-
	#30	TPS	5.7	10.2	35.7	64.8	☐	-
	#10	SLA	☐	☐	11.6*	21.3	☐	-
Diamond burs	#24	TPS	☐	☐	18.2	54.0	☐	-
	#23	SLA	1.16*	3.20	5.41*	16.25	☐	-
Diamond polishers	#24	TPS	☐	☐	4.6	?	☐	-
Carbide burs	#23	SLA	1.14*	3.20	4.44*	16.25	☐	-
Air abrasive/air polisher	#30	TPS	6.8	10.2	37.0	64.8	☐	-
	#34	SLA	0.69	0.70	☐	☐	☐	0

[1] Ra: mean roughness defined as the arithmetic mean of the departure of the profile from the mean line

[2] Rz: predominant crest mean index defined as the average of all peal-to-valley heights in the assessment length

[3] Pt: all profile deviations from the linear compensations

[4] +: surface rougher than the control; -: surface smoother than the control; 0: surface comparable to the control

tx: treated surface; c: control surface

? data not given; ☐ not applicable; * calculated by the authors of this review

Table 4. Methodological quality scores of the selected studies.

Quality criteria	External validity			Internal validity				Statistical validity				Author's estimated risk of bias
Study number	Representative surface *	Validation of the evaluation method	Reproducibility data provided	Random treatment allocation	Blinded to examiner*	Blinding during statistical analysis	Appropriate comparison conditions *	Sample size and power calculation	Point estimates presented for primary outcome measurements*	Measures of variability presented for the primary outcome	Statistical analysis/appraisal*	
#1	+	-	NA	-	+	NA	+	-	-	-	-	High
#2	+	-	NA	-	?	NA	+	-	-	-	-	High
#3	+	-	-	-	+	?	+	-	+	+	+/☺	Low
#4	-	-	NA	-	?	NA	+	-	-	-	-☺	High
#5	+	-	NA	-	+	NA	+	-	-	-	-	High
#6	+	-	NA	-	?	NA	+	-	-	-	-	High
#7	+	-	NA	-	?	NA	+	-	-	-	-	High
#8	+	-	NA	-	?	NA	+	-	-	-	-	High
#9	+	-	NA	-	?	NA	+	-	-	-	-	High
#10	+	+	-	-	?	?	+	-	+	-	+/☺	Moderate
#11	+	-	NA	-	?	NA	+	-	-	-	-	High
#12	-	-	NA	-	?	NA	+	-	-	-	-	High
#13	+	-	NA	-	+	?	+	-	-	-	+/?	High
#14	+	+	-	-	?	NA	+	-	+	-	-	High
#15	+	-	NA	-	?	?	+	-	-	-	+/?	High
#16	+	-	NA	+	?	?	+	-	+	+	+/☺	Moderate
#17	+	-	NA	+	?	NA	+	-	-	-	-	High
#18	+	-	NA	-	+	NA	+	-	-	-	-	High
#19	+	-	NA	-	?	NA	-	-	-	-	-	High

Quality criteria	External validity			Internal validity				Statistical validity				Author's estimated risk of bias
Study number	Representative surface *	Validation of the evaluation method	Reproducibility data provided	Random treatment allocation	Blinded to examiner*	Blinding during statistical analysis	Appropriate comparison conditions *	Sample size and power calculation	Point estimates presented for primary outcome measurements*	Measures of variability presented for the primary outcome	Statistical analysis/appraisal*	
#20	+	-	NA	-	+	?	+	-	+	+	+/☺	Low
#21	+	-	NA	-	+	NA	+	-	-	-	-	High
#22	+	-	NA	?	?	NA	+	-	-	-	-	High
#23	+	+	-	+	?	?	+	-	+	+	+/☺	Moderate
#24	+	+	-	-	?	NA	+	-	+	+	-	High
#25	+	-	NA	-	?	NA	-	-	-	-	-	High
#26	-	-	NA	+	+	NA	+	-	-	-	-	High
#27	+	+	-	-	+	?	+	-	+	+	+/☺	Low
#28	+	+	-	-	+	?	+	-	-	-	+/☺	Moderate
#29	-	-	NA	-	?	?	-	-	-	-	-	High
#30	+	+	-	-	?	?	+	-	+	-	-	High
#31	+	+	-	-	?	?	+	-	+	+	+/☺	Moderate
#32	+	+	-	-	+	?	-	-	-	-	+/☺	High
#33	-	-	NA	+	+	NA	-	-	-	-	-	High
#34	-	+	-	+	+	?	+	-	+	+	+/☺	Moderate

?: Not specified/unclear; +: Yes; -: No; *: Items used to estimate potential risk of bias;
☺: Valid statistical method

Table 5. GRADE evidence profile for impact mechanical instruments compared to control on smooth and rough implant surfaces from the presented systematic review

GRADE	Smooth surfaces			
	Non-metal instruments	**Metal instruments**	**Rubber cups**	**Air abrasives**
Risk of bias	High	High	High	High
Consistency	Fairly consistent	Consistent	Consistent	Inconsistent
Directness	Generalizable	Generalizable	Generalizable	Generalizable
Precision	Undeterminable	Undeterminable	Undeterminable	Undeterminable
Publication bias	Not detected	Not detected	Not detected	Not detected
Strength of recommendation	**Weak**	**Moderate**	**Moderate**	**Weak**

GRADE	Rough surfaces*		
	Non-metal instruments	Metal instruments	Air abrasives
Risk of bias	High	High	High
Consistency	Consistent	Consistent	Inconsistent
Directness	Generalizable	Generalizable	Generalizable
Precision	Undeterminable	Undeterminable	Undeterminable
Publication bias	Not detected	Not detected	Not detected
Strength of recommendation	**Moderate**	**Moderate**	**Weak**

* Refers to TPS and SLA surfaces

Chapter 3

The effects of mechanical instruments on contaminated titanium dental implant surfaces: a systematic review

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Clinical Oral Implants Research 2014 25: 1149-1160.

Introduction

After successful osseointegration and in order to be functional, oral implants must pierce the mucosa and enter the oral cavity, thus establishing a transmucosal connection between the internal and external environment. The implant components that are in contact with the soft tissue and are exposed to the oral environment are smooth. Hence, preservation of implant health implies keeping smooth surfaces clean (Mombelli, 2002). Plaque accumulation induces inflammatory changes in the soft tissues around them, which may lead to the loss of supporting bone and ultimately implants loss (Esposito et al. 2010). Long term maintenance care, especially for the high risk groups, is essential to reduce the risk of peri-implant infections (Atieh et al. 2012). If peri-implantitis is diagnosed, a therapeutic intervention should be initiated as soon as possible (Esposito et al. 1999).

Ideally, the instruments used to effectively clean smooth surfaces should cause minimal or no surface damage, should not create a surface that is more conducive to bacterial colonisation, and should not affect the implant-soft tissue interface. If, however, the soft tissue attachment is disrupted, the instrumentation procedure should maintain a surface that is conducive to re-establishment of the soft tissue seal (Kuempel et al. 1995).

In case of peri-implantitis, the implant threads, which generally have a roughened surface to promote osseointegration, can become exposed to oral micro-organisms and bacterial colonisation of the titanium surface can occur, leading to the loss of osseointegration. The treatment of peri-implantitis includes among others the decontamination of the surface exposed to the biofilm to eliminate inflammation and to render the exposed surface biocompatible, with re-osseointegration as the ultimate goal.

In a recent systematic review (Louropoulou et al. 2012), the effects of different mechanical instruments on the characteristics and roughness of smooth and structured (i.e., rough) titanium surfaces were evaluated. Non-metal instruments and rubber cups were found to cause minimal or no damage to smooth implant surfaces. Similarly, non-metal instruments and air-abrasives were the instruments of choice for structured surfaces when maintenance of the surface integrity was required. Metal instruments and burs were recommended only in cases that required smoothing of the surface roughness.

Whereas this review addressed in detail the issue of surface alterations, it still remains unclear how effective mechanical instruments are at cleaning contaminated titanium implant surfaces. Surface alterations may be of secondary interest if the means of instrumentation prove to be ineffective in removing accretions.

Therefore, the aim of this comprehensive review was to systematically evaluate, based on the existing literature, the ability of different mechanical instruments to clean contaminated titanium surfaces.

Materials and Methods

This systematic review was conducted according to the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA-statement) (Moher et al. 2009).

Search strategy

Three internet sources were used to identify publications that met the inclusion criteria: the National Library of Medicine, Washington, D.C. (MEDLINE-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). The search was conducted up to May, 2013 and was designed to include any published study that evaluated the efficacy of mechanical instruments on cleaning contaminated titanium surfaces. To achieve this goal, a comprehensive search was performed. All reference lists from the selected studies were manually searched by two reviewers (A.L & G.A.W) for additional papers that met the eligibility criteria. The terms used in the search strategy are presented in Box 1.

Screening and selection

Papers written in English were accepted. Letters, human case reports and reviews were not included in the search. The titles and abstracts were first screened independently by two reviewers (A.L & G.A.W) for eligibility. Following selection, full-text papers were carefully read by the two reviewers. The papers that fulfilled all of the selection criteria were processed for data extraction. Disagreements were resolved by discussion. If disagreements persisted, the judgment of a third reviewer (D.E.S) was decisive. The following eligibility criteria were used:

- Controlled studies
- Titanium surfaces of dental implants or implant components, discs, strips or cylinders simulating such surfaces
- Contamination of the titanium surfaces, including biofilm grown with a standardised technique, a single bacterial species or bacterial products, such as lipopolysaccharide (LPS), or/and calcified deposits

- Treatment with mechanical instruments, including curettes and/or scalers, (ultra)sonic instruments, titanium brushes, air abrasives/polishers, rubber cups/points and burs/polishers
- Outcome parameters for surface cleanliness, including residual biofilm (RB) area, residual lipopolysaccharide, colony forming units (CFU) and scanning electron microscope (SEM) observations.

Assessment of heterogeneity

The following factors were evaluated to assess heterogeneity:

- Titanium surfaces
- Surface contamination method
- Treatment performed
- Outcome variables
- Funding

Box 1. Search terms used for PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE. The search strategy was customized according to the database been searched.

{‹Subject› AND ‹Adjective› AND ‹Intervention›}

{‹Subject: (dental implants [MeSH terms] OR (dental implant OR {/dental OR oral\ AND implant}[textword]) ›
AND
‹Adjective: (biofilms OR dental plaque OR dental deposits [MeSH terms] OR smooth OR structure OR texture OR roughness OR surface OR biofilm OR plaque index OR dental plaque OR plaque OR dental deposit* OR biocompatibility [textword]) ›
AND
‹Intervention: (dental scaling OR decontamination OR laser [MeSH terms] OR ultrasonic OR curette OR scaling OR laser OR polishing OR debridement OR curettage OR air abrasion OR air polisher OR cleaning OR instrumentation OR decontamination OR air powder OR bur OR brush [textword])›}

Quality assessment

Two reviewers (A.L & D.E.S) scored the methodological quality of the studies selected for analysis. Assessment of methodological quality was performed as proposed by the RCT checklist from the Dutch Cochrane Centre (2009) and was further extended using quality criteria obtained from the CONSORT statement (Schulz et al. 2010), the Delphi List (Verhagen et al. 1998), the Jadad scale (1996), the ARRIVE guidelines (Kilkenny et al. 2010) and the position papers by Moher et al. (2001) and Needleman (2002). Most of the proposed criteria were combined as described by Louropoulou et al. (2012).

Data extraction and analysis

The data were extracted from the selected papers by two reviewers (A.L & D.E.S). Disagreements were resolved via discussion. If the disagreement persisted, the judgment of a third reviewer (G.A.W) was considered decisive. After a preliminary evaluation of the selected papers, considerable heterogeneity was found in the study characteristics, instruments used, outcome variables and results. Only few studies presented quantifiable data. Consequently, it was impossible to perform valid quantitative analyses of the data or a subsequent meta-analysis. Therefore, a descriptive presentation of the data was adopted.

In order to evaluate the sample size of the included studies, the Mead's resource equation was used. This equation is often used for estimating sample sizes of laboratory experiments. It may not be as accurate as using other methods in estimating sample size, but gives a hint of the appropriate sample size where parameters such as expected standard deviations or expected differences in values between groups are unknown or very hard to estimate (Kirkwood et al. 2010). The Mead's resource equation is: E= N-B-T, where N is the total number of included units (minus 1), T is the number of treatment groups, including the control group, (minus 1), B is the blocking component (minus 1) and E is the degree of freedom, which should be equal to or more than 10.

Grading the 'body of evidence'

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system proposed by the GRADE working group was used to grade the collected evidence and to rate the strength of the recommendations (Guyatt et al. 2008).

Results

Search and selection

The PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE searches identified in total, 1,893 unique papers using the specified search terms (Figure 1). The initial screening of the titles and abstracts resulted in 20 full-text papers that met the inclusion criteria. After reading the full-text articles, six of the papers were excluded. Table 1 shows the reasons for exclusion. Additional hand-searching of the reference lists from the selected studies did not yield any additional papers. Fourteen papers were ultimately processed for data extraction.

Assessment of heterogeneity

Information regarding the study characteristics is provided in Table 2. The table includes a short summary of the study design, the results of the selected studies and the authors' conclusions. Eleven of the included studies (Parham et al. 1989; Zablotsky et al. 1992; Dennison et al. 1994; Pereira da Silva et al. 2005; Schwarz et al. 2005, 2009; Nemer Vieira et al. 2012; Schmage et al. 2012; Tastepe et al. 2013; Idlibi et al. 2013; and John et al. 2014) had an *in vitro* design. Two studies (Gantes & Nilveus 1991; and Speelman et al. 1992) were *in situ* studies using an animal model and one (Kawashima et al. 2007) was an *in situ* study in humans.

Titanium surfaces and surface contamination

The titanium surfaces that were evaluated varied between the selected studies. Both smooth and structured titanium surfaces were used. Implant abutments/bodies with polished/machined surfaces or titanium discs/sheets/cylinders simulating those surfaces were evaluated in eight studies (Gantes & Nilveus 1991; Speelman et al. 1992; Dennison et al. 1994; Pereira da Silva et al. 2005; Kawashima et al. 2007; Nemer Vieira et al. 2012; Schmage et al. 2012; Idlibi et al. 2013). Five studies (Schwarz et al. 2005, 2009; Schmage et al. 2012; Tastepe et al. 2013; John et al. 2014) used titanium discs with sand-blasted and acid-etched surfaces (SLA) and two studies (Nemer Vieira et al. 2012; Schmage et al. 2012) used titanium implants and titanium discs respectively with an acid-etched surface. Implant bodies and implant specimens produced from bodies with titanium plasma-sprayed (TPS) surfaces were used in two studies (Parham et al. 1989; Dennison et al. 1994). Pereira da Silva (2005) studied surfaces blasted with aluminium oxide particles of different diameters, and Zablotsky et al. (1992) and Schmage et al. (2012) used titanium strips or discs with a grit-blasted titanium alloy surface.

The methods of surface contamination also differed between the selected studies. Lipopolysaccharide from *Escherichia coli* or *Porphyromonas gingivalis* was used in two studies (Zablotsky et al. 1992; Dennison et al. 1994, respectively). Four studies used single-species biofilm, such as *Streptococcus mutans* (Schmage et al. 2012), *Streptococcus sanguis* (Pereira da Silva et al. 2005; Nemer Vieira et al. 2012) or *Actinomyces viscosus* (Parham et al. 1989). Eight studies used an *in situ* model to contaminate titanium surfaces with supragingival plaque by placing titanium discs in splints in the mouth of either beagle dogs (Gantes & Nilveus 1991; Speelman et al. 1992) or volunteers (Schwarz et al. 2005, 2009; Tastepe et al. 2013; Idlibi et al. 2013; John et al. 2014). Finally, in one study subgingival plaque was left to accumulate on healing abutments placed in the mouth of patients with implants (Kawashima et al. 2007). The period of plaque accumulation varied considerably between the studies from 24 hours up to 16 days.

Treatment

Metal (stainless-steel) curettes were evaluated in two studies (Speelman et al. 1992; John et al. 2013). Non- metal curettes/scalers and rubber cups with pumice were evaluated in two studies (Speelman et al. 1992; John et al. 2013). (Ultra)sonic scalers were tested with metal (Speelman et al. 1992; Schmage et al. 2012) and non-metal tips (Gantes & Nilveus 1991; Zablotsky et al. 1992; Kawashima et al. 2007; Schmage et al. 2012), while two studies (Schwarz et al. 2005; Kawashima et al. 2007) used the Vector™ ultrasonic system with a PEEK (polyether etherketone fibre) tip. Rotating titanium brushes were tested in one study (John et al. 2013). The air powder abrasive system was the instrument mostly evaluated, as it was tested in nine out of the fourteen included studies (Parham et al. 1989; Zablotsky et al. 1992; Dennison et al. 1994; Pereira da Silva et al. 2005; Schwarz et al. 2009; Nemer Vieira et al. 2012; Schmage et al. 2012; Tastepe et al. 2013; Idlibi et al. 2013). A sodium bicarbonate powder was used in the majority of the studies (Parham et al. 1989; Zablotsky et al. 1992; Dennison et al. 1994; Pereira da Silva et al. 2005; Schwarz et al. 2009; Nemer Vieira et al. 2012), while amino acid glycine powders were tested in four studies (Schwarz et al. 2009; Schmage et al. 2012; Tastepe et al. 2013; Idlibi et al. 2013). Finally, three other powders (TiO2 powder, hydroxylapatite sintered powder and calcium phosphate powder) were used in one study (Tastepe et al. 2013). Speelman et al. (1992) tested a composite bur (Stainbuster®) in combination with sodium bicarbonate powder and Schmage et al. (2012) tested a prophylaxis brush (Sonic Flex Clean®). Differences were observed in the treatment time and treatment mode (e.g., number

of stokes, distance of the tip from the surface, and angulation of the tip). No study was found evaluating the cleaning efficacy of titanium curettes.

Funding

Six studies (Parham et al. 1989; Zablotsky et al. 1992; Dennison et al. 1994; Pereira da Silva et al. 2005; Schwarz et al. 2005; Idlibi et al. 2013) were supported by a non-industrial funding and two (Zablotsky et al. 1992; Schwarz et al. 2009) were supported by an industrial grant. In four studies (Pereira da Silva et al. 2005; Kawashima et al. 2007; Nemer Vieira et al. 2012; Idlibi et al. 2013), the authors declared no conflict of interest. In five studies (Speelman et al. 1992; Dennison et al. 1994; Schwarz et al. 2009; Schmage et al. 2012; Idlibi et al. 2013), some of the materials used were donated by companies. Two studies (Tastepe et al. 2013; and John et al. 2014) provided no information about funding.

Outcomes

The outcome variable for five studies (Parham et al. 1989; Gantes & Nilveus 1991; Speelman et al. 1992; Kawashima et al. 2007; Schmage et al. 2012) was SEM observations. Idlibi et al. (2013) evaluated the quantity of residual biofilm by quantification of the total protein content and scanning electron microscopy. Four studies (Schwarz et al. 2005, 2009; Tastepe et al. 2013; John et al. 2014) used the residual biofilm areas and one study (Zablotsky et al. 1992) the residual LPS levels. Nemer Vieira et al. (2012) reported on the percentage of bacterial removal, Pereira da Silva et al. (2005) evaluated the colony forming units (CFU) before and after treatment and Dennison et al. (1994) used a radioimmunoassay to evaluate the removal of endotoxin. The results of all studies are presented in Table 2. Only two studies (Kawashima et al. 2007; Tastepe et al. 2013) provided information regarding the validation of the evaluation method (Table 3).

Speelman et al. (1992) evaluated the effectiveness of scaling with metal and plastic scalers and ultrasonic scalers with metal tips at cleaning the buccal surface of abutments with a machined surface contaminated with plaque and calculus. SEM photographs were taken and abutments were assigned a "cleanliness" score ranking from 0 (unused abutment) to 5 (surface not clean). The authors reported that although a 90 s treatment with metal, plastic or ultrasonic instruments with metal tip appeared clinically to result in a clean surface, the SEM analysis showed a surface that was still covered to various extents with thin layers of amorphous materials, calculus, and/or bacterial colonies. None of these cleaning methods created

a cleanliness score better than 3 and none of them appeared to be superior to the other. In the same study single polishing with a composite bur (Stainbuster®) in combination with sodium bicarbonate powder was found to have the least cleaning potential (score 5), while weekly rubber cup polishing with pumice for 10 s once a day for three months resulted in the highest surface cleanliness (score 1,2).

John et al. (2014) compared the effectiveness of a rotating titanium brush to that of a stainless steel curette on SLA titanium discs contaminated with supragingival plaque. Both cleaning procedures showed a significant decrease in residual plaque areas. However, the mean residual biofilm area in the titanium brush group (8.57% ± 4.85%) was significant lower than in the curette group (28.99 ± 5.51%), while being gentler to the implant surface than the metal curette.

Schmage et al. (2012) evaluated the cleaning efficacy of different cleaning instruments, among which non-metal curettes (plastic, carbon), sonic and ultrasonic scalers with non-metal (PEEK, carbon) tips, air-abrasive with amino acid glycine powder and rubber cup with pumice, on titanium discs with four different surfaces: polished, acid-etched, grit-blasted/acid-etched and grit-blasted. The specimens were contaminated with a monoclonal biofilm of *Streptococcus mutans*. The best cleaning was seen with (ultra)sonic scalers with a PEEK tip and the air abrasive with amino acid glycine powder on all implant surfaces, whereas the poorest cleaning was seen with the non-metal curettes and the rubber cup with pumice.

Kawashima et al. (2007) evaluated the treatment of polished implant abutment surfaces with three piezoelectric scalers with metal, plastic or carbon tip (Vector™ scaler), in vivo. After one week of plaque accumulation in the mouth of patients that underwent implant treatment, the subgingival area of the abutments was treated for 60 s with the three ultrasonic scalers. After instrumentation, the abutments were removed and the amount of remaining plaque and calculus in the mesial proximal area was estimated using the same ranking score as in the study of Speelman et al. (1992).The authors reported that all three instruments successfully removed plaque from the abutment surfaces. All piezoelectric scalers resulted in a cleanliness score better than 3.

Schwarz et al. (2005) tested the Vector™ system with a carbon-fibre tip and polishing fluid (HA particles $< 10\ \mu m$) on titanium discs with SLA surfaces contaminated with supragingival plaque. Cleaning efficacy was evaluated by measuring the residual biofilm (RB) area. Treatment with the Vector system resulted in a significant decrease in initial biofilm covered (IPB) area (mean RB: 36.8 ± 4.5% versus mean IPB: 97.5 ± 0.9; $p < 0.001$).

Sonic scalers with plastic tips were also tested in two other studies (Gantes & Nilveus 1991; Zablotsky et al. 1992). Gantes & Nilveus (1991) used a sonic plastic scaler for less than 5 s on titanium cylinders with a highly polished surface contaminated with supragingival plaque and concluded that this instrument was able, based on SEM observations, to completely remove plaque from the surface of highly polished titanium. In Zablotsky et al. (1992), a sonic scaler with plastic tip was used on grit-blasted titanium alloy strips contaminated with *E. coli* LPS. The residual LPS levels were measured. A 60 s application with the plastic sonic scaler tip resulted in significantly reduced residual LPS levels compared to the untreated control (63 mean residual LPS counts/min/mm^2 versus 197 counts/min/mm^2; $p < 0.05$). This study also evaluated the detoxifying effects of a 30 s application of an air powder abrasive system with a sodium bicarbonate powder. This treatment removed significantly greater amounts of LPS compared to the plastic sonic scaler (12 LPS counts/min/mm^2 for air abrasive versus 63 LPS counts/min/mm^2 for the plastic scaler; $p < 0.05$).

Dennison et al. (1994) used the air abrasive with sodium bicarbonate powder on cylindrical implants with TPS or machined surfaces contaminated with *P. gingivalis* LPS for a single (60 s) and a repeated treatment (120 s) and showed that the air abrasive resulted in a significant reduction in endotoxin levels compared to the baseline on both surfaces. On TPS surfaces, the air abrasive removed 84.2% of the endotoxin after one treatment and 91.8% after the second treatment ($p < 0.05$). On the machined surface, the reduction was 98.5% and 99.4%, respectively ($p > 0.05$). The air abrasive was shown to be more effective in removing endotoxin from machined than TPS surfaces.

Parham et al. (1989) showed that a 5 s application of the air-abrasive with a sodium bicarbonate powder on implant specimens with TPS surfaces contaminated with *A. viscosus* resulted in complete removal of bacteria.

Pereira da Silva et al. (2005) investigated the efficacy of a decontamination protocol for bacterial removal from titanium surfaces contaminated with *S. sanguis* using a high-pressure sodium bicarbonate device for 60 s. They used titanium sheets with three different levels of surface roughness. Group 1 was composed of titanium sheets with a machined surface, and group 2 and 3 of titanium sheets blasted with aluminium oxide particles with different diameters: group 2 was blasted with 65-μm particles (moderate rough surface) and group 3 with 250- μm particles (very rough surface). The colony forming units were counted before and after treatment, and no viable cells were detected after treatment in all of the surfaces

examined. Nemer Vieira et al. (2012) used a similar high-pressure sodium bicarbonate device for 60 s on implants contaminated with *S. sanguis*, with either a machined or an acid-etched surface. Removal of all bacterial cells was observed regardless of the surface roughness.

Schwarz et al. (2009) used the air abrasive with sodium bicarbonate or amino acid glycine powders with different particle sizes (range of mean particle size 20-75 μm) on titanium discs with a SLA surface contaminated with supragingival plaque at two distances and two angulations for single (20 s) and repeated treatments (40 s). The residual biofilm (RB) areas (%) were assessed. Comparable mean RB areas were observed within and between groups after single (RB: 0.0 ± 0.0 % to 5.7 ± 5.7%) and repeated treatments (RB: 0.0 ± 0.0 %). The authors concluded that all of the powders investigated were equally effective in cleaning the SLA titanium surfaces.

Tastepe et al. (2013) also tested the air abrasive on intraorally contaminated SLA titanium discs. Four different powders were used: titanium dioxide (TiO2), amino acid glycine powder (particle size 20-65 μm), hydroxylapatite sintered (HA) and calcium phosphate powder. All powders decreased the initial amount of biofilm significantly, although the TiO2 powder was not as efficient as the others. All applications resulted in remnants of the powder particles left or impacted on the surface.

Finally, Idlibi et al. (2013) evaluated the efficacy of an air abrasive with amino acid glycine powder (mean particle size: 20 μm) in removing biofilm formed *in situ* on machined titanium discs. A 60s treatment of the machined surfaces with the air abrasive resulted in significant decrease in the amount of biofilm. The average percentage of residual biofilm in relation to the untreated control was 2.5%.

Quality assessment and grading the 'body of evidence'

The quality assessment of the various studies is presented in Table 3. Of the fourteen studies that evaluated the cleaning efficacy, ten were considered to have a high potential risk of bias and four were considered to have a moderate risk. Most of the studies used titanium discs, sheets or strips, which are considered to be less clinically representative. Five studies provided data regarding randomisation of the treatment, but no study provided data regarding the allocation concealment.

Regarding the sample size of the included studies, twelve studies used an adequate sample size, as it was calculated by the reviewers using the Mead's resource equation, while two studies (Parham et al. 1989; Gantes & Nilveus 1991) did not fulfill the abovementioned

criteria. However, exclusion of these studies does not affect the outcome of the review.

The following criteria were used to rate the quality of evidence and strength of the recommendations according to GRADE (Guyatt et al. 2008, GRADE working group): potential risk of bias, consistency, directness, precision of the estimate and publication bias. There were sufficient available data regarding the use of air abrasive with sodium bicarbonate or amino acid glycine powder to clean titanium surfaces. The available data were consistent, indirect and rather precise and had a high potential risk of bias. As a result, the strength of recommendation was considered to be weak. The data reporting on the cleaning efficacy of the other mechanical instruments were limited, which made grading of the evidence not feasible. A formal testing for publication bias, as proposed by Egger et al. (1997), could not be used owing to insufficient statistical power because of the limited number of studies evaluating each instrument and the lack of sufficient quantitative data.

Discussion

The present review focused on the effectiveness of different mechanical instruments to clean contaminated titanium implant surfaces. This issue has been approached mainly by *in vitro* experiments. Metal (stainless steel) curettes were found to be ineffective in removing calcified deposits from machined surfaces (Speelman et al. 1992), but effective in removing non-calcified deposits from SLA surfaces (John et al. 2014). Different non-metal curettes were found to be ineffective in removing bacteria as well as calcified deposits from smooth as well as rough titanium surfaces (Speelman et al. 1992; Schmage et al. 2012). Similar results are reported in the literature and in the case of cylindrical implants with a TPS surface and screw-shaped implants with a machined surface (Augthun et al. 1998). This study showed that it was impossible to remove the plaque from the depth of the screw-like threads or the plasma-sprayed surfaces with plastic curettes. The inadequate effect of these instruments has been attributed to their limited flexibility, which prevents exact placement and application, particularly in the case of threaded implants (Augthun et al. 1998). These results are also corroborated to a certain extent by the findings from two other studies that evaluated the effectiveness of plastic curettes in combination with chlorhexidine gluconate (CHX) to remove supragingival biofilm grown on titanium discs with Osseotite or SLA titanium surfaces (Schwarz et al. 2006 and 2005, respectively). Subsequent to instrumentation, the mean residual plaque biofilm area was 58.5 ± 4.9% for the Osseotite and 61.1 ± 11.4 % for the

SLA surfaces, which showed the inability of the plastic curette to effectively clean implant surfaces, even in combination with CHX.

The Vector scaler, a piezoelectric scaler with a carbon tip, seems to be effective in removing biofilm from SLA (Schwarz et al. 2005) and polished titanium surfaces (Kawashima et al. 2007). These results are supported to a certain extent by the findings from one other study that evaluated the effectiveness of an ultrasonic scaler with the same carbon tip in combination with chlorhexidine gluconate (CHX) to remove plaque biofilm grown on titanium discs with Osseotite surfaces (Schwarz et al. 2006). Sato et al. (2004) compared the effectiveness of the Vector scaler to that of conventional piezoelectric scalers with a metal and with a plastic tip to remove artificial debris from abutments with a polished titanium alloy surface *in vitro*. After 60 s, removal of artificial debris was significantly better when using the Vector system compared to the conventional scalers with metal and plastic tips. However, these results are different to that of Kawashima et al. (2007) who compared the effectiveness of the same piezoelectric scalers on the same abutments *in vivo.* No significant differences were observed between the scalers after treatment for 60 s. These authors (Kawashima et al. 2007) concluded that all scalers produced clean surfaces. The apparent discrepancies may be due to the differences between removing artificial debris and plaque and the inherent differences between *in vitro* and *in vivo* settings. The friction during removal of the treated abutments from the mouth of the patients in order to be microscopically evaluated may have affected the amount of remaining biofilm on the surface.

(Ultra)sonic scalers with metal tip were quite effective in removing plaque from polished and highly polished surfaces (Gantes & Nilveus 1991; Kawashima et al. 2007). However, these results should be used with caution. In a systematic review evaluating the effect of different mechanical instruments on titanium implant surfaces (Louropoulou et al. 2012), (ultra)sonic scalers with metal tips were found to cause major damage to smooth surfaces. The surface roughness produced by these instruments may promote new biofilm formation and impede the preservation of implant health.

A rotating titanium brush seems to be an effective instrument for mechanical cleansing of SLA surfaces, while inducing no surface alteration (John et al. 2014). These results are supported to an extent by the findings from another study that assessed the effect of rotating titanium brushes in combination with four chemical agents on titanium surfaces covered by a *Staphylococcus epidermidis*-based biofilm. Three different titanium surfaces were used: SLA surfaces, specimens mimicking Ti-Unite™ surfaces and specimens mimicking OsseoSpeed™

surfaces. The combination of the titanium brushes with the chemical agents resulted in a greater reduction of the biofilm compared to the use of the same chemical agents alone (Gustumhaugen et al. 2014).

All studies evaluating the cleaning efficacy of an air powder abrasive reported consistent results. This device when used with a sodium bicarbonate powder was found to be very effective in removing bacteria and bacterial products from machined, SLA, grit-blasted and TPS titanium surfaces. All studies reported more than 84% removal of bacteria or bacterial products irrespective of the surface type. When comparing the air-abrasive with sodium bicarbonate powder to a plastic curette (Augthun et al. 1998) or a sonic scaler with a plastic tip (Zablotsky et al. 1992), the air-abrasive was found to be more effective than the other treatment modalities, independent of the surface characteristics. These results are in agreement with a recently published literature review focusing on the air abrasive (Tastepe et al. 2012). The authors of this review reported: *"In vitro cleaning efficacy of air powder abrasive treatment on titanium strips, discs or implants is high."* Promising results for the air abrasive were also reported in a review evaluating the decontamination of infected implants by mechanical, chemical and physical methods (Meyle et al. 2012). This review included in vitro, animal and human studies and the authors concluded that "for *decontamination of infected implant surfaces air-abrasive treatment seems to work".*

Beside the classical sodium bicarbonate powder, good results are also reported for other powders. A less abrasive amino acid glycine powder seems to be effective in removing single bacteria species and plaque from titanium discs with smooth and structured surfaces (Schwarz et al. 2009; Schmage et al. 2012; Tastepe et al. 2013; Idlibi et al. 2013). Moreover, this powder has been found to be gentler to the implant surface than the sodium bicarbonate powder. Repeated use of the different amino acid glycine powders on SLA surfaces (density= 2.16 g/cm^3) was not associated with any surface alterations compared to a sodium bicarbonate powder (density= 1.61 g/cm^3), which resulted in a flattening of the sharp-edged elevations of the surface after repeated treatments (Schwarz et al. 2009). Similarly, the air-polishing treatment with glycine powder of titanium abutment surfaces caused no detrimental surface alterations on the smooth surface, while an increased surface roughness with crater formation was observed when a sodium bicarbonate powder was used (Cochis et al. 2012). When comparing the air-abrasive with amino acid glycine powder with different hand, sonic and ultrasonic instruments with metal and non-metal tips, the air abrasive with amino acid glycine powder was found to be equally effective as a sonic instrument with a

PEEK tip on both smooth and structured surfaces (Schmage et al. 2012).

The powder seems to be an important parameter for the efficacy of the air abrasive. The use of an air abrasive device without powder (only water) resulted in significantly less biofilm removal compared to the use of the same device with different powders (Tastepe et al. 2013). However, deposition of powder particles has been observed on the treated surfaces (Mouhyi et al. 1998; Tastepe et al. 2013). The latest study (Mouhyi et al. 1998), in which failing implants were cleaned with an air-abrasive with sodium bicarbonate powder, showed that although a clean surface was observed on SEM, the elemental composition of the original surface was not re-established. This treatment resulted in a marked contamination with sodium (38%), which was found as deep as 87 nm into the implant, and only 1% of titanium could be detected on the surface (Mouhyi et al. 1998).The residual powder particles may interfere with cell responses and thus, affect the biocompatibility of the treated titanium surface.

