THE UNIVERSITY OF
SYDNEY

THE UNIVERSITY OF SYDNEY

The Long Term Stability of Soft and Hard Tissues Surrounding Brånemark Dental Implants

Khai Quang Nguyen BDS (Syd)

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Clinical Dentistry (Periodontics)

Discipline of Periodontics
Faculty of Dentistry
The University of Sydney, New South Wales

Australia 2009

OCTOBER 2014

CANDIDATE'S CERTIFICATE

This is to certify that the work presented in this thesis was carried out by the candidate in the Faculty of Dentistry, University of Sydney at the Sydney Dental Hospital. Any contribution made to the research by others with whom I have worked with is explicitly acknowledged in the treatise. The work presented in this treatise has been submitted only to the University of Sydney for a higher degree.

Khai Quang Nguyen

ACKNOWLEDGEMENTS

Firstly, I would like to thank my supervisor Associate Professor Axel Spahr, as well as Associate Professor Norton Duckmanton and Mr. Tim Badgery-Parker for their invaluable guidance, support and time provided throughout the preparation and completion of this project.

This project would not have been possible without the assistance and co-operation of all the dental assistants and administrative support staff of the Periodontics Department at Sydney Dental Hospital.

Funding for this project was also graciously granted by the Australian Periodontology Research Foundation (APRF).

For their forbearance over the length of this course, I would also like to thank my fellow registrars; Dr. Alex Kalos, Dr. Eugeniya Kelloway, and Dr. Leon Gershenfeld – I really could not have asked for or chosen a better crew myself!

Last, but definitely not least, I would like to thank my family and friends for their unwavering love, encouragement and support throughout this time.

ABSTRACT

Background: Dental implants are an increasingly popular treatment modality in the replacement of teeth. With the greater uptake and longevity of implants, there is also a likely increase in the incidence of biological complications. Limited data exists concerning longitudinal (20+ years) clinical peri-implant parameters, including marginal bone level changes in edentulous and partially edentulous patients.

Objectives: The aim of this retrospective cohort study was to examine the outcomes of implant treatment in fully and partially edentulous patients with respect to clinical peri-implant parameters, including marginal bone level changes in patients with dental implants after at least 20 years.

Materials and Methods: Twenty-two partially and fully edentulous patients, of 278 originally treated individuals who could be tracked and recalled were reviewed after receiving turned-surface ø3.75mm Brånemark implants® (Nobel Biocare AB, Göteborg, Sweden) of various lengths between 1981 and 1985. These implants were restored with various suprastructures including: overdentures, full fixed dentures, partial fixed dentures and single crowns. At review, the following clinical implant parameters were assessed: plaque scores, bleeding scores, probing depths, peri-implant mucosal recession, probing attachment levels, bleeding on probing and radiographic marginal bone loss.

Results: The 22 patients examined had received 97 implants. Seven implants (14%) in 3 patients were lost. The patients had a mean age at insertion of 48.5 years and the mean age at examination was 73 years. A mean probing depth of 3.3mm (SD 1.0) was measured with 39% (SD 30) of the implants showing bleeding on probing. Significantly more mucosal inflammation and plaque were seen at implants supporting full fixed dentures and partial fixed dentures (p = 0.006

and p <0.001 respectively). Over a median of 22 years of service, the observed mean bone loss was 1.1mm (SD 0.9). Marginal bone loss was significantly greater in smokers and ex-smokers compared to never smokers (p <0.001). Although below statistical significance, there was a tendency for more bone loss around implants supporting overdentures (1.2mm, SD 1.1) compared to implants restored with full fixed dentures (1.0mm, SD 0.8), partial fixed dentures (0.7mm, SD 0.9), and single crowns (0.4mm, SD 0.6).

Conclusion: Good clinical outcomes can be achieved with turned surface Brånemark implants over 20 years, with only minimal soft tissue inflammation and minimal radiographic bone loss being observed.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Part A: Review of the literature

1. INTRODUCTION

Dental implants are an increasingly popular treatment modality in the replacement of teeth. With the rapid uptake of this treatment modality, complications may also arise. Although dental implants are considered to be a relatively reliable treatment modality for complete and partial edentulism, complications of a technical (mechanical) and/or biological nature can occur[1], which can contribute towards implant failure. It has been reported that the incidence of biological and technical complications may be somewhat underestimated[1]. A review of clinical complications (biologic and technical) of implant-supported fixed partial dentures concluded that *"variations in study design and reporting procedures limit the available data and therefore precluded proper analysis of certain complications*[2]*"*.

However, it has been noted that there is still limited information available regarding the incidence, prevalence, and risk factors that are associated with peri-implant diseases[3, 4]. This discrepancy can be partially attributed to by a lack of longitudinal studies capturing this information. In the 2012 VIII European Workshop on Periodontology, similar sentiments regarding a lack of long term clinical data was identified by participants where they were also surveyed regarding their opinions concerning the reporting of outcome domains in future dental implant studies[5]. Here, it was identified that future dental implant research should identify and measure patient reported outcomes[6], peri-implant health[7, 8], as well as restorative outcomes[9].

