Peri-implant health:

the effect of implant design and surgical procedure on bone and soft tissue stability

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CHAPTER 1

GENERAL INTRODUCTION

Achieving osseointegration of a dental implant is no longer the key issue in research related to oral implantology. Due to improvements in biomaterials and clinical procedures, implant therapy is currently predictable, with an 89.5 to 99.2% survival rate of functional rehabilitation.[1-6]

Despite high survival rates given in the literature, the scientific community seems heavily affected by the escalating discussion on peri-implantitis. This has divided the scientific community and risks to ruin the good reputation of implant dentistry. Some of these disagreements are related to the inconsistency in the case definition, case selection, and the variability in diagnostic thresholds for disease.[7-9] Two recent systematic reviews indicated that homogeneity in peri-implantitis reporting is still lacking.[10,11] One of the systematic reviews listed nine different threshold levels for radiographic bone loss applied to diagnose peri-implantitis and the other review detected ten case definitions for peri-implantitis.

In addition, the focus of clinical research has shifted from predominately survival-oriented to patient-centred outcomes and peri-implant health. The latter is paramount for long-term success. A prerequisite for peri-implant health is peri-implant bone stability. Stable peri-implant bone levels preserves soft tissue, prevents recession and possible esthetic burdens, and minimizes the risk for complications such as 'peri-implantitis', implant fractures, and eventually implant loss.[12,13] The peri-implant bone level could be affected by patient-, implant-, and site-specific factors. In the paragraphs below we will outline how these factors influence implant success and what the remaining gaps in the literature are.

PATIENT-RELATED FACTORS

Besides the issues mentioned above, patient-related factors such as the inability to perform oral hygiene are related to peri-implantitis[14] and regular maintenance is key for the prevention of this disease.[15] These findings are confirmed by a meta-analysis including 13 papers. The authors concluded that a more regular, individually tailored peri-implant maintenance therapy prevents possible biologic complications over time and improves the long-term outcome of implants.[16] Recent systematic reviews investigated the relationship between additional patient-related factors and the implant treatment outcome. Amongst these factors, smoking habits have

been shown to affect implant failure irrespective of the implant surface, increase the risk of postoperative infection and yield more marginal bone loss especially in the maxilla.[17] Moreover, the history of periodontal disease was suggested as a second important patient-related factor. Increased susceptibility for periodontitis may translate into an increased susceptibility for implant loss, loss of supporting bone and/or postoperative infection.[18] Interestingly, no significant relation was found between diabetes and implant failure.[19]

IMPLANT-RELATED FACTORS

In addition to patient-related factors, implant-related factors could influence peri-implant bone stability. Several modifications in implant macro-design and micro-design have been introduced to optimize peri-implant bone stability. One of the most investigated and debated implant-related micro-design factors over the last decades is surface topography and composition. Both factors have their influence on implant surface roughness, which is expressed in a Sa value. This three-dimensional value expresses an absolute difference in the height of each point compared to the arithmetical mean of the surface.[20] In the early years of implant dentistry two types of implant surfaces were used, namely the minimally rough surface (Sa = 0.5–1 µm) and the microporous titanium plasma-sprayed surface (Sa > 2 µm). The former was coined as smooth, while the latter was denoted as a rough implant surface.

Manufactures performed modification of the implant surface by sandblasting, acid-etching, anodic oxidation, or hydroxyapatite coating. These techniques resulted in a moderately rough implant surface (Sa = 1–2 µm), which is nowadays the most used roughness in dental implants. These modifications were necessary to improve the osteoconductive and osteoinductive properties of the implant. Studies showed that the moderately rough implant surface had better blot cloth stabilisation, enhanced production of biological mediators, stimulated osteogenic maturation leading to higher bone-to-implant contact, and increased bonding strength of the bone to the implant.[21,22] Additionally, the modifications also led to a lower clinical failure rate,[23] and researchers observed a higher removal torque compared to the smooth implant surfaces.[24] Hence, this surface modification made it possible to load the implant earlier or even immediately

after the surgery. The resulting surface enlargement allowed shorter implants to be used without jeopardizing the prognosis and reduced the necessity for bone grafting procedures.[25] Besides the afore-mentioned benefits, related to faster osseointegration and enlarged indication, rough implant systems have been linked to increased bacterial adhesion in vitro.[26] However, the applied model in the latter study does not mimic the clinical reality. Nevertheless, two Cochrane systematic reviews suggested, albeit with limited evidence, that smooth surfaces had a 20% reduced risk of being affected by peri-implantitis over a three-year period.[27,28]

Besides the above-mentioned micro-design factor implant surface roughness the manufactures also adjusted macro- design features of the implant to improve the clinical outcome of implant treatment. An implant macro-design feature, which has been modified over time as well, is the type of abutment connection. Different abutment connections have been used, in order to overcome abutment screw loosening, to enhance long-term bone stability, and to minimize crestal bone loss. In the early years of implant dentistry, the most common abutment connection was the flat-to-flat abutment to implant connection, with an external hexagon to prevent abutment rotation. Nowadays, an internal conical connection or a Morse taper with an internal anti-rotation element is mostly used. A large review of 52 articles by Schmitt and colleagues[29] concluded from in-vitro techniques that: (1) no connection yields a 100% perfect seal for bacterial contamination; (2) the implant-abutment interface geometry seems to be an influencing factor for stress and strain transmission around the implant; (3) the conical implant-abutment connection seems to be more resistant to abutment movement and microgap enlargement and has higher torque loss resistance in addition to high resistance to fatigue loading and maximum bending; and (4) the conical implant-abutment connection seems to have lower abutment screw stresses than with the external hexagon connection, but it is comparable to internal hexagon connections. Furthermore, the authors also concluded from in-vivo studies that: (1) conical and non-conical systems are comparable in terms of implant success and survival, and (2) in most cases, conical connection systems seems to produce a lower marginal bone loss. In addition to the implant-abutment connection type, thread design at the coronal part of the implant is claimed to affect crestal bone loss. Several in vitro studies using finite element analysis showed better stress distribution on the surrounding crestal bone for microthreaded compared to non-microthreaded implants.[30,31] Multiple in vivo clinical studies showed less crestal bone loss for

microthreaded implants compared to non-microthreaded implant.[32-35] However, most of the aforementioned studies did not control for other implant design factors. Moreover, the compared implants differed in more than one confounding factor, potentially biasing the outcome of the study.

SITE-SPECIFIC FACTORS

Other factors that could influence peri-implant bone stability are site-specific factors. The effect of peri-implant mucosal tissue thickness on peri-implant bone stability has been described in animals. These studies suggested a certain minimum width of peri-implant mucosa as a prerequisite, allowing a stable soft tissue attachment.[36] Studies in humans confirmed this finding and concluded that a soft tissue thickness of 2 mm or less resulted in crestal bone loss up to 1.45 mm[37]. More recently, Vervaeke and co-workers concluded that the initial bone remodeling was affected by soft tissue thickness.[38] Furthermore, they suggested that an unforeseen exposure of the implant surface during initial bone remodeling should be avoided by adapting the vertical position of the implant during surgical placement in relation to the available preoperative soft tissue thickness. In the light of the hype that currently exists around peri-implantitis, it has been questioned whether the early exposure of implant surfaces to soft tissues could hamper peri-implant health or may pose a risk for the future development of peri-implantitis. Galindo-Moreno and co-workers concluded in an 18-month study that early implant surface exposure was predictive for additional bone loss.[39] Another clinical study, examining 105 implants in 21 patients, concluded that initial bone loss and surface exposure at 2 years of function was identified as a predictor for further bone loss after 10 years of function.[40]

ORAL HEALTH-RELATED QUALITY OF LIFE

While there are many patient-related, implant-design, and site-specific factors that affect the success of implant treatment. The success of an implant treatment should also be determined by the improvement in Oral Health-Related Quality of Life (OHRQoL).[41] To measure this improvement, the Oral Health Impact Profile-14 (OHIP-14) questionnaire is a widely used tool. The tool consists of a questionnaire

to measure the impact of medical care on social and functional well-being.[42] Allen and McMillan reported significant improvement in satisfaction and health-related quality of life for patients who received implant-retained prostheses compared to those who received conventional dentures.[43] However, patient satisfaction is highly individual and satisfaction with an implant-supported overdenture is never guaranteed. Hence, the decision to propose an implant-supported overdenture should be based on proper individual assessment.[44]

By and large the success of a dental implant is affected by the inconsistency in the existing literature in case definition, case selection, and the variability in diagnostic thresholds for peri-implant diseases. Besides these factors, the success could be influenced by patient-related factors, as well as site-specific and implant-related factors. Finally, the OHRQoL is likewise a crucial factor determining the effect and success of implant treatment.

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CHAPTER 2

AIMS OF THIS THESIS

The research questions in this PhD project are focused on the above-mentioned factors.

- Scrutinize whether the commonly used biologic diagnostic parameters correspond to the long-term outcome in terms of implant survival and reported peri-implantitis prevalence **(STUDY I, CHAPTER 3)**.
- Scrutinize whether long-term peri-implant bone loss is affected by implant surface roughness **(STUDY II, CHAPTER 4)**.
- Study the effect of implant surface roughness on crestal bone remodeling, peri-implant health **(STUDY III, CHAPTER 5)**.
- Study the effect of adapting the vertical position of implants on peri-implant bone stability and peri-implant health **(STUDY III AND IV, CHAPTER 5 AND 6)**.
- Study the effect of implant neck (microthreaded versus non-microthreaded) as well as the type of connection (internal conical versus external flat to flat) on peri-implant bone stability and peri-implant health **(STUDY V, CHAPTER 7)**.
- Assess the Oral Health-Related Quality of Life in patients restored with mandibular implant-retained overdentures **(STUDY III AND IV, CHAPTER 5 AND 6)**.

CHAPTER 3

How do peri-implant biologic parameters correspond with implant survival and peri-implantitis? A critical review.

This chapter is based on the publication:
How do peri-implant biologic parameters correspond with implant survival and peri-implantitis?
A critical review.

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ABSTRACT

Objectives: The aim of this critical review was to evaluate whether commonly used biologic diagnostic parameters correspond to implant survival and peri-implantitis prevalence.

Materials and methods: Publications from 2011 to 2017 were selected by an electronic search using the Pubmed database of the US National Library of Medicine. Prospective and retrospective studies with a mean follow-up time of at least 5 years and reporting prevalence of peri-implantitis as well as mean bone loss and standard deviation were selected. The correlation between reported prevalence of peri-implantitis and reported implant survival, mean follow-up time, mean bone loss, mean probing depth, and mean bleeding on probing was calculated. Mean bone loss and standard deviation were used for estimation of proportion of implants with bone loss exceeding 1, 2, and 3 mm.

Results: Full-text analysis was performed for 255 papers from 4,173 available ones, and 41 met all the inclusion criteria. The overall mean weighted survival rate was 96.9% (89.9%–100%) and the reported prevalence of peri-implantitis ranged between 0% and 39.7%, based on 15 different case definitions. The overall weighted bone loss was 1.1 mm based on 8,182 implants and an average mean loading time ranging from 5 to 20 years. No correlation was found between mean bone loss and the reported prevalence of peri-implantitis. The estimated prevalence of implants with bone loss above 2 mm was 23%. The overall weighted mean probing depth was 3.3 mm, and mean weighted bleeding was 52.2%. Only a weak correlation was found between survival and function time ($r = -0.49$). There was no relation between the probing depth or bleeding and the mean bone loss, mean follow-up time, and reported prevalence of peri-implantitis.

Conclusion: Biologic parameters mean probing depth and mean bleeding on probing do not correlate with mean bone loss and this irrespective of follow-up. Case definition for peri-implantitis varied significantly between studies indicating that an unambiguous definition based on a specified threshold for bone loss is not agreed upon in the literature.

INTRODUCTION

Dental implants are widely used to restore partial and full edentulism. Due to a continuous improvement of implant designs, implant surface topographies, and prosthetic components, implant dentistry today yields excellent long-term results in terms of implant survival. Doornewaard and colleagues performed a systematic review including papers with above 5-year follow-up yielding a 97.3% weighted implant survival rate.[1] Numerous clinical studies with a 10-year follow- up yield survival rates of over 95%.[2-6] For single tooth replacements on turned implants, cumulative survival rates of 96.8% after 17–19 years and 91.5% after 16–22 years were reported.[7,8] In fully edentulous jaws, a 97% implant survival after on average 14 years has been reported.[9] Up to 20 years, implant survival rates in the range of 80%–95% have been reported with turned implants in fully edentulous jaws.[10-13] Chappuis and colleagues reported in a prospective study 89.5% survival of titanium plasma-sprayed implants after 20 years of function in partially edentulous cases.[14] Compared with the era of introduction of dental implants in clinical practice half a century ago, implant survival is today predictable, regardless of implant length, implant diameter, bone quality, available bone volume, surgical, or prosthetic treatment protocol.[15] Apart from restoring function and esthetics, this has also affected patient-reported quality of life.[16]

This positivity has over the last decade been affected by the escalating discussion on peri-implantitis, which has divided the scientific community and risks to ruin the good reputation of implant dentistry. Some of these disagreements are related to the inconsistency in the case definition, case selection, and the variability in diagnostic thresholds for disease.[17-19] Two recent systematic reviews indicated that homogeneity in peri-implantitis reporting is still lacking. Tomasi and Derks listed nine different threshold levels for radiographic bone loss applied to diagnose peri-implantitis, and Ramanauskaite and Juodzbalys detected 10 case definitions for peri-implantitis.[20,21] It is doubtful whether this is beneficial for the patient in the long run given the clinical treatment consequences that may follow, which could lead to unnecessary surgical treatment or even implant removal.

It is evident that patient-related factors such as the inability to perform oral hygiene are related to peri-implantitis and that regular maintenance is key for

prevention.[22,23] This is confirmed by a meta-analysis including 13 papers concluding that a more regular, individually tailored peri-implant maintenance therapy prevents possible biologic complications over time and improves the long-term outcome of implants.[24] Recent systematic reviews scrutinized additional patient-related factors and their association with implant treatment outcome. Among them, smoking habits have been shown to affect implant failure irrespective of implant surface, increase the risk of postoperative infection, and yield more marginal bone loss especially in the maxilla.[25] The history of periodontal disease was suggested as a second important patient-related factor. An increased susceptibility for periodontitis may translate into an increased susceptibility for implant loss, loss of supporting bone, and/or postoperative infection.[26] No significant relation could be identified between diabetes and implant failure as no differences were observed between patients with and without diabetes.[27] As concluded in multiple articles, the difference in occlusal loading between immediate non-functional and immediate functional loading may not affect the survival of these implants and no significant effect on the marginal bone loss has been reported.[28] Furthermore, peri-implant mucositis can also be induced by residual cement in the sulcus or be related to implant/prosthetic factors and lead to peri-implantitis.[29,30] In a systematic review including 79 papers, it was suggested that the implant factor surface roughness had an impact on peri-implant bone loss.[1] The bone loss around the moderately rough and minimally rough surface implants was less than around rough surface implants. The additional meta-analysis confirmed that a history of periodontal disease and smoking leads to more peri-implant bone loss.

Definition of peri-implant disease

Peri-implant mucositis is defined by the 6th European Workshop of Periodontology as a reversible inflammation of the peri-implant soft tissue with no signs of loss of the supporting bone. In the 7th European Workshop, it was diagnosed as bleeding on gentle probing.[31] Peri-implantitis is defined as inflammation of the soft tissues in combination with ongoing loss of the supporting peri-implant bone beyond the physiological bone adaptation.[32] The latter takes place as a consequence of biologic width establishment during initial healing. In the 3rd EAO consensus conference, it was stated that this initial bone remodeling may be unrelated to infection and is not necessarily peri-implantitis.[33] It was therefore suggested that monitoring of implant performance should not be based on radiographs taken

after implant placement but should relate to baseline recordings once tissue homeostasis has been established, in essence 3 months after completion of the treatment.[34] Today, there is a general consensus that a baseline radiograph is required for the assessment of bone changes over time.[31] It is unfortunate that, this baseline radiograph is not always available when clinicians assess the peri-implant tissue condition. For these conditions, a pragmatic clinical approach for peri-implantitis diagnosis was suggested by the 8th European Workshop for Periodontology.[35] The consensus report suggested a 2 mm additional loss beyond the "expected" bone level as a threshold in situations where baseline radiographic bone level assessment is lacking.

Bone loss

Although the threshold for bone loss as a diagnostic criterion for disease is not exactly specified in the previous EFP or EAO consensus meetings, there is agreement on the fact that stable crestal bone levels are most important for implant success because it is paramount for long-term survival, esthetics, as well as peri-implant health. Klinge and colleagues advised that critical bone loss ≥ 2 mm from the time of placement of the prosthetic device, in combination with bleeding on probing, should be interpreted as a "red flag" for the clinician to critically evaluate whether any intervention is indicated in the individual case and whether follow-up and reassessment are required to confirm ongoing bone loss.[34]

De Bruyn and colleagues reviewed radiographic assessment of modern implants and suggested that this mean bone loss assessment in patients with multiple implants yields very limited information on the condition of individual implants.[36] However, it may be valid to benchmark implant systems. Given the fact that a majority of implants have very stable crestal bone levels over time and in a majority of cases sometimes no bone loss at all, the statistical interpretation of mean values often hides the condition of individual implants. It may be the reason why in the early studies, with mostly multiple implant cases for complete jaw rehabilitations, disease may have been overlooked. This is obvious from a radiographic follow-up study of 640 patients with 3,462 turned implants.[37] The mean bone loss after 5 years was 0.8 mm, and insignificant changes were reported in the years thereafter. However, the prevalence of implants with bone level located 3 mm apical to the implant-abutment junction was 2.8% at the time

of prosthesis insertion but increased to 5.6%, 10.8%, 15.2%, 17.2%, and 23.5% after 1, 5, 10, 15, and 20 years, respectively. Vervaeke and colleagues performed a prospective study, whereby 50 full-arch rehabilitations were immediately loaded the day of surgery on 5-8 implants in the maxilla and mandible and followed for 9 years.[38] Implant survival was 99.2%, and the total mean bone loss, including initial remodeling, was calculated on patient level being limited to 1.7 mm. However, on implant level, 30% of the individual implants had lost more than 2 mm, figures largely affected by the inclusion of smokers and patients with a periodontal history. Hence, in the context of peri-implantitis, the mean crestal bone values calculated on patient level are not appropriate to detect disease around individual implants. The same holds true for cross-sectional evaluation at a given time point when the baseline radiograph is lacking and bone levels are used as surrogate for peri-implantitis detection. A recent report of Pettersson and Sennerby revealed that 15% of the implants showed more than 2 mm bone loss after 5 years.[39] Applying the criteria published in a paper written for the European Workshop on Periodontology in 2012 by Sanz and colleagues, these implants could be diagnosed with peri-implantitis.[35] However, in this particular study, 25% of the implants had already bone loss up to 2 mm due to the specific implant design and over time there was stability or even improvement of the bone level.

Probing depth

Periodontal probing is a common basic diagnostic tool in periodontal diagnosis around teeth. Ericsson and Lindhe had described distinct differences between teeth and implants in soft tissue composition, organization, and attachment between the gingiva and the root surface on one hand and between the peri-implant mucosa and the implant surface on the other.[40] Therefore, this affects the interpretation of probing depth measurements. In healthy tissue, the probe penetration is more advanced around implants, although this is depending on the probing force.[41-44] Soft tissue around implants has also been found thicker than around teeth. This was first described in animals and confirmed by human biopsies.[45,46] Parpaiola and colleagues assessed the dimensions of the soft tissue cuff present at various aspects around teeth and implants using human biopsies.[47] The soft tissue cuff that surrounded a tooth varied between 2 mm at flat surfaces and 4 mm at proximal surfaces, while at implant sites, the mucosa at proximal as well as flat surfaces was 1–1.5 mm greater. The probing depth (PD) was greater at proximal than at facial or palatal/lingual surfaces at tooth sites

and frequently also at implant sites. Furthermore, the PD and the soft tissue thickness were greater at implant than at adjacent tooth sites. Another study confirmed soft tissue thickness ranging between 0.85 mm and 6.85 mm and papilla heights of 7 mm to 9 mm under healthy conditions.[48] Kan and colleagues measured an average interproximal thickness of the mucosa of 6 mm with a large range.[49] Gallucci, Belser, Bernard and Magne found mesial and distal PD often ranging between 4 and 8 mm depending on how scalloped the mucosa is.[50] Animal studies have shown that conditions of mild inflammation already yield deeper pockets around implants compared to teeth and this does not necessarily coincide with actual bone loss.[51] A multilevel analysis performed in a group of 52 patients with screw-retained restorations on 92 implants revealed that deeper PD is associated with higher tendency to bleed. This would indicate that an increase in PD in the absence of additional bone loss may be indicative of peri-implant mucositis.[43] Also, Lang and colleagues concluded that the probe penetrates into the connective tissue in situations of mucositis.[44] A few studies have looked for correlations between bone loss and clinical parameters among them probing. They concluded that probing depths are of limited value in predicting future peri-implant bone loss.[8,52,53] Long-term clinical studies have clearly shown that the probing depth of healthy peri-implant mucosa is not always smaller than 4 mm but very often up to 6 mm.[8,54,55] In an 18-year follow-up of single turned implants, pockets of up to 9 mm were found despite the absence of bone loss.[7] Also, Dierens and colleagues could not demonstrate correlations between PD and marginal bone levels around single implants functional for 16–22 years.[8] Deep (>5 mm) and shallow (<4 mm) pockets were found in all bone level groups explaining the poor predictive value of probing in the peri-implantitis diagnosis when based on bone loss alone.

Probing is hindered by the location of the implant restoration especially in case of partial or full jaw reconstructions. This may be the reason while in some studies patients with multiple implant cases are diagnosed more often with peri-implantitis. Dalago and colleagues speculated that this could be attributed to less adequate oral hygiene or possible inclusion of more patients with periodontal history.[56] Also, Serino and Strom proved that 65% of the implants with no good accessibility for oral hygiene showed peri-implantitis compared to 18% when oral hygiene was feasible.[22] It is obvious that incorrect probing may lead to iatrogenic bleeding. De Bruyn and colleagues evaluated full jaw patients with

implants placed in onlay grafts in the maxilla after a mean follow-up of more than 9 years.[57] To assess the peri-implant health, they removed the screw-retained reconstruction; 11% of the implants presented with a PD ≥ 5 mm despite more than 39% of the implants with BoP. There was no correlation between the registered BoP 39% and the bone loss, but the PD reflected the bone loss. Serino, Turri and Lang demonstrated differences in PD with or without the implant construction in place.[58] The PD showed a high correlation with bone loss when the reconstruction was removed. The presence of the construction impeded the accuracy of the PD registration, and only in 37% of the sites, similar results were obtained with probing with or without the construction. They concluded that PD reflects the bony defect only when access for probing is ideal. However, full jaw prosthesis often present with overhang, which may lead to inaccurate probing and false-positive diagnosis. In addition, the measurement error encountered with probing is higher around implants than around teeth and the type of implant may affect the absolute PD value.[41,59]

The aforementioned studies all suggest that the use of an absolute PD threshold to diagnose the soft tissue around implants should be performed with great caution. Based on the current evidence, the PD value alone cannot be considered a reliable indicator for defining peri-implantitis.[58] When actual bone loss is not correctly taken into account, due to the absence of a baseline radiograph, and when the PD is the only determining factor in the diagnosis, this may undoubtedly account for the high reported prevalence of peri-implantitis in some studies. It is obvious that change in PD over time, once a physiological steady state in the soft tissue has been established, may be regarded as an indicator of disease activity. Huang and colleagues suggested that a baseline PD should be established as a basis for comparison over time because initial implant location may affect the PD.[60] A recent systematic review concluded that the use of progressively deepening probing depth is more meaningful than using absolute PD values of ≥ 4 or 5 mm.[61]

Bleeding on probing

Bleeding on probing is used in periodontal diagnosis. It is a poor predictor of disease progression, but the absence of BoP is a good predictor of future tissue stability.[62] Lekholm and colleagues reported that neither deep pockets nor BoP was found to be accompanied by accelerated marginal bone loss.[55] The probability

of a peri-implant site to bleed upon probing is associated with PD, implant position, and gender.[63] A paper by Jepsen and colleagues revealed no difference in BoP between sites with progressive bone loss or stable sites.[64] They pointed out that probing might also provoke a nonspecific bleeding that is unrelated to the amount of inflammation and most probably related to the presence of the microgap between implants and abutments or reconstruction. Indeed, studies comparing teeth and implants, with respect to soft tissue healing, revealed that peri-implant healing as determined by crevicular molecular composition differs from periodontal healing. It is suggested that peri-implant tissues represent a higher pro-inflammatory state.[65] An analysis of 987 implants followed for 9–14 years demonstrates that signs of mucositis (BoP) are evenly distributed among implants with or without peri-implantitis. There was actually no difference in the proportion of implants with the absence or presence of bleeding/suppuration in relation to bone loss, bone gain, or bone stability.[66] Another large cohort study, including 4,591 implants from 2,060 subjects, indicated that minimal bleeding did not correlate with bone loss but multipoint bleeding, profuse bleeding, or suppuration did.[67] The use of a dichotomous diagnostic criterion (bleeding yes or no) is probably the reason why often high figures of mucositis are reported. Dierens revealed 80% of BoP-positive implants after 16–22 years of follow-up despite a prevalence of peri-implantitis as low as 5% and found no correlation between BoP and peri-implantitis.[8] Renvert, Lindahl and Persson evaluated 86 individuals at an examination after 9–14 years and furthermore after 21–26 years of function; 58% of the individuals with no bone loss during the interval had been diagnosed with mucositis during the first examination. On the other hand, nearly 22% of the patients without any sign of mucositis after 9–14 years had developed peri-implantitis at a later stage.[68] Data analysis failed to show that a diagnosis of mucositis after 9–14 years was predictive for development of peri-implantitis after 21–26 years. This recent paper is in contradiction with the suggestion of Jepsen and colleagues that mucositis is a precursor for peri-implantitis.[69] This contradiction does not imply that one should become negligent and should not strive for the prevention of mucositis with good oral hygiene.

Prevalence of peri-implantitis

The prevalence of peri-implant diseases significantly varies among clinical studies due to the inconsistent definitions, reporting methods and study characteristics. One of the first publications on the prevalence of peri-implant diseases by

Zitzmann and Berglundh based on only two cross-sectional studies reported 28–77% on patient level and 12–43% on implant sites with peri-implantitis.[70] Mombelli, Muller and Cionca calculated the prevalence of peri-implantitis, based on 29 papers, in the order of 10% of the affected implants and 20% patients during 5–10 years after implant placement.[71] Another review summarizing 10 papers reporting on the 10-year clinical outcome with implants treated by sandblasting, grit blasting, acid-etching, or combined treatments revealed that the survival was above 95% and < 5% were diagnosed with purulent infection or peri-implantitis.[72] A 10-year follow-up study including nearly 300 implants in 100 subjects revealed similar figures.[73] They concluded that implant sites with radiographically confirmed marginal bone loss of ≥ 1 mm were not common and that peri-implantitis defined as bone loss > 0.5 mm, BoP^+, and PD ≥ 6 mm was detected in 12% of patients and only 5% of implants. Atieh and colleagues performed a systematic review including information of 1,497 patients with 6,283 implants and reported a respective prevalence of 18.8% on patient level and 9.6% on implant level.[74] Derks and Tomasi performed a systematic review including 11 clinical studies and reported a broad range in the prevalence of peri-implant mucositis (19%–65%) and peri-implantitis (1%–47%).[19] The meta-analyses estimated a weighted mean prevalence of peri-implantitis affecting 22% of the implants. The meta-regression showed a positive relationship between prevalence of peri-implantitis and function time. This report was critically appraised in a paper by Jemt, mentioning that the broad range in the prevalence could be attained to different thresholds for bone loss (range 0.4 mm - 5 mm) used in the various case definition applied in the selected papers, in combination with a high dropout rate and the use of bone levels at a cross-sectional time point instead of absolute bone loss.[75] The systematic review of Lee and colleagues included 47 studies whereby the bone level thresholds for disease ranged from 1 to 5 mm and lead to a weighted mean implant-based and subject-based peri-implantitis of 9.2% and 19.8%, respectively.[61]

Aim

The aim of this critical review was to describe whether the commonly used biologic diagnostic parameters correspond to long-term outcome in terms of implant survival and reported peri-implantitis prevalence.

MATERIAL AND METHODS

Search strategy

The focus of this study was on diagnostic aspects in relation to peri-implant health and clinical outcome in long-term perspective. Given the overall consensus that progressive bone loss is the most important biologic parameter in the diagnosis of peri-implantitis, it was decided to conduct a broad literature search using Pubmed database of the US National Library of Medicine for articles. Publications from 2011 up to September 2017 were selected using the general search algorithm: ((((((“bone loss”) OR “peri-implantitis”)) OR “periimplant”)) AND dental implant). Cross-sectional reports were excluded because they report on bone levels and not on bone loss. The papers had to be published in English, report on peri-implantitis prevalence together with mean bone loss on implant level (compared to a baseline measurement). No distinction was made based on study design (prospective or retrospective, RCT, or case series) or surgical or prosthetic treatment protocol as long as they included at least 10 patients after a minimal mean follow-up time of 5 years. Only studies discussing implant treatment in systemically healthy patients were included, but studies with smokers, patients with periodontal history, controlled diabetes, or implants in sinus lifted bone were allowed. Studies describing implant treatment in tumor-resected areas, studies involving extensive bone grafts or zygomatic or mini-implants were excluded. An independent selection was performed based on the title and detailed information given in the abstract by two assessors (RD & HDB) who discussed jointly and reached a consensus in case of disagreement over the inclusion/exclusion of a paper.

Data analysis

Papers were descriptively analyzed, and case definitions of peri-implantitis were extracted. Analysis was performed on implant level. In the overall statistical analysis of implant survival and bone loss, the number of implants was used to weight the study or study groups throughout this review. A bivariate correlation analysis was performed using the Pearson r correlation coefficient. A correlation coefficient ranging from 0.01–0.19, 0.20–0.29, 0.30–0.39, 0.40–0.69, and above 0.70 represent a negligible, weak, moderate, strong, and very strong relationship, respectively. Correlation was calculated between the outcomes (i) reported prevalence of peri-implantitis and (ii) mean implant survival, mean time in function, mean

bone loss, mean PD, and mean BoP. Based on studies reporting on skewness and distributions it could be expected that data, most commonly, are not normally distributed. This is caused by outliers, which could lead to large standard deviations, rather caused by chance than population. Therefore, the standard deviations on population level are not used in weighing of studies. The variability between studies is more reduced due to the lesser effect of outliers on the mean compared to the effect on the standard deviation and the amount of studies. Therefore, the Pearson correlation coefficients calculated, chosen as measure for a linear relationship between measures, are exploratory and could only be descriptively interpreted in conjunction with the graphical representations. If papers mentioned multiple case definitions, the one with the smallest bone loss threshold was applied in the correlation analysis. Papers with incomplete data reporting were not used for these analyses. In addition, the proportion of implants with bone loss above 1, 2, and 3 mm was estimated based on reported means and standard deviations. If the paper gave a frequency distribution for bone loss, the outcome of the frequency distribution was compared with the calculated proportion of implants with bone loss above 2 mm. Descriptive statistics were performed using MatLab R2015b version (8.6.0.267246; The MathWorks, Inc., Natick, MA, USA).

RESULTS

Selection and data reporting

The search yielded 4.173 papers whereof 255 publications were selected for full article reading. At last, 41 fulfilled the inclusion criteria, and the extracted data are summarized in Table 1. The peri-implantitis case definitions applied in the respective articles are illustrated in Table 2. In total, 41 articles, 21 prospective and 20 retrospective, report on 56 treatment groups. They represent in total 4,198 patients initially treated with 9,657 implants of various brands and with a variety of treatment protocols. A total of 6,246 implants were retrospectively analyzed, and 3,411 implants were prospectively analyzed. Table 3 shows the number of papers and their respective reported parameters.

Survival rate and follow-up time

Thirty-eight of the 41 papers reported on survival rate in 49 treatment groups. The overall weighted mean survival rate was 96.9% (89.5%–100%) and 97.2% and 96.2% for retrospective and prospective studies, respectively. In 39 and

nine treatment groups, the reported implant survival rate was ranging between 95.0%–100% and 90.0%–94.9%, respectively. Only one treatment group reported an implant survival below 90%. The weighted mean follow-up time for the 56 treatment groups was 9.0 years with a range of 3–24.4 years. The weighted mean follow-up was 9.2 (3–24.4) and 8.7 (5–21) years for retrospective and prospective groups, respectively. Thirty of the 56 treatment groups, representing initially 5,886 implants, had a follow-up time between 5 and 9.9 years with 4,894 implants at follow-up (dropout 16.9%). In total, 24 treatment groups had a mean follow-up time ranging between 10 and 14.9 years, with 3,498 implants at baseline and 3,025 implants at follow-up (dropout 13.5%). Only two treatment groups had a mean follow-up time of 15 years or longer, with 273 implants at baseline and 263 at follow-up (dropout rate of 3.7%).

Reported prevalence and case definition of peri-implantitis

For all the included 56 treatment groups, the prevalence of peri-implantitis on implant level ranged between 0% and 39.7% as shown in Table 1 and was based on 15 different case definitions of peri-implantitis. The case definitions varied considerably, mostly due to heterogeneous thresholds for bone loss and ranging from any detectable bone loss to 3.5 mm. Of the 41 papers, only 27 had a clearly defined threshold for bone loss, most commonly 2 mm. Some authors used more than one threshold and also gave more than one prevalence.[76-78] Tey and colleagues made a distinction between clinical peri-implant disease definitions according to Pjetursson et al. and the prevalence of peri-implantitis based on radiographic diagnosis.[78,79] Derks and colleagues used a combination of BoP and/or suppuration with a bone loss threshold of 0.5 mm and diagnosed 24.9% with peri-implantitis.[76] However, when they used a bone loss threshold of 2.0 mm, only 7.8% of the implants were diagnosed with peri-implantitis. Also, Donati used two different bone loss thresholds.[77] Peri-implantitis was diagnosed in 2.9% or 5.7% of the implants when applying 2 or 1 mm thresholds for bone loss, respectively. The highest prevalence of peri-implantitis (although coined incidence in the paper) was found in the study by Renvert, Lindahl and Rutger Persson, originally reporting on 234 implants of two different brands after 7 years of function in 54 patients.[80] After 13 years, 164 implants were available for radiographic evaluation, which resulted in a dropout rate of 29.9% on implant level. The mean bone loss for the two study groups was 0.8 mm and 1.0 mm, respectively. Peri-implantitis was detected in nearly 40% of the implants based on a bone loss threshold above 1 mm following the first year after implant placement.

Table 1: The number of papers and summarized relevant clinical information.

Article number	Author	Study design	Treatment subgroups	Mean follow-up years (range)	Patients baseline	Implants baseline	Survival %	Implants for BL follow-up
1	Shi et al.[98]	R		10.1 (8-14.6)	67	98	96.6	95
2a	Sener-Yamaner et al.[90]	P	1: early loaded SLA	6.8	55	107	99.0	106
2b			2: early loaded SLA-active	6.8		68	97.0	66
3	Galindo-Moreno et al.[105]	P		5	69	97	95.9	93
4a	den Hartog et al.[86]	P	1: smooth neck	5	31	31	96.2	26
4b			2: rough neck	5	31	31	100	28
4c			3: scalloped rough neck	5	31	31	96.2	26
5	Froum & Khouly[87]	R		8.5	52	52	100	28
6a	Ayna et al.[106]	P	1: all-on 4 mandible metal ceramic	7	16	64	100	60
6b			2: all-on 4 mandible bar retained	7	16	64	100	64
7a	Taschieri et al.[107]	R	1a: P-PRP Immediat Loading	5	71	30	97.5	11
7b			1b: P-PRP Delayed loading	5		49		28
7c			2a: non P-PRP immediat loading	5	38	11	97.9	9
7d			2b: non P-PRP delayed loading	5		37		10
8	Cassetta et al.[89]	P		5	270	576	94.1	542
9	Ekfeldt et al.[92]	R		10.5 (10-11)	23	30	100	30
10	Jensen et al.[96]	R		8 (3-16)	26	52	91.7	43
11	Tey et al.[78]	R		5.9	194	266	100	266
12	Cosyn et al.[108]	P		5	22	22	95.0	17
13	Glibert et al.[109]	P		6.2 (5.4-6.9)	40	112	99.1	111

Time of baseline radiograph	Mean implant BL in mm (SD)	Info on PPD	Mean PPD (mm)	Bleeding index used	Bleeding score %	Reported suppuration	Reported PI prevalence % on implant level	Definition of PI
1	1.19 (1.07)	Mean	3.7	BoP	33.4	No	8.5	11
0	0.71 (0.35)					No	1.0	X
	0.53 (0.28)					No	3.0	
0	0.15 (0.95)	0.20 mm PPD reduction		BoP	57.5	No	0.0	X
0	1.26 (0.90)	Mean	3.5	BoP	79.2	No	7.7	11
	1.20 (1.10)	Mean	3.3	BoP	59.3	No	14.2	
	2.28 (0.97)	Mean	4.3	BoP	87.5	No	11.5	
0	0.30 (0.73)	Mean	2.2	BoP	53.6	No	3.6	3
0	0.74 (0.17)	Mean	3.3	BoP	18.8	No	0.0	X
	0.76 (0.15)	Mean	3.6	BoP	32.8	No	0.0	
0	0.8 (0.35)					No	3.8	6
	1.02 (0.27)					No		
	0.6 (0.16)					No	10.4	
	0.8 (0.89)					No		
1	0.59 (1.34)					No	4.9	X
1	0.26 (0.60)	30% PPD > 4 mm		BoP	13.0	No	13.0	5 with cut-off bone loss of 0.6 mm
0	0.9 (1.0)	Mean	3.3	mBI = 0.7		No	8.7	5 with cut-off bone loss of 2mm
9	1.05 (1.07)	Fd: 7.1% PPD ≥ 6 mm		BoP	95.0	No	7.1	3
0	0.19 (0.30)	Mean	3.1	BoP	32.0	No	0.0	X
0	0.35 (0.45)					No	0.9	11

Table 1: Continued

Article number	Author	Study design	Treatment subgroups	Mean follow-up years (range)	Patients baseline	Implants baseline	Survival %	Implants for BL follow-up
14	Derks et al.[83]	R		8.9	596	2367	97.0	1578
15a	Sanchez-Siles et al.[104]	R	1: smooth neck	6.44	171	515	100	515
15b			2: whitout smooth neck	5.61	229	729	100	729
16	Donati et al.[77]	P		12	40	45	97.0	35
17a	Canullo et al.[84]	P	1: steam cleaning abutment	5	15	15	100	15
17b			2: Plasma of Argon cleaning abutment	5	15	15	100	15
18	Vandeweghe et al.[9]	R		14.3 (10-21)	33	203	97.0	197
19	Nedir et al.[110]	P		10	17	25	100	23
20	van Velzen et al.[97]	P		10	250	506	99.7	367
21	Trullenque-Eriksson & Guisado-Moya[111]	R		13.19 (8.46-24.37)	105	342	90.6	342
22	Meijer et al.[93]	P		10	150	240	95.3	240
23	Schropp et al.[112]	P		10	63	63		47
24	Mangano et al.[113]	R		15.2 (10-20)	49	178	97.2	178
25	Simion et al.[114]	R		12	29	59	93.2	59
26	Meyle et al.[94]	P		10	20	54	96.3	54
27	Anitua et al.[115]	R		10.3 (7.2-11.4)	75	111	98.9	87
28	Donati et al.[77]	P		5	151	161	95.6	140
29	Gelb et al.[116]	R		7.33 (7-8)	57	107	100	107
30	Chappuis et al.[14]	R		20	67	95	89.5	85
31a	Renvert et al.[80]	R	1: TiOblast	13	27	132		80
31b			2: TiUnite	13	27	102		84
32	Frisch et al.[95]	R		14.1 (10.2-18.9)	22	89	98.9	89

Time of baseline radiograph	Mean implant BL in mm (SD)	Info on PPD	Mean PPD (mm)	Bleeding index used	Bleeding score %	Reported suppuration	Reported PI prevalence % on implant level	Definition of PI
1	0.72 (1.15)	16.9% PPD ≥ 6 mm		BoP	60.9	No	24.9	15
9	1.12 (1.24)			only for implants with PI		Yes	2.9	5
	2.51 (1.57)			only for implants with PI		Yes	14.4	
1	0.61 (2.10)			BoP	25.0	No	8.6	11
1	0.65 (0.36)			BoP	6.6	No	0.0	X
	0.21 (0.21)			BoP	20.0	No	0.0	
0	1.73 (1.54)	Mean	3.6	BoP	47.2	No	4.1	3
0	1.00 (0.90)					Yes	8.7	X
0	1.21 (0.94)	Mean	3.7	BoP	52.5	No	7.0	10
1	1.84 (1.35)					No	1.7	13
1	1.10 (1.10)	Mean	3.4	mBI = 0.3		No	20.3	11
0	0.67 (0.98)	Fd: 36% PPD ≥ 5 mm		BoP	70.0	No	4.3	9
1	1.80 (0.60)					Yes	2.3	12
1	1.34 (0.79)	Mean	2.9	BoP	54.7	No	0.0	8
1	0.60 (0.26)	Mean	3.3	BoP	27.0	No	23.8	5
0	0.95 (0.65)					Yes	0.9	X
0	0.32 (1.15)	Fd: 3.2% PPD ≥ 6 mm		BoP	13.0	No	2.9	11
0	1.49 (1.03)			BoP	4.7	No	0.0	X
0	0.14 (1.09)	Mean	3.1	sBI = 0.1		Yes	20.0	X
1	0.80 (-)	Mean	2.6	BoP	82.1	Yes	32.1	4 with cut-off bone loss of 1mm
	1.0 (-)	Mean	3.1	BoP	89.7	Yes	39.1	
1	1.80 (1.50	Mean	3.1	BoP	21.0	No	8.0	1 with PPD ≥ 5 mm and BoP

Table 1: Continued

Article number	Author	Study design	Treatment subgroups	Mean follow-up years (range)	Patients baseline	Implants baseline	Survival %	Implants for BL follow-up
33	Lops et al.[91]	P		13.2 (10-21)	121	257	92.3	207
34	Ormianer[117]	R		10	46	173	99.4	172
35a	Ravald et al.[118]	P	1: TiOblast	13.5 (12-15)	66	184	95.0	136
35b			2: Machined	13.5 (12-15)	66	187	94.7	116
36	Ostman et al.[88]	P		10	46	121	99.2	106
37a	Arnhart et al.[85]	R	1: TiUnite	6.7 (5.3-9.8)	47	136	98.5	136
37b			2: Machined	8.2 (5.3-9.8)		52	96.2	52
38	Lai et al.[119]	R		10	168	231	98.3	231
39	Levine et al.[120]	P		5	20	21	100	21
40a	Rodrigo et al.[121]	P	1: immediate placement	5	22	34		26
40b			2: delayed placement	5		34		26
41a	Roccuzzo et al.[122]	P	1: periodontally healthy	10	112	61	96.6	59
41b			2: moderately periodontally compromized	10	112	95	92.7	88
41c			3: severely periodontally compromized	10	112	90	90.0	81

Time of baseline radiograph	Mean implant BL in mm (SD)	Info on PPD	Mean PPD (mm)	Bleeding index used	Bleeding score %	Reported suppuration	Reported PI prevalence % on implant level	Definition of PI
1	1.85 (1.55)	Mean	2.2			No	8.7	X
9	0.18 (-)					No	2.3	X
0	0.70 (-)	Fd: 19% PPD ≥ 6 mm upper jaw and 11% PPD ≥ 6 mm lower jaw				Yes	6.0	X
	0.40 (-)	Fd: 3% PPD ≥ 6 mm upper jaw and 4% PPD ≥ 6 mm lower jaw				Yes	5.0	
0	0.70 (1.35)			BoP	9.2	Yes	1.9	4
1	1.53 (0.25)	Mean	3.1	BoP	76.8	No	0.0	X
	2.42 (0.34)	Mean	2.9	BoP	23.2	No	1.9	
0	0.63 (0.68)					No	2.0	14
0	0.58 (-)					No	0.0	X
1	2.20 (0.90)	Fd: 2.5% PPD ≥ 5 mm		BoP	14.2	No	8.8	7
	2.10 (1.00)	Fd: 0% PPD ≥ 5 mm		BoP	13.7	No	2.9	
0	0.75 (0.88)	Mean	3.1	BoP	12.0	No	4.7	2
	1.14 (1.11)	Mean	3.5	BoP	31.0	No	11.2	
	0.98 (1.22)	Mean	3.9	BoP	30.9	No	15.1	

Abbreviations: BL bone loss; PI peri-implantitis; IL immediate loading; DL delayed loading; IP immediate placement; DP delayed placement; R retrospective; P prospective; mBI mean bleeding index; sBI sulcus bleeding index; BoP bleeding on probing; Fd frequency distribution; PPD probing pocket depth. Time of baseline radiograph: 0 after surgery 1; variable time point after loading; 9 unknown. # In the Derks paper only implants with bone loss data were extracted. Definition of peri-implantitis: refer to Table 2

Table 2: Overview of the different definitions for peri-implantitis used in the retrieved papers.