Limitations

Reviewing the literature for studies on mechanical cleaning of titanium dental implant surfaces retrieved limited evidence. Only thirteen studies were identified addressing this issue. Most instruments were evaluated in only one or two studies. The majority of the studies used titanium discs, sheets, strips and cylinders simulating the surface of implant bodies or abutments. Although these specimens mimic exactly the microstructure of the surface, the macrostructure (threads shape) are not identical. As a result of these differences, the cleaning of actual implant surfaces may be more difficult.

In almost all studies that used biofilm contamination, the titanium surfaces were contaminated with non-mineralised supragingival plaque. However, the composition of the subgingival plaque may vary and mineralised deposits may be present in clinical cases. Only one study (Speelman et al. 1992) used surfaces contaminated with plaque and calculus and showed the inability of the tested instruments to adequately remove mineralised deposits. Several of the studies used bacterial products (e.g., LPS) and single species-biofilm to contaminate the surfaces. These contaminants may not adequately represent actual clinical situations compared to *in situ* biofilm growth.

The impact of sponsorship may be an important issue, as there is literature showing that industry sponsorship may affect biomedical research outcomes (Popelut et al. 2010). In the present review, two studies (Zablotsky et al. 1992; Schwarz et al. 2009) were supported by an

industrial grant. In the study of Schwarz et al. (2009) the air abrasive system and the powders used were provided by a grant of the manufacturer, while the study of Zablotsky et al. (1992) was supported in part by the implant company. Furthermore, in four studies (Speelman et al. 1992; Dennison et al. 1994; Schmage et al. 2012; Idlibi et al. 2013), the implant specimens used were donated by the implant companies. Two studies investigated the effectiveness of a commercial device, the Vector™ scaler (Schwarz et al. 2005; Kawashima et al. 2007). In the first study the authors declare no conflict of interest, while the second one was supported by a non-industrial grant. In a systematic review on the treatment of peri-implantitis (Esposito et al. 2012) the authors report that in the trials sponsored by manufacturers "there might be some commercial 'pressure' to evaluate some interventions and not others".

Quantifiable results are fundamental for effective comparisons of study outcomes (Field et al. 2010). In five studies SEM observations were used to evaluate the cleaning effect of the different instruments. This method is clearly not quantitative and thus does not allow us to draw any definitive conclusions.

Randomization and allocation concealment are aspects shown to have a great impact on bias. However, for the quality appraisal of the studies included in this review (Table 3), neither allocation concealment or sequence generation (randomization) were considered as items to be used to estimate the risk of bias. Although the authors of this review recognize that this is an important issue, they are also aware that reporting on randomization and allocation concealment in the dental literature has not been a critical item up until the recent past. Therefore, including these items would result in an overestimation of the risk of bias. From the fourteen studies included in this review, only six (Schwarz et al. 2005, 2009; Schmage et al. 2012; Tastepe et al. 2013; Idlibi et al. 2013; John et al. 2014), provided information about the randomization. All are recent studies that are published starting from 2005. None of the included studies provided information about the concealment of allocation. It should, however, be emphasized that for future studies it is imperative that researchers provide information on these important aspects.

Different instruments, among which mechanical instruments, have been suggested for the decontamination of implant surfaces. All of these methods have been associated with advantages and disadvantages, with no definitive gold standard. This finding does not mean that all current treatments are ineffective (Esposito et al. 2012), but there is still no consensus among clinicians regarding the best available treatment. The term "contamination" is ambiguous. Most clinicians use this term to imply the transfer of microorganisms or bacterial

products, such as polysaccharide, onto the implant surfaces. Any contamination of the titanium surface significantly reduces the surface free energy, which is believed to compromise the biocompatibility of the implant (Kasemo 1983; Sennerby et al. 1989). Thus, the removal of plaque biofilm or bacterial products from the implant surfaces constitutes an important element in the prevention and treatment of peri-implant infections. It should, however, be kept in mind that instruments used to remove contaminants may also leave deposits on the treated surfaces. Air abrasive powders, the Vector™ scaler and non-metal instruments were found to leave deposits on the treated surfaces (Louropoulou et al. 2012). Whether such residues influence healing events is still unknown.

In this systematic review an attempt was made to evaluate the available evidence on mechanical instruments and their cleaning efficacy on titanium implant surfaces in a controlled manner (Table 4).The conclusions are based mainly on *in vitro* studies and refer to observations at a microscopic level. In clinical situations, there are factors that render the accessibility of the titanium surfaces more difficult, such as the design of the implant, the design of the suprastructure and the soft and hard tissues surrounding the implants. In a clinical setting, the cleaning efficacy of the instruments may, thus, be more limited. Although complete biofilm removal should not be expected, especially in clinical situations when sufficient access to the surface is sometimes difficult, some mechanical instruments have been proven to reduce the amount of biofilm present on the surface satisfactory. This decrease in the bacterial load may be enough to re-establish equilibrium between the peri-implant microbiota and the host defense and thus, a stable clinical situation over time (Mombelli, 2002).

Conclusions

- Metal curettes seem to be ineffective in removing calcified deposits from machined surfaces but effective in removing non-calcified deposits from SLA surfaces.
- Non-metal curettes seem to be ineffective in removing bacteria from polished/machined, acid-etched and grit-blasted titanium surfaces.
- (Ultra)sonic scalers with metal tip seem to be effective in removing plaque from polished titanium surfaces. In the presence of calcified deposits, the cleaning potential of these instruments appears to be very limited.
- (Ultra)sonic scalers with non-metal tip seem to be effective in removing single bacteria species and non-calcified deposits from polished and highly polished titanium surfaces. Controversial results are presented for grit-blasted surfaces.

- The Vector™ scaler with a carbon tip seems to be effective in removing plaque from polished and SLA titanium surfaces.
- Rotating titanium brushes seem to be effective in removing non-mineralised deposits from SLA surfaces.
- Single use of rubber cup with pumice on both smooth and rough titanium surfaces does not clean these surfaces effectively.
- Air powder abrasive with either sodium bicarbonate or amino acid glycine powder appears to clean machined, SLA, TPS and grit-blasted titanium surfaces effectively.

Different surfaces may require treatment with different instruments. When choosing the most appropriate instruments for each surface other parameters should also be taken into account like the localization the surface, the accessibility of the surface, the alterations produced by the instrumentation and the effect of instrumentation on the biocompatibility of the treated surface. It is obvious that an instrument would be of no value if it renders the surface non-biocompatible.

Implications for further research

In this systematic review an attempt was made to evaluate the available evidence on mechanical instruments and their cleaning efficacy on titanium implant surfaces in a controlled manner. Although the formulation of concrete conclusions appears to be difficult, this review clearly points out that some mechanical instruments may be valuable instruments in the maintenance of implants and the treatment of peri-implantitis. As this systematic review has shown that mechanical instruments cannot be expected to achieve complete biofilm removal, combination treatments should also be tested. Mechanical instruments could be combined with chemical agents for killing the bacteria remaining on the titanium surfaces. Well-performed *in vitro* and eventually *in vivo* studies with adequate sample size and appropriate design to allow comparisons are necessary in order to establish an evidence-based protocol for the use of mechanical instruments in the maintenance of implants and the treatment of peri-implantitis.

Practical Implications

The available data suggested that the air abrasive may remove plaque effectively from machined, SLA and TPS titanium surfaces. Positive results were also observed for ultrasonic scalers with non-metal tip on polished and SLA surfaces and rotating titanium brushes on SLA surfaces.

Acknowledgements

Declaration of interest

The authors declare that they have no conflict of interest.

The research was self-funded by the authors and their institution

Authors' contributions:

A. Louropoulou contributed to the conception, design, acquisition, analysis, interpretation of data, drafted the manuscript.

D.E. Slot contributed to the design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

G.A. van der Weijden contributed to the conception, design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

All authors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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* Studies included in the review

Figure 1. Databases search and literature selection

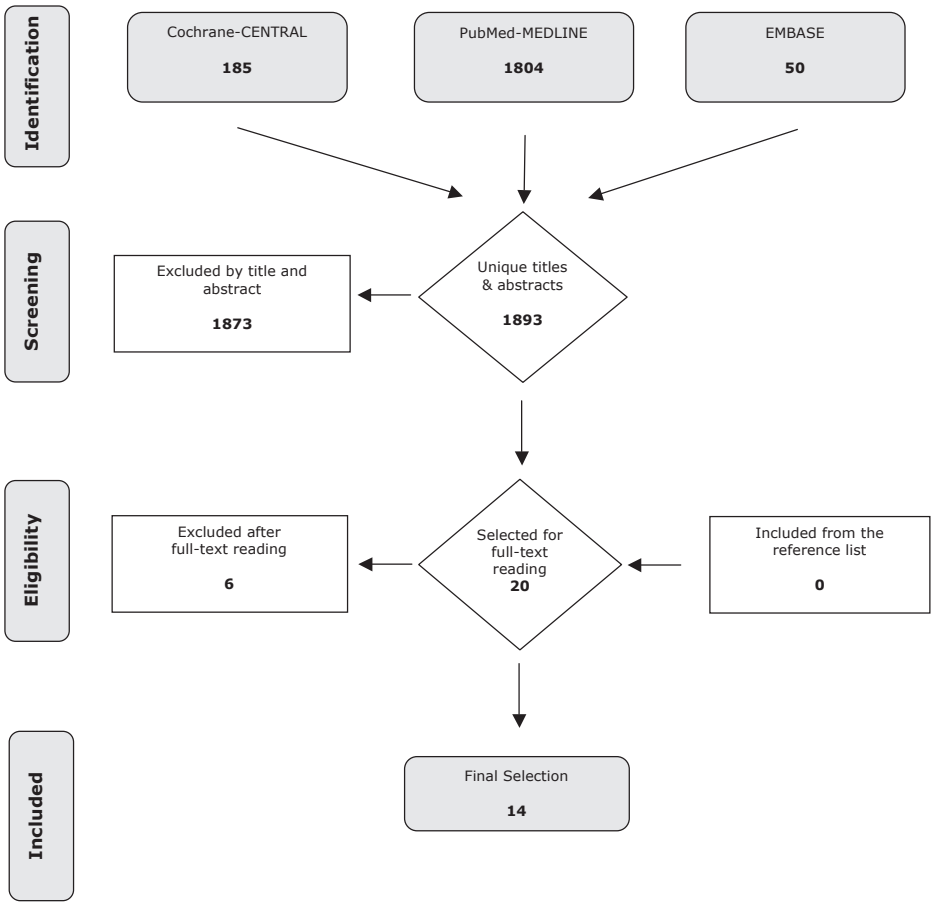

Table 1. Overview of the studies that were excluded after full-text reading and the reason for exclusion

Reason for exclusion	Authors (year)
Not controlled and non-standardized biofilm growth	Bain (1998) Mouhyi et al. (1998) Augthun et al.(1998) Matsuyama et al. (2003)
Contamination with ink	Sahrmann et al. (2013)
Combination of mechanical and chemical treatment/ no mechanical instruments	Baumhammers et al. (1975)

Table 2. Summary of studies evaluating the cleaning efficacy of mechanical instruments on titanium surfaces

Author (year)	Component/ Surface(s)/ Contamination	Treatment/ Control (n= # of treated surfaces)	Outcome parameter	Conclusions
John et al. (2014)	Titanium discs SLA surface Contaminated with supragingival plaque by placement of splints in volunteers	- Rotating titanium brush (n= 30) - Metal curette (n= 30) - Pre-treatment control (n= 60)	Residual biofilm areas	Both cleansing procedures showed a significant decrease in residual biofilm areas. The rotation titanium brush was more effective in removing plaque than the steel curette.
Idlibi et al. (2013)	Titanium discs Machined surface Contaminated with supragingival plaque by placement of splints in volunteers	- Air abrasive with amino acid glycine powder (n= 20) - Contaminated and untreated control (n= 20)	Percentage of residual biofilm Total protein content	The air abrasive showed the best efficacy at removing oral biofilm. The percentage of residual biofilm was 2.5% of the untreated control.
Nemer Vieira et al. (2012)	Titanium implants Machined surface Acid-etched surface Contaminated with *Streptococcus sanguis*	- Air abrasive with sodium bicarbonate powder (n= 20) - Pre-treatment control (n= 20)	Percentage of bacterial removal	After the application of the decontamination protocol, all bacterial cells were removed from the tested implants, regardless of surfaces roughness.
Tastepe et al. (2013)	Titanium discs SLA surface Contaminated with supragingival plaque by placement of splints in volunteers	- Air powder abrasive with four different powders: (1) TiO2 powder (n= 6) (2) Amino acid glycine powder (n= 6) (3) HA powder (n= 6) (4) Calcium phosphate powder (n= 6) - Pre-treatment control (n=24)	Residual biofilm areas	The calcium phosphate, HA and amino acid glycine powders can almost totally remove the biofilm from the titanium surfaces. The TiO2 powder is less efficient.

Author (year)	Component/ Surface(s)/ Contamination	Treatment/ Control (n= # of treated surfaces)	Outcome parameter	Conclusions
Schmage et al. (2012)	Titanium discs Polished surface Acid-etched surface Grit-blasted/acid-etched surface Grit-blasted surface Contaminated with *Streptococcus mutans*	- Plastic curette (n= 20) - Carbon curette (n= 20) - Prophylaxis brush (n= 20) - Rubber cup with paste (n= 20) - Sonic scaler with PEEK tip (n= 20) - Ultrasonic scaler with PEEK tip (n= 20) - Ultrasonic scaler with carbon curette (n=20) - Ultrasonic scaler with metal tip (n= 20) - Air abrasive with amino acid glycine powder (n= 20) - Non contaminated and untreated control (n= 20)	SEM observations Ranking score: 1 (no bacteria or remaining particles) to 3 (many remnants of bacteria of particles)	The best cleaning was found for the air abrasive and the sonic scaler with PEEK tip on all implant surfaces. The carbon curette provided the worst cleaning.
Schwarz et al. (2009)	Titanium discs SLA surface Contaminated with supragingival plaque by placement of splints in volunteers	- Air powder abrasive with amino acid glycine or sodium bicarbonate powder (n=128) - Pre-treatment control (n=128)	Residual biofilm areas	All powders investigated were equally effective.
Kawashima et al. (2007)	Healing abutments Polished surface (Ti-6Al-4V) Contaminated by subgingival plaque by placement in the mouth of patients	- Ultrasonic scaler with metal tip (n= 7) - Ultrasonic scaler with plastic tip(n= 7) - Ultrasonic scaler with carbon tip (n= 7) - Contaminated and untreated control (n= 21)	SEM observations Ranking score: 0 (untreated abutment) to 5 (surface not clean)	The modified remaining plaque and calculus scores differed significantly when the treatment groups compared to controls. No significant differences were observed between the treatment groups.
Schwarz et al. (2005)	Titanium discs SLA surface Contaminated with supragingival plaque by placement of splints in volunteers	- Ultrasonic scaler with PEEK tip and polishing fluid (n=20) - Pre-treatment control (n=20)	Residual biofilm areas	Specimens treated with the ultrasonic scaler showed a significant decrease in biofilm covered areas.
Pereira da Silva et al. (2005)	Titanium sheets Machined surface Titanium surface blasted with 65 μm aluminum oxide particles Titanium surface blasted with 250 μm particles Contaminated with *Streptococcus sanguis*	- Air abrasive with sodium bicarbonate powder (n= 21) - Contaminated and untreated control (n= 9)	Colony forming units	After application of the decontamination protocol no viable cells were detected for all surfaces examined.

Author (year)	Component/ Surface(s)/ Contamination	Treatment/ Control (n= # of treated surfaces)	Outcome parameter	Conclusions
Dennison et al. (1994)	Implant bodies TPS surface Machined surface Contaminated with *Porphyromonas gingivalis* LPS	- Air powder abrasive with sodium bicarbonate powder (n= 6) - Pre-treatment control (n= 6)	Radioactive endotoxin (radioimmuno assay)	Significant decrease in endotoxin levels after treatment on both titanium surfaces. Air abrasive was more effective in removing endotoxin from machined than from TPS surfaces.
Speelman et al. (1992)	Healing abutments Machined surface Contaminated with plaque and calculus by placement in beagle dogs	- Metal curette (n= 4) - Plastic scaler (n= 4) - Ultrasonic scaler with metal tip (n= 5) - Single polishing with composite bur and sodium bicarbonate powder (n= 5) - Rubber cup with pumice (n= 3) - Non contaminated and untreated control (n= 1)	SEM observations Ranking score: 0 (untreated abutment) to 5 (surface not clean)	The weekly rubber cup polishing resulted in the highest surface cleanliness. The single polishing with composite bur resulted in the lowest surface cleanliness followed by the plastic scaler. None of the three scaling methods created a cleanliness score better than 3.
Zablotsky et al. (1992)	Titanium strips Grit-blasted titanium alloy surface Contaminated with *Escherichia coli* LPS	- Sonic scaler with plastic tip (n= 3) - Air powder abrasive with sodium bicarbonate powder (n= 3) - Contaminated and untreated control (n= 3)	Residual LPS levels measured by liquid scintillation spectrometry	Both treatments resulted in significantly less amounts of LPS compared to the untreated control. The air powder abrasive removed significantly greater amounts of LPS than the sonic plastic scaler.
Gantes et al. (1991)	Titanium cylinders Highly polished surface Contaminated with supragingival plaque by placement in beagle dogs	- Sonic scaler with plastic tip (n=6) - Contaminated and untreated control (n= 2)	SEM observations	The sonic plastic scaler was able to completely remove the contaminants from the surface of polished titanium.
Parham et al. (1989)	Implant specimens TPS surface Contaminated with *Actinomyces viscosus*	- Air powder abrasive with sodium bicarbonate powder (n= 4) - Contaminated and untreated control (n= 4)	SEM observations	Specimens treated with the air abrasive system showed 100% removal of bacteria.

TPS, titanium plasma-sprayed; SLA, sand-blasted and acid-etched; LPS, lipopolysaccharide; SEM, scanning electron microscope; PEEK, polyether etherketone fiber; TiO2, titanium dioxide; HA, hydroxylapatite

Table 3. Methodological quality scores of the selected studies

Quality criteria		External validity			Internal validity					Statistical validity				Author's estimated risk of bias
	Author (year)	Representative surface *	Validation of the evaluation method	Reproducibility data provided	Sequence generation (randomization)	Concealment allocation	Blinded to examiner*	Blinding during statistical analysis	Preparation, manipulation and treatment of the surface identical, except for the intervention *	Adequate sample size[i]	Point estimates presented for primary outcome measurements*	Measures of variability presented for the primary outcome	Statistical analysis*	
Cleaning Efficacy	John et al. (2014)	-	?	?	+	?	+	?	+	+	+	+	+	Moderate
	Idlibi et al. (2013)	-	?	?	+	?	?	?	+	+	+	+	+	High
	Nemer Vieira et al. (2012)	+	-	?	-	?	?	?	+	+	-	-	?	High
	Tastepe et al. (2013)	-	+	?	+	?	?	?	+	+	-	-	+	High
	Schmage et al. (2012)	-	?	?	+	?	?	?	+	+	-	-	-	High
	Schwarz et al. (2009)	-	?	?	+	?	+	?	+	+	+	+	+	Moderate
	Kawashima et al. (2007)	+	+	?	-	?	+	?	+	+	-	-	+	Moderate

Quality criteria		External validity			Internal validity					Statistical validity				Author's estimated risk of bias
	Author (year)	Representative surface *	Validation of the evaluation method	Reproducibility data provided	Sequence generation (randomization)	Concealment allocation	Blinded to examiner*	Blinding during statistical analysis	Preparation, manipulation and treatment of the surface identical, except for the intervention *	Adequate sample size[1]	Point estimates presented for primary outcome measurements*	Measures of variability presented for the primary outcome	Statistical analysis*	
Cleaning Efficacy	Schwarz et al. (2005)	-	?	?	+	?	+	?	+	+	+	+	+	Moderate
	Pereira da Silva et al. (2005)	-	?	?	-	?	?	?	+	+	+	-	?	High
	Dennison et al. (1994)	+	?	?	-	?	?	?	+	+	+	+	+	High
	Speelman et al. (1992)	+	?	?	-	?	+	?	+	+	-	-	-	High
	Zablotsky et al. (1992)	-	?	?	-	?	?	?	+	+	+	-	+	High
	Gantes et al. (1991)	+	?	?	-	?	?	?	+	-	-	-	-	High
	Parham et al. (1989)	-	?	NA	-	?	?	?	+	-	-	-	NA	High

+: yes, -: no, ?: not specified/unclear

*: Items used to estimate potential risk of bias

NA: not applicable, visual assessment without scoring of the outcome

[1] The authors of the review calculated the sample size of all the include studies by using the Meads's resource equation

Table 4. Summary of the outcomes of the included studies

Author	John et al. (2014)	Idlibi et al. (2013)	Nemer Vieira et al. (2012)	Tastepe et al. (2013)	Schmage et al. (2012)	Schwarz et al. (2009)
Surface	SLA§	Machined	Machined Acid-etched	SLA	Polished Acid-etched Acid-etched/ grit-blasted Grit-blasted	SLA
Contamination	Plaque biofilm	Plaque biofilm	Single species biofilm	Plaque biofilm	Single species biofilm	Plaque biofilm
Treatment						
Metal curette	+					
Non-metal curette					0	
Ultrasonic with metal tip						
Ultrasonic with non-metal tip					+/- For all surfaces	
Vector scaler with carbon tip						
Rotating titanium brush	+					
Air abrasive with sodium bicarbonate powder			+/- For all surfaces			+
Air abrasive with amino acid glycine powder		+		+	+/- For all surfaces	+
Air abrasive with HA powder				+		
Air abrasive with calcium phosphate powder				+		
Rubber cup with pumice					0 Single use	

+: positive effect reported and statistically significant difference compared to control

+/-: positive effect reported, without statistical analysis

0: no statistically significant difference compared to control or observation without statistical analysis with surface still (partially) covered with biofilm

TPS, titanium plasma-sprayed; SLA, sand-blasted and acid-etched; LPS, lipopolysaccharide; HA: hydroxylapatite

	Kawashima et al. (2007)	Schwarz et al. (2005)	Pereira da Silva et al. (2005)	Dennison et al. (1994)	Speelman et al. (1992)	Zablotsky et al. (1992)	Gantes et al. (1991)	Parham et al. (1989)
	Polished	SLA	Machined Grit-blasted	Machined TPS	Machined	Grit-blasted	Highly polished	TPS
	Plaque biofilm	Plaque biofilm	Single species biofilm	LPS	Plaque biofilm and calculus	LPS	Plaque biofilm	Single species biofilm
					0			
					0			
	+				0		+/-	
	+					+		
	+	+						
			+ For all surfaces	+ For all surfaces		+		+/-
					+/- Weekly use for 3months			

Chapter 4

Influence of mechanical instruments on the biocompatibility of titanium dental implant surfaces: a systematic review

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Clinical Oral Implants Research 2015; 26: 841-850.

Introduction

The reaction of cells and tissues to biomaterials depends on the material's properties, surface topography, elemental composition and its behaviour upon contact with the body fluids. Pristine implants, which are made of commercially pure titanium, are covered by a layer of titanium oxide that forms on the surface of the metal within milliseconds of exposure to air, water or other electrolytes (Steinemann, 1998). This oxide layer increases the surface free energy, which facilitates adsorption of biomolecules and subsequent cellular attachment and spreading (Donley & Gillette 1991; Baier, 1988).

Bacterial contamination has been shown to affect cell behaviours and alter the elemental composition of a titanium surface (Kawahara et al. 1998a, 1998b; Mouhyi et al. 2000). Next to bacterial contamination, treatment modalities used to decontaminate the titanium surface can also affect its surface topography and chemical composition (Mouhyi et al. 1998). In addition, it has been shown that some of the instruments used to clean contaminated surfaces may deposit themselves to the treated surfaces, which in turn might disturb cell attachment (Schwarz et al. 2003). Alterations of the titanium surface due to contamination and/or after instrumentation have been shown to induce changes in the oxide layer, resulting in a lower surface energy (Kasemo & Lausmaa 1988). This process appears to impair cell adhesion and affects the biocompatibility of the implant (Baier et el. 1988; Fox et al. 1990; Dmytryk et al. 1990; Mouhyi et al. 1998).

Cleaning of contaminated implant surfaces constitutes an important part in the treatment of peri-implant infections. This review is part of a series of reviews on the effect of mechanical instruments on titanium dental implant surfaces. The cleaning efficacy of these instruments and the surface alterations produced by the instrumentation has been previously published (Louropoulou et al. 2012, 2014). However, a question that arises is which consequences instrumentation has for the attachment of peri-implant tissues. An important goal of the different cleaning procedures is to render the exposed titanium surface biocompatible, with re-osseointegration being the ultimate goal. In addition, if the soft tissue attachment is disrupted during instrumentation, the instrumentation procedure should maintain a surface that is conducive to re-establishment of the soft tissue seal (Kuempel et al. 1995). Therefore, the aim of this review was to systematically evaluate, based on the available evidence, the effect of different mechanical instruments on the biocompatibility of titanium dental implant surfaces.

Materials and Methods

This systematic review was conducted according to the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA-statement) (Moher et al. 2009).

Focused question

What is the effect of mechanical instruments on the biocompatibility of titanium dental implant surfaces, as assessed by cell responses, compared with untreated (pristine) titanium surfaces?

Search strategy

Three internet sources were used to identify publications that met the inclusion criteria: the National Library of Medicine, Washington, D.C. (MEDLINE-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). The search was conducted up to December 2013 and was designed to include any published study that evaluated cell responses on contaminated and non-contaminated titanium dental implant surfaces after treatment with different mechanical instruments. To achieve this goal, a comprehensive search was performed. All reference lists from the selected studies, as well as those of review articles on implants, were manually searched by two reviewers (A.L & G.A.W) for additional papers that met the eligibility criteria. The terms used in the search strategy are presented in Box 1.

Screening and selection

Papers written in English were accepted. Letters, human case reports and reviews were not included in the search. The titles and abstracts were first screened independently by two reviewers (A.L & G.A.W) for eligibility. Following selection, full-text papers were carefully read by the two reviewers. The papers that fulfilled all of the selection criteria were processed for data extraction. Disagreements were resolved by discussion. If disagreements persisted, the judgment of a third reviewer (D.E.S) was decisive. The following eligibility criteria were used:

- Controlled studies, presence of an untreated control
- Titanium surfaces of dental implants or implant components or discs, strips or cylinders simulating such surfaces
- In case of contaminated surfaces, contamination with biofilm grown with a standardised technique, single bacterial species or bacterial products, such as lipopolysaccharide (LPS), or/and calcified deposits

- Treatment with mechanical instruments, including curettes and/or scalers, (ultra)sonic instruments, titanium brushes, air abrasives/polishers, rubber cups/points and burs/polishers
- Outcome parameters for cell responses, including cell counts, cell growth, cell attachment, cell spreading, cell viability, surface area of cell coverage, and cell morphology

Assessment of heterogeneity

The following factors were evaluated to assess heterogeneity:

- Titanium surfaces
- Surface contamination method, in case of contaminated surfaces
- Cell culture and incubation period
- Treatment performed
- Outcome variables
- Funding

Box 1. Search terms used for PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE. The search strategy was customized according to the database been searched.

{‹Subject› AND ‹Adjective› AND ‹Intervention›}

{‹Subject: (dental implants [MeSH terms] OR (dental implant OR {/dental OR oral\ AND implant}[textword]) ›

AND
‹Adjective: (biofilms OR dental plaque OR dental deposits [MeSH terms] OR smooth OR structure OR texture OR roughness OR surface OR biofilm OR plaque index OR dental plaque OR plaque OR dental deposit* OR biocompatibility [textword]) ›

AND
‹Intervention: (dental scaling OR decontamination OR laser [MeSH terms] OR ultrasonic OR curette OR scaling OR laser OR polishing OR debridement OR curettage OR air abrasion OR air polisher OR cleaning OR instrumentation OR decontamination OR air powder OR bur OR brush [textword])›}

Quality assessment

Two reviewers (A.L & D.E.S) scored the methodological quality of the studies selected for analysis. Assessment of methodological quality was performed as proposed by the RCT checklist from the Dutch Cochrane Centre (2009) and was further extended using quality criteria obtained from the CONSORT statement (Schulz et al. 2010), the Delphi List (Verhagen et al. 1998), the Jadad scale (1996), the ARRIVE guidelines (Kilkenny et al. 2010) and the position papers by Moher et al. (2001) and Needleman (2002). Most of the proposed criteria were combined as described by Louropoulou et al. (2012).

Data extraction and analysis

The data were extracted from the selected papers by two reviewers (A.L & D.E.S). Disagreements were resolved via discussion. If the disagreement persisted, the judgment of a third reviewer (G.A.W) was considered decisive. After a preliminary evaluation of the selected papers, considerable heterogeneity was found in the study characteristics, instruments used, outcome variables and results. Only few studies presented quantifiable data. Consequently, it was impossible to perform valid quantitative analyses of the data or a subsequent meta-analysis. Therefore, a descriptive presentation of the data was adopted.

Grading the 'body of evidence'

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system proposed by the GRADE working group was used to grade the collected evidence and to rate the strength of the recommendations (Guyatt et al. 2008).

Results

Search and selection

The PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE searches identified in total, 1,893 unique papers using the specified search terms (Figure 1). The initial screening of the titles and abstracts resulted in eleven full-text papers that met the inclusion criteria. Additional hand-searching of the reference lists from the selected studies and those of review articles did not yield any additional papers. Eleven studies were ultimately processed for data extraction.

Assessment of heterogeneity

Information regarding the study characteristics is provided in Tables 1 and 2. The tables include a short summary of the study design, the results of the selected studies and the authors' conclusions. After a preliminary evaluation, considerable heterogeneity was found between the selected studies, which precluded any statistical analysis of the data. Therefore, a descriptive manner of data presentation was used. All included studies were *in vitro* studies. The selected studies could further be divided in two groups: studies evaluating cell behaviours on non-contaminated smooth and structured titanium surfaces after instrumentation with different mechanical instruments and studies evaluating cellular behaviours on smooth and structured titanium surfaces that were contaminated and subsequently cleaned.

Biocompatibility of *non-contaminated* titanium surfaces after instrumentation

The studies included in this section evaluate the impact of instrumentation on cell responses. Six studies were included in this section. Information on these studies is provided in Table 1.

Four studies (Dmytryk et al. 1990; Kuempel et al. 1995; Shibli et al. 2003; Schwarz et al. 2003) evaluated machined titanium surfaces and three studies (Parham et al. 1989; Rühling et al. 2001; Schwarz et al. 2003) used structured titanium surfaces; SLA (sand-blasted and acid-etched) or TPS (titanium plasma sprayed) surfaces.

Cell cultures and incubation periods varied between the studies. Human or mouse fibroblasts were used in four studies (Parham et al. 1989; Dmytryk et al. 1990; Rühling et al. 2001; Shibli et al. 2003). Schwarz et al. (2003) used osteoblast-like cells (SAOS-2 cells) and Kuempel et al. (1995) rat gingival epithelial cells. The incubation period varied from 24 hours up to 7 days.

Smooth surfaces

Dmytryk et al. (1990) examined the ability of tissue culture fibroblasts to attach and colonize smooth titanium surfaces following instrumentation with curettes of dissimilar composition. The smooth transmucosal extension of IMZ implants was scaled with a stainless-steel, titanium alloy or plastic (acetal plastic) curette and then immersed in a cell suspension of mouse fibroblasts. The number of attached cells was counted at 24 and 72 hours and the implants were then processed for scanning electron microscopy (SEM). At 24 hours, only surfaces scaled with a stainless-steel curette showed a significant reduction in number of attached cells. At 72 hours, significantly fewer cells attached to the surfaces treated with the

stainless-steel and titanium alloy curettes (14.6 ± 2.5, 20.9 ± 4.8, respectively) compared to the untreated control and plastic scaler instrumented surfaces (24.3 ± 2.8, 28.1 ± 6.0, respectively). The greatest reduction in cell attachment was observed on the stainless-steel instrumented surfaces. SEM observations showed that the morphology of cells on titanium-alloy and plastic curette instrumented surfaces was similar to that seen on untreated control surfaces. Fibroblasts on stainless-steel instrumented surfaces tended to show to some extent a rounded morphology and a relatively reduced degree of spreading. The authors attributed the impaired cell attachment after treatment with the stainless-steel curette to an alteration in the surface chemistry produced by the contact of two dissimilar metals.

Kuempel et al. (1995) investigated the ability of epithelial cells to grow on titanium discs simulating the smooth surface of an abutment at the soft tissue interface after instrumentation with stainless-steel, gold-coated and plastic curettes. Rat gingival epithelial cells were used. After 5 days of growth, the epithelial cell surface area coverage (mm2) was measured on photographed specimens using a computer digitizing system. The extent of epithelial cell growth did not differ significantly between the stainless-steel, plastic and untreated control groups (74.4 ± 3.9 mm^2, 61.2 ± 4.4 mm^2 and 72.4 ± 3.3 mm^2, respectively). However, the surfaces treated with the gold-coated curette supported significantly less epithelial growth than the stainless steel and control surfaces (56.7 ± 5.7 mm^2), which was thought to be due to changes in the elemental composition of the titanium surface because of damage of the coating of the curette. The slightly reduced epithelial growth on the plastic scaled specimens was attributed by the authors to deposition of particles of the plastic curette on the treated titanium surface.

Treatment of the machined surface of healing abutments with an air powder abrasive system with sodium bicarbonate powder resulted in a reduced proliferation of fibroblasts on the treated surfaces (Shibli et al. 2003). The test group presented a significantly reduced amount of cells (35.31 ± 28.14) as compared to the control group (71.44 ± 31.93) ($p = 0.001$). This reduced proliferation was attributed by the authors to the release of toxic ions from titanium or the presence of powder particles on the instrumented surfaces. However, no significant differences in cell morphology were found between the groups ($p > 0.05$), which was considered by the authors a sign of good cell adhesion.