Whilst there has been an explosion in implant research conducted up to a 10 year follow up, limited data exists for longer observation periods extending up to 20 years[10]. Even less so are studies exceeding a 20 year follow up period, where there have only been three[11-13] published. Therefore, more studies capturing peri-implant data (patient-reported outcomes, peri-implant

health, and restorative outcomes[5]) for implants exceeding a 20 year observation period is required.

In the formulation of my clinical research question, it was proposed that a long term clinical study be performed to identify and report on peri-implant health related parameters on a pre-existing cohort here at Sydney Dental Hospital to provide meaningful contribution to this pool of data. This chosen cohort is unique on several facets:

1. They were among the earliest recipients of dental implants in Australia, and were a mixture of both public and private patients.

2. They have all been treated by the same group of clinicians (surgeons and restoring dentists) – all of whom were working in the same institution at the time.

3. They were recipients of turned surface Brånemark implants® (Nobel Biocare AB, Götheborg, Sweden) inserted at least twenty years ago.

In a previous retrospective follow-up study conducted on this same cohort on the long-term survival of dental implants and prosthetic suprastructures[14], the cumulative survival of implants and implant-supported prostheses following 20 years of placement and the impact of the type of prosthetic suprastructure on implant survival was evaluated. Here it was revealed that the 20 year implant estimated cumulative survival was 92%, with a patient-based implant survival of 80%. The prosthetic estimated cumulative survival rate was reported to be 94% for single crowns, 80% for fixed partial prosthesis, 50% for fixed full prostheses, and 22% for overdentures. It was concluded that implants supporting overdentures were significantly more likely to be lost compared to implants restored with fixed full reconstructions.

Following on from this investigation, additional clinical questions were also raised:

1. What is the prevalence and severity of peri-implant bone loss/peri-implant diseases on the surviving implants of this aforementioned cohort following 20+ years after placement?

2. Are there any risk factors contributing to the incidence and severity of peri-implant bone loss/peri-implant diseases, as identified in the patient's medical history (e.g. diabetes, smoking)?

3. Does the suprastructure have any effect on the extent of peri-implant bone loss and the development of peri-implant disease?

4. Does the implant location have any effect on bone loss and the development of peri-implant diseases?

This paper will consequently review the nature of peri-implant diseases, examining any contributory effects that the patient's medical history may have on the prevalence of peri-implant diseases.

2. DEFINITIONS

As a treatment modality, dental implants rely on the concept of osseointegration – first described by Branemark[15]. Osseointegration can be defined as *"a process whereby clinically asymptomatic rigid fixation of alloplastic materials that is achieved and maintained, in bone during functional loading"*[16].

The outcome of implant therapy is often reported in success and survival rates. Commonly accepted criteria for the assessment of implant success were proposed by Albrektsson and co-workers[17], identifying clinical evidence of successful osseointegration. This assessment can be based on survival rates, continuous prosthesis stability, radiographic bone loss, and absence of infection in the peri-implant soft tissues.

Although implants are considered to be a relatively reliable treatment modality of complete and partial edentulism, complications of a technical (mechanical) and biological nature can occur[1], which can contribute towards implant failure.

2.1. Biological complications

'*Biological complications*' refer to disturbances in implant function characterised by biological processes that affect the supporting peri-implant tissues. Such examples of biological complications include soft tissue dehiscence, peri-implant bone loss exceeding 2 mm, peri-implant mucositis, inflammation under the fixed prosthesis, and hypertrophy/hyperplasia of soft tissue.

These complications also include early and late implant failures and adverse reactions in the peri-implant hard and soft tissues, whilst implant loss is also classified as a biological complication.

2.2. Technical complications

'*Technical complications*' is a collective term referring to mechanical damage of the implant, implant components and suprastructures. Technical complications of implant components or prostheses frequently occur and the incidence of some technical complications may be specific to certain implant systems[18].

2.3. Success

'*Success*' can further be defined as a surviving (i.e. present) osseointegrated implant that is capable of satisfying other criteria, including functionality (being able to chew effectively), absence of tissue pathology (maintain osseointegration in the absence of pain and pathology), as well as meeting the patient's satisfaction (satisfactory gingival and prosthetic aesthetics and absence of discomfort). Success parameters are often related to implant survival, peri-implant soft tissue, prosthetic outcomes, and the patient's subjective evaluation. Many classification systems have been proposed in the reporting of treatment outcomes on dental implant therapy[19], encompassing the evaluation of implant longevity/survival, as well as patient-centred aspects of the treatment outcome (physiological, psychological, economic impact). However, the clinician's objective evaluation and the patient's subjective perception of a successful outcome often do not agree[20].