Definition number	Reference	Definition of peri-implantitis	Cut-off bone loss (mm)	Cut-off PPD (mm)	BoP/Sup	Frequency distribution of definition	Article number
1	Albrektsson et al., 1986	Bone loss 1.5 mm for the first year and 0.2 mm anually there after	1.5			1	32
2	Albrektsson and Isidor 1994: 1st EWOP	Inflammatory reactions associated with loss of supporting bone around an implant in function			BoP	1	41
3	Berglundh et al., 2002	PPD > 6 mm in combination with bleeding on probing/suppuration and attachment loss/bone loss of 2.5 mm	2.5		BoP/Sup	3	5, 11, 18
4	Lindhe and Meyle 2008: 6th EWOP	A mucosal lesion often associated with suppuration and deepened pockets, but always accompanied by loss of supporting marginal bone			BoP/Sup	2	31, 36
5	Lang and Berglundh 2011: 7th EWOP	Changes in the level of the crestal bone in conjunction with bleeding on probing with or without concomitant deepening of periimplant pockets. Pus is a common finding in peri-implantitis sites.			BoP	4	9, 10, 15, 26
6	Self-reported definition 1	Inflammatory lesion in the peri-implant mucosa, associated with plaque, BoP and radiographic evidence of bone loss at mesial or distal aspect of implants			BoP	1	7
7	Self-reported definition 2	Significance bone loss, PPD ≥ 4mm and BoP		4	BoP	1	40
8	Self-reported definition 3	Crater-like bone defect, PPD ≥ 4mm and BoP/Sup		4	BoP/Sup	1	25
9	Self-reported definition 4	Bone loss > 1mm, PPD ≥ 5mm and BoP/Sup	1	5	BoP/Sup	1	23
10	Self-reported definition 5	Bone loss > 1.5 mm and BoP	1.5		BoP	1	20
11	Self-reported definition 6	Bone loss > 2 mm and BoP/Sup	2		BoP/Sup	6	1, 4, 16, 22, 28
12	Self-reported definition 7	Bone loss ≥ 2.5mm, PPD ≥ 6mm, profuse bleeding/suppuration and pain	2.5	6	BoP/Sup	1	24
13	Self-reported definition 8	Bone loss > 3mm, PPD > 5mm and BoP/Sup	3	5	BoP/Sup	1	21
14	Self-reported definition 9	PPD > 6 mm and BoP/Sup		6	BoP/Sup	1	38
15	Self-reported definition 10	1) Bone loss > 0,5 mm and BoP 2) moderate/severe = bone loss > 2mm and BoP	0.5 or 2		BoP	1	14

The article number refers to the reference provided in Table 1

Table 3. Number of papers and the respectively reported clinical parameters

Clinical Parameter	Number of papers
Bone loss (BL)	41
Survival rate (SR)	38
Bleeding (B)	28
Probing pocket depth (PPD)	25
Suppuration (S)	8
Bone loss, survival rate and B + PPD + S	1
Bone loss, survival rate and 2 of the 3 parameters	21
Bone loss, survival rate and 1 of the 3 parameter	8
Bone loss and survival rate	8
Bone loss and B + PPD + S	1
Bone loss and 2 of the 3 parameters	2

Mean bone loss

The weighted overall mean bone loss as reported in the papers was 1.1 mm (SD 1.0) and 1.3 mm (SD 1.1) and 0.9 mm (SD 1.0) for the retrospective and prospective studies, respectively. Time point of baseline radiographs was inconsistent. Baseline radiographs for bone loss calculation were taken immediately after implant placement in 22 papers, several months after the placement in 15 papers and three papers did not provide information about the time point. Figure 1 summarizes the mean bone loss in relation to the follow-up time. With the reported mean and standard deviation, the estimation of the proportion of implants with cutoff bone loss above 1, 2, and 3 mm was calculated per treatment group and amounted to 51%, 23%, and 8%, respectively (Figure 2).

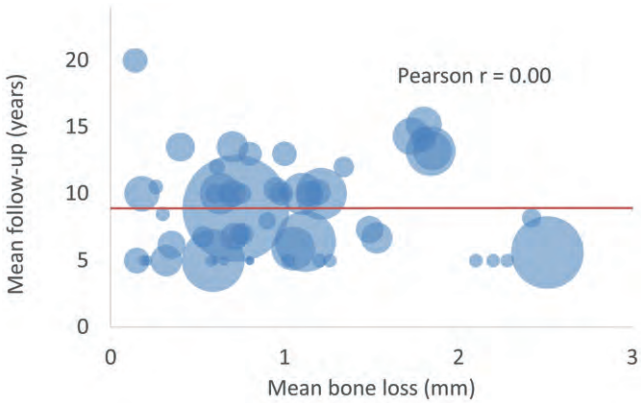

Figure 1: Mean bone loss (mm) in relation to the mean follow-up time (years) of the treatment groups; the size of the bullets reflects the number of implants reported in the treatment group

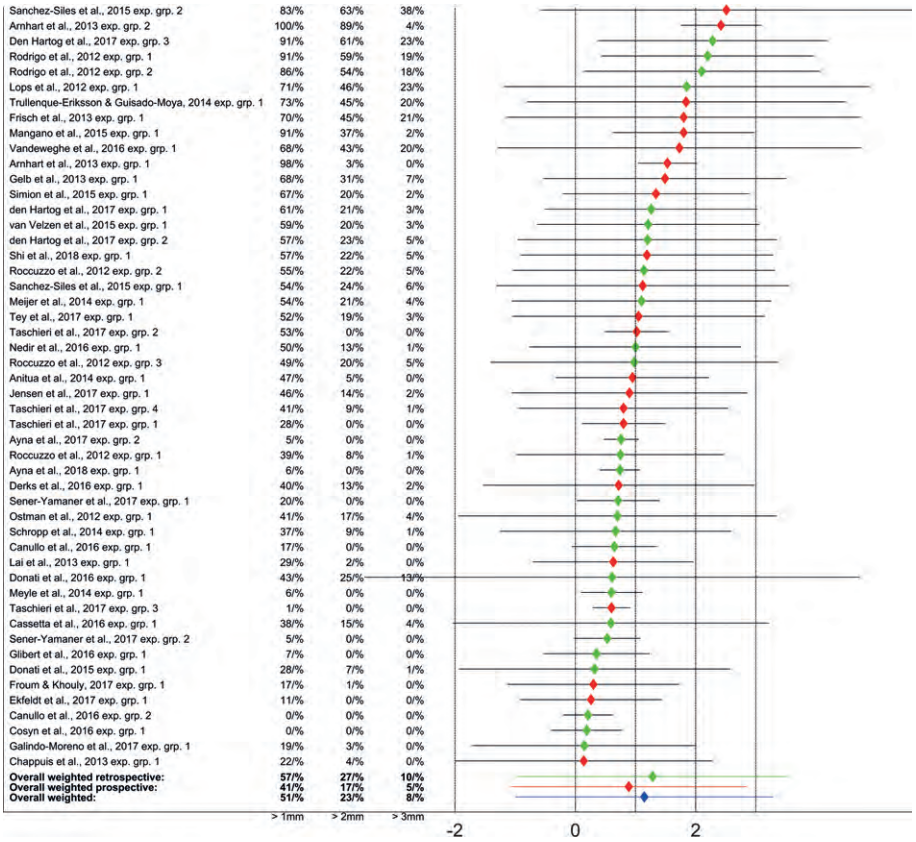

Figure 2: Mean bone loss (mm) per treatment group and estimated proportion of implants with bone loss above 1, 2, and 3 mm (green = retrospective study design; red = prospective study design)

Mean peri-implant probing depth and bleeding scores

In 25 papers, representing 34 treatment groups, the mean peri-implant probing depth was reported. The overall mean weighted PD was 3.3 mm; 75% of the treatment groups reported a mean PD between 3.0 and 3.9 mm and only one treatment group reported a mean PD above 4 mm. The majority of papers reported the mean PD. However, four papers gave a detailed frequency distribution as can be seen in Table 4. Twenty-eight of the 41 included papers (38/56 treatment groups) reported mean bleeding scores around implants using various indices. Twenty-four papers (34/56 treatment groups) reported mean peri-implant bleeding on probing with a weighted mean of 52.2%, ranging from 4.7% to 95.0%. The BoP around implants was <25% for 13 treatment groups,

ranging from 25% to 49.9% for eight treatment groups and ranging from 50% to 74.9% for six treatment groups. In seven treatment groups, a BoP ≥ 75% was reported. Two papers reported the modified bleeding index,[81] one the Sulcus bleeding,[82] and one gave only information about bleeding for implants diagnosed with peri-implantitis.

Table 4: Frequency distribution op probing pocket depth (mm), between brackets percentage of implants with BoP.

Article number	Author	Treatment groups	Percentage probing pocket depth (% implants BoP)				
			≤ 3 mm	3.1 – 4 mm	4.1 – 5 mm	5.1 – 6 mm	> 6 mm
11	Tet al.[78]		39.5 (89.5)	38.3 (99)	15.0 (95)	4.1 (100)	3.0 (100)
16	Donati et al.[77]		80	16.8			3.2
35a	Ravald et al.[118]	Tioblast upper jaw	49	32			19
		Tioblast lower jaw	66	23			11
35b		Machined upper jaw	47	50			3
		Machined lower jaw	70	26			4
40a	Rodrigo et al.[121]	Immediate placement	82.9	14.2	2.4	0.5	
40b		Delayed placement	81.1	15.6	2.4	0.9	

The article number refers to the reference provided in Table 1

Suppuration

Eight papers (Table 5) reported that 0%–20% of the implants showed suppuration independently from BoP. In four papers, this percentage corresponds nicely with the reported prevalence of peri-implantitis (~10%–40%), but in the other four papers, it did not. The high prevalence of 20% in the paper of Chappuis et al. (2013) is explained by the inclusion of six previously lost implants as well as 13 successfully treated ones.[14]

Correlation between reported prevalence of peri-implantitis and biologic parameters

Figures 3-5 report the Pearson r correlation coefficient, visualize the correlation between the different biologic parameters, and reported prevalence of peri-implantitis and follow-up time. The dimension of the different bullets in the figures reflects the weight of the study.

Table 5: Suppurating implants (%) in relation to the reported peri-implantitis prevalence.

Article number	Author	Treatment group	Suppurating implants / total number (%)	Reported PI prevalence on implant level (%)
15	Sanchez-Siles et al.[104]		2/1244 (0.2)	9.6
19	Nedir et al.[110]		0/ 25 (0.0)	8.7
24	Mangano et al.[113]		4/178 (2.2)	2.3
27	Anitua et al.[115]		1/111 (0.9)	0.9
30	Chappuis et al.[14]		19/ 95 (20)	20.0
31a	Renvert et al.[80]	1: TiOblast	(1.2)	32.1
31b		2: TiUnite	(3.8)	39.1
35a	Ravald et al.[118]	1: TiOblast	2/136 (1.5)	6.0
35b		2: Machined	2/116 (1.7)	5.0
36	Ostman et al.[88]		2/106 (1.9)	1.9

The article number refers to the reference provided in Table 1

Figure 3 visualizes mean bone loss versus the reported peri-implantitis prevalence, the mean PD, and mean BoP quoted in the selected studies. The treatment group with the highest weight, being 1,578 implants (Derks et al., 2016), reported a prevalence of 25% with a mean bone loss of 0.7 mm, 61% of the implants showing BoP, and 17% of the implants with a PPD ≥ 6 mm.[83] The smallest treatment group included 15 implants (Canullo et al., 2016) and detected no peri-implantitis with a limited mean bone loss (0.2 mm) and 20% of the implants showing BoP.[84] Overall, the reported peri-implantitis prevalence (Figure 3a) was in the majority of studies lower than 10%. There was no distinct correlation between mean bone loss and peri-implantitis prevalence. The range of mean bone loss up to 2.5 mm may explain the large range in reported prevalence from 0% up to approximately 40%. The highest prevalence of nearly 40% was presented by Renvert and colleagues, despite a mean bone loss of 1 mm after an average 13 years of follow-up.[80] However, they defined peri-implantitis using a threshold for bone loss of 1 mm. Arnhart reported a prevalence of only 2% with a much higher mean bone loss of 2.4 mm, but they did not define a threshold for bone loss.[85] In addition, data suggested the absence of a distinct relationship between the biologic factors mean PD and mean BoP with mean bone loss. Some studies reported a high mean bone loss despite lower percentages of bleeding on probing. Den Hartog reported a mean bone loss of 2.3 mm after a follow-up of 5-year with a corresponding 87.5% BoP.[86] Arnhart gave a comparable mean bone loss of 2.4 mm after 8.2 years with only 23.2% BoP.[85] Tey and colleagues reported the highest mean BoP score of 95% with a mean bone loss of only 1 mm and 7.1% of implants demonstrated peri-implantitis.[78] On

the other hand, mean BoP showed a large range (4.7%–95%) irrespective of mean bone loss or mean PD (Figure 3c).

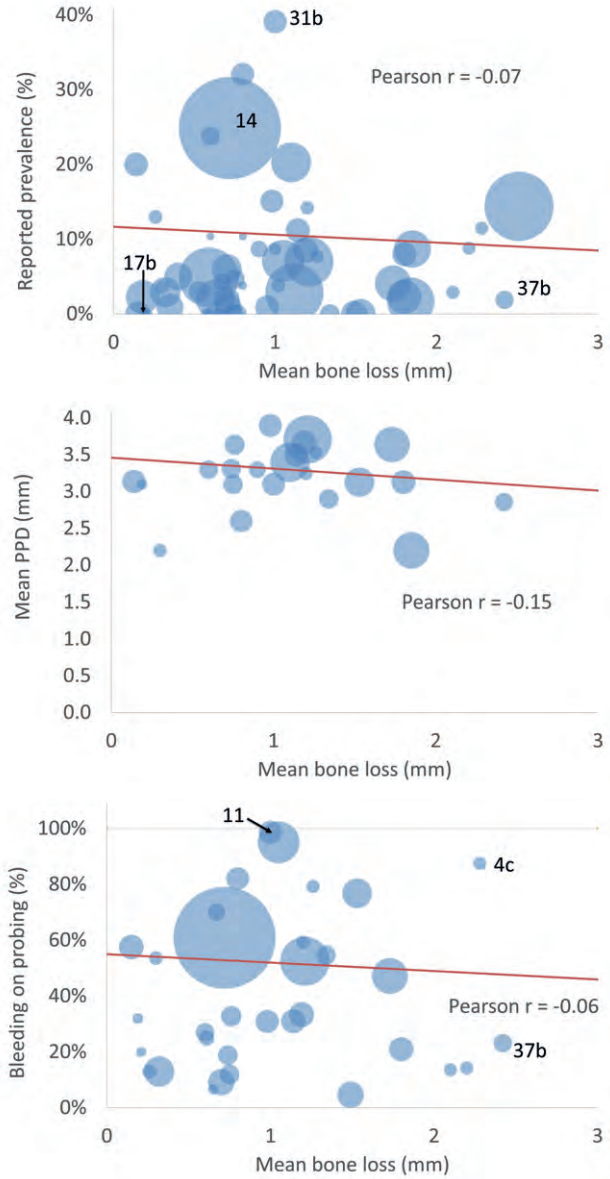

Figure 3: (a) Mean bone loss (mm) in relation to the reported prevalence of peri-implantitis (%); r = –0.07 (negligible correlation). (b) Mean bone loss (mm) in relation to probing pocket depth (mm); r = –0.15 (negligible correlation). (C) Mean bone loss (mm) in relation to bleeding on probing (%): r = –0.06 (negligible correlation); the size of the bullets reflects the number of implants reported in the treatment group; the number in the bullets refers to the article number provided in Table 1

Figures 4a and b illustrate the lack of a relationship between the reported prevalence of peri-implantitis and mean PD. Froum and Khouly reported the lowest mean PD (2.2 mm) and a corresponding reported prevalence of peri-implantitis of 3.6%.[87] Den Hartog and colleagues reported the highest mean PPD (4.3 mm) and a reported prevalence of peri-implantitis of 11.5%.[86] Mean BoP showed a strong correlation with peri-implantitis (Pearson r = 0.45). Tey reported 95% BoP with only 7.1% of the implants demonstrating peri-implantitis.[78] The paper of Renvert reported a similar 90% BoP with a mean PD of 3 mm but nevertheless 39% peri-implantitis.[80] Another Swedish report came up with 9% of BoP and only 2% of peri-implantitis, but PD values were missing.[88]

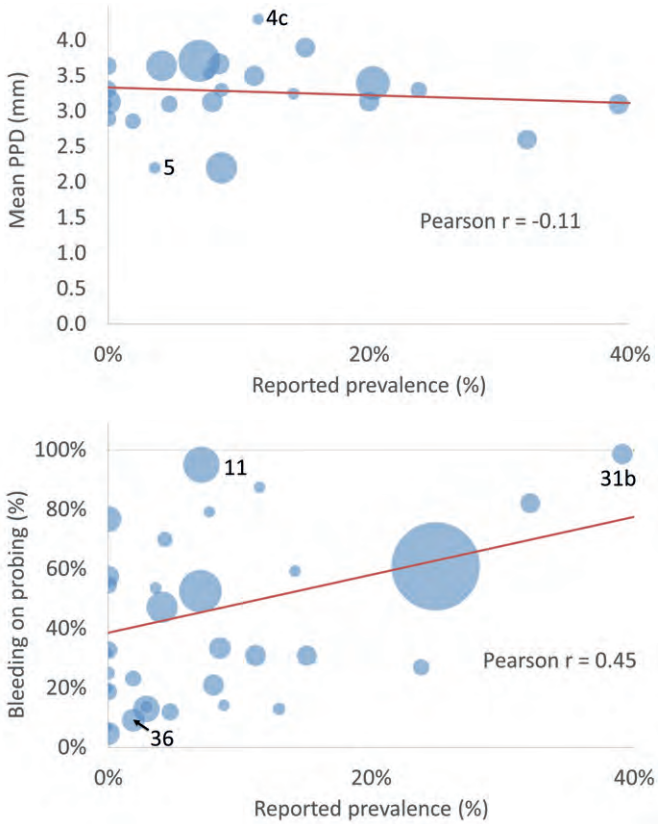

Figure 4: (a) Reported prevalence of peri-implantitis (%) in relation to mean probing pocket depth (mm): r = –0.11 (negligible correlation). (b) Reported prevalence of peri-implantitis (%) in relation to bleeding on probing (%): r = 0.45 (strong correlation); the size of the bullets reflects the number of implants reported in the treatment group; the number in the bullets refers to the article number provided in Table 1

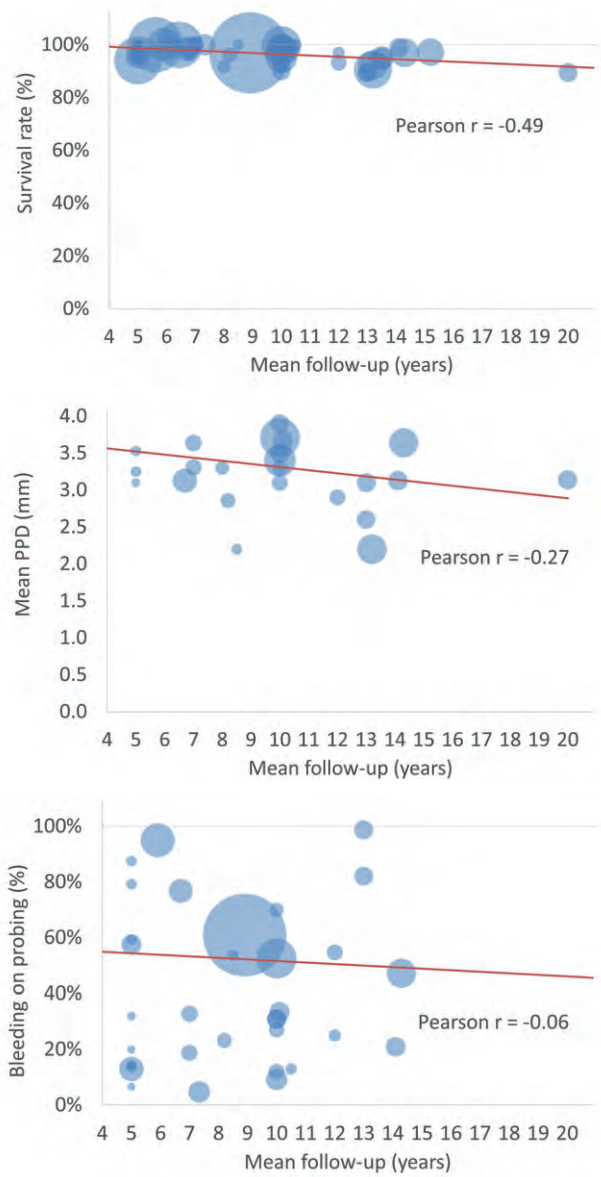

Figure 5: (a) Mean follow-up time (years) in relation to survival rate (%): r = 0.49 (strong correlation). (b) Mean follow-up time (years) in relation to probing pocket depth (mm): r = –0.27 (weak correlation). (c) Mean follow-up time (years) in relation to bleeding on probing (%): r = –0.06 (negligible correlation); the size of the bullets reflects the number of implants reported in the treatment group

Figure 5 visualizes the parameters survival rate, mean PD, and mean BoP in correlation with the mean function time. The survival rate shows negative strong

correlation with the mean function time (Pearson $r = -0.49$). The correlation between mean PD and mean function time is weak (Pearson $r = -0.27$). There is no indication of correlation between the mean function time and mean BoP (Pearson $r = -0.06$).

DISCUSSION

This review focused on reported peri-implantitis prevalence and diagnostic parameters considered important for long-term outcome. Biologic complications often coined as peri-implantitis may cause patient discomfort and may result in implant failure. For the current critical review, the search was limited from 2011 to September 2017, which coincides with the scientific debate on peri-implantitis. It was decided to include all types of studies to be as inclusive as possible. This may better reflect daily clinical practice when compared to well-controlled academic studies. Because peri-implantitis occurs commonly after longer function time, studies were included when at least 5 years of mean follow-up was reported. Over the last decade, there has been a tremendous increase in the use of dental implants in daily clinical practice and consequently also scientific interest has increased. In 2011, twice as many papers appeared compared to 2006 and from 2011 until 2017 as many papers appeared than in the previous 35 years as visualized in Figure 6. Despite 4,173 initially selected papers, only 255

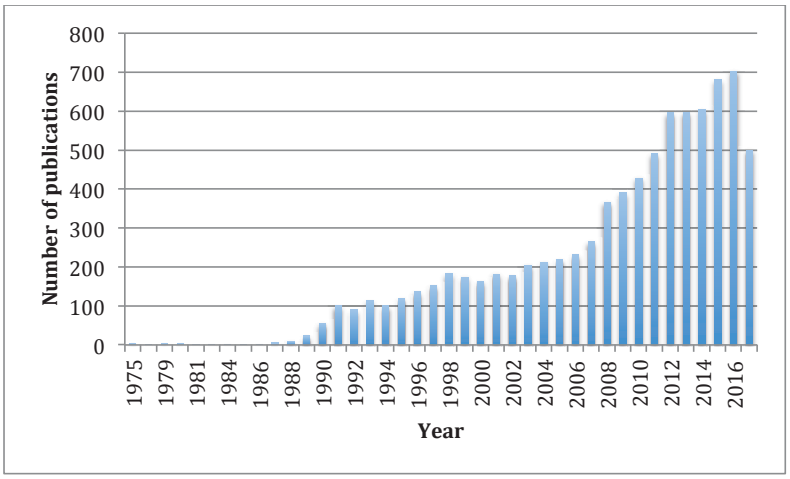

Figure 6: Number of publications per year from the search string applied in this systematic review

were selected for full reading and only 41 withstood the quality check. This is a disappointingly low proportion for a topic with such a significant impact for patients, clinicians, and implants industry.

The included material in this paper is strongly skewed toward retrospective studies, with 6,246 retrospective and 3,411 prospective analyzed implants. One could address that this leads to a higher inclusion of lower quality data. The high amount of retrospective included implants is mainly caused by the large study of Derks and colleagues with 2,367 implants at baseline.[83] However, the results showed a similar survival rate for retrospective and prospective analyzed implants, 97.2% and 96.2%, respectively, and in view of the large standard deviation, the difference in overall mean weighted bone loss between retrospective and prospective studies is not conclusive. Due to the large heterogeneity in the definition of peri-implantitis, it was not possible to calculate whether there was a difference in the reported peri-implantitis prevalence between retrospective and prospective analyzed implants.

Regarding the statistical analysis, it was opted to use the Pearson correlation coefficient. Although the justification of this correlation coefficient instead of the Spearman's relation coefficient could be a point of debate when data are possibly not normally distributed, the distribution at the level of the separate studies is most often skewed, when reported, and the presence of outliers cannot be excluded. This results in the distinct difference in variability of the different studies and the unreliability of estimates of the standard deviation for the individual studies. To circumvent the problem of unreliable estimates of the standard deviation, weighting by sample size was performed. At the level of the studies, though, no real outliers are present. The Pearson correlation coefficient is a measure of linear approximation, and the Spearman correlation coefficient is a measure of association that is not immediately translates to linearity. In view of the attempt to demonstrate the absence or presence of linear relations, the Pearson correlation was chosen together with the graphical representation to visually assess the relation described by the coefficient. Testing of the correlation coefficient would have required normality at both levels and reliable estimates of the within variability and between study variability. It is clear that, these requirements were not met, and therefore, the presented results are exploratory and descriptive in nature.

The overall weighted mean implant survival in the selected studies was 96.9% based on remaining implants at the time of evaluation. This shows that dental implant treatment today can be considered predictable. Few papers report on implant failure caused by peri-implantitis alone. In five treatment groups (Arnhart et al., 2013; Cassetta, Driver, Brandetti & Calasso, 2016; Sener-Yamaner, Yamaner, Sertgoz, Canakci & Ozcan, 2017), 5%, 1%, 3%, 0%, and 2% of the implants were lost due to peri-implantitis.[85,89,90] Sener-Yamaner and colleagues reported peri-implantitis related failures after 5 years of loading especially in smokers.[90] The paper of Arnhart mentioned the loss of two implants after 5 and 10 years because of peri-implantitis.[85] The aforementioned three papers did not report prevalence of peri-implantitis for the remaining implants and were therefore excluded from the current review. Only two studies reported the prevalence for peri-implantitis of both lost and functioning implants. Lops described eight of 257 (3.1%) implants with mobility due to severe peri-implantitis and ten other implants were successfully treated during the 20-year follow-up period.[91] Chappuis and colleagues reported 19 of 95 implants (20%) with peri-implantitis whereof six implants were lost and 13 underwent a successful anti-infectious therapy and were maintained with no further signs of acute infection.[14] Both studies included the treated peri-implantitis implants in the reported prevalence figures despite successful treatment. In the other 36 papers, prevalence of peri-implantitis was related to surviving implants and dropouts or lost implants prior to the moment of assessment are not taken into account. One can conclude that information of peri-implantitis in lost implants is scarce, and hence, the reported prevalence may be underestimated in the available literature.

In this review, the prevalence of peri-implantitis on implant level ranged between 0% and 40%. The case definitions varied considerably between studies, mostly due to heterogeneous thresholds for bone loss, ranging from any detectable bone loss to 3.5 mm. This makes comparisons between studies difficult. Reflecting on the results presented in Table 6, it is obvious that reported prevalence figures are larger when the threshold is low. Using the same implant design, Swedish studies that applied a threshold bone loss of approximately 0.5 mm concluded that 13%–25% of the implants were affected.[83,92] Thresholds of bone loss of 2–3 mm yield much lower prevalence in the order of 5%–10%. However, the paper of Meijer, Raghoebar, de Waal and Vissink seems contradictory in this respect.[93] With a 2 mm threshold, they detected 20% despite a mean bone loss limited to

1 mm. Their material consisted of IMZ and TPS implants from the first generation, known to be prone to bone loss over time. Meyle and colleagues reported a similarly high prevalence of 24% but a low mean bone loss of 0.60 mm also after 10 years.[94] The threshold of bone loss for the diagnosis for peri-implantitis was any bone loss and this could explain the high reported prevalence. If one were to apply the guidelines of the 8th European Workshop on Periodontology on their material, the prevalence would not be 23.8% but 0%. Also, Renvert reported peri-implantitis prevalence of 32.1% and 39.7% for both treatment groups, respectively.[80] The implants evaluated after 13 years showed a mean bone loss of 0.8 mm for TiOblast surfaces and 1.0 mm for TiUnite surfaces of peri-implantitis in both treatment groups. Despite this low mean bone loss, high bleedings scores around the implants of 82% and 90% were reported.

Table 6: Overview of studies giving a frequency distribution for implants with bone loss > 2mm in relation to prevalence of peri-implantitis and cut-off bone loss.

Article number	Author	Mean bone loss (SD)	% Implants with estimated bone loss> 2 mm based on given mean and SD	Frequency distribution of implants with bone loss > 2mm as reported in the paper	Reported prevalence of peri-implantitis	Cut-off bone loss (mm)
1	Shi et al.[98]	1.19 (1.07)	22%	8.5%	8.5%	2
4a	den Hartog et al.[86]	1.26 (0.90)	21%	17.3%	7.7%	-
4b		1.20 (1.10)	23%	16.%	14.2%	-
4c		2.28 (0.97)	61%	64.0%	11.5%	-
8	Cassetta et al.[89]	0.59 (1.34)	15%	13.3%	4.9%	-
9	Ekfeldt et al.[92]	0.26 (0.60)	0%	3.33%	13.0%	0.6
11	Tey et al.[78]	1.05 (1.07)	19%	18.0%	7.1%	2.5
14	Derks et al.[83]	0.72 (1.15)	13%	9.9	24.9	0.5
16	Donati et al.[77]	0.61 (2.10)	25%	9.0%	8.6%	2
20	van Velzen et al.[97]	1.21 (0.94)	20%	5.99%	7.0%	1.5
22	Meijer et al.[93]	1.10 (1.10)	21%	16.0%	20.3%	2
25	Simion et al.[114]	1.34 (0.79)	20%	10.0%	0.0%	-
30	Chappuis et al.[14]	0.14 (1.09)	4%	0.0%	20.0%	-
32	Frisch et al.[95]	1.80 (1.50)	45%	35.0%	8.0%	3.5
36	Ostman et al.[88]	0.70 (1.35)	17%	11.3%	1.90%	-

The article number refers to the reference provided in Table 1

A serious problem in this review is the heterogeneity of the data and the variation of the follow-up time within each study. This was recognized by previous authors (Frisch, Ziebolz & Rinke, 2013; Eriksson & Guisado-Moya, 2014) and obvious from the study of Jensen, Meijer, Raghoebar, Kerdijk and Cune.[95,96] The latter had a mean

follow-up time of 8 years based on implants in function from 3 years up to 16 years of follow-up. One could debate whether it is appropriate to sample implants with a large range in function time as being one group or whether cohort analysis based on function periods would be more justified.

Bone loss is in most of the studies expressed as a mean value with a standard deviation, which may hide outliers in the analysis. When reporting mean values of bone loss in a study population, it implies that the data are normally distributed. If this were the case, the mean and standard deviation would suffice to estimate the percentage of implants with a defined bone loss. Doornewaard and colleagues applied this in a systematic review and calculated the proportion of implants with bone loss over 1, 2 and 3 mm, respectively.[1] The same approach was applied as a post hoc analysis using the 13 papers that reported both the mean and standard deviation and also gave a frequency distribution of bone loss as presented in Table 6. We observed that the calculated proportion of implants with bone loss was an overestimation when compared to the frequency distribution reported. Hence, bone loss is probably not normally distributed within the study population but positively skewed. Hence, nonparametric statistics is appropriate including statistical parameters median, interquartile ranges as well as frequency distributions. This could refine the prevalence figures in scientific reports. Only four of the 13 previously mentioned papers reported their data in this proposed way (Donati et al., 2015; Ekfeldt et al., 2017; Frisch et al., 2013; van Velzen, Ofec, Schulten & Ten Bruggenkate, 2015) and all reported lower medians than means.[77,92,95,97] This may suggest that few implants with an extensive bone loss have a big impact on the mean and the standard deviation. This is confirmed by Donati who detected three of the 35 evaluated implants with bone loss of 5, 7, and 9 mm.[77] They reported a median of 0.2 mm and an interquartile range of –0.7 to 0.5 mm. Ekfeldt and colleagues showed comparable results where only two of the 30 evaluated implants lost, respectively, 1.8 mm and 2.4 mm bone.[92] This resulted in a higher mean bone loss of 0.26 mm compared to a median of 0.0 mm. It is obvious that the methodology applied in our review yielded overestimated proportions of implants with a certain threshold of bone loss.

The pooled data from this review did not demonstrate a relationship between mean function time and mean implant survival or peri-implantitis prevalence. This could be partially explained by dropouts of implants that are not further assessed during follow-up.

This review contains four papers that reported the Kaplan–Meier survival analysis. Chappuis reported a sudden increase after 12 years, the latter related to a combination of biologic and technical failures.[14] Jensen analyzed the implants retrospectively with a start of the measurement after 3 years and reported all losses before 5 years.[96] Also, the other two papers by Meyle and Shi showed a downhill Kaplan–Meier survival rate in relation to follow-up time.[94,98] It seems therefore appropriate to conclude that implants do fail over time, although in small numbers.

The mean PD reported in 25 of the 41 papers varied between 2.2 mm and 4.3 mm, with only one study reporting a mean PD above 4 mm. It is obvious from the results presented in this review that a relationship between mean PD and mean bone loss or peri-implantitis prevalence is absent. From a clinical perspective, one should realize that probing is technique sensitive and may be affected by probing force, probing direction, design of the restorations, design of implant, and type of prosthetic components. Obviously, the prosthetic reconstruction may jeopardize probing due to incorrect probing direction or restorations' overhangs. This may potentially also provoke iatrogenic bleeding. Serino and colleagues examined the PD before and after removal of the prosthetic reconstruction.[58] While the PD before removal had a poor correlation with bone loss, it correlated well with the PD after removal as assessed during surgery. Christiaens concluded in a recent published paper that probing depth around peri-implantitis affected implants significantly underestimated the true bone level by 1 mm.[99] Garcia-Garcia and colleagues showed a significant underestimation of the interproximal bone level by intra-oral radiography of 1.3 mm on average.[100] Merli concluded that assessment of bone loss by three clinicians showed the highest intraclass correlation coefficient while the intraclass correlation coefficient for PD and BoP was low.[101] The paper of Coli and colleagues concluded, based on evidence from animal as well as human studies, that it is unreliable to simply diagnose an implant as having peri-implantitis because of a pre-established PD.[18] It is well known that values of 6–9 mm PD have been described in association with long-term successful dental implants. Human studies have shown that in healthy peri-implant mucosa, the probing depths are in most of the cases (60%–63%) above 4 mm and even up to 6 mm.[7,55] One should also keep in mind that the interproximal probing depth measurement is affected by a significant papilla regrowth after crown installation. These findings support the importance of a combination of diagnostic parameters when diagnosing peri-implantitis.

This critical review revealed mean BoP ranging from 4.7%–95%. Gerber and colleagues concluded that BoP is highly dependent on the probing pressure, which strengthens the difficulty of interpreting probing assessments.[102] When the probing pressure increased from 0.15N to 0.25N, BoP increased with 14% at implant sites. This increase was found to be significantly higher when compared to tooth sites (6.6%). A low probing force of 0.15N resulted in similar findings at implants and tooth sites. None of the selected papers gave detailed information on probing force. Only the paper by Chappuis used the sulcus bleeding index instead of BoP.[14] By doing so, there is no de-attachment of the mucosa around the implant as it is carried out without using a high force. This could explain the low bleeding score.

Merli and colleagues evaluated the peri-implant BoP together with PD scoring. They observed a 39% BoP and an increase in odds ratio by 1.8 for each 1 mm increment of PD.[103] For pockets of 3 mm, 30%–40% were BoP-positive. Over 80% of the pockets of 7 mm were bleeding. Also, the paper of Farina confirmed an odds ratio for BoP of 1.6 for each 1 mm increment of PD.[63] In both studies, also similar proportion of BoP-positive sites was detected for pockets of 4 mm (27%) and 7 mm (60%). It is therefore obvious that deeper pockets have a higher tendency to bleed. A recent large retrospective cohort study of nearly 5,000 Straumann implants placed in 2,060 patients with up to 10-year follow-up concluded that time alone and minimal bleeding did not correlate with bone loss but that care should be taken for implants with profuse bleeding or suppuration.[67] They found the highest mean bone loss around implants with suppuration and minor changes for implants with minimal to moderate or profuse bleeding. They concluded that BoP around implants is a weak indicator of ongoing or future loss of crestal bone. The fact that BoP is a binary analysis of bleeding (bleeding or no bleeding) may possibly explain high false-positive bleeding scores. They suggested the use of an ordinal scale assessment to overcome this issue. In our review, only three of the 41 included papers used an ordinal scale, which may explain why the review could not find a significant correlation between reported prevalence and mean BoP and mean bone loss.

Suppuration is an unequivocal sign of inflammation that may be indicative of bone loss. In most clinical papers, suppuration as a diagnostic parameter is grouped together with bleeding and denoted as "BoP and/or suppuration." Only

eight of 41 selected papers gave information about suppuration separately. Sanchez- Siles, and colleagues reported only two suppurating implants of the 120 implants diagnosed with peri-implantitis.[104] On the other hand, in four other papers, the prevalence of suppurating implants strongly correlated with the reported prevalence. This latter finding is in accordance with the results of the study of French.[67] They specified that suppuration was detected in implants with the highest bone loss and suggested it could be useful for clinical diagnosis. Confirmation in more studies seems essential to confirm this assumption.

CONCLUSIONS

There is a large variation in the peri-implantitis case definitions, and reporting of biologic parameters is incomplete. Mean bone loss did not correlate with diagnostic parameters mean PD, mean BoP, and peri-implantitis prevalence. Only mean BoP correlated strong, with reported prevalence of peri-implantitis. Survival rate showed a substantial correlation with function time, with minor implant loss over time. Inconsistent reporting of peri-implantitis prevalence needs to be addressed, and an unambiguous case definition for peri-implantitis is of utmost importance for science as well as clinical practice.

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CHAPTER 4

Long-Term Effect of Surface Roughness and Patients' Factors on Crestal Bone Loss at Dental Implants. A Systematic Review and Meta-Analysis.

This chapter is based on the publication: Long-Term Effect of Surface Roughness and Patients' Factors on Crestal Bone Loss at Dental Implants. A Systematic Review and Meta-Analysis.

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ABSTRACT

Publications from 2011 to 2015 were selected to evaluate effect of implant surface roughness on long-term bone loss as surrogate for peri-implantitis risk. 87 out of 2,566 papers reported the mean bone loss after at least 5 years of function. Estimation of the proportion of implants with bone loss above 1, 2, and 3 mm as well as analysis the effect of implant surface roughness, smoking, and history of periodontitis was performed. By means of the provided statistical information of bone loss (mean and standard deviation) the prevalence of implants with bone loss ranging from 1 to 3 mm was estimated. The bone loss was used as a surrogate parameter for "peri-implantitis" given the fact that "peri- implantitis" prevalence was not reported in most studies or when reported, the diagnostic criteria were unclear or of dubious quality. The outcome of this review suggests that peri-implant bone loss around minimally rough implant systems was statistically significant less in comparison to the moderately rough and rough implant systems. No statistically significant difference was observed between moderately rough and rough implant systems. The studies that compared implants with comparable design and different surface roughness, showed less average peri-implant bone loss around the less rough surfaces in the meta-analysis. However, due to the heterogeneity of the papers and the multifactorial cause for bone loss, the impact of surface roughness alone seems rather limited and of minimal clinical importance. Irrespective of surface topography or implant brand, the average weighted implant survival rate was 97.3% after 5 years or more of loading. If considering 3 mm bone loss after at least 5 years to represent the presence of "peri- implantitis," less than 5% of the implants were affected. The meta-analysis indicated that periodontal history and smoking habits yielded more bone loss.

INTRODUCTION

Today, achievement of osseointegration is no longer the only key issue in research related to oral implantology as the predictability of implant therapy is high due to improvements of biomaterials and clinical procedures. Multiple long-term studies show successful treatment outcomes in terms of functional rehabilitations with survival rates ranging from 89.5 to 99.2%.[1–6] Instead, the focus has shifted to peri-implant bone stability, which is paramount for long-term success. Bone loss may lead to complications such as soft tissue recession, "peri-implantitis," implant fractures, and eventually loss of the implant.