Schwarz et al. (2003) investigated the effects of an ultrasonic scaler (Vector™ system) with a straight carbon fibre tip and polishing fluid (HA particles $< 10\ \mu m$) on the biocompatibility of titanium discs with machined surfaces in cultures of human osteoblast-like cells

(SAOS-2). After an incubation period of 7 days, cells were counted using a reflected light microscope and the cell density per mm^2 was calculated. The number of attached cells was significantly reduced on the surfaces treated with the Vector™ system compared to the untreated controls ($p < 0.001$). No differences were observed in the morphology of the cells between test and control groups. The surfaces treated with the Vector™ system showed deposits of the carbon fibre tip used. The authors attributed the reduced cell numbers in the Vector™-treated group to the cytotoxic effect of these fragments from the carbon fibre tip.

Structured surfaces

Schwarz et al. (2003) also examined the effect of the same ultrasonic scaler (Vector™ system) on the growth of SAOS-2 cells on rough titanium surfaces. SLA and TPS surfaces were used. The attachment of SAOS-2 cells on the treated surfaces was significantly reduced ($p < 0.001$), which was, like in the case of machined surfaces, attributed to the cytotoxic effect of the deposits from the used carbon fibre tip. No difference in cell morphology was observed between test and control groups.

Parham et al. (1989) evaluated the attachment of fibroblasts on TPS implant surfaces after treatment with an air powder abrasive system with sodium bicarbonate powder. There were no statistically significant differences in the number of attached cells between treated and control groups. In both treatment groups all specimens were uniformly covered with fibroblasts.

Sometimes the removal of the coating of a rough titanium surface may be necessary, especially when rough implant surfaces become supragingivally exposed. The effect of this treatment on cell behaviour has been addressed in one study (Rühling et al. 2001). These authors investigated the growth of human gingival fibroblasts on the titanium surfaces exposed after the removal of the rough TPS coating using diamond-coated files of different roughness depths. The growth of human gingival fibroblasts on the instrumented surfaces was possible. The cells were ultimately associated to each other, and compared to culture controls on cover glasses, demonstrated good adhesion with strict orientation to the microstructure of the scoring left by instrumentation.

Biocompatibility of *contaminated* titanium surfaces after instrumentation

The studies on contaminated titanium surfaces deal with the impact of both instrumentation and bacterial contamination on cell responses. These studies are more representative of

a clinical situation. Five studies were included in this section. Information on these studies is provided in Table 2.

SLA titanium surfaces were used in the majority of the included studies (John et al. 2014; Schwarz et al. 2009, 2005; Kreisler et al. 2005). Implants with either TPS or machined surfaces were tested in one study by Augthun et al. (1998).

Four studies used an *in situ* model to contaminate titanium surfaces with supragingival plaque by placing titanium discs in splints in the mouth of volunteers (John et al. 2014; Schwarz et al. 2009, 2005; Augthun et al. 1998), while Kreisler et al. (2005) used contamination with single-species biofilm of *Porphyromonas gingivalis*.

Cell cultures and incubation periods varied between the studies. Human or mouse fibroblasts were used in two studies (Kreisler et al. 2005 and Augthun et al. 1998, respectively) and osteoblast-like cells (SAOS-2 cells) in three studies (John et al. 2014; Schwarz et al. 2009, 2005). The incubation period varied from 24 hours up to 7 days.

Smooth surfaces

Augthun et al. (1998) examined the growth of mouse fibroblasts on the machined surface of a screw-type implant contaminated with supragingival plaque after cleaning the surface with a plastic curette or an air abrasive system with sodium bicarbonate powder. In the implant treated with the air abrasive, the percentage of viable cells was nearly the same as in the control group (100%). Cell counting showed 570 cells/mm^2 for the smooth titanium screw and 580 cells/mm^2 for the control implants. Good cell spreading could also be observed. This was attributed to the cleaning efficacy of the air abrasive, which was found to yield a completely plaque-free surface. In contrast, the cell number/mm2 was significantly reduced on the implant treated with the plastic scaler (290 cells/mm^2) ($p < 0.001$). The viable cells showed limited spreading and were located between residual amorphous material and fungus-like structures, which were thought to be due to insufficient cleaning by the plastic curette. However, it should be kept in mind that in this study threaded implants with a machined surface were used. Therefore, these results cannot be directly extrapolated to the smooth surfaces of the healing abutments or transmucosal components.

Structured surfaces

Augthun et al. (1998) also examined the growth of fibroblasts on the TPS surface of a hollow-cylinder implant after using the same instruments. Similar results to the machined surfaces

were observed. The implant treated with the plastic curette showed significantly reduced number of vital cells compared to the implant treated with the air abrasive and the control implant (275 cells/mm^2, 550 cells/mm^2 and 580 cells/mm^2 respectively) ($p < 0.001$). Reduced cell spreading was observed on the implant treated with the plastic curette.

Kreisler et al. (2005) evaluated the biocompatibility of SLA surfaces contaminated with a suspension of *Porphyromonas gingivalis* after treatment with an air abrasive system with sodium bicarbonate powder (Kreisler et al. 2005). After treatment, human gingival fibroblasts were incubated on the specimens. The proliferation rate was determined by means of fluorescence activity of a redox indicator which is reduced by metabolic activity related to cellular growth. Proliferation was determined up to 72h. On air powder-treated specimens cell growth was not significantly different from that on sterile specimens.

Schwarz et al. (2009) evaluated the influence of different air-abrasive powders on cell viability at SLA surfaces contaminated with supragingival plaque. Sodium bicarbonate and amino acid glycine powders with different particle sizes were applied on the SLA surfaces. Specimens were incubated with osteoblast-like cells for 7 days and cell viability, expressed as mitochondrial cell activity (MA) (counts/s), was assessed. All treatments resulted in reduced cell viability compared to the non-contaminated and untreated control group ($p < 0.001$). However, sodium bicarbonate powder resulted in significantly higher viability than the amino acid glycine powders of different particle sizes ($p < 0.001$). The cell viability in the amino acid glycine group tended to increase with the particle size of the powder, but these differences did not reach statistical significance ($p > 0.05$). The authors concluded that the SAOS-2 cell viability at contaminated titanium surfaces was mainly influenced by the particle type of the powder and they suggested that a certain amount of surface ablation might improve cell viability at contaminated titanium implants. The reduced cell viability was attributed by the authors to changes in the chemical composition of the titanium surface and in the presence of powder particles on the instrumented surfaces.

Schwarz et al. (2005) evaluated the biocompatibility of titanium discs with SLA surfaces after treatment with an ultrasonic scaler(Vector™ system) with a polyether ethercetone fibre tip (PEEK) and a polishing fluid (HA particles<10 μm). The discs were contaminated with supragingival plaque and after treatment they were incubated with osteoblast-like cells for 3 days. Cell viability was measured by means of mitochondrial cell activity (MA) (counts/s). The discs treated with the ultrasonic scaler showed significantly reduced cell viability compared to the non-contaminated and untreated controls ($p < 0.001$). This reduced biocompatibility

was attributed to the residual plaque biofilm and to changes of the surface topography (damage) produced by the instrumentation.

John et al. (2014) evaluated the biocompatibility of contaminated SLA surfaces after treatment with a stainless-steel curette or a rotating titanium brush. The biocompatibility of the treated surfaces was evaluated by measuring the viability of SAOS-2 cells by the use of a luminescence assay after 3 and 6 days of incubation. Both treatments resulted in significantly reduced cell viability compared to the non-contaminated and untreated control groups. The cell viability in the stainless-steel curette group was higher than in the corresponding titanium brush group on both dates. However, the differences between these two groups were not statistically significant.

Quality assessment and GRADE

The methodological quality assessment of the various studies is presented in Table 3. Of the eleven included studies, seven were considered to have a high potential risk of bias, three were considered to have a moderate risk of bias and one was considered to have a low risk of bias. Eight studies used titanium discs, sheets or platelets, which are considered to be clinically less representative. Five studies provided data regarding randomisation of the treatment, but no study provided data regarding the allocation concealment. In three studies the examiner was blinded to the experimental conditions.

The following criteria were used to rate the quality of the body of evidence and the strength of the recommendations according to GRADE (Guyatt et al. 2008, GRADE working group): potential risk of bias, consistency, directness, precision of the estimate and publication bias. A formal testing for publication bias, as proposed by Egger et al. (1997), could not be used owing to insufficient statistical power because of the limited number of studies evaluating each instrument and the lack of sufficient quantitative data. Five studies reported data regarding the biocompatibility of titanium dental implant surfaces after treatment with an air-powder abrasive system with sodium bicarbonate powder on titanium dental implant surfaces. The available data were rather consistent, indirect and rather precise and had a moderate/high potential risk of bias. As a result, the strength of recommendation was considered to be weak. Three studies reported data regarding the use of stainless-steel curette. The available data were rather inconsistent, indirect and had a moderate to high potential risk of bias. The strength of recommendation is therefore weak. The data reporting on other mechanical instruments were limited, which made grading of the evidence not feasible.

Discussion

The present review focused on the biocompatibility of titanium dental implant surfaces after treatment with different mechanical instruments. This issue has been approached by *in vitro* experiments.

The reaction of cells and tissues to biomaterials depends on the material's properties, surface topography, elemental composition and its behaviour upon contact with the body fluids. It has been shown that osteoblast-like cells attach more readily to rough surfaces while epithelial cells and fibroblasts prefer smooth and finely textured surfaces (Bowers et al. 1992; Könönen et al. 1992). It has been observed that the surface microstructure can influence epithelial growth and attachment of fibroblasts (Chehroudi et al. 1989, 1990; Brunette & Chehroudi 1999). Therefore, alterations in surface topography may have a selective influence on the attachment of epithelial cells and fibroblasts, thus having an impact on the maintenance or re-establishment of the soft tissue seal around implants after treatment. Kuempel et al. (1995) and Dmytryk et al. (1990) showed that instrumentation of machined titanium surfaces with curettes of dissimilar composition has different impact on epithelial cells and fibroblasts. While instrumentation with stainless-steel curette did not seem to affect the epithelial cell growth, it seems to have an adverse effect on the growth of fibroblasts. Stainless-steel instrumented surfaces showed significantly fewer attached fibroblasts than untreated controlled surfaces (Dmytryk et al. 1990).

One important step in establishing cellular attachment is a chemical attachment between glycoproteins and the titanium oxide layer of the implant (Donley & Gilette 1991). Treatment modalities may sometimes adversely affect the surface topography and/or alter the chemical composition of a titanium surface which in turn may affect the ability of the surface to support cell attachment and spreading. This may be due to contamination of the surface by debris of the instrument deposited on the surface. This seems to be the explanation for the reduced cell numbers observed after treatment of titanium surfaces with a gold-coated curette (Kuempel et al. 1990) or non-metal instruments (Kuempel et al. 1990; Schwarz et al. 2003). The contact of two dissimilar metals could be the reason for the reduced attachment of fibroblasts on implant surfaces instrumented with steel instruments and titanium-alloy curettes compared to non-instrumented control surfaces (Dmytryk et al. 1990).

In clinical situations, the implant surfaces are contaminated with bacterial deposits. Reduced cell growth and cell viability have been observed after treatment of contaminated machined or structured (SLA or TPS) titanium surfaces with either a plastic curette or ultra-

sonic scalers with non-metal tips (Augthun et al. 1998; Schwarz et al. 2005). These results are corroborated to a certain extent by the findings from two other studies that evaluated the viability of osteoblast-like cells cultured on SLA and Osseotite surfaces after treatment with a plastic curette in combination with chlorhexidine gluconate (CHX) (Schwarz et al. 2005, 2006 respectively). In both studies reduced cell viability was observed after treatment with the plastic scaler and CHX compared to the untreated control ($p < 0.001$). Similar results were also reported in a study where an ultrasonic scaler with the same PEEK tip was used in combination with CHX for the treatment of Osseotite surfaces contaminated with plaque (Schwarz et al. 2006). The inability of plastic instruments to restore the biocompatibility of previous contaminated titanium surfaces seems to be due to deposition of debris of these instruments on the titanium surfaces but also to the inability of these instruments to effectively clean especially the structured titanium surfaces (Louropoulou et al. 2014). The alteration of the surface resulting from the cleansing procedure and the biofilm remaining after cleansing seems to be the reason for the reduced cell viability observed after treatment of SLA surfaces with a rotating titanium brush or a steel curette (John et al. 2014). Mouhyi et al. (1998) tested the surface composition of failed and retrieved machined titanium implants after various cleaning procedures. Although some of the tested methods resulted in a macroscopically clean surface, all of them failed to re-establish the original surface elemental composition.

The air-powder abrasive with sodium bicarbonate powder was the treatment modality mostly evaluated and appears to have the least influence on the biocompatibility of titanium surfaces after treatment. When different powders were used on contaminated SLA surfaces, the sodium bicarbonate powder resulted in higher cell viability than amino acid glycine powders of different sizes. This was attributed by the authors to a certain amount of surface ablation (Schwarz et al. 2009). It seems that the more abrasive sodium bicarbonate powder may clean structured SLA titanium surfaces more effectively than the less abrasive amino acid glycine powders, which in turn improves cell viability. Similar results were also observed in the study by Kreisler et al. (2005) that used the same sodium bicarbonate powder on SLA surfaces contaminated with a single bacterial species. However, the use of sodium bicarbonate powder on smooth (machined) titanium surfaces resulted in a significant decrease in the number of attached fibroblasts compared to the untreated control surfaces, although the morphology of the cells was not altered indicating that the adhesion of fibroblasts was not significantly affected (Shibli et al. 2003). This observation may be due to alterations of the surface morphology produced by the abrasive sodium bicarbonate powder (Louropoulou et

al. 2012) or to the presence of powder particles on the instrumented surfaces (Mouhyi et al. 1998). The less abrasive amino-acid glycine powders, which did not affect the surface morphology of smooth titanium surfaces, may affect the biocompatibility of smooth titanium surfaces differently.

Limitations

Reviewing the literature for studies evaluating the biocompatibility of titanium dental implant surfaces after instrumentation with different mechanical instruments in the absence or presence of contamination retrieved limited evidence. From the available ultrasonic and sonic scalers with metal and non-metal tips, only the Vector™ system has been tested. No studies were found testing rubber cups.

Regarding the cells used, fibroblasts were used in the majority of studies (6/10) followed by the osteoblast-like cells (4/10). The behaviour of epithelial cells, which constitute an important component of the peri-implant soft tissue seal, was evaluated in one study only. The use of fibroblast cell lines in the majority of the studies can be explained by the rapid proliferation of the cells (reducing the probability of contamination), the infinite life-span of cells, allowing many repetitions of experiments, and the fact that these cells are easier to grow and maintain. Although it can be assumed that fibroblasts can provide a valid indication as to how mechanical instruments affect the biocompatibility of different titanium surfaces, other cells may respond differently.

Only three studies (Schwarz et al. 2009; Shibli et al. 2003; Parham et al. 1989) provided information regarding the blinding of the examiner to the experimental conditions. The other eight studies either provided no information on this subject or the information was unclear. Although in this kind of *in vitro* studies it is not common to report on the blinding of the examiners, the authors of this review think that such information is provided.

Summary and Conclusions

Different animal studies indicate that although mechanical debridement of contaminated implant surfaces can result in resolution of the inflammatory lesion, it fails to achieve significant re-osseointegration along the previously contaminated implant surface (Claffey et al. 2008). This means that although the equilibrium between the peri-implant microbiota and the host defence can be re-established leading to an improvement in the clinical parameters,

the implant surfaces are not biocompatible enough to allow direct apposition of new bone and re-osseointegration. The reduced biocompatibility after treatment has been attributed to changes in the surface topography and chemical composition of the titanium surface produced by the instrumentation, but also to the residual biofilm.

In the present study an attempt was made to evaluate the available evidence on the influence of mechanical instruments on the biocompatibility of titanium implant surfaces in a controlled manner. Although the formulation of concrete conclusions is difficult because of the limited available data, it is carefully concluded that:

- Instrumentation may have a selective influence on the attachment of different cells.
- Plastic instruments fail to restore the biocompatibility of contaminated titanium surfaces because of deposition of debris from the instrument on the surface and limited cleansing efficacy, especially in the case of structured titanium surfaces.
- Treatment of contaminated SLA surfaces with either a metal curette or a rotating titanium brush fail to restore the biocompatibility of the surface.
- The air powder abrasive with sodium bicarbonate powder affects the fibroblast-titanium surface interaction after treatment of smooth or structured titanium surfaces the least, even in the presence of plaque contamination. Cell viability on SLA surfaces is influenced by the type of the powder particles used.

Implications for further research and practical implications

In this review an attempt was made to evaluate the available evidence on the biocompatibility of titanium implant surfaces after treatment with mechanical instruments. The formulation of concrete conclusions is difficult because of the limited available evidence. However, the cell responses and the mechanism of cellular adhesion on instrumented surfaces require further investigation. The understanding of the biological consequences of instrumentation for the attachment of peri-implant tissues constitute an important first step in understanding the clinical responses and the absence of significant re-osseointegration observed in both animal and human studies. Since the maintenance of the soft tissue seal is of major importance for the long term stability of implants, well-performed *in vitro* and eventually *in vivo* studies are needed to address the effects of instrumentation procedures on cell attachment in order to establish an evidence-based protocol for the use of mechanical instruments in the maintenance of implants and the treatment of peri-implantitis. Especially, epithelial cells deserve further attention as they constitute an important part of this connective tissue seal.

Acknowledgements

Declaration of interest

The authors declare that they have no conflict of interest.

The research was self-funded by the authors and their institution

Authors' contributions:

A. Louropoulou contributed to the conception, design, acquisition, analysis, interpretation of data, drafted the manuscript.

D.E. Slot contributed to the design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

G.A. van der Weijden contributed to the conception, design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

All authors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure 1. Databases search and literature selection

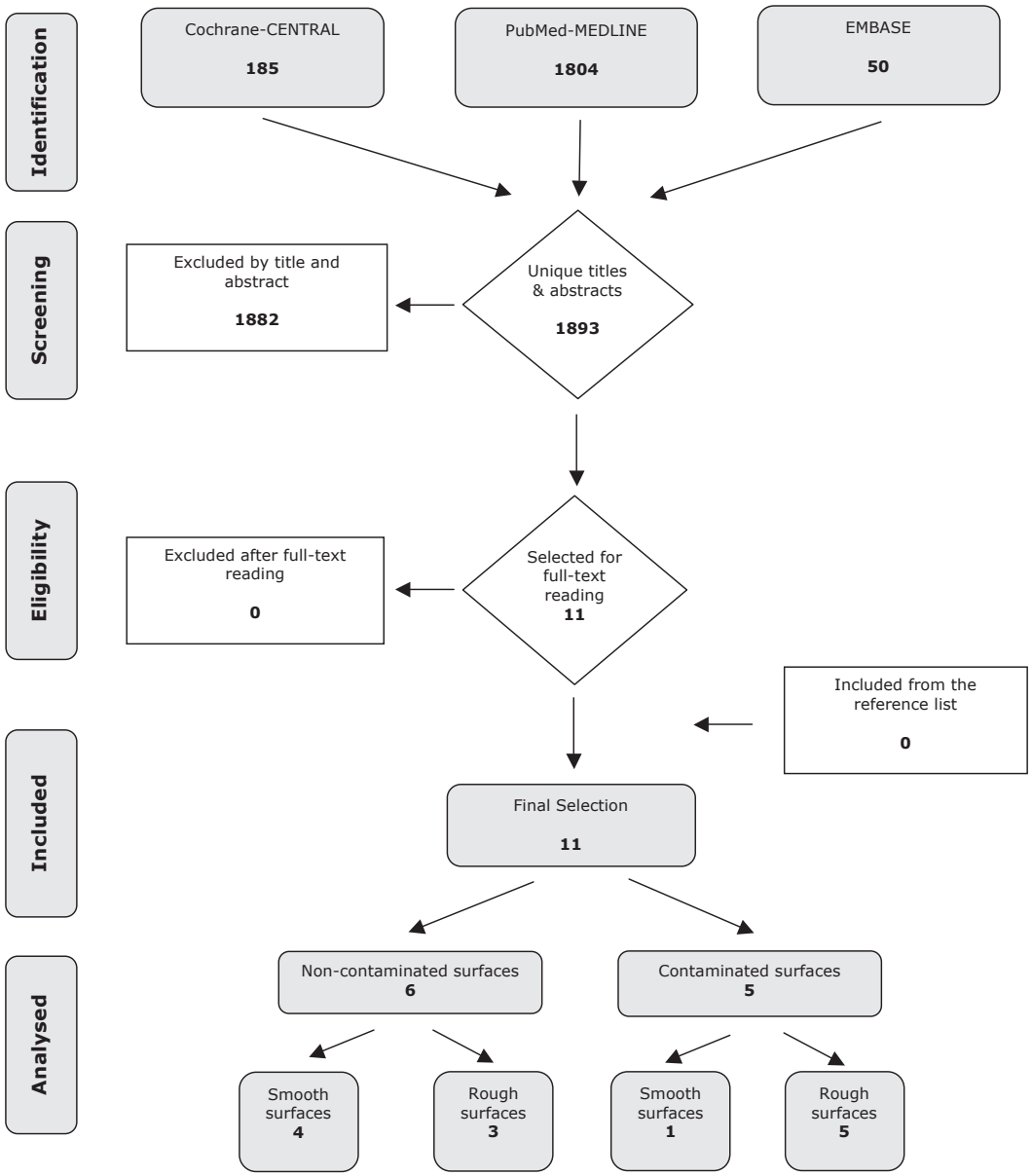

Table 1. Summary of studies evaluating the biocompatibility of *non-contaminated* titanium surfaces after instrumentation

Author (year)	Component/ Surface(s)	Treatment/Control (n= # of treated surfaces)	Cell culture/ Incubation period	Outcome parameter (assessment method)	Authors' conclusions
Schwarz et al. (2003)	Titanium discs Machined surface SLA surface TPS surface	- Ultrasonic system with straight carbon fibre tip and polishing fluid (n=16 per surface) - Untreated control (n=16 per surface)	Osteoblast-like cells 7 days	Counts of attached cells (cell density/ mm2) Cell morphology (SEM)	Statistically significant decrease in the number of cells that attached to the implant surfaces treated with the ultrasonic system compared to control. No difference in cell morphology between test and control.
Shibli et al. (2003)	Titanium abutments Machined surface	- Air powder abrasive with sodium bicarbonate powder (n=11) - Untreated control (n=11)	Fibroblasts (McCoy cell line) 24 hours	Counts of attached cells (number of cells on an area of approximately 200 um2) Cell morphology (SEM)	The use of an air-abrasive prophylaxis system on the surface of titanium healing abutments reduced the cells proliferation but did not influence cell morphology.
Rühling et al. (2001)	Flat titanium specimens TPS surface	- Instrumentation with diamond-coated files (n=5) - Untreated control (n=5)	Human gingival fibroblasts 2 days	Cell growth (SEM)	Cells were associated with one another and, compared to culture controls, demonstrated good adhesion with strict orientation to the microstructure of the scoring left by the instrumentation.

Author (year)	Component/ Surface(s)	Treatment/Control (n= # of treated surfaces)	Cell culture/ Incubation period	Outcome parameter (assessment method)	Authors' conclusions
Kuempel et al. (1995)	Titanium discs Machined surface	- Stainless-steel curette (n=10) - Gold-coated curette (n=10) - Plastic scaler (n=10) - Untreated control (n=10)	Rat gingival epithelial cells 5 days	Cell growth (surface of epithelial cell coverage in mm2) Cell morphology (SEM)	Epithelial surface area coverage on stainless-steel, plastic and control groups did not vary significantly among groups. The gold-coated curette exposed surfaces supported significantly less epithelial growth than the stainless steel and control surfaces.
Dmytryk et al. (1990)	Implant neck Machined surface	- Stainless-steel curette (n=10) - Titanium-alloy curette (n=10) - Plastic curette (n=10) - Untreated control (n=10)	Mouse fibroblasts 24 and 72 hours	Counts of attached cells (mean number of attached cells) Cell morphology (SEM)	At 72 hours, stainless steel and titanium-alloy curette instrumented surfaces showed significantly fewer attached cells than untreated control surfaces. Fibroblasts on stainless steel instrumented surfaces tended to show somewhat rounded cell morphology and a relatively reduced degree of spreading
Parham et al. (1989)	Implant specimens TPS surface	- Air powder abrasive with sodium bicarbonate powder (n=6) - Untreated control (n=6)	Human gingiva fibroblasts 48 hours	Counts of attached cells (SEM)	Similar numbers of attached cells in control and test. In both groups specimens were uniformly covered by fibroblasts.

TPS, titanium plasma-sprayed; SLA, sand-blasted and acid-etched; SEM, scanning-electron microscope

Table 2. Summary of studies evaluating the biocompatibility of contaminated titanium surfaces after being mechanically cleaned

Author (year)	Component/ Surface(s)/ Contamination	Treatment/control (n= # of treated surfaces)	Cell culture/ Incubation period	Outcome parameter (assessment method)	Authors' conclusions
John et al. (2014)	Titanium discs SLA surface Contaminated with supragingival plaque by placement of splints in volunteers	- Rotating titanium brush (n=10) - Stainless-steel curette (n=10) - Non-contaminated and untreated control (n=10)	Osteoblast-like cells 6 days	Cell viability (luminescence assay)	In all treatment groups cell viability was significantly lower compared to the control group. Higher cell viability in the steel curette group than in the titanium brush group.
Schwarz et al. (2009)	Titanium discs SLA surface Contaminated with supragingival plaque by placement of splints in volunteers	- Air powder abrasive with amino acid glycine or sodium bicarbonate powder (n=128) - Non contaminated and untreated control (n=8)	Osteoblast-like cells 7 days	Cell viability (mitochondrial cell activity)	In all treatment groups cell viability was significantly lower compared to the control group. Higher cell viability in the sodium bicarbonate group.
Schwarz et al. (2005)	Titanium discs SLA surface Contaminated with supragingival plaque by placement of splints in volunteers	- Ultrasonic scaler with PEEK tip and polishing fluid (n=20) - Non contaminated and untreated control (n=20)	Osteoblast-like cells 3 days	Cell viability (mitochondrial cell activity)	Treatment with the ultrasonic scaler resulted in significantly lower cell viability compared to control.

Author (year)	Component/ Surface(s)/ Contamination	Treatment/control (n= # of treated surfaces)	Cell culture/ Incubation period	Outcome parameter (assessment method)	Authors' conclusions
Kreisler et al. (2005)	Titanium platelets SLA surface Contaminated with *Porphyromonas gingivalis*	- Air powder abrasive with sodium bicarbonate powder (n=12) - Non contaminated and untreated control (n=12) - Contaminated and untreated control (n=12)	Human gingival fibroblasts 72 hours	Cell proliferation (fluorescence activity of a redox indicator)	Cell growth on the air powder treated specimens was not significantly different from that on non-contaminated and untreated specimens.
Augthun et al. (1998)	Implants TPS surfaces Machined surface Contaminated with supragingival plaque collected by placement of stents in volunteers	- Plastic scaler (n=2) - Air powder abrasive with sodium bicarbonate powder (n=2) - Non contaminated control (n=2)	Mouse fibroblasts 24 hours	Cell vitality (vital staining)	The percentage of vital cells on implants treated with the air abrasive system was nearly the same as on the control implants. Significantly less vital cell were observed on implant surfaces treated with the plastic scaler.

TPS, titanium plasma-sprayed; SLA, sand-blasted and acid-etched; PEEK, polyether etherketone fibre

Table 3. Methodological quality and risk of bias scores of the selected studies

Quality criteria		External validity			Internal validity					Statistical validity				Author's estimated risk of bias
	Author (year)	Representative surface *	Validation of the evaluation method	Reproducibility data provided	Sequence generation (randomization)	Concealment allocation	Blinded to examiner*	Blinding during statistical analysis	Preparation, manipulation and treatment of the surface identical, except for the intervention *	Adequate sample size[1]	Point estimates presented for primary outcome measurements*	Measures of variability presented for the primary outcome	Statistical analysis*	
Biocompatibility **Non-contaminated surfaces**	Schwarz et al. (2003)	-	?	?	+	?	+	?	+	+	-	-	+	**High**
	Shibli et al. (2003)	+	+	?	+	?	+	?	+	+	+	+	+	**Low**
	Rühling et al. (2001)	-	?	NA	?	?	?	?	+	-	NA	NA	NA	**High**
	Kuempel et al. (1995)	-	?	?	?	?	?	?	+	+	+	+	+	**High**
	Dmytryk et al. (1990)	+	?	?	?	?	?	?	+	+	+	+	+	**Moderate**
	Parham et al. (1989)	-	?	?	?	?	+	?	+	+	+	-	+	**Moderate**

Quality criteria		External validity			Internal validity					Statistical validity				Author's estimated risk of bias
	Author (year)	Representative surface *	Validation of the evaluation method	Reproducibility data provided	Sequence generation (randomization)	Concealment allocation	Blinded to examiner*	Blinding during statistical analysis	Preparation, manipulation and treatment of the surface identical, except for the intervention *	Adequate sample size[1]	Point estimates presented for primary outcome measurements*	Measures of variability presented for the primary outcome	Statistical analysis*	
Biocompatibility **Contaminated surfaces**	John et al. (2014)	-	?	?	+	?	?	?	+	+	+	+	+	**High**
	Schwarz et al. (2009)	-	?	?	+	?	?	?	+	+	-	-	+	**High**
	Schwarz et al. (2005)	-	?	?	+	?	?	?	+	+	+	+	+	**High**
	Kreisler et al. (2005)	-	?	?	?	?	?	?	+	+	-	-	+	**High**
	Augthun et al. (1998)	+	?	?	?	?	?	?	+	-	+	-	+	**Moderate**

+: yes, -: no, ?: not specified/unclear

*: Items used to estimate potential risk of bias

NA: not applicable, visual assessment without scoring of the outcome

[1] The authors of the review calculated whether the sample size was adequate by using the Meads's resource equation (see Louropoulou et al. 2014)

Chapter 5

Influence of various air-abrasive powders on the viability and density of periodontal cells: an *in vitro* study

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This study is submitted

Introduction

Air-abrasive treatment uses an abrasive powder brought into a stream of compressed air to clean and polish all kinds of surfaces by removing deposits or smoothing its texture (Moëne et al. 2010). The air-abrasive devices are commonly used during nonsurgical treatment for supra- and subgingival biofilm removal from teeth and implants (Petersilka et al. 2003). These devices have also been used with promising results during periodontal flap surgery as well as during the surgical treatment of peri-implantitis (Horning et a. 1987; Toma et al. 2014).
The air-abrasive devices can be used with different powders. Since the 1980's, sodium bicarbonate has been used and has been proven to be safe and efficient for removing supragingival plaque and stains from intact enamel surfaces (Petersilka 2011). However, sodium bicarbonate can be extremely abrasive to root cementum and dentin and may induce changes on implant surfaces (Petersilka et a. 2003; Louropoulou et al. 2012).

To facilitate the removal of biofilm from dental root and implant surfaces whilst minimizing trauma to hard and soft tissues, a less abrasive amino acid glycine powder was introduced (Petersilka et al. 2003). This powder has been shown to induce minimum tooth and implant surface alterations while still removing biofilm efficiently *in vitro* and *in vivo* (Louropoulou et al. 2012, 2014). Since the introduction of glycine powders other types of presumably low-abrasive powders began to appear in the market, like powders based on aluminum trioxide or calcium carbonate (Petersilka, 2011). More recently an erythritol-containing powder with chlorhexidine gluconate as preservative (CHX) (0.3%) has also been introduced for use with air-polishing devices (Hägi et al. 2013).

Scarce and small powder remnants have been detected on surfaces after powder treatment *in vitro* (Schwarz et al. 2009; Tastepe et al. 2013; John et al. 2016). Also, in clinical situations remnants of the powder are expected in peri-implant and periodontal pockets or in the tissues surrounding teeth and implants during surgery. It has been speculated that these fragments have an effect on the biocompatibility of the treated surfaces and may affect biologic responses during healing (Schwarz et al. 2009; Tastepe et al. 2013; John et al. 2016).
The aim of the present *in vitro* study was to investigate the possible effect of five commercially available air-abrasive powders, on the viability and density of three types of cells: epithelial cells (EC), gingival fibroblasts (GF) and periodontal ligament fibroblasts (PDLF).

Materials and Methods

Powders and solutions

In the present study, five commercially available powders, developed for use with a dental air-abrasive system, were evaluated. Table 1 provides an overview of the study products and details regarding main ingredients and particle size. A sodium bicarbonate powder (SBP), two amino acid glycine powders with the same particle size from two different manufacturers (AGP-1 and AGP-2), an amino acid glycine and tricalcium phosphate powder (TCP) and an erythritol powder, in which chlorhexidine gluconate was added as preservative, (ECP) were used.

Suspensions of these powders in three different concentrations were prepared in culture medium: the maximum soluble concentration, the maximum diluted 10-times (1:10) and 100-times (1:100). Details regarding the maximum soluble concentration and pH of this suspension for the different powders can be found in Table 1. The criterion used to define the maximum soluble concentration was the highest degree of powder solubility, beginning from the 3gr/60ml, which is the ratio of powder/water emitted from the nozzle of the air-powder device, as given by the manufacturer.

Cell types

Three cell types were used: epithelial cells from a human buccal epithelial cell line (epithelial cell line -Tr146), human gingival fibroblasts (primary gingival cells- Gin) and human periodontal ligament fibroblasts (primary periodontal ligament cells-PDL).

The two types of fibroblasts were derived from one donor and harvested from an extracted third molar. Informed consent was obtained from the donor. The cells were taken from a site without signs of inflammation and periodontal attachment loss (probing pocket depth ≤3 mm, no bleeding on probing and no loss of attachment). The cell propagation was performed as described by de Vries et al. (2006).

Time point

A pilot study was conducted to evaluate the effect of SBP and AGP-1 powders on the viability and cell density of epithelial cells and gingival fibroblasts, when the cells were cultured in the presence of the powders' suspensions. Three different time points were tested: two hours, six hours and three days. No effect was observed for any of the powders after two hours, whereas some effect on both cell viability and cell density, as compared to the control,

was observed after six hours and three days of incubation. Based on the results of the pilot study, in the present study the effect of the different powders after six hours of incubation was investigated.

Culturing

Cells were cultured in culture medium in 96 well plates with 15.000 cells/well. The culture medium used was DMEM (Thermo Fisher Scientific, Walthan, MA) supplemented with 10% fetal clone serum (HyClone I, Thermo Fisher Scientific) and 1% penicillin-streptomycin (Sigma-Aldrich, St. Louis, MO). After overnight culturing the medium was replaced with the media with or without the different powders and incubated for six hours. The medium without powder served as a control. Four replicates were plated per condition.

Cell Viability

The viability was assessed by measuring the mitochondrial activity using an Alamar blue assay (Life Technologies, Carlsbad, CA), according to the manufacture's protocol.