Implant success or failure is influenced by several factors, which can be divided into being either 'local' or 'systemic' in nature[21, 22]. These factors are listed in Table 2.3-A and can be influential in either the early or late phases of implant therapy.

Table 2.3-A: Factors associated with success and failures in implant dentistry

Local factors	Interdental space
	Infected sites
	Soft tissue morphology
	Width of keratinised soft tissue
Systemic factors	Oral lichen planus, ectodermal dysplasia, and Sjögren's syndrome
	Psychiatric diseases
	Transplantation
	Cardiovascular disease
	Diabetes
	Osteoporosis
	Bisphosphonates
	Radiotherapy

2.4. Failure

'*Failure*' on the other hand is defined as the point at which an implant, measured in some quantitative way, has failed to meet a defined acceptable level[23]. This definition includes a great variety of clinical situations, ranging from symptomatic mobile implants, to those with greater than 0.2mm of bone loss after the first year of loading[17], to those exhibiting bleeding on probing from pocket depths greater than 5mm[24]. Failures can be further classified into biological failures,

mechanical failures, iatrogenic failures, or inadequate patient adaptation. These sub classifications are as elaborated below in Table 2.4-A:

Table 2.4-A: Classification of dental implant failures

Biological		
	Early (before loading)	Represents a failure to establish osseointegration
	Late (after loading)	Represents a failure to maintain the achieved osseointegration
Mechanical		Failure of components (implant, connecting screws, bridge frameworks, coatings, suprastructure failures)
Iatrogenic		A stable and osseointegrated implant that cannot be used due to malpositioning (also includes nerve damage)
Inadequate patient adaptation		Failure of components (implant, connecting screws, bridge frameworks, coatings, suprastructure failures)

2.5. Biological failure

'Biological failure' is defined as an inadequacy of the host tissue in establishing or maintaining osseointegration. This can also be further subdivided into early and late failures, where an early failure represents a failure to establish osseointegration due to an interference with the healing process, and a late failure is representative of a failure to maintain osseointegration – i.e. there are processes contributing to the breakdown of osseointegration.

Early failures are often the result of a disruption to the initial healing process, resulting in fibrous scar tissue formation between the implant surface and the surrounding bone[25]. Consequently, this can allow the down-growth of epithelium, resulting in implant mobility, before leading to eventual failure. On the other hand, late failures are affected by a combination of factors, including the microbial environment, along with the prosthetic restoration.

This loss of osseointegration is clinically evident in the form of either implant mobility or radiographically as a peri-implant radiolucency, which is the result of replacement of the bone tissue with a fibrous connective tissue capsule that is unable to meaningly contribute to the functional capacity of the bone-implant unit.

3. RISK FACTORS AND THEIR CONTRIBUTION TO SUCCESS AND FAILURE OF DENTAL IMPLANTS

3.1. Local Factors

3.1.1. Interdental space

Dental implant placement requires careful three-dimensional analysis of the surgical site, with careful attention paid to the available restorative space, bone volume and root positions of the adjacent teeth. Placement of a dental implant that encroaches on the root surfaces of the neighbouring teeth can lead to complications affecting the peri-implant hard and soft tissues as well as the neighbouring teeth, which would result in an aesthetic compromise with potential loss and thus failure of the implant or tooth[26].

As a general guide, dental implants should be installed within the alveolar envelope. The implant position in relation to the bucco-oral and mesio-distal dimensions of the alveolar ridge is a factor thought to influence the degree of bone remodelling following implant placement[27]. Such remodelling may consequently have a negative influence on the soft tissue topography and the aesthetic outcome of the implant therapy[28].

The respect for these biological concepts has led to several clinical guidelines regarding the correct implant positioning in relation to bucco-oral and mesio-distal bone dimensions[29]. For the bucco-oral dimension, it is suggested that the buccal bone thickness should be at least 2mm, and even preferably 4mm. In the mesio-distal dimensions, it is suggested that the distance between a tooth and an implant should not be <1.5mm and between two implants, not <3mm. In order to fulfil these criteria, bone augmentation procedures, orthodontics, enameloplasty, or restorative materials are often recommended[29].

3.1.2. Previously infected sites

Immediate implants have been popular in the past to assist in streamlining patient care and attempted to maximise the amount of available bone following tooth extraction[30]. Clinical studies have demonstrated immediate implant placement into extraction sockets can be successful[31]. However, when implants are placed into an infected site that has been debrided, different outcomes may be encountered. An infected site is defined as one that has exhibited a range of the following symptoms: pain, periapical radiolucency, fistula formation, and/or suppuration.

Truninger et al.[32] conducted a prospective clinical study reporting the survival of immediate implants to replace teeth exhibiting periapical pathology. In his study, one group of 17 patients were treated with immediate implants placed into sites with pre-existing periapical pathology (pain, periapical radiolucency >1mm, fistula formation, and/or suppuration), whereas the control group of 17 patients received the same immediate implants placed into pathology-free sites. The implants were subsequently loaded and restored 3 months after placement. The authors reported that 5 of the patients were removed from the study due to the inability to attain primary stability during placement, while the remaining patients had a 100% survival rate at 12 and 36 months. It was concluded that there were no statistical differences in complications or survival when comparing immediate implants placed in the two different site types.