Although dental implants have demonstrated favourable long-term results,[7–12] failures do occur and can be related to different factors. For instance, early implant failures have been related to excessive surgical trauma, an impaired healing ability, premature loading, and infection. In addition, late failures are mostly attributed to occlusal overload and/or progressive peri-implant bone loss.[13] Most patients of today have lost one or a few teeth and have high demands on the esthetic outcome. Peri- implant bone stability is a prerequisite for soft tissue preservation and hence, bone loss may lead to soft tissue recession and a poor esthetic outcome.[14,15]

Likewise periodontitis, peri-implantitis is a multi- factorial disease but associated with pathogens colonizing the subgingival biofilm, and the host response.[16] Peri-implant mucositis has been described as a reversible inflammation of the peri-implant soft tissues without signs of loss of the supporting bone. Peri-implantitis is defined as inflammation of the soft tissues in combination with ongoing loss of the supporting peri-implant bone beyond the physiological bone adaptation.[17] The reasons for the inflammation is multifactorial and under debate and especially diagnostic thresholds or diagnostic methods in general, are currently leading to biased reports on peri-implantitis prevalences. Some authors look on "peri-implantitis" as a biofilm induced disease while others regard this as an imbalanced foreign body response. However, not every single implant presenting peri-implant bone loss can be defined as peri-implantitis. It is well documented that the initial bone loss is an inevitable reaction to surgery and loading and known clinically as the establishment of a soft tissue seal called "biologic width."[18–20]

Poor oral hygiene is known as an important risk factor in the development and progression of periodontal disease.[21] Poor oral hygiene initiates a persistent gingivitis, which results in a 46-times higher risk for tooth loss.[22] Similarly, there is evidence that good oral hygiene should be recommended to prevent bleeding and pocket formation around implants.[23] Patient less compliant with maintenance are also more prone to implant failure.[24]

Different systematic reviews have shown that patients with existing or ongoing periodontitis are more likely to experience implant failure and biological complications.[25–32] This could be related to the type of microbiota in these patients and the ability of forming biofilms. It could also reflect a stronger immunological response to foreign bodies such as biofilm, plaque, and implant components. However, it is difficult to draw strong conclusions due to the high heterogeneity among the studies and methodological variability.[33]

Tobacco smoke contains nearly 4,000 chemicals such as carbon monoxide, hydrogen cyanide, and reactive oxidizing radicals. Some of those chemicals are known to be toxic and as a consequence smoking harms nearly every organ in the body including the tissues within the oral cavity. The negative effect of smoking is attributed to the impaired vascularity of the periodontal tissues rather than a vasoconstrictive effect.[34] By affecting the revascularization it may lead to an impaired healing after surgery. Different systematic review identified smoking as a factor affecting implant survival and peri-implant bone loss.[27,35,36] Additionally, Lindquist and colleagues identified smoking the predominant factor affecting peri-implant bone loss. However, good oral hygiene reduced the pernicious effects of smoking while poor oral hygiene aggravated bone resorption.[37]

Besides, the above-mentioned patient-related factors, implant-related factors can possibly influence implant treatment outcome. Today, most marketed implant surfaces are moderately rough with Sa values between 1.1 and 2 µm. A brief overview of various surface roughness for some implant brands is given in Table 1. Increasing implant surface roughness, induces qualitative and quantitative changes in biofilm formation.[38] Quirynen and colleagues suggested that implants with increased surface roughness may be more prone to peri-implant bone loss and consequently, late implant failure.[28] Conversely, Chappuis and colleagues showed that even rough TPS-coated implants can

be very successful presenting very limited peri-implant bone loss after 20 years follow-up in a well-maintained population.[39] One can conclude that the literature is inconclusive about the effect of implant surface roughness on implant success.

Table 1: Surface roughness and corresponding Sa values (µm) and some implant brands

Surface roughness	Sa value	Some implant brands
Smooth	< 0.5 µm	Experimental not clinically available
Minimally rough	0.5 - 1 µm	Machined Brånemark implants, Osseotite, Nanotite
Moderately rough	> 1 - 2 µm	SLA, TiUnite, Osseospeed, TiOblast, Southern
Rough	> 2 µm	IMZ, TPS, Ankylos, Friadent, Xive

Hence the aim of this study was to scrutinize whether long-term peri-implant bone loss, beyond physiologic bone adaptation, is affected by implant surface roughness and/or patient-related factors such as smoking and history of periodontitis.

MATERIALS AND METHODS

Paper Selection

Since it was the aim of the paper to assess long-term bone loss as surrogate variable for peri-implantitis and to scrutinize the type of studies and the level of quality of reporting, it was decided to conduct a broad literature search using the Pubmed database of the US National Library of Medicine for articles. Publications from 2011 up to December 24, 2015 were selected using the general search algorithm: ((((((“bone loss”) OR “peri-implantitis”)) OR “peri implant”)) AND dental implant). It was opted not to perform a strict review using the terminology “Peri- Implantitis” [Mesh] as search criterion due to the limitation of the generated output to only 426 papers. Because most surface-modified implants were launched commercially at the time of the millennium change, the time frame was set to 2011 to 2015 because this increased the probability to select predominantly currently commercially available implant brands and various rather new surfaces. Furthermore, it seemed logical to have a literature search cut-off at 2011 because peri-implantitis is reported after longer follow-up times and the scientific community has taken special interest in clinical research on peri-implantitis after consensus meetings with specific guidelines for research from 2006 onwards.[40–43]

The list of generated articles was obtained through elimination based on the title and detailed information given in the abstract. Further evaluation and refining of the selected papers was performed by reading the papers and registering the described results in the data set. In case of disagreement over the inclusion/exclusion, both evaluators (RD & VC) discussed and reached a consensus or, in case of further doubt, a third evaluator was consulted (HDB).

To be included in the study, the papers had to be published in English, report on bone loss compared to a baseline measurement and include at least 10 patients after a minimal mean follow-up time of 5 years. Only studies discussing straightforward implant treatment in systemically healthy patients, as the test strategies were included. Hence, studies describing implant treatments in tumor-resected areas, studies involving extensive bone grafts or zygomatic implants were excluded. Exceptional, experimental or uncommon implant designs, as well as implants with unknown surface topography, were excluded. Studies were additionally rejected when statistical evaluation was hampered because of incomplete data reporting, such as lacking failure rate, implant or patient numbers, bone loss and standard deviation calculated on implant level. However, studies lacking standard deviation on bone loss were included for calculating implant survival.

Table 2 gives an overview of exclusion criteria and the references of the excluded papers. The review did not exclude studies with smokers, patients with periodontal history, controlled diabetes, or implants in sinus lifted bone. These procedures are today considered part of daily good clinical practice. To avoid a biased selection and to ensure that the papers reflected the daily clinical situation, no distinction was made based on study design (prospective or retrospective) or surgical or prosthetic treatment protocol.

Statistical Analysis

For each study the mean bone loss was used together with the number of implants to calculate the weight of the study in the overall statistical analysis of bone loss and to estimate the proportion of implants with bone loss above 1, 2, and 3 mm. Analysis was performed additionally per implant surface roughness group and qualified as minimally rough, moderately rough, rough, or mixed/unknown. The latter included studies with unspecified implant surface roughness

Table 2: Excluded papers and exclusion reasons

Follow up < 5 years	
Kan et al.[44]	2011
Lopez-Piriz[45]	2012
Soardi et al.[46]	2012
Paul et al.[47]	2013
Dagorne et al.[48]	2014
Ata-Ali et al.[49]	2015
Jervoe-Storm et al.[50]	2015
< 10 patients per treatment group at baseline	
Zafiropoulos et al.[51]	2013
Romanos et al.[52]	2013
< 10 patients per treatment group after at least 5 years	
Vanlioglu et al.[53]	2012
Bahat et al.[54]	2012
Romeo et al.[55]	2014
Incomplete data about bone loss after at least 5 years	
Cortellini et al.[56]	2011
Ozkan et al.[57]	2011
Ozkan et al.[58]	2011
Akoglu et al.[59]	2011
Stacchi et al.[60]	2012
Maló et al.[61]	2012
Fugazzotto[62]	2012
Swierkot et al.[63]	2012
Degidi et al.[64]	2012
Ormianer et al.[65]	2012
Rocci et al.[66]	2012
Covani et al.[67]	2012
Wilson et al.[68]	2013
Harel et al.[69]	2013
Romanos et al.[70]	2013
Harel et al.[71]	2013
Canullo et al.[72]	2016
Felice et al.[73]	2014
Frisch et al.[74]	2014
Woelber et al.[75]	2016
Maló et al.[76]	2015
Trullenque-Eriksson et al.[77]	2015
Jemt et al.[78]	2015
Melo et al.[79]	2015
Incomplete data about number of patients and/or implants	
Yaltirik et al.[80]	2011
Ueda et al.[81]	2011
Stoker et al.[82]	2012
Krennmair et al.[83]	2011
Oliva et al.[84]	2012
Moeintaghavi et al.[85]	2012

Table 2: Continued

Incomplete data about number of patients and/or implants	
Pettersson et al.[86]	2015
Sivolella et al.[87]	2013
Berberi et al.[88]	2014
Mangano et al.[89]	2014
Rossi et al.[90]	2015
Vázquez Alvarez et al.[91]	2014
Nack et al.[92]	2015
Korfage et al.[93]	2014
Cavalli et al.[94]	2015
Maló et al.[95]	2014
Anitua et al.[96]	2016
Ebinger et al.[97]	2016
Jeong et al.[98]	2015
Konstantinidis et al.[99]	2015
Fretwurst et al.[100]	2015
Krebs et al.[101]	2015
Quaranta et al.[102]	2015
Rossi et al.[103]	2016
Incomplete data about follow up time	
Mijiritsky et al.[104]	2013
Zirconia implants	
Grassi et al.[105]	2015
Autologous onlay grafted bone	
Dasmah et al.[106]	2013
De Bruyn et al.[107]	2013
Sbordone et al.[108]	2012
Stellingsma et al.[109]	2014
Duttenhoefer et al.[110]	2015
Patients treated with implants after oral tumors	
Zou et al.[111]	2015
No consensus about bone loss	
Hjalmarsson et al.[112]	2011

or where data were presented without making distinction between implant brands or surface topography.

For the descriptive statistics the results of the individual studies were weighted by the number of implants to prevent studies with extremely homogenous groups dominating the results. After the descriptive followed the assessment of the inter study variability. Preliminary analysis performed showed that the multitude of intervening factors jeopardized the successful reduction of the intra study variability by means of a meta-regression. As argument to sustain this statement

the heterogeneity estimates of the random effects model were included and the results of meta-regression models predicting mean bone loss through mediating factors, such as smoking and roughness were presented. The aim of meta-analysis is the recombination of results of several studies through increased power and to detect influences that otherwise would appear to be statistically insignificant. Extreme heterogeneity of the studies does not allow for the straightforward application of meta-analytic statistics and testing strategies. Therefore, a subgroup analysis was conducted for roughness, smoking, and periodontal history based on studies that allowed for "paired" comparisons. Null-hypotheses were the equality of bone loss between minimally rough and moderately rough implant surfaces, smokers and non-smokers, and healthy patients and patients with a periodontal history, respectively. Throughout the meta-analytic analysis the study results are weighted by the inverse of the variance of the effect sizes. Heterogeneity was considered to be high if I^2 exceeded 70%, between 50% and 70% the heterogeneity was considered to be medium, and below 50% small. When the heterogeneity was revealed to be statistically significant ($p < .05$) the random effects model was interpreted. If not significant, the fixed model was evaluated.

Descriptive statistics and the recombination of results were performed using MatLab R2015b version (8.6.0.267246) (The MathWorks, Inc., Natick, MA, USA). The meta-regression and fixed and random effects modeling were performed using the statistical package R version 3.1.0 (2014-04-10) (The R foundation for Statistical Computing), platform: x86_64-w64-mingw32/x64 (64-bit) with "metaphor" package (version 1.9-7) for meta-regressions and the package "meta" version 4.3-2 for random and fixed effect modeling.

RESULTS

Selection of Papers

The literature search yielded 6,445 studies starting in 1972 up to 2015. Of the last 2,566 publications between 2011 and August 14, 2015, in total 156 were deemed appropriate and selected by the two examiners taking the initial selection criteria into account. A further selection after reading of the paper disqualified another 69 papers for several reasons, among others the lack of standard deviation on bone loss. This was an essential factor to allow statistical estimation of the proportion of implants with an arbitrarily selected threshold for bone loss (Table 2).

Table 3: Overview of finally included papers with study design

Author	Year	Study design	Treatment subgroups	Mean follow-up years	Patients at baseline	Implants at baseline	Implants at follow-up
Becker et al.[113]	2016	P		6.5	31	84	40
Imburgia & Del Fabbro[114]	2015	R		8.8	41	205	205
Hoeksema et al.[115]	2016	P	1: older patients	10		106	64
			2: young patients	10	105	104	99
Vandeweghe et al.[116]	2016a	R		7.5	46	211	211
Vandeweghe et al.[117]	2016b	R	1: moderately rough	14.3		121	121
			2: smooth	14.3	33	76	76
Nedir et al.[118]	2016	P		10	17	25	23
Park et al.[119]	2015	R		10	74	242	242
Eerdekens et al.[120]	2015	P		5	10	60	10
Perrotti et al.[121]	2015	P	1: tuberplant	10	97	67	67
			2: bioplant	10		59	59
Romanos et al.[122]	2014	P	1: immediate loading	10.1	12	30	30
			2: delayed loading	10.4		30	30
Zhao et al.[123]	2016	R		6.2	45	45	45
Crespi et al.[124]	2014	P	1: screw retained	8	28	136	136
			2: cement retained	8		136	136
van Velzen et al. [125]	2015	P		10	250	506	367
Trullenque-Eriksson & Guisado-Moya[126]	2014	R		13.19	105	342	342
Joda et al.[127]	2015	R		5	98	316	316
Meijer et al.[128]	2014	P		10	150	240	240
Slotte et al.[129]	2015	P		5	32	86	71
Schropp et al.[130]	2014	P		10	72	63	47
Gholami et al.[131]	2014	P	1: partial cases	5	20	35	23
			2: full cases	5		23	35
Cooper et al.[132]	2014a	P		5	19	23	18
Vervaeke et al.[133]	2016	P		9	50	320	245
Mangano et al.[134]	2015	R		20	49	178	178
Simion et al.[135]	2015	R		12	29	59	59
Tealdo et al.[136]	2014	P	1: immediate loading	6.2	49	163	159
			2: delayed loading	6.2		97	90
Covani et al.[137]	2014	P		5	47	47	45
Cooper et al.[138]	2014b	P	1: immediate placement	5	113	55	55
			2: delayed placement	5		58	58
Leventi et al.[139]	2014	R		7.7	41	102	102
Meyle et al.[140]	2014	P		10	20	54	54
Pozzi et al.[141]	2014	R		8.82	73	167	160
Anitua et al.[142]	2014	R		10.3	75	111	87

Implant brand	Surface	Baseline radiograph time	Mean implant bone loss (mm)	Standard deviation bone loss (mm)	Implant survival rate %	Surface roughness
Nobel Biocare	Mixed	1	-0.10		94.60%	mixed
Nobel Biocare	TiUnite	0	0.43	1.15	96.10%	3
Straumann	TPS	1	1.20	1.20	93.40%	4
Straumann	TPS	1	1.20	1.10	97.10%	4
Southern	Mod rough	0	1.17	0.49	99.50%	3
Southern	Mod rough	0	1.73	1.54	97.00%	3
Southern	Machined	0	1.41	0.92		2
Straumann	SLA	0	1.00	0.90	100.00%	3
Implantium Dental Implant	Moderately rough	0	0.28	0.78	97.90%	3
Ankylos	Ankylos	1	0.60	1.12	96.70%	4
Oralplant	TPSS	1	1.31	0.74	98.60%	4
Oralplant	TPSS	1	0.74	0.92	100.00%	4
Ankylos	Ankylos	9	0.57	1.06	100.00%	4
Ankylos	Ankylos	9	1.12	1.30	100.00%	4
Straumann	SLA	1	1.10	0.92	100.00%	3
Outlink	TPS	0	0.42		98.50%	4
Outlink	TPS	0	0.67		100.00%	4
Straumann	SLA	0	1.21	0.94	99.70%	3
Mixed	Mixed	1	1.84	1.35	90.60%	mixed
Ankylos	Ankylos	1	1.02	1.25	97.20%	4
Mixed	Mixed	1	1.10	1.10	95.30%	mixed
Straumann	SLA	1	0.53	0.34	92.20%	3
Biomet/3I	Osseotite	0	0.67	0.98	unknown	2
Thommen	Moderately rough	0	1.10	0.60	98.40%	3
Thommen	Moderately rough	0	1.50	0.90		3
Astra Tech	Osseospeed	0	0.18	0.79	96.50%	3
Astra Tech	TiOblast	0	1.68	2.08	99.20%	3
Mac System	Unknown	1	1.80	0.60	97.20%	unknown
Nobel Biocare	Machined	1	1.34	0.79	93.20%	2
Unknown	Rough	0	1.12	1.12	93.90%	4
Unknown	Rough	0	1.94	1.44	95.90%	4
Khono Implants	Unknown	0	1.08	0.43	95.70%	unknown
Astra Tech	Osseospeed	0	0.43	0.63	95.00%	3
Astra Tech	Osseospeed	0	0.38	0.62	98.00%	3
Calcitek	Calcitek	0	1.28	1.06	99.00%	4
Frialit	Friadent	1	0.60	0.26	96.30%	4
Nobel Biocare	TiUnite	0	1.58	1.61	100.00%	3
BTI	Unknown	0	0.95	0.65	98.90%	unknown

Table 3: Continued

Author	Year	Study design	Treatment subgroups	Mean follow-up years	Patients at baseline	Implants at baseline	Implants at follow-up
Rasperini et al.[143]	2014	R	1: periodontally compromized non smoking	10	120	20	20
			2: periodontally compromized smoking	10		10	10
			3: periodontally compromized non smoking	10		20	20
			4: periodontally compromized smoking	10		10	10
			5: periodontally healthy non smoking	10		20	20
			6: periodontally healthy smoking	10		10	10
			7: periodontally healthy non smoking	10		20	20
			8: periodontally healthy smoking	10		10	10
Mozzati et al.[144]	2015	R		11	90	209	168
Zou et al.[145]	2013	R	1: telescopic overdenture	8	44	112	106
			2: bar overdenture	8		105	95
Donati et al.[146]	2015	P		5	151	161	140
Rocci et al.[147]	2013	P	1: TiUnite	9	44	66	51
			2: Machined	9		55	39
Dhima et al.[148]	2013	R		9	81	81	81
Krennmair et al.[149]	2013	R		5.5	42	152	152
Akca et al.[150]	2013	R	1: ball abutment overdenture	5	29	38	38
			2: locator abutment overdenture	5		20	20
Gelb et al.[151]	2013	R		7.33	57	107	107
Schwarz et al.[152]	2014	P		7.2	37	185	126
Wagenberg et al.[153]	2013	R		10.18	541	1187	1181
Chappuis et al.[39]	2013	R		20	67	95	85
Sayardoust et al.[154]	2013	R	1: smokers, TiUnite	5	80	56	56
			2: never smokers, TiUnite	5		52	52
			3: smokers, Machined	5		78	78
			4: never smokers, Machined	5		66	66

Implant brand	Surface	Baseline radiograph time	Mean implant bone loss (mm)	Standard deviation bone loss (mm)	Implant survival rate %	Surface roughness
Nobel Biocare	Machined	1	2.32	0.41	95.00%	2
Nobel Biocare	Machined	1	3.47	1.09	90.00%	2
Straumann	TPS	1	2.32	0.41	85.00%	4
Straumann	TPS	1	3.77	1.43	80.00%	4
Nobel Biocare	Machined	1	1.43	0.38	95.00%	2
Nobel Biocare	Machined	1	2.65	0.41	90.00%	2
Straumann	TPS	1	1.95	0.42	95.00%	4
Straumann	TPS	1	2.51	0.31	100.00%	4
Nobel Biocare	TiUnite	0	0.60	1.17	97.10%	3
Straumann	TPS	9	1.30	0.40	100.00%	4
Straumann	TPS	9	1.20	0.60	100.00%	4
Astra Tech	Osseospeed	0	0.32	1.15	95.60%	3
Nobel Biocare	TiUnite	0	1.40		95.50%	3
Nobel Biocare	Machined	0	1.70		85.50%	2
Nobel Biocare	TiUnite	0	-0.94	0.99	100.00%	2
Camlog	Camlog	0	1.21	0.36	100.00%	3
Straumann	SLA	9	0.77	0.31	97.00%	3
Straumann	SLA	9	0.59	0.13	100.00%	3
Nobel Biocare	TiUnite	0	1.49	1.03	100.00%	3
Frialoc system	Frialit	0	1.10	1.20	89.20%	4
Nobel Biocare	Machined	0	0.52	0.79	99.62%	2
Straumann	TPS	0	0.14	1.09	89.50%	4
Nobel Biocare	TiUnite	1	1.16	1.80	92.90%	3
Nobel Biocare	TiUnite	1	1.26	1.08		3
Nobel Biocare	Machined	1	1.54	1.85		2
Nobel Biocare	Machined	1	0.84	1.14		2

Table 3: Continued

Author	Year	Study design	Treatment subgroups	Mean follow-up years	Patients at baseline	Implants at baseline	Implants at follow-up
Calvo-Guirado et al.[155]	2014	P		10	64	86	86
Lops et al.[156]	2013	P	1: titanium abutment	6	85	47	47
			2: zirconium abutment	6		38	38
Dam et al.[157]	2014	P		5.5	174	378	378
Buser et al.[158]	2013	P		7	41	41	41
Lee et al.[159]	2012	R		5.7	175	116	259
Nickenig et al.[160]	2013	P	1: non polished collar	5.2	34	70	70
			2: polished collar	5.2		63	63
Kokovic et al.[161]	2014	P	1: immediate loading	5	12	36	36
			2: early loading	5		36	36
Mertens et al.[162]	2012	R		10.1	14	52	52
Renvert et al.[163]	2012	R	1: TiOblast	13	41	80	80
			2: TiUnite	13		84	84
Mordenfeld et al.[164]	2014	P		10.2	20	53	53
Mir-Mari et al.[165]	2012	R		6.7	68	217	217
Horwitz et al.[166]	2012	P		5	19	74	39
Deporter et al.[167]	2014	P		20	52	53	53
Dierens et al.[168]	2013	R		18.5	53	62	59
Buser et al.[169]	2012	R		10	303	511	511
Frisch et al.[170]	2013	R		14.1	22	89	89
Camargos et al.[171]	2012	R		5	44	73	70
Lops et al.[172]	2012	P		13.2	121	108	207
Ormianer[173]	2012	R		10	46	108	172
Lang et al.[174]	2014	P		5	20	20	15
Ravald et al.[175]	2013	P	1: TiOblast	5	66	184	170
			2: Machined	5		187	175
Deporter et al.[176]	2012	P		10	24	48	30
Jungner et al.[177]	2014	R	1: TiUnite	6.8		154	154
			2: Machined	6.8	103	133	133
Francetti et al.[178]	2014	P		6	22	54	49
Ostman et al.[179]	2012	P		10	46	121	106
Arnhart et al.[180]	2013	R	1: TiUnite	6.7	47	136	136
			2: Machined	8.2		52	52
Lai et el.[181]	2013	R		10	168	231	231
Hayacibara et al.[182]	2013	R		8	71	74	74
Degidi et al.[183]	2012	P	1: delayed placement	10	48	84	84
			2: immediate placement	10		74	74
Levine et al.[184]	2012	P		5	20	21	21

Implant brand	Surface	Baseline radiograph time	Mean implant bone loss (mm)	Standard deviation bone loss (mm)	Implant survival rate %	Surface roughness
Biomet/3I	Osseotite	0	1.01	0.22	97.10%	2
Astra Tech	TiOblast	1	0.50	0.30	100.00%	3
Astra Tech	TiOblast	1	0.40	0.20	100.00%	3
Straumann	Mixed	0	1.12	1.10	unknown	mixed
Straumann	SLA	0	0.38	0.72	100.00%	3
Mixed	Mixed	9	0.93	0.15	unknown	?
Nobel Biocare	TiUnite	0	0.70		unknown	3
Nobel Biocare	TiUnite	0	1.40			3
Straumann	SLA	0	0.40	0.24	100.00%	3
Straumann	SLA	0	0.80	0.19	100.00%	3
Astra Tech	TiOblast	1	0.30	0.50	100.00%	3
Astra Tech	TiOblast	1	0.80		unknown	3
Nobel Biocare	TiUnite	1	1.00		unknown	3
Nobel Biocare	Machined	1	1.60	1.00	86.00%	2
Nobel Biocare	Machined	1	0.26		unknown	2
MIS implant technologies	Moderately rough	0	1.41	0.67	unknown	3
SPS dental implants	Rough	9	0.67		73.40%	4
Nobel Biocare	Machined	1	0.82	1.45	91.50%	2
Straumann	SLA	0	1.52	0.66	98.80%	3
Nobel Biocare	Mixed	1	1.80	1.50	98.90%	mixed
Unknown	Unknown	0	1.80		95.90%	unknown
Straumann	TPS	1	1.85	1.55	92.30%	4
Zimmer Dental	Unknown	9	0.18		99.00%	unknown
Zimmer Dental	Unknown	0	0.70	0.26	94.00%	unknown
Astra Tech	TiOblast	0	0.70		95.00%	3
Nobel Biocare	Machined	0	0.40		94.70%	2
Mixed	Moderately rough	9	1.20		95.50%	3
Nobel Biocare	TiUnite	9	2.00	0.90	99.40%	3
Nobel Biocare	Machined	9	1.80	0.80	94.70%	2
Nobel Replace	TiUnite	0	0.76	0.47	97.96%	3
Nobel Biocare	TiUnite	0	0.70	1.35	99.20%	3
Nobel Biocare	TiUnite	1	1.53	0.25	98.53%	3
Nobel Biocare	Machined	1	2.42	0.34	96.15%	2
Straumann	SLA	0	0.63	0.68	98.30%	3
Straumann	TPS	0	1		100.00%	4
Nobel Biocare	TiUnite	0	1.93	0.40	98.05%	3
Nobel Biocare	TiUnite	0	1.98	0.37	96.52%	3
Straumann	SLA	0	0.58		100.00%	3

Table 3: Continued

Author	Year	Study design	Treatment subgroups	Mean follow-up years	Patients at baseline	Implants at baseline	Implants at follow-up
Rodrigo et al.[185]	2012	P	1: immediate placement	5	22	34	26
			2: delayed placement	5		34	26
Heschl et al.[186]	2012	P		10	30	30	120
Lethaus et al.[187]	2011	P		5	14	60	54
Heschl et al.[188]	2011	P		5	39	156	152
Browaeys et al.[189]	2013	R		5	83	501	106
Turkyilmaz et al.[190]	2011	P	1: early loading	7	26	24	24
			2: delayed loading	7		24	24
Glauser et al.[191]	2013	P		7	38	102	73
Soardi et al. [192]	2013	R		5	538	376	376
Calvo-Guirado et al.[193]	2011	P		5	64	86	83
Kowar et al.[194]	2013	R	1: completely edentulous maxilla	5	264	447	162
			2: completely edentulous mandible	5		644	219
			3: partially edentulous maxilla	5		146	78
			4: partially edentulous mandible	5		119	69
Geckili et al.[195]	2011	R		5	71	159	159
Cochran et al.[196]	2011	P		5	200	626	542
Mertens et al.[197]	2011	P		8	17	106	99
Roccuzzo et al.[198]	2012	P	1: periodontally healthy	10	112	61	59
			2: moderately periodontally compromized	10		95	88
			3: severely periodontally compromized	10		90	81

Implant brand	Surface	Baseline radiograph time	Mean implant bone loss (mm)	Standard deviation bone loss (mm)	Implant survival rate %	Surface roughness
Straumann	SLA	1	2.20	0.90	unknown	3
Straumann	SLA	1	2.10	1.00	unknown	3
Xive	Xive	1	1.80	0.65	98.30%	4
Straumann	SLA	1	0.77	0.66	96.70%	3
Xive	Xive	0	1.44	0.78	99.40%	4
Biomet/3I	Osseotite	0	1.57	1.10	92.10%	2
Nobel Biocare	TiUnite	0	1.29	0.20	100.00%	3
Nobel Biocare	TiUnite	0	1.33	0.20	100.00%	3
Nobel Biocare	TiUnite	0	1.51	1.00	97.10%	3
Unknown	Unknown	0	1.98		94.90%	unknown
Certain Prevail 3i	Osseotite	0	0.97	0.39	97.10%	2
Nobel Biocare	Mixed	1	0.60	0.46	94.90%	mixed
Nobel Biocare	Mixed	1	0.60	0.47	100.00%	mixed
Nobel Biocare	Mixed	1	0.60	0.47	97.60%	mixed
Nobel Biocare	Mixed	1	0.40	0.50	100.00%	mixed
Mixed	Mixed	1	0.99		98.74%	mixed
Straumann	TPS	1	0.18	0.88	99.40%	4
Astra Tech	TiOblast	1	0.30	0.72	99.00%	3
Straumann	TPS	0	0.75	0.88	96.60%	4
Straumann	TPS	0	1.14	1.11	92.70%	4
Straumann	TPS	0	0.98	1.22	90.00%	4

(p = prospective; r = retrospective), mean follow-up (years), number of patients and implants at baseline, implants at follow-up, mean implant bone loss (mm) and standard deviation, implant survival rate (%) and surface roughness (1 = unknown or mixture of surfaces, 2 = smooth, 3 = moderately rough, 4 = rough)

Quality of the Papers

The paper search revealed in total 87 included studies (summarized in Table 3) that reported a mean bone loss on implant level over a 5 to 20 year follow-up time; 48 were prospective and 39 were retrospective. Some papers compared different treatment protocols, which were considered as separate study groups for the statistical analysis of implant survival or bone loss calculation because some pertained to different surface or implant types as well as different treatment protocols. In the 123 treatment groups in total 15,695 implants were inserted in 6,755 patients and information about mean bone loss at the last examination visit was available from 13,970 implants after at least 5 years of implant function. The total drop-out of implants from baseline to the evaluation time point was 11% for the 87 selected papers.

Fifty-three out of 87 studies pertained to 10,533 originally placed implants from the portfolio of the three world leading companies Dentsply, Nobel Biocare and Straumann representing proportionally 67.1% from the total material. With 9,136/10,533 initially placed implants remaining at follow-up, the dropout rate was 13.3%.

Information on probing depth and bleeding on probing was available in only 40 and 49 of the included studies, respectively. Twenty-seven out of 87 papers reported peri-implantitis prevalence on implant level (Table 4) ranging between 0% and 39.7%. This large range can be explained by the arbitrarily chosen thresholds and diagnostic parameters for disease. The cut-off bone loss for peri-implantitis ranged from 1 to 3 mm and the cut-off probing pocket depth ranged from 4 to 6 mm. However, only 19/27 papers reported bleeding on probing, 16/27 reported probing depth, and only 11/27 actually defined peri-implantitis.

Implant Survival

From the 87 included papers and 123 study groups, the survival was reported in 79 papers and 107 study groups and ranged between 73.4% and 100%. Figure 1, A–C summarizes the implant survival rate and corresponding function time for the three surface roughness groups. In 44% of the studies the implant survival rate was between 95% and 100%, in half of the studies the survival ranged between 90% and 94.9%. Only in 6% of the studies the survival was below 90% with 73.4% survival after 20 years being the lowest one with a porous titanium alloy implant having a rough

Table 4: Studies discussing mean bone loss (expressed as positive value in mm) and standard deviation, survival rate (%), mean probing pocket depth (mm), bleeding on probing (%) and self-reported peri-implantitis prevalence

Author	Mean bone loss (SD)	Survival rate	Mean probing pocket depth (mm)	BoP	Prevalence peri-implantitis
Vandeweghe et al.[117]	1.41 (0.92)	97.00%	3.64		4.10%
Nedir et al.[118]	1.00 (0.90)	100.00%	-		8.70%
van Velzen et al.[125]	1.21 (0.94)	99.70%	3.71		7.00%
Trullenque & Guisado[126]	1.84 (1.35)	90.60%	-		21.00%
Meijer et al.[128]	1.10 (1.10)	95.30%	3.4		20.30%
Schropp et al.[130]	0.67 (0.98)	-	-	70.00%	4.30%
Mangano et al.[134]	1.80 (0.60)	97.20%	-		1.10%
Simion et al.[135]	1.34 (0.79)	93.20%	2.9	54.00%	0.00%
Meyle et al.[140]	0.60 (0.26)	96.30%	3.3	27.00%	23.80%
Anitua et al.[142]	0.95 (0.65)	98.90%	-		0.90%
Donati et al.[146]	0.32 (1.15)	95.60%	-	13.00%	2.90%
Gelb et al.[151]	1.49 (1.03)	100.00%	-	4.70%	0.00%
Schwarz et al.[152]	1.10 (1.20)	89.20%	-	60.00%	4.30%
Chappuis et al.[39]	0.14 (1.09)	89.50%	3.14		6.30%
Renvert et al.[163]	0.80 (-)	-	-	80.00%	32.10%
	1.00 (-)	-	-	94.00%	39.70%
Frisch et al.[170]	1.80 (1.50)	98.90%	3.13	21.00%	8.00%
Camargos et al.[171]	1.80 (-)	95.90%	2.3	59.00%	4.30%
Lops et al.[172]	1.85 (1.55)	92.30%	2.3		8.30%
Ormianer et al.[173]	0.18 (-)	99.00%	-		2.30%
Ravald et al.[175]	0.70 (-)	95.00%	-		6.00%
	0.40 (-)	94.70%	-		5.00%
Jungner et al.[177]	2.00 (0.90)	99.40%	1.8		1.80%
Ostman et al.[179]	0.70 (1.35)	99.20%	-	9.20%	1.00%
Arnhart et al.[180]	2.42 (0.34)	96.20%	2.86	23.20%	1.90%
Lai et al.[181]	0.63 (0.68)	98.30%	-		2.00%
Levine et al.[184]	0.58 (-)	100.00%	-		0.00%
Rodrigo et al.[185]	2.20 (0.90)	-	-	14.20%	8.80%
	2.10 (1.00)	-	-	13.70%	2.90%
Roccuzzo et al.[198]	0.75 (0.88)	96.60%	3.1	12.00%	4.70%
	1.14 (1.11)	92.70%	3.5	31.00%	11.20%
	0.98 (1.22)	90.00%	3.9	31.00%	15.10%

surface.[167] The average weighted implant survival was 97.3% including all studies and 96.4% for rough (Figure 1A), 98.4% for moderately rough (Figure 1B), and 97.6% for minimally rough (Figure 1C).

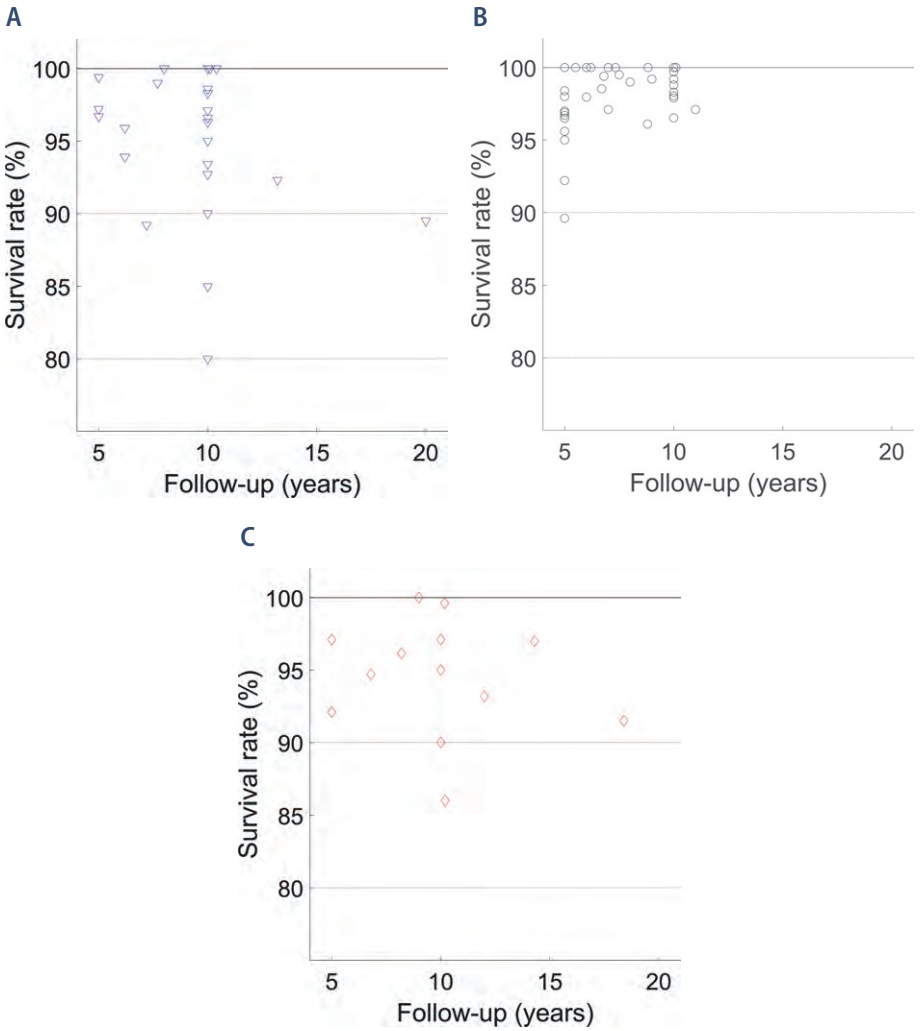


Figure 1 A: Implant survival in relation to loading time and surface roughness for rough surface implants. B. Implant survival in relation to loading time and surface roughness for moderately rough surface implants. C. Implant survival in relation to loading time and surface roughness for minimally rough surface implants

Bone Loss and Surface Roughness

Of the 123 treatment groups, 21 treatment groups were treated with a minimally rough implant surface (0.5 – 1 µm), 52 treatment groups with a moderately rough implant surface (1 – 2 µm), and 31 treatment groups with a rough implant surface (>2 µm); 19 groups reported a mixture of implants or did not report the surface. There were no studies with smooth surfaces available because these were merely experimental surfaces not used in the clinic.

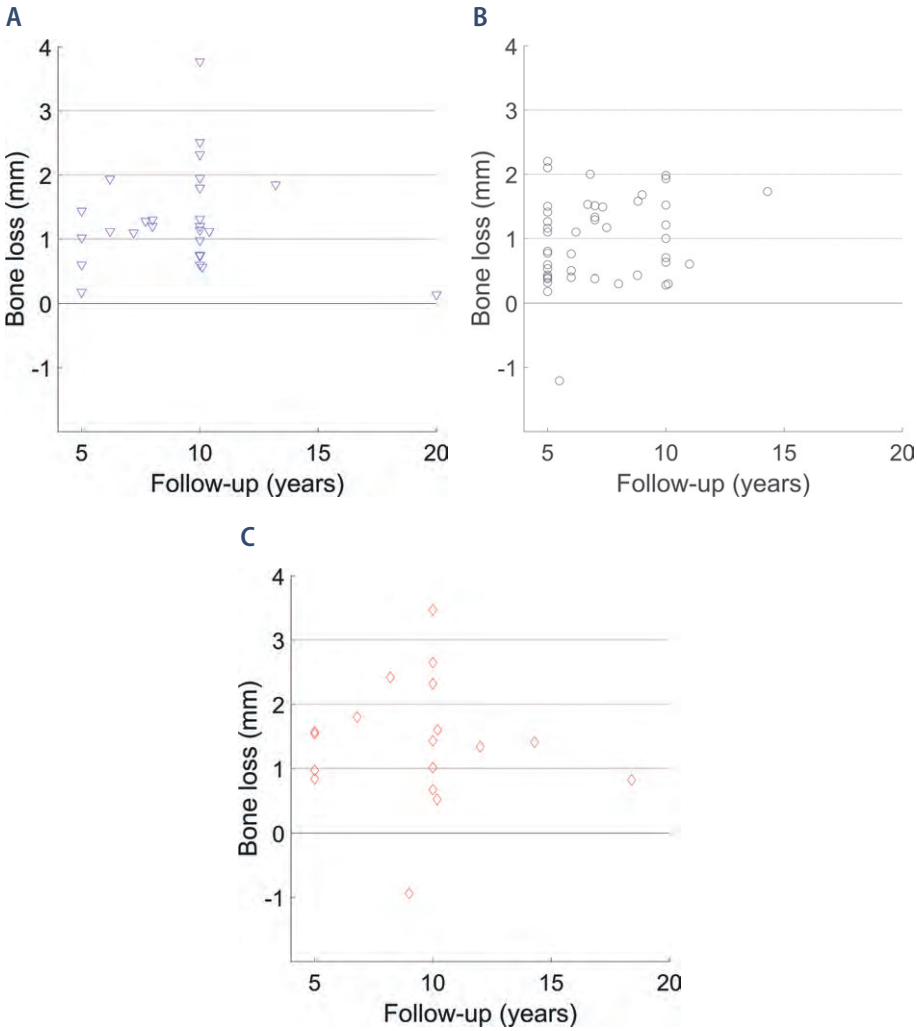


Figure 2 A: Bone loss (expressed as positive value in mm) in relation to loading time for rough surface implants. B. Bone loss (expressed as positive value in mm) in relation to loading time for moderately rough surface implants. C. Bone loss (expressed as positive value in mm) in relation to loading time for minimally rough surface implants.