Cell density

After measuring the viability the medium was removed, cells were washed once with PBS and subsequently lysed by adding 100 ul of Cyquant Lysis buffer per well. The amount of DNA, as a measure for cell density was measured using the Cyquant cell proliferation kit (Life Technologies, Carlsbad, CA), according to the manufacture's protocol. More specifically, the above technique is based on a sensitive nucleic acid stain-based assay for determining numbers of cells in culture, since the cellular nucleic acid content is considered a reasonable indicator of cell number (Jones et al. 2001).

Statistical analysis

A software package (SPSS for Windows, 21.0, SPSS Inc., Chicago, MA, USA) was used for the statistical analysis. The experimental groups were considered to be independent. Mean values and standard deviations were calculated for each group. One Way Analysis of Variance (1-Way ANOVA) was applied with Bonferroni's correction for detecting the significance among the multiple comparisons within and between groups. Results were considered statistically significant at $p < 0.05$.

Results

In the present study, the effect of five commercially available air-abrasive powders on cell density and viability of epithelial cells (EC), periodontal ligament fibroblasts (PDLF) and gingival fibroblasts (GF) was assessed. Three different suspensions of the powders were prepared. The results for the maximum soluble concentration of the powders are presented in Figures 1-2. Data for the two other dilutions are provided in Figures 3-6.

Sodium bicarbonate powder (SB)

In the maximun concentration, sodium bicarbonate powder resulted in an significant decrease in both cell density and cell viability of all types of cells (Figure 1,2). There was at least a 5-time reduction in the number of cells compared with the control (Figure 1). The viability remained reduced in the other two dilutions (Figure 4, 6). Only in the case of gingival fibroblasts and in the highest dilution of the powder (100-time), differences with the control could no longer be observed (Figure 6). Regarding cell density, the reduction in numbers was less pronounced with the powder 10-time diluted, while no difference compared with control was observed, when the powder was diluted 100-times.

Amino acid glycine powders (AGP-1, AGP-2)

The amino acid glycine powders had different effects on the cells. The AGP-1 powder in the maximum soluble concentration resulted in a statistically significant reduction in the number of all cells (Figure 1) When diluted 10-times, reduced numbers of epithelial cells and PDL fibroblasts were noted. When 100-time diluted, the cell density for all cells was comparable with the control (Figure 3, 5).

The AGP-2 powder at the maximum soluble concentration caused a significant reduction only in the number of PDLF fibroblasts (Figure 1). Further, no effect on the cell density was observed (Figure 1, 3, 5).

Regarding viability, epithelial cells and fibroblasts exhibited different responses. More specifically, both glycine-based powders resulted in a significant reduction in the viability of epithelial cells, irrespective of the concentration of the powder. A reduction in the viability of PDL fibroblasts was noted with the AGP-1 powder, when diluted. Both glycine-based powders had no effect on the viability of gingival fibroblasts, regardless the concentration of the powder (Figure 2, 4, 6).

Amino acid glycine with tricalcium phosphate powder (TCP)

The density of gingival and PDL fibroblasts was not affected, when the amino acid glycine powder with tricalcium phosphate was used. Interestingly enough, and for all concentrations tested, increased numbers of epithelial cells compared with the control were observed (Figure 1, 3, 5). However, the viability of the epithelial cells was significantly reduced, in the maximum soluble concentration and 10-time dilution. No significant effect on the viability of both types of fibroblasts could be observed (Figure 2, 4, 6).

Erythritol powder (ECP)

In the maximum soluble concentration, a significant reduction in both cell number and viability was observed, for all cell types. The viability of epithelial cells and PDL fibroblasts was reduced also when the powder was diluted (Figure 2, 4).

Effect on epithelial cells

All powders and in all concentrations reduced the viability of epithelial cells (Figure 2, 4, 6). The only exception was the TCP powder 100-time diluted. Interestingly enough, increased numbers of epithelial cells were observed. AGP-2 powder had no significant effect in the cell density. Compared to the other two glycine-containing powders (AGP-2, TCP), AGP-1 had a more pronounced effect on the counts of epithelial cells. SB, AGP-1 and EC reduced the numbers of epithelial cells, especially in the highest concentration (Figure 1, 3, 5).

Effect on gingival fibroblasts

The glycine-based powders (AGP-1, AGP-2, TCP) did not have any effect on the viability of gingival fibroblasts, irrespective of the concentration of the powder. The AGP-2 and TCP powders also had no significant effect on the cell density. A decrease in the number of cells was noted with the maximum concentration of the AGP-1 powder. The other two powders (sodium bicarbonate and erythritol) caused a decrease in the numbers and viability of gingival fibroblasts, when used in the highest concentration. This effect could no longer be observed in the other, lower concentrations.

Effect on PDL fibroblasts

Reduction in the viability was observed when the sodium bicarbonate and erythritol powders were used, independent of the concentration. When the glycine-based powders were used, no effect on the viability was observed with the TCP and AGP-2 powders. Reduced viability was noted with the AGP-1 powder diluted. The TCP powder had no effect on the number of fibroblasts. The other powders in the maximum concentration caused a reduction in the number of these cells.

Discussion

The use of air-abrasive devices can lead to residual powder fragments on the treated surfaces and in the surrounding tissues. It has been speculated, especially in the case of implants, that these powder remnants may account, at some level, for changes in the biocompatibility of the implant surfaces and may, therefore, affect the biologic responses. In the present study we investigated the possible influence of five commercially available air-abrasive powders on periodontal tissue cells. Due to their important role in wound healing both epithelial cells and fibroblasts were included. What the concentration is of the powder remaining in the tissues or on the treated surfaces is not known. That is why we used three different suspensions of the powders. The results of the present study indicate that the effect of the different kinds of powders on the various cell types may differ considerably depending on the cell type and the type and concentration of the powder used.

The present study indicates that sodium bicarbonate powder decreases the viability and the number of human gingival fibroblasts. These findings are in accordance with the findings of Shibly and colleagues (2003). In their study it was shown that fibroblasts' counts were reduced after treatment of machined titanium surfaces with a sodium bicarbonate powder. In the present study a significant reduction in the number of gingival fibroblasts was also observed when one of the two tested amino acid glycine based powders (AGP-1) was used. No effect was observed when the AGP-2 powder was used. The AGP-1 and the AGP-2 are both amino acid glycine based powders with a slight difference in their composition (3-4% approximately, according to the information provided by the manufacturers). This small difference in composition, for which the manufacturers provided no details, could be an explanation for the difference observed on the gingival fibroblasts.

It has been shown that cells residing within the periodontal ligament have phenotypic

characteristic of osteoblast-like cells, exhibiting potential osteoblastic activity (Basdra et al. 1997). We observed that sodium bicarbonate powder causes a significant reduction in both cell density and viability of these cells. Also, one of the amino acid glycine powders (AGP-1) reduced the viability of these cells. This is in accordance with the findings of Schwarz and colleagues (2009). These authors assessed the effect of different air-abrasive powders on the viability of osteoblast-like cells (SAOS2) at biologically contaminated titanium implant surfaces. The powders used were a sodium bicarbonate powder and amino acid glycine powders with different particle sizes. One of the glycine powders that they tested was the AGP-1 powder that we used in our study. They observed a reduction in the viability on the SAOS2 cells, which was more pronounced in the case of the amino acid glycine powders. However, another study that assessed the viability of SAOS2 cells after treatment of titanium discs with the same (AGP-1) glycine powder reported similar or increased cell viability compared with the controls after three and six days of incubation respectively (Toma et al. 2016).

To the best of our knowledge, this is the only *in vitro* study that investigated the possible effect of different air-abrasive powders on epithelial cells. These cells are an important component of the soft tissue seal and are the first cells that come in contact with the powders during non-surgical treatment. According to the results of this study all powders reduce the viability of epithelial cells. The most pronounced reduction was observed with the sodium bicarbonate and erythritol powders especially when respectable amounts of the powder come in contact with the epithelial cells.

Sodium bicarbonate and amino acid glycine powders are commonly used. However, new powders are being developed based on different ingredients such as erythritol or tricalcium phosphate, which are considered to be less abrasive. The erythritol-containing powder in its commercially available form is combined with chlorhexidine gluconate as preservative (CHX) (0.3%). This was the powder used in our study (ECP). An *in vitro* study evaluating the above combination of erythritol and CHX showed that this combination seems to be a viable alternative to glycine treatment for biofilm removal since it constitutes a combination of an antimicrobial substance (CHX) with an antibiofilm substance (erythritol) (Drago et al. 2014). In the present study we investigated the effect of this powder on three different types of cells. In the maximum soluble concentration a reduced density and viability was observed for all types of cells. To which of the compounds of the powder these results could be attributed is not clear. Erythritol is a four-carbon sugar alcohol and can be found naturally in many organisms, which indicates that it is a byproduct of metabolism of sugar. However, a possible

contribution to the abovementioned negative effect cannot be excluded. Chlorhexidine gluconate is a cationic polybiguanide (bisbiguanide) and it is primarily used as its salts (e.g., the dihydrochloride, diacetate and digluconate) with antiseptic and bacteriostatic properties. There are a number of studies that examined the possible effect of chlorhexidine gluconate (CHX) on various types of cells. Different studies have shown that direct exposure of cells to CHX resulted in inhibition of growth even when CHX was used at very low concentrations (0.0025 to 0.01%) (Helgeland et al. 1971; Cline et al. 1992; Lessa et al. 2010).

Another novel powder that was tested in the present study was TCP, a combination of amino acid glycine and tricalcium phosphate. A rational for using this type of powder is the less abrasive nature of the powder and its possible osteoconductive properties. More specifically, tricalcium phosphate is considered to have excellent biological properties (osteoconduction, osteoinduction), adequate setting time, excellent moldability for surgical applications and the capability to deliver different bone-enhancing proteins (Ambard & Mueninghoff 2006). A recently published study concluded that decontamination with glycine and tricalcium phosphate powder seems to be more efficient than treatment with glycine or sodium bicarbonate alone (John et al. 2016). At the cellular level it has been shown that tricalcium phosphate enhances the cellular performance of osteoblast-like cells, leading to the reconstruction of hard tissues (Oh et al. 2010; Wu et al. 2014). We observed that this powder did not have any effect on the cell density. Interestingly enough, increased numbers of epithelial cells and to a certain extent of PDL fibroblasts were noted. Also no adverse effect in the viability of both gingival and PDL fibroblasts were noted. It has been suggested that if remnants of this powder remain on the surface or in the tissues after treatment this may have a beneficial effect on tissue responses (Tastepe et al. 2013; John et al. 2016). The results of the present study are in support of this supposition.

An important limitation of this study is that only fibroblasts from one donor have been used. Therefore, the results regarding the fibroblasts should be interpreted with caution. This is not the case for epithelial cells, as for these cells an epithelial cell line was used.

In conclusion, different effects were observed on different types of cells. All powders caused a reduction in the viability of the epithelial cells. The most pronounced effect was observed with the sodium bicarbonate and erythritol-containing powders and for the highest concentration. When the glycine powder with tricalcium phosphate was tested with fibroblasts, no adverse effect on both the viability and cell density was observed. Within the limitation of this study, it seems that while some of the powders may adversely affect the

counts and viability of periodontal cells some other powders may have a beneficial effect on the cells. It can thus be speculated that in clinical situations a careful selection of the powder should be done by the clinician, depending on the area that the powder is going to be used, i.e. supragingivally, subgingivally or during flap procedures. The clinical significance of this finding in terms of tissue healing should be the subject of further investigation.

Acknowledgements

Declaration of interest

The authors declare that they have no conflict of interest.

The research was self-funded by the authors and their institution

Authors' contributions:

E. Sygkounas contributed to the design, acquisition, analysis, interpretation of data, drafted the manuscript.

A. Louropoulou contributed to the conception, design, acquisition, analysis, interpretation of data, drafted the manuscript.

T. Schoenmaker contributed to the design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

T.J. de Vries contributed to the design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

G.A. van der Weijden contributed to the conception, design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

All authors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Toma S, Lasserre J, Brecx MC, Nyssen-Behets C. (2016) In vitro evaluation of peri-implantitis treatment modalities on SAOS-2 osteoblasts. *Clinical Oral Implants Research* **27**: 1085-1092.

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Table 1. Powder characteristics and properties of the suspension with the maximum soluble powder concentration

Powder	Abbreviation	Main ingredient(s)	Mean particle size (μm)	Manufacturer	Concentration (mg/ml) ¶	pH*
Air Flow® Classic	SBP	Sodium bicarbonate	65 μm	EMS, Nyon, Switzerland	17	8.3
Air Flow® Perio	AGP-1	Amino acid glycine	25 μm	EMS, Nyon, Switzerland	50	7.8
AIR-N-GO® Perio	AGP-2	Amino acid glycine	25 μm	SATELEC SAS, ACTEON group, Bordeaux, France	50	7.7
Air Flow® Plus	ECP	Erythritol Chlorhexidine gluconate (0.3%)	14 μm	EMS, Nyon, Switzerland	50	8.5
Clinpro® Prophy Powder	TCP	Amino acid glycine Tricalcium phosphate	25 μm 45 μm	3M ESPE, Bracknell, Berkshire, United Kingdom	5	7.8

¶ maximum soluble powder concentration

* pH of the suspension with the maximum soluble powder concentration

Figure 1. Effect of air-abrasive powders on cell density (maximum soluble concentration)

DNA (ng/ml) was measured after six hours of incubation with the maximum soluble concentration of the air-abrasive powders. Averages +/- SE are shown. The * indicates statistical significance when compared to control ($p < 0.05$). The ⌐ indicates statistical significance when the three glycine-containing powders were compared to each other ($p < 0.05$)

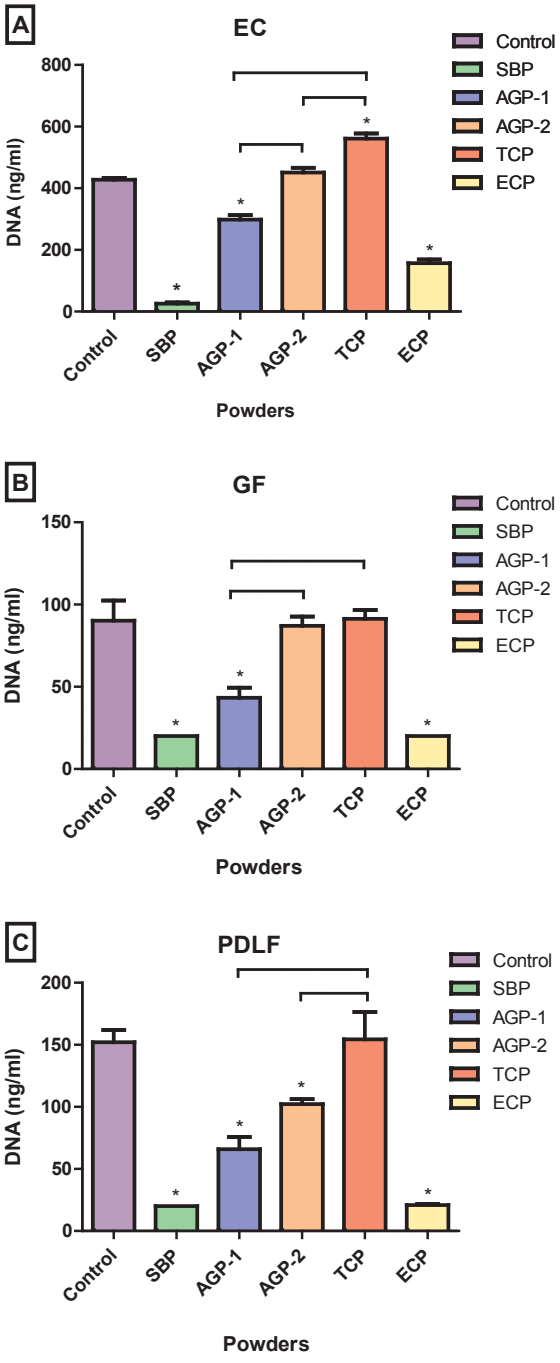


Figure 2. Effect of air-abrasive powders on cell viability (maximum soluble concentration)

Viability (in arbitrary units) was measured after six hours of incubation with the maximum soluble concentration of the air-abrasive powders. Means +/- SE are shown. The * indicates statistical significance when compared to control ($p < 0.05$). The ⌐ indicates statistical significance when the three glycine-containing powders were compared to each other ($p < 0.05$)

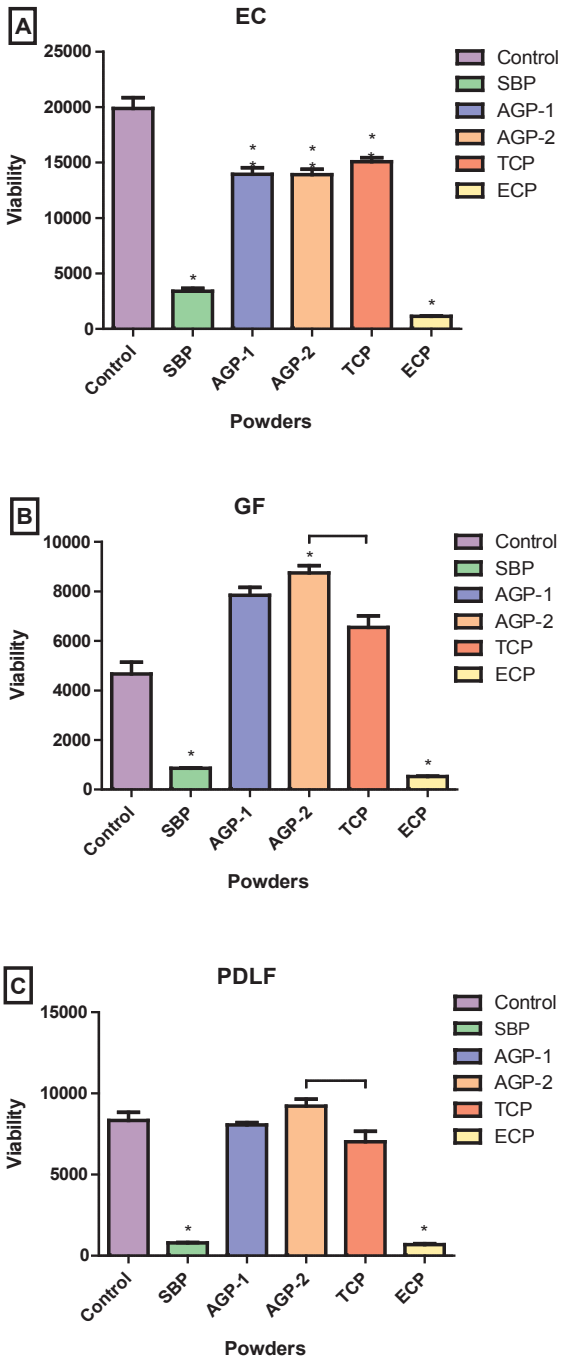


Figure 3. Effect of air-abrasive powders on cell density (10-times dilusion)

DNA (ng/ml) was measured after six hours of incubation with the maximum soluble concentration of the air-abrasive powders diluted 10 times (1:10). Averages +/- SE are shown. The * indicates statistical significance when compared to control ($p < 0.05$). The ⌐¬ indicates statistical significance when the three glycine-containing powders were compared to each other ($p < 0.05$).

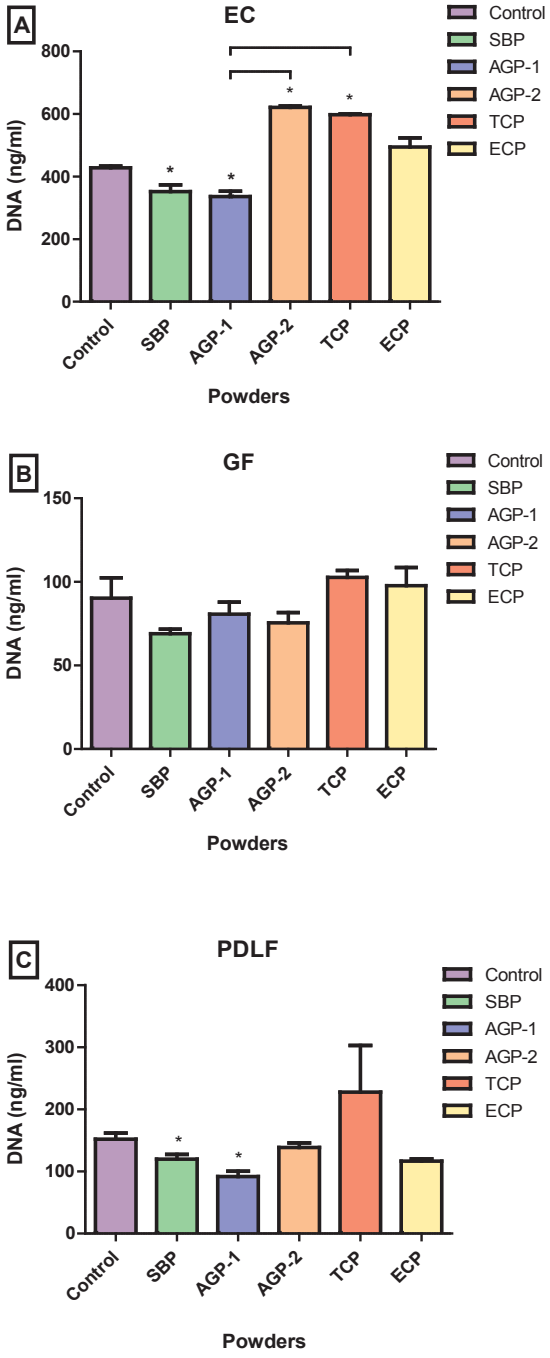


Figure 4. Effect of air-abrasive powders on cell viability (10-times dilusion)

Viability (in arbitrary units) was measured after six hours of incubation with the maximum soluble concentration of the air-abrasive powders diluted 10 times (1:10). Means +/- SE are shown. The * indicates statistical significance when compared to control ($p < 0.05$). The ⌐ indicates statistical significance when the three glycine-containing powders were compared to each other ($p < 0.05$).

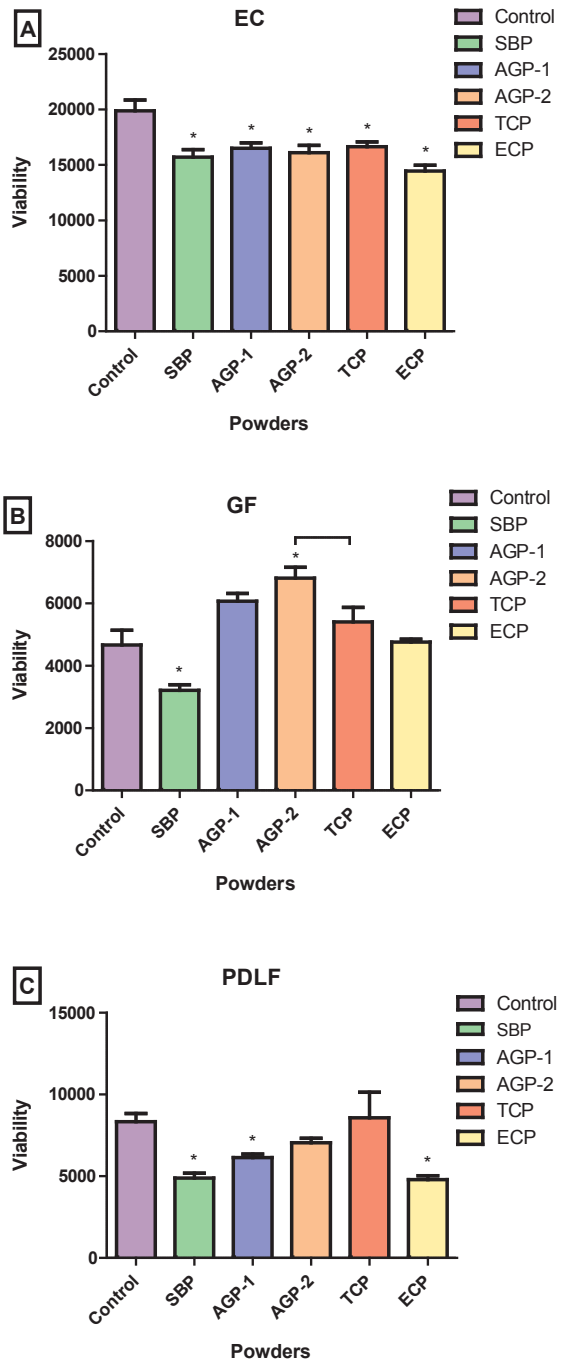


Figure 5. Effect of air-abrasive powders on cell density (100-times dilusion)

DNA (ng/ml) was measured after six hours of incubation with the maximum soluble concentration of the air-abrasive powders diluted 100 times (1:100). Averages +/- SE are shown. The * indicates statistical significance when compared to control ($p < 0.05$). The ⌐ indicates statistical significance when the three glycine-containing powders were compared to each other ($p < 0.05$).

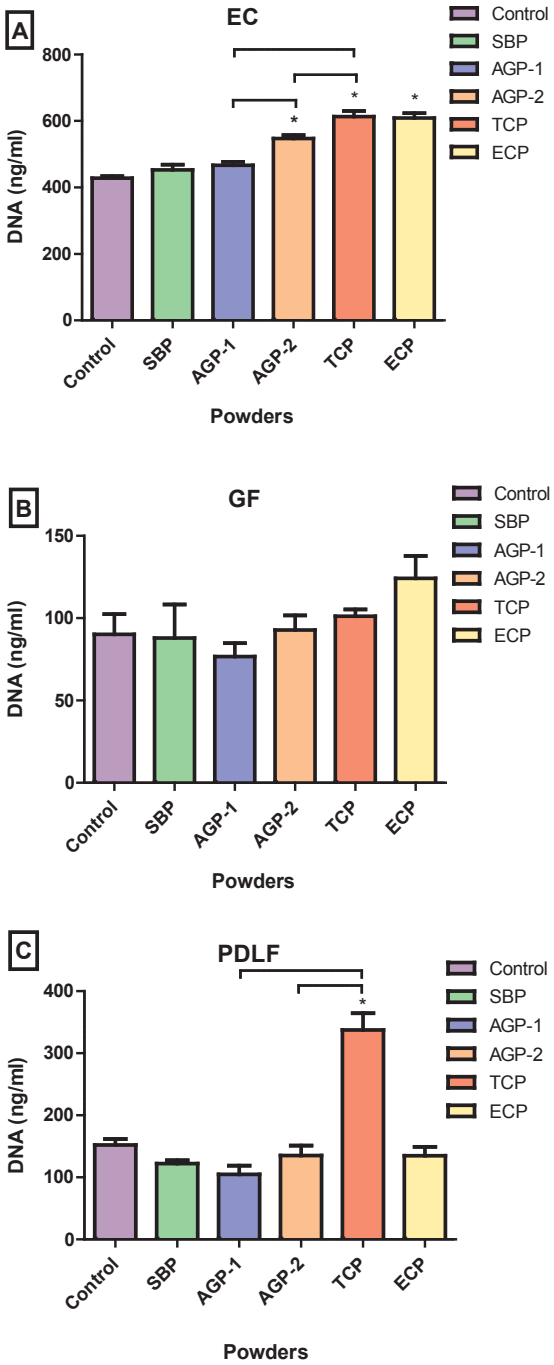
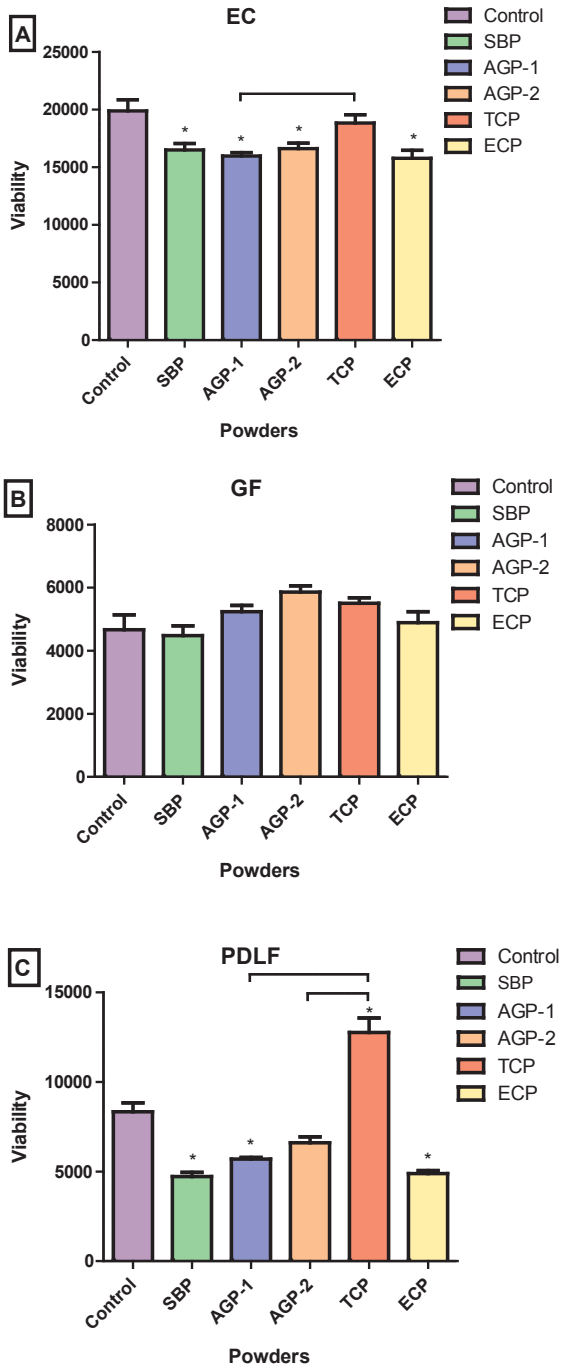


Figure 6. Effect of air-abrasive powders on cell viability (100-times dilusion)

Viability (in arbitrary units) was measured after six hours of incubation with the maximum soluble concentration of the air-abrasive powders diluted 100 times (1:100). Means +/- SE are shown. The * indicates statistical significance when compared to control ($p < 0.05$). The ⌐ indicates statistical significance when the three glycine-containing powders were compared to each other ($p < 0.05$).



Chapter 6

The effect of chemotherapeutic agents on contaminated titanium surfaces: a systematic review

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G.A. van der Weijden

Clinical Oral Implants Research 2011; 22: 681-690.

Introduction

Oral implantology is a dynamic field of modern dentistry. Dental implants have various indications and present high survival and success rates. Lambert et al. (2009) reported overall implant survival rates ranging from 94% (1 year) to 87.7% (15 years). Certain characteristics of the implant surface play a determining role in the longevity of the implants, with rough surfaces demonstrating higher success and survival rates than smooth surfaces (Lambert et al. 2009). It has been shown that surfaces with a roughness of approximately 1.5 mm, which corresponds to moderately rough implant surfaces, have the strongest biomechanical bond with alveolar bone (Albrektsson & Wennerberg 2004).

On the other hand, rough surfaces may promote bacterial colonization and biofilm formation. Bacterial accumulation induces inflammatory changes in the soft tissues surrounding oral implants (peri-implant mucositis), which may lead to progressive destruction of the supporting bone (peri-implantitis), and ultimately, to implant failure (Esposito et al. 2006). Peri-implant mucositis, a reversible inflammation of the soft tissues surrounding a functional implant (Albrektsson & Isidor 1994), occurs in approximately 50% of all implants (Zitzmann & Berglundh 2008). Peri-implantitis is an inflammatory reaction associated with bone loss around a functional implant (Albrektsson & Isidor 1994) and affects from 12% (Fransson et al. 2005) to 43% (Roos-Jansåker et al. 2006) of peri-implant tissues. Astrand et al. (2004) reported a higher frequency of peri-implantitis for implants with a rougher surface. To avoid a bacterial shift towards more pathogenic flora, the use of a relatively smooth abutment and implant surface has been suggested (Quirynen et al. 2002).

There is insufficient evidence concerning the most effective intervention for the treatment of peri-implant diseases (Esposito et al. 2008) despite several attempts to determine the optimal treatment protocol for the complete resolution of peri-implantitis (Claffey et al. 2008). Renvert et al. (2009) reviewed the literature for evidence of any re-osseointegration of previously contaminated implant surfaces. The authors concluded that no method could predictably accomplish the complete resolution of the peri-implant defect. Although there is evidence that some treatments can be effective against peri-implantitis, the most effective intervention methods are presently unknown. Furthermore, among the interventions with similar degrees of effectiveness, the available research does not identify the treatments with fewer side effects, or those that are simpler and cheaper to use (Esposito et al. 2008).

The removal of bacterial deposits and the reduction of micro-organisms to a level compatible with health is the first step in the treatment of peri-implant diseases (Lindhe & Meyle

2008). Because the available evidence for combination treatments is inconclusive (Claffey et al. 2008; Esposito et al. 2008), it is wise to examine the effectiveness of single treatments. Mechanical treatment alone is incapable of removing bacterial biofilms due to the screw-shaped design and surface roughness of dental implants. Furthermore, the suprastructure of the implant often hinders the access of mechanical instruments (Renvert et al. 2008). Thus, the use of different chemotherapeutic agents has been proposed for the treatment of infected implant surfaces (Renvert et al. 2008). A recent systematic review evaluated different treatments of peri-implantitis *in vivo*. No single method of implant surface decontamination was found to be superior (Claffey et al. 2008). Most of the studies included in recent reviews (Claffey et al. 2008; Esposito et al. 2008; Renvert et al. 2009) were not controlled or evaluated a combination rather than a single treatment. Furthermore, those studies did not assess the decontamination of implant surfaces but instead determined the effectiveness of each treatment based on cumulative parameters such as clinical outcomes. To identify the most effective chemical treatment, controlled studies with outcome variables related to the reduction of microorganisms on contaminated titanium surfaces are needed. Therefore, the aim of the present review was to systematically collect the available evidence, and based on the associated findings, evaluate the ability of different chemotherapeutic agents to decontaminate biofilm-contaminated titanium surfaces.

Material and methods

Focused question

What is the efficacy of various chemotherapeutic agents in decontaminating biofilm-contaminated titanium surfaces as compared with a control?

Search strategy

Two internet sources were used to search for papers that met the inclusion criteria: the National Library of Medicine, Washington, DC (PubMed-MEDLINE) and the Cochrane Central Register of Controlled Trials (CENTRAL). Both databases were searched for studies conducted during or before June 2010. The search was designed to include any published study that evaluated the effects of chemotherapeutic agents on contaminated titanium surfaces. To achieve this goal, a wide and comprehensive search was performed. All possible treatment interventions for the decontamination of titanium surfaces were included, which ensured

the inclusion of papers that used treatment methods other than chemical solutions (but which may have provided chemical treatment as an alternative). All reference lists of the selected studies were handsearched for additional papers that might meet the eligibility criteria for inclusion in this study.