Similarly, Villa et al.[33] also examined immediate implants placed into the extraction sockets of maxillary infected teeth. Here, an infected tooth was defined as demonstrating clinical or radiographic evidence of advanced endodontic or periodontal lesions, or root fracture. In total, 33 patients over one year were observed, with 76 implants being placed into infected sites, while 24 were placed into pathology-free sites. Here, the authors defined an implant as 'surviving' when it was stable when tested individually, with no pain or signs of infection being detected during clinical examination and no radiographic evidence of peri-implant pathology was observed. It was

reported that there were no statistically significant differences between the 2 groups after an observation period of 1 year.

Lindeboom et al.[34] performed a randomised prospective trial placing 50 immediate implants into 50 patients with hopeless teeth that demonstrated radiographic evidence of apical periodontitis. Patients were randomised into 2 even groups: immediate placement, and delayed placement (3 months post-extraction). In both groups, all the implants were submerged without loading for a period of 6 months. The authors used the following success criteria in their studies: no implant mobility at second stage surgery, no radiographic evidence of peri-implant pathology, and no bone loss exceeding 2mm. 32 of the implants were placed in the anterior maxilla and 18 were placed in the premolar region. It was reported that the success rate after 6 months was 92% in the immediate placement group, and 100% in the delayed placement group.

In animal models, histomorphometric studies on immediate implants placed into sites with periapical pathology have revealed little difference in the percentage of bone-implant contact when compared to non-diseased controls[35].

There seem to be several factors that play an important role in the success of immediate dental implants placed into infected sites, including the surgical technique, achieving primary stability, additional augmentation required, and adequate debridement and degranulation of the infected tissues. Unfortunately, most of these aforementioned studies report only short follow up times.

3.1.3. Antibiotics

Some dental implant failures may be due to bacterial contamination at implant insertion[16]. Infections around dental implants are difficult to treat and almost all infected implants have to be removed[36].

In general, antibiotic prophylaxis in surgery is recommended for patients at risk of infectious endocarditis; for patients with reduced host response, where surgery is being performed in infected sites; in cases of extensive and prolonged surgical interventions; and when large foreign materials are implanted. In order to minimise infection after dental implant placement, various prophylactic systemic antibiotic regimens have been suggested.

A statistically and clinically significant difference in implant failures was found in a meta analysis of six randomised controlled trials by Esposito[37]. Their meta analyses also suggests that 2g or 4g of Amoxicillin administered orally as a single administration one hour preoperatively had a 0.33 risk ratio of reduced dental implant failure. No significant adverse effects were reported neither. The authors also concluded that it is still unknown as to whether postoperative antibiotics are beneficial, and which dosage, duration and type of antibiotic is the most effective.

3.1.4. Soft tissue morphology

Mucosal recession surrounding dental implants has been reported in the literature as being a soft tissue complication. In a prospective clinical study by Evans and Chen[38], the aesthetic outcomes of immediately placed implants was evaluated, based upon the gingival biotype. Of the 42 patient included in the study, 24 of these patients were classified as having a thin biotype with the remaining 18 patients having a thick biotype. Patients with a thin biotype demonstrated greater mucosal recession compared to thick biotype subjects (1.0mm vs. 0.7mm respectively), however this difference lacked statistical significance. Buccal recession was also more prevalent in thin biotypes, than that of thick biotypes (85.7% vs. 66.7%).

3.1.5. Width of keratinised soft tissue

Aesthetic outcomes in implant dentistry are of major concern, and soft tissue morphology is an important factor to consider when working within the aesthetic zone. The presence of an

adequate zone of keratinised mucosa has often been mentioned as essential for the aesthetic success and long term survival of dental implants. It has been assumed that keratinised gingiva and non-keratinised oral mucosa differ in their resistance towards bacterial infection, particularly at the implant-mucosa interface. An adequate zone of keratinised gingiva has been defined as having ≥2mm of masticatory mucosa with ≥1 mm of attached gingiva[39].

However, only limited studies are available evaluating the impact of the width of keratinised tissue on implant survival/success. Bouri et al.[40] conducted a cross sectional study involving 200 implants placed in 76 patients that had been restored for a minimum of 12 months. Bouri's objective was to determine if there was a relationship between the width of keratinised mucosa surrounding a dental implant and the health of the surrounding peri-implant soft and hard tissues. Within this cohort, 110 implants were found to have ≥2mm of keratinised tissue, while the remaining 90 had <2mm. The authors consequently reported that those patients with <2mm had significantly more bleeding on probing and a significantly higher mean alveolar bone loss than for those patients with ≥2mm zone of keratinised tissue.