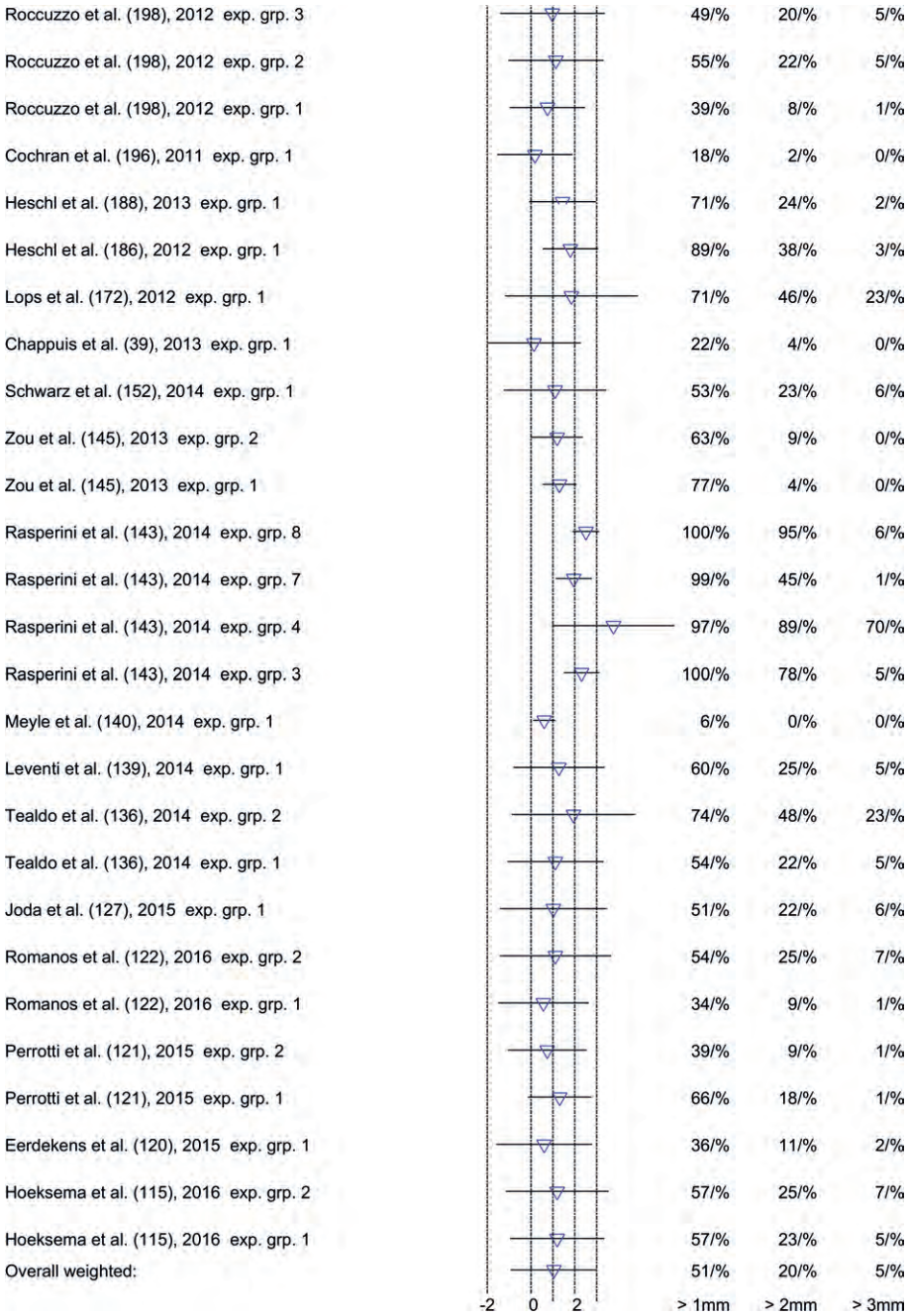
Implant roughness and/or implant system were not reported or unknown and hence all these studies/ treatment groups were considered as a separate group.[134,137,142,171,174,192] Some papers presented in their results a mixture of implants with various surface roughnesses and did not make specific distinction between them and therefore were also excluded for the detailed roughness versus bone loss evaluation.[113,126,128,17,159,170,193-195] Additionally, studies which did

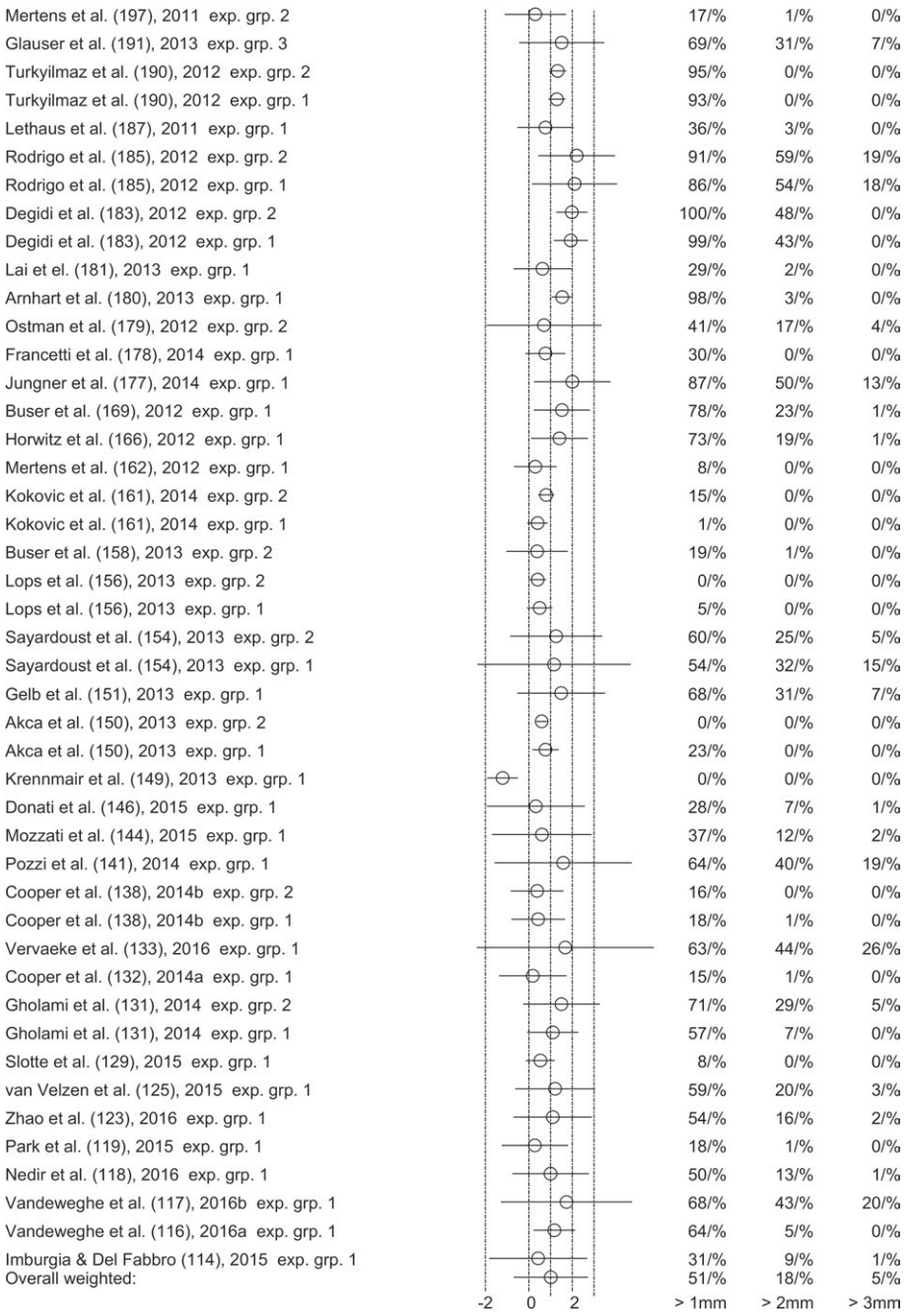
not mention the standard deviation of bone loss were excluded because calculation of proportions of bone loss was impossible.[124,147,160,163,165,167,171,175,176,182]

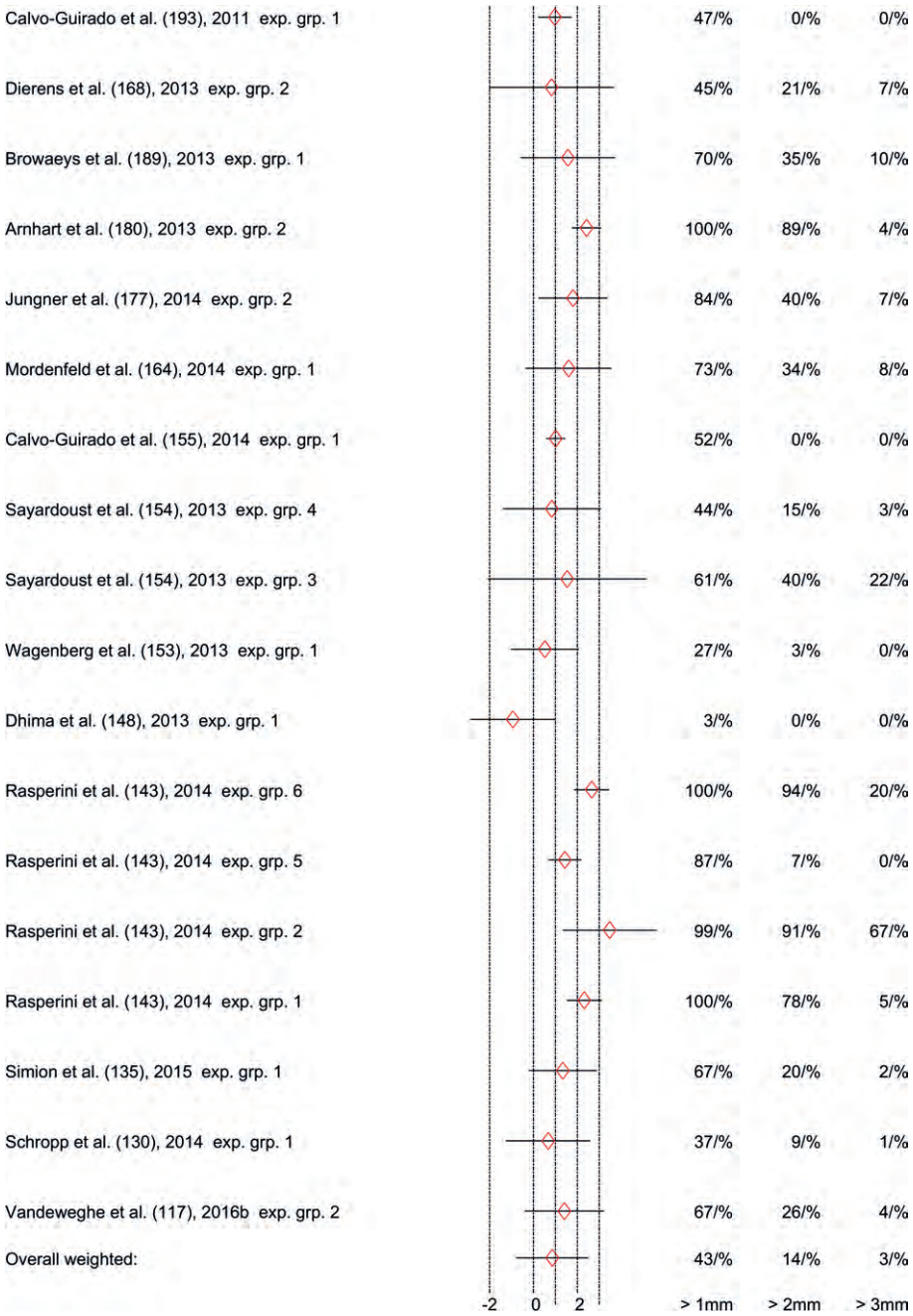
Figure 2, A–C summarize the bone loss in relation to the follow-up time including all 87 studies of this review. The overall mean bone loss was 1.01 mm (95% CI 1.00 – 1.03; SD 0.89 and ranging between -0.94 and 3.47 mm). In the total material, 49% of the implants lost more than 1 mm bone, 18% of the implants lost more than 2 mm, and 5% lost more than 3 mm bone. A distinction was made per implant surface roughness and shown in Figure 3, A–C for rough, moderately or minimally rough surfaces and Figure 3D for the mixed/unknown surfaces. The mean bone loss, standard deviation and proportion of implants losing more than 1, 2, or 3 mm bone is given per study. Table 5 shows per surface roughness the mean bone loss pointing to 1.04 mm, 1.01 mm, and 0.86 mm for the rough, moderately, and minimally rough surfaces, respectively. Between minimally and moderately or rough there was a statistically significant difference, but this was not observed between moderately and rough surfaces. Taking bone loss above 2 mm as arbitrary cut-off point reflecting a higher chance for peri-implant disease, the proportion was 20% for rough (Figure 3A), 18% and for moderately rough (Figure 3B), and 14% for minimally rough (Figure 3C).

Unfortunately among the 87 selected papers for this review, there was only one prospective study that compared machined minimally rough Brånemark implants with moderately rough TiUnite implants in conjunction with immediate loading.[147] The TiUnite surface yielded a superior cumulative implant survival of 95.5% compared to 85.5% in the machined group but the corresponding 1.4 and 1.7 mm bone loss was not statistically different. Unfortunately, this study did not report the standard deviation of the mean bone loss and hence could not be included in prevalence calculation.

There are four retrospective studies in this review that compared implants with comparable design, often from the same implant brand, but with different surface roughness.[117,154,177] Vandeweghe and colleagues[117] evaluated 197 Southern Implants with either smooth or minimally rough surface after 10 to 21 years of loading with the baseline at time of implant placement. Multivariate analysis demonstrated that the rougher surface yielded more peri-implant bone loss than the smooth surface implant. Prevalence of bone loss above 3 mm, as reported in


Roccuzzo et al. (198), 2012 exp. grp. 3 49/% 20/% 5/%
Roccuzzo et al. (198), 2012 exp. grp. 2 55/% 22/% 5/%
Roccuzzo et al. (198), 2012 exp. grp. 1 39/% 8/% 1/%
Cochran et al. (196), 2011 exp. grp. 1 18/% 2/% 0/%
Heschl et al. (188), 2013 exp. grp. 1 71/% 24/% 2/%
Heschl et al. (186), 2012 exp. grp. 1 89/% 38/% 3/%
Lops et al. (172), 2012 exp. grp. 1 71/% 46/% 23/%
Chappuis et al. (39), 2013 exp. grp. 1 22/% 4/% 0/%
Schwarz et al. (152), 2014 exp. grp. 1 53/% 23/% 6/%
Zou et al. (145), 2013 exp. grp. 2 63/% 9/% 0/%
Zou et al. (145), 2013 exp. grp. 1 77/% 4/% 0/%
Rasperini et al. (143), 2014 exp. grp. 8 100/% 95/% 6/%
Rasperini et al. (143), 2014 exp. grp. 7 99/% 45/% 1/%
Rasperini et al. (143), 2014 exp. grp. 4 97/% 89/% 70/%
Rasperini et al. (143), 2014 exp. grp. 3 100/% 78/% 5/%
Meyle et al. (140), 2014 exp. grp. 1 6/% 0/% 0/%
Leventi et al. (139), 2014 exp. grp. 1 60/% 25/% 5/%
Tealdo et al. (136), 2014 exp. grp. 2 74/% 48/% 23/%
Tealdo et al. (136), 2014 exp. grp. 1 54/% 22/% 5/%
Joda et al. (127), 2015 exp. grp. 1 51/% 22/% 6/%
Romanos et al. (122), 2016 exp. grp. 2 54/% 25/% 7/%
Romanos et al. (122), 2016 exp. grp. 1 34/% 9/% 1/%
Perrotti et al. (121), 2015 exp. grp. 2 39/% 9/% 1/%
Perrotti et al. (121), 2015 exp. grp. 1 66/% 18/% 1/%
Eerdekens et al. (120), 2015 exp. grp. 1 36/% 11/% 2/%
Hoeksema et al. (115), 2016 exp. grp. 2 57/% 25/% 7/%
Hoeksema et al. (115), 2016 exp. grp. 1 57/% 23/% 5/%
Overall weighted: 51/% 20/% 5/%
-2 0 2
> 1mm > 2mm > 3mm


Mertens et al. (197), 2011 exp. grp. 2 17/% 1/% 0/%
Glauser et al. (191), 2013 exp. grp. 3 69/% 31/% 7/%
Turkyilmaz et al. (190), 2012 exp. grp. 2 95/% 0/% 0/%
Turkyilmaz et al. (190), 2012 exp. grp. 1 93/% 0/% 0/%
Lethaus et al. (187), 2011 exp. grp. 1 36/% 3/% 0/%
Rodrigo et al. (185), 2012 exp. grp. 2 91/% 59/% 19/%
Rodrigo et al. (185), 2012 exp. grp. 1 86/% 54/% 18/%
Degidi et al. (183), 2012 exp. grp. 2 100/% 48/% 0/%
Degidi et al. (183), 2012 exp. grp. 1 99/% 43/% 0/%
Lai et el. (181), 2013 exp. grp. 1 29/% 2/% 0/%
Arnhart et al. (180), 2013 exp. grp. 1 98/% 3/% 0/%
Ostman et al. (179), 2012 exp. grp. 2 41/% 17/% 4/%
Francetti et al. (178), 2014 exp. grp. 1 30/% 0/% 0/%
Jungner et al. (177), 2014 exp. grp. 1 87/% 50/% 13/%
Buser et al. (169), 2012 exp. grp. 1 78/% 23/% 1/%
Horwitz et al. (166), 2012 exp. grp. 1 73/% 19/% 1/%
Mertens et al. (162), 2012 exp. grp. 1 8/% 0/% 0/%
Kokovic et al. (161), 2014 exp. grp. 2 15/% 0/% 0/%
Kokovic et al. (161), 2014 exp. grp. 1 1/% 0/% 0/%
Buser et al. (158), 2013 exp. grp. 2 19/% 1/% 0/%
Lops et al. (156), 2013 exp. grp. 2 0/% 0/% 0/%
Lops et al. (156), 2013 exp. grp. 1 5/% 0/% 0/%
Sayardoust et al. (154), 2013 exp. grp. 2 60/% 25/% 5/%
Sayardoust et al. (154), 2013 exp. grp. 1 54/% 32/% 15/%
Gelb et al. (151), 2013 exp. grp. 1 68/% 31/% 7/%
Akca et al. (150), 2013 exp. grp. 2 0/% 0/% 0/%
Akca et al. (150), 2013 exp. grp. 1 23/% 0/% 0/%
Krennmair et al. (149), 2013 exp. grp. 1 0/% 0/% 0/%
Donati et al. (146), 2015 exp. grp. 1 28/% 7/% 1/%
Mozzati et al. (144), 2015 exp. grp. 1 37/% 12/% 2/%
Pozzi et al. (141), 2014 exp. grp. 1 64/% 40/% 19/%
Cooper et al. (138), 2014b exp. grp. 2 16/% 0/% 0/%
Cooper et al. (138), 2014b exp. grp. 1 18/% 1/% 0/%
Vervaeke et al. (133), 2016 exp. grp. 1 63/% 44/% 26/%
Cooper et al. (132), 2014a exp. grp. 1 15/% 1/% 0/%
Gholami et al. (131), 2014 exp. grp. 2 71/% 29/% 5/%
Gholami et al. (131), 2014 exp. grp. 1 57/% 7/% 0/%
Slotte et al. (129), 2015 exp. grp. 1 8/% 0/% 0/%
van Velzen et al. (125), 2015 exp. grp. 1 59/% 20/% 3/%
Zhao et al. (123), 2016 exp. grp. 1 54/% 16/% 2/%
Park et al. (119), 2015 exp. grp. 1 18/% 1/% 0/%
Nedir et al. (118), 2016 exp. grp. 1 50/% 13/% 1/%
Vandeweghe et al. (117), 2016b exp. grp. 1 68/% 43/% 20/%
Vandeweghe et al. (116), 2016a exp. grp. 1 64/% 5/% 0/%
Imburgia & Del Fabbro (114), 2015 exp. grp. 1 31/% 9/% 1/%
Overall weighted: 51/% 18/% 5/%
-2
0
2
> 1mm
> 2mm
> 3mm


Calvo-Guirado et al. (193), 2011 exp. grp. 1 47/% 0/% 0/%
Dierens et al. (168), 2013 exp. grp. 2 45/% 21/% 7/%
Browaeys et al. (189), 2013 exp. grp. 1 70/% 35/% 10/%
Arnhart et al. (180), 2013 exp. grp. 2 100/% 89/% 4/%
Jungner et al. (177), 2014 exp. grp. 2 84/% 40/% 7/%
Mordenfeld et al. (164), 2014 exp. grp. 1 73/% 34/% 8/%
Calvo-Guirado et al. (155), 2014 exp. grp. 1 52/% 0/% 0/%
Sayardoust et al. (154), 2013 exp. grp. 4 44/% 15/% 3/%
Sayardoust et al. (154), 2013 exp. grp. 3 61/% 40/% 22/%
Wagenberg et al. (153), 2013 exp. grp. 1 27/% 3/% 0/%
Dhima et al. (148), 2013 exp. grp. 1 3/% 0/% 0/%
Rasperini et al. (143), 2014 exp. grp. 6 100/% 94/% 20/%
Rasperini et al. (143), 2014 exp. grp. 5 87/% 7/% 0/%
Rasperini et al. (143), 2014 exp. grp. 2 99/% 91/% 67/%
Rasperini et al. (143), 2014 exp. grp. 1 100/% 78/% 5/%
Simion et al. (135), 2015 exp. grp. 1 67/% 20/% 2/%
Schropp et al. (130), 2014 exp. grp. 1 37/% 9/% 1/%
Vandeweghe et al. (117), 2016b exp. grp. 2 67/% 26/% 4/%
Overall weighted: 43/% 14/% 3/%
-2 0 2 > 1mm > 2mm > 3mm

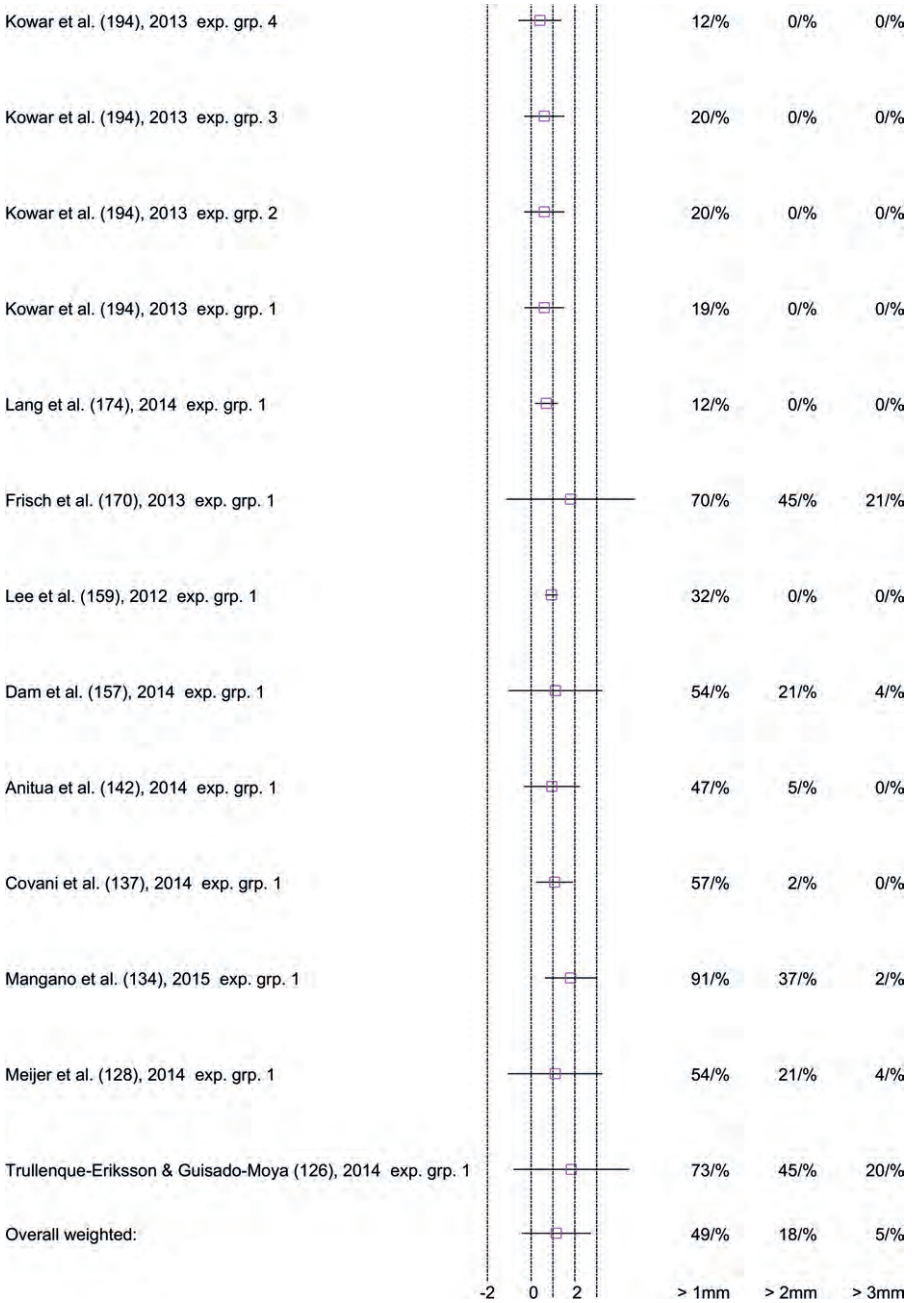


Figure 3 A: Clinical studies and bone loss (expressed as positive value in mm) for rough surface implants including proportions of implants with bone loss above 1, 2, or 3 mm. B. Clinical studies and bone loss (expressed as positive value in mm) for moderately rough surface implants including proportions of implants with bone loss above 1, 2, or 3 mm. C. Clinical studies and bone loss (expressed as positive value in mm) for minimally rough surface implants including proportions of implants with bone loss above 1, 2, or 3 mm. D. Clinical studies and bone loss (expressed as positive value in mm) for unknown/mixed surface implants including proportions of implants with bone loss above 1, 2, or 3 mm

Figure 3, B and C, was 20% versus 4%. Nevertheless, when combining bleeding and probing depth in the analysis only 4.1% of the implants were diagnosed with peri-implantitis. The other three studies and four study groups compare TiUnite moderately rough with machined minimally rough Bra˚nemark implants.

Patient-Related Risk Factors

In the smoking group of the Sayardoust study,[154] as well as in the Arnhart study,[180] TiUnite showed a better outcome whereas in the Sayardoust the non-smokers group and the Jungner group[177] the machined implants led to less bone loss. In the study of Arnhart[180] 72% of the patients reported to smoke and also had a history of periodontal disease. This could also explain 89% of the machined surface implants with bone loss above 2 mm. For the meta-analysis the Arnhart study[180] was excluded because of the synergistic effect of smoking and periodontal history in a majority of cases.

Some papers assessed bone loss around similar implants and roughness in patients with various periodontal conditions. Roccuzzo and colleagues[198] demonstrated that periodontally healthy patients lost significantly less bone compared to patients with a history of moderate or severe periodontal disease. This outcome was also reflected by 8% versus 20% to 22% of the implants with bone loss above 2 mm, as can be seen in Figure 3A. Rasperini and col- leagues[143] compared machined Brånemark surfaces and Straumann TPS surfaces after 10 years of function in four patient groups being either periodontally healthy or periodontally compromised and with or without smoking as cofactor (Figure 3, A and C). Bone loss above 2 mm was found in 89% to 95% of the implants placed in smokers, irrespective of the implant surface or the periodontal condition. And in 78% of both implant types in periodontally compromised non-smoking patients. In the periodontally healthy and non-smokers, the TPS surface yielded 45% of the implants above 2 mm bone loss compared to only 7% in the machined smooth group. It seems that patient related risk factors affect bone loss to a bigger extent than surface roughness.

Meta-Analysis of Data

Heterogeneity. The estimated amount of total heterogeneity t^2 of all included study groups was equal to 0.54 (SE = 0.084). The variability explained through the variability between groups was significant and high I^2 5 99.38% (Q = 13,950.7, df = 89, $p < .001$). When the research groups were restricted to those with known

surface roughness and inclusion or exclusion of smokers $t^2 = 0.56$ (SE = 0.093) was significant and the variability between groups remains high $I^2 = 99.36\%$ (Q = 11,272.9, df = 76, $p < .0001$). The roughness of the surface was significant as mediating factor (QM = 7.43, df = 2, $p = .024$). The residual heterogeneity remained significant $t^2 = 0.5187$ (SE = 0.0878) and the variability between groups high $I^2 = 99.27\%$ (Q = 10,956.63, df = 74, $p < .0001$). The mediator roughness introduced a reduction in residual homogeneity of 0.09%. The inclusion of smokers in the study did not lead to a significant decrease in heterogeneity. Note that the inclusion of smokers does not mean that a research group solely consisted of smokers and that the amount of smoking was not taken into account because was seldom reported objectively.

Meta-Analysis. For studies testing differences in surface roughness using one implant design the het- erogeneity I^2 between the studies was not significant (Q = 0.45, df = 2, $p = .8001$). The fixed effect model showed a significant difference in mean bone loss between minimally rough and moderately rough implant surfaces (Figure 4) with less bone loss for the former (z = 3.1716, $p = .0015$).

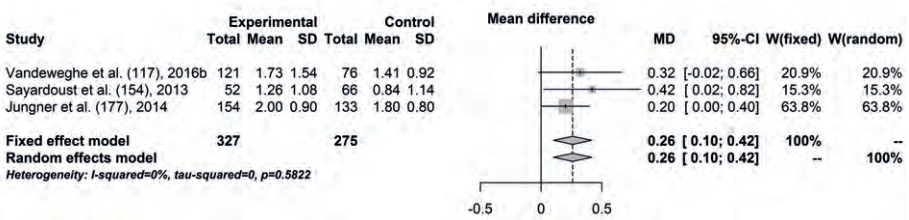


Figure 4: Forest plot for additional bone loss (expressed as positive value in mm) and moderately rough implant surfaces (experimental group) and minimally rough (control group)

Heterogeneity I^2 =88.5% for the studies evaluating the influence of periodontal history was significant equal to and the t^2 medium (66.6%) (Q = 32.55, df = 2, $p = .0002$). The random effects model showed a significant difference in mean bone loss between patient groups with a periodontal history and without a periodontal history (z=2.1793, $p = .029$) (Figure 5). When only the rough surfaces were maintained the heterogeneity I^2 was no longer significant (Q = 1.76, df = 1, $p = .1849$). The random fixed effect model showed a significant difference with

higher mean bone loss in patient groups with a periodontal history compared to periodontally healthy patients (z = 3.1822, $p = .0015$) (Figures 5 and 6).

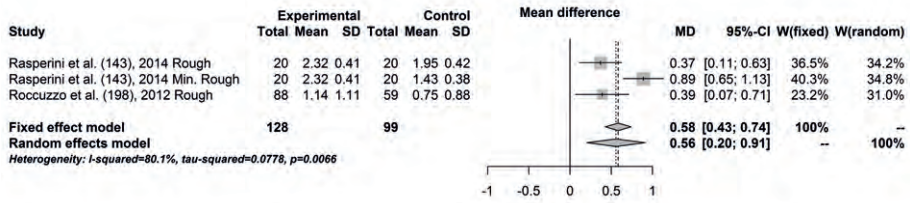


Figure 5: Forest plot for additional bone loss (expressed as positive value in mm) between patient groups with a periodontal history (experimental group) and without a periodontal history (control group) including one study using implants with a minimally rough surface and two studies using a rough surface

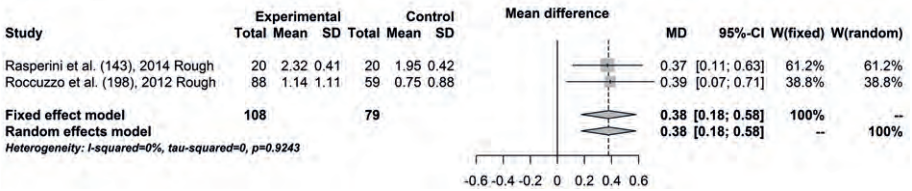


Figure 6: Forest plot for additional bone loss (expressed as positive value in mm) between patient groups with a periodontal history (experimental group) and without a periodontal history (control group) reduced to the two studies using implants with a rough surface

Heterogeneity I2 = 90.8 of the studies comparing smoking and non-smoking with respect to bone loss was significant (Q = 32.55, df = 3, p < .0001) and t2 high (70.4%). The random effects model showed a significant difference in mean bone loss between smokers and non-smokers (z = 2.3008, p = .0214) (Figure 7).

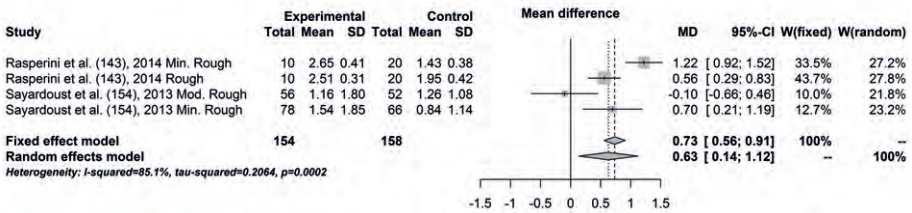


Figure 7: Forest plot for additional bone loss (expressed as positive value in mm) between smokers (experimental group) and non-smokers (control group)

DISCUSSION

This paper scrutinized the literature on peri-implant bone loss in relation to implant surface roughness. The main focus was on bone loss for two reasons. First, ongoing bone loss is a prerequisite in the diagnosis of peri-implantitis and second, stability of peri- implant bone is considered a crucial determinant for implant success.

Because the process of bone level changes due to disease may take some years before being diagnosed clinically,[199] a minimal 5 year follow-up was set as inclusion criterion. Furthermore, since most of the surface modified implants have been launched commercially at the time of the millennium change and the scientific community has started to show serious interest in the peri-implantitis issue after some consensus meetings dating back to 2006[200] and onwards,[40–43] the authors decided to limit the search to papers published over the last 6 years to increase the likelihood of finding relevant papers. This also seems logical because some extra time passes before clinical research is reported and published in scientific journals. It is important to recall that the studies selected in this review reflect daily reality and are not limited to strictly selected patient groups. It may be an advantage that the inclusion was kept as broad as possible to ensure that all types of clinical studies were included. Conversely, this approach may also yield criticism and voice opposition based on how the literature was chosen. It may also account for the heterogeneity of the studies.

During data analysis we struggled especially with the time point of the first radiographic assessment of the bone level, used as baseline for bone loss comparisons. Indeed, it is well known that peri-implant bone loss may be affected by the time point considered as baseline for the evaluation. There is consensus that a radiograph should at least be taken at the time of loading to register the bone level as baseline for future comparison to ensure that bone loss can be calculated.[43] Often this delayed assessment approach leads to an underestimation of the total bone loss because initial crestal bone remodeling is not included.[201] Different authors described initial crestal bone loss as a consequence of biologic width re- establishment after implant placement in patients with thin soft tissues.[19,202] Another effect on the crestal bone loss could be the microcap between the implant and abutment in 2 piece implants.[203,204] This crestal bone

loss is not only caused by the size and location of the microgap but also by the movement of the implant components.[14,205]

Bacterial colonization of the exposed implant surface[206–208] may increase the risk for peri-implantitis. Vervaeke and colleagues[133] showed ongoing bone loss up to 9 years of function around implants with early bone loss in patients with other risk factors such as smoking and history of periodontitis.[133] Vandeweghe and colleagues[209] demonstrated that initial bone remodeling around immediately loaded implants occurs during the first 3 months in conjunction with biologic width establishment. Also with a one-stage surgery and delayed loading the soft tissue and bone healing starts at time of implant placement, yet this is not monitored when the baseline is taken at placement of the restoration several months later. For this review, however, we accepted the bone loss calculations based on a baseline at any given time point between implant installation and the first year. Additionally, it was impossible to control many other factors that may affect bone loss such as implant design, surgical technique, expertise level, prosthetic treatment protocols.[210] And last but not least, not all studies have the same follow-up time nor comparable patients' profiles with respect to risk factors such as smoking habits or periodontal history. It is our belief, however, that this flaw affects all studies irrespective of implant system or implant surface roughness and hence is of secondary importance in the context of the comparison of various surface roughness and its effect on bone loss.

One of the observations of the review was that very few papers actually report on peri-implantitis prevalence and those that do so often use different diagnostic thresholds or have incomplete data reporting and missing parameters. Only 6 papers of the 87 quoted all diagnostic parameters, suggested as essential to diagnose peri-implantitis.[43] This reflects that some studies yield extremely high "self-quoted" prevalence of peri-implantitis despite extremely low mean bone loss values,[140,163] which is indicative of low bone loss thresholds, whereas others have extremely low prevalence percentage despite contradictory high bone loss values.[163,189] These findings question the reliability of those self-reported prevalences, especially when incomplete data are presented, and point to the necessity of using more straightforward and objective parameters, such as bone loss over time. It can be concluded that researchers deliberately pay less attention to the assessment of parameters to diagnose peri-implantitis and that

there is still no consensus on the criteria to define peri-implantitis.

By and large, the mean weighted bone loss ranged between 0 and 2 mm in 90% of the study groups (Figure 3, A–C). Only in 9/123 study groups (7.3%) was the mean bone loss above 2 mm as reported in 3 studies. However, since mean values may hide the real problematic cases, the statistical analysis using mean value and standard deviation allowed calculation of number of implants with an arbitrarily chosen bone loss threshold of above 1, 2, or 3 mm. We adopted the 2 mm bone loss threshold as proposed by Klinge and colleagues[211] since this could be suggestive of "risk-zone" cases.

The overall results demonstrate that 49% and 18% of all implants in the 87 studies lost more than 1 mm and 2 mm bone, respectively, during function above 5 years. It seems logical to conclude that setting a threshold for disease below this value is unrealistic and probably leads to false positive diagnosis of dis- ease. Only 5% of the implants lost more than 3 mm bone. The proportion of implants losing above 2 mm bone is 14%, 18%, and 20% for minimally rough, moderately rough, and rough surfaces, respectively. Of course, the prevalence of 2 or 3 mm bone loss does not necessarily equals peri-implantitis. The approach applied in our paper may even overestimate the prevalence of peri-implantitis because bone loss should be accompanied by inflammation of the surrounding tissues as demonstrated by the presence of bleeding or pus. This explains why self-reported peri- implantitis prevalence (Table 4) does not always correspond with the prevalence of bone loss above 2 to 3 mm as reported in Table 3. The paper of Roc- cuzzo[198] demonstrates nicely that implants placed in patients with aggressive periodontal disease history have 15.1% peri-implantitis but only 1% of bone loss above 2 or 3. Meyle and colleagues[140] has no implants with bone loss above 2 mm yet finds 24% of peri-implantitis due to 27% bleeding. This seems suggestive of mucositis diagnosis instead of peri-implantitis. The parameters bleeding or the bone loss threshold taken for disease seem to have a very decisive effect in rocketing peri-implantitis upwards in many studies. Interestingly, in an 18-year follow-up study, Dierens and colleagues[212] demonstrated that bleeding on probing is a bad predictor for bone loss or peri-implantitis.

Table 5: Summary of implant survival % and mean bone loss (expressed as positive value in mm), standard deviation and standard error for each surface roughness and corresponding proportion of implants estimated to loose bone >1 mm, >2 mm and >3 mm. T-test was used for statistical comparison with p≤0.05 being statistically significant.

Surface roughness	Mean bone loss (mm) [95% CI; SD; SE]	T-test				Proportion % implants bone loss			Implant survival %
						>1 mm	>2 mm	>3 mm	
All studies	1.01 [1.00-1.03; 0.89; 0.0092]					49	18	5	97.3
Unknown surface	1.15 [1.11-1.19; 0.81; 0.021]			p=0.0002		49	18	5	95.8
Rough	1.04 [1.00-1.08; 1.01; 0.0189]	p=0.28			p<0.00001	51	20	5	96.4
Moderately rough	1.01 [0.98-1.04; 0.87; 0.0148]		p<0.00001	p<0.00001		51	18	5	98.4
Minimally rough	0.86 [0.81-0.90; 0.84; 0.0212]					43	14	3	97.6

There is a statistically significant difference in the mean bone loss calculated between the various roughness groups with a trend for higher bone loss for the rougher implant surface (Table 5). Whether this is of clinical significance remains disputable taking heterogeneity of the studies into account. Furthermore, one should take into consideration a 0.3 to 0.5 mm measurement error when performing radiographic bone assessments.

Hence, a better approach is to compare implants with equal design but only differing in surface topography in prospective randomized controlled trials. Unfortunately, the only available prospective trial[147] was excluded because of missing standard deviation, required to do the statistics. The other three studies, albeit of retrospective design, were testing minimally rough surfaces and moderately rough surfaces with similar implant designs. Hence, these three studies were apt for meta-analysis as shown in Figure 4. The minimally rough surface was statistically better in minimizing bone loss. However, the amount of studies is scarce and more research is required to confirm this finding.

CONCLUSIONS

Although rough surface implants induce statistically significant more bone loss according to the present meta-analysis, the clinical impact of surface roughness on bone loss is limited in the majority of the papers. The multifactorial cause for bone loss and the heterogeneity of the studies, related to inclusion of risk patients as well as poor data reporting, make it difficult to draw strong conclusions regarding the effect of implant surface roughness on bone loss over time. Nevertheless, independent of surface or implant brand, bone loss above 3 mm occurs in less than 5% of all implants after at least 5 years in function. Moreover, the meta-analysis indicates that co-factors such as smoking or periodontal disease increase the risk for bone loss.

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CHAPTER 5

Improvement of Quality of Life with Implant-Supported Mandibular Overdentures and the Effect of Implant Type and Surgical Procedure on Bone and Soft Tissue Stability: A Three-Year Prospective Split-Mouth Trial.

This chapter is based on the publication:
Improvement of Quality of Life with Implant-Supported Mandibular Overdentures and the Effect of Implant Type and Surgical Procedure on Bone and Soft Tissue Stability: A Three-Year Prospective Split-Mouth Trial.

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ABSTRACT

In fully edentulous patients, the support of a lower dental prosthesis by two implants could improve the chewing ability, retention, and stability of the prosthesis. Despite high success rates of dental implants, complications, such as peri-implantitis, do occur. The latter is a consequence of crestal bone loss and might be related to the implant surface and peri-implant soft tissue thickness. The aim of this paper is to describe the effect of implant surface roughness and soft tissue thickness on crestal bone remodeling, peri-implant health, and patient-centered outcomes. The mandibular overdenture supported by two implants is used as a split-mouth model to scrutinize these aims. The first study compared implants placed equicrestal to implants placed biologically (i.e., dependent on site-specific soft tissue thickness). The second clinical trial compared implants with a minimally to a moderately rough implant neck. Both studies reported an improvement in Oral Health-Related Quality of Life and a stable peri-implant health after three years follow-up. Only equicrestal implant placement yielded significantly higher implant surface exposure, due to the establishment of the biologic width. Within the limitations of this study, it can be concluded that an implant supported mandibular overdenture significantly improves the quality of life, with limited biologic complications and high survival rates of the implants.

INTRODUCTION

Edentulousness is widely spread worldwide. According to the WHO the prevalence in the elderly population is 26% in the USA and between 15% and 78% in European countries. Among the edentulous population, a strong negative impact of poor oral conditions on daily life has been described. Edentulism could lead to diet changes where food rich in saturated fats and cholesterol are preferred. Besides diet changes, edentulousness is an independent risk factor for weight loss and could lead to social handicaps related to communication.[1]

The support of a dental prosthesis by two implants could improve the chewing ability, retention, and stability of the prosthesis, which could lead to higher satisfaction and health-related quality of life. Dental implants have been used since the early sixties to replace missing teeth by fixed or removable prostheses. Nowadays, this yields a predictable treatment outcome with success over 95% after 10 years of function.[2]

To measure the improvement in health-related quality of life, the Oral Health Impact Profile (OHIP) is a widely used tool to assess currently applied dental procedures. It has also been used for evaluating the quality of life in more invasive surgical interventions in oral surgery.[3] The tool consists of a questionnaire to measure the impact of medical care on functional and social wellbeing.[4] Allen and McMillan reported significant improvement in satisfaction and health-related quality of life for patients who received implant-retained prostheses compared to those who received conventional dentures.[5] A panel of experts published a consensus statement where they described overwhelming evidence for a 2-implant supported overdenture as the first choice of treatment for the edentulous mandible instead of a conventional denture.[6]

A recent review focusing on the Patient-Reported Outcome Measures (PROMs) showed compelling evidence to support that the fully edentulous patients experience higher satisfaction with an implant-supported overdenture in the mandible compared to a conventional denture.[7] These findings were confirmed by several other recent systematic reviews and meta-analyses.[8-10]

De Bruyn and co-workers also concluded that patient satisfaction is highly individual and satisfaction with an implant-supported overdenture is never guaranteed. Hence, the decision to propose an implant-supported overdenture should be based on proper individual assessment.[7]

Despite the improvement of the patient's quality of life and high survival and success rates of dental implants in patients with overdentures, dental implants are not free of complications. The most common complications following implant therapy are peri-implant mucositis (bleeding on probing and inflammation of the peri-implant soft tissues), and peri-implantitis (clinical and radiographic bone loss with or without suppuration). To detect inflammatory changes around the implant, several biologic parameters (plaque, bleeding, and suppuration) must be monitored during the patient's follow-up visits.[11]

According to the latest consensus report of the "World Workshop on the Classification of Periodontal and Peri-implant Diseases and Conditions", the main clinical characteristic of peri-implant mucositis is bleeding on gently probing.[12] Erythema, swelling, and/or suppuration may also be present.[13] There is strong evidence from animal and human experimental studies that plaque is the etiological factor for peri-implant mucositis.[11,14-18] Peri-implantitis is described as a plaque-associated pathologic condition occurring in tissues around dental implants, characterized by inflammation in the peri-implant mucosa and subsequent progressive loss of supporting bone. Peri-implantitis sites exhibit clinical signs of inflammation, bleeding on probing, and/or suppuration, increased probing depths and/or recession of the mucosal margin in addition to radiographic bone loss.[19] Peri-implantitis is a consequence of crestal bone loss. Two recent consensus meetings highlighted the influence of implant material, shape and surface characteristics on the occurrence and progression of peri-implantitis. However, evidence for these suggestions is weak and future long-term studies are necessary to analyze these potential risk factors.[20,21] Beside these implant factors also other important factors like surgical, prosthetic, patient-related factors and foreign body reactions may contribute to crestal bone loss.[21]

The composition and the topography of the implant surface have been a matter of debate during the last decades. Both composition and topography have their influence on implant surface roughness. The implant surface roughness

is expressed in a Sa value. This three-dimensional value expresses an absolute difference in the height of each point compared to the arithmetical mean of the surface.[22] In the early years of implant dentistry two types of implant surfaces were used, the machined/turned surface (Sa = 0.5–1 µm) and the microporous titanium plasma-sprayed surface (Sa > 2 µm). The first one is smooth and the latter could be described as a rough implant surface.