The following terms were used in the search strategy for both databases:

{Subject AND Adjective AND Interventiong f*Subject:* (Dental implant [MesH] OR Dental implant [textword])
AND
Adjective: (Smooth OR structure OR texture OR roughness OR surface OR biofilm OR plaque index OR dental plaque OR plaque OR dental depositn [textword])
AND
Intervention: (Ultrasonic OR curette OR scaling OR acid OR laser OR polishing OR debridement OR curettage OR chlorhexidine OR air abrasion OR cleaning OR cleansing agents OR instrumentation OR Ardoz-X OR decontamination OR citric acid OR phosphoric acid OR CPC OR Cetylpyridinium chloride OR SLS OR sodium lauryl sulfate OR EDTA OR ethylenediaminetetraacetic acid OR Chlortetracycline OR Demeclocycline OR Doxycycline OR Lymecycline OR Methacycline OR Minocycline OR Oxytetracycline OR Rolitetracycline OR Tetracycline OR Tetracyclines OR Hydrogen peroxide OR H202 OR Sodium perborate OR Peroxyborate OR Peroxycarbonate [textword])}

The eligibility criteria:

- Controlled studies
- Standardized approach to the growth of biofilms on titanium surfaces
- Intervention: Treatment of contaminated titanium surfaces with a chemotherapeutic agent
- Evaluation parameters for surface decontamination: Residual biofilm, residual lipopolysaccharide (LPS), confocal laser scanning microscope (CLSM) or scanning electron microscope (SEM) observations

Screening and selection

Only papers written in English were accepted for further evaluation. Letters and narrative/historical reviews were not included in the search. Two reviewers (A.L & V.I.N) independently screened the papers for eligibility, first by title and abstract. If the search keywords were present in the title, the abstract was selected for reading. If the abstract was not present but the title contained keywords of interest or suggested that the article was related to the objectives of this review, the paper was also selected for full-text reading. In the case of disagreement, the opinion of a third reviewer (G.A.W) was decisive. Following selection, full-text papers were read in detail by two reviewers (G.A.W & V.I.N). Those papers that fulfilled all selection criteria were processed for data extraction. Disagreements were resolved by discussion. If disagreement persisted, the judgment of a third reviewer (D.E.S) was decisive. Two reviewers (G.A.W & V.I.N) hand-searched the reference lists of all included studies for additional papers.

Assessment of heterogeneity

Factors that were evaluated to assess heterogeneity across the selected studies were as follows:

- Titanium surfaces, contamination methods
- Chemical agents tested, concentrations, method and duration of application
- Outcome variables

Quality assessment

Two reviewers (D.E.S & V.I.N) scored the methodological quality of the studies selected for analysis. This assessment of methodological quality combined several proposed criteria (RCT-checklist of the Dutch Cochrane Center [2009], the MOOSE statement by Stroup et al. (2000), the STROBE statement by Von Elm et al. (2007), Esposito et al. (2001), Needleman et al. (2000), Verhagen et al. (1998), Jadad et al. (1996) and the CONSORT statement March (2010). Criteria were described for each of the three domains: external validity, internal validity and statistical methods. Each item was scored with either a ''+'' for an informative description of the issue and a study design that met the quality standards, ''–'' for an informative description but a study design that failed to meet the quality standards or ''?'' for lacking or insufficient information. A study was classified as having a low risk of bias when the surface material

was clinically representative; reproducibility data were provided; treatments were randomly allocated; preparation, manipulation and treatment of the surface were identical except for the intervention; point estimates were presented for the primary outcome measurements; and statistical analyses were described. Studies that lacked one of these six criteria were classified as having a moderate potential risk of bias and those that lacked two or more of these criteria indicated a high potential risk of bias (van der Weijden et al. 2009).

Data extraction and analysis

Data were extracted from the selected papers by two reviewers (D.E.S & V.I.N). Disagreements were resolved by discussion. If disagreement persisted, the judgment of a third reviewer (G.A.W) was decisive. After a preliminary evaluation of the selected papers, considerable heterogeneity was found in the study designs, characteristics, outcome variables and measurements. Furthermore, one out of the four studies had descriptive outcome variables. Consequently, it was not possible to perform a meta-analysis. Therefore, a descriptive summary of the data had to be adopted.

Results

Search and selection

The PubMed-MEDLINE and Cochrane-CENTRAL searches resulted in 2288 and 168 papers, respectively (Figure 1). In total, 2425 unique papers were found, and 31 papers were identical in both searches. The initial screening of titles and abstracts resulted in 12 full-text papers. After fulltext reading, eight papers were excluded. Table 1 shows the reasons for exclusion. Additional hand-searching of the reference lists of selected studies yielded no additional papers. Ultimately, four papers were processed for data extraction.

Assessment of heterogeneity

Information regarding the study characteristics is presented in Table 2. This table presents a short summary of the study design and the results of the selected papers. The considerable heterogeneity of these studies made comparisons between them difficult. Owing to the lack of uniform data presentation, the results of the studies could only be evaluated separately.

Titanium surfaces

Surface roughness is a determining factor in both biofilm formation and decontamination (Korber et al. 1997). The roughness of the titanium surfaces used varied among the studies. Zablotsky et al. (1992a) studied grit-blasted titanium surfaces that had an average surface roughness of 3.62 mm (Rønold et al. 2003). Machined and plasma-sprayed surfaces were used by Dennison et al. (1994). Titanium plasma-sprayed (TPS) surfaces display a roughness of 5.2 mm, according to Schwartz et al. (2001). Mouhyi et al. (2000) used commercially pure titanium foils with a textured surface of unknown roughness and finally, Chin et al. (2007) used machined surfaces with a mean surface roughness of approximately 182 nm.

The method of contamination also differed between the selected studies. Two studies used LPS from *Eschericia coli* or *Porphyromonas gingivalis* (Zablotsky et al. 1992a and Dennison et al. 1994, respectively). Mouhyi et al. (2000) used an *in situ* model to contaminate titanium foils by placing them in dentures in the mouths of volunteers. Finally, Chin et al. (2007) grew human saliva biofilms on titanium surfaces.

Treatment and outcome

Concerning the chemical agents tested, differences were observed in the concentrations and the methods and durations of application. Zablotsky et al. (1992a) and Dennison et al. (1994) used 0.12% chlorhexidine digluconate (CHX). Chin et al. (2007) also used CHX but at a higher percentage (0.2%). Citric acid was tested in a saturated (Dennison et al. 1994) or supersaturated (Mouhyi et al. 2000) solution. Zablotsky et al. (1992a) evaluated citric acid with a pH of 1, but the concentration was not mentioned.

Zablotsky et al. (1992a) and Dennison et al. (1994) burnished the chemotherapeutic agents on the titanium surface with a cotton pellet, whereas Chin et al. (2007) immersed the implant samples in the chemotherapeutic agents. Mouhyi et al. (2000) applied the chemicals with a pipette. The outcome variable for the first two studies (Zablotsky et al. 1992a and Dennison et al. 1994) was the residual radioactive LPS. Mouhyi et al. (2000) used SEM in their study, and Chin et al. (2007) used CLSM analysis to quantify the residual biofilm. In the CLSM analysis, the biofilm samples were sonicated and dispersed in demineralized water. Next, they were stained with a live/dead stain, and the remaining bacteria were enumerated (van der Mei et al. 2006).

Quality assessment

Quality assessments of the various studies reviewed are presented in Table 3. The estimated risk of bias is considered to be high for all four studies. The study by Mouhyi et al. (2000) did not fulfill any of the criteria established to determine quality, whereas the remaining three studies provided descriptions of the statistical analyses but did not report data concerning the reproducibility and did not randomly allocate the treatments. Representative titanium surfaces were used by Dennison et al. (1994) and Chin et al. (2007). Chin et al. (2007) did not carry out the preparation, manipulation and treatment of the surfaces identically except for the intervention because they used an untreated surface instead of a negative control. Dennison et al. (1994) did not present point estimates for the primary outcome measures.

Data extraction and analysis

Zablotsky et al. (1992a) used grit-blasted titanium alloy strips contaminated with *E. coli* LPS. In their study, 21 titanium strips were treated for 1 min with 0.12% CHX, 1.64% stannous fluoride, tetracycline HCl, 1% chloramine T, 3% saline, hydrogen peroxide (H_2O_2) or citric acid. The results are presented in Table 4. The residual LPS levels were measured by liquid scintillation spectrometry. Chloramine T, saline, H_2O_2 and citric acid treatments all resulted in lower LPS counts than the untreated controls. Stannous fluoride appeared to increase the LPS counts. Chloramine T and citric acid resulted in lower amounts of residual LPS compared with the saline control, but these differences failed to reach statistical significance.

Dennison et al. (1994) studied machined and TPS implants contaminated with radioactive P. gingivalis LPS. Three implants of each type were treated for 2 min with deionized water, saturated citric acid solution or 0.12% CHX. The results are presented as the percentage of the initial endotoxins removed (Table 5). The treatments (citric acid, CHX) were significantly more effective than the untreated control, but they demonstrated no statistically significant differences compared with deionized water (d-H_2O) in terms of their effectiveness on machined and plasma-sprayed surfaces.

Mouhyi et al. (2000) placed eight commercially pure titanium foils on dentures in volunteers. After 24 h in the volunteers' mouths with no oral hygiene, the foils were collected and treated with supersaturated citric acid (three times for 30 s each), 10 mM H_2O_2 (2 min), or a combination of H_2O_2 (2 min) followed by citric acid (three times for 30 s each). Following all treatments, the discs were rinsed with ultrapure water. Eight non-contaminated, commercially pure titanium foils served as controls. SEM was used to assess the surface decontami-

nation. According to the authors, citric acid treatment resulted in a clean surface. However, some areas of bacterial contamination remained. H_2O_2 demonstrated no obvious cleaning effect. The combined treatment with citric acid and H_2O_2 resulted in some decontamination, but small dehydrated and burned debris remained attached to the surface. This study did not go beyond a descriptive analysis and provided no data.

Chin et al. (2007) used five commercially available, self-tapping micro-implants (pure titanium or titanium alloy) with machined surfaces. Human saliva was collected from 20 healthy volunteers. Saliva biofilms were grown on the implants for 20 h in an aerobic incubator. The contaminated implants were then treated with 0.2% CHX or 0.055% sodium fluoride mouth rinses for 1 min. Residual biofilms were sonicated and dispersed in demineralized water and stained with a live/dead stain, and the remaining bacteria were enumerated using a CLSM microscope. The data are presented in Table 6. Before the treatment, all of implants harboured an average of 57% viable microorganisms. The biofilms on the micro-implants treated with CHX and fluoride mouth rinses contained comparable numbers of viable organisms but significantly (80%) fewer viable organisms compared with the untreated micro-implants. Neither mouth rinse significantly reduced the number of bacteria. Thus, these mouth rinses kill but do not effectively remove bacteria from titanium implants.

In Table 7, we attempt to summarize the statistical analysis of the effects of various chemotherapeutic agents (versus their relevant controls) for the purposes of comparison. Among the different agents, the most data were available for citric acid and CHX. Three studies demonstrated a positive effect of citric acid on LPS and bacteria removal as compared with an untreated surface. However, one of these studies also compared citric acid with water treatment and did not establish a significant difference. The three studies that evaluated biofilm removal following the use of CHX showed no significant effect as compared with the control. However, Chin et al. (2007) noted the efficacy of CHX in bacterial killing.

Discussion

Although peri-implantitis is currently recognized as a distinct disease entity, the proposed treatments for this condition are still based on evidence obtained from the treatment of periodontitis. The rationale behind this practice is that the tissues surrounding dental implants are very similar to the tissues that surround the teeth (Berglundh et al. 1991). On the other hand, the titanium surface is dissimilar from the root surface and the direct application

of periodontal treatment measures to implants might be less effective. The screw-shaped design and roughness of implant surfaces may facilitate biofilm formation during exposure to the oral environment (Renvert et al. 2008) and may limit the effectiveness of mechanical debridement (Karring et al. 2005). The available evidence suggests the use of a chemotherapeutic agent as an adjunct to mechanical therapy (Kozlovsky et al. 2006; Renvert et al. 2008).

Persson et al. (2001) used two-part implants in dogs, induced peri-implantitis and replaced the contaminated portion of the implant with a pristine part. Their study reported a complete re-osseointegration and suggested that decontamination of the titanium surface is of decisive importance for re-osseointegration. However, to date, human and animal studies have failed to identify one chemotherapeutic agent as the gold standard for implant surface decontamination (Claffey et al. 2008). Thus, the aim of this review was to search the literature for evidence regarding the most effective chemotherapeutic agent for the decontamination of infected titanium surfaces.

To re-establish titanium surface biocompatibility, it is imperative to remove the bacterial deposits (Kozlovsky et al. 2006). Some treatments may achieve this goal but simultaneously render the titanium surface non-biocompatible. Conventional techniques used to clean natural tooth surfaces usually cause irreversible and detrimental changes to the implant (Burchard et al. 1991), thus compromising the biocompatibility (Schwarz et al. 2005). One advantage of the chemical approach is that the titanium surface is not instrumented and therefore runs only a minimal risk of damage (Strooker et al. 1998). Hydroxyapatite-coated titanium surfaces treated with citric acid showed a greater number of attached fibroblasts than sterile and untreated controls (Wittrig et al. 1992; Zablotsky et al. 1992b). CHX has also been shown to promote gingival fibroblast attachment equivalent to that observed with saline treatment (Burchard et al. 1991). Nevertheless, studies have shown that titanium surfaces may still suffer reduced biocompatibility after various chemical treatments. Zablotsky et al. (1992b) and Wittrig et al. (1992) found that CHX, hydrogen peroxide and stannous fluoride treatments resulted in significantly less fibroblast coverage of hydroxyapatite titanium surfaces compared with sterile and untreated controls, respectively.

In the present review, only four eligible papers were identified. In vivo studies failed to fulfill the eligibility criteria because the biofilm formation on these titanium surfaces could not be standardized. Moreover, under such conditions, it is difficult to formulate a control treatment or untreated controls. The evaluation parameters used in these types of studies tend to be stated in terms of clinical outcomes such as the resolution of inflammation, prob-

ing depth, clinical attachment gain, radiographic data (such as bone fill) and histological parameters (such as re-osseointegration). To date, no in vivo studies have demonstrated a way to assess titanium surface decontamination in a ''controlled'' fashion.

To find evidence of the effectiveness of chemical treatments in decontaminating titanium surfaces, in vitro studies were reviewed as ''a proof of principle''. In vitro studies provide the first measurable evidence that an investigational product might work in humans. Furthermore, in vitro tests allow for the inclusion of controls in the study without the addition of any moral or ethical concerns (Ulrey et al. 2005). Only when a specific treatment is solidly proven to be superior in vitro should in vivo studies, preferably randomized clinical trials, be initiated. The studies that were eligible for the present review did not go beyond the in vitro design, and all of them were considered to have a high potential level of bias.

Negative controls, or blanks, are substances such as sterile, deionized water, saline or other media that are expected to cause little or no change in the test system. All manipulations specified in the protocol (including removal of the tested solutions) should also be conducted using the negative control (Ulrey et al. 2005). The use of negative controls provides valuable information that is highly useful in interpreting the results obtained in in vivo and in vitro studies (Ulrey et al. 2005). Zablotsky et al. (1992a) and Dennison et al. (1994) evaluated both an untreated control and a control treatment against the various interventions. Whereas some interventions were significantly better than the untreated control, no intervention was better than the control treatment. Mouhyi et al. (2000) and Chin et al. (2007) only compared their treatments with an untreated control.

The most frequently used chemotherapeutic agents in the four studies included in this review were CHX and citric acid. The 0.12% CHX did not achieve a significant reduction of LPS on contaminated titanium surfaces as compared with untreated controls (Zablotsky et al. 1992a). Dennison et al. (1994) found that 0.12% CHX treatment removed 94.6% of the LPS from machined, contaminated implant surfaces, but less LPS (37.1%) from plasma-sprayed, contaminated implant surfaces. The effect of CHX was not significantly different from the water control treatment. Finally, Chin et al. (2007) found that 0.2% CHX was effective in killing multispecies biofilms and resulted in 79.5% fewer viable microorganisms compared with the untreated controls. On the other hand, CHX was only modestly effective in removing the biofilm.

Animal studies (Wetzel et al. 1999; Schou et al. 2003; You et al. 2007) have investigated the effects of a titanium surface treatment with CHX and saline. Low levels of re-osseointegration were achieved for non-machined implant surfaces (Claffey et al. 2008). These studies

did not assess decontamination of the implant surfaces, but the effect of CHX on clinical outcomes appears to be questionable. CHX has also been used for the treatment of peri-implant mucositis. A single professional irrigation of the sulci (Schenk et al. 1997; Porras et al. 2002) was not beneficial, but a self-administrated irrigation achieved significantly greater clinical improvement than rinsing (Felo et al. 1997).

In the study reported by Mouhyi et al. (2000), citric acid resulted in a cleaner titanium surface as observed by SEM than that associated with the untreated control. Citric acid was effective in the removal of LPS from titanium surfaces when compared with untreated controls, but it was not significantly more effective than saline or water (Zablotsky et al. 1992a; Dennison et al. 1994). The effectiveness of citric acid in LPS removal has been shown to be significantly greater on machined surfaces (90%) than on plasma-sprayed surfaces (34.4%) (Dennison et al. 1994). Zablotsky et al. (1992a) and Dennison et al. (1994) reported similar results. Citric acid showed no statistically significant differences in effectiveness as compared with water or saline. A possible explanation for this result is the small sample sizes used in both studies (three surfaces per treatment), which could be responsible for the lack of power and thus the lack of significant results.

An *in vivo* study in monkeys used citric acid as the chemotherapeutic agent for the treatment of TPS surface implants in combination with autogenous bone grafts and e-PTFE membranes (Schou et al. 2003). In that study, almost total bone fill was observed in all groups, and bone-to-implant contact ranged from 39% to 46%. Citric acid treatment did not differ significantly from CHX in that in vivo study. Khoury & Buchmann (2001) combined citric acid with CHX, H2O2 and saline to decontaminate implant surfaces before the placement of bone grafts and membranes. Neither of these studies was controlled, and decontamination was not assessed. Finally, Kolonidis et al. (2003) and Alhag et al. (2008) placed smooth and minimally rough (0.76 mm, on average) implants in dogs. They allowed some threads to protrude in the oral cavity to permit plaque accumulation and the development of peri-implant disease. The contaminated parts of each implant were treated using three different techniques: (1) swabbing with citric acid for 30 s, (2) cleansing with a toothbrush and saline for 1 min and (3) swabbing with 10% hydrogen peroxide for 1 min. Next, the treated implants and one pristine implant (control) were installed to the full implant length on the contralateral sides of the mandibles. The amount of osseointegration did not vary significantly, either between the different treatment modalities or in comparison with the new, sterile implant. These studies demonstrated that the method of decontamination used for the titanium surface might not

be a determining factor if the recipient site is healthy. Nevertheless, the implants used had a smooth or a minimally rough surface that facilitated the decontamination process (Dennison et al.1994). Furthermore, in clinical reality, peri-implant tissues are likely to be inflamed, which can impair healing.

H_2O_2 has been used in clinical protocols for the treatment of infected implant surfaces (Mombelli & Lang 1998). *In vitro* studies of H_2O_2 decontamination have revealed conflicting results. Zablotsky et al. (1992a) showed that 3% H_2O_2 removes significantly more LPS from titanium surfaces when compared with untreated controls. In contrast, Mouhyi et al. (2000) found that 3% H_2O_2 had no obvious cleaning effect on contaminated titanium surfaces. In a clinical trial, Leonhardt et al. (2003) used H_2O_2 in combination with antibiotics and access surgery and observed healing in 58% of the implants.

Zablotsky et al. (1992a) and Dennison et al. (1994) utilized bacterial LPS to contaminate titanium surfaces. The rationale behind this choice was twofold. First, although the binding of endotoxin to the root surface appears to be weak (Nakib et al. 1982), Nelson et al. (1997) observed that LPS had a high affinity for titanium biomaterials. Further, endotoxin is a characteristic component of the cell wall of gram-negative bacteria and it plays a significant role in the binding process of these bacteria and in initiation of the host response. LPS from oral bacteria has a marked effect on most types of cells found in the periodontal tissues, including macrophages, lymphocytes, fibroblasts and osteoblasts (Wilson 1995). Bacterial endotoxin has been shown to inhibit fibroblastic growth and attachment to root surfaces (Layman & Diedrich 1987). Zablotsky at el. (1992a) showed that the removal of LPS from hydroxyapatite-coated titanium surface promoted more effective human gingival fibroblast growth and attachment compared with the untreated control. Whether this effect also occurs on uncoated titanium surfaces remains unknown. The results reported by Nouneh et al. (2001) indicated that the presence of LPS did not significantly alter osteoblast attachment to titanium or titanium alloy surfaces, irrespective of whether the exposure occurred before or after cellular adherence. The biological and clinical significance of removing bacterial components like LPS require further validation. In addition, the use of LPS removal as an outcome variable might not adequately represent the overall ability of the tested chemotherapeutic agents to remove the biofilm and vice versa. In our opinion, it is more clinically relevant to grow biofilms on titanium surfaces to test various chemical treatments. Furthermore, this approach can provide information regarding both the killing and removal abilities of these agents. The only study to investigate the killing capacities of antimicrobials was that reported by Chin et al.

(2007). The greatest shortcoming of that study was the use of machined titanium surfaces. Machined titanium surfaces are mostly limited to the neck of the implants, but peri-implant disease often involves exposure of the rough titanium surface to the oral environment.

Quantifiable results are fundamental for effective comparisons of study outcomes (Field et al. 2010) and therefore they reflect the quality of the study. Mouhyi et al. (2000) used titanium surfaces that were contaminated biologically by placing the discs in dentures in the mouths of volunteers. Further, they used SEM to evaluate the cleaning effect of the different chemicals. This method is clearly not quantitative and thus does not allow us to draw any definitive conclusions.

The real incidence of peri-implantitis is probably underestimated (Esposito et al. 2007). The high number of dental implants placed and their longer follow-up periods will inevitably lead to more cases of diagnosed peri-implantitis. Thus, the need for efficient treatment and further maintenance of successfully treated implants will increase in the near future. The interventions tested in the various studies presented herein are mostly empirical, and the study outcomes are inconsistent and unpredictable. This finding does not mean that all current treatments are ineffective (Esposito et al. 2008), but there is still no consensus among clinicians regarding the best treatment. In our opinion, a systematic approach to the treatment of contaminated implant surfaces should be initiated. The available treatment modalities should be categorized and evaluated separately in a controlled manner. Reviewing the literature for this type of studies on chemical decontamination of titanium surfaces was rather disappointing. Considering the number of studies that have been published on the technical aspects and aesthetic outcomes of implant surgery, it is striking that so little controlled research has been undertaken to determine how the titanium implants should be maintained in order to reduce the chances of biological complications (perimucositis and peri-implantitis) and further how to treat the titanium surfaces in the event of such complications. Additional work in this area of research is imperative. Finally, the greatest challenge will be to determine the treatment protocol that best balances decontamination (Persson et al. 2001) and re-establishment of the biocompatibility of the titanium surface with the stimulation and promotion of healing in peri-implant tissues (Kolonidis et al. 2003; Alhag et al. 2008).

Conclusion

The data reported on the efficacy of chemotherapeutic agents for the treatment of contaminated titanium surfaces are scarce, which precludes the generation of any firm conclusions. Based on the limited available evidence, we cautiously conclude that citric acid seems to be the chemotherapeutic agent with the highest potential for the removal of biofilms from contaminated titanium surfaces *in vitro*, although complete removal was not achieved. To date, the killing effect of citric acid has not been investigated on titanium surfaces.

Implications for future research

Owing to the limited and weak evidence that is available, further research is required. Future studies should include an appropriate negative control, and titanium surfaces should be preferably contaminated with bacterial biofilms rather than bacterial components such as LPS. Additionally, the assessment of surface decontamination should involve quantification of the residual biofilm. The results obtained using rough titanium surfaces are more clinically relevant and increase the applicability of the findings. Finally, *in vivo* studies should be performed to test the *in vitro* findings and to establish an evidence-based protocol for the treatment of peri-implant diseases.

Acknowledgements

This paper was prepared as a part of the obligation of the first author to fulfill the requirements of the ACTA master's program in Periodontology and Implantology. *Conflict of interest and source of funding statement*: The authors declare that they have no conflict of interest. This study was self-funded by the authors and their institutions.

Authors' contributions:

V.I. Ntrouka contributed to the conception, design, acquisition, analysis, interpretation of data, drafted the manuscript.

D.E. Slot contributed to the design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

A. Louropoulou contributed to the conception, design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

G.A. van der Weijden contributed to the conception, design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

All authors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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* Studies included in the review

Table 1. Overview of the studies that were excluded after complete reading and the reason for exclusion

Reason for rejection	Author(s) (year)
Combination of mechanical and chemical treatment	Schwarz et al. (2005)
Surface preparation, not chemical treatment	Kilpadi et al. (2000)
Hydroxyapatite-coated titanium strips (not a titanium surface)	Wittrig et al. (1992)
	Zablotsky et al. (1992b)
	Zablotsky et al. (1992c)
Non-contaminated titanium surfaces	Burchard et al. (1991)
	Kozlovsky et al. (2006)
Not controlled and non-standardized biofilm growth (failed implants)	Mouhyi et al. (1998)

Figure 1. Database search and literature selection.

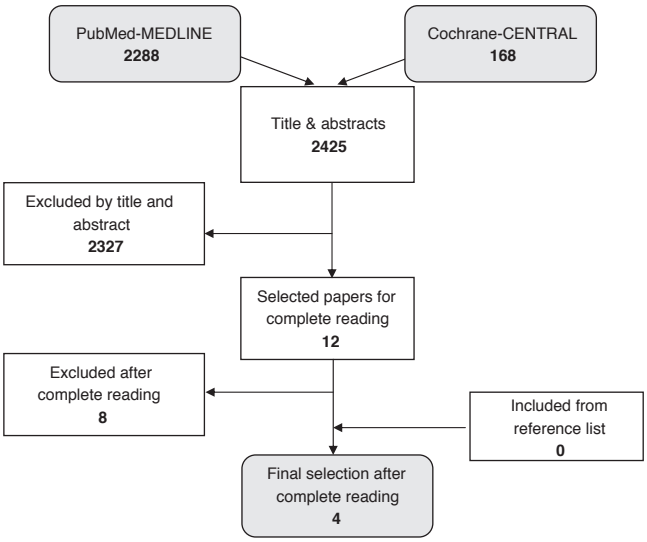

Table 2. Details of the selected studies

Author (year) Title	Surface	# of surfaces treated	Treatment	Outcome measure	Conclusion
Zablotsky et al. (1992a) Detoxification of endotoxin-contaminated titanium and hydroxyapatite-coated surfaces utilizing various chemotherapeutic and mechanical modalities	Contaminated with *Eschericia coli* LPS Grit-blasted titanium alloy strips	3 3 3 3 3 3 3	Chlorhexidine gluconate (0.12%) Stannous fluoride (1.64%) Tetracycline HCl (50 mg/ml) Chloramine T (1%) Saline (3%) Hydrogen peroxide (3%) Citric acid (pH 1)	Residual lipopolysaccharide levels measured by liquid scintillation spectrometry	Citric acid was significantly superior for the removal of LPS from grit-blasted titanium alloy when compared with the untreated control. Citric acid treatment resulted in the lowest amount of residual LPS, but when compared with saline, it failed to reach statistical significance
Dennison et al. (1994) Contaminated implant surfaces: an *in vitro* comparison of implant surface coating and treatment modalities for decontamination	Contaminated with *Porphyromonas gingivalis* LPS Machined and plasma-sprayed titanium implants	6 6 6	d-H_2O Saturated citric acid Chlorhexidine gluconate (0.12%)	Radioactive endotoxin (radioimmunoassay)	Citric acid and CHX were superior to an untreated control and equally effective as water for machined and plasma-sprayed titanium surfaces

Author (year) Title	Surface	# of surfaces treated	Treatment	Outcome measure	Conclusion
Mouhyi et al. (2000) Re-establishment of the atomic composition and the oxide structure of contaminated titanium surfaces by means of carbon dioxide laser and hydrogen peroxide: An *in vitro* study	Contaminated by placement on dentures in volunteer patients Commercially available pure titanium foils Textured surface	2 2 2 2	Untreated control Supersaturated citric acid followed by rinsing with ultrapure water H_2O_2 (10 mM) followed by rinsing with ultrapure water Supersaturated citric acid, water rinsing, H_2O_2, water rinsing	Observations using a Scanning electron microscope	Citric acid treatment resulted in a clean surface, but some areas of bacterial contamination remained H_2O_2 had no obvious cleaning effect The combination of citric acid and H_2O_2 treatment resulted in some decontamination, but remnants of debris were attached to the titanium surface
Chin et al. (2007) Biofilm formation on surface characterized micro-implants for skeletal anchorage in orthodontics.	Contaminated with saliva biofilm Four Commercially available, self-tapping micro-implants (Two pure titanium, two titanium alloy) Machined surface	12 12 12	Untreated control Chlorhexidine digluconate (0.2%) Sodium fluoride (0.055%)	CLSM analysis of dispersed biofilms	Biofilms on micro-implants treated with chlorhexidine and fluoride mouth rinses contained comparable numbers of viable organisms but significantly (80%) fewer than those detected in untreated micro-implants. The amount of bacteria in the biofilm was not significantly reduced

LPS, lipopolysaccharide; CSLM, confocal laser scanning microscopy.

Table 3. Methodological quality scores of the selected studies

Author: **Quality criteria:**	**Zablotsky et al. (1992a)**	**Dennison et al. (1994)**	**Mouhyi et al. (2000)**	**Chin et al. (2007)**
External validity				
Representative surface material*	–	+	–	+
Validation of the model	?	?	?	?
Validation of the evaluation method	+	+	–	+
Reproducibility data provided*	–	–	–	–
Internal validity				
Random treatment allocation*	?	?	?	?
Blinded to examiner	?	?	?	?
Blinding during statistical analysis	?	?	?	?
Preparation, manipulation and treatment of the surface identical, except for the intervention*	+	+	–	–
Statistical validity				
Sample size and power calculation	?	?	?	?
Point estimates presented for primary outcome measurements	+	–	–	+
Measures of variability presented for the primary outcome	–	–	–	+
Statistical analysis*	+	+	–	+
Author's estimated risk of bias	**High**	**High**	**High**	**High**

*Items used to estimate potential risk of bias.

?, not specified/unclear; +, yes; –, no.

Table 4. Mean residual LPS counts on grit-blasted titanium alloy strips, and levels of significance for the treatments compared with the untreated control (adapted from Zablotsky et al. 1992a)

Treatment	# titanium strips	LPS counts/min/mm^2	% Removal relative to untreated control ◇	Level of significance
SnF_2 (1.64%)	3	302*	NA	<0.05
Untreated control ■	3	197	NA	NA
CHX (0.12%)	3	170	13.7%	NS
Tetracycline	3	141	28.4%	NS
H_2O_2 (3%)	3	108	45.2%	<0.05
Saline ■	3	98	50.2%	<0.05
Chloramine T	3	86	56.3%	<0.05
Citric acid	3	68	65.5%	<0.05

*Significantly greater amounts of LPS than in the untreated control ($p<0.05$).

◇, calculation by the authors of this review; NA, not applicable; NS, not significant;

■, untreated and saline-treated controls; LPS, lipopolysaccharide.

Table 5. Reduction of endotoxin level relative to baseline values on machined and plasma-sprayed titanium surfaces, and level of significance for the treatments compared with water (adapted from Dennison et al. 1994)

Treatment	Machined		Plasma sprayed		Level of significance
	#	%	#	%	
d-H_2O ■	3	92.4*	3	42.1*	NA
CHX	3	94.6*	3	37.1*	NS
Citric acid	3	90*	3	34.4*	NS

*Significant compared with baseline.
■, water-treated control; NA, not applicable; NS, not significant.

Table 6. Mean percentage of viable organisms remaining on machined titanium surfaces after treatment, and level of significance compared with untreated controls (adapted from Chin et al. 2007)

Treatment	# Titanium surfaces	% Mean (SD)	Significance levels
Untreated control ■	12	57 (4.5)	NA
CHX (0.2%)	12	11.7 (4.7)	<0.05
NaF (0.055%)	12	10.5 (5.3)	<0.05

NA, not applicable.
■, untreated control.

Table 7. Summary of the outcomes of the included papers, treatments and comparisons

Author	Zablotsky et al. (1992a)		Dennison et al. (1994)		Mouhyi et al. (2000)◊	Chin et al. (2007)	
Outcome parameter	Removal of LPS		Removal of LPS		Clean surface at SEM	Removal	Killing
Comparison	Untreated	Saline	Untreated	d-H_2O	Untreated	Untreated	
Treatment							
CHX (0.12%)	–	–	+	–			
CHX (0.2%)						–	+
SnF_2 (1.64%)	–	–					
Tetracycline	–	–					
Chloramine (1%)	+	–					
Saline (3%)	+						
H_2O_2 (3%)	+	–			–		
Citric acid	+	–	+	–	+		
NaF (0.055%)						–	+
Citric acid and H_2O_2					+		

+, statistically significant difference; –, no significant difference;
■, not applicable;
◊, no statistical analysis was performed; LPS, lipopolysaccharide; SEM, scanning electron microscopy. This reflects a descriptive summary.

Chapter 7

Mechanical self-performed oral hygiene of implant supported restorations: a systematic review

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Journal of Evidence Based Dental Practice 2014; 14(suppl): 60-69.

Introduction

Biofilm accumulation is associated with inflammatory changes around implants (Zitzmann et al. 2001). Consequently, regular and effective plaque removal constitutes an important issue in the prevention of such responses. Several studies have shown that consistent professional maintenance and the standard of the patients' home care are key factors for long term stability of dental implants and the prevention of biological complications (Bauman et al. 1991; Silverstein et al. 2006; Serino & Ström 2009).

In a longitudinal multicenter study, failing implants were associated with higher plaque biofilm levels than successful implants (van Steenberghe et al. 1993). In a prospective 15-year follow-up study, Lindquist et al. (1996) reported an association between poor oral hygiene and peri-implant bone loss. More bone loss was observed around implants supporting fixed bridges in edentulous patients with poor oral hygiene than in those with better oral hygiene (Lindquist et al. 1996). In a study analyzing risk variables for peri-implant disease in a Brazilian population, very poor oral hygiene was highly associated with peri-implantitis with an OR of 14.3 (95% CI: 2.0-4.1) (Ferreira et al. 2006). In the consensus meeting of the Sixth European Workshop on Periodontology regarding peri-implant diseases it was concluded that insufficient oral hygiene is an important risk factor for developing peri-implant infections (Heitz-Mayfield, 2008).