A similar finding was also reported by Chung and co-workers[41] in their retrospective cross sectional study involving 69 patients. They also investigated the relationship between the presence of keratinised mucosa and the long term maintenance of 339 implants of different surfaces. Clinical parameters including probing depth and radiographic evaluation were analysed. The authors reported a higher occurrence of inflammation and plaque accumulation in keratinised and attached mucosa widths <2mm, while the lack of an adequate attached mucosa zone only had minor effects on alveolar bone levels.

Roos-Jansaker et al.[42] echoed similar sentiments in their report on 999 implants with a follow-up period ranging between 9 and 14 years. The authors reported that the amount of keratinised mucosa was greatly associated with mucositis and bone loss exceeding 3 implant threads.

In contrast, Wennstrom et al.[43] evaluated the soft tissue health surrounding 171 implants in relation to the width of keratinised mucosa. Despite 61% of the implants having no attached gingiva surrounding the implants, they found this to have had no bearing upon the peri implant health of the tissues. It was thus concluded that the lack of attached mucosa presented no issues in the maintenance of the health of peri-implant soft tissues.

As can be seen, there is still controversy regarding the need for keratinised/attached gingiva surrounding an implant, and whether or not this characteristic contributes to its long term survival.

3.1.6. Implant stability

Implant stability is an important factor that influences the long term success of an implant. Esposito et al.[44] performed a systematic review examining implant success rates in immediate, early, and conventionally loaded implants. The authors concluded that a high degree of primary stability is a requirement for successful immediate or early loading.

Orenstein and co-workers[45] completed a prospective study of 3,111 implants placed in 800 patients, in which they focussed upon the 3 year survival of 89 implants that exhibited clinical mobility at the time of placement. This mobility was assessed by gently applying pressure to the implant to determine if it could be depressed or rotated. The authors defined survival as being clinically stable with an absence of pain and infection and reported survival rates for 2 time periods – from implant insertion to prosthetic restoration (loading), and from prosthetic restoration to 3 years. Implant survival of 78.8% was reported from insertion to loading and 95.9% from prosthetic restoration to the 3 year recall. The authors also concluded that the survival was closely related to mobility of the implant at the time of insertion.

Molly[46] conducted a review to evaluate the relationship between bone density and primary stability in implant therapy. It was concluded that there was no evidence supporting any means of defining primary stability, or that any particular threshold could be used to provide a predictive value of future implant outcomes. The primary stability of an implant at placement will remain a critical factor in the survival of an implant, however, the critical level needed to ensure implant survival is still yet to be defined.

3.2. Systemic Factors

Systemic diseases may affect oral tissues by increasing their susceptibility to other diseases or by interfering with healing. Additionally, systemic conditions may be treated with medications or other therapies that potentially affect implants and the peri-implant tissues.

3.2.1. Oral lichen planus, ectodermal dysplasia, Sjögren's syndrome, and psychiatric diseases

There is little evidence to evaluate the impact of scleroderma[47, 48], oral lichen planus[49], ectodermal dysplasia[50, 51], Sjögren's syndrome[52] and neuropsychiatric disorders on the success of dental implant therapy. No controlled studies to date can be found regarding these conditions that demonstrate any positive or negative effect on the outcome of implant therapy. For all these conditions, only case reports or case series could be identified. Similarly, only case reports on selected psychiatric diseases, neurologic disabilities, or genetic disorders – such as Down syndrome[53], autism[54], Huntington disease, and schizophrenia[55] – have been published.

3.2.2. HIV/AIDS

Several case reports have demonstrated successful implant-prosthetic rehabilitation in AIDS and/or HIV patients. A recent report concluded that no medication for routine dental treatment is needed in HIV positive patients, provided that their immune status is stable. A short term study

investigating the clinical outcome of a group of HIV-positive patients compared to a HIV-negative control group found the success rates for both groups were 100% with no differences in clinical outcomes being noted between the two groups[56].

3.2.3. Transplantation

Patients receiving transplanted organs generally undergo long-term immunosuppressive therapy, usually consisting of Cyclosporine A and often also combined with steroids. Several animal studies have demonstrated that Cyclosporine may negative influence bone healing around dental implants and may even impair the mechanical retention of dental implants previously integrated in bone[57, 58].

3.2.4. Osteoporosis

Osteoporosis is defined as a decrease in bone mass and bone density, manifesting with an increased risk and/or incidence of fracture[59]. There are multiple case control studies on the efficacy of dental implants in patients with osteoporosis.

Sixteen women, all with a diagnosis of osteoporosis (low bone density or the occurrence of low-trauma fractures), were assessed in one retrospective study investigating the success of implants placed between 6 months and 11 years previously. The overall success rates were 97.0% for maxillary implants and 97.3% for mandibular implants[60].

Corticosteroids or other endocrinopathies can cause osteoporosis. Corticosteroids are used for a variety of conditions, including Crohn's disease, asthma, pemphigus, and polyarthritis. There have been case reports of dental implants placed and successfully maintained in patients with these conditions[61-63].