Surface modification was done to enlarge the surface, resulting in a greater bone-to-implant contact area. Implant surface modifications were done by sandblasting, acid-etching, anodic oxidation or hydroxyapatite coating. These techniques resulted in a moderately rough implant surface (Sa = 1–2 µm), which is nowadays the most used surface roughness. Beside the higher bone-to-implant contact,[23] a lower clinical failure rate[24] and a higher removal torque was observed compared to the smooth implant surfaces.[25] Hence, the surface modification made it possible to load the implant earlier or even immediately after the surgery. The resulting surface enlargement allowed shorter implants to be used, without jeopardizing the prognosis and with a reduced necessity for bone grafting procedures.[2] Beside the aforementioned benefits, related to faster integration, rough implant systems have been linked to increased bacterial adhesion.[26] The applied model in the latter study does not always mimic the clinical reality. However, A Cochrane systematic review suggested limited evidence that smooth surfaces had a 20% reduced risk of being affected by peri-implantitis over a three-year period.[27,28] This finding led to the commercial production of hybrid dental implants, combining the best of both systems. Hybrid dental implants have a minimally rough coronal part to decrease biofilm formation in the soft tissue crevice and a moderately rough implant body to enhance bone healing and speed up the osseointegration. These hybrid surfaces combine the effect of both surface roughnesses in the same implant. A short-term study indicated that the moderately rough and smooth coronal part showed the same crestal bone remodeling in the initial healing phase.[29] However, long-term studies to describe clinical parameters and peri-implant health are not yet available.

Some patient-related factors, such as certain metabolic syndrome components, medical conditions and/or the use of medication are known to have an effect on implant treatment outcome. Systematic reviews reveal that hyperglycemia has an increased risk for peri-implantitis,[30,31] although the risk for more implant failures

is comparable with the one observed in healthy patients.[32] There is inconsistent and controversial evidence about the association with cardiovascular diseases.[31] Another meta-analysis revealed that there was no difference in implant survival rate between patients with and without osteoporosis. However, increased peri-implant bone loss was observed.[33] The intake of bisphosphonates, related to the treatment of osteoporosis, was not associated with an increased implant failure rate.[34] On the other hand, the same systematic review revealed an increased risk for implant failure with the intake of certain selective serotonin reuptake inhibitors and proton pump inhibitors.[34] Patients that are periodontally compromised are at higher risk for implant failure and crestal bone loss when compared with periodontally healthy subjects.[35]

Another patient factor related to the failure of integrated implants is smoking. De Bruyn and Collaert described in a large retrospective study significantly higher failure rates of dental implants in smokers compared to non-smokers, both before and after functional loading, especially in the maxilla.[36] These findings are in agreement with a large meta-analysis of 18 studies showing an odds-ratio of 2.17 for implant failures in smokers were compared to non-smokers.[37] Besides implant failure smokers are more prone to peri-implant bone loss.[38,39]

Also, biologic variances between patients could influence crestal bone loss around dental implants. Especially, soft tissue dimensions could play an important role in bone remodeling. The effect of peri-implant mucosal tissue thickness on the crestal bone loss was described in an animal study suggesting a certain minimal width of peri-implant mucosa may be required, and that bone resorption may take place allowing a stable soft tissue attachment.[40] The latter was confirmed in a human clinical trial, when there was a soft tissue thickness of 2 mm or less, crestal bone loss up to 1.45 mm may occur.[41]

More recently Vervaeke and co-workers concluded that the initial bone remodeling was affected by the thickness of the peri-implant soft tissue.[42] They suggested that bone loss directly after implant placement, due to crestal bone remodeling, precludes the biologic width re-establishment and can be controlled by adapting the vertical depth position of the implant in the bone in relation to the soft tissue thickness at the time of implant placement. Hence, in thin tissues, a deeper subcrestal position in the bone may prevent partial exposure of the crestal

part of the implant. Although crestal bone remodeling is a given fact after implant placement, related to the surgical trauma from periosteal elevation, as well as the drilling procedure, it is from a preventive point of view important to have the bone covering the implant as much as possible. Initial crestal bone loss, resulting in the absence of bone contact, can predict a future bone loss in patients prior to the disease. Galindo-Moreno and co-workers concluded that 96% of implants with a marginal bone loss above 2 mm at 18 months had lost 0.44 mm or more at six months post loading.[43] A critical long-term study where implants were placed in the partially edentulous mandible, indicated that bone loss in patients with thin (<2 mm) and a thick mucosa (>2 mm) was identical, when the implants were installed subcrestally to anticipate on the biologic width re-establishment.[44]

Another subject of debate is the predictive value of biologic parameters around dental implants. Bleeding on probing, suppuration, plaque formation and probing pocket depth are the most widely used clinical parameters to describe health and/or disease around dental implants. These biologic parameters are most of the times included in the definition of peri-implantitis. However, a largely critical review showed the absence of a correlation between bone loss and the biologic parameters mean probing pocket depth and mean bleeding on probing. The authors also reported inconsistency and incompleteness in reporting on these parameters in the literature, which could affect decision-making in clinical practice.[45]

Hence, the aim of this paper is to describe, by means of two prospective clinical split-mouth cohort studies, the effect of implant surface roughness and surgical implant depth positioning on crestal bone remodeling, peri-implant health, and patient-centered outcomes. The mandibular overdenture supported by two dental implants is used as a split-mouth model to scrutinize these aims.

EXPERIMENTAL SECTION

Patient Population and Surgical/Prosthetic Procedures

This paper includes two prospective split-mouth studies. Both studies included edentulous patients in need of a two-implant supported overdenture in the lower jaw. The same inclusion and exclusion were used for both studies. Inclusion criteria

include: (1) Total complete edentulism for at least four months and (2) presence of sufficient residual bone volume to install two implants of 3.5 to 4.0 mm diameter and 8 to 11 mm length. Patients were excluded if they were: (1) Younger than 21, (2) suffered from systemic diseases, (3) current smokers and (4) had general contraindications for oral surgery (full dose head and neck radiation, intravenous administrated bisphosphonates, and ongoing chemotherapy). All patients were treated at the Ghent University Hospital by the same surgeon between January 2013 and September 2014. Twenty-six patients (study 1) received two moderately rough dental implants (Astra Tech Osseospeed TX™, Dentsply implants, York, Pennsylvania, USA). The control implant was installed equicrestally (group 1), according to the manufacturer's guidelines with the rough implant surface completely surrounded by bone. The vertical position of the test implant (group 2) was adapted to the soft tissue thickness, allowing at least 3 mm space for biologic width establishment.[42]

Another 23 patients (study 2) received two dental implants with a difference in implant surface roughness of the coronal part of the implant (Figure 1). All 46 implants were biologically guided taking the soft tissue thickness into account whereby care was taken to ensure a 3 mm soft tissue seal in contact with the abutment. All patients received one moderately rough implant (group 3) (Sa = 1.3 µm) (DCC, Southern implants, Irene, South Africa) and one test implant (group 4). The latter was a hybrid dental implant with a minimally rough coronal neck of 3 mm (Sa = 0.9 µm) combined with a moderately rough body (Sa = 1.3 µm) (MSC, Southern implants, Irene, South Africa).

Although two different brands were used in both studies, all 98 implants installed in the 49 patients were identical at the level of the abutment-implant connection. Implants had the same integrated platform-shift with a smooth implant bevel, the same internal deep conical connection and a similar macro design of the micro-threads on the implant neck.

Implants were immediately restored if primary stability was achieved (insertion-torque > 25 Ncm). Implants were restored either with locator abutments (study 1) or definitive titanium abutments (Compact Conical Abutments; Southern Implants, Irene, South Africa) and a healing cap with a standard abutment height of 4 mm (study 2).

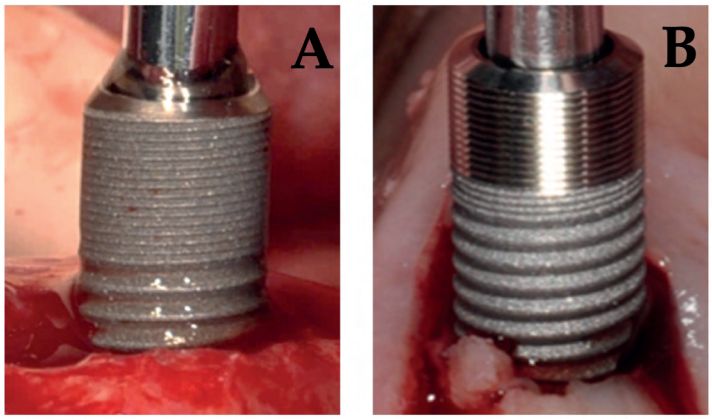

Figure 1: Placement of an implant with a moderately rough surface (A) and a hybrid implant with a minimally rough coronal neck (B)

Before surgery, all patients received new removable dentures in the mandible and maxilla to achieve a correct occlusion, appropriate teeth position, and appropriate smile line. The removable dentures were adapted after surgery to connect with the implants by one experienced prosthodontist. The surgical and prosthetic procedures have been described previously by Vervaeke and co-workers and Glibert and co-workers.[29,46]

The clinical trial has been conducted in full accordance with the Helsinki Decleration (1975) as revised in 2000. All patients were thoroughly informed and signed written informed consent. The study protocol was approved by the ethical committee of the Ghent University Hospital.

Clinical and Radiographic Examination

Follow-up visits were planned at 1 week, 1, 3, 6, 12, 24, and 36 months after surgery. After soft tissue healing was fully established, three months after surgery, peri-implant health was monitored and probing pocket depths, bleeding on probing and plaque scores were assessed on four implants sites: Midmesial, middistal, midbuccal, and midlingual. The bleeding- and plaque scores were measured on a dichotomous scale (0 = absence of bleeding on probing/absence of plaque; 1 = bleeding on probing/plaque). From the site level scores both for bleeding and plaque mean scores on implant level were calculated.

Digital peri-apical radiographs were taken at baseline (implant placement), at 3, 6, 12, 24, and 36 months using a guiding system in order to obtain the X-rays perpendicular to the film. The radiographic measurements were calibrated using the length of the implant, the distance between the threads or the diameter of the implant. Bone levels were determined as the distance from a reference point, which corresponds with the lower edge of the smooth implant bevel at the implant-abutment interface, to the most crestal bone-to-implant contact point. The baseline bone-to-implant contact levels are assessed from the implant-abutment interface. The baseline from the four experimental groups was logically comparable. Bone loss was determined by the difference of the bone level directly after implant placement and the bone level at the follow-up visit.

If necessary, calculus and plaque were removed and oral hygiene was reinforced during follow-up visits. Instructions with a (electric) toothbrush and interdental brushes were given based on the need, preferences and dexterity or motoric skills of the patient.

To measure the change in Oral Health-Related Quality of Life the Oral Health Impact Profile-14 questionnaire (OHIP-14) is assessed before surgery, 3, and 12 months after connection of the prosthesis with the implants (Table 1). The questionnaire is based on 14 questions capturing seven domains: Functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. Of these seven domains, two questions need to be answered on a Likert scale. Score 4 is indicating a highly negative answer to the question and 0 means that there is no discomfort at all. The total score of the 14 questions can balance between 56 (maximally negative) to 0 (maximally positive).

Statistics

Outcomes are reported with descriptive statistics (mean, SD, median, range, and 95% CI) and boxplots. All analyses concern pair-wise comparisons within patients. For continuous variables paired *t*-tests were applied, for dichotomous variables the McNemar test was used. The 95% confidence intervals are given to show the precision of an estimate of a certain effect.

Table 1: OHIP-14 questionnaire divided per domain

Domain 1: functional limitation	
1	Have you had trouble pronouncing any words because of problems with your teeth, mouth, or denture?
2	Have you felt that your sense of taste has worsened because of problems with your teeth, mouth, or denture?
Domain 2: physical pain	
3	Have you had painful aching in your mouth?
4	Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth, or denture?
Domain 3: psychological discomfort	
5	Have you been self-conscious because of your teeth, mouth, or denture?
6	Have you felt tense because of problems with your teeth, mouth, or denture?
Domain 4: physical disability	
7	Has been your diet been unsatisfactory because of problems with your teeth, mouth, or denture?
8	Have you interrupt meals because of problems with your teeth, mouth, or denture?
Domain 5: psychological disability	
9	Have you found it difficult to relax because of problems with your teeth, mouth or denture?
10	Have you been a bit embarrassed because of problems with your teeth, mouth, or denture?
Domain 6: social disability	
11	Have you been a bit irritable with other people because of problems with your teeth, mouth, or denture?
12	Have you had difficulty doing your usual jobs because of problems with your teeth, mouth, or denture?
Domain 7: handicap	
13	Have you felt that life, in general, was less satisfying because of problems with your teeth, mouth, or denture?
14	Have you been totally unable to function because of problems with your teeth, mouth, or denture?

The sample size for both studies was calculated using SAS Power and Sample size calculator for related samples based on an effect size of 1 mm and a standard deviation of 0.60, with the level of significance set at 0.05 and $\beta = 0.80$. The effect estimation was based on findings Vervaeke et al. 2014.[42]

For the OHIP-14 outcome, the impact of the change was assessed by calculating the "effect size" with the following formula:
((mean-OHIP before surgery) – (mean-OHIP three months after connection))/SD before surgery

As proposed by Cohen 1977 an "effect size" of 0.2 could be interpreted as a small change, 0.6 as a moderate change and > 0.8 as a large change.

RESULTS

Study Population

A sample size of 14 patients for each study was calculated. Hence, minimums of 20 patients (= 40 implants) were consequently included to anticipate future dropouts.

Twenty-six patients in study I were initially treated with one equicrestally (group 1) and one subcrestally (group 2) placed implant. In study II, 23 patients were initially treated with one implant with a moderately rough implant neck (group 3) and one implant with a minimally rough implant neck (group 4). In total four experimental treatment groups were assessed. After a follow-up of at least three years, one patient was excluded, due to anatomical constraints requiring deviation of the surgical protocol. Two patients were excluded after starting smoking and one did not respond to the follow-up invitation. Hence, 45 patients with two implants each were available after a follow-up of three years and none of the implants had failed (survival 100%). A flowchart of the patients' distribution is shown in Figure 2. The study population consisted of 24 men and 21 women with a mean age at implant placement of 64 years (SD = 9.25, range = 43–85).

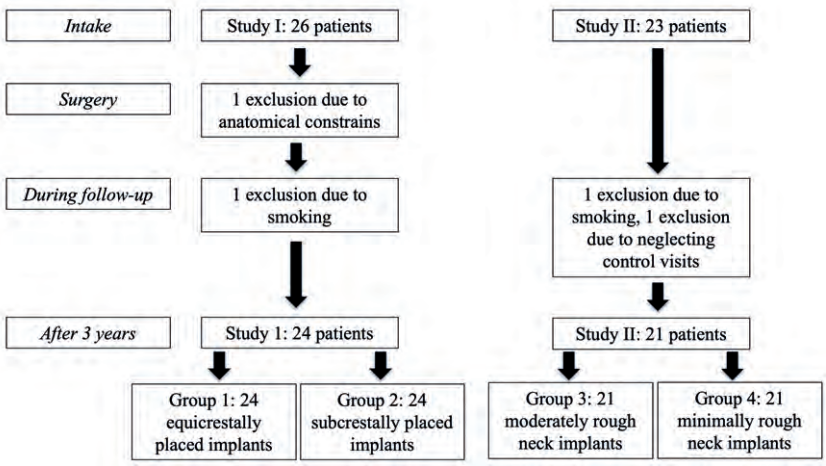

Figure 2: Flowchart of both study populations

Mean Bone Level Difference

Table 2 shows the mean bone level and the corresponding changes of the four treatment groups at baseline and after 6, 12, 24, and 36 months. Initially, the bone level of the implants in the four groups is comparable and basically located at the implant crest. In the first six months bone remodeling was 0.7 mm for equicrestally placed implants and ranging from 0–0.3 mm in the other three subcrestally placed groups. Over time no further statistically significant bone level changes occurred in all groups (Figures 3–6). Figures 5 and 6 gives a schematic view of the bone remodeling over time, with the visible implant surface exposure in the equicrestally placed implant group (group 1).

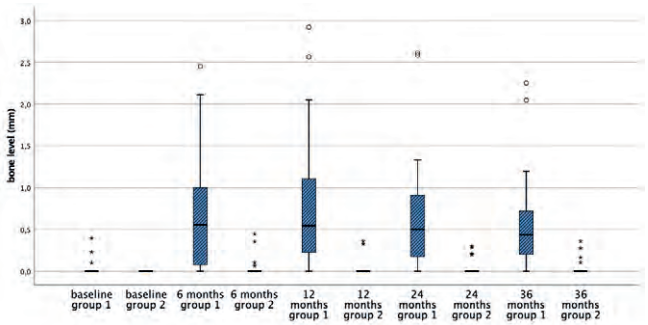

Figure 3: Boxplots representing the bone level at subsequent time points for the equicrestally (group 1) and subcrestally placed implants (group 2). * Outliers (≥ 3×IQR above third quartile), ° suspected outliers (between 1.5×IQR and 3×IQR above third quartile)

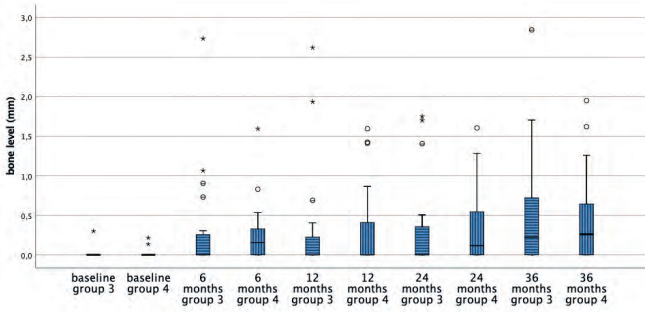

Figure 4: Boxplots representing the bone level at subsequent time points for the implants with a moderately rough neck (group 3) and minimally rough neck (group 4). * Outliers (≥ 3×IQR above third quartile), ° suspected outliers (between 1.5×IQR and 3×IQR above third quartile)

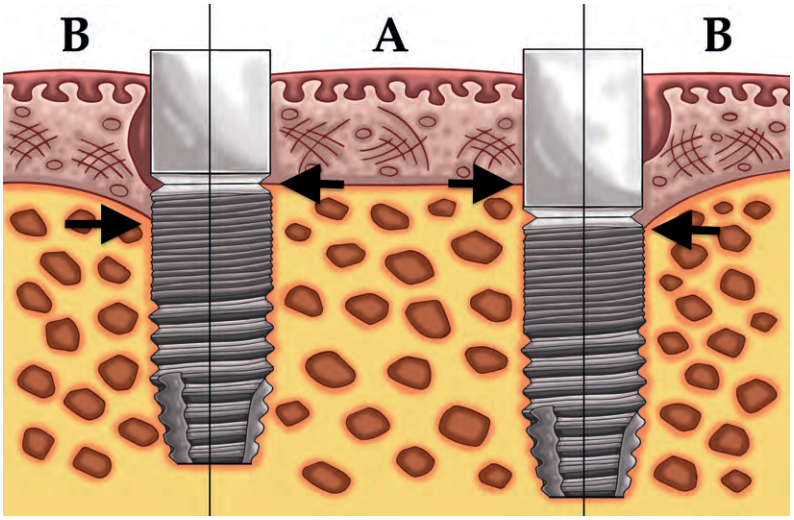

Figure 5: Schematic illustration of study 1, left equicrestally placed implant (group 1) and right subcrestally placed implant (group 2); showing the bone level at baseline (A) and bone level after bone remodeling (B)

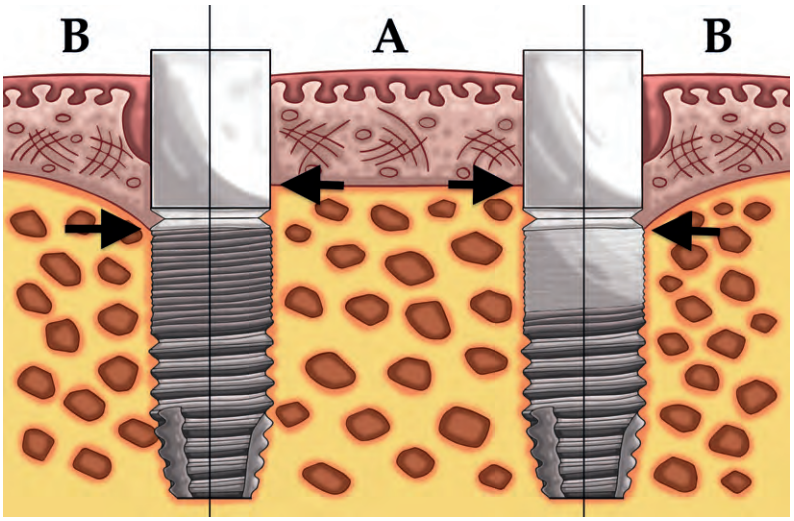

Figure 6: Schematic illustration of study 2, left implant with a moderately rough neck (group 3) and right implant with a minimally rough neck (group 4); showing the bone level at baseline (A) and bone level after bone remodeling (B)

Between groups the subcrestally placed implants of group 2 lost no bone at all. Groups 3 and 4 showed comparable bone remodeling. Hence, implant surface roughness did not affect initial nor long-term bone remodeling (Figures 4, 6).

Table 2: Mean bone level for each study group and the bone level difference between respectively equicrestally versus subcrestally placed implants and implants with moderately rough versus minimally rough neck; $p < 0.05$ indicates a statistically significant difference (paired t-test)

Bone Level											
	Group 1: Equicrestal				Group 2: Subcrestal				Paired difference		
	Mean (SD)	Median	Min	Max	Mean (SD)	Median	Min	Max	Mean dif	95% CI	P
Baseline	0.03 (0.09)	0.00	0.00	0.40	0.00 (0.00)	0.00	0.00	0.00	0.030	(-0.009,0.070)	0.123
6 months	0.72 (0.74)	0.59	0.00	2.45	0.04 (0.11)	0.00	0.00	0.45	0.678	(0.360,0.996)	<0.001
12 months	0.78 (0.81)	0.54	0.00	2.92	0.03 (0.10)	0.00	0.00	0.36	0.746	(0.397,1.096)	<0.001
24 months	0.69 (0.70)	0.51	0.00	2.61	0.04 (0.10)	0.00	0.00	0.30	0.644	(0.337,0.951)	<0.001
36 months	0.59 (0.59)	0.44	0.00	2.25	0.04 (0.10)	0.00	0.00	0.36	0.549	(0.297,0.802)	<0.001
	Group 3: Moderately rough neck				Group 4: Minimally rough neck				Paired difference		
	Mean (SD)	Median	Min	Max	Mean (SD)	Median	Min	Max	Mean dif	95% CI	P
Baseline	0.01 (0.07)	0.00	0.00	0.30	0.02 (0.05)	0.00	0.00	0.22	-0.002	(-0.424,0.037)	0.9P2
6 months	0.33 (0.64)	0.00	0.00	2.74	0.27 (0.38)	0.18	0.00	1.60	0.064	(-0.118,0.245)	0.474
12 months	0.34 (0.68)	0.00	0.00	2.62	0.34 (0.53)	0.00	0.00	1.61	0.009	(-0.191,0.209)	0.926
24 months	0.36 (0.58)	0.00	0.00	1.75	0.37 (0.49)	0.23	0.00	1.60	-0.014	(-0.170,0.142)	0.853
36 months	0.51 (0.74)	0.22	0.00	2.84	0.45 (0.58)	0.26	0.00	1.95	0.066	(-0.114,0.246)	0.453

Biologic Parameters

On implant level only a statistically significant difference could be measured for the plaque score at 24 months ($p = 0.042$), with significantly less plaque for the equicrestally placed compared with subcrestally placed implants. However, at all other time points the plaque–and bleeding scores were not statistically significantly different, indicative of peri-implant health (Table 3).

Table 3: Mean plaque and bleeding on probing on implant level at 6, 12, 24 and 36 month for each study group and mean difference between respectively equicrestally versus subcrestally placed implants and implants with moderately rough versus minimally rough neck.

	Plaque				
	Group 1: Equicrestal	**Group 2: Subcrestal**		**Paired difference**	
	Mean (SD)	Mean (SD)	Mean dif	95% CI	P
6 months	0.44 (0.47)	0.52 (0.45)	-0.083	(-0.221,0.055)	0.224
12 months	0.45 (0.39)	0.56 (0.44)	-0.115	(-0.285,0.056)	0.178
24 months	0.42 (0.40)	0.51 (0.40)	-0.091	(-0.178,-0.003)	0.042
36 months	0.39 (0.43)	0.41 (0.42)	-0.022	(-0.148,0.104)	0.724
	Group 3: Moderately rough neck	**Group 4: Minimally rough neck**		**paired difference**	
	Mean (SD)	Mean (SD)	Mean dif	95% CI	P
6 months	0.38 (0.33)	0.40 (0.31)	-0.025	(-0.144,0.094)	0.666
12 months	0.37 (0.31)	0.35 (0.31)	0.017	(-0.136,0.169)	0.818
24 months	0.57 (0.36)	0.52 (0.36)	0.054	(-0.030,0.137)	0.189
36 months	0.39 (0.41)	0.43 (0.38)	-0.038	(-0.147,0.072)	0.481
	Bleeding on probing				
	Group 1: Equicrestal	**Group 2: Subcrestal**		**paired difference**	
	Mean (SD)	Mean (SD)	Mean dif	95% CI	P
6 months	0.15 (0.22)	0.15 (0.22)	0.000	(-0.093,0.0933)	1.000
12 months	0.19 (0.18)	0.19 (0.18)	0.000	(-0.125,0.125)	1.000
24 months	0.23 (0.30)	0.20 (0.28)	0.023	(-0.090,0.136)	0.680
36 months	0.30 (0.33)	0.23 (0.25)	0.076	(-0.048,0.200)	0.216
	Group 3: Moderately rough neck	**Group 4: Minimally rough neck**		**paired difference**	
	Mean (SD)	Mean (SD)	Mean dif	95% CI	P
6 months	0.24 (0.31)	0.23 (0.24)	0.013	(-0.110,0.135)	0.834
12 months	0.20 (0.32)	0.23 (0.24)	-0.033	(-0.189,0.122)	0.653
24 months	0.25 (0.29)	0.30 (0.37)	-0.054	(-0.243,0.136)	0.551
36 months	0.08 (0.14)	0.07 (0.12)	0.013	(-0.084,0.109)	0.789

$p < 0.05$ indicates a statistically significant difference (paired t-test)

For the probing pocket depth at implant level only at 24 months a statistically significant difference between equicrestally placed compared to subcrestally placed implants could be observed (Table 4). After three years all groups are comparable indicative of peri-implant health.

Table 4: Mean probing pocket depth on implant level at 6, 12, 24 and 36 months for each study group and the mean difference between respectively equicrestally versus subcrestally placed implants and implants with a moderately rough versus minimally rough neck.

	Probing pocket depth								
	Group 1: Equicrestal			Group 2: Subcrestal			Paired difference		
	Mean (SD)	Min	Max	Mean (SD)	Min	Max	Mean dif	95% CI	P
6 months	1.88 (0.53)	1.00	3.25	2.01 (0.66)	1.00	3.75	-0.135	(-0.311,0.041)	0.125
12 months	1.70 (0.44)	1.00	2.50	1.83 (0.53)	1.00	2.75	-0.130	(-0.312,0.051)	0.149
24 months	2.30 (0.66)	1.50	4.50	2.57 (0.84)	1.25	4.50	-0.261	(-0.473,-0.048)	0.018
36 months	2.42 (0.69)	1.00	4.00	2.59 (0.71)	1.00	3.75	-0.163	(-0.0378,0.052)	0.130
	Group 3: Moderately rough neck			Group 4: Minimally rough neck			Paired difference		
	Mean (SD)	Min	Max	Mean (SD)	Min	Max	Mean dif	95% CI	P
6 months	2.93 (0.71)	1.75	5.25	2.88 (0.65)	1.75	4.75	0.050	(-0.142,0.242)	0.592
12 months	2.65 (0.72)	1.75	4.75	2.68 (0.68)	1.75	4.50	-0.033	(-0.221,0.154)	0.709
24 months	2.48 (0.58)	1.25	3.50	2.34 (0.60)	1.00	3,25	0.143	(-0.114,0.401)	0.252
36 months	2.10 (0.68)	1.25	4.25	2.01 (0.58)	1.00	3.00	0.088	(-0.259,0.434)	0.603

$p < 0.05$ indicates a statistically significant difference (paired t-test).

Oral Health-Related Quality of Life

Based on 45 edentulous patients, receiving an implant-supported overdenture, the OHIP-14 index reduced from 13.37/56 (SD 9.97) at baseline to 4.42/56 (SD 4.94) after three months of functional loading. This result in a large effect size of 0.90, suggesting a strong improvement in Oral Health-Related Quality of Life. Between 3 and 12 months, no further changes were observed, resulting in small effect size (0.04), indicative of a very stable result over time (Figure 7). The reduction was statistically significant for all seven domains after three months (Table 5). For

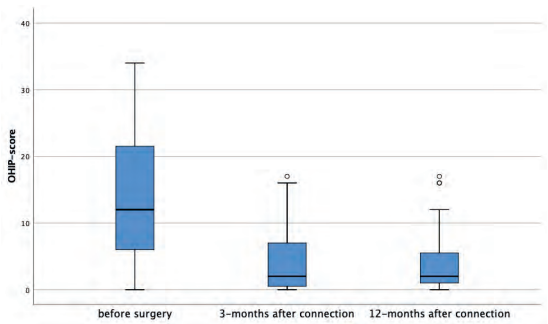

Figure 7: Boxplots representing the Oral Health Impact Profile-14 (OHIP-14) total score before surgery, 3 and 12 months after connection of the prosthesis with the implants. A score of 56 represents a maximal negative appreciation. ° Suspected outliers (between 1.5×IQR and 3×IQR above third quartile)

functional limitation, physical disability and handicap the effect size was moderate. For the other four domains, a large effect size was observed and most expressed for physical pain with an effect size of 1.04. The latter is logically given the fact that improved denture retention results in less mucosal irritation and consequently fewer complaints related to pain suffering.

Table 5. Mean OHIP score and the mean difference for each of the seven domains before surgery and three months after connection with the calculated effect-size.

Domain	mean-OHIP (SD)		Paired difference			Effect-size
	Before surgery	3-months after connection	Mean dif	95% CI	P	
Functional limitation	2.30 (1.85)	1.14 (1.42)	1.16	(0.540,1.785)	0.001	0.63
Physical pain	3.37 (2.06)	1.21 (1.55)	2.16	(1.440,2.886)	<0.001	1.04
Psychological discomfort	2.52 (2.35)	0.65 (1.43)	1.87	(1.034,2.687)	<0.001	0.80
Physical disability	2.12 (2.16)	0.44 (0.85)	1.68	(0.971,2.378)	<0.001	0.78
Psychological disability	2.21 (1.91)	0.58 (0.93)	1.63	(0.930,2.326)	<0.001	0.85
Social disability	1.67 (1.49)	0.16 (0.49)	1.51	(1.007,2.016)	<0.001	1.01
Handicap	1.42 (1.48)	0.26 (0.66)	1.16	(0.683,1.642)	<0.001	0.78

DISCUSSION

The current paper focuses on implant treatment outcome in patients, which were completely edentulous in both jaws. Retention of the lower denture is a typical problem in this category of patients, especially in the mandible as compared to the maxillary denture. The denture in the mandible is less retentive because of a smaller crestal bone support, a more expressed degree of bone resorption, and unfavorable distribution of occluding forces, as well as additional pressure of the tongue yielding dislocating forces. Often this results in functional discomfort and pain, the latter because of the absence of keratinized mucosa. In the maxilla, the denture is supported on the crest and on the hard structure of the palate, which is covered by keratinized tissue. A vacuum present during mastication, between the palatal coverage of the denture and the underlying tissues, improves the retention. Consequently, fully edentulous patients have more complaints with mandibular dentures and an overdenture retained on two implants has therefore been suggested as of minimal care in order to provide functional comfort [6].

Implant treatment in denture wearing patients can be used for a split-mouth study, as was the case in the two clinical studies presented in the present paper. The focus was on implant type and surgical procedure, defined as implant survival, crestal bone loss and biologic peri-implant health. The latter is an important aspect because peri-implant diseases may jeopardize treatment outcome in the long run and are often related to aesthetic appreciation. Additionally, the patient-centered outcome was assessed by using a validated Oral Health Related Quality of Life questionnaire.

After three years of follow-up, no implant failures could be recorded in the present study and all remaining patients remained fully functional. This 100% implant survival is in line with current literature on implant overdenture therapy.[47]

Initial bone remodeling is a healing phenomenon related to the surgical procedure mainly the exposure of bone and periosteum during implant placement, as well as the depth placement in the bone. Given the fact that implant survival with currently available dental implant systems is successful and quite predictable, the research focuses on implant success. Implant treatment is considered a success when high implant survival is combined with bone stability over time, because the latter reflects the health of the peri-implant tissues. Indeed, worldwide consensus defined that peri implantitis, a disease condition of the implant resulting in pocket formation between the implant and soft tissue, is always preceded by the bone loss.[12] Additionally, soft tissue health also affects the aesthetic outcome, especially in the partially edentulous patient. Although aesthetics was not the key issue in the present paper, the study conditions tested may provide clinical guidelines that do affect aesthetics, as well as peri-implant health outcomes.

In the present paper, minimal initial bone remodeling ranging from 0–0.7 mm was assessed. After the physiological initial bone remodeling, no further bone loss could be observed up to three years of function. The effect of soft tissue thickness and implant surface roughness on the crestal bone loss was evaluated. The applied split-mouth study design corrects for inter-individual variability from the estimates of the treatment effect.[48] The results showed that the initial bone remodeling was affected by the originally present soft tissue thickness, but not by the implant surface roughness. After implant installation, a minimum of 3 mm soft tissue dimensions seems to be necessary for the re-establishment of the so-called

"biologic width", indicative of the importance of the biologically guided implant placement. These findings are in accordance with an earlier published systematic review, including meta-analysis. There it is stated that implants placed with an initially thicker peri-implant soft tissue have less radiographic marginal bone loss in the short term.[49] Additionally, an increased early bone remodeling leads to implant surface exposure in patients with thin soft tissues, which increases the risk of on-going bone loss as shown by Vervaeke and colleagues in a nine year follow-up. A greater implant surface exposure increases the bacterial colonization of the implant surface, which could enlarge the chance to induce peri-implantitis.[50] From a clinical point of view, it is highly suggested that the surgeon adapts the surgical position of the implant in relation to the available pre-operative soft-tissue thickness.

It is generally accepted that osseointegration of moderately rough implants is enhanced as compared to minimally rough implants. This resulted in faster treatment protocols and reduced early failures. More recently, it was suggested that a minimally rough implant surface yields less crestal bone loss and less peri-implantitis on the long-term. A recent systematic review, including studies up to 10 years, reported on the survival rate and marginal bone loss of implants with different surface roughness. Implant survival was higher for moderately rough surfaces, but minimally rough surfaces showed the least marginal bone loss.[51] This outcome is in contrast to the outcome presented in another systematic review with meta-analysis. The latter evaluated the influence of the implant collar surface on marginal bone loss and revealed less bone loss for the rougher implant systems. However, 10 out of the 12 included studies showed results with less than five years of function. The only study with 10 years of follow-up showed less bone loss for the implants with a smooth collar compared to the implants with a rough collar. Yet, the authors stated that the results of their systematic review needed to be interpreted cautiously, due to several confounding factors.[52] Another systematic review with meta-analysis, which included only studies with at least, a five-year follow-up showed significantly less bone loss around smooth implant surfaces compared to moderately rough and rough implant surfaces.[38] Recently Donati and co-workers published the results of a 20-year follow-up RCT to evaluate the effect of a modified implant surface. In 51 patients at least one implant with a minimally rough surface and one with a modified surface was installed. The difference in mean bone level change between the two implant-systems was not

statistically significant, and the moderate increase of implant surface roughness has no beneficial effect on long-term preservation of the peri-implant marginal bone level. A more detailed analysis of the paper revealed, however, that none of the 32 evaluated smooth implants showed more than 3 mm bone loss, whereas 3 out of the 32 modified implants showed bone loss between 3 and 6 mm. Only two smooth surface implants were diagnosed with peri-implantitis compared with five implants with a modified surface.[53]

The findings of our paper are in accordance with the paper of Donati and co-workers, concluding that the surface roughness of the implant neck has no effect on bone level up to three years. The hybrid implant system used in our study combines the benefits of faster osseointegration, due to the moderately rough implant body, and the minimally rough surface around the implant neck suggests it is less prone to develop peri-implantitis.[54] Additionally, several studies conclude the beneficial effect of a smoother surface with a lower incidence of peri-implantitis and less bone loss on the long term. A further long-term follow-up of the current study population will elucidate the latter.

Besides implant survival and bone level stability, also peri-implant health is considered a perquisite for treatment success. Peri-implant health is defined on two levels. Plaque accumulation yields minor inflammation of the soft tissue surrounding the implant- restorative interface, coined as mucositis. It is diagnosed with bleeding of the tissues after probing the crevice between implant and mucosa. In a recent consensus report, the diagnosis of peri-implantitis has been redefined as a combination of probing pocket depths of at least 6 mm in combination with bleeding on probing or a bone level of at least 3 mm apical of the most coronal portion of the intraosseous part of the implant.[12] In our study, no patients showed ongoing bone-loss in combination with bleeding and increasing probing pocket depths. Hence, the incidence of peri-implantitis was 0.0%.

The absence of peri-implantitis was found despite a high plaque level. This could be explained by the elderly, fully edentulous patient population. De Waal and colleagues revealed that edentulous patients restored with implants showed more plaque compared to partially edentulous patients restored with implants. However, the plaque in the fully edentulous patients harbours a potentially less pathogenic peri-implant micro-flora.[55,56]

Another explanation for the relatively high plaque scores could be the dexterity problems inducing imperfect cleaning abilities in elderly patients. On the other hand, plaque is screened at a given moment in time during the clinical inspection and this may be several hours after cleaning and not necessarily reflects the overall hygiene of the patient over time.

This is the reason why the bleeding index is considered more useful. It reflects the degree of inflammation as a result of the long-term plaque control and is less momentarily. The current study revealed that high plaque score did not result in high bleeding scores.

The support of a mandibular overdenture by two implants has a significant positive effect on the quality of life. The OHIP-14 score was calculated irrespective of the implant group because it is a patient-related outcome variable. On all the seven domains measured with the OHIP-14 questionnaire a statistically significant difference was measured, all in favor of the support of a mandible overdenture by two implants. These findings are in accordance with a clinical trial reporting a significant improvement in satisfaction and health-related quality of life when subjects who received two implants are compared with subjects requesting a new conventional denture. Besides the improvement in the quality of life, they reported that patients requesting implants reported that tooth loss and denture wearing problems had a much greater impact in their quality of life than patients seeking conventional dentures.[5]

CONCLUSIONS

Within the limitations of this study, it can be concluded that an implant supported mandibular overdenture significantly improves the quality of life, with limited biologic complications and a high survival rate of the implants. All seven domains of the OHIP-14 questionnaire significantly reduced when the mandible overdenture is supported by two implants. No differences were observed in crestal bone remodeling between minimally rough and moderately rough implant surfaces. However, initial bone remodeling was affected by initial soft tissue thickness. Anticipating biologic width re-establishment by adapting the vertical position of the implant in relation to the available soft tissue thickness may avoid peri-implant bone loss. The biologic variance of the patient might be more important compared to the configuration of the implant surface. Long-term follow-up of the study

is necessary to determine the influence of early implant surface exposure and implant surface roughness on crestal bone loss, biologic parameters, mechanical complication, and implant survival.

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CHAPTER 6

The Long-Term Effect of Adapting the Vertical Position of Implants on Peri-Implant Health: A 5-Year Intra-Subject Comparison in the Edentulous Mandible Including Oral Health-Related Quality of Life.

This chapter is based on the publication: The Long-Term Effect of Adapting the Vertical Position of Implants on Peri-Implant Health: A 5-Year Intra-Subject Comparison in the Edentulous Mandible Including Oral Health-Related Quality of Life.

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ABSTRACT

Despite high success rates of dental implants, surface exposure may occur as a consequence of biologic width establishment associated with surgery. This prospective split-mouth study evaluated the effect of early implant surface exposure caused by initial bone remodeling on long-term peri-implant bone stability and peri-implant health. Additionally, Oral Health-Related Quality of Life (OHRQoL) was assessed by means of the Oral Health Impact Profile-14 (OHIP-14). Twenty-six patients received two non-splinted implants supporting an overdenture in the mandible by means of locators. One implant was installed equicrestally (control) and the second one was installed subcrestally, taking at least 3 mm soft tissue thickness into account (test). During initial bone remodeling (up to 6 months postoperatively), equicrestal placement yielded 0.68 mm additional surface exposure compared to subcrestal placement ($p < 0.001$). Afterwards, bone level and peri-implant health were comparable in both treatment conditions and stable up to 5 years. The implant overdenture improved OHRQoL ($p < 0.01$) and remained unchanged thereafter ($p = 0.51$). In conclusion, adapting the vertical position of the implant concerning the soft tissue thickness prevents early implant surface exposure caused by initial bone remodeling, but in a well-maintained population, this has no impact on long-term prognosis. The treatment of edentulousness with an implant mandibular overdenture improves OHRQoL.

INTRODUCTION

To provide functional comfort in the edentulous patient, an overdenture retained on two implants has been suggested as the first choice of treatment for the edentulous mandible.[1] The recent literature yields treatment success over 95% after 10 years of function.[2] Success could be determined by implant factors such as long-term peri-implant bone stability and the absence of inflammation in the peri-implant tissues or by patient factors such as the Oral Health-Related Quality of Life (OHRQoL).

The effect of peri-implant mucosal tissue thickness on peri-implant bone stability has been described in animals and suggests a certain minimum width of peri-implant mucosa as a prerequisite, allowing a stable soft tissue attachment.[3] This was confirmed in humans and refined with the conclusion that a soft tissue thickness of 2 mm or less resulted in crestal bone loss up to 1.45 mm.[4] More recently, Vervaeke and co-workers concluded that the initial bone remodeling was affected by soft tissue thickness.[5] Furthermore, they suggested that an unforeseen exposure of the implant surface during initial bone remodeling should be avoided by adapting the vertical position of the implant during surgical placement in relation to the available preoperative soft tissue thickness. In the light of the hype that currently exists around peri-implantitis, it has been questioned whether the early exposure of implant surfaces to soft tissues could hamper peri-implant health or may pose a risk for the future development of peri-implantitis. Galindo-Moreno and co-workers concluded in an 18-month study that early implant surface exposure was predictive for additional bone loss.[6] Another clinical study, including 105 implants in 21 patients, concluded that initial bone loss and surface exposure at 2 years of function was identified as a predictor for further bone loss after 10 years of function.[7]

Another subject of debate lies in the predictability of biologic peri-implant health parameters in relation to future risk for disease development or progression. Jepsen and co-workers could not demonstrate a difference in bleeding on probing between stable sites and sites with progressive bone loss.[8] However, bleeding on probing was characterized by a high negative predictive value, and thus an absence of inflammation can be an indicator for stable peri-implant conditions. In a long-term follow-up study of single implants functional for 16–22

years, Dierens and co-workers described very stable long-term bone stability with a 6% incidence of peri-implantitis. Despite this low incidence, 80% of the implants presented signs of inflammation with bleeding on probing.[9] Furthermore, they found a low correlation between probing pocket depth and bone levels. Hence, they concluded that probing depths are of limited value in predicting future peri-implant bone loss. Recently, based on 4951 implants, it was concluded that only profuse bleeding or suppuration did correlate with long-term bone loss, but no positive correlation was found for minimal bleeding and bone loss.[10] The above-mentioned findings of the clinical studies are in accordance with a recently published critical review by Doornewaard and co-workers.[11] This review included 41 articles representing 4198 patients initially treated with 9657 implants and showed the absence of a correlation between bone loss and the biologic parameters mean probing pocket depth and mean bleeding on probing. It needs to be mentioned that the outcomes of the latter study could have been biased by the fact that biologic parameters are reported very often in an inconsistent and incomplete manner.