Several methods may be used for self-performed plaque control with implants and are based on the knowledge that is available with respect to cleaning of natural teeth. The mechanical plaque control may involve the use of manual or power toothbrushes as well as proximal cleaning dental devices (Eskow & Smith 1999). The purpose of this study was to review and evaluate the literature, in a systematic way, with respect to various self-performed mechanical, oral hygiene modalities around implant-supported dental restorations in relation to peri-implant soft tissue health.

Materials and Methods

This systematic review was conducted according to the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (PRISMA-statement) (Moher et al. 2009).

Search strategy

Three internet sources were used to identify publications that met the inclusion criteria: the National Library of Medicine, Washington, D.C. (MEDLINE-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). The final search was conducted up to October 1st 2013 and was designed to include any published study that evaluated self-performed mechanical home care of dental implants. The search strategy was customized according to the requirements of each database (for details on the search terms used see Box 1).

Screening and selection

Only papers written in English were included. The titles and abstracts were first screened independently by two reviewers (D.E.S & G.A.W) to identify eligible studies. When the abstract was not clear or no abstract was available but the title seemed to be relevant, the paper was selected for full-text reading. Following selection, full-text papers were carefully read by two reviewers (A.L & G.A.W). Disagreements were resolved by discussion. If disagreements persisted, the judgment of a third reviewer (D.E.S) was decisive. The papers that fulfilled all of the selection criteria were processed for data extraction. All reference lists of the selected studies were hand searched by two reviewers (A.L & D.E.S) for additional published work that could possibly meet the eligibility criteria of the study. The following eligibility criteria were used:

- Randomized controlled clinical trials (RCTs) or controlled clinical trials (CCTs) or cohort studies
- Conducted in humans
  - ≥ 18 years of age
  - Good general health
  - Having at least one dental implant
- Intervention: self-performed mechanical cleaning of dental implant-supported restorations

- Clinical outcome parameters including plaque indices, bleeding indices, gingiva health indices, probing pocket depth and gingival recession.

Box 1. Search terms used for PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE. The search strategy [<structure> AND <device>] was customized appropriately for each of the additional databases being used taking into account differences in controlled vocabulary and syntax rules.

The following terms were used in the search strategy:

[<*structure*: [MeSH terms /all subheadings] Dental Implants OR [textwords] dental implant>

AND

<*device*: [MeSH terms /all subheadings] toothbrushing OR Dental Devices, Home Care OR [textwords] toothbrush OR toothbrushing OR toothbrush* OR Floss OR Dental floss OR Flossing OR Tape OR Dental tape OR Superfloss OR Ultrafloss OR Toothpick* OR woodstick* OR wooden interdental cleaner OR wedge stimulator* OR wooden stimulator* OR interproximal brushing OR interproximal brushes OR interproximal brush OR interproximal brush* OR interdental brushing OR interdental brushes OR interdental brush OR interdental brush* OR interdental cleaning devices OR interspace brushing OR interspace brushes OR interspace brush OR interspace brush* OR proxabrush OR oral irrigation OR oral irrigator OR oral irrigation jet OR water jet irrigator OR dental water jet OR water pick OR water pik OR waterpik OR perio pik OR pick pocket OR pickpocket OR pik pocket OR monojet oral irrigator OR subgingival irrigation OR subgingival tip OR dental irrigator OR dental irrigation OR Interdental cleaning devices OR Interproximal cleaning devices OR Interspace cleaning devices>]

The asterisk (*) was used as a truncation symbol

Assessment of heterogeneity

The following factors were evaluated to assess heterogeneity:

- Study design
- Characteristics of the participants
- Clinical outcome parameters
- Funding

Quality assessment

Two reviewers (A.L & D.E.S) scored the methodological quality of included studies. This assessment was performed according to the method that has been described in detail by Keukenmester et al. (2013). In short, when random allocation, defined eligibility criteria, blinding of examiners, blinding of patients, balanced experimental groups, identical treatment between groups (except for the intervention), reporting of loss of follow-up and the subject as unit of statistical analysis were present, the study was classified as having a low risk of bias. When one of these criteria was missing, the study was considered to have a moderate risk of bias. When two or more of these criteria were missing, the study was considered to have a high risk of bias, as proposed by van der Weijden et al. (2009).

Data extraction and analysis

Studies were analyzed for similarities and suitability for meta-analysis. After a preliminary evaluation of the selected papers, it was found that considerable heterogeneity was present in the study designs, characteristics, outcome variables and results. It was, therefore, not possible to perform a quantitative analysis of the data and subsequent meta-analysis; accordingly a descriptive analysis of the data was performed.

Grading the 'body of evidence'

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as proposed by the GRADE working group (Guyatt et al. 2008) was used to rank the evidence emerging from this review regarding self-performed mechanical home care of dental implants. Two reviewers (A.L & G.A.W) rated the quality of the evidence as well as the strength of the recommendations according to the following aspects: risk of bias of the individual studies, consistency and precision among the study outcomes, directness of the study results and detection of publication bias. Any disagreement between the two reviewers was resolved after additional discussion.

Results

Search and selection

The PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE searches identified in total 375 unique papers using the specified search terms (Figure 1). The initial screening of the titles and abstracts resulted in seven full-text papers that met the inclusion criteria. After reading the full-text articles, two papers were excluded, one because it was a survey (Orelud et al. 2012) and one because the mechanical cleaning was performed by a dental professional (Chongcharoen et al. 2012). Additional hand-searching of the reference lists from the selected studies did not yield any additional papers. Five papers were ultimately processed for data extraction.

Assessment of heterogeneity

Information regarding the study characteristics is provided in Table 1. The table includes a short summary of the study design, information regarding the participants (number, age, smoking habits, number of implants and type of implant-supported restoration) and the authors' conclusions. Information regarding the changes within each group for the various outcome parameters is presented in Table 2.

Study design, characteristics of the participants and outcome parameters

Two studies were cohort studies (Vandekerckhove et al. 2004; Rasperini et al. 2008), two were randomized controlled clinical trials (Wolff et al. 1998; Tawse-Smith et al. 2002) and one study (Truhlar et al. 2000) was a multicentre controlled clinical trial.

In a prospective cohort study Rasperini et al. (2008) (study IV) evaluated over a 12-month follow-up period an oscillating/rotating powered toothbrush in patients with implant-supported restorations in the aesthetic area. One third of the subjects were smokers. Papillary bleeding index, recession and probing pocket depth were measured at baseline and at 3, 6, and 12 months. An improvement on both bleeding score and clinical attachment level was reported over time (Table 2).

Similar results were also reported in another prospective cohort study by Vandekerckhove et al. (2004) (study V). This study assessed the efficacy of an oscillating/rotating powered toothbrush in patients rehabilitated with fixed prostheses on implants. Sulcus bleeding index, probing pocket depth, periodontal pocket bleeding index and gingival recession was measured at baseline and at 3, 6, and 12 months and showed that all parameters improved

over the course of the study (Table 2). Changes of similar magnitude were observed over time on these parameters irrespective of the presence or absence of keratinized mucosa around the implants.

Tawse-Smith et al. (2002) (study I) compared in a 6-week single-blinded, randomized, cross-over study the clinical effectiveness of a manual and an oscillating/rotating powered toothbrush in a group of elderly, non-smoking, patients with implant-supported mandibular overdentures. Modified plaque and bleeding indexes were recorded at the start and end of the experimental period. The results of this study revealed comparable efficacy of the 2 types of toothbrushes with regard to mean plaque and bleeding scores (Table 2).

Truhlar et al. (2000) (study II) evaluated in a multicentre controlled clinical trial the effectiveness of a counter-rotational powered toothbrush with that of a conventional manual toothbrush and interdental aids on indexes of periodontal health in patients with implant-supported restorations. Plaque index, gingival index, probing pocket depth and recession were measured. The powered toothbrush was found to be superior to the conventional toothbrush in combination with interdental aids in reducing plaque and bleeding scores and probing pocket depth over a 2-year period (Table 3).

Similar results were also reported in a 6-month single-blinded, randomized, parallel study by Wolff et al. (1998) (study III) that compared a sonic toothbrush with a manual one. The sonic toothbrush was found to reduce plaque and bleeding significantly better than the manual toothbrush over time. Moreover, the sonic toothbrush was found to be more effective than the manual toothbrush in reducing probing depths and gingival inflammation over time, although differences in these parameters did not reach statistical significance (Table 2). However, the difference between the two groups at the end of the study was not significant for all parameters evaluated (Table 3).

Funding

In two studies (I, IV) the materials that were used were provided by companies. Three studies (II, III, V) reported involvement of a third party. This was either an industrial grant (II, III) or a co-author being related to the industry (V).

Quality assessment and grading the 'body of evidence'

The quality assessment of the various studies is presented in Table 4. All studies were considered to have a high potential risk of bias. Studies I and II used the site as the experimental

unit for data analysis, while in studies III, IV and V the unit for data analysis was the subject. Only study I provide information about excluding subjects from further analysis because of non-compliance (per protocol analysis). Study III used an intention-to-treat analysis, including subjects in the analysis that used other cleaning devices next to the ones they were assigned to in the study.

The following criteria were used to rate the quality of evidence and strength of the recommendations according to GRADE (Guyatt et al. 2008): potential risk of bias, consistency, directness, precision of the estimate and publication bias. Only the controlled trials were included in this analysis (studies I, II, III). All studies had a high potential risk of bias. The available data for the powered toothbrush were rather consistent and rather precise. However, it is difficult to decide whether the results of the included studies can be generalized to other populations. As a result, the strength of recommendation was considered to be weak. A formal testing for publication bias, as proposed by Egger et al. (1997), could not be used owing to insufficient statistical power because of the limited number of studies.

Discussion

The present systematic review focused on the mechanical self-performed oral hygiene of implant-supported restorations. Powered toothbrushes were found to result in an improvement in clinical parameters over time. Three controlled clinical trials (I, II, III) compared a powered to a manual toothbrush. Study I revealed comparable efficacy of the 2 types of toothbrushes in elderly edentulous subjects with implant-supported overdentures, while, in subjects rehabilitated with fixed prostheses, powered toothbrushes gave superior results compared to the manual toothbrushes over time (II, III). However, these studies differ in several aspects. Results obtained in edentulous subjects do not necessarily reflect the situation in partially-dentate subjects. Edentulism, subjects' age and brushing dexterity may have influenced the results. It is also known that study duration affects outcomes when manual and powered toothbrushes are compared (Aass & Gjermo 2000). Hence, the short-term (6-week) design that was employed in study I may be less likely to demonstrate significant differences. Furthermore, this study had a cross-over design with a wash-out period of two weeks, while studies II and III used a parallel design, which is the simplest type of randomized trial. An advantage of a cross-over design is that each participant acts as his or her own control, eliminating between-participant variation. However, statistically, cross-over trials are not

appropriate due to the likelihood of a carry-over effect. Cross-over studies using therapeutic agents are at risk of showing a period effect that is greater than the effect of interest. A wash-out period of two weeks may not be sufficient and longer wash-out periods are preferable (Senn, 2002). Thus, the results of this study should be interpreted with caution.

Study II compared a powered toothbrush to a manual toothbrush in combination with interproximal aids. Study III included in the analysis subjects that used other devices next to the toothbrushes assigned to the participants in the study. In study V, in addition to the powered toothbrush, subjects were allowed to use their usual interdental cleaning devices. These additional procedures may have influenced the results obtained. Although the powered toothbrushes gave superior results than the manual toothbrushes over time (study II, III), the difference between the two groups at most visits was not significant (study I, III). Thus the comparison of a power toothbrush to a manual toothbrush in combination with additional interdental cleaning devices should be interpreted with diligence since the comparison is not truly valid.

There is paucity of studies investigating interproximal devices. None of the included studies evaluated interproximal cleaning as a separate intervention. Chongcharoen et al. (2012) evaluated in a randomized controlled, double-blind cross-over study the effectiveness of two different interdental brushes in cleaning the interproximal surfaces of implants placed in the posterior region of the mouth. All cleaning procedures were performed by a trained dental surgery assistant, which was the reason of exclusion from the present review. The purpose of this study was to evaluate the efficacy of the interdental brush itself and not the capacity of the subject to clean interproximally. Under these circumstances both devices were found to be effective in purely interproximal cleaning. However, the ability of subjects to properly use these devices was not evaluated.

While there has been extensive research into all aspects of dental implant placement, little has been done to investigate the essential aspect of the maintenance of implant-supported restorations by patients. The patient's ability to perform regular and effective oral hygiene has an impact on the long-term success of implants (Cagna et al. 2011). It becomes obvious that there is a lack of evidence with respect to optimal self-performed oral hygiene around dental implants, especially in terms of the use of interproximal devices. Self-performed home care around implants is, at present, mainly based on the knowledge that is available from the periodontal literature, with respect to cleaning of natural teeth. However, often, implant-supported restorations present contours and shapes that render

plaque removal difficult, even by the most capable individuals (Cagna et al. 2011). Additionally a pocket around an implant is anatomically different from pocket around a natural tooth which may require specific attention. Consequently well performed clinical trials, evaluating different oral hygiene products alone or in combination, are needed regarding this topic.

Based on the limited available data, powered toothbrushes seem to be effective in cleaning both fixed and removable implant-supported restorations. No hard evidence was found that powered toothbrushing is superior to manual toothbrushing, although powered toothbrushing may help to overcome limitations in manual dexterity and accessibility.

Acknowledgements

Declaration of interest

The authors declare no conflict of interest. The research was funded by the authors and their institutions.

Authors' contribution

A. Louropoulou contributed to the conception, design, acquisition, analysis, interpretation of data, drafted the manuscript.

D.E. Slot contributed to the design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

G.A. van der Weijden contributed to the conception, design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

All authors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Figure 1. Databases search and literature selection

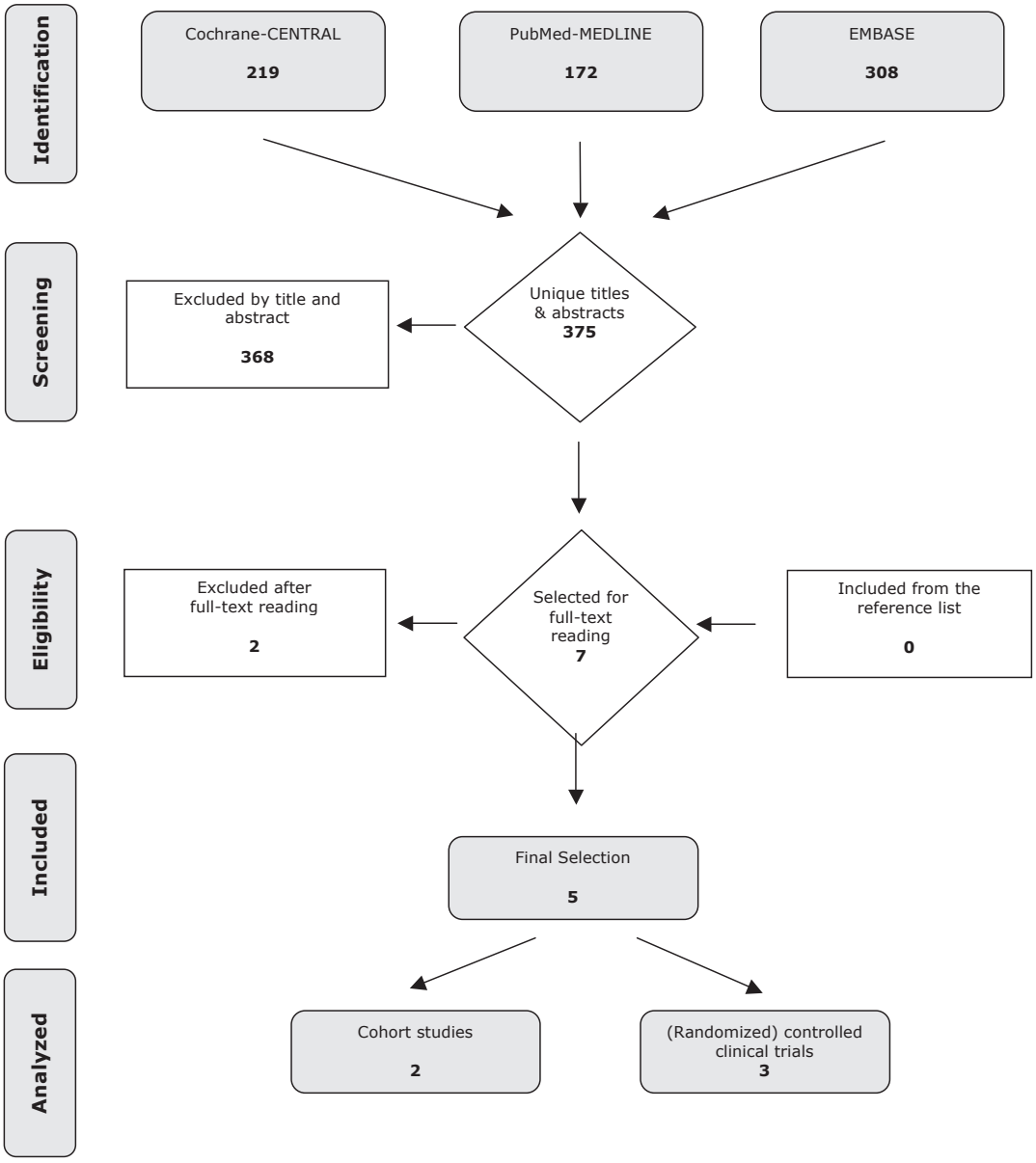

Table 1. Summary of studies evaluating the self-performed mechanical plaque control

	No Author (reference)	Study design Duration	Subjects' characteristics No of subjects baseline (end) Mean age(range) Smoking Type of implant-supported restoration No of implants	Groups Regimen	Authors' Conclusions
(RANDOMIZED) CONTROLEED CLINICAL TRIALS	I.Tawse-Smith et al. (17)	RCT Cross-over 2w- WOP Single blind 6 weeks	Elderly subjects n=40 (36) Mean age: 65.8 (55-80) Non-smokers Patients fully edentulous with 2 unsplinted mandibular implants supporting a complete removable overdenture opposed by a maxillary complete denture 80 implants	- Oscillating/rotating powered toothbrush (Braun Oral-B Plaque Remover 3-D) - Manual toothbrush (Oral-B Squish-grip brush) 2x daily for 30s	Manual and powered brushes were found to be of comparable efficacy with regard to improvement in peri-implant plaque and bleeding indices.

	No Author (reference)	Study design Duration	Subjects' characteristics No of subjects baseline (end) Mean age(range) Smoking Type of implant-supported restoration No of implants	Groups Regimen	Authors' Conclusions
(RANDOMIZED) CONTROLEED CLINICAL TRIALS	II. Truhlar et al. (18)	CT Parallel Multicenter 24 months	n=? Mean age: ? Smoking: ? Patients rehabilitated partially or fully with implant-supported restorations 2,966 implants	- Counter-rotational powered toothbrush (Interplak Power Toothbrush Conair Corp.) - Soft manual toothbrush (TrueSoft Lactona Co.) and either regular dental floss or specialized implant dental floss and end-tufted brushes (End-Tuft Lactona Co.) or interproximal brushes (Proxabrush John O. Butler Co.) No recommended regimen	The counter-rotational powered toothbrush was more effective than a manual toothbrush plus interproximal aids, both in terms of clinical indexes and implant survival.
	III. Wolff et al. (19)	RCT Parallel Single blind 24 weeks	Adults n=31 Mean age: 56.3 (21-75) Smoking: ? Type of restoration: ? 96 implants	- Sonic toothbrush (Sonicare®, Optriva Corp., Bellevue, WA) - Manual toothbrush (Crest® Complete, The Proctor & Gamble Co., Cincinetti, OH) 2x daily for 2min	Sonic toothbrushing significantly reduced plaque, gingival inflammation and bleeding, and probing pocket depths around implants over the 6-month trial period.

	No Author (reference)	Study design Duration	Subjects' characteristics No of subjects baseline (end) Mean age(range) Smoking Type of implant-supported restoration No of implants	Groups Regimen	Authors' Conclusions
COHORT STUDIES	IV. Rasperini et al. (20)	Prospective Cohort 12 months	Adults n=100 (98) Mean age: 56 (?) One third smokers Implants in the esthetic area between the 1st premolars Patients rehabilitated partially or fully with fixed prosthesis 100 implants	- Oscillating/rotating toothbrush (Braun Oral-B Professional Care 7000, Proctor & Gamble, Ohio, USA) 2x daily	All parameters improved over the course of the study. The electric toothbrush appears to be safe for patients with fixed prostheses on implants in the aesthetic area.
	V. Vanderkerckhove et al. (21)	Prospective Cohort 12 months	Adults n=100 (80) Mean age: 56.3 (18-80) Smoking: ? Patients rehabilitated partially or fully with fixed prosthesis 361 implants	- Oscillating/rotating powered toothbrush (Braun Oral-B Plaque Control Ultra (D9), Kronberg, Germany) Regular interdental cleaning which mostly consisted of interdental brushes and Superfloss 2x daily for 2min	All parameters improved over the course of the study. The powered toothbrush investigated is effective for patients rehabilitated by means of oral implant-supported prostheses.

RCT: randomized controlled clinical trial; CT: controlled clinical trial; WOP: wash-out period

Table 2. Extracted data of the selected studies by plaque indices, bleeding indices, gingival health indices, probing pocket depths and recessions.

Model	Study no	Index (reference)	Intervention Groups	Mean (SD)			Statistically significant within groups
				Baseline	End	Difference	
Plaque index							
CONTROLLED CLINICAL TRIALS	I	Modified plaque index by Mombelli (26)	Powered toothbrush	0.9 (0.67)	0.9 (0.73)	1.0 ◊	No
			Manual toothbrush	0.8 (0.64)	0.8 (0.67)	0.0 ◊	No
	II	Silness and Löe plaque index (27)	Powered toothbrush	?	?	?	?
			Manual toothbrush and inter-dental aids	?	?	?	?
	III	Silness and Löe plaque index (27)	Sonic toothbrush	1.31 (0.48)	0.46 (0.50)	- 0.83*	Yes
			Manual toothbrush	1.27 (0.47)	0.60 (0.45)	- 0.68*	Yes

Model	Study no	Index (reference)	Intervention Groups	Mean (SD)			Statistically significant within groups
				Baseline	End	Difference	
Bleeding index							
CONTROLLED CLINICAL TRIALS	I	Modified sulcus bleeding index by Mombelli (26)	Powered toothbrush	0.4 (0.38)	0.5 (0.52)	0.1◊	No
			Manual toothbrush	0.4 (0.49)	0.5 (0.51)	0.1◊	No
	III	Gingival bleeding index by Pihlström (28)	Sonic toothbrush	1.47 (0.31)	0.66 (0.64)	- 0.78*	Yes
			Manual toothbrush	1.46 (0.72)	0.67 (0.56)	- 0.82*	Yes
COHORT TRIALS	IV	Papillary bleeding index (29)	Powered toothbrush	1.5 (1.6)	0.7 (1.0)	- 0.8◊	Yes
	V	Sulcus bleeding index (29)	Powered toothbrush and inter-dental aids	0.31 (?)	0.14 (?)	- 0.17◊	Yes
		Periodontal bleeding index (30)		0.55 (?)	0.38 (?)	- 0.17◊	Yes

Model	Study no	Index (reference)	Intervention Groups	Mean (SD)			Statistically significant within groups
				Baseline	End	Difference	
Gingival index							
CONTROLLED CLINICAL TRIALS	II	Löe and Silness gingival index (31)	Powered toothbrush	?	?	?	?
			Manual toothbrush and inter-dental aids	?	?	?	?
	III	Löe and Silness gingival index (31)	Sonic toothbrush	1.46 (0.27)	0.87 (0.54)	- 0.60*	Yes
			Manual toothbrush	1.58 (0.42)	0.94 (0.49)	- 0.63*	Yes
Probing pocket depth							
CONTROLLED CLINICAL TRIALS	II	Probing pocket depth (18)	Powered toothbrush	?	?	?	?
			Manual toothbrush and inter-dental aids	?	?	?	?
	III	Probing pocket depth (19)	Sonic toothbrush	3.32 (0.70)	2.87 (0.76)	- 0.43*	Yes
			Manual toothbrush	3.10 (0.75)	2.73 (0.68)	- 0.39*	Yes

Model	Study no	Index (reference)	Intervention Groups	Mean (SD)			Statistically significant within groups
				Baseline	End	Difference	
Probing pocket depth							
COHORT TRIALS	IV	Probing pocket depth (20)	Powered toothbrush	3.8 (1.1)	3.5 (1.2)	- 0.3◊	Yes
	V	Probing pocket depth (21)	Powered toothbrush and inter-dental aids	3.32 (?)	3.02 (?)	- 0.3◊	Yes
Recession							
CONTROLLED CLINI-CAL TRIALS	II	Recession (18)	Powered toothbrush	?	?	?	?
			Manual toothbrush and inter-dental aids	?	?	?	?
COHORT TRIALS	IV	Recession (20)	Powered toothbrush	11.9 (2.5)	11.7 (2.3)	- 0.2◊	No
	V	Recession (21)	Powered toothbrush and inter-dental aids	0.97 (?)	0.87 (?)	- 0.1 ◊	Yes

?: no data available * Reduction in clinical parameter is adjusted for baseline

◊ calculated by the authors of this review

Table 3. A descriptive summary of the statistical significance of powered toothbrushes to a comparison

Study no	Test group	Control group	Plaque Index	Bleeding Index	Gingival Index	Probing Pocket Depth	Recession
I	Powered toothbrush	Manual toothbrush	0	0			
II	Powered toothbrush	Manual toothbrush and interproximal aids	+		+	+	+
III	Sonic toothbrush	Manual toothbrush	0	0	0	0	0

+: significant difference at the end of the study period in favor of the test group ; 0: no significant difference at the end of the study between the groups

Table 4. Methodological validity and quality scores of the included studies

Study Quality criteria		Tawse-Smith et al. (2002)	Truhlar et al. (2000)	Wolff et al. (1998)	Rasperini et al. (2008)	Vandekerck-hove et al. (2004)
Internal validity	Random allocation *	+	-	+	NA	NA
	Allocation concealment	?	-	?	NA	NA
	Blinded to patient *	NA	NA	NA	NA	NA
	Blinded to examiner *	+	?	+	NA	NA
	Blinding during statistical analysis	?	?	?	?	?
	Balanced experimental groups *	+	?	+	NA	NA
	Reported loss to follow up *	+	-	+	+	+
	No (%) of drop-outs	4(10%)◊	-	0	2(2%)◊	20(20%)◊
	Treatment identical, except for intervention *	+	-	-	NA	NA
External validity	Representative population group	-	-	+	+	+
	Eligibility criteria defined *	+	+	+	+	+
Author's estimated risk of bias		**High**	**High**	**High**	**High**	**High**

Study Quality criteria		Tawse-Smith et al. (2002)	Truhlar et al. (2000)	Wolff et al. (1998)	Rasperini et al. (2008)	Vandekerck-hove et al. (2004)
Statistical validity	Research model used	Cross-over	Multicenter Parallel	Parallel	Cohort	Cohort
	Sample size calculation and power	-	-	-	-	-
	Point estimates	+	-	+	+	+
	Measures of variability presented for the primary outcome	+	-	+	+	
	Unit of analysis *	Site	Site	Subject	Subject	Subject
	Include a per protocol analysis	+	?	-	?	?
	Include an intention-to-treat analysis	-	?	+	?	?
Author's estimated risk of bias		**High**	**High**	**High**	**High**	**High**

Criteria were designated for each domain of internal validity, external validity and statistical methods. Each aspect of the score list was given a rating of '+' for an informative description of the item at issue and a study design meeting the quality standard, '-' for an informative description without a study design that met the quality criteria and '?' for lacking or insufficient information.

+: yes; -: no; ?: not specified/unclear

◊: percentage of drop-outs calculated by the authors of this review

NA: not applicable

* reporting criteria for estimating the potential risk of bias

Chapter 8

Prevention and Treatment of Peri-implant diseases - An Epitome of the Dutch Guideline -

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Introduction

Implant therapy is a useful and successful extension of the dental armamentarium for the treatment of patients with missing teeth. However, clinicians should expect to see both biological and technical complications in their daily practice (Heitz-Mayfield et al. 2014). This paper is based on a clinical guideline that has recently been published in the Netherlands on the prevention and management of biological complications. The Dutch Society of Periodontology and the Dutch Society of Implantology appointed the working group. The merit of this working group was to provide answers and make recommendations for clinical practice focusing on the aspects of diagnosis, prevention and treatment of peri-implant diseases. The guideline was developed taking into account the Appraisal of Guidelines for Research and Evaluation (AGREE) II Instrument (Brouwers et al. 2010) and a Dutch guideline for the development of guidelines (Richtlijn voor Richtlijnen, 2012).

Peri-implant diseases may occur in two forms, peri-implant mucositis and peri-implantitis (Lang & Berglundh 2011). Peri-implant mucositis is defined as the presence of inflammation in the mucosa around implants without loss of supportive bone. In contrast, peri-implantitis also affects the supporting bone, causing progressive bone loss beyond the normal biologic remodelling (AAP-Academy-Report, 2013). Currently, the prevalence of peri-implant diseases represents a 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 to be 43% (range, 19% to 65%), whereas for peri-implantitis this amounted to 22% (range, 1% to 47%) (Derks & Tomasi 2015). Differences in case definition, with varying thresholds for the assessment of bone loss and reference time points from which the bone loss occurred, result in a wide range of prevalence of peri-implant diseases reported in the literature. It is, therefore, difficult to globally estimate the true magnitude of the disease (Salvi et al. 2017).

The presence of a biofilm that contains 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 & Décaillet 2011). Peri-implant diseases may be initiated or maintained by iatrogenic factors e.g. 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. Furthermore, bone loss induced at the time of implant placement by traumatizing the pristine bone beyond its adaptive capacity may also persist (Lang & Ber-

glundh 2011). In a recent review paper (Vasconcelos et al. 2016), it has been concluded that metal particles and metal ions may induce immunologic response that may lead to bone loss and implant failure. Moreover, patient-related factors, like untreated or refractory periodontitis, systemic diseases, smoking, level of oral hygiene, compliance with maintenance and site-related factors e.g. poor bone quality are important parameters that may contribute to the initiation and/or progression of peri-implant diseases (De Bruyn et al. 2016).

Risk indicators for peri-implant disease

There is substantial evidence that poor oral hygiene, smoking and history of periodontitis are important risk indicators for peri-implant diseases (Heitz-Mayfield, 2008).

History of periodontitis

Patients with a history of periodontitis are at greater risk for peri-implant diseases (van der Weijden et al. 2005; Karoussis et al. 2007; Quirynen et al. 2007). In periodontitis susceptible patients, residual pockets (PPD ≥ 5 mm) at the end of active periodontal therapy were found to represent a significant risk for the development of peri-implantitis and implant loss. Moreover, patients developing re-infections during supportive periodontal treatment were found to be at greater risk for peri-implantitis and implant loss than patients maintaining a stable periodontal condition (Pjetursson et al. 2012). Successful treatment of periodontitis prior to implant placement lowers the risk for peri-implantitis (Renvert & Quirynen 2015).

Oral Hygiene/Accessibility to clean

A prospective study reported an association between poor oral hygiene and peri-implant bone loss at 10-year follow-up (Lindquist et al. 1997). Very poor oral hygiene has been associated with peri-implantitis with an OR=14.3, 95% CI 9.1–28.7 (Ferreira et al. 2006). Furthermore, the accessibility for proper oral hygiene at the implant site seems to be related to the presence or absence of peri-implantitis (Serino & Ström 2009). It is, therefore, very important to educate the patients rehabilitated with dental implants in proper plaque control and to establish regular maintenance. Prosthesis design must allow accessibility for proper oral hygiene at the implants. Whenever possible margins of implant- supported restorations should be placed at or above the mucosal margin to facilitate access for plaque control. Implant-supported restorations with poor access for plaque removal should be adjusted or replaced by restorations that allow for optimal oral hygiene (Salvi & Ramseier 2015).

Smoking and alcohol consumption

It is indicated that smokers have an enhanced risk for biologic complications. Smoking has been associated with the onset of peri-implantitis and smokers showed more marginal bone loss compared to non-smokers (Strietzel et al. 2007; Chrcanovic et al. 2015; Renvert & Quirynen 2015). Regarding alcohol consumption, one prospective study reported that peri-implant marginal bone loss was significantly related to a daily consumption of > 10g alcohol (Galindo-Moreno et al. 2005).

Diabetes mellitus

Diabetes may be associated with peri-implantitis (Renvert & Quirynen 2015). A systematic review on dental implants and diabetes mellitus reported that, in the long-term observation, peri-implant inflammation seems to be increased in diabetic patients, especially if diabetes is poorly controlled (Naujokat et al. 2016).

Genetic traits

There are studies showing a synergistic effect between genetic traits and smoking on the development of peri-implant diseases (Feloutzis et al. 2003; Gruica et al. 2004; Jansson et al. 2005). The negative effect of smoking seems to be more pronounced in patients with a positive IL-1 genotype (Feloutzis et al. 2003). Although genetic traits may influence the inflammatory response, available data on the relationship between peri-implantitis and genetic traits are at present unclear (Renvert & Quirynen 2015).

Occlusal overload

Implants are considered less tolerable to non-axial forces compared to teeth because of the lack of periodontal ligament (AAP-Academy-Report, 2013). Excessive stress can cause microfractures within bone and eventually bone loss (Stanford & Brand 1999). Occlusal overload was found to be positively associated with marginal bone loss around implants (Fu et al. 2012). It has also been suggested that bruxism may be associated with an increased risk of implant failure (Chrcanovic et al. 2016). The AAP-Academy Report (2013) stated that the influence of occlusal overload on peri-implantitis needs further investigation. In this respect, also a more precise definition of occlusal overload is needed. Although hard evidence for the impact of occlusal overload on peri-implantitis is lacking, it seems advisable to include an evaluation of the patients' occlusion during maintenance visits (Renvert & Quirynen 2015).

Implant surface

Dental implants are available with a range of surface characteristics. So far, there is no evidence available that the type of implant surface can have a significant effect on the initiation of peri-implantitis. However, there is some evidence that surface characteristics may have an effect on the progression of established peri-implantitis (Renvert et al. 2011). Data available from human studies suggest that implants with relatively smooth (machined) surfaces may to be less prone to bone loss due to chronic infection than implant with much rougher surfaces (titanium plasma sprayed) (Renvert et al. 2011; Esposito et al. 2014). Furthermore, animal studies, whereby a ligature-induced peri-implantitis model was used, suggest that some moderately rough surfaces (Sa= 1.1- 2.0 μm) might be more susceptible to disease progression than other surfaces (Berglundh et al. 2007; Albouy et al. 2008, 2009).