Von Wowern and Gotfredsen[64] evaluated implant therapy in subjects with and without a diagnosis of osteoporosis by measuring changes in mineral content of the mandibular bone in 7 osteoporotic and 11 non-osteoporotic women 5 years after functional loading of their implants. No implant failures were observed for any patient, but a statistically significant difference in marginal bone loss over the observation period was noted for the osteoporotic group (0.47mm vs. 0.01mm).

Becker et al.[65] compared a case population of 49 individuals who had experienced implant loss to a control population consisting of 49 successful recall patients. Ten patients in the test group and 7 in the control group had a history of osteoporosis. On analysing the factors associated with implant integration failure they found no association between bone density, assessed at the radius and ulna and the risk of implant failure.

3.2.5. Bisphosphonates

Bisphosphonates reduce or even suppress osteoclast function, and are used in the treatment of such disorders as malignancies affecting the bone (including multiple myeloma and bone metastases of breast and prostate cancer) and for treatment of osteoporosis and Paget's disease. Intravenous bisphosphonates therapy is considered a major risk factor for bisphosphonate-related osteonecrosis of the jaw (BRONJ)[66]. The insertion of dental implants is contraindicated for subjects on this type of medication[67, 68].

The risk of BRONJ appears to be much lower for oral than for intravenous drug administration, but appears to increase with the duration of bisphosphonate therapy[66]. The risk of implant failure in patients taking oral bisphosphonates is currently unknown and remains the subject of controversy.

A controlled study[69] found no statistically significant difference between a group of patients with dental implants receiving oral bisphosphonates (Alendronate or Risedronate) compared to a control group of dental implant patients over the course of at least 3 years. After the observation period, 100 % of the implants in the test group and 99.2% of the implants in the control group (no bisphosphonates) were considered successful.

A retrospective study[70] found similar implant failure rates for patients taking oral bisphosphonates to that observed for a healthy control population. The authors concluded that oral bisphosphonates represent no risk factor for osteonecrosis in implant surgery. They limited this conclusion to a duration of bisphosphonate intake of no longer than 3 years and also warned against simultaneous medication with corticosteroids.

3.2.6. Radiotherapy

When analysing radiotherapy as a risk factor for dental implant placement, two aspects need to be considered: the effect of the cancer or disease, and the effect of its treatment on the tissues containing the implants. Radiotherapy treatment may have been provided before the implants were placed, or treatment may have been in subjects with already existing implants.

Several factors may influence success rates in irradiated patients. These include, but are not limited to: the source, dose, and fractionation of irradiation, concomitant therapies (i.e. chemotherapy, hyperbaric oxygen therapy), the anatomic region of implantation, and the timing of medical and dental therapies[71].

Colella and co-workers[72] compared the implant failure rates of pre-implant radiotherapy and post-implant radiotherapy. This systematic review found similar failure rates (3.2 % vs. 5.4% respectively). The authors acknowledged the difficulty in comparing the studies included due to the heterogeneity of disease conditions, combinations of treatments (radiotherapy and

chemotherapy), sequence of events, time of follow-up, differences in the exact site of implant placement in relation to the region of radiotherapy, implant systems used, confounding variables (systemic disease, smoking, parafunction), and parameters used for assessment. The authors did not find evidence in the literature to support delaying implant placement after radiotherapy for 6 to 12 months to maximise implant success. No implant failures were found to occur below a radiation dose of 45Gy.

A retrospective study reported the survival rates of 631 implants inserted in cancer patients over a mean follow-up period of 6.3 years[73]. This group of irradiated patients were compared to a control group of non-irradiated patients receiving implants at the same clinic during the same period. During this period, 147 implants in patients undergoing radiotherapy were lost (23.3%) and 76 implants (12.4%) failed in the control group. High implant failure rates were especially seen after high dose radiotherapy and a long time after irradiation. Failures occurred in all craniofacial regions, but the greatest risk of implant failures was found for the frontal bone, zygoma, mandible, and nasal maxilla.

There is a risk of osteoradionecrosis in irradiated patients when placing dental implants. Esser and Wagner[74] reported 2 cases of osteoradionecrosis from a total of 249 implants in the irradiated maxilla and mandible. Three patients from a group of 64 patients rehabilitated had necrosis of soft tissues in the floor of the mouth following implant placement. Osteoradionecrosis resulted in continuity defects of the mandible and loss of implants in the region.

Hyperbaric oxygen (HBO) therapy has been advocated to improve the survival and success rates, as well as to minimise the risk of osteoradionecrosis associated with dental implant placement in irradiated bone[75]. Nevertheless, the use of HBO in irradiated patients remains controversial in the literature. In a recent Cochrane systematic review, Esposito et al.[76] compared the success, morbidity, patient satisfaction and cost effectiveness of dental implant treatment performed with

and without HBO in irradiated patients. They concluded that HBO therapy in irradiated patients requiring dental implants may not offer any clinical benefits.