In addition to peri-implant health parameters, the success of an implant treatment should be determined by the Oral Health-Related Quality of Life (OHRQoL).[12] In dentistry, the Oral Health Impact Profile-14 (OHIP-14) questionnaire is a widely used and validated instrument focusing on the impact of medical care on social and functional well-being.[13]

Hence, the aim of this prospective split-mouth clinical study is to evaluate the long-term effect of adapting the vertical position of implants on peri-implant bone stability and peri-implant health, and secondarily to assess the OHRQoL of patients restored with mandibular implant-retained overdentures.

The short-term data regarding the peri-implant bone stability and peri-implant health were earlier published by Vervaeke and co-workers.[5]

EXPERIMENTAL SECTION

Patient Population and Surgical/Prosthetic Procedures

This prospective split-mouth study included edentulous patients in need of a two-implant supported overdenture in the mandible. The patient selection, surgical, and prosthetic procedures have been described previously by Vervaeke and co-workers.[5]

Patients received two dental implants (Astra Tech Osseospeed TX™, Dentsply implants, Mölndal, Sweden) inserted using a one-stage surgical procedure with an open flap. One control implant was installed equicrestally (group 1), according to the manufacturer's guidelines. The vertical position of the test implant (group 2) was adapted to the soft tissue thickness, allowing at least 3 mm space for biologic width re-establishment. For example, if mucosal thickness was 2 mm, the test implant was installed 1 mm subcrestally. A systematic non-random assignment was applied to determine the position of the test and control implants by alteration of the experimental site for every consecutively included patient. If sufficient primary stability could be achieved, implants were immediately restored with locator abutments (Locator, ZEST Anchors LLC, Escondido). In the case of insufficient primary stability (<20 Ncm) in one or both implants, a two-stage protocol was preferred for both implants and were restored with locator abutments after 3 months. The crestal bone was slightly adapted around the subcrestally placed implant to install the locator abutments without direct contact between bone and abutment.

To achieve a balanced occlusion and articulation, appropriate teeth position, and appropriate smile line, all patients received new removable dentures in the mandible and maxilla before surgery. After surgery, the removable dentures were adapted to connect with the implants by one experienced prosthodontist (C.M.).

All patients were treated at the Ghent University Hospital by the same surgeon (S.V.) and prosthodontist (C.M.) between January 2013 and September 2014. Patient follow-up and supportive professional maintenance was done by two calibrated periodontists (S.V. and R.D.) and one prosthodontist (C.M.) for the technical follow-up. All patients were thoroughly informed and signed written informed consent, and the clinical trial has been conducted in full accordance

with the Helsinki Declaration (1975) as revised in 2000. The ethical committee of the Ghent University Hospital approved the study protocol under registration number B670201215160.

Clinical and Radiographic Examination

The clinical and radiographic examination up to two years has been described previously by Vervaeke and co-workers.[5] Follow-up visits after surgery were planned at 1 week as well as at 1, 3, 6, 12, 24, 36, 48, and 60 months. Three months after surgery, when soft tissue healing was fully established, and during later control visits, peri-implant health was monitored by measuring probing pocket depths, bleeding on probing, and plaque scores on four implant sites: midmesial, middistal, midbuccal, and midlingual. Bleeding on probing and the presence of plaque were assessed on a dichotomous scale with 0 being absent and 1 being present. The scores were used to recalculate the parameters per implant.

Digital peri-apical radiographs were taken immediately after implant placement (baseline) and after 3, 6, 12, 24, 36, 48, and 60 months using a guiding system in order to obtain the X-rays perpendicular to the film (Rinn XCP, Dentsply Sirona, Charlotte, NC, USA). The radiographs were calibrated using the length of the implant, the distance between the threads of the implant, or the diameter of the implant. Bone levels were determined as the distance from a reference point, which corresponds with the lower edge of the smooth implant bevel at the implant–abutment interface, to the most crestal bone-to-implant contact point. The bone loss is determined by the difference of the bone level directly after implant placement and the bone level at the follow-up visit.

If necessary, calculus and plaque were removed, and oral hygiene was reinforced during follow-up visits. Instructions with a (electric) toothbrush and interdental brushes were given based on the need, preferences, and dexterity or motoric skills of the patient.

The Oral Health Impact Profile-14 questionnaire (OHIP-14) was used to measure the change in Oral Health-Related Quality of Life over time. It consists of 2 questions per domain scored using a Likert scale and capturing functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. Score 0 means no discomfort at all, and score 4 is indicative

for a highly negative answer to the question. The total score of the questionnaire can range from 0 (maximally positive on all items) to 56 (maximally negative). The questionnaire was assessed before surgery as well as 3 and 60 months after connection of the prosthesis with the implant. The impact of the change was assessed by calculating the "effect size" with the use of the following formula: ((mean-OHIP before surgery) - (mean-OHIP three months after connection))/SD before surgery. As proposed by Cohen 1977, an "effect size" > 0.8 is interpreted as large, 0.6 is interpreted as moderate, and 0.2 is interpreted as small.

Statistical Analysis

Data analysis was performed in SPSS Statistics 26 (SPSS Inc., Chicago, IL, USA). Outcomes are reported with descriptive statistics (mean, standard deviation (SD), median, range) and visualized through boxplot representation. All analyses concern pair-wise comparisons within patients. For dichotomous variables, the McNemar test was used, and for continuous variables, paired t-tests were applied. The 95% confidence intervals (95% CI) are given to show the precision of an estimate of a certain effect. The sample size was calculated using an SAS Power and Sample size calculator for related samples based on an effect size of 1 mm mean bone level difference between test and control and a standard deviation of 0.60, with the level of significance set at 0.05 and $\beta = 0.80$. The effect estimation was based on findings published previously .[14]

An analysis of the measurement error for the continuous variable bone level between the observer S.V. and R.D. was performed by the use of a scatterplot representation and a paired-t-test. The random error, or duplicate measurement error (DME), was calculated with the formula $SD/\sqrt{2}$.

Incidence of peri-implantitis is based on the definition of peri-implantitis according to the 2017 Consensus report of the World Workshop on the classification of Periodontal and Peri-Implant Diseases and Conditions.[15] Implant success was defined in two ways: firstly, as 2 mm bone loss in combination with bleeding on probing as proposed by Klinge et al.,[16] and secondly, as 1 mm additional bone loss after initial bone remodeling.

RESULTS

Study Population

Twenty-six patients were initially included in the study. One patient was excluded after starting smoking during the healing phase. In another patient with a knife-edge crest, both implants were installed subcrestally in order to have both implants completely surrounded by crestal bone. As a result of the absence of a control condition, this patient was excluded for further statistical analysis. Hence, 24 patients with two implants each (48 implants) were available for the 5-year follow-up. For 19 cases, the primary stability was high enough to use a one-stage protocol. In five patients, the primary stability required a two-stage submerged protocol. The baseline for these patients was the moment of abutment connection, which was approximately 3 months after implant placement.

The study population consisted of 13 men and 11 women with a mean age at implant placement of 65 years (SD = 9.38, range = 43–81). It was known that 16 out of the 24 patients had lost their teeth due to periodontal disease; for the other eight patients, the reason for tooth loss was unknown. Of the 24 included patients, only one patient could not attend the 3- and 4-year follow-up visit due to medical reasons, and another patient did not show up for the 4-year follow-up visit; however, all 24 patients attended the 5-year follow-up visit.

Survival Rate, Mean Bone Level Difference, and Mean Bone Loss

All implants were present after at least 5-years of follow-up, which resulted in a survival rate of 100%. The analysis of the measurement error for bone level between the two observers (S.V. and R.D.) showed a mean difference of 0.024 with a 95% CI of between –0.0004 and 0.0484, resulting in a *p*-value of 0.054, which was indicative for no significant structural error. The standard error, or duplicate measurement error, was 0.046, which could be interpreted as low. The outcome of the structural error and random error are both indicative for a high inter examiner agreement.

The mean bone level and the corresponding changes for both placement protocols at baseline and after 6, 12, 24, 36, 48, and 60 months are shown in Table 1. A boxplot representation of the bone level for both treatment protocols at the subsequent time points is given in Figure 1. Initially, the bone level of the implants in both treatment protocols is comparable and basically located at the implant crest.

Table 1: Mean bone level for each placement protocol and the bone level difference between respectively equicrestally and subcrestally placed implants; p is a result of a paired t-test comparing the bone level between placement protocols.

	Bone Level										
	Group 1: Equicrestal				Group 2: Subcrestal				paired difference		
	Mean (SD)	Median	Min	Max	Mean (SD)	Median	Min	Max	Mean dif	95% CI	p
Baseline	0.03 (0.09)	0.00	0.00	0.40	0.00 (0.00)	0.00	0.00	0.00	0.030	(-0.009,0.070)	0.123
6 months	0.72 (0.74)	0.59	0.00	2.45	0.04 (0.11)	0.00	0.00	0.45	0.678	(0.360,0.996)	<0.001
12 months	0.78 (0.81)	0.54	0.00	2.92	0.03 (0.10)	0.00	0.00	0.36	0.746	(0.397,1.096)	<0.001
24 months	0.69 (0.70)	0.51	0.00	2.61	0.04 (0.10)	0.00	0.00	0.30	0.644	(0.337,0.951)	<0.001
36 months	0.59 (0.59)	0.44	0.00	2.25	0.04 (0.10)	0.00	0.00	0.36	0.549	(0.297,0.802)	<0.001
48 months	0.56 (0.54)	0.46	0.00	2.21	0.07 (0.13)	0.00	0.00	0.41	0.487	(0.236,0.737)	0.001
60 months	0.62 (0.66)	0.44	0.00	2.66	0.12 (0.22)	0.00	0.00	0.86	0.500	(0.219,0.782)	0.001

At all other time points, a statistically significant bone level difference could be observed, all in favor of the subcrestally placed implants.

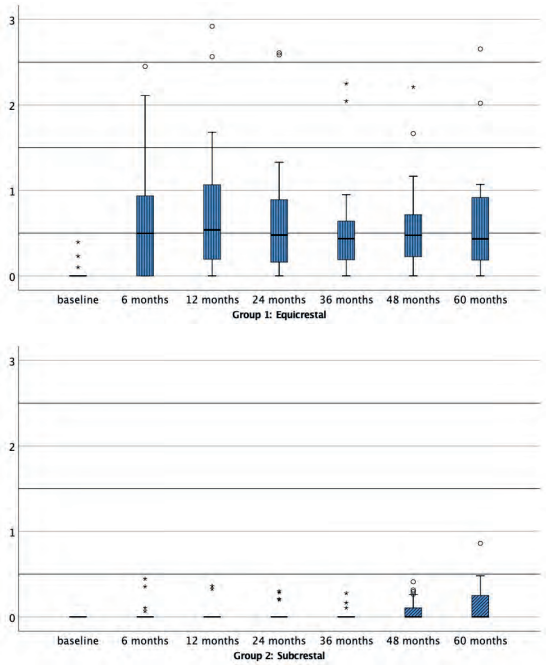

Figure 1: Boxplots representing bone level at subsequent time points for the equicrestally (Group 1) and subcrestally placed implants (Group 2). * Outliers (≥3× IQR above third quartile), ◦ suspected outliers (between 1.5 and 3× Inter Quartile Range above third quartile).

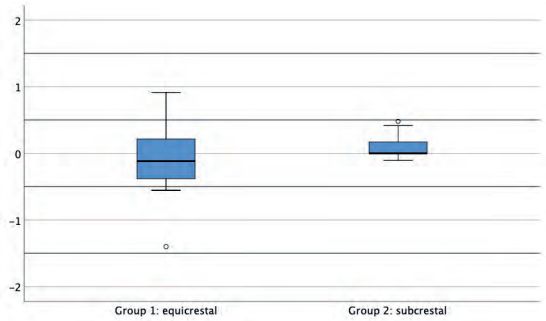

Figure 2. Boxplots representing bone level change between 6 and 60 months for the equicrestally (Group 1) and subcrestally placed implants (group 2). ◦ Suspected outliers (between 1.5× IQR and 3× IQR above third quartile), a negative number is indicative for bone gain.

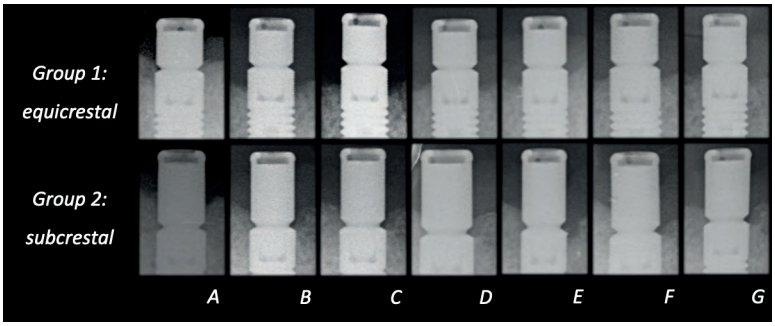

Figure 3: X-ray representing one and the same patients with the bone level directly after placement (A) and after 6 (B), 12 (C), 24 (D), 36 (E), 48 (F), and 60 (G) months for the equicrestally (Group 1) and subcrestally placed implants (Group 2).

In the first six months, bone remodeling was 0.7 mm for the equicrestally placed implants and 0.0 mm in the subcrestally placed implants. Six months is the time period considered appropriate for initial bone remodeling, following biologic width establishment. Figure 2 shows the mean bone loss between 6 and 60 months for both groups. For the equicrestally placed implants, this was –0.09 mm (SD 0.47) with a maximum additional bone loss of 0.92 mm. The negative number of the mean is indicative for a small but statistically and clinically irrelevant bone gain (p = 0.335). For the subcrestally placed implants, this change was 0.08 mm (SD 0.16) with a maximum loss of 0.48 mm after initial bone remodeling. Although this change was statistically significant (p=0.021), it can be considered clinically irrelevant. When both treatment protocols are compared, the difference in bone loss between 6 and 60 months was not statistically significant (p = 0.077). Figure 3 is illustrative for the bone remodeling over time in both placement protocol, with the visible implant surface exposure in the equicrestally placed implant.

Peri-Implant Health

After 60 months, the overall mean plaque score based on all implants was 0.39 (SD 0.35 range 0.00–1.00), with a mean plaque score of 0.39 for the equicrestally placed implants (SD 0.34, range 0.00–1.00) and 0.39 for the subcrestally placed implants (SD 0.37, range 0.00–1.00). At 60 months, the mean plaque score of equicrestally and subcrestally placed implants was not statistically significantly different (p = 1.00). The overall mean bleeding on probing off all implants was 0.18 (SD 0.24, range 0.00–1.00), with a mean bleeding on probing of 0.20 (SD

0.26, range 0.00–0.75) for the equicrestally placed implants and 0.16 (SD 0.23, range 0.00–1.00) for the subcrestally placed implants. At 60 months, the mean bleeding on probing of equicrestally and subcrestally placed implants was not statistically significantly different ($p = 0.590$). The overall mean probing pocket depth based on all implants was 2.04 mm (SD 0.53, range 1.00–3.25), with a mean probing pocket depth of 1.98 mm (SD 0.52, range 1.00–3.00) for the equicrestally placed implants and 2.09 mm (SD 0.55, range 1.25–3.25) for the subcrestally placed implants. At 60 months, the mean probing pocket depth between of equicrestally and subcrestally placed implants was not statistically significantly different ($p = 0.257$).

Prevalence of Peri-Implantitis

According to the 2017 Consensus report of the World Workshop on the classification of Periodontal and Peri-Implant Diseases and Conditions, the incidence for peri-implantitis in both study populations is 0%. None of the implants showed bone levels ≥ 3 mm apical of the most coronal portion of the intraosseous part of the implant and/or probing pockets depths ≥ 6 mm.

If a cross-sectional analyses after 5 years is performed and taking bone loss of 2 mm with bleeding on probing and/or suppuration to define disease as proposed by Klinge and colleagues,[16] only one implant in the present study showed a bone level of more than 2 mm in combination with bleeding on probing (Table 2), resulting in a success of 97.9% of all implants, respectively 95.8% for the equicrestally and 100% for the subcrestally placed implants.

Table 2: Implant distribution at 5 years according to mean bone level and mean probing pocket depth; numbers between brackets show implants with bleeding on probing.

Probing pocket depth (mm)	Mean bone level (mm)						
	<0.5	0.5 - 0.99	1.00 - 1.49	1.50 - 1.99	2.00 - 2.49	≥ 2.5	Total
≤1	1	1	0	0	0	0	2
1.1 - 2.0	17 (9)	2 (1)	3 (1)	0	0	1	23 (11)
2.1 - 3.0	17 (8)	4 (2)	0	0	1 (1)	0	22 (11)
3.1 - 4.0	1 (1)	0	0	0	0	0	1 (1)
4.1 - 5.0	0	0	0	0	0	0	0
> 5.0	0	0	0	0	0	0	0
Total	36 (18)	7 (3)	3 (1)	0	1 (1)	1	48 (23)

When a longitudinal analysis is performed with bone loss over time, the maximum bone loss after initial bone remodeling was 0.92 mm for the equicrestal and 0.48 mm for the subcrestal treatment protocol. When considering 1 mm of bone loss after initial bone remodeling as a success, 100% of the implants in both treatment protocols were considered a success.

Oral Health-Related Quality of Life

The mean OHIP-14 score before surgery was 10.08 (SD 9.42, range 0–34). Three months after connection, the mean score reduced to 3.46 (SD 4.60, range 0–17); this reduction was statistically significant ($p < 0.01$) and indicative for an improvement in OHRQoL. The reduction was statistically significant for all seven domains, with a large effect size for physical pain and social disability. For the other domains, the effect size was moderate (Table 3).

Table 3: Mean Oral Health Impact Profile (OHIP) score and the mean difference for each of the seven domains before surgery and three months after connection with the calculated effect size.

Domain	Mean-OHIP (SD)		Paired difference			effect-size
	before surgery	3-months after connection	Mean dif	95% CI	P	
Functional limitation	2.04 (1.90)	0.79 (1.10)	1.25	(0.431,2.069)	0.004	0.66
Physical pain	3.13 (2.23)	0.88 (1.45)	2.25	(1.206,3.294)	<0.001	1.01
Psychological discomfort	2.50 (2.81)	0.54 (1.64)	1.96	(0.592,3.325)	0.007	0.70
Physical disability	1.63 (2.02)	0.29 (0.62)	1.34	(0.492,2.175)	0.003	0.66
Psychological disability	2.00 (2.17)	0.42 (0.78)	1.58	(0.506,2.661)	0.006	0.73
Social disability	1.45 (1.47)	0.13 (0.45)	1.32	(0.655,2.012)	<0.001	0.90
Handicap	1.33 (1.52)	0.33 (0.76)	1.00	(0.353,1.647)	0.004	0.66

At 60 months, the mean OHIP-14 score was 4.33 (SD 5.92, range 0–15). Between 3 and 60 months, no statistically significant difference was observed ($p = 0.51$), which is indicative of a stable OHRQoL over time.

DISCUSSION

This prospective split-mouth clinical study evaluated the effect of long-term implant surface exposure, which is induced by biologic width re-establishment, on peri-implant bone stability and peri-implant health in patients treated with an implant-supported overdenture in the mandible. The applied split-mouth

design corrects for inter-individual variability from the estimates of the treatment effect.[17]

The difference in this study population in mean bone level between equicrestally and subcrestally placed implants at 6 months is 0.68 mm. The 95% confidence interval of the mean shows a 95% chance that the mean difference in the true population will be between 0.36 and 1.00 mm. Even the lower number of the mean difference of the true mean is already suggestive for clinically relevant differences in mean bone level. For all other time intervals, the same conclusion could be made.

Compared to the short-term follow-up earlier published by Vervaeke and co-workers,[5] no significant changes could be observed regarding peri-implant bone stability and peri-implant health when the 2-year data are compared with the 5-year data, which is indicative of stable peri-implant health over time.

A recent systematic review and meta-analysis of 16 studies concluded in a quantitative analysis that subcrestal and equicrestal implant placement yield comparable peri-implant bone loss.[18] However, in the presence of a thin tissue, a subcrestal placement of the implant is preferred, because it may reduce the risk for implant exposure in the future, thus avoiding peri-implant pathologies. More studies suggested a certain minimum width of peri-implant mucosa as a prerequisite, allowing a stable soft tissue attachment.[4,19-22] The results of the present study are in agreement with the aforementioned papers. Hence, one should anticipate for the preferred biologic width establishment to prevent early implant surface exposure caused by initial bone remodeling by adopting implant depth positioning in relation to soft tissue thickness.

A recent clinical trial tried to overcome the initial bone remodeling due to biologic width re-establishment by using a soft tissue tenting technique.[23] These implants were placed equicrestal with soft tissue tenting over 2 mm healing abutments. The implants in the control group were placed 1.5 mm subcrestally. The bone loss between both groups was statistically significantly different and in favor of the subcrestally placed implants. They concluded that soft tissue tenting could increase soft tissue thickness. However, the latter technique is leading to greater bone loss compared to the subcrestal placement of the implants. Based on the

present paper in line with the available evidence, it is advised to adapt the surgical position of the implant in relation to the available pre-operative soft-tissue thickness. This contradicts the protocols often advised by implant manufacturers suggesting that implant design features alone may prevent bone loss.

Radiographic analysis of the subcrestally and equicrestally placed implants showed a minimal bone loss over time after the initial bone remodeling, although it was not clinically relevant. The findings of this paper are in accordance with earlier published papers, showing comparable results for peri-implant bone stability in patients treated with a two-implant overdenture in the mandible .[24-26]

The present study demonstrated only small and clinically irrelevant differences for the biological parameters between equicrestally and subcrestally placed implants at all time intervals. Despite direct exposure of the implant threads, this did not lead to further bone loss, since there was no statistically significant difference in bone level between 6 and 60 months. One should keep in mind that all patients in the present study were fully edentulous and were compliant with oral hygiene. Whether this outcome is also valid in non-compliant patients is questionable as suggested by scarce evidence. It is highly unlikely that scientifically sound, randomized control trials in humans could be initiated in non-compliant patients given the unethical approach this would require. However, some evidence in the literature is in contradiction with the present finding. In partially edentulous patients, an early exposure of the implant surface was indicative for future bone loss.[6] It is tempting to suggest that partially edentulous patients harbor potentially more pathogenic peri-implant microflora explanatory for more bone loss in case of exposed implant surfaces.[27] Another 10-year follow-up study included 25 patients with an edentulous mandible restored with five implants and a fixed prosthetic rehabilitation. Not all of their patients complied with professional peri-implant maintenance therapy between year 3 and 10. Additionally, with a fixed prosthetic rehabilitation, maintaining a good oral hygiene was more demanding.[7] The positive effect of a regular peri-implant maintenance therapy has been described in a systematic review with meta-analysis by Monje and colleagues.[28] It is well understood that regular peri-implant maintenance therapy is mandatory to prevent biologic complications and ameliorates the long-term success rate.

As far as peri-implant health is concerned, the current findings are in accordance with other papers, which found no difference in BoP and/or PPD between equicrestally and subcrestally placed implants.[29,30] When the parameters of the mean bone level, bleeding on probing, and probing pocket depth are combined, only one implant in the present study showed a bone level of more than 2 mm in combination with bleeding on probing. However, a low probing pocket depth was scored for this implant, and the bone level stayed stable over time. The cross-sectional analysis to detect disease compared to the longitudinal analysis gave an overestimation for detecting disease. Despite a bone level above 2 mm after 60 months in combination with bleeding on probing, the bone loss after initial bone remodeling for this implant was below 1 mm, and the implant could be considered a success.

It is questionable if the parameter mean, which is derived from four values per implant, is the best parameter to use for a statistical comparison of biologic parameters. This was also raised in the 5th EAO consensus conference where it was addressed that mean peri-implant bleeding scores and mean probing pocket depths are not adequate outcomes to measure health and disease. Frequency distributions of sites with a certain threshold of deep probing depths or sites demonstrating inflammation reflected by bleeding on probing are considered more appropriate.[31] The frequency distribution (Table 2) of the data from the current paper shows probing pocket depths, which are all indicative of peri-implant health. The findings of the weak correlation between biologic parameters and bone level are in accordance with the paper by Doornewaard and co-workers and indeed suggest that the single use of a periodontal index not combined with (ongoing) bone loss seems not to be a reliable indicator to measure the peri-implant health.[11]

The outcome of the OHRQoL is in accordance with earlier published papers. All papers indicate the superiority of an implant-supported overdenture compared to a conventional complete denture regarding the quality of life.[32-35] Moreover, a recent published paper investigating the difference in OHRQoL between patients with an implant fixed complete denture and patients with an implant overdenture could not find a significant difference in OHIP score between the two treatment groups.[36] The above-mentioned findings confirm the McGill consensus statement where it is stated that an implant-retained overdenture is

the first choice of treatment for the edentulous mandible. It could be concluded that if patients are well maintained, this treatment protocol yields high success rates regarding patient quality of life and peri-implant health.

CONCLUSIONS

Within the limitations of this study, it can be concluded that adapting the vertical position of the implant in relation to the soft tissue thickness prevents early implant surface exposure caused by initial bone remodeling. In a well-maintained population with regular peri-implant maintenance therapy, the effect of early implant surface exposure caused by initial bone remodeling on peri-implant bone stability and biologic parameters seems to be limited after a follow-up of 5 years.

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CHAPTER 7

Four-implant-supported overdenture treatment in the maxilla. Part I: A randomized controlled split mouth trial assessing the effect of microthreads and abutment connection type on 4 years peri-implant health.

This chapter is based on the publication: Four-implant-supported overdenture treatment in the maxilla. Part I: A randomized controlled split mouth trial assessing the effect of microthreads and abutment connection type on 4 years peri-implant health.

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ABSTRACT

Background: According to literature, peri-implant bone loss is minimized on implants with microthreaded neck design and internal type of abutment connection. However, most clinical studies may be biased due to confounding factors.

Purpose: This nonblinded RCT assessed the effect of implant neck (microthreaded vs non-microthreaded) as well as the type of abutment connection (internal conical vs external flat-to-flat) on peri-implant bone stability and peri-implant health after at least 36 months.

Materials and methods: Twenty-five patients were treated with a maxillary implantsupported bar-retained overdenture on four different implant types: internal connection with microthreads (I-MT), internal connection without microthreads (I-NMT), external connection with microthreads (E-MT), and external connection without microthreads (E-NMT). To control confounding factors, all other design features were similar. A linear mixed-model analysis or mixed-model logistic regression analysis was used to determine the effect of implant type on bone level, probing pocket depth, bleeding on probing, and plaque.

Results: Four out of 98 implants (4.1%) placed in 25 patients failed during provisionalization and were replaced. Mean overall bone loss after 6 months was 0.39 mm (SD 0.62, range 0.00–3.48) with limited additional bone loss of 0.04 mm (SD 0.54, range 1.80–1.63) after at least 3 years. Microthreads or connection type had no effect on the bone level, probing pocket depth, bleeding on probing, nor plaque.

Conclusions: With 96% of implant survival, the maxillary overdenture supported with a bar on four implants yield a predictable outcome and the implant–abutment connection type (internal vs external) and implant neck design (microthreaded vs nonmicrothreaded) have no influence on peri-implant bone remodeling after initial bone remodeling nor up to 4 years of function. Peri-implant bone levels are within international success standards and peri-implant health is indicative of absence of peri-implantitis.

INTRODUCTION

Nowadays, the support of an overdenture by dental implants is a widely used treatment procedure to provide higher functional comfort in the edentulous patient. Moreover, the mandibular two-implant overdenture is already for a long time considered as standard care for the edentulous patient.[1] Success rates over 95% after 10 years of function are presented for overdentures in the mandible.[2] A systematic review and meta-analysis reported an implant survival ranging from 73.5% to 100% for maxillary implants supporting an overdenture.[3] They also concluded that a minimum of four implants is required to ensure high implant survival rates. Another systematic review with meta-analysis reported an implant survival of 98.1% per year in the case of ≥6 implants and splinted anchorage, a survival rate of 97.0% per year in case of ≤4 implants and a splinted anchorage, and a survival rate of 88.9% per year in case of ≤4 implants and a nonsplinted anchorage. They concluded an increased risk for implant loss for a nonsplinted anchorage with less than four implants.[4] Success of the implant treatment is mostly determined by implant factors, such as survival rate, long-term peri-implant bone stability, and the absence of inflammation in the peri-implant tissues, or by patient factors such as the Oral Health-Related Quality of Life (OHRQoL). Part II of this study describes the patient-related outcome, more specifically Oral Health-Related Quality of Life (OHIP-14) as well as subjective opinion on speech by patients and objective speech analysis by professional speech therapists. The OHRQoL improved after connection with the implant-overdenture and this remained unchanged afterward. However, despite subjective registered improvements in speech, a professional scrutiny detected some disorders indicative of adaptation problems.

Different abutment connections have been used over time, in order to overcome abutment screw loosening, enhance long-term bone stability, and minimize crestal bone loss. In the early years of implant dentistry the most common abutment connection was the flat-to-flat abutment to implant connection, with an external hexagon to prevent abutment rotation. Nowadays, an internal conical connection or a Morse taper with an internal antirotation element is mostly used. A large review of 52 articles by Schmitt and colleagues concluded from in vitro techniques that (1) no connection yields a 100% perfect seal for bacterial contamination; (2) the implant–abutment interface geometry seems to be an influencing factor for stress

and strain transmission around the implant; (3) the conical implant–abutment connection seems to be more resistant to abutment movement and microgap enlargement and has higher torque loss resistance in addition to high resistance to fatigue loading and maximum bending; (4) the conical implant–abutment connection seems to have lower abutment screw stresses than with external hexagon connection are detected but it is comparable to internal hexagon connections. The same review concluded from in vivo studies that (1) conical and non-conical systems are comparable in terms of implant success and survival and (2) in most cases conical connection systems seem to produce a lower marginal bone loss.[5]

Besides the implant–abutment connection type, also thread design at the coronal part of the implant is claimed to influence crestal bone loss. Several in vitro studies, using finite element analysis, showed better stress distribution on the surrounding crestal bone for microthreaded compared to non-microthreaded implants.[6,7] Multiple in vivo clinical studies showed less crestal bone loss for microthreaded implants compared to non-microthreaded implants.[8–11] However, most of the aforementioned studies did not control other implant design factors and often the compared implants differed in more than one confounding factor thereby possible biasing the outcome of the study.

No connection has a 100% bacterial seal. However, evidence showed that conical connection systems seem to be superior in terms of bacterial seal. Conical implant–abutment connection systems seem to be more resistant to abutment movement and microgap enlargement under loading. Internal and external hexagonal connection systems seem to be inferior in terms of abutment movement and microgap formation. Conical connection systems have higher torque loss resistance than other systems. Conical connection systems have high resistance to fatigue loading and maximum bending. Conical connection systems seem to have lower abutment screw stresses than external hexagonal connection systems and are comparable to internal hexagonal systems. The cone compensates high stresses and protects the screw from overloading. The implant–abutment interface geometry seems to be an influencing factor for stress and strain transmission around the implant. Hence, this prospective clinical study assessed the 4–5 years effect of implant neck (microthreaded vs non-microthreaded) as well as the type of connection (internal conical vs external flat to flat) on peri-implant bone stability and peri-implant health.

The preliminary short-term data regarding peri-implant bone stability and peri-implant health are earlier published Glibert and colleagues.[12] The latter study showed data up to 15–23 months and only pertaining to 15 patients. The Glibert study is a preliminary report of the current study whereby now all cases are followed for 36 months.

MATERIALS AND METHODS

Patient population and surgical/prosthetic procedures

Fully edentulous patients in the maxilla in need of a four-implant- supported overdenture were included in this prospective clinical split-mouth study. The patient selection, surgical, and prosthetic procedure have been described in detail previously by Glibert and colleagues.[12]

To study the effect of a microthreaded neck design and an internal abutment connection on peri-implant bone stability and peri- implant health, the commercially available Deep Conical Cylindrical implant (DCC, Southern Implants, Irene, South Africa) served as a basis for the other three experimental implants (Southern Implants). All implants were straight-wall implants with a thread pitch of 0.6 mm and had the same implant surface roughness (1.3 µm) and the same

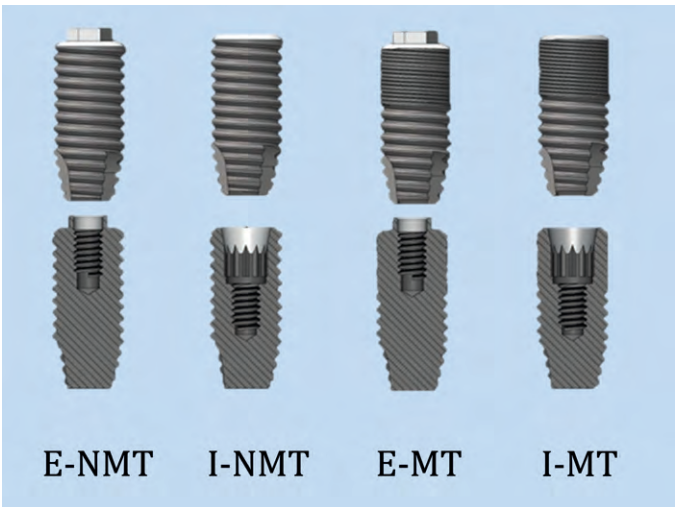

Figure 1: Schematic drawing of the four study implants

integrated platform shift with smooth implant bevel. For the purpose of this study the experimental implants differed only in one factor as clarified in Figure 1. The commercially available implant (DCC, Southern Implants) has an internal connection and microthreaded neck (I-MT), the three experimental implants (Southern Implants) existed of an implant with an internal connection and without microthreaded neck (I-NMT), an implant with an external connection and with microthreaded neck (E-MT), and an implant with an external connection and without microthreaded neck (E-NMT). All implants used for this study had a diameter of 4 mm and a length of 9 or 11 mm.

Each patient received all four study implants in the edentulous maxilla in a one-stage surgical procedure with open flap. The preferred implant locations were the canine and first molar region. However, in case of insufficient bone at the molar region the second premolar site was chosen. Implant types were allocated by means of a computerized randomization scheme. Directly after implant placement, a definitive titanium implant abutment with a height of 4 mm (Compact Conical Abutments, Southern Implants) was installed, using a 20 Ncm torque. These abutments were temporary covered with healing caps.

After implant surgery, the conventional denture was adjusted with a soft reliner (Coe Soft, GC Europe, Leuven, Belgium) in direct contact with the healing caps. The direct contact of the prosthesis with the healing caps could be considered as an immediate functional loading with a provisional removable denture. The occlusion and articulation as well as the fit of the denture were checked every 2–3 weeks to avoid overload and the soft reliner was renewed whenever required. To control the clinical osseointegration the titanium implant abutments were torqued at 30 Ncm after a minimal healing period of 4 months. If good clinical osseointegration was achieved, impression was taken on abutment level, and a titanium bar was designed and milled using CAD-CAM technology. The maximum allowed extension of the bar was 8 mm. All final prosthesis had a metal frame and a partial coverage of the palate.

The ethical committee of the Ghent University Hospital approved the study protocol under the Belgium registration number B670201524372. All patients were thoroughly informed about the treatment, signed written informed consent, and were treated between September 2015 and September 2017 at the Ghent

University hospital. This clinical trial has been conducted in full accordance with the Helsinki Declaration (1975) as revised in 2000.

Clinical and radiographic examination

The clinical and radiographic examination of a smaller study cohort up to 21 months has been described previously by Glibert and colleagues.[12] After implant placement (t0, baseline) follow-up visits were planned at 3, 6(t1, initial remodeling), 12, 24, and 36(t2) months. Peri-apical radiographs were taken after implant placement (t0, baseline), and after 3, 6(t1, initial bone remodeling), 12, 24, and 36(t2) months. The time period between t0 and t1 is the period considered appropriate for initial bone remodeling, following biologic width establishment. After delivery of the final prosthesis, the measurement of probing pocket depths, bleeding on probing, and plaque scores were executed on four sites per implant to monitor the peri-implant health. The presence of plaque and bleeding on probing was assessed on a dichotomous scale.

Peri-apical radiographs were analyzed after implant placement (t0), after initial remodeling at 6 months (t1), and after 36 months (t2). To standardize the peri-apical radiographs an individualized x-ray holder and Rinn-Sett was used (Rinn XCP, Dentsply Sirona, Charlotte, NC). The radiographs were calibrated preferably by using the length of the implant, otherwise the distance between the threads of the implant, or the diameter of the implant was used. The bone level was determined as the distance between the most crestal bone-to-implant contact and the lower edge of the smooth implant bevel at the implant–abutment interface. The distance was measured on the peri-apical radiograph at the distal and mesial side of the implant and recalculated to a mean bone level on implant level. The bone loss was calculated by the difference of the bone level between two time points.

During all follow-up visits, calculus and plaque were removed and oral hygiene instructions were given tailored to the need of the patient. All patients were advised to use interdental brushes and (electric) toothbrush to maintain the bar construction.

Incidence of peri-implantitis was assessed according to the criteria proposed in the 2017 Consensus report of the World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.[13]

Statistical analysis

Data analysis was performed in SPSS statistics 26 (SPSS Inc., Chicago, IL) and R Core Team 2019 (R: a language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria). Outcomes are reported with descriptive statistics (mean, standard deviation [SD], median, and range) and visualized through boxplot representation. The analysis on bone level is carried out after 6(t1) and 36(t2) months using a linear mixed-model analysis. The mean bone level per implant type at t1 and t2 were the dependent variables and the patient as random intercept. The independent variables for this analysis were the bone level at baseline (t0), implant type (I-MT, I-NMT, E-MT, and E-NMT), and implant position (anterior and posterior).

An analysis of the measurement error for the continuous variable bone level between the different observers (S.S., M.G., and R.D.) was performed by the use of a scatterplot representation and a paired *t* test. The random error or duplicate measurement error (DME) was calculated with the formula: (sd of differences)/√2. Also, the paired samples correlation between the observers was calculated.

The analysis on probing pocket depth, bleeding on probing and plaque were, respectively, carried out after 36 months using a linear mixed-model analysis for the probing pocket depth and a mixed-model logistic regression analysis for bleeding on probing and plaque. The probing pocket depth, bleeding on probing and plaque at site level was the dependent variable and both to the implant and patient a random intercept was assigned. The independent variables for this analysis were implant type (I-MT, I-NMT, E-MT, and E-NMT) and implant position (anterior and posterior). To show the effect of the fixed factor, the fixed effects estimates (linear mixed-model analysis) and the odds ratios (mixed-model logistic regression analysis), all with their confidence limits and *p*-value, are given. The level of significance was set at 0.05.

RESULTS

Study population

Initially, 25 patients were included in this study (Figure 2). The study population consisted of 15 men and 10 women with a mean age of 62 years (SD 9.98, range

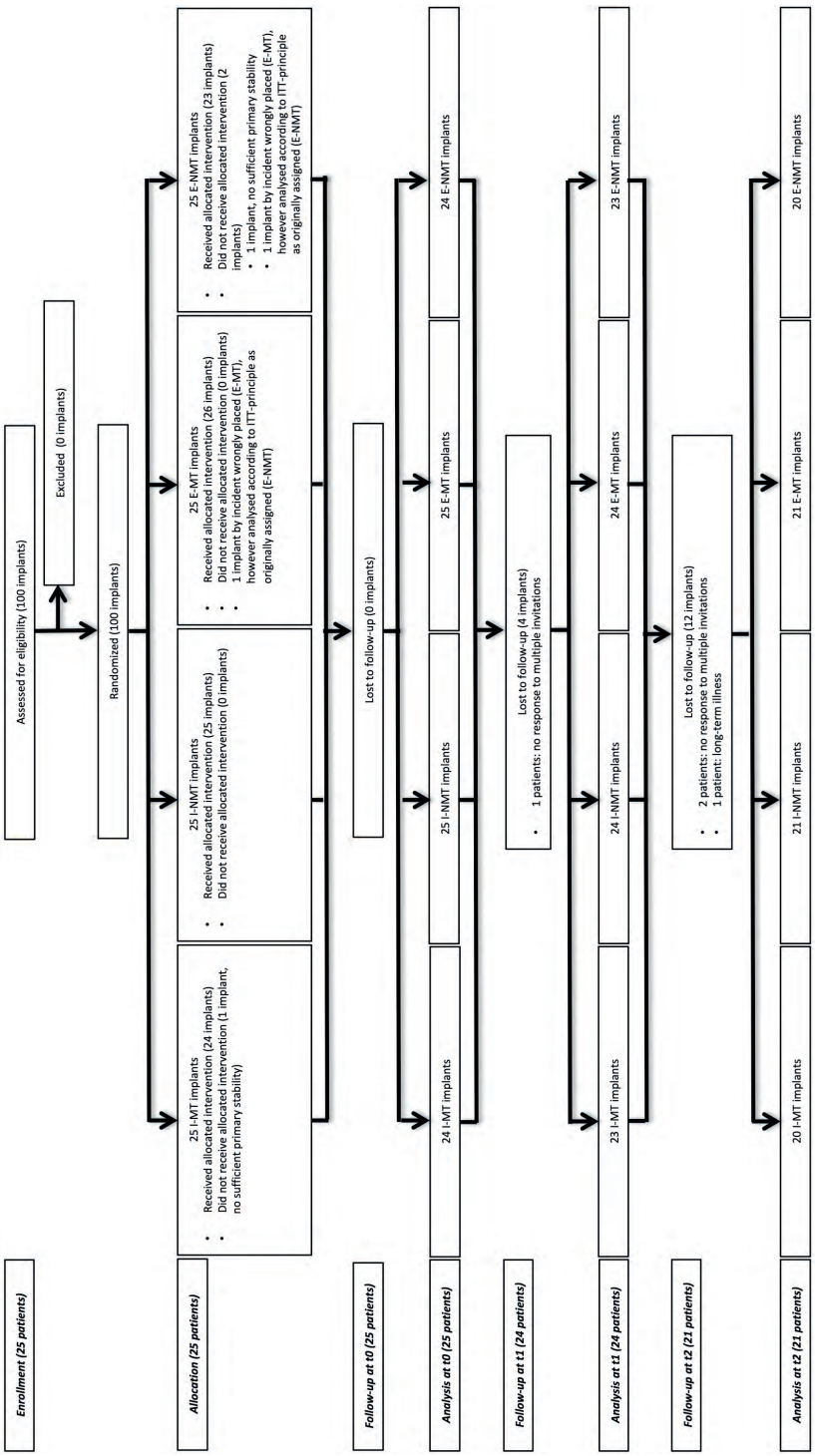

Figure 2: Flowchart of the study population

42–83) at implant placement (t0). Two implants in two patients were excluded for further analysis, because placement of a study implant was not possible. Both implant sites required a 5-mm diameter implant to achieve sufficient primary stability (≥20 Ncm). Hence, 98 implants were available for follow-up after implant placement. Unfortunately by mistake, one patient received two E-MT and no E-NMT implant. However by respecting the intention-to-treat principle, the wrongly placed implant is analyzed according to the group it was originally assigned, resulting in the analysis of 24 I-MT, 25 I-NMT, 25 E-MT, and 24 E-NMT implants.

In all cases immediate provisional loading was possible and after a mean of 7.0 months (SD 2.05, range 3–11) after implant placement the final bar retained implant overdenture was placed. Twenty-four patients were available at the clinical and radiographic evaluation of t1. At t2, one patient could not attend the follow-up due to long-term illness and three patients did not respond to multiple invitations. Hence, 21 patients (82 implants) were available for follow-up at t2. Most visits planned at t2 were not carried out at 36 months but postponed due to the Covid-19 pandemic, resulting in a mean follow-up time of 45.5 months (SD 4.82, range 35–58) after implant placement.