Keratinized mucosa

A recent systematic review concluded that the presence of an adequate zone of keratinized tissue (≥ 2mm) around the implant-supported restoration might be necessary because it has been associated with better peri-implant tissue health (Brito et al. 2014).

Excess cement

Excess cement may act as a foreign body and thus provoke an inflammatory reaction in the peri-implant tissues. The use of cement-retained implant restorations was found to frequently result in leaving excess cement in peri-implant tissues despite of careful clinical control following cementation of the crown (Linkevicius et al. 2013b); the deeper the position of the crown margin, the greater the amount of undetected cement discovered (Linkevicius et al. 2013a). Although few papers exist on the association between excess cement and peri-implantitis, the data clearly indicate that excess cement may be a contributing factor to the development of peri-implantitis (Renvert & Quirynen 2015).

Diagnosis of peri-implant diseases

After the delivery of the definite implant-supported restoration, baseline data representing homeostasis should be established (Lang & Berglundh 2011). For this a radiograph should be obtained to determine alveolar bone level after physiologic remodelling, and peri-implant probing assessments should be performed. According to the Dutch approach, a clinical

photograph may help to visualize changes of the soft peri-implant tissues and to evaluate the position, form and thickness of the peri-implant mucosa. Recorded baseline data will be the reference from which the peri-implant condition can be followed in subsequent examinations and early development of peri-implant disease can be timely recognized (Table 1).

Radiographs

The time of the prosthesis installation should be chosen to obtain a radiograph. This radiograph can also be used to control the proper fitting of the restoration/abutment or the present of cement remnants, in case of cement-retained restorations. A new radiograph should be made one year after the prosthesis installation in order to determine alveolar bone level after physiologic remodelling and establish radiographic baseline after this remodelling. It is assumed that further bone loss occurring after this initial remodelling is mainly due to bacterial infection (Lang & Berglundh 2011).

A radiograph taken some years after the installation of the implant-supported restoration without any possible reference to a baseline radiograph cannot be used to diagnose disease, or to assess progressing marginal bone loss. This clearly requires a series of radiographs, taken at different time points, displaying ongoing loss of marginal bone. The latter is an important criterion for the diagnosis of peri-implantitis (Albrektsson et al. 2016). In the absence of previous radiographic records, a vertical distance of 2 mm from the expected marginal bone level following remodelling has been suggested as an appropriate threshold level, provided peri-implant inflammation was evident (Sanz & Chapple 2015).

Intraoral and panoramic radiographs are widely used for peri-implant diagnosis and both are reliable to assess bone levels around dental implants (Kullman et al. 2007). However, intraoral radiographs provide a more detailed picture and higher resolution and, therefore, should be preferred. Nonetheless, both methods cannot monitor facial and lingual bone levels, have low sensitivity in the detection of early bone loss and underestimate the marginal bone level (De Smet et al. 2002). In addition, radiographs do not provide information on the condition of the soft tissues. Hence, a thorough clinical examination is mandatory for complete diagnosis.

Probing Depth

Probing depth measurement, after the initial soft tissue healing upon loading, should be established and monitored over time (Padial-Molina et al. 2014). Human and animal stud-

ies have shown that a soft tissue barrier adjacent to an implant-supported restoration is completely established within 8 weeks (Tomasi et al. 2014; Chrcanovic et al. 2016). Hence, to allow this initial soft tissue healing to occur, according to the Dutch approach, the baseline measurement should be performed around 8 weeks after the prosthesis installation, in order to give the peri-implant mucosa around the restoration the necessary time to mature. Progressive changes in probing depth compared to previous measurements can be an alarming sign. In experimental peri-implantitis studies, an increase in probing depth over time has been associated with clinical attachment and bone loss around implants (Lang et al. 1993; Schou et al. 2004).

Peri-implant tissues are sensitive to probing force variations (Ericsson et al. 1993; Mombelli et al. 1997). In the past, it has also been suggested that probing around implants would damage the soft tissue seal around them. However, Etter and colleagues (2002), in an experimental study, evaluated the healing following standardized peri-implant probing using a force of 0.25 N and observed complete re-establishment of the junctional epithelium within 5 days. The findings of this study clearly imply that peri-implant probing using a probe with a light pressure of 0.25 N will not cause damage to the peri-implant tissues and is recommended for the evaluation of the peri-implant tissue health status. There are no data available whether the material of the probe (metal or plastic) or the probe design can influence peri-implant probing measurements (Heitz-Mayfield, 2008). Empirically, a plastic probe appears more favourable because it is flexible and can follow the bulging contour of the implant-supported restoration more easily.

In contrast to natural teeth, for which average periodontal probing depth has been reported, the physiologic probing depth of the peri-implant sulcus has been a matter of debate (Salvi & Lang 2004). Probing depths around implants can be influenced by different factors such as probing force, thickness of the peri-implant mucosa, placement level and type/design of implant, abutment or restoration (Lang et al. 1994; Salvi & Lang 2004). Generally, probing pocket depths can vary between implant systems, aesthetic placement depths, bone levels to adjacent teeth, healing time, surgical protocol (one or two stages), and loading protocol (Padial-Molina et al. 2014). Platform switching may lead to shallower measurements because the probe tip may stop on the neck of the implant. In the aesthetic zone, where implants are placed deeper for a better emergence profile, probing depths of ≥ 5 may be accepted, if not accompanied by other symptoms or signs of inflammation (e.g. bleeding on probing, suppuration, pain or discomfort). However, it must be kept in mind that pockets of ≥ 5 mm repre-

sent niches where anaerobic bacteria can be found (Misch et al. 2008). Regular maintenance is, thus, mandatory to preserve a stable peri-implant condition. Long-term investigations in humans have shown that the probing depth of a healthy peri-implant sulcus is not always < 4mm but in fact, often > 4 mm and sometimes ≥ 6 mm (Coli et al. 2017). Therefore, single probing depth measurements, solely, should not be considered a diagnostic tool for the presence of disease, but should always be combined with other clinical signs of disease, e.g. bleeding on probing, suppuration, as well as, radiographic evidence of ongoing bone loss. Nevertheless, it should be realized that, at present, peri-implant pocket probing provides the clinician with the best information in order to evaluate the condition of the peri-implant soft tissues.

Bleeding on probing

Bleeding on gentle probing (≤ 0.25 N) is considered a useful parameter for monitoring the peri-implant mucosal tissue condition and for the diagnosis of mucosal inflammation around implants (Luterbacher et al. 2000). Bleeding on probing (BOP) has a high negative predictive value. In other words, absence of BOP is a good indicator of a stable peri-implant condition (Jepsen et al. 1996). Bleeding upon gentle probing (≤ 0.25 N) is considered a key parameter for the diagnosis of peri-implant mucositis (Lang & Berglundh 2011). However, it should be kept in mind that stable peri-implant sites, in some cases, also slightly bleed on probing which may be the result of disrupting the epithelial junction.

Suppuration

The presence of pus indicates the presence of inflammation. Pus is frequently associated with progressive bone loss and peri-implantitis (Roos-Jansåker et al. 2006; Fransson et al. 2008) and is a common finding in peri-implantitis sites (Lang & Berglundh 2011).

Prevention

The key for the long-term success of implants is prevention of peri-implant diseases based on proper implant design, proper placement and correct contours for ease of oral hygiene, along with meticulous maintenance care by both the dental care professional and the patient (Tarnow, 2016). Attendance to a regular supportive periodontal therapy program (SPT) has been found to be strongly related to implant survival (Anner et al. 2010) and reduces the risk

for the development of peri-implant disease, especially in subjects affected by periodontitis (Roccuzzo et al. 2012).

During SPT, an update of the medical and dental history, a thorough examination of the peri-implant and periodontal tissues and an inspection of the implant-supported restoration should be performed (Heitz-Mayfield et al. 2014). The level of patient's self-performed oral hygiene should also be evaluated. Examination of the peri-implant tissues should include assessment of the presence of plaque, probing pocket depth, presence and severity of bleeding on gentle probing and/or suppuration. The colour and tonus of the peri-implant mucosa should also be evaluated. The probing depth measurements should be compared to previous examinations. Progressive changes compared to previous measurements are an alarming sign. When changes in clinical parameters indicate disease, a radiograph should be taken to evaluate possible bone loss compared to previous examinations (Lang & Berglundh 2011). Possible reasons to take a radiograph could be an increase in probing depth of ≥ 2mm compared to previous examination (Roos-Jansåker et al. 2006), which may be accompanied with severe bleeding and/or suppuration; suspected mobility of the implant; or patient 's discomfort/pain.

In every follow-up visit, the frequency of the maintenance should be determined, on the basis of an individual risk analysis, taking into account local and patient-related factors. In every follow-up visit, the recall interval should be revised and, if necessary, adapted.

Peri-implant health is defined as the absence of clinical signs of inflammation, absence of radiographic bone changes of more than 2 mm compared to the baseline radiograph after physiologic bone remodelling, absence of pain upon function and absence of mobility (Misch et al. 2008; Heitz-Mayfield et al. 2014). In this case, a recall frequency of twice a year is recommended, precluding that local and/or systemic factors require more frequent intervals (Monje et al. 2016) (Figure 1). Professional cleaning, including reinforcement of the oral hygiene is recommended as a preventive measure (Heitz-Mayfield et al. 2014).

The removal of biofilm from implant components exposed to the oral environment, which have mostly a smooth surface, constitutes an important part of the professional supportive therapy. Ideally, the instruments used to effectively clean smooth surfaces should cause minimal or no surface damage, should not create a surface that is more conducive to bacterial colonization and should not affect the implant–soft tissue interface. If, however, the soft tissue attachment is disrupted, the instrumentation procedure should maintain a surface that is conducive to re-establishment of the soft tissue seal (Louropoulou et al. 2014).

Based on the available *in vitro* data, air-abrasive devices with less abrasive powders and sonic and ultrasonic devices with non-metal tips appear to be effective in removing non-calcified deposits from smooth implant surfaces, without causing noticeable changes on the structure of the implant surface. Summarizing the evidence, air abrasive devices are, at present, the most effective instruments in removing biofilm from smooth surfaces (Louropoulou et al. 2012, 2014). In a six-month randomized clinical trial air-abrasive debridement with glycine powder was compared to manual debridement with plastic curettes and chlorhexidine administration for the maintenance of peri-implant status. The authors concluded that the air-abrasive treatment with glycine powder seems adequate and more effective than manual instrumentation in removing the peri-implant biofilm and in maintaining the health of peri-implant tissues (Lupi et al. 2016).

Treatment of peri-implant diseases

Peri-implant mucositis

Peri-implant mucositis is defined as the presence of inflammation in the mucosa, evident by bleeding on probing, with or without deepening of the peri-implant pocket and without radiographic evidence of bone loss compared to the baseline radiograph. In general, peri-implant mucositis can be managed with nonsurgical treatment. However, current data indicate that complete resolution of the inflammation, as evident by absence of bleeding on probing, is not always possible (Jepsen et al. 2015). Improvement of the oral hygiene of the patients and professionally-administered mechanical cleaning of the implant components, employing different hand or powered instruments with or without air-abrasive devices, should be considered the standard of care for the management of peri-implant mucositis (Jepsen et al. 2015) (Figure 1). The adjunctive use of local antiseptics or antibiotics (i.e. local and systemic) does not seem to improve the efficacy of mechanical plaque removal in improving the clinical parameters in mucositis sites (Schwarz et al. 2015; Salvi et al. 2015).

Sometimes, iatrogenic factors are present and play an important role in the initiation of peri-implant mucositis. Removal of these factors is mandatory in order to achieve improvement. Cement remnants, if present, should be removed and prosthodontic issues like inadequate abutment/restoration seating or over-contoured restorations should be corrected. In case of implant mal-positioning, surgical correction of the hard and soft tissues may be necessary to reduce the inflammation and to improve the accessibility for proper oral hygiene (Figure 1).

After treatment, enrolment in a maintenance program is necessary to maintain a stable peri-implant condition. The absence of maintenance in individuals treated for peri-implant mucositis has been associated with a higher risk for developing peri-implantitis (Costa et al. 2012).

Peri-implantitis

Peri-implantitis is defined as the presence of changes in the level of crestal bone over time, accompanied by bleeding on probing and/or suppuration with or without concomitant deepening of the peri-implant pocket (Lang & Berglundh 2011). Sometimes, these symptoms are accompanied by redness and swelling of the peri-implant mucosa and patient's symptoms like discomfort or pain.

When peri-implantitis is diagnosed, proper treatment should be started, as soon as possible (Figure 1). The ideal goal of the treatment would be the resolution of inflammation with no suppuration or bleeding on probing, no further bone loss, and the reestablishment and maintenance of healthy peri-implant tissues (Heitz-Mayfield et al. 2014). "A composite outcome of disease resolution including the absence of deep pocket depth with bleeding and suppuration" can be considered (Sanz & Chapple 2015). However, peri-implant pocket depth can be influenced by different factors, as discussed above, and, therefore, the classification of a "deep" pocket needs to be done on an individual basis (Schwarz et al. 2015).

The treatment of peri-implantitis starts with a nonsurgical therapy, consisting of improvement of the oral hygiene of the patient and professional cleaning of the infected implant components (Figure 1). Any co-existing periodontal disease should also be treated. From the existing literature on nonsurgical therapy of peri-implantitis, it seems that limited clinical improvements can be achieved following mechanical therapy alone using specially designed carbon-fiber curettes, ultrasonic devices and titanium instruments (Renvert & Polyzois 2015). Glycine powder air polishing appears to improve the efficacy of nonsurgical treatment of peri-implantitis. Glycine powder air polishing was associated with a significant improvement in bleeding scores over the control measures investigated (Schwarz et al. 2015a).

A recent systematic review showed that adjunctive local antibiotics/antimicrobials might improve the efficacy of conventional mechanical debridement (Schwarz et al. 2015). Better results regarding bleeding on probing and probing depths, were observed, although

the lesion was not resolved in all cases. From a clinical perspective, this combined therapy may serve as an alternative therapy when surgical intervention is not possible (Renvert & Polyzois 2015).

Regarding the use of systemic antibiotics, a number of case series suggest an improvement in clinical parameters (Mombelli & Lang 1992; Khoury & Buchmann 2001). The available data are very limited and do not allow any definite conclusions, as the studies include both local and systemic use of antimicrobials/antibiotics (Renvert & Polyzois 2015).

In case of peri-implantitis, nonsurgical treatment is often not sufficient to resolve the inflammation. This is due to the inaccessibility for proper decontamination of the infected implant surface. In many cases, a surgical treatment is also necessary (Renvert et al. 2008). Nevertheless, nonsurgical therapy should always be performed before surgical interventions. A preparatory phase allows the clinician to evaluate the patient's ability to perform good oral hygiene. If adequate oral hygiene cannot be obtained, the clinician may consider other treatment options. It remains however possible that the initial nonsurgical therapy may resolve the problem (Renvert & Polyzois 2015). A recent study systematically evaluated the effectiveness of nonsurgical therapy for the treatment of peri-implant diseases including both, mucositis and peri-implantitis lesions. It was concluded that although nonsurgical treatment for peri-implant mucositis seems to be effective, modest and not-predictable outcomes are expected for peri-implantitis lesions. Limitations of this study include different peri-implant diseases definitions, treatment approaches, as well as different implant designs/surfaces and defect characteristics (Suárez-López et al. 2016).

The main goal of surgery is to provide better access to the contaminated rough implant surface. Different instruments, including mechanical instruments and chemical agents, have been used for the decontamination of the infected surfaces. Clinical improvements have been reported for air-abrasive devices or lasers, but the available evidence is still very weak (Renvert & Polyzois 2015). A retrospective study evaluating the effect of an air-abrasive device during surgical treatment of peri-implantitis compared with plastic curettes and cotton pellets impregnated with saline reported that, although both groups revealed a significant improvement in clinical parameters, the air abrasive group yielded better improvements regarding bleeding scores and probing depths at 12 months (Toma et al. 2014). In the surgical treatment of peri-implantitis, chlorhexidine failed to show superior clinical results compared to placebo-control, although it resulted to a greater suppression of anaerobic bacteria in short term (De Waal et al. 2013).

If surgery is required, resective or regenerative techniques may be used, depending on the clinical situation. A resective treatment approach may also be combined with surface modification including removal of implant threads. In this study, radiographic assessment of marginal bone levels have shown that implantoplasty combined with resective surgery resulted in significantly better results and a stabilization of the bone level 3 years after surgery compared with resective surgery alone (Romeo et al. 2007).

Serino and Turri (2011) evaluated the outcome of a surgical procedure based on pocket elimination and bone re-contouring combined with plaque control before and after surgery in the treatment of peri-implantitis. Two years after treatment 48% of the patients had no signs of peri-implantitis. However, 42% of the treated implants presented peri-implant disease despite treatment and 7 implants with bone loss ≥ 7 mm had to be removed during the follow-up period. The authors concluded that complete disease resolution seems to be dependent on the initial bone loss at implants and that disease progression was observed for the implants that still showed signs of disease after treatment (Serino & Turri 2011).

Resective techniques are mostly the treatment of choice in the non-aesthetic areas of the mouth. In the aesthetic zone, in which exposed implant threads would be an undesirable complication, other treatment approaches may be required (Renvert & Polyzois 2015). If retentive bone defects are present, open flap debridement and decontamination of the implant surface may be accompanied by regenerative techniques in order to restore the osseous defect (Claffey et al. 2008). A number of grafting materials, with or without barrier membranes, as well as the use of membranes alone, have been advocated over the years, in an attempt to regenerate the lost bone and establish re-osseointegration. Although, an improvement in the clinical parameters has been observed, with pocket depth reduction and radiographic bone fill, failures have also been reported (Renvert & Polyzois 2015). The outcomes of therapy may be influenced by several local factors, mainly including the physicochemical properties of the bone filler, the defect configuration, and the implant surface characteristics (Schwarz et al. 2015). To date, limited evidence is available on the long-term effects of regenerative procedures (Schwarz et al. 2009; Roos-Jansåker et al. 2011). In a 4-year follow-up study of 11 patients, it was concluded that clinical improvements could be maintained after treatment with a xenograft and a collagen membrane (Schwarz et al. 2009). The ability of the patient to maintain good levels of oral hygiene after treatment seems to be a prerequisite for long-term stability (Schwarz et al. 2009; Roos-Jansåker et al. 2011).

A mobile implant should always be removed because there is no chance that osseointegration will occur again. It is important to be sure that the implant itself is mobile and not the prosthetic components.
In case of advanced peri-implantitis or persisting peri-implantitis or in case of extreme implant mal-positioning, removal of the implant should be considered (Figure 1).

After active treatment, enrolment in regular supportive therapy results in the maintenance of stable peri-implant conditions in the majority of patients and implants. However, in some patients recurrence of peri-implantitis may be observed (Heitz-Mayfield et al. 2016).

Oral Hygiene

Proper maintenance of implant-supported restorations is to a large extent in the control of the patient and is dependent on his/her daily oral hygiene. Powered toothbrushes seem to be effective in cleaning both fixed and removable implant-supported restorations. However, there is no hard evidence that powered toothbruhing is superior to manual toothbrushing. Nevertheless, powered toothbrushing may help to overcome limitations in manual dexterity and accessibility (Louropoulou et al. 2014).

The evidence on interproximal cleaning around implant-supported restorations is very limited. Interdental brushes, when used by a trained dental professional, seem to be effective in removing plaque from interproximal areas (Chongcharoen et al. 2012). One study reported that using a water jet stream device resulted in greater reduction in bleeding compared to traditional floss (Magnuson et al. 2013). However, the lack of controlled clinical trials makes it difficult to draw any firm conclusions on their relative effectiveness. Chemical agents have also been tested in combination with mechanical plaque control. However, the data on the adjunctive effect of these agents is not conclusive (Salvi et al. 2015).

Self-performed home care around implants is, at present, mainly based on the knowledge that is available from the periodontal literature, with respect to cleaning of natural teeth. Individually tailored oral hygiene instructions should be given to patients rehabilitated with dental implants. The design of the implant-supported restorations should also allow accessibility for proper oral hygiene at the implants. Otherwise, the restorations should be adapted or replaced by cleansable restorations (Salvi et al. 2015).

Conclusions

Good oral hygiene and regular maintenance are key factors for long-term success with dental implants. Baseline clinical and radiographic recordings are necessary for the long-term follow-up of implants. Regular monitoring of the peri-implant tissues includes assessment of the peri-implant probing depth, bleeding on gentle probing and/or presence of suppuration. If necessary, based on the clinical findings, the bone level should be evaluated. A single measurement of one factor cannot be used to differentiate health from disease. Changes over time, compared to previous recordings, can be an alarming sign.

If disease is diagnosed, treatment should be initiated, as soon as possible. The treatment consists of reinforcement of the oral hygiene and nonsurgical therapy for the decontamination of the implant surface, followed if necessary by surgery. Local antimicrobials/antibiotics may be used as adjunct in the nonsurgical treatment of peri-implantitis.

The treatment of peri-implant mucositis is considered to be predictable. However, it should be kept in mind that complete resolution of the inflammation is not always possible and that some implants will remain to present with bleeding on probing after treatment. Supportive therapy is necessary to maintain a stable peri-implant condition and to reduce the risk for relapse. The treatment of peri-implantitis is not always predictable and may sometimes include removal of the infected implant.

Acknowledgments

The authors gratefully acknowledge the expert contribution of Prof. Dr. Daniel Wismeijer, and Dr. Yvonne de Waal, members of the working group, for the development of the Dutch clinical guideline.

Declaration of interest

The authors declare no conflict of interest. The research was funded by the authors and their institutions.

Authors' contributions

A. Louropoulou contributed to the conception, design, acquisition, analysis, interpretation of data, drafted the manuscript.

G.A. van der Weijden contributed to the conception, design, analysis, interpretation of data, critically revised the manuscript for important intellectual content.

All authors gave final approval and agree to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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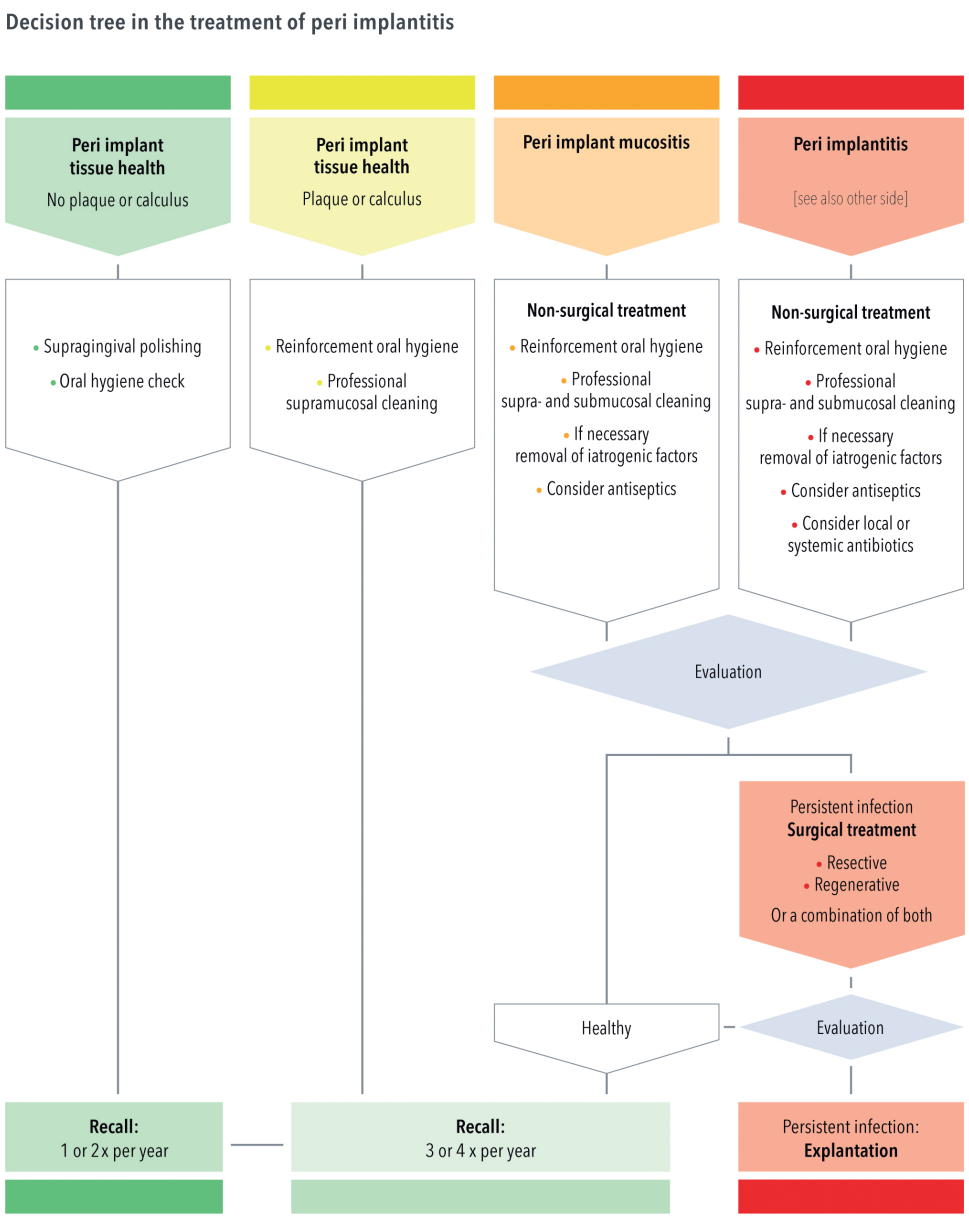
Table 1. Parameters that should be evaluated during baseline clinical assessment. Similar assessments should be done in any subsequent evaluation.

Baseline assessment around 8 weeks after placement of the implant-supported restoration: • Assess pocket depth • Assess bleeding on gentle probing • 1st radiograph (if not already taken immediately after placement of the implant-supported restoration) • Clinical photograph • Exudate/Suppuration • Implant mobility • Cleansability • Control Occlusion

Figure 1. Flow chart for the treatment of peri-implant diseases adapted from the Dutch clinical guideline.



Chapter 9

/ Summary, Discussion & Conclusions /

Titanium implant surfaces

The implant construction that supports the intra-oral restoration consists of two components with distinctive surfaces: the abutment or transmucosal part, which is exposed to the oral cavity and has a smooth surface and the implant itself or implant body, which is the part inserted into the bone and most frequently has a rough surface.

During the first twenty years the implant market was dominated by two implant systems with two discrete surfaces: the machined implant introduced by Brånemark and the titanium plasma sprayed implants introduced by Schroeder (Buser et al. 2017). Nowadays, dental implants are available in different materials, sizes, and lengths and with different surface properties and coatings (Esposito et al. 2014). The currently available implant systems from the major implant manufacturers differ from their respective predecessors in microroughness, physicochemical properties and nanoroughness (Wennerberg & Albrektsson 2010).

The original Brånemark implant had a turned surface. These surfaces are those produced by the turning machine process of a titanium rod and are considered to be smooth surfaces (Wennerberg & Albrektsson 2009). Machined surfaces span a wide range of surface textures (Stout et al. 1990). In implant dentistry the term 'machined' is mostly used to describe turned, milled or polished surfaces (Wennerberg & Albrektsson 2009). Implant surface modifications have led to improved bone-to-implant contact and better and stronger bone responses. They have allowed for reduced healing periods and predictable treatment outcomes in numerous treatment indications, such as immediate placement and immediate loading (De Bruyn et al. 2017). The modification methods can be divided into subtractive and additive processes. The subtractive techniques remove material from the implant surface creating pits or pores on the surface and result in a concave profile. Examples for these techniques are electropolishing, mechanical polishing, blasting, etching and oxidation. The additive techniques add material and create a surface with bumps and a convex profile. Examples of these techniques are hydroxylapatite and other calcium phosphate coatings, titanium plasma spraying and ion deposition (Wennerberg & Albrektsson 2009).

Surface roughness is often described in terms of Ra, a two-dimensional measurement, or preferably Sa, the corresponding three-dimensional parameter. These parameters describe the height of a surface structure, i.e. the average mean deviation of a profile (Ra) or surface (Sa) (Wennerberg & Albrektsson 2009). According to their surface roughness, dental implant surfaces are classified into four different groups. Smooth implant surfaces refer to a Sa value

of less than 0.5 μm; minimally rough surfaces refer to Sa values of 0.5 to less than 1.0 μm; moderately rough surfaces refer to Sa values between 1.0–2.0 μm; and rough surfaces have an Sa value of more than 2.0 μm (Albrektsson & Wennerberg 2004). Currently, minimally and moderate rough surfaces are accepted as the preferred surfaces for the part of the implant inserted into the bone (Wennerberg & Albrektsson, 2010; Buser et al. 2017).

On all implant surfaces a biofilm can form. However, surface properties may influence its formation. The roughness of the implant surface, as well as its chemical composition and surface free energy, has an impact on the amount and quality of plaque formation. Rougher surfaces and surfaces with high free energy, which is a characteristic of titanium, accumulate and retain more plaque. The initial adhesion of bacteria starts at locations with high wettability, which is also a characteristic of titanium, and from surface irregularities, like pits and grooves, where bacteria are protected from shear forces (Teughels et al. 2006). Consequently implant surfaces have been found to accumulate more plaque than natural teeth (Quirynen & Bollen 1995), and roughened titanium surfaces are considered to accumulate and retain more plaque than smooth surfaces (Quirynen et al. 1993). A Ra value of $\approx$ 0.2 μm has been suggested as a threshold roughness value below which no further significant changes in the amount of adhering bacteria can be observed (Bollen & Quirynen 1997).

Surface roughness also influences the quality of the soft tissue seal. The surface of a transmucosal abutment should be smooth to establish a long-lasting soft tissue seal and to avoid adverse soft tissue reactions (Sawase et al. 2000). Nevertheless a certain surface roughness is required for an optimal soft tissue seal. Highly polished abutments favour less plaque retention but they have been found to negatively affect the soft tissue seal due to interactions between surface structure and fibroblast and/or epithelial cell attachment and proliferation (Bollen et al. 1996). Thus implant components exposed to the oral cavity should have a smooth surface to avoid plaque accumulation and to promote an optimal soft tissue seal. The Ra values of the transmucosal part of most implant systems, nowadays, range from 0.1 to 0.3 μm, which is within the range of a smooth enamel surface and/or polished restorative materials (Quirynen et al. 1994a). Yet, because of the limited hardness of titanium there is, in theory, a risk of surface roughening during self-performed or professional cleaning (Quirynen et al. 2002).

Surface topography can affect the cell shape, orientation, proliferation and function (Könönen et al. 1992). Surface chemical composition is also important for tissue interactions (Sawase et al. 2000). It is generally accepted that the outermost atomic layer of the implant

surface is an essential factor for the interaction with tissues. A major problem associated with the removal of plaque from implant surfaces is the possible damage to the implant surfaces. Any damage to the surface induces changes in the chemical oxide layer (Kasemo & Lausmaa 1988) which in turn may affect the biocompatibility of the implant and consequently impair cell adhesion (Mouhyi et al. 1998). When the surface topography changes also the surface chemistry or physics may change simultaneously. Furthermore, when the surface microtopography is changed, the nanotopography of the same surface usually also changes. All these factors may affect biological responses (Wennerberg & Albrektsson 2009).

Mechanical instruments

Prevention of peri-implantitis implies keeping smooth surfaces of the implant supported restoration clean. Ideally, the instruments used to effectively clean smooth surfaces should cause minimal or no surface damage, should not create a surface that is more conducive to bacterial colonization and should not affect the implant–soft tissue interface. If the soft tissue attachment is disrupted, the instrumentation procedure should maintain a surface that is conducive to re-establishment of the soft tissue seal. When bone is lost, rough surfaces become exposed resulting in the bacterial colonization of these surfaces. The decontamination of these surfaces is mandatory to achieve healing, with re-osseointegration being the ultimate goal (Mombelli, 2002). In order to reduce microbial adherence and colonization on those rough surfaces that remain exposed to the oral environment, removal of the macroscopic and microscopic retentions is suggested (Jovanovic et al. 1993). The effect of mechanical instruments on smooth and rough titanium surfaces with respect to surface alterations, cleaning efficacy and biocompatibility has been evaluated in the studies presented in **chapters 2, 3 and 4**.

Surface alterations

Chapter 2 scrutinized the available evidence on the effect of instrumentation on the surface roughness. Because of the nature of the question, experimental and mostly *in vitro,* studies were included in the analysis. Regarding smooth surfaces, a roughening of the surface was observed when these surfaces were treated with metal curettes or sonic and ultrasonic devices with metal tips. Although with titanium curettes this occurs to a lesser extent the use of these instruments on smooth surfaces is not advisable. Similar findings were reported in

an experimental study using a bone defect-simulating model. Scanning electron microscopy (SEM) images revealed significant changes on the morphology of smooth surfaces when metal curettes and ultrasonic devices with metal tips were used (Sahrmann et al. 2015). In contrary, a recent study by Schmidt et al. (2016) reported no changes on the machined surface of an implant neck after a single use of an ultrasonic device with a metal tip, except for a tendency towards a smoother surface compared to the control. The implants were embedded into plastic models, which were then attached to a phantom head. This study setup, the handling of the instruments and the subjective nature of the ranking method used to evaluate changes may account for the observed differences.

A variety of non-metal curettes and inserts for sonic and ultrasonic devices have been developed and tested on smooth titanium surfaces, like plastic, teflon-coated, carbon or polyetheretherketone (PEEK) composite instruments. The use of non-metal instruments does not seem likely to produce a considerable level of surface roughening, although some roughening of the surface can be seen after multiple use. This damage can vary depending on the instrument used. The material of the instrument seems to be an important factor for the amount of the damage seen. When different non-metal instruments and inserts for sonic and ultrasonic devices were tested on titanium discs with polished surface, the least damage was seen with the carbon curette (Schmage et al. 2012).

Rubber cups do not seem to alter a smooth surface. It even seems possible to remove minor scratches and to restore the integrity of surfaces that have been slightly altered as a result of professional instrumentation by using rubber cups with flour of pumice paste or other polishing agents. This is dependent on the abrasiveness of the material.