4. MECHANICAL FAILURES AND COMPLICATIONS

Technical (or mechanical) complications that can be encountered include: screw loosening/fracture, veneering material chipping/fracture, wear and/or total replacement of acrylic resin teeth, framework fracture, loss of screw access filling material, fracture of the opposing restoration, or patient dissatisfaction. These may be further categorised into implant-related and prosthesis-related.

The most frequent implant related technical complication reported by Papaspyrikakos and co-workers[77] for implant-supported fixed complete dental prostheses was abutment/occlusal screw loosening. From a total of 752 implants analysed, screw loosening was reported to occur in 31 implants. The estimated annual complication rate for 5 and 10 years were 10.4% and 20.8% respectively. They also found that the second most common implant-related technical complications was screw fracture. Parafunction resulting in occlusal overload, cyclic stress loading fatigue from occlusal forces and framework misfit have been suggested reasons of screw fracture. The 5 and 10 year estimated complication rates were 9.3% and 18.5% respectively.

Screw-related complications are indeed commonly reported. In their meta-analysis, Bozini et al.[78] reported estimated rates of abutment and prosthetic screw fracture after 15 years of 6.3% and 11.7%, respectively. Implant screw joints are susceptible to screw loosening or fracture because of the magnitude and direction of oral forces and the strength limitation of the components. Factors that may contribute to screw complications include: inadequate preloading on the screws, over tightening of the screws leading to stripping and/or screw deformation, and/or occlusal overload from parafunction, occlusal interferences, or excessively long cantilevers.

Dudic and Mericske-Stern[79] categorised prosthetic problems with overdentures into the following groups: complications and failures of implant-retained parts (abutments, bars and anchors, retainers, occlusal screws), mechanical and structural failures of prostheses (denture base, teeth,

prosthetic design, fabrication of new dentures), prosthesis-related adjustments (relining, occlusion, aesthetics, hyperplasia).

A meta-analysis of the prosthodontic complications rates of implant supported fixed dental prostheses in edentulous patients[78] reported veneer fractures representing the most frequent prosthodontic complication with estimated cumulative rates of veneer fractures over an observation period of 5, 10 and 15 years of 30.6%, 51.9% and 66.6%, respectively. Acrylic resin veneers require sufficient material thickness and support from their underlying frameworks to withstand forces in the oral cavity. Veneer fractures may be caused by material failure, design issues, and/or technical errors[80]. The estimated rates for framework fractures, material wear, and aesthetic deficiencies during the same follow-up period were 8.8%, 43.5%, and 9%, respectively. The frequency of both acrylic resin fractures and wear is influenced by such factors as the opposing dentition and the presence of parafunctional habits[81, 82].

Fracture of the metal framework is a non-reversible complication that presents to a lesser extent. Commonly cited reasons for their occurrence are poor alloy choice and decreased cross-sectional dimension distal to the most posterior implant[83]. Most fractures occurred at the beginning of the cantilever arms[84]. Thus attention should be given to the selection of the alloy type, the framework design, and the height of the framework[85].

5. SHORT AND REDUCED DIAMETER IMPLANTS

Ideal implant placement requires an adequate osseous housing within the residual ridge. Often, due to the physiological resorptive effects that ensue following tooth extraction[86], this residual ridge is inadequate. In such cases, augmentation procedures are required either simultaneously or preceding implant placement. Bone augmentation techniques such as guided bone regeneration (GBR)[87], block grafts[88], sinus elevation[89], and distraction osteogenesis[90] have been proposed – all of which can lead to successful increases in bone volume of the residual ridge for implant placement. As a result, alternative treatment modalities have been suggested to overcome this challenge, including the placement of short dental implants or reduced diameter implants[91]. The advantage of such alternatives includes the avoidance of vital anatomic structures, reduced surgical mortality, reduced treatment time and costs, which also contributes to increased patient satisfaction[92]. Further benefits include a reduced risk of sinus perforation and mandibular paraesthesia. Both short and reduced diameter implants have been reported to have quite successful outcomes.

There is a general lack of consensus within the literature defining the dimensional limits of a short implant. Various dimensional cut-offs range from 11mm[93], 10mm[94], down to 8mm[95] have been employed. It has also been argued that because an implant can be placed at differing horizontal levels, a short implant should be defined as an implant that has been designed with an *intra-bony length of 8mm* or less[96].

Short implants have been demonstrated in the literature to be a predictable and reliable alternative to bone augmentation procedures[96]. In terms of survival rates, short implants have relatively high survival rates of 99.1% over a mean, albeit short observational period of 3.2 ± 1.7 years[97]. They also have lower reported failure rates when compared to longer implants[98, 99]. The high survival rate is however dependent upon confounding factors, such as bone density, patient

factors (systemic diseases, smoking status, parafunctional habits), the implant surface, timing of implant placement and prosthetic factors[100, 101]. Most implant failures have been reported in the literature to be early failures – that is occurring during the healing phase, at abutment connection, or during the first year of function[102]. Jaw shape and bone quality have been considered to be the most important determinants of early failures in Brånemark Dental Implants[103].