Mean bone level, mean bone loss, and peri-implant health

Four implants (2x E-NMT, 1x E-MT, 1x I-NMT) in three patients failed during the period of osseointegration, resulting in a survival of 95.9% on implant level. However, all failed implants were successfully rep- laced with the same type of implant after 3 months of healing and were included in further analysis.

The applied test for the inter examiner agreement on the measurement of the variable bone level resulted in a paired samples correlation ranging between 0.937 and 0.976 for the three observers. The random measurement error for this variable ranged between 0.09 and 0.16. Details of mean bone level, SD, median, and range per study implant at different time intervals is provided in Table 1. The mean bone loss for all implants between t0 and t1 was 0.39 mm (SD 0.62, range 0.00 - 3.48). The mean additional bone loss between t1 and t2 was 0.04 mm (SD 0.54, range -1.80 – 1.63). The negative number in the range is indicative for bone gain between t1 and t2. The bone loss between the different time points per implant type is given in Table 2. The linear mixed-model analysis (Table 3) with mean bone level

Table 1: Mean bone level, standard deviation (SD), median, and range per study implant at different time intervals

	T0				T1				T2			
Implant type	**N**	**Mean (SD)**	**Median**	**Range**	**N**	**Mean (SD)**	**Median**	**Range**	**N**	**Mean (SD)**	**Median**	**Range**
E-NMT	24	0.01 (0.04)	0.00	(0.00-0.22)	23	0.35 (0.55)	0.00	(0.00-2.34)	20	0.52 (0.56)	0.40	(0.00-1.93)
I-NMT	25	0.00 (0.00)	0.00	(0.00-0.00)	24	0.33 (0.61)	0.00	(0.00-2.62)	21	0.43 (0.62)	0.21	(0.00-2.47)
E-MT	25	0.05 (0.14)	0.00	(0.00-0.64)	24	0.50 (0.78)	0.13	(0.00-3.48)	21	0.40 (0.54)	0.26	(0.00-1.80)
I-MT	24	0.01 (0.02)	0.00	(0.00-0.12)	23	0.45 (0.60)	0.21	(0.00-2.22)	20	0.50 (0.52)	0.36	(0.00-2.08)

Table 2: Mean bone level change, standard deviation (SD), median, and range per study implant at different time interval

Implant type	**T0 - t1**			**T1 - t2**		
	Mean (SD)	**Median**	**Range**	**Mean (SD)**	**Median**	**Range**
I-MT	0.45 (0.61)	0.18	(0.00-2.22)	0.01 (0.47)	0.02	(-0.86-0.72)
I-NMT	0.33 (0.61)	0.00	(0.00-2.62)	0.07 (0.60)	0.11	(-1.80-1.59)
E-MT	0.45 (0.77)	0.10	(0.00-3.48)	-0.10 (0.58)	0.00	(-1.68-0.90)
E-NMT	0.34 (0.51)	0.00	(0.00-2.13)	0.19 (0.48)	0.05	(-0.47-1.63)

at t1 as dependent variable showed that the factors "bone level at t0" and "implant position posterior" had a significant effect on the mean bone level. A posteriorly placed implant reduced the mean bone level with 0.21 mm compared to an anteriorly placed implant. However, this very small estimate with the small range of the confidence limits makes this difference clinically irrelevant. No significant effect on the bone level at t2 was found for the factors "bone level at t0,""implant type," and "implant position."

The overall mean probing pocket depth at t2 was 3.15 mm (SD 0.88, range 1.50–5.25), with an overall mean bleeding on probing of 0.20 (SD 0.26, range 0.00–0.75), and an overall mean plaque score of 0.22. The linear mixed-model analysis (Table 3) with probing pocket depth at t2 as dependent variable showed no significant impact for the factor "implant type" on probing pocket depth (Table 3). However, this analysis showed a significant impact for the factor "implant position" in favor of the posterior implant with an estimate pocket reduction of 0.338 mm, although this difference is significant it seems to be clinically irrelevant. A logistic regression analysis with bleeding on probing and plaque as dependent variables showed that "implant type" or "implant position" had no significant impact on the odds at t2.

Prevalence of peri-implantitis

The maximum bone loss calculated at t2 compared to t1 (initial remodeling) was 1.63 (Table 2). For 74 implants combined data were available at t2 for bone level, probing pocket depth as well as bleeding on probing. When bone level <2 mm in combination with the absence of bleeding on probing and/or suppuration is considered as success, only one implant did not fulfill these criteria, resulting in a success of 98.6% (Table 4). Moreover, none of these implants showed bone levels ≥3 mm apical of the most coronal portion of the intraosseous part of the implant and/or probing depths ≥6 mm. It could be stated that the incidence of peri-implantitis in the study population is 0% according to the 2017 Consensus report of the World Workshop on the Classification of Periodontal and Per-Implant Diseases and Conditions.[13]

Table 3: Mixed-model analyses with mean bone loss at t1 (n = 94), mean bone loss at t2 (n = 82), and for probing pocket depth at t2 (n = 75) as dependent variables. And a mixed-model logistic regression with bleeding on probing at t2 and plaque at t2 (n = 75) as dependent variables

Bone level at t1				
Factor		**Estimate**	**Confidence limits**	**P**
Bone level at t0		1.098	(0.092,2.109)	**0.032**
Implant type	**E-NMT**	reference		
	I-NMT	0.132	(-0.081,0.344)	0.224
	E-MT	0.177	(-0.024,0.377)	0.084
	I-MT	0.126	(-0.070,0.322)	0.207
Implant position	**Anterior**	reference		
	Posterior	-0.212	(-0.365,-0.060)	**0.006**
Bone level at t2				
Factor		**Estimate**	**Confidence limits**	**P**
Bone level at t0		1.828	(-0.358,4.024)	0.101
Implant type	**E-NMT**	reference		
	I-NMT	-0.079	(-0.381,0.223)	0.608
	E-MT	-0.168	(-0.449,0.114)	0.244
	I-MT	-0.044	(-0.321,0.234)	0.759
Implant position	**Anterior**	reference		
	Posterior	-0.021	(-0.238,0.197)	0.854
Probing pocket depth at t2				
Factor		**Estimate**	**Confidence limits**	**P**
Implant type	**E-NMT**	reference		
	I-NMT	0.038	(-0.349,0.425)	0.224
	E-MT	-0.152	(-0.509,0.204)	0.084
	I-MT	0.003	(-0.357,0.190)	0.207
Implant position	**Anterior**	reference		
	Posterior	-0.338	(-0.617,-0.059)	**0.017**
Bleeding on probing at t2				
Factor		**Odds ratio**	**Confidence limits**	**P**
Implant type	**E-NMT**	reference		
	I-NMT	1.252	(0.393,3.986)	0.704
	E-MT	1.280	(0.441,3.713)	0.649
	I-MT	0.845	(0.275,2.594)	0.768
Implant position	**Anterior**	reference		
	Posterior	1.094	(0.462,2.588)	0.838
Plaque at t2				
Factor		**Odds ratio**	**Confidence limits**	**P**
Implant type	**E-NMT**	reference		
	I-NMT	1.114	(0.215,5.761)	0.898
	E-MT	1.323	(0.325,5.394)	0.695
	I-MT	2.595	(0.616,10.930)	0.194
Implant position	**Anterior**	reference		
	Posterior	0.875	(0.273,2.807)	0.822

Table 4: Implant distribution at t2 according to mean bone level and mean probing pocket depth; numbers between brackets show implants with bleeding on probing

Probing Pocket Depth (mm)	Mean Bone Level (mm)						
	< 0.5	0.5 - 0.99	1.00 - 1.49	1.50 - 1.99	2.00 - 2.49	≥ 2.5	total
≤ 1	0	0	0	0	0	0	**0**
1.1 - 2.0	8 (3)	1 (0)	0	0	0	0	**9 (3)**
2.1 - 3.0	23 (9)	7 (4)	1 (1)	0	1 (1)	0	**32 (15)**
3.1 - 4.0	12 (6)	3 (3)	2 (0)	4 (3)	0	0	**21 (12)**
4.1 - 5.0	6 (1)	0	2 (1)	0	1 (0)	0	**9 (2)**
> 5.0	1 (0)	2 (1)	0	0	0	0	**3 (1)**
Total	**50 (19)**	**13 (8)**	**5 (2)**	**4 (3)**	**2 (1)**	**0**	**74 (33)**

DISCUSSION

This prospective clinical split-mouth study evaluated the (long-term) effect of a microthreaded neck design and an internal abutment connection on peri-implant bone stability and peri-implant health in patients treated with an implant-supported overdenture on four implants in the maxilla. To minimize confounding factors, all study implants were similar but for one specific design factor, namely the internal versus external connection and microthreaded versus nonmicrothreaded neck design. Besides controlling the confounding factors, the split-mouth design corrects for inter-individual variability from the estimates of the treatment effect.[14]

The present study shows an implant survival of 95.9%, which is in accordance with earlier published RCTs and systematic reviews.[3,4,15] All implant failures were early failures during healing and possibly caused by overloading of the nonsplinted implants. It should be stressed that implants were provisionally loaded. The abutments plus healing caps were located above the mucosal level and despite soft relining and regular check-ups overload during healing cannot be excluded. For future studies immobilization of the implants by splinting or lower prosthetic components are advised to overcome the limitation in this study protocol. One may suggest the use of healing abutments at mucosal level to avoid premature loading but this was not possible because in the context of controlling experimental confounders, the use of final abutments was advocated.

The time period between t0 and t1 is the period considered appropriate for initial bone remodeling, following biologic width establishment. After initial bone remodeling, the linear mixed-model analysis showed no clinical relevant effect of the implant type on the bone level at the t1 and t2. Although the implant position showed a significant effect on the bone level at t1 in favor of a posterior placed implant, the confidence limit (-0.365, -0.060) is suggestive for a clinically irrelevant difference. Moreover, at t2 no effect of implant position could be found.

Between t1 and t2 all implant types showed no relevant bone level change, indicative for a stable bone level over time after initial bone remodeling. However, some implants with high bone loss at t1 showed bone gain at t2. This could be explained by the effect of splinting the implants with a titanium bar after t1. The positive effect on bone level by splinting the implants was described earlier by De Bruyn and colleagues.[16]

The linear mixed-model analysis applied for probing pocket depth and the model logistic regression analysis applied for bleeding on probing and plaque showed no clinical relevant difference for implant type and implant position at t2. Only the probing pocket depth seems to be influenced by implant position, in favor of the posterior placed implant; however, the confidence limit (-0.617, -0.059) is suggestive of a clinically irrelevant difference.

Furthermore, it needs to be stated that these results have been established with the precondition that (1) all implants are placed in relation to the soft tissue thickness and (2) due to the use of the specific abutment a platform-shift between implant and abutment was created. The effect of adapting the vertical position of the implant in relation to the soft tissue thickness is published in several studies.[17–22] It could prevent early implant surface exposure by initial bone remodeling. The results of this study are in according to the aforementioned studies. The philosophy of a platform-shift between implant and abutment is to move the inflammatory cell away from the bone. A large meta-analysis of 28 publications with 1216 platform-switched implants and 1157 nonplatform-matched implants showed a significant effect on marginal bone loss in favor of the platform-shifted implants. However, they suggest a careful interpretation of the results due to the presence of uncontrolled con- founding factors.[23]

Bone level in the present study is comparable with a recent published RCT by Slot and colleagues with a 5-year follow-up of 29 patients treated with four of six implants in the maxillary posterior region to support a bar retained overdenture.[15] The mean bone loss between the placement of the overdenture and 5-year evaluation was 0.58 mm (SD 0.51) for the four-implant group. The present study showed a mean probing pocket depth of 4.5 mm and 45% (33 out of the 74 implants) showed bleeding on probing. The study by Slot and colleagues showed comparable findings, with a mean probing of 4.3 mm and 48% of the implants scored positive on the bleeding index. Mean loss of peri-implant bone between baseline and the 5-year evaluation was 0.58 ± 0.51 mm in the four-implant group.[15]

Regarding the implant–abutment connection, the results of the present study are not in accordance with a systematic review and meta-analysis with 11 included studies, which compares the effect of an internal or external implant–abutment connection on bone loss.[24] The systematic review concluded that internal connections had lower marginal bone loss when compared to external connections. However, several included studies used a study design where confounding factors such as design factors like implant brand, implant surface, thread design, and platform-shift were not controlled. Due to the presence of more than one different design factor between the study implants, the interpretation of these results should be interpreted with caution. Two other systematic reviews also concluded that internal connections exhibit lower marginal bone loss than implants with external connections; however, they discussed that these findings are probably related to the platform switching, which is more frequently found in implants with internal connections.[25,26]

A systematic review with meta-analysis concluded that a microthreaded neck design reduces the amount of marginal bone loss.[27] The three RCTs in the meta-analysis represent in total 57 implants in each treatment group in only partially edentulous patients. Only two out of the three studies found a statistically significant difference in marginal bone loss between the two study implants. The overall mean difference in the meta-analysis was significant and in favor of the implants with micothreaded neck design. However, the difference was only -0.09 mm with a 95%CI of -0.18, -0.01 and it is questionable if this statistically significant difference is clinically relevant. Furthermore, the authors of the meta-analysis concluded that the evidence was insufficient to draw a definite conclusion on

the effect of the microthreaded design because too few RCTs with low risk for bias were available. Moreover, they suggest that more RCTs with an adequate control for confounding factors for design are needed, because many studies have compared not only the microthread design but also other designs. To our knowledge, no more recent meta-analysis or RCTs other than the present study population could be found on PubMed when the search string "(microthread) AND (implant)" was used. The results from our paper confirm and strengthen the outcome described in the avail- able meta-analysis.

Today, only a few studies report on peri-implantitis incidence in patients with implant-supported overdentures in the maxilla. One study reported an incidence of 8.3% on patient level when restored with a maxillary overdenture on four implants in the anterior region and 4.5% on patient level for patients restored with a maxillary over- denture on six implants in the anterior region after 5 years of function.[28] The same author published in a recent RCT an incidence of 17.2% for patients restored with a maxillary overdenture on four implants in the posterior region and 9.7% for patients restored with a maxillary overdenture on six implants in the posterior region after 5 years of function.[15] They explained that the difference in incidence between anterior and posterior placed implants could be due to the fact that anterior placed implants are easier to maintain for the patient. The incidence of peri-implantitis in the present study is 0% on implant level, and thus 0% on patient level. However, the low incidence in the present study is based on another definition. The pre- sent paper based the incidence of peri-implantitis on the definition of peri-implantitis according to the 2017 Consensus report of the World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions.[13] In this classification, bone loss above 3 mm is considered as threshold for disease. The papers by Slot and colleagues based the incidence of peri-implantitis on the consensus from the Seventh European Workshop on Periodontology,[29] applying the threshold for marginal bone loss at ≥2 mm. If we apply the definition of the Seventh European Workshop on our study population and use a threshold of ≥2 mm in combination with bleeding on probing and/or suppuration, only one implant fulfilled this criteria resulting in an incidence of 1.4% on implant and on patient level.

An important limitation in this study could be the relatively short follow-up time. A recent study by Windael and colleagues suggests that bone loss at 2 years is

a predictor for bone loss at 10 years.[30] The present study showed a minimum bone loss up to 6 months (t1) and hardly any bone loss after initial remodeling (t1) up to the latest follow-up visit (t2). Provided that professional maintenance and compliance is taken care of, it is to be expected that further bone level changes related to the implant design are rather limited. Another limitation in clinical trials is the number of included patients. This is often limited because of affordability reasons. The follow-up time and number of patients in the current study is comparable with the included papers in the above-mentioned systematic reviews and meta-analyses.[24–27] In addition the split mouth design of the study helps to minimize the aforementioned limitations.

CONCLUSION

Within the limitations of this study, it can be concluded that in a well-maintained edentulous population restored with a four- implant-supported overdenture in the maxilla with a platform-shift implant–abutment interface, the implant–abutment connection type (internal vs external), implant neck design (microthreaded vs non- microthreaded), and implant position (anterior vs posterior) have (1) no influence on peri-implant bone remodeling after implant placement and have (2) no influence on peri-implant bone level after initial remodeling, and have (3) no influence on peri-implant health parameters (probing pocket depth, bleeding on probing, and plaque score) when implants are installed in relation to soft tissue thickness.

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CHAPTER 8

General discussion

This thesis discussed how peri-implant health could be affected by patient-, implant and site-specific factors. Peri-implant health is reflected by peri-implant bone stability. The stability of peri-implant bone is considered a crucial factor for implant success. The available scientific evidence was assessed systematically **(STUDY I AND II, CHAPTER 3 AND 4),** focussing on the long-term effect of implant surface roughness and patient' factors on crestal bone loss. In addition, we assessed how peri-implant biologic parameters correspond with implant survival and peri-implantitis diagnosis. Only studies with at least five years of follow-up were included because peri-implantitis is more likely to occur after a few years of function and exposure to bacterial load. The three clinical studies **(STUDY III, IV, AND V, CHAPTER 5, 6, AND 7)** scrutinized the effect of implant macro- and micro design, and the surgical procedure on peri-implant bone and soft tissue stability. In **Study III and IV (CHAPTER 5 AND 6)** the patient-reported outcome related to quality of life was reported.

The three clinical studies were a collaborative multidisciplinary research effort. Short-term data about implant survival and peri-implant health were previously published within the research group regarding surgical aspects. [1-3] Moreover, the group has published studies on prosthetic-related aspects, including cost-effectiveness, patient-related outcome, prosthetic aftercare,[4] and patient-related outcome measures reflecting on oral-health related quality of life and speech.[5,6]

Diagnostic Criteria to Describe Clinical Implant Outcome

Study I focused on the large variability in case definition of per-implantitis. Furthermore, the prevalence of peri-implant mucositis and peri-implantitis in the existing literature is examined. To reflect daily clinical practice and to be as inclusive as feasible, not only well-controlled academic studies, but all types of studies were included. With the used search algorithm, 4,173 papers were found between 2011 and 2017, of which 255 were selected for further assessment. Unfortunately, only 41 could be included for further analysis. This is a low proportion, given the significant impact it has on patients and clinicians. From 2011 to 2017 as many papers appeared as in the previous 35 years, which is indicative for the growing scientific interest for peri-implant health and disease. The scientific interest is apparently still growing, because more papers were published in 2020 compared to 2017. This rise in interest is probably caused by the increase in the use of dental implants in daily clinical practice. **Study I** delved

into the case definitions, thresholds applied for diagnosis of peri-implantitis, and whether commonly used biologic diagnostic parameters, such as mean bone loss, probing pocket depth, and bleeding on probing correspond to implant survival and peri-implantitis prevalence.

Study I showed that the included papers used 15 different peri-implantitis definitions. The case definitions varied considerably between studies, primarily due to heterogeneous thresholds for bone loss, ranging from any detectable bone loss to 3.5 mm. Low thresholds for bone loss lead to a higher prevalence of peri-implantitis on implant level than when higher thresholds are used. In addition to bone loss, other commonly used parameters to define peri-implantitis were arbitrarily selected thresholds for probing pocket depth, and bleeding on probing and/or suppuration. Moreover, 15 out of the 41 papers reported peri-implantitis prevalence on implant level without giving a specific case definition. These differences in thresholds make comparisons between studies difficult and lead to an over- or underestimation of peri-implantitis. Therefore, **Study I** concluded that many authors report extremely high 'self-quoted' prevalence of peri-implantitis despite extremely low mean bone loss values.[7-9]

This considerable variation in scientific reporting induces unreliable figures of the prevalence of peri-implantitis and may contribute to inadequate clinical actions. To illustrate, we applied the different definitions on our clinical data of **Study IV**. Nine definitions for peri-implantitis were applicable on our data (TABLE 1) and six were non-applicable (Table 2). Given the applicable definitions, the prevalence of peri-implantitis on implant level in the study population of **Study IV** has a range of 0% and 29.2%. Clinically this means that over a fourth of the implant the implant tissues diagnosed as diseased are healthy.

Table 3 summarizes the proportion of implants examined in **Study IV** concerning bone level, probing pockets depth, and bleeding on probing. The single implant variables were calculated as the mean of site measurements, respectively two radiographical bone values or four clinical peri-implant sites. A cross-table presents bone loss around each individual implant in relation to the probing depth or bleeding. Thirty-six implants presented with less than 0.5 mm bone loss after 5 years. In fact, 22 implants had no bone loss at all and only 9 out of these 22 showed bleeding on probing. All implants yielded less than 4 mm probing depth

Table 1: Overview of the 9 different definitions for peri-implantitis applicable on our own data.

Definition number	Reference	Definition of peri-implantitis	Cut-off bone loss (mm)	Cut-off PPD (mm)	BoP/Sup	Frequency distribution of definition	Prevalence of peri-implantitis according to the given definition for the study population in Study IV
1	Albrektsson et al., 1986	Bone loss 1.5 mm for the first year and 0.2 mm annually thereafter	1.5			1	2.1%
3	Berglundh et al., 2002	PPD > 6 mm in combination with bleeding on probing/ suppuration and attachment loss/bone loss of 2.5 mm	2.5	6	BoP/Sup	3	0%
5	Lang and Berglundh 2011: 7th EWOP	Changes in the level of the crestal bone in conjunction with bleeding on probing with or without concomitant deepening of peri-implant pockets. Pus is a common finding in peri-implantitis sites.			BoP	4	29.2%
9	Self-reported definition 4	Bone loss > 1mm, PPD ≥ 5mm and BoP/Sup	1	5	BoP/Sup	1	0%
10	Self-reported definition 5	Bone loss > 1.5 mm and BoP	1.5		BoP	1	2.1%
11	Self-reported definition 6	Bone loss > 2 mm and BoP/Sup	2		BoP/Sup	6	2.1%
13	Self-reported definition 8	Bone loss > 3mm, PPD > 5mm and BoP/Sup	3	5	BoP/Sup	1	0%
14	Self-reported definition 9	PPD > 6 mm and BoP/Sup		6	BoP/Sup	1	0%
15	Self-reported definition 10	1) Bone loss > 0,5 mm and BoP	0.5 or 2		BoP	1	10.4%
		2) Moderate/severe = bone loss > 2mm and BoP					2.1%

Table 2: Overview of the 6 different definitions for peri-implantitis not applicable on our own data.

Definition number	Reference	Definition of peri-implantitis	Cut-off bone loss (mm)	Cut-off PPD (mm)	BoP/Sup	Frequency distribution of definition	Why not applicable
2	Albrektsson and Isidor 1994: 1st EWOP	Inflammatory reactions associated with loss of supporting bone around an implant in function			BoP	1	No cut-off bone loss
4	Lindhe and Meyle 2008: 6th EWOP	A mucosal lesion often associated with suppuration and deepened pockets, but always accompanied by loss of supporting marginal bone			BoP/Sup	2	No cut-off probing pocket depth
6	Self-reported definition 1	Inflammatory lesion in the peri-implant mucosa, associated with plaque, BoP and radiographic evidence of bone loss at mesial or distal aspect of implants			BoP	1	Plaque not used as parameter in study IV
7	Self-reported definition 2	Significance bone loss, PPD ≥ 4mm and BoP		4	BoP	1	No cut-off bone loss
8	Self-reported definition 3	Crater-like bone defect, PPD ≥ 4mm and BoP/Sup		4	BoP/Sup	1	No cut-off bone loss,
12	Self-reported definition 7	Bone loss ≥ 2.5mm, PPD ≥ 6mm, profuse bleeding/ suppuration and pain	2.5	6	BoP/Sup	1	No registration of pain in study IV

and only one had bone loss above 2.5 mm. One should consider that these bone loss measurements are calculated with the date of placement as the baseline, hence including initial bone remodeling after surgery. The strict follow-up and regular check-ups of the patients may add to good compliance and consequently to the good peri-implant health assessed in the study.

Table 3: Implant distribution of study IV at 5 years according to calculated bone level and probing pocket depth; numbers between brackets show implants with bleeding on probing.

Probing pocket depth (mm)	Bone level (mm)						
	<0.5	0.5 - 0.99	1.00 - 1.49	1.50 - 1.99	2.00 - 2.49	≥ 2.5	**Total**
≤1	1	1	0	0	0	0	2
1.1 - 2.0	17 (9)	2 (1)	3 (1)	0	0	1	23 (11)
2.1 - 3.0	17 (8)	4 (2)	0	0	1 (1)	0	22 (11)
3.1 - 4.0	1 (1)	0	0	0	0	0	1 (1)
4.1 - 5.0	0	0	0	0	0	0	0
> 5.0	0	0	0	0	0	0	0
Total	36 (18)	7 (3)	3 (1)	0	1 (1)	1	48 (23)

More recently, new definition for peri-implantitis were given by the 2017 Consensus report of the World Workshop on the classification of Periodontal and Peri-Implant Diseases and Conditions.[10] This consensus report was not available yet at the moment of preparation of Study I and II. Using the new internationally accepted criteria with bone levels ≥ 3mm apical of the most coronal portion of the intraosseous part of the implant and/or probing depths ≥ 6 mm, the prevalence of peri-implantitis on implant level in **Study III, IV and V** is 0%.

In addition, **Study I** was critically appraised in the 5th EAO Consensus Conference and used for clinical recommendations and research directions.[11] The panel of experts highlighted the importance of an internationally accepted case definition for peri-implantitis. Without accepted international definitions, evidence-based knowledge on the prevalence of peri-implantitis is lacking. Moreover, the panel addressed the debate on the diagnostic validity of probing pocket depth and bleeding on probing. These parameters are accepted evidence-based tools to diagnose and define periodontal health and disease. However, these parameters may not have the same diagnostic value for the diagnosis of peri-implantitis. Therefore, the second part of **Study I** focussed on the correlation between the prevalence of peri-implantitis and the biologic parameters mean bone loss, mean probing pocket depth and mean bleeding on probing. In addition, we

also examined how mean bone loss correlated with mean probing pocket depth and mean bleeding on probing. No significant correlation was found between mean bone loss and the prevalence of peri-implantitis. The results showed no significant correlation between mean bleeding on probing and prevalence of peri-implantitis or mean probing pocket depths and prevalence of peri-implantitis. The panel of experts advised in their research directions that the use of the currently available diagnostic tools, reporting mean or median values of diagnostic parameters is not sufficient per se to describe the extent of biologic complications in epidemiologic research. Therefore, future studies should report (1) a case definition that is internationally accepted, (2) validated assessments (repeated measurements, calibrated examiners), (3) baseline registrations for probing pocket depth, bleeding on probing, and bone level, (4) frequency distributions combining the different diagnostic parameters, and (5) percentage of disease according to case definition, based on the implant and patient level. This extensive reporting makes it possible to compare studies and include more studies in meta-analyses. This, in turn, could lead to a more precise estimate of the extent of biologic complications and a smaller prevalence range of peri-implantitis given in the literature.

Clinical Implant Outcome

Initially a total of 196 implants were included in the three clinical studies presented in the thesis (**Study III – V**). Table 4 gives an overview of all the included implants regarding implant survival and crestal bone level at the latest follow-up visit. Only **Study V** showed four early failures, possibly caused due to overloading of non-splinted implants. The overall survival of all implants included in this study was 98.0%. This survival rate is comparable with the results described in the systematic reviews (**Study I and II**). These systematic reviews included respectively 9,457 and 15,695 implants and reported an overall weighted survival rate of respectively 96.9% and 97.3%. This is in accordance with other earlier published RCT's and systematic reviews.[12-14]

At the latest follow-up visit the mean crestal bone level for the different study groups of **Study III, IV, and V** ranged between 0.12 and 0.62 mm. In all groups the median was lower than the mean, indicative that the mean was influenced by a few implants with more extensive bone loss. As previously discussed, the mean is not an adequate measure for peri-implant health or disease. The median,

Table 4: Implant survival and bone level at latest follow-up visit of the 3 clinical studies

		#Patients at intake	#Initially placed implants	Latest follow-up (months)	#Implants at latest follow-up	Bone level at latest follow-up visit			#Implant loss during osseo-integration	#Implant loss after osseo-integration	Survival per study on implant level
						Mean (SD)	Median	Range			
Study III	Moderately rough implant neck	23	23	36	21	0.50 (0.74)	0.22	(0.00 - 2.84)	0	0	100%
	Minimally rough implant neck	23	23	36	21	0.45 (0.58)	0.26	(0.00 - 1.95)	0	0	
Study IV	Equicrestally placed implants	26	26	60	24	0.62 (0.66)	0.44	(0.00 - 2.66)	0	0	100%
	Subcrestally placed implants	26	26	60	24	0.12 (0.22)	0.00	(0.00 - 0.86)	0	0	
Study V	Internal connection with microthreads	25	24	36	20	0.50 (0.52)	0.36	(0.00 - 2.08)	0	0	95.6%
	Internal connection without microthreads	25	25	36	21	0.43 (0.62)	0.21	(0.00 - 2.47)	1	0	
	External connection with microthreads	25	25	36	21	0.40 (0.54)	0.26	(0.00 - 1.80)	1	0	
	External connection without microthreads	25	24	36	20	0.52 (0.56)	0.40	(0.00 - 1.93)	2	0	
TOTAL			196		172				4	0	98.0%

interquartile range, and maximum bone loss at the latest follow-up visit are given in figure 1. None of the implants had a bone level over 3 mm and only five implants showed a bone level above 2 mm. In all treatment groups 75% of the implants, represented by the first three quartiles, showed a bone level of less than 1 mm after respectively 36 months for **Study III** and 60 months for **Study IV**.

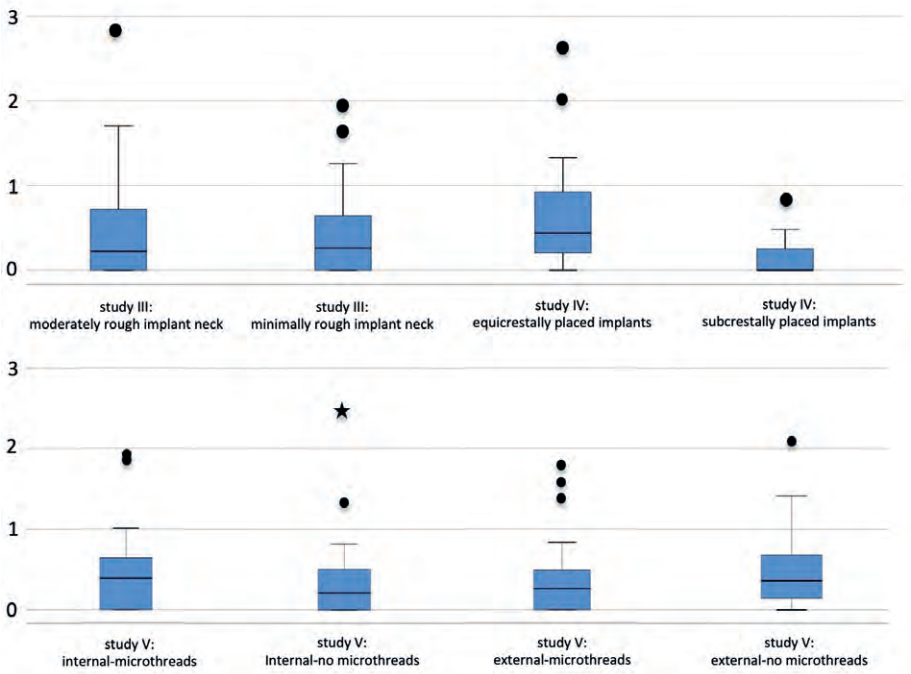

Figure 1: Boxplots representing bone level at the latest follow-up visit of the 3 clinical studies. * Outliers (≥ 3×IQR above third quartile), ° suspected outliers (between 1.5 and 3×IQR above third quartile)

PATIENT-RELATED FACTORS

The meta-analysis of **Study II** concluded that 'smoking' and 'history of periodontitis' yielded significantly more crestal bone loss. This is in agreement with the available literature. Besides more crestal bone loss, the above-mentioned patient-related factors also affected implant survival.[15-25] Smoking and untreated periodontitis were exclusion criteria for the clinical studies of this thesis, which could explain the low failure rate (table 3).

IMPLANT-RELATED FACTORS

The systematic review and meta-analysis of **Study II** focussed on the long-term effect of implant surface roughness on peri-implant bone stability. Only 3 out of the 87 included studies were appropriate for inclusion in the meta-analysis.[26-28] The result showed a significant difference in the long-term mean bone loss between minimally rough versus moderately rough and minimally rough versus rough implant systems. However, there was no significant difference between moderately and rough surfaces.

Shortly after the publication of **Study II**, Donati and co-workers published a 20-year follow-up of an RCT evaluating minimally rough and moderately rough implant surfaces.[29] Their results showed no statistically significant difference in mean bone level change between the two implant surfaces. A more detailed analysis of the results showed that 10% of the moderately rough implants lost more than 3 mm bone compared to 0% of the minimally rough implants. The authors reported a peri-implantitis incidence of respectively 16% and 6%. Another systematic review that evaluated the effect of implant collar surface on marginal bone loss,[30] revealed less bone loss for rougher implant systems. However, 10 out of the 12 studies were short term (less than five years in between follow-up). The only study with 10 years of follow-up showed less bone loss for the implants with a smooth collar compared to the implants with a rough collar. Moreover, the authors stated that their results needed to be interpreted with caution, due to confounding factors in the included papers.

As can be seen, more research is required to confirm the effect of implant surface roughness on peri-implant bone stability. However, the implant-industry did not wait for this research confirmation but recently developed a hybrid dental implant designs. This hybrid dental implant combine the presumably positive effect of minimally rough surface on bone stability and less susceptibility to develop peri-implantitis.[31] These benefits were confirmed in several Cochrane reviews.[32,33] The moderately rough surface is known to yield a greater bone-to-implant contact area, leading to faster osseointegration. Therefore, **Study III** compared a commercially available implant with an experimental hybrid implant in a split-mouth design, correcting for inter-individual variability, to test bone and soft tissue stability. Both implants were from the same brand and all design features of the implant were

similar except the roughness of the implant neck to control confounding factors (Figure 2).

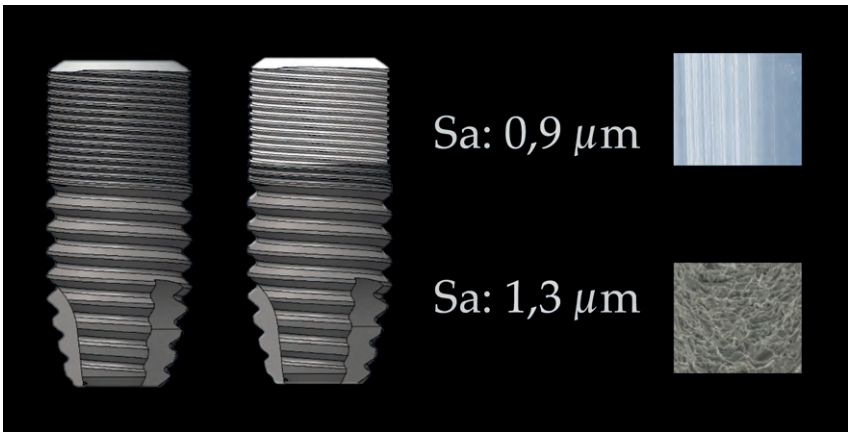

Figure 2: Study implants of study III, moderately rough surface implant (right) and hybrid surface with minimally rough coronal part and moderately rough implant body (left)

Study III concluded that there was no effect of the implant surface roughness on bone level up to three years and, none of the implants was diagnosed with peri-implantitis. A recent systematic review and meta-analysis concluded that implants with a rough surface in patients with a history of periodontal disease showed lower implant survival and higher crestal bone loss than in patients without a history of periodontal disease. [34] However, implants with a minimally rough surface responded similarly irrespective of periodontal history. It is tempting to conclude that a hybrid-implant system may be beneficial in patients with a higher individual risk for implant loss or peri-implantitis.

Study V focussed on macro design features with respect to bone stability and peri-implant health, namely, the effect of microthreaded versus non-microthreaded implant neck. In addition, we investigated the effect of implant-abutment connection, namely internal conical versus external flat-to-flat. For this purpose, a commercially available implant was compared with three specially produced experimental implants. All design features of the implant were similar except one to minimize confounding factors. A split-mouth study design was used to correct for inter-individual variability. After implant placement regular follow-up visits were planned at 3, 6, 12, 24, and 36 months, to ensure that the patients were

well compliant with maintenance. Statistical analysis was performed during three visits, namely directly after implant placement (t0, baseline), at 6 months (t1, initial remodeling), and at 36 months (t2). However, most visits planned according to protocol at 36 months (t2) were postponed due to the COVID-19 pandemic. This explains the mean follow-up time of 45.5 months (SD 4.82, range 35 – 58).

After initial bone remodeling due to biologic width establishment, the linear mixed-model analysis applied in this study showed no clinically relevant effect of the implant type on the bone level at t1 and t2. Although the implant position (posterior versus anterior) showed a significant effect on the bone level at t1 in favour of a posteriorly placed implant, the confidence limits (-0.365, -0.060) are suggestive of a clinically irrelevant difference. Moreover, we found no effect of implant position at t2. Between t1 and t2, all implant types showed no further relevant bone level change, indicative of a stable bone level once initial bone remodeling took place. Some implants with high bone loss at t1 showed bone gain at t2. This latter could be explained by the effect of splinting the implants with a titanium bar after t1. A similar positive effect of splinting the implants was described earlier by De Bruyn and co-workers.[35]

Regarding the implant-abutment connection the results of the present study are not in accordance with a systematic review and meta-analysis.[36] Based on 11 studies, the authors concluded that internal connections had lower marginal bone loss when compared to external connections. However, several of the included studies used a study design that did not control for confounding factors, such as design factors like implant brand, implant surface, thread design, and platform-shift. Due to the presence of more than one different design factor between the study implants, these results should be interpreted with caution.

Two other systematic reviews also concluded that internal connections exhibit lower marginal bone loss than implants with external connections. However, they discussed that these findings are probably related to platform switching, which is more frequently found in implants with internal connections.[37,38]

A systematic review with meta-analysis concluded that a microthreaded neck reduces the amount of marginal bone loss.[39] The three RCTs in the meta-analysis represent in total 57 implants in each treatment group in only partially edentulous

patients. Only two out of the three studies found a statistically significant difference in marginal bone loss favouring the implants with microthreaded neck design. However, the difference was only -0.09 mm with a 95%CI of -0.18, -0.01. Thus, it is questionable if this statistically significant difference is clinically relevant. Furthermore, the authors of the meta-analysis concluded that the evidence was insufficient to draw a definite conclusion on the effect of the microthread design because too few RCTs with low risk for bias were available. Moreover, they suggested that more RCTs with adequate control for confounding factors for design are needed because many studies have compared other designs in addition to the microthread design. To our knowledge, no more recent meta-analyses or RCTs other than the present study population could be found on PubMed when the search string '(microthread) AND (implant)' was used. The results from our paper confirm and strengthen the outcome described in the available meta-analysis.

It is noteworthy that the results in **Study III and Study V** have been established with the precondition that (1) due to the use of the specific abutment, a platform-shift between implant and abutment was created and (2) all implants were placed in relation to the soft tissue thickness. A large meta-analysis on 28 publications with 1,216 platform-shifted implants and 1,157 non-platform-shifted implants showed a significant effect on marginal bone loss favouring platform-shifted implants. However, the authors also suggested a careful interpretation of the results due to uncontrolled confounding factors.[40]

SITE-SPECIFIC FACTORS

The effect of adapting the vertical position of the implant in relation to soft tissue thickness was investigated in a part of **Study III** and in **Study IV.**

The difference in this study population in mean bone level between equicrestally and subcrestally placed implants at 6 months was 0.68 mm. The 95% confidence interval of the mean showed a 95% chance that the mean difference in the true population would be between 0.36 and 1.00 mm. Even the lower number of the mean difference of the true mean is already suggestive for clinically relevant differences in mean bone level. For all other time intervals, the same conclusion could be made.

Compared to the three-years follow-up of **Study III** no further changes occurred regarding peri-implant bone stability and peri-implant health.

A recent systematic review and meta-analysis of 16 studies concluded in a quantitative analysis that subcrestal and equicrestal implant placement yielded comparable peri-implant bone loss.[41] However, in the presence of a thin tissue, a subcrestal placement of the implant is preferred, because it may reduce the risk for implant exposure in the future, thus avoiding peri-implant pathologies. More studies suggested a certain minimum width of peri-implant mucosa as a prerequisite, allowing a stable soft tissue attachment.[42-46] The results of **Study III and IV** are in line with the aforementioned papers. Hence, one should anticipate the preferred biologic width establishment to prevent early implant surface exposure caused by initial bone remodeling by adopting implant depth positioning in relation to soft tissue thickness.

Radiographic analysis of the subcrestally and equicrestally placed implants showed a minimal bone loss over time after the initial bone remodeling, although it was not clinically relevant. The findings of **Study III and IV** are in accordance with earlier published papers, showing comparable results for peri-implant bone stability in patients treated with a two-implant overdenture in the mandible.[47-49]

Part of **Study III** and **Study IV** showed that equicrestally placed implants yielded significant more bone loss during initial remodeling. The boxplot representation in **Study IV** showed that 75% percent of the equicrestelly placed implants had a bone level between 0 and almost 1 mm at 6 months. Moreover, 25% of this treatment group showed a bone level between 1 and 2.45 mm, resulting in a median bone level of 0.59 mm compared to a median bone level of 0.00 mm for the subcrestally placed implants. One could conclude a higher risk for implant surface exposure to the soft tissues in the equicrestally placed implant group.

There was no statistically significant difference in bone level change between 6 and 60 months, despite direct exposure of the implant threads. One should keep in mind that all patients in the present study were fully edentulous and compliant with oral hygiene. Whether this outcome is also valid in non-compliant patients is questionable, as suggested by scarce evidence. It is improbable, that scientifically sound, randomized controlled trials in humans could be initiated in non-compliant

patients, given the unethical approach this would require. Namely, regular peri-implant maintenance therapy is mandatory to prevent biologic complications and ameliorates the long-term success rate. The positive effect of regular peri-implant maintenance therapy has been described in a systematic review with meta-analysis by Monje and colleagues.[50]

ORAL HEALTH-RELATED QUALITY OF LIFE

Study III and Study IV included measuring the change in OHRQoL for patients treated with an implant-supported overdenture in the mandible. The outcome of the OHRQoL is in line with earlier published papers. All papers indicated the superiority of an implant-supported overdenture over a conventional complete denture regarding the quality of life.[4,51-53] Moreover, a recently published paper investigating the difference in OHRQoL between patients with an implant fixed complete denture and patients with an implant overdenture did not find a significant difference in OHIP-49 score.[54] The findings mentioned above confirm the McGill consensus statement, where it is stated that an implant-retained overdenture is the first choice of treatment for the edentulous mandible.[55]

STUDY LIMITATIONS

An important limitation in the clinical studies of this thesis could be the relatively short follow-up time. As described in **Study II** the bone level changes due to disease may take some years before being diagnosed clinically.[56] Hence, a longer follow-up of the study population of **Study III** and **Study V** is required to assess the long-term effect of implant-related factors on the prevalence of peri-implantitis. On the other hand, a recent study by Windael and colleagues assessed fixed implant bridges on five to eight implants in fully edentulous jaws. They suggested that bone loss at two years is a predictor for bone loss at ten years.[57] The **Studies III, IV** and **V** showed a minimum bone loss in the first six months and hardly any bone loss after initial remodeling up to the last follow-up visit. Moreover, concerning the study of Windael and colleagues, it could be expected that performing good oral hygiene is easier for patients treated with a removable overdenture compared to those restored with a fixed bridge. Provided that professional maintenance and

compliance is taken care of, it is to be expected that further bone level changes related to the implant design are limited.

Another limitation in the clinical trials presented in this thesis is the number of included patients. This number is often limited because of financial reasons. On the other hand, the follow-up time and number of patients in **Study III, IV and V** are comparable to samples included in other papers in the field.[36-39] Moreover, the applied split-mouth design of the studies may help to minimize the aforementioned limitations.