Air polishing seems to cause no marked surface changes. Yet, some studies reported roughening of the surface. Differences in treatment time, angulation of the tip and distance from the surface may account for the reported differences. In the majority of the studies included in **chapter 2**, the air-abrasive device was used in combination with a sodium bicarbonate powder, which is rather abrasive. Increased surface roughness with crater formation has been reported when a sodium bicarbonate powder was used on titanium abutment surfaces (Cochis et al. 2013). Nowadays, less abrasive powders like amino acid glycine powders with different particle sizes, tricalcium phosphate powders and an erythritol powder are commercially available. *In vitro* studies have shown that these powders cause slight no or slight changes on smooth surfaces (Cafiero et al. 2016; Sarhmann et al. 2015; Schmage et al. 2012; Schmidt et al. 2016).

The studies included in **chapter 2** evaluated two types of rough surfaces: a moderate rough (SLA) and a rough (TPS) surface. Burs and metal instruments smoothen both surfaces by removing a part of the coating while non-metal instruments cause no visible changes. Air abrasive devices with a sodium bicarbonate powder seem to slightly smoothen SLA surfaces by flattening the sharp-edged elevations. No visible changes were observed on TPS surfaces. Similarly, the application of less abrasive amino acid glycine powders with different particle sizes on SLA surfaces does not seem to cause major changes on the surface roughness. Although sometimes a slight rounding of the sharp edges has been observed (Schwarz et al. 2009; Tastepe et al. 2013; Sahrmann et al. 2015). In general, air abrasive devices do not seem to cause major changes on moderate rough and rough surfaces. The slight changes that can sometimes be observed are dependent on the powder used, the angulation of the tip and the treatment time.

From **chapter 2** it becomes obvious that mechanical instruments can have an effect on the various titanium surfaces. Some instruments induce minimal, scarcely visible changes in surface topography while others account for more pronounced changes. The effect of mechanical instruments on the surface structure is dependent on various parameters related to the instrument used, but also to the surface itself. The degree of change that might be inflicted by an instrument is dependent on the material of the instrument, the treatment time and treatment mode (e.g. handling pressure, speed and direction of movement, angulation of the tip, hardness of tips or powders used). It should be kept in mind that what seems as a minor change after a single use may become a major change after repeated application of an instrument on the same surface. This is important for surfaces that are exposed to the oral environment and for instruments that are causing a roughening of the surface, especially since frequent maintenance is recommended for patients having dental implants. Depending on the surface and its localization, the best suitable instrument for this surface should be chosen. From the available instruments the air polisher seems at this moment the most suitable instrument for both smooth and rough surfaces, when preservation of the surface structure is required.

Surface decontamination

The effect of mechanical instruments on the surface structure may be of secondary importance, in case an instrument is not effective in removing accretions from the surface. A successive systematic review was performed in **chapter 3** to evaluate the ability of various

mechanical instruments to clean contaminated implant surfaces. Based on the available evidence non-metal curettes were found to be ineffective in removing bacteria and/or bacterial products from both smooth and rough titanium surfaces. Better results have been observed for sonic and ultrasonic devices with non-metal tips. These instruments were more effective in cleaning smooth than rough titanium surfaces. The effectiveness seemed to be dependent on the composition of the tip.

Rotating titanium brushes showed promising results on SLA surfaces. The best results were observed for the air-abrasive devices. These devices, when used with a sodium bicarbonate powder, were found to be effective in removing bacteria and bacterial products for both smooth and rough surfaces. All studies reported more than 84% removal of deposits irrespective of the surface type. Similar results were also observed when the less abrasive amino-acid glycine powders were used. However, complete biofilm removal should not be expected. These results are in agreement with another review on air abrasive devices (Tastepe et al. 2012). The authors of this review reported: "*In vitro*, the cleaning efficacy of air-powder abrasive treatment on titanium strips, discs or implants is high". Promising results for the air abrasive were also reported in a review evaluating the decontamination of infected implants by mechanical, chemical and physical methods (Meyle 2012). This review included *in vitro*, animal and human studies, and the authors concluded: "For decontamination of infected implant surfaces air-abrasive treatment seems to work".

In clinical situations, several factors, such as the soft and hard tissues surrounding the implant, the implant/abutment design or the design of the restoration may render the accessibility of the titanium surfaces more difficult and may limit the cleaning efficacy of an instrument. The accessibility of an air abrasive device with glycine powder to clean minimally rough implant surfaces was assessed in models imitating peri-implantitis with different defect morphologies. The authors concluded: " Although a complete cleaning of the implant surfaces was not possible in any of the defect models, it was possible to clean the biggest part of the surface up to more than 95% in easy accessible defects. In broad defects of 60° and 90° defect angulations, it was even possible to get access to more than 75% of the lower faces of the implant threads". Narrow defects ($< 30^{o}$) and the area under the threads were difficult to reach (Sarhmann et al. 2013). In a subsequent study using the same model, the air-abrasive device was compared with other modalities as a stainless-steal curette and an ultrasonic device with metal tip. For implants with a smooth neck and a body with SLA surface the air abrasive device showed a superior cleaning potential as compared to the debridement

with ultrasonic and manual instruments. In wide defects, the differences between the instruments were more pronounced (Sahrmann et al. 2015). The two-abovementioned studies simulated condition similar to an open-flap debridement. Recently, the same research group published another study using a bone defect-model that includes a custom-made mucosa mask in order to simulate the conditions of nonsurgical implant surface debridement, which made the access to the implant even more difficult. The air abrasive with a glycine powder and a subgingival nozzle provided superior cleaning results compared to a metal curette or an ultrasonic device with a metal tip. Again the differences between the instruments were more pronounced in the wider defects irrespective of the operator's experience (Ronay et al. 2016). Air pressure seems to be the most important parameter that influences the cleaning efficiency of the air abrasive device. It has been shown that in order to get the best results when used subgingivally the device should be used with high pressure, deep insertion of the nozzle and enough water flow. The cleaning effect of the device reaches deeper than the nozzle physically reaches and the movement of the nozzle improves the cleaning efficiency, irrespective of the direction of the movement (Tastepe et al. 2016).

Surface biocompatibility

Bacterial contamination has been shown to affect cell behaviours and to alter the elemental composition of a titanium surface. Kawahara et al. (1998a, 1998b) investigated cell contact to titanium surfaces and adhesive strength of epithelial cells and fibroblasts in the presence of plaque extracts. The plaque extracts had a greater effect in decreasing the growth rate of fibroblasts than that of epithelial cells. Mouhyi et al. (2000) indicated that biofilm increases the amount of carbon (C) at the titanium oxide layer. The elemental composition of unused commercially pure titanium foils was 9% titanium (Ti), 48% carbon (C), 40% oxygen (O) and traces of 10% nitrogen (N) and chlorine, whereas intraorally contaminated foils exhibited 70% C, 20% O, 10% N and only traces of titanium (<1%). Next to bacterial contamination, treatment modalities used to decontaminate the titanium surface can also affect its surface topography and chemical composition. The surface composition of failed and retrieved machined titanium implants after various cleaning procedures has been evaluated in a study. Although some of the tested methods resulted in a macroscopically clean surface, all of them failed to re-establish the original surface elemental composition (Mouhyi et al. 1998). In addition, residues of the instruments may deposit themselves to the treated surfaces, which in turn might disturb cell attachment (Schwarz et al. 2003). Residues of various curettes and

inserts for ultrasonic devices, as well as powder remnants after the use of air abrasive devices, have been found on the titanium surfaces after instrumentation (Schwarz et al. 2003; Schwarz et al. 2009; Tastepe et al. 2013).

Alterations to the titanium surface due to contamination and/or after instrumentation may affect biological responses. It is obvious that an instrument would be of no value if it renders the surface non-biocompatible, i.e. intervene with the normal tissue healing. Subsequently a third systematic review was conducted in **chapter 4** and concluded that all instruments reduce the biocompatibility of the surface irrespective of the presence or absence of plaque. However, none of them has a deleterious effect.

The air-abrasive devices seem to have the least effect on the biocompatibility. This is based mainly on studies on rough (SLA and TPS) titanium surfaces and with the utilization of sodium bicarbonate powder. This conclusion is in accordance with a recently published study that evaluated the biocompatibility of SLA surfaces after treatment with a plastic curette, an air abrasive device with glycine powder, a titanium brush or implantoplasty (Toma et al. 2016). No treatment modality did impede the biocompatibility of the titanium surface. The air abrasive device showed slightly better results that the other modalities. This study has also reported promising results for the use of implantoplasty on SLA surfaces. This modality induced titanium alloy purity and hydrophily without altering osteoblast proliferation and production of cytokines potentials (Toma et al. 2016). Another study also reported that implantoplasty applied on SLA surfaces was associated with an undisturbed viability of gingival fibroblasts and an elemental composition comparable to machined surfaces, and caused minimal reduction of the implant diameter (Schwarz et al. 2016). Similarly, an earlier animal study employing the ligature-induced peri-implantitis defect model demonstrated the creation of a smooth surface, which supported a close adhesion of the sub-epithelial connective tissue (Schwarz et al. 2011).

Taking together the results of the systematic reviews in **chapters 2, 3, 4** it seems, based on the currently available *in vitro* data, that air-abrasive devices represent the most promising tool in the treatment of peri-implant infections. They are effective in biofilm removal, without causing major changes on the surface topography or having detrimental effect on the biocompatibility of a titanium surface. These results are corroborated to a certain extent by findings from animal studies. Mechanical cleaning with an air abrasive device appeared to provide adequate decontamination to allow for some new bone formation in direct contact with the implant surface (Roos-Jansåker et al. 2003).

A number of clinical studies have also evaluated the efficacy of air polishing compared with other treatments on changing signs of inflammation in patients with peri-implant mucositis or peri-implantitis. These studies have been summarized in a recently published systematic review. The available data suggest that air polishing used as an adjunctive measure or as monotherapy can result in significant clinical improvements in terms of bleeding scores, following a single or repeated nonsurgical treatment of peri-implant mucositis and/or peri-implantitis. At mucositis sites, glycine air polishing seems to be as effective as conventional mechanical debridement with non-metal instruments with or without local antiseptics. For the non-surgical treatment of peri-implantitis, glycine powder air polishing was associated with a significant improvement in bleeding scores over the control measures investigated (Schwarz et al. 2015). A retrospective study evaluating the effect of an air abrasive device during surgical treatment of peri-implantitis compared with plastic curettes and cotton pellets impregnated with saline reported that, although both groups revealed a significant improvement in clinical parameters, the air abrasive group yielded better results regarding bleeding scores and probing depths at 12 months (Toma et al. 2014).

Air abrasive powders

The type of the powder seems to be of importance for the biological responses. Glycine powders seem to reduce the biocompatibility more than sodium bicarbonate, when used on SLA surfaces (Schwarz et al. 2009). It has been shown that tricalcium phosphate, when used as an additive to powders, may increase the cleaning efficiency of the air abrasive (Tastepe et al. 2013). These results are also supported by the findings from another study that evaluated the effectiveness of a powder consisting of glycine and tricalcium phosphate, in comparison to two established powders based on glycine and sodium bicarbonate, in biofilm removal from SLA titanium surfaces (John et al. 2016). However, all powders that were tested affected the biocompatibility and the extent to which this was influenced depended on the powder used. The less abrasive powders (glycine and glycine with tricalcium phosphate) reduced the viability of SAOS-2 cells more than sodium bicarbonate; but the observed differences were not statistically significant (John et al. 2016). This finding has been attributed to the hardness and bigger particle size of sodium bicarbonate, which has also been observed to induce surface changes. It was speculated that a certain amount of surface ablation might improve the biocompatibility of moderate rough surfaces (Schwarz et al. 2009).

Another possible explanation for the reduced biocompatibility that has been reported in the literature is small particles of the powders embedded at the implant surface (Tastepe et al. 2013). What can be the possible effect of these remnants is not clear yet. In the study in **chapter 5**, the aim was therefore to assess 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. This study showed that powders might indeed have different effects on various cells. The use of tricalcium phosphate containing powder seems promising. It has been speculated that tricalcium phosphate residues on the implant surface could improve biocompatibility and support wound healing (Tastepe et al. 2013; John et al. 2016). The results of **chapter 5** seem to support this notion. However, more studies are necessary in this area.

Chemotherapeutica

Surface decontamination

Chemotherapeutic agents, alone or in combination with mechanical instruments, have also been used for cleaning implant surfaces. **Chapter 6** reviewed the literature for evidence regarding the ability of different chemotherapeutic agents to decontaminate titanium surfaces. The available data were very limited and precluded any firm conclusions. Yet, it seems that citric acid has the highest potential to remove bacteria and bacterial products from titanium surfaces. It should however be kept in mind that chemical agents are less capable in removing biofilm than mechanical instruments. In an *in vitro* study evaluating the effectiveness of different products with chemotherapeutic agents (EDTA, citric acid, cetylpyridium chloride, Ardox-X, hydrogen peroxide, chlorhexidine) to decontaminate machined and SLA titanium surfaces, citric acid showed the highest decontamination potential with respect to both killing and removing bacteria (Ntrouka et al. 2011). These results are to a certain extent corroborated by the findings of another study that evaluated the ability of three chemical agents, citric acid, chlorhexidine and EDTA/sodium hypochlorite, to decontaminate rough implant surfaces contaminated with biofilm grown from in-vivo peri-implantitis sites. The antimicrobial effect was greater for citric acid and EDTA/sodium hypochlorite groups, followed by the chlorhexidine group (Kotsakis et al. 2016). In an earlier study different results with respect to the killing potential of citric acid were reported. In this study the antibacterial efficacy of several antimicrobials on the oral microflora attached to titanium specimens

with a machined surface after overnight contamination in the oral cavity of volunteers was assessed. All agents used were shown to significantly reduce the total number of attached bacteria after immersion for 1 minute. However, citric acid showed less bactericidal effect compared to the other agents. It was concluded that the antiseptics sodium hypochlorite, hydrogen peroxide, citric acid, chlorhexidine, and essential oils might have some beneficial effect in reducing the bacteria load on titanium surfaces (Gosau et al. 2010).

Surface biocompatibility

Chemotherapeutic agents may have an effect on the elemental composition of the titanium surface, which subsequently may affect the biocompatibility of the surface and the biologic responses. Elemental contaminants or salts have been found on titanium surfaces after treatment with chemical agents (Mouhyi et al. 1998; Kotsakis et al. 2016). An *in vitro* study assessed the effect of different chemical agents (citric acid, hydrogen peroxide, chlorhexidine, tetracycline, doxycycline, sodium fluoride and peroxyacetic acid) on the oxide layer morphology of titanium. The treatments consisted of immersion of samples in a solution or rubbing them on with cotton swabs. Rubbing with swabs led to signs of titanium oxide damage in a pH-related manner (Wheelis et al. 2016).

One study investigated the attachment and proliferation of epithelial cells on smooth titanium surfaces treated with citric acid, hydrogen peroxide and chlorhexidine. Treatment with citric acid and hydrogen peroxide resulted in respectively similar or enhanced proliferation of epithelial cells compared to an untreated control. Less favourable results were observed with chlorhexidine due to adsorption on the titanium surface (Ugvári et al. 2010). It is also reported that chlorhexidine significantly impaired the proliferation of osteoblasts on treated titanium surfaces. Based on these findings the use of chlorhexidine is not recommended because it produces cytotoxic effects and may thus compromise the biocompatibility of the surface (Kotsakis et al. 2016).

A clinical study demonstrated that the application of a 35% phosphoric etching gel at pH 1 adjunctive to the use of carbon curette and rubber cup resulted at 5 months in a higher reduction in gingival index scores and a lower number of colony-forming units compared to control treatment (Strooker et al. 1998). In patients with peri-implant mucositis, professionally administered chlorhexidine (irrigation, gel application or combination of both) failed to show adjunctive beneficial effects compared with mechanical debridement alone (Porras et al. 2002; Heitz-Mayfield et al. 2011). Similarly, in the surgical treatment of peri-implantitis

chlorhexidine resulted to a greater suppression of anaerobic bacteria in short term but failed to show superior clinical results compared to placebo-control (De Waal et al. 2013).

Self-performed mechanical home care

Proper maintenance of implant-supported restorations is to a large extent in the control of the patient and is dependent on the daily oral hygiene. In the study in **chapter 7**, the available evidence with respect to the patient-administered measures for mechanical plaque removal around implant-supported restorations was scrutinized. Compared to the studies focussing on placing dental implants the scientific literature on how to maintain them is very limited. All studies reported an improvement in the clinical parameters over time. Powered toothbrushes seem to be effective in cleaning both fixed and removable implant-supported restorations. No hard evidence was found that powered toothbruhing is superior to manual toothbrushing, although powered toothbrushing may help to overcome limitations in manual dexterity and accessibility. These findings are in accordance with the recommendations of the Ninth European Workshop on Periodontology regarding patient-administered measures in the management of peri-implant mucositis (Jepsen et al. 2015) and a Cochrane systematic review on interventions aiming at maintaining and recovering soft health around dental implants (Grusovin et al. 2010). The evidence on interproximal cleaning around implant-supported restorations is scarce. Interdental brushes, when used by a trained dental care professional, seem to be effective in removing plaque from interproximal areas (Chongcharoen et al. 2012).

Often implant-supported restorations present contours and shapes that render plaque removal difficult, even by the most capable individuals. A clinical retrospective study showed that high proportions of implants diagnosed with peri-implantitis were associated with inadequate plaque control or lack of accessibility for oral hygiene measures whereas peri-implantitis was rarely diagnosed at implants supporting cleansable restorations or when proper plaque control was performed (Serino & Ström 2009). Like Salvi and Ramseier (2015) stated: “Individually tailored oral hygiene instructions should be given to patients rehabilitated with dental implants. Whenever possible, margins of implant- supported restorations should be placed at or above the mucosal margin to facilitate access for plaque control and implant-supported restorations with poor access for plaque removal should be adjusted or replaced by cleansable restorations”. Anyhow at present, home care recommendations are based mainly on the knowledge that is available with respect to cleaning of natural teeth. It

becomes evident that there is an urgent need for academic institutions and industry to initiate and support high quality randomized controlled clinical trials on this topic in the near future.

Clinical Guideline

The consensus report of the Eleventh European Workshop on Periodontology on effective prevention of periodontal and peri-implant diseases stated that primary prevention of peri-implantitis is managing peri-implant mucositis. Consensus was reached on recommendations for patients with dental implants and dental care professionals with regard to the efficacy of measures to prevent or manage peri-implant mucositis. It was particularly emphasized that implant placement and prosthetic reconstructions need to allow proper personal cleaning, proper monitoring of the peri-implant tissues and professional plaque removal (Jepsen et al 2015). **Chapter 8** is an epitome of a clinical guideline developed in the Netherlands on behalf of the Dutch Society of Periodontology and the Dutch Society of Oral Implantology regarding the diagnosis, prevention and treatment of peri-implant diseases.

A "Clinical Practice Guideline" (CPG) has been defined as a "systematically developed statement to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances." (Field & Lohr 1990). Practically, guidelines attempt to distil a large body of medical expertise into a convenient readily usable format (Cook et al. 1997). Briefly, the development of a CPG includes the following five steps: Determination of the scope and the intended audience; Definition of the problem and formulation of focused questions; Search for, selection and combination of the available evidence and evaluation of the quality of the available evidence. This step is done in a way analogous to that used for systematic reviews. The strength of the recommendations is in part dependent on the quality of the available evidence but also on other factors like the balance between desirable and undesirable consequences of specific treatments and cost-effectiveness. Continuous implementation and evaluation of the guideline is mandatory to remain up to date.

Conclusions

Decontamination of an implant surface constitutes an important component in the prevention and treatment of peri-implant diseases. Depending on the surface characteristics, the localization of the surface and the goal of the treatment, the best suitable instrument for each surface should be chosen. Based on the available *in vitro* data, air abrasive devices with sodium bicarbonate powder appear to be effective in removing biofilm from both smooth and rough titanium surfaces, without causing major changes on the surface structure, especially in the case of rough surfaces. Amino acid glycine powders are less abrasive but seem to be similarly effective in removing biofilm. Newly developed powders, like powders containing tricalcium phosphate and an erytritol powder, seem also effective in removing biofilm from implant surfaces. For rough surfaces that are going to become exposed to the oral environment after treatment implantoplasty seems to be a realistic option if the surfaces is sufficiently accessible. All mechanical instruments affect the biocompatibility of the treated surfaces but none of them seem to have a deleterious effect. The best results have been reported for the air abrasive devices. The selection of the powders seems to be of importance. Powders with tricalcium phosphate as additive may have a beneficial effect on the biological responses.

From the available chemotherapeutic agents, citric acid and hydrogen peroxide seem to have the best potential.

There is much discussion on the aetiology, prevalence and treatment modalities for peri-implantitis, but everybody agrees on one thing; regular controls and meticulous maintenance from both the patients and dental care professionals are mandatory to avoid problems. Baseline clinical and radiographic recordings are important to be able to follow implants over time and to differentiate between health and disease. According to the "*Dutch approach*", the first time to assess probing pocket depths around implants should be around 8 weeks after prosthetic installation in order to give the soft tissue the necessary time to adapt. Changes in clinical and/or radiographic parameters can be an alarming sign.

Proper maintenance of the peri-implant soft tissue health is largely in the control of the patient and is depended on the daily self-care. Patients with dental implants should receive individually tailored instructions for optimal oral hygiene. The current home care recommendations are based on the knowledge that is available with respect to cleaning of natural teeth. Subsequently oral hygiene around dental implants should be one of the priorities on the research agenda in dentistry.

Prevention and early diagnosis of problems is the key for long-term success with dental implants. Like Garber already in 1991 stated:

"Implants; the name of the game is still maintenance".

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/ Nederlandse samenvatting /

Serendipiteit

Het is allemaal begonnen met een toevalsbevinding. In 1952 ontdekte Per-Ingvar Brånemark het principe van verankering van titanium celkamers in bot. Hij noemde het fenomeen osseointegratie. In 1965 werden door hem de eerste titanium implantaten bij een patiënt in de mond geplaatst. Sinds de jaren 1980 wordt er als onderdeel van de tandheelkundige zorg steeds vaker geïmplanteerd.

Calamiteit

Hoewel de implantaten een valide en succesvolle behandeloptie zijn gaan vormen, zijn deze niet vrij van complicaties. De biologische complicaties hiervan, de zogenoemde peri-implantaire ziektes vormen een belangrijk bedreiging voor het behoud van de implantaten. De peri-implantaire ziektes zijn ontstekingsprocessen in de weefsels rondom implantaten. Er worden naar analogie in de parodontologie twee processen onderscheiden: peri-implantaire mucositis en peri-implantitis (respectievelijk gingivitis en parodontitis). Peri-implantaire mucositis is een reversibele ontsteking van de peri-implantaire mucosa. Bij peri-implantitis is er naast de ontsteking van de zachte peri-implantaire weefsels ook sprake van botafbraak rond het implantaat.

Onderzoek laat zien dat hoewel de prevalentie lastig te bepalen is, toch kan worden aangenomen dat de gemiddelde prevalentie van peri-implantaire mucositis ongeveer 43% is, terwijl de gemiddelde prevalentie van peri-implantitis rond de 22% is. Als belangrijkste risicofactoren voor het ontstaan van peri-implantaire ziektes worden in de literatuur aangegeven: onvoldoende mondhygiëne, onbehandelde parodontitis in de rest van de mond en roken.

Behandelbaarheid

De behandeling van peri-implantitis is niet eenvoudig en het resultaat ervan blijft onvoorspelbaar. Voorkomen is daarmee beter dan genezen. Primaire preventie is gebaseerd op selectie van de juiste patiënten, goede planning en uitvoering van de behandeling maar ook op regelmatige controles van de implantaat-gedragen constructies en zorgvuldige onderhoud door zowel de patiënten als de mondzorg professionals.

Reinigbaarheid

Een tandheelkundig implantaat bestaat uit twee delen: het transmucosale deel dat door de mond slijmvlies (tandvlees) in de mondholte steekt en blootgesteld is aan het orale milieu, en het implantaat zelf dat met schroefwindingen onder het tandvlees direct contact met het kaakbot heeft. Het oppervlak van het transmucosale deel is glad, terwijl het deel van het implantaat dat botcontact maakt voornamelijk een ruw oppervlak heeft. Dit laatste heeft als doel de osseointegratie te bevorderen. Het verwijderen van biofilm van implantaatoppervlakken (door zelfzorg en door tandheelkundige zorgprofessionals) is essentieel om peri-implantaire ziektes te voorkomen en te behandelen. Bij de nazorg en de behandeling van peri-implantaire mucositis moet er normaal gesproken een glad (titanium) oppervlak gereinigd worden. De instrumenten die op de transmucosale implantaatoppervlakken gebruikt kunnen worden, mogen deze oppervlakken niet beschadigen omdat dit anders rekolonisatie met micro-organismen zou kunnen bevorderen. Dit is met name belangrijk voor die onderdelen van het implantaat die blootgesteld zijn aan het orale milieu. De hulpmiddelen die ervoor het meest gebruikt worden zijn mechanische instrumenten en chemische middelen. Bij een ernstige peri-implantaire ontsteking kan het zo zijn dat door botverlies ook het ruwe deel van het implantaat boven het botniveau komt te liggen. Dan moeten de windingen van het implantaat en het ruwe oppervlak gereinigd worden. Dit is niet eenvoudig omdat micro-organismen zich in het ruwe en het soms poreuze oppervlak kunnen verschuilen en onbereikbaar zijn voor de instrumenten van de tandheelkundige zorgprofessionals..

Instrumentatie

In diverse onderzoeken van de afgelopen decennia zijn verschillende mechanische instrumenten op verschillende implantaatoppervlakken getest: metalen handinstrumenten, niet-metalen handinstrumenten, (ultra)sone scalers met metalen of niet-metalen tips, air polishers met diverse poeders, polijstcupjes/puntjes met of zonder polijstpasta en diamant-/carbideboren.

In **hoofdstuk 2** werd in de literatuur gezocht naar wetenschappelijk bewijs voor de te verwachten effecten van diverse mechanische instrumenten op de oppervlaktestructuur van gladde en ruwe titaniumoppervlakken. De uitkomsten van dit review tonen dat air polishers, niet-metalen instrumenten en rubber polijst cupjes geen of minimale schade aan gladde titaniumoppervlakken toebrengen en daardoor veilig toegepast kunnen worden in de nazorg van patiënten met implantaten. Als er geen veranderingen in de oppervlaktestructuur van

ruwe implantaatoppervlakken mag worden aangebracht, lijken niet-metalen instrumenten en de air polisher de meest geschikte instrumenten. Als het doel is het ruwe implantaatoppervlak juist gladder te maken en bijvoorbeeld ook de schroefwindingen te verwijderen, dan worden diamant-/carbideboren aanbevolen. Dit bijvoorbeeld ten behoeve van implantoplastie wanneer het ruwe implantaatoppervlak is blootgesteld aan het orale milieu. Of dit laatste ook noodzakelijk is, staat momenteel ter discussie.

Misschien nog belangrijker dan het effect van een instrument op de oppervlakte structuur is of een instrument effectief is in het reinigen van het oppervlak. In **hoofdstuk 3** werd bekeken welke mechanische instrumenten effectief zijn in het reinigen van het implantaatoppervlak en het verwijderen van biofilm. De resultaten van deze review duiden erop dat air polishers de meest effectieve instrumenten zijn voor het verwijderen van biofilm van zowel gladde als ruwe titaniumoppervlakken. Met minder bewijs werden ook positieve resultaten gevonden voor roterende titaniumborstels op (ruwe) SLA-titanium-oppervlakken en (ultra) sone scalers met niet-metalen tips op gepolijste oppervlakken. De literatuur laat verder zien dat de effectiviteit van alle mechanische instrumenten bij het verwijderen van tandsteen beperkt is.

Bacteriële contaminatie kan de chemische samenstelling van een titaniumoppervlak veranderen. Ook kan instrumentatie een ongunstig invloed hebben op de samenstelling en oppervlaktestructuur van een titaniumoppervlak. Dit kan de biocompatibiliteit van het implantaat negatief te beïnvloeden. In **hoofdstuk 4** werd bekeken wat het effect van de diverse mechanische instrumenten op de biocompatibiliteit van het implantaatoppervlak is. Alle instrumenten reduceren de biocompatibiliteit van het titaniumoppervlak. Van alle geteste instrumenten blijkt de air-polisher het minst negatieve effect te hebben.

De air-polisher kan met diverse poeders gebruikt worden. In **hoofdstuk 5** werd onderzocht wat de invloed van de diverse poeders op de cellen die in het peri-implantaire weefsel voorkomen kan zijn. Het blijkt dat de diverse cellen verschillend reageren op de geteste poeders. De selectie van het meest geschikte poeder lijkt van belang te zijn voor de genezing.
Geen van de mechanische instrumenten blijkt alle biofilm van het titaniumoppervlak te verwijderen, zeker als het oppervlak moeilijk bereikbaar is. Er kan dus ook overwogen worden om de behandeling met chemische middelen te combineren. Hiermee kunnen dan de bacteriën die op de titaniumoppervlakken zijn achtergebleven alsnog mee worden gedood. In **hoofdstuk 6** werden chemische middelen geëvalueerd in relatie tot de biofilm op het titaniumoppervlak. In dit hoofdstuk werd bekeken welke middelen effectief zijn in het verwijderen

en afdoden van biofilm van titanium implantaatoppervlakken. Het gebruik van een zuur (etsgel) lijkt hierbij op dit moment het meest effectief.

Zelfzorg

Het onderhoud van de implantaat-gedragen constructies is grotendeels de verantwoordelijkheid van de patiënt en het is afhankelijk van de dagelijkse plaque-beheersing. In **hoofdstuk 7** werd in de literatuur gezocht hoe een patiënt het beste een implantaat-gedragen constructie zou kunnen reinigen. Hoewel elektrisch poetsen niet superieur blijkt te zijn vergeleken met poetsen met een handtandenborstel, kan het helpen om beperkingen in de handvaardigheid te beperken en de toegankelijkheid van de te reinigen constructies te verbeteren. Wat de interdentale reiniging betreft, is floss geen goed middel als een ruwe implantaatoppervlak blootgesteld is aan het orale milieu. Het gebruik van een rager of stoker is hiervoor beter geschikt.

Van systematische reviews tot een klinische richtlijn

De laatste jaren wordt in de medische wereld de ontwikkeling van klinische richtlijnen nagestreefd. **Hoofdstuk 8** betreft de samenvatting van een klinische richtlijn die vanuit de Nederlandse Vereniging voor Parodontologie (NVvP) en de Nederlandse Vereniging voor Orale Implantologie (NVOI) is ontwikkeld met betrekking tot de preventie, diagnostiek en behandeling van peri-implantaire ziektes. Periodieke controles en zorgvuldig onderhoud zijn van groot belang om peri-implantaire ziektes te voorkomen of ze vroegtijdig te diagnosticeren. Vroegtijdige diagnose van ontsteking en botverlies rondom implantaten is essentieel om tijdig adequate therapie te bieden. Echter door de grote variatie in type van implantaten, methodiek van plaatsing ten opzichte van omliggende structuren zoals bot en zachte weefsels maar ook de vorm van de vervaardigde constructie, is er geen universeel referentiepunt voor het vaststellen van gezond of ongezond. Daarmee is deze 'nulmeting' een onmisbaar onderdeel voor de start van de controles van de implantaat-gedragen constructies. De klinische 'nulmeting' vindt bij voorkeur ongeveer acht weken na het plaatsen van de suprastructuur plaats, zodat het peri-implantaire weefsel zich eerst aan de constructie heeft kunnen adapteren.

Al met al geeft dit proefschrift kort samengevat aan dat:

het voorkomen van peri-implantaire infecties beter is dan genezen!

Acknowledgements

A “thank you” note for a journey towards knowledge.

“As you set out for Ithaka, hope the journey is a long one,
Full of adventure, full of discovery.”
C.P. Cavafy, ITHAKA

My journey started many years ago when as a dental student I started working in the periodontal practice of George Makris in Thessaloniki, Greece. His work and enthusiasm inspired me to become periodontist. Of course nothing would have happened if Ubele van der Velden and Bruno Loos did not give me the chance to start my journey and become periodontist. For that I own them gratitude.

My journey would have been a short one if I had not met Dick Barendregt. He believed in me and gave me the opportunity to work with him. He gave me as young periodontist at that time the space and freedom to expand my knowledge and skills in clinical periodontology; but always supervising from a distance ready to help, if necessary. I thank him for his mentorship and for the confidence he showed in me.

Thanks to Dick I came in contact with Fridus van der Weijden, a visionary, a true scientist who is continuously seeking new knowledge. My cooperation with Fridus made possible a dream to come true. Fridus became my companion in the most challenging part of my journey. He introduced me into the world of science, stimulating me with not only scientific but also philosophical discussions, coaching and motivating me. His guidance is still invaluable.

All journeys have surprises, hidden treasures that one is grateful to discover. The hidden “pearl” in my journey was Dagmar Else Slot. Dagmar was always there for me ready to help. She has an unbelievable gift in finding solutions even for the most challenging situations. The quality of her supervising is much more than I ever wished for.

Last but not least I want to thank my parents Dimitis and Athina and my husband Pavlos, my steady companions in my pursuit of knowledge. Thank you for all the sacrifices you did, the psychological and physical support and the encouragement you provided me.

" Keep Ithaka always in your mind.
Arriving there is what you are destined for.
But do not hurry the journey at all.
Better if it lasts for years,
So you are old by the time you reach the island,
Wealthy with all you have gained on the way,
Not expecting Ithaka to make you rich.

Ithaka gave you the marvelous journey.
Without her you would not have set out.
She has nothing left to give you now.

And if you find her poor, Ithaka won't have fooled you.
Wise as you will have become, so full of experience,
You will have understood by then what these Ithakas mean."

C.P. Cavafy, ITHAKA

As an introduction but also epilogue to this note I chose a poem from the Greek poet Cavafy. Reaching the destination is not the most important part of the journey. The knowledge and experience acquired and the people you come across along the way is what actually matters. When I started this thesis I thought that its completion would be the end of my journey but now I realise that my journey towards knowledge has just begun. I thank you all for everything you did for me.

List of publications

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Honours

Graduate Research in EFP (2nd prize)

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Curriculum Vitae

Anna Louropoulou received her DDS degree from the Dental School of the Aristotle University of Thessaloniki, in 2002. She practiced then general dentistry in a private office in Thessaloniki for almost two years. In 2004 she was enrolled in the postgraduate program for Periodontology and Implant Dentistry at the Academic Centre for Dentistry Amsterdam (ACTA), which she finished in 2007. After graduation she started working as periodontist and implantologist in a private practice for Periodontology and Implant Dentistry, in Rotterdam and in Utrecht, The Netherlands. In 2008 she started her PhD research at the department of Periodontology at ACTA, concerning the prevention and treatment of peri-implant diseases and more specifically the cleaning of titanium implant surfaces.

PERIODONTOLOGY

Anna Louropoulou