GENERAL CONCLUSIONS

1. Various peri-implantitis definitions are used in the literature, and reporting of biological parameters is often incomplete. Consistent reporting of peri-implantitis is required for scientific purposes as well as for clinical practice.
2. The peri-implantitis prevalence based on various case definitions did not correlate with the diagnostic parameters 'mean probing pocket depth', 'mean bleeding on probing', and 'mean bone loss'. The survival rate showed a substantial correlation with function time, but implant loss over time is low.
3. In the current literature, less than 5% of the implants showed bone loss above 3 mm after at least five years in function. This result was independent of surface or implant brand, suggesting that currently reported peri-implantitis prevalence is exaggerated.
4. Rough implant systems are more prone to crestal bone loss. However, the multifactorial cause for bone loss and the heterogeneity of the studies make it difficult to draw firm conclusions. Nevertheless, more papers show less bone loss in favour of minimally rough implant systems.
5. Co-factors such as smoking or a history of periodontal disease increase the risk of bone loss.
6. The implant neck design (microthreaded vs non-microthreaded) has no influence on peri-implant bone remodeling when implants are installed in relation to soft tissue thickness allowing the formation of a 3 to 4 mm biological seal.
7. The implant-abutment connection type (internal vs external) has no

influence on peri-implant bone remodeling when implants are installed in relation to soft tissue thickness allowing the formation of a 3 to 4 mm biological seal.

8. Implant surface roughness (minimally rough vs moderately rough) influences peri-implant bone remodeling nor additional bone loss when implants are installed in relation to soft tissue thickness allowing the formation of a 3 to 4 mm biologic seal.
9. Peri-implant health parameters (probing pocket depth, bleeding on probing, and plaque score) are not affected by implant design, surface texture, or abutment-connection features when implants are installed in relation to soft tissue thickness.
10. Anticipating biologic width re-establishment by adapting the vertical position of the implant in relation to the available soft tissue thickness may prevent initial peri-implant bone loss.
11. In a well-maintained population, the effect of early implant surface exposure caused by initial bone remodeling on peri-implant bone stability and biological parameters seems to be limited.
12. Implant-supported mandibular overdentures significantly improve the quality of life, with little biological complications and a high survival rate of the implants.

FUTURE RESEARCH RECOMMENDATIONS

Based on the conclusions of this thesis the following research recommendations are given.

1. An internationally accepted panel of experts, such as the EAO, EWOP and ADA, need to provide research guidelines with a minimum of required parameters necessary for the publication of a clinical study. Based on these guidelines and in relation to scientific integrity, the author, reviewer, editor and publisher share the responsibility that clinical data of published studies are suitable and accessible for further analysis in systematic reviews and meta-analysis.
2. Given that mean values are not sufficient to describe the extent of biological complications and disease, implant research concerning peri-implant health minimally requires:

- Baseline registration and further measurement of bone level, probing pocket depth, bleeding on probing and plaque at well-defined time intervals
- An internationally accepted case definition for disease
- The percentage of disease according to the case definition, based on implant level and patient level
- Proper statistical analysis

3. Clinical studies presented in this thesis need to be prolonged to describe the long-term outcome of implant-related factors, site-specific factors, and early implant surface exposure on crestal bone loss, biologic parameters, and implant survival.
4. For hybrid implant systems, the length of the coronal smooth part needs to be examined.
5. Clinical studies, reflecting the reality of daily practice, are needed to determine whether hybrid-implant systems and macro design modifications are beneficial in patients prone to peri-implantitis.

CLINICAL RECOMMENDATIONS

The following clinical recommendations based on the results of this thesis and the included literature could be given.

1. Peri-implantitis diagnosis should be made on more than one clinical parameter. Preferably, crestal bone loss or the crestal bone level and bleeding measurement around the implant are used.
2. The baseline radiograph should be made after crestal bone remodeling due to biologic width reestablishment. This results in a timeline of 3 to 6 months after implant surgery in a one-stage procedure and 3 to 6 months after second-stage surgery.
3. Implants should be installed regarding the soft tissue thickness to prevent early surface exposure due to biologic width reestablishment. The advice is to take at least 3 to 4 mm soft tissue thickness into account.
4. When bone level implants are placed, the use of an implant system with a platform shift between the implant and abutment is advised.
5. In risk patients, the use of a hybrid implant system is likely beneficial.
6. Implant treatment, including peri-implant maintenance therapy, should

be carried out by a team of dental care professionals including oral hygienists, general dentists, prosthodontists and periodontists. It is important to work with clear guidelines accepted by all dental care professionals and emphasize effective communication between each of these professionals.

SOCIAL RELEVANCE

Implant dentistry is becoming more challenging in its complexity. Firstly, patients become more demanding, not only with high expectations in terms of functionality, but also in terms of aesthetics and costs. Secondly due to the increase of implant manufactures, all with different implant designs, claiming to be the best. In daily practice the dental surgeon needs to deal with the constant pressure of new products on the market. They must choose from all these implant manufacturers based on their own preferences, costs, the service of the company, and scientific evidence. Most of the time, sound scientific evidence of new design features is missing when the product is launched on the commercial market. This makes it questionable if the changes are beneficial for the patient, if they fulfil the patient's higher expectations and if these changes are made out of commercial interest. On the other hand, some design improvements in the past led to better implant survival and an improvement in crestal bone stability.

This thesis tried to give a critical reflection, out of an evidence perspective, on implant design. The outcome is that not implant design but biological factors take precedence in the successful outcome of implant therapy. Hopefully, this thesis could make implant treatment less complex for the dental surgeons by showing that not the choice of implant manufacturer or design defines the success of implant surgery, but rather proper education and understanding of the reactions of oral tissues on implant surgery.

In addition, this thesis tried to clarify the problems that exist when the field lacks an internationally accepted definition for peri-implantitis. Nowadays, it is still difficult to give a clear answer to the patient about how big the risk of peri-implantitis is. Moreover, it could harm the good reputation of implant treatment if scientific papers with high percentages of peri-implantitis based on poor definitions are used in the media.

PERSONAL REFLECTION ON RESEARCH

In this final paragraph of the general discussion, I want to ask attention to an article published in the Guardian in May 2015 (Will traditional science journals disappear?). This article promoted a new way of publishing, which can overcome the problems I faced in **Study I and Study II**. These two literature studies showed that nowadays the number of publications is high. However, the number of included studies in meta-analyses remains low. This is often related to the exclusion of many studies based on inconsistent study designs or incomplete data reporting. The article in the Guardian suggested that it could be valuable to improve research design of studies prior to the start of the study rather than criticizing studies once they have been done.

In addition, the paper pleaded for more transparency between the planned scientific approach and the exploratory analyses based on the registration of the research plan. Once the research plan is reviewed the protocol can be executed. The article highlighted two more advantages after publication of the study protocol. Firstly, the researcher can solicit collaborators for the study. This can overcome the important limitation of underpowered studies. Secondly, collaborative working or multicentre studies generally enhance the reproducibility of findings. When the study is completed, the editor could do the review by checking that the authors have followed the protocol. If the latter is done, no further review is required.

In my opinion, the advantages of publishing in this way are considerable: it brings the scientific community together, makes it more transparent, can stop the overload of studies with mediocre data analysis, and increases the power of the studies, leading to clearer answers to the research questions. Moreover, when centres work together, logistics and knowledge will be shared, resulting in high-quality studies and reduced costs for society.

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CHAPTER 9

SUMMARY IN ENGLISH

SUMMARY IN DUTCH

LIST OF ABBREVIATIONS

SUMMARY

Over the last decade, the focus of clinical implant research shifted from predominately survival orientated to peri-implant health and patient-centred outcomes. A stable peri-implant bone level is a prerequisite to achieve long-term implant success. Peri-implant bone level is affected by patient-, implant-, and site-specific factors. In addition, the success of an implant treatment could also be determined by the improvement in Oral Health-Related Quality of Life (OHRQoL). The introduction **(Chapter 1)** scrutinizes and clarifies the current literature focusing on these factors. The existing literature gives an ambiguous effect of implant-related and site-specific factors on peri-implant bone stability, showing the need for more research.

Chapter 2 presents the aims of this dissertation. This thesis's first two literature studies **(Chapter 3 and 4)** systematically assessed the available scientific evidence. The assessment focused on whether commonly used biological parameters correspond to long-term outcomes of implant survival and reported peri-implantitis prevalence. Additionally, it also examined whether long-term peri-implant bone loss is affected by implant surface roughness. The clinical studies in this thesis **(Chapter 5, 6, and 7)** aimed to evaluate the effect of implant related factors such as implant micro-design (implant surface roughness), macro-design (microthreads and implant-abutment connection), and site-specific factors (soft-tissue thickness) on long-term peri-implant bone stability and peri-implant health. Additionally, we paid attention to the Oral Health-Related Quality of Life in patients restored with mandibular implant-retained overdentures.

Chapter 3 (Study I) is a critical review of the literature published between 2011 and 2017, regarding the biological peri-implant parameters bleeding on probing, probing pocket depth, and bone loss. The search algorithm highlighted 4,173 papers available for further analysis, 255 papers for full article reading, and 41 fulfilled the inclusion criteria. In these 41 articles, 15 different case definitions for peri-implantitis were used. The reported prevalence of peri-implantitis ranged between 0% and 39.7%, with an overall mean weighted implant survival rate of 96.9% (89.9% - 100%).

Based on 8,182 implants, the overall weighted mean bone loss was 1.1 mm after a loading time ranging from 5 to 20 years. The mean bone loss did not correlate with the reported prevalence of peri-implantitis, and the diagnostic parameters mean probing pocket depth and mean bleeding on probing. Moreover, the reported peri-implantitis prevalence did not correlate with mean probing pocket depth. However, a strong correlation was found between the reported prevalence of peri-implantitis and bleeding on probing. The survival rate showed a substantial correlation with function time, showing minor implant loss over time. We concluded that the case definition for peri-implantitis varied significantly between studies, indicating that an unambiguous definition based on a specified threshold for bone loss is not agreed upon in the literature.

Chapter 4 (Study II) scrutinized the literature on long-term peri-implant bone loss and the relation with implant surface roughness and patient-related factors such as smoking and history of periodontitis. Implant systems are categorised based on the surface roughness expressed in Sa-value; minimally rough (Sa value: 0.5 – 1 µm), moderately rough (Sa value: 1 – 2 µm), and rough (Sa value: > 2 µm). In implant dentistry's early days, only minimally rough and microporous titanium plasma-sprayed rough implant systems were available.

However, over time several implant modifications were done by sandblasting, acid-etching, anodic oxidation, or hydroxyapatite coating resulting in a moderately rough implant system. These modifications improved the osteoconductive and osteoinductive properties of the implant. The surface of the moderately rough implant system showed better blot cloth stabilisation, enhanced production of biological mediators, stimulate osteogenic maturation leading to higher bone-to-implant contact, and increased bonding strength of the bone to the implant. On the other hand, rougher implant systems are linked to increased bacterial adhesion with a higher risk of being affected by peri-implantitis.

The search yielded 2,566 studies and 156 were selected for further reading. Only 87 reported information about surface roughness of the implants and mean bone loss after at least five years of function. In these papers in total 15,695 implants were inserted in 6,755 patients. The average weighted survival rate for these implants was 97.3% after at least 5 years of function. If 3 mm bone loss was used as a threshold to quantify peri-implantitis, less than 5% of the implants were affected.

Regarding implant surface roughness, the systematic review suggests that peri-implant bone loss around minimally rough implant systems was statistically significantly less than the moderately rough and rough implant systems. No statistically significant difference was observed between moderately rough and rough implant systems. The meta-analyses showed less average peri-implant bone loss around smoother surfaces. However, due to the heterogeneity of the papers and the multifactorial cause for bone loss, the impact of surface roughness alone seems somewhat limited and of minimal clinical importance. In addition, the meta-analysis showed that smoking and history of periodontitis increased the risk for bone loss.

Chapter 5 (Study III) includes two prospective split-mouth studies. Both studies included edentulous patients in need of a two-implant-supported overdenture in the mandible. The first part of **Study III** described the effect of the site-specific factor 'soft-tissue thickness' on crestal bone remodeling and peri-implant health. Twenty-six patients received two moderately rough implants. According to the manufacturer's guidelines, the control implant was installed equicrestally. The test implant was placed below crestal level to ensure at least 3 mm space for biologic width establishment on the abutment part. Initially, 26 patients were treated with one equicrestally and one subcrestally placed implant. After 36 months, 24 patients were available for follow-up.

The second part of **Study III** determined the effect of implant surface roughness on crestal bone remodeling. As concluded in **Study II**, crestal bone loss might be related to the implant surface roughness. The existing literature suggests higher survival rates for moderately rough implants compared to minimally rough implants. On the other hand, recent literature and the findings of **Study II** suggest that implants with a minimally rough surface yield less long-term crestal bone loss.

An implant with a hybrid surface combines the benefit of a moderately rough implant body and a minimally rough implant neck. To determine the effect of implant surface roughness on crestal bone loss, 23 patients received two implants: an implant with a moderately rough surface (Sa value: 1.3 µm) and a hybrid implant with a minimally rough coronal neck of 3 mm (Sa value: 0.9 µm) combined with a moderately rough body (Sa value: 1.3 µm). Apart from the difference in implant

surface roughness, the two implants were identical. After 36 months, 21 patients were available for follow-up.

The implant survival rate was 100% after 36 months. No differences were observed in crestal bone remodeling between the hybrid and moderately rough implant. However, initial bone remodeling was affected by initial soft tissue thickness because the equicrestal implants had implant threads exposed above bone level. Anticipating the biological width re-establishment by adapting the vertical position of the implant in relation to the available soft tissue thickness may prevent that implant threads are not fully covered by peri-implant bone. However, long-term follow-up of the study is necessary to determine the influence of early implant surface exposure and implant surface roughness on crestal bone loss, biological parameters, and implant survival.

Study III also included Oral Health-Related Quality of Life for edentulous patients restored with a two-implant-supported mandibular overdenture. This patient-centred outcome was assessed with the Oral Health Impact Profile-14 (OHIP-14). The study concluded that a two-implant-supported mandibular overdenture in comparison with a conventional removable denture yields a significant improvement in the quality of life.

Chapter 6 (Study IV) presented the five-year follow-up of the first part of study III, determining the effect of soft tissue thickness on crestal bone remodeling and peri-implant health. Twenty-four patients were available for the five-year follow-up. The survival rate was 100%, and only one implant showed a mean bone level higher than 2 mm. During initial bone remodeling equicrestal placement yielded 0.68 mm additional surface exposure compared to subcrestal placement. Afterwards, bone level and peri-implant health were comparable in both treatment conditions and stable up to five years. Hence, **Study IV** concluded that adapting the vertical position of the implant concerning the soft tissue thickness prevents early implant surface exposure caused by initial bone remodeling. However, in a well-maintained population, this has no impact on long-term prognosis. In addition, the Oral Health-Related Quality of Life was assessed using the Oral Health Impact Profile-14 (OHIP-14), concluding a stable Oral Health-Related Quality of Life over time.

Chapter 7 (Study V) determines the effect of implant neck (microthreaded versus non-microthreaded) as well as the type of connection (internal conical versus external flat-to-flat) on peri-implant bone stability and peri-implant health. According to the literature, peri-implant bone loss is minimized on implants with microthreaded neck design and internal type of abutment connection, albeit that many clinical studies are biased due to confounding factors.

Twenty-five patients were treated with a maxillary implant-supported bar-retained overdenture on four different implant types. Each patient received one implant with an internal connection with microthreads (I MT), one with an internal connection without microthreads (I NMT), one with an external connection with microthreads (E MT), and one with an external connection without microthreads (E NMT). Other design features, as well as surgical and prosthetic protocol, were consistent.

After at least 36 months, the survival rate was 96%. It was concluded that the implant-abutment connection type (internal vs external) and the implant neck design (microthreaded vs non-microthreaded) have no clinical effect on peri-implant bone remodeling, peri-implant bone level after the initial remodeling. Furthermore, it also had no clinical effect on peri-implant health parameters, at least when implants are installed according to soft tissue thickness.

Chapter 8 is the general discussion and includes clinical and future research recommendations. In addition, it highlights the social relevance of the undertaken scientific work in conjunction with a personal reflection. This PhD thesis concludes that:

1. Various peri-implantitis definitions are used in the literature, and reporting of biological parameters is often incomplete. Consistent reporting of peri-implantitis is required for scientific purposes as well as for clinical practice.
2. The peri-implantitis prevalence based on various case definitions did not correlate with the diagnostic parameters 'mean probing pocket depth', 'mean bleeding on probing', and 'mean bone loss'. The survival rate showed a substantial correlation with function time, but implant loss over time is low.
3. In the current literature, less than 5% of the implants showed bone loss above 3 mm after at least five years in function. This result was independent

of surface or implant brand, suggesting that currently reported peri-implantitis prevalence is exaggerated.

4. Rough implant systems are more prone to crestal bone loss. However, the multifactorial cause for bone loss and the heterogeneity of the studies make it difficult to draw firm conclusions. Nevertheless, more papers show less bone loss in favour of minimally rough implant systems.
5. Co-factors such as smoking or a history of periodontal disease increase the risk of bone loss.
6. The implant neck design (microthreaded vs non-microthreaded) has no influence on peri-implant bone remodeling when implants are installed in relation to soft tissue thickness allowing the formation of a 3 to 4 mm biological seal.
7. The implant-abutment connection type (internal vs external) has no influence on peri-implant bone remodeling when implants are installed in relation to soft tissue thickness allowing the formation of a 3 to 4 mm biological seal.
8. Implant surface roughness (minimally rough vs moderately rough) influences peri-implant bone remodeling nor additional bone loss when implants are installed in relation to soft tissue thickness allowing the formation of a 3 to 4 mm biologic seal.
9. Peri-implant health parameters (probing pocket depth, bleeding on probing, and plaque score) are not affected by implant design, surface texture, or abutment-connection features when implants are installed in relation to soft tissue thickness.
10. Anticipating biologic width re-establishment by adapting the vertical position of the implant in relation to the available soft tissue thickness may prevent initial peri-implant bone loss.
11. In a well-maintained population, the effect of early implant surface exposure caused by initial bone remodeling on peri-implant bone stability and biological parameters seems to be limited.
12. Implant-supported mandibular overdentures significantly improve the quality of life, with little biological complications and a high survival rate of the implants.

SAMENVATTING

In het afgelopen decennium is de focus van klinisch implantaatonderzoek verschoven van overwegend overlevingsgericht onderzoek naar onderzoek met de focus op de gezondheid van de weefsels rondom de implantaten en patiëntgerichte uitkomsten. Een stabiel botniveau rondom het implantaat is een voorwaarde voor een succesvolle implantaatbehandeling op de lange termijn. Het botniveau rondom het implantaat wordt beïnvloed door patiënt-, implantaat- en plaats-specifieke factoren. Daarnaast zou het succes van een implantaatbehandeling ook bepaald kunnen worden door de verbetering van de 'Oral Health-Related Quality of Life' (OHRQoL). In de introductie **(hoofdstuk 1)** wordt de bestaande literatuur met betrekking tot bovengenoemde factoren onder de loep genomen en verduidelijkt. Deze literatuur geeft geen eenduidig effect van implantaat gerelateerde en plaats-specifieke factoren op de botstabiliteit rondom het implantaat. De afwezigheid van een eenduidig effect toont de noodzaak van meer onderzoek.

Hoofdstuk 2 beschrijft de doelstellingen van dit proefschrift. De eerste twee literatuurstudies van dit proefschrift **(Hoofdstuk 3 en 4)** evalueerden systematisch het beschikbare wetenschappelijke bewijs omtrent de onderzoeksvragen of veelgebruikte biologische parameters overeenkomen met langetermijnuitkomsten van implantaatoverleving en gerapporteerde peri-implantitis prevalentie. Daarnaast werd ook onderzocht of de huidige literatuur een antwoord geeft of het botniveau rondom implantaten op lange termijn wordt beïnvloed door ruwheid van het implantaatoppervlak. De klinische studies in dit proefschrift **(Hoofdstuk 5, 6 en 7)** richten zich op het evalueren van het effect van implantaat gerelateerde factoren zoals implantaat micro-design (ruwheid implantaatoppervlak), macro-design (microthreads en implantaat-abutmentverbinding), en plaats-specifieke factoren (dikte van zacht weefsel) op het botniveau en de gezondheid van de weefsels rondom het implantaat op de lange termijn. Daarnaast is er aandacht besteed aan de kwaliteit van leven gerelateerd aan de mondgezondheid bij patiënten die zijn behandeld met een implantaatgedragen overkappingsprothese in de onderkaak.

Hoofdstuk 3 (Studie I) is een kritisch analyse van de tussen 2011 en 2017 gepubliceerde literatuur met betrekking tot de biologische parameters bloeding

bij sonderen, sonderen van pocketdiepte en botverlies. Het zoekalgoritme bracht 4.173 artikelen aan het licht die beschikbaar waren voor verdere analyse; 255 artikelen zijn geselecteerd voor verdere analyse en uiteindelijk voldeden 41 artikelen aan de vooropgestelde inclusiecriteria van de studie. In deze 41 artikelen werden 15 verschillende definities voor peri-implantitis gebruikt. De gerapporteerde prevalentie van peri-implantitis varieerde tussen 0% en 39,7%, met een algemeen gemiddeld gewogen implantaat overlevingspercentage van 96,9% (89,9% - 100%). Op basis van 8.182 implantaten was het totale gewogen gemiddelde botverlies 1,1 mm na variërend van 5 tot 20 jaar overleving. Het gemiddelde botverlies correleerde niet met de gerapporteerde prevalentie van peri-implantitis. Ook was er geen correlatie tussen het gemiddeld botverlies en de diagnostische parameters gemiddelde pocketdiepte en bloeding bij het sonderen. Bovendien correleerde de gerapporteerde prevalentie van peri-implantitis niet met de gemiddelde pocketdiepte. Er werd echter een sterke correlatie gevonden tussen de gerapporteerde prevalentie van peri-implantitis en bloedingen bij sonderen. Het overlevingspercentage vertoonde een substantiële correlatie met functietijd, met een beperkt implantaatverlies in de loop van de tijd. We concludeerden dat de definitie voor peri-implantitis significant varieerde tussen de onderzoeken, wat aangeeft dat een eenduidige definitie op basis van een gespecificeerde drempel voor botverlies niet wordt aanvaard in de literatuur.

Hoofdstuk 4 (Studie II) onderzocht de literatuur met de vraag of botverlies rondom het implantaat op de lange termijn wordt beïnvloed door ruwheid van het implantaatoppervlak. Tevens is onderzocht of de bestaande literatuur aantoont of patiënt gerelateerde factoren zoals roken en een voorgeschiedenis van parodontitis invloed hebben op het botverlies rondom implantaten.

Implantaatsystemen kunnen worden ingedeeld op basis van de oppervlakteruwheid van het implantaatoppervlak. Deze oppervlakteruwheid wordt uitgedrukt in een bepaalde Sa-value; minimaal ruw (Sa-value: 0,5 – 1 µm), gemiddeld ruw (Sa-value: 1 – 2 µm) en ruw (Sa-value: > 2 µm). In de beginjaren van de implantaattandheelkunde waren er voornamelijk minimaal ruwe en microporeuze titanium plasmagespoten ruwe implantaatsystemen beschikbaar.

Na verloop van tijd werden er echter verschillende modificaties aan het implantaatoppervlak uitgevoerd. Deze modificaties werden gedaan door middel

van zandstralen, etsen met zuur, anodische oxidatie of hydroxyapatietcoating, wat resulteerde in een gemiddeld ruw implantaatsysteem. Deze modificaties verbeterden de osteoconductieve en osteo-inductieve eigenschappen van het implantaat. Het gemiddeld ruwe implantaatoppervlak vertoonde een betere stabilisatie van het bloedstolsel, verbeterde productie van biologische mediatoren en stimuleerde de osteogenese, wat leidde tot een hoger bot-tot-implantaatcontact en verhoogde bindingssterkte van het bot aan het implantaat. Aan de andere kant zijn er bewijzen dat er meer bacteriën kunnen hechten aan ruwere implantaatsystemen, wat kan leiden tot een hoger risico op peri-implantitis.

De zoekopdracht voor deze studie leverde 2.566 studies op en 156 werden geselecteerd voor verdere analyse. Slechts 87 rapporteerden informatie over oppervlakteruwheid van de implantaten en gemiddeld botverlies na ten minste vijf jaar functioneren. In deze publicaties werden in totaal 15.695 implantaten geplaatst bij 6.755 patiënten. Na tenminste vijf jaar was de gemiddelde gewogen overlevingskans van deze implantaten was 97,3%. Als botverlies van 3 mm werd gebruikt als drempel om peri-implantitis te kwalificeren, kon minder dan 5% van de implantaten gediagnosticeerd worden met peri-implantitis. Wat betreft de oppervlakteruwheid van implantaatoppervlak, toonde de systematische review aan dat het botverlies rond minimaal ruwe implantaatsystemen statistisch significant minder was dan gemiddeld ruwe en ruwe implantaatsystemen. Er werd geen statistisch significant verschil waargenomen tussen gemiddeld ruwe en ruwe implantaatsystemen. De meta-analyse toonde gemiddeld minder botverlies rondom implantaatsystemen met een minimaal ruw oppervlak. Vanwege de heterogeniteit van de artikelen en de multifactoriële oorzaak van botverlies rondom implantaten, lijkt de impact van oppervlakteruwheid alleen enigszins beperkt en van minimaal klinisch belang. Wel toonde de meta-analyse aan dat roken en een voorgeschiedenis van parodontitis het risico op botverlies significant verhogen.

Hoofdstuk 5 (Studie III) omvat twee prospectieve split-mouth studies. Beide onderzoeken includeerden edentate patiënten met de zorgvraag voor een implantaat gedragen overkappingsprothese in de onderkaak. Het eerste deel van **Studie III** beschrijft het effect van de plaats-specifieke factor 'zacht weefsel dikte' op de remodellering van het crestale bot en de gezondheid van de weefsels rondom implantaten. Zesentwintig patiënten kregen twee gemiddeld

ruwe implantaten in functie van een overkappingsprothese in de onderkaak. Volgens de richtlijnen van de fabrikant werd het controle-implantaat equicrestaal geplaatst. Het testimplantaat werd subcrestaal geplaatst om te zorgen voor ten minste 3 mm ruimte voor de instelling van de biologische breedte ter hoogte van het implantaat en het abutment. Initieel werden 26 patiënten behandeld met één equicrestaal en één subcrestaal geplaatst implantaat. Na 36 maanden waren er 24 patiënten beschikbaar voor verdere opvolging.

In het tweede deel van **Studie III** werd het effect bepaald van de oppervlakteruwheid van het implantaatoppervlak op de remodellering van het crestale bot. Zoals geconcludeerd in **Studie II**, zou verlies van crestaal bot gerelateerd kunnen zijn aan de ruwheid van het implantaatoppervlak. De bestaande literatuur suggereert hogere overlevingspercentages voor gemiddeld ruwe implantaten in vergelijking met minimaal ruwe implantaten. Aan de andere kant suggereren recente literatuur en de bevindingen van **Studie II** dat implantaten met een minimaal ruw oppervlak minder crestaal botverlies op de lange termijn opleveren.

Een implantaat met een hybride oppervlak combineert het voordeel van een gemiddeld ruw implantaatoppervlak voor het onderste gedeelte van het implantaat en een minimaal ruwe implantaathals. Om het effect van de oppervlakteruwheid van het implantaat op het crestale botverlies te bepalen, kregen 23 patiënten twee implantaten: een implantaat met een gemiddeld ruw oppervlak (Sa-value: 1,3 µm) en een hybride implantaat met een minimaal ruwe coronale hals van 3 mm (Sa-value: 0,9 µm) gecombineerd met een gemiddeld ruw oppervlak voor het overige gedeelte van het implantaat (Sa-waarde: 1,3 µm). Afgezien van het verschil in oppervlakteruwheid van het implantaat, waren de twee implantaten identiek. Na 36 maanden waren 21 patiënten beschikbaar voor verdere opvolging.

Het overlevingspercentage van het implantaat was 100% na 36 maanden. Er werden geen verschillen waargenomen in de bot remodellering van het crestale bot tussen het hybride en het gemiddeld ruwe implantaat. Het eerste gedeelte van **Studie III** toonde echter wel aan dat de initiële botremodellering werd beïnvloed door de initiële dikte van het zachte weefsel, resulterend in een hogere kans voor het niet geheel bedekt zijn met bot van de hals van het implantaat als het implantaat equicrestaal geplaatst is. Door te anticiperen op het herstel van de biologische breedte door de verticale positie van het implantaat aan

te passen aan de beschikbare pre operatieve dikte van het zachte weefsel, kan worden voorkomen dat het de implantaathals niet volledig wordt bedekt met bot. Opvolging op lange termijn van deze studie is echter noodzakelijk om de invloed van vroege blootstelling van het implantaatoppervlak aan de zachte weefsels en de ruwheid van het implantaatoppervlak op crestaal botverlies, biologische parameters en implantaatoverleving te bepalen.

Studie III onderzocht ook de mondgezondheid gerelateerde kwaliteit van leven voor edentate patiënten die werden behandeld met een implantaat gedragen overkappingsprothese in de onderkaak. Deze patiëntgerichte uitkomst werd beoordeeld door middel van een vragenlijst: Oral Health Impact Profile-14 (OHIP-14). De studie concludeerde dat een implantaatgedragen overkappingsprothese op twee implantaten in vergelijking met een conventionele uitneembare prothese een significante verbetering van de kwaliteit van leven oplevert.

Hoofdstuk 6 (Studie IV) beschrijft de vijf jaar durende opvolging van het eerste deel van **Studie III**, waarin het effect van de dikte van zacht weefsel op de remodellering van het crestale bot en de gezondheid van de weefsels rondom het implantaat werd onderzocht. Vierentwintig patiënten waren beschikbaar voor de opvolging van vijf jaar. Het overlevingspercentage was 100% en slechts één implantaat vertoonde een gemiddeld botniveau hoger dan 2 mm. Tijdens de initiële botremodellering leverde equicrestale plaatsing 0,68 mm extra oppervlakteblootstelling op in vergelijking met subcrestale plaatsing. Daarna was het botniveau en de gezondheid van de weefsels rondom het implantaat vergelijkbaar en stabiel tot vijf jaar voor zowel het equicrestaal als het subcrestaal geplaatst implantaat. **Studie IV** concludeert dat het aanpassen van de verticale positie van het implantaat met betrekking tot de dikte van het zachte weefsel vroege blootstelling van het implantaatoppervlak veroorzaakt door initiële botremodellering voorkomt. In een goed onderhouden populatie heeft het blootliggende implantaatoppervlak geen invloed op de prognose van het implantaat op de lange termijn. Daarnaast werd ook na vijf jaar de mondgezondheid gerelateerde kwaliteit van leven beoordeeld met behulp van een vragenlijst, de Oral Health Impact Profile-14 (OHIP-14). Er werd geen significante verandering in de mondgezondheid gerelateerde kwaliteit van leven waargenomen ten opzichte van de resultaten van **Studie III**.

In **Hoofdstuk 7 (Studie V)** wordt het effect van de implantaathals (microthreaded versus niet-microthreaded) en het type verbinding (inwendig conisch versus uitwendig plat-op-plat) op de botstabiliteit en gezondheid van de zachte weefsels rondom het implantaat besproken. Volgens de literatuur wordt botverlies rondom het implantaat geminimaliseerd door implantaten met een microthreaded halsontwerp en een interne abutmentverbinding. Hierbij moet echter worden opgemerkt dat veel klinische onderzoeken een vertekend beeld geven door de aanwezigheid van zogenoemde 'confounding factors' in de onderzoeksopzet.

Vijfentwintig patiënten met de zorgvraag voor een implantaatgedragen overkappingsprothese in de bovenkaak werden geïncludeerd in **Study V**. Elke patiënt kreeg vier verschillende implantaattypes: één implantaat met een interne verbinding met microthreads (I MT), één met een interne verbinding zonder microthreads (I NMT), één met een externe verbinding met microthreads (E MT) en één met een externe verbinding zonder microthreads (E NMT). Andere ontwerpkenmerken, evenals het chirurgische en prothetische protocol, waren gelijk, om de kans op 'confounding factors' te minimaliseren.

Na ten minste 36 maanden was het overlevingspercentage 96%. Er werd geconcludeerd dat het type implantaat-abutmentverbinding (intern versus extern) en het ontwerp van de implantaathals (microthreaded versus niet-microthreaded) geen klinisch effect heeft op de initiële botremodellering en de botstabiliteit rondom het implantaat na de initiële botremodellering. Bovendien had het implantaatontwerp ook geen klinisch effect op de gezondheidsparameters rondom het implantaat, mits de implantaten worden geïnstalleerd met inachtneming van de initiële dikte van het zachte weefsel.

Hoofdstuk 8 is de algemene discussie en bevat aanbevelingen voor de praktijk en toekomstig onderzoek. Daarnaast benadrukt het de maatschappelijke relevantie van het ondernomen wetenschappelijke werk in combinatie met een persoonlijke reflectie op het uitvoeren van onderzoek. Dit proefschrift concludeert dat:

1. In de literatuur worden verschillende definities van peri-implantitis gebruikt en de rapportage van biologische parameters is vaak onvolledig. Consistente rapportage van peri-implantitis is zowel voor wetenschappelijke doeleinden als voor de klinische praktijk vereist.

2. De prevalentie van peri-implantitis op basis van verschillende casusdefinities correleerde niet met de diagnostische parameters 'gemiddelde pocketdiepte', 'gemiddelde bloeding bij sonderen' en 'gemiddeld bot-verlies'. Het overlevingspercentage vertoonde een substantiële correlatie met functietijd, maar implantaatverlies in de tijd is laag.
3. In de huidige literatuur vertoonde minder dan 5% van de implantaten botverlies van meer dan 3 mm na ten minste vijf jaar in functie. Dit resultaat was onafhankelijk van het merk van het oppervlak of implantaat, wat suggereert dat de momenteel gerapporteerde prevalentie van peri-implantitis overdreven is.
4. Ruwe implantaatsystemen zijn vatbaarder voor crestaal botverlies. De multifactoriële oorzaak van botverlies en de heterogeniteit van de onderzoeken maken het echter moeilijk om harde conclusies te trekken. Desalniettemin tonen meerdere studies minder botverlies ten gunste van minimaal ruwe implantaatsystemen.
5. Cofactoren zoals roken of een voorgeschiedenis van parodontitis verhogen het risico op botverlies.
6. Het ontwerp van de implantaathals (microthreaded vs niet-microthreaded) heeft geen invloed op de botremodellering rondom het implantaat, mits implantaten worden geïnstalleerd in verhouding tot de dikte van zacht weefsel, waardoor een biologische afdichting van 3 tot 4 mm kan worden gevormd.
7. Het type implantaat-abutmentverbinding (intern vs. extern) heeft geen invloed op peri-botremodellering rondom het implantaat, mits implantaten worden geïnstalleerd in verhouding tot de dikte van zacht weefsel, waardoor de vorming van een biologische afdichting van 3 tot 4 mm mogelijk is.
8. De ruwheid van het implantaatoppervlak (minimaal ruw versus matig ruw) heeft geen invloed op de initiële bot remodellering, noch op het botverlies op de lange termijn, mits implantaten worden geïnstalleerd in verhouding tot de dikte van zacht weefsel, waardoor de vorming van een biologische afdichting van 3 tot 4 mm mogelijk is.
9. Peri-implantaatgezondheidsparameters (pocketdiepte, bloeding bij sonderen en plaquescore) worden niet beïnvloed door implantaatontwerp, oppervlaktetextuur of abutmentverbinding mits implantaten worden geïnstalleerd in relatie tot de dikte van zacht weefsel.

10. Door te anticiperen op herstel van de biologische breedte door de verticale positie van het implantaat aan te passen aan de beschikbare dikte van het zachte weefsel, kan initieel botverlies rondom het implantaat worden voorkomen.
11. In een goed onderhouden populatie lijkt het effect van vroege blootstelling aan het implantaatoppervlak, veroorzaakt door initiële botremodellering, op de botstabiliteit en biologische parameters rondom het implantaat beperkt te zijn.
12. Implantaat-ondersteunde overkappingsprothesen in de onderkaak verbeteren de kwaliteit van leven aanzienlijk, met weinig biologische complicaties en een hoge overlevingskans van de implantaten.

LIST OF ABBREVIATIONS

- ADA American Dental Association
- BL bone loss
- BoP Bleeding on Probing
- CAD-CAM Computer Aided Design – Computer Aided Manufacturing
- CI Confidence Interval
- DCC Deep Conical Connection
- DDS Doctor of Dental Surgery
- DME Duplicate Measurement Error
- E MT External connection, Microthreaded implant
- E NMT External connection, Non-Microthreaded implant
- EAO European Association for Osseointegration
- EFP European Federation of Periodontology
- EWOP European Workshop on Periodontology
- I MT Internal connection, Microthreaded implant
- I NMT Internal connection, Non-Microthreaded implant
- IQR Inter Quartile Range
- Max Maximum
- Mean diff Mean difference
- Min Minimum
- mm millimetres
- MSC Machined Surface Collar
- MSc Master of Science
- Ncm Newton centimetre
- OHIP-14 Oral Health Impact Profile – 14 questionnaire
- OHIP-49 Oral Health Impact Profile – 49 questionnaire
- OHRQoL Oral Health-Related Quality of Life
- PD probing depth
- PhD Doctor of Philosophy
- PROMs Patient-Reported Outcome Measures
- RCT: Randomized Controlled Clinical Trial
- Sa value Surface area – Value
- SD Standard Deviation
- Sup Suppuration
- µm micrometre

CHAPTER 10

CURRICULUM VITAE

LIST OF PUBLICATIONS

RESEARCH DATA MANAGEMENT PLAN

PHD PORTFOLIO

ACKNOWLEDGEMENTS/ DANKWOORD

CURRICULUM VITAE

Ron Doornewaard was born on October 22, 1984 in Papendrecht, the Netherlands. He finished secondary school in 2003 at 'Willem de Zwijger College' in Papendrecht. He started studying dentistry at ACTA (Academisch Centrum Tandheelkunde Amsterdam) during the same year. In September 2008, he obtained his master's degree in dentistry with honour.

After five years of work experience in general practice, he decided to follow a three-year full-time master in advanced dentistry with a major in periodontics at Ghent University, Belgium. After obtaining his diploma with great honour, he worked in various dental practices for periodontology and oral implantology in Belgium and the Netherlands.

Besides his work as a clinician, Ron started his joint PhD-programme at Gent University and Radboud University (Nijmegen, the Netherlands) in September 2017. During his PhD track, he was a supervisor in the field of periodontology at both universities. Moreover, during this time he was the author and co-author of several international publications.

LIST OF PUBLICATIONS

Peer reviewed full-text publications

In this thesis

How do peri-implant biologic parameters correspond with implant survival and peri-implantitis?A critical review.
Doornewaard R, Jacquet W, Cosyn J, De Bruyn H.
Clinical Oral Implants Research. 2018;29 Suppl 18:100-123.

Long-Term Effect of Surface Roughness and Patients' Factors on Crestal Bone Loss at Dental Implants. A Systematic Review and Meta-Analysis.
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Improvement of Quality of Life with Implant-Supported Mandibular Overdentures and the Effect of Implant Type and Surgical Procedure on Bone and Soft Tissue Stability: A Three-Year Prospective Split-Mouth Trial.
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Other

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Seyssens L, Eghbali A, Christiaens V, De Bruyckere T, **Doornewaard R**, Cosyn J.
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Clinical Implant Dentistry and Related Research. 2019;21(5):835-844.

A multicenter cohort study on the association of the one-abutment one-time concept with marginal bone loss around bone level implants.
Lambrechts T, **Doornewaard R**, De Bruyckere T, Matthijs L, Deschepper E, Cosyn J.
Clinical Oral Implants Research. 2021;32(2):192-202.

DATA MANAGEMENT PLAN

The studies presented in **Chapter 5, 6, and 7** of this dissertation are based on human studies. The clinical trials have been conducted in full accordance of the Helsinki Declaration (1975) as revised in 2000. All clinical data are obtained at Ghent University. The ethical committee of the Ghent University Hospital approved the study protocols under the Belgium registration numbers B670201422878 **(part of Study III)**, B670201215160 **(part of Study III and Study IV)**, and B670201524372 **(Study V)**. All patients were thoroughly informed about the treatment, signed written informed consent, and were treated between January 2013 and September 2017 at the Ghent University Hospital. This project is stored on the Radboudumc department server: (H:)THKdata$\\UMCFS012\Leerstoel I&P\Ron Doornewaard.

The paper data made during the clinical examination and at each follow-up appointment were stored in the department of Periodontology and Oral Implantology of Ghent University. The privacy of the participants is assured by the use of encrypted and unique individual subject codes. The code was stored separately from the study data.

All data related to the analysis and publications for **Study I, II, III, IV, and V** are stored in on the Radboudumc department server: (H:)THKdata$\\UMCFS012\Leerstoel I&P\Ron Doornewaard. These data will be saved for 15 years after the termination of the study. The datasets analysed during the studies in **Chapter 3, 4, 5, 6, and 7** are available from the corresponding author on reasonable request.

PHD PORTFOLIO

Institute for Health Sciences
Radboudumc

Name of PhD student: Ron Doornewaard
PhD period: September 2017 – April 2022
PhD Promotors: Prof. Dr. H. de Bruyn (Radboud Universiteit Nijmegen)
Prof. Dr. S. Vandeweghe (Universiteit Gent)
PhD Co-promotor: Dr. S. Vervaeke (Universiteit Gent)

Training activities		
Courses & Workshops	**Year**	**ECTS**
Human Quality Management course (HQM)	2019	0.5
RIHS - Introduction course for PhD candidates	2019	0.5
Radboud UMC Scientific Integrity	2020	1
Radboud UMC Mindfulness based stress reduction	2021	1
Seminars & Lecturers	**Year**	**ECTS**
ITI dutch Annual Section Meeting (online event)	2021	0.1
Research seminars dentistry	2019-2021	0.1
Symposia & Congresses	**Year**	**ECTS**
The EAO's 25th annual scientific meeting (Paris, France, poster presentation)	2016	1
International Osteology symposium (Monaco)	2016	1
BVP congress (zaventem, Belgium)	2017	0.5
EuroPerio9 (Amsterdam, the Netherlands)	2018	1
Southern Implants International Forum (Hermanus, South Africa)	2018	1
Symposium 'Parodontale en Implantologische Zorgen Voor Morgen' (Nijmegen, the Netherlands)	2019	0.2
International Osteology symposium (Barcelona, Spain)	2019	1

Teaching activities		
Lecturing	**Year**	**ECTS**
Response lecture students in preventive oral healthcare (Arteveldehogeschool, Ghent, Belgium)	2017	0.5
VUNIT course 'Kiezen van het juiste implantaat en abutment' (Ghent, Belgium)	2019	0.5
Symposium 'Parodontale en Implantologische Zorgen Voor Morgen' (Nijmegen, the Netherlands)	2019	0.5
ITI dutch Annual Section Meeting (online event)	2021	0.5
Supervision	**Year**	**ECTS**
Co-promotor masterthesis in oral implantology (Ghent University/Ghent, Belgium)	2019-2021	3
Supervisor 'master klinikek' in the field of periodontology and implantology (AKMA department of the Radboud University/Nijmegen, the Netherlands)	2020-2021	8.5
Supervisor 'master kliniek' in general dentistry (Radboud University/Nijmegen, the Netherlands)	2020	2.9
Supervisor 'paroprofiel' (Radboud University/Nijmegen, the Netherlands)	2020-2021	2.9
Total		26.2

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