When comparing survival rates of implants placed in augmented sites to that of short implants placed in native bone, more favourable results are yielded with shorter implants. The implant survival rates of when placed in augmented sites ranged from 92.1-100% for guided bone regeneration; from 90-100% for distraction osteogenesis and from 76-100% for onlay bone grafts over 1-7 years[104]. SLA implants placed in sites with residual bone heights of 5mm requiring transmucosal sinus floor elevation yielded a 5 year cumulative survival rate of 95.71%, in comparison with 98.2% for short implants with the same surface being installed in similar maxillary sites[105]. Similar findings were also published by Tonetti and co-workers[106]. Thus, the use of short implants as an alternative to additional grafting procedures could be advocated to solve specific problems.

Short implants have been demonstrated to have greater micro-movements, especially in the osseous regions in contact with the compression surfaces (the side away from the force vector)[107]. In addition, it has also been demonstrated that the straighter the alignment of the implant, the greater the potential for bending and flexure of the implant[108]. This in effect transfers the greatest stress potential on the crestal third of the implant, especially when the implant is subjected to lateral forces, with very little of the stress being transferred to the apical portion[109]. In fact, it has been demonstrated that the maximum bone stress is a constant force that is concentrated around the coronal cortical anchorage point. This was also a feature that was independent of the implant length and bicortical anchorage[107]. In addition, the first 3-5 threads are mostly involved in the

stress absorption[107]. Furthermore, the increase in implant length from 7mm to 10mm did not significantly improve its anchorage[110]. These aforementioned studies however, do suggest that an optimal implant should be wider rather than longer. Therefore, implant diameter, rather than length may be more critical in the distribution of prosthetic loads to the bone-implant interface.

Similar to short implants, the choice of implant diameter is dependent upon the type of edentulism, the volume of residual bone, the available space for prosthetic reconstruction, the emergence profile, along with the occlusion. Narrow diameter implants (those defined as having a diameter less than 3.75mm), are indicated where there is reduced interradicular bone or a thin alveolar crest, and for the replacement of teeth with a small cervical diameter. Here, the placement of a narrow diameter implant – like short implants – can be an alternative to additional bone-augmentation surgeries. The same surgical and prosthetic guidelines applied to regular sized implants (diameter ≥3.75mm) can be applied to narrow diameter implants, with a few studies analysing the clinical outcomes of such implants. These reports have demonstrated good medium and long term results. Vigolo and Givani[111] presented a 5 year retrospective study on 52 mini-implants with diameters ranging from 2.9-3.25mm that were used for single tooth restorations. Here, they reported a total implant survival rate of 94.2%. This was then preceded by a subsequent 7 year prospective study of the same type of narrow diameter implants for single tooth or partial prostheses, where similar survival rates were achieved (95.3%)[112]. Similar survival rates were reported by Zinsli and co-workers[113] examining 298 3.3mm diameter implants restored with a variety of prostheses (single crowns, fixed partial or complete prosthesis, or overdentures). They reported a cumulative survival rate of 98.7% and 96.6% after 5 and 6 years respectively. The investigators also noted that the failures of these narrow diameter implants were infrequent, and that prosthetic complications that occurred were mainly due to fatigue fractures, which were unrelated to the use of narrow diameter implants.

It has also been suggested that the implant diameter may also be an influencing factor in the survival rates of implants, with wider implants being hypothesised as having greater mechanical stability and osseointegration as a result of the bicortical stabilisation, which increases the surface area for osseointegration, and higher contact bone-implant contact area[114]. This also leads to better stress distribution within the surrounding bone[115]. Finite element analysis have revealed a 3.5 fold reduction in crestal strain[116]. The same study also noted a 1.65 fold reduction in crestal strain with increasing implant length. Other studies have also refuted the claim that implant diameter can compensate for implant length however[98, 117]. Renouard and Nissand's[95] review paper noted that narrow diameter implants reported low failure rates collectively. The authors also concluded that the levels of evidence provided by the literature remains low, with very few randomised controlled studies being available to investigate the relationships between bone density, implant length and diameter, and survival rates. From a biomechanical perspective, short implants are a predictable treatment modality in oral rehabilitation, with lower failure rates often being achieved.

Prosthetically, a wider implant diameter can aid in decreasing the cantilever that may be encountered in the restoration of wide edentulous spaces by facilitating more favourable distribution of occlusal forces[118]. The use of a wide implant diameter will also facilitate a more optimum emergence profile in such situations, thus aiding in aesthetics, whilst also facilitating oral hygiene measures[119]. Conversely, where narrow diameter implants are used for the restoration of wide edentulous spaces, increased strain at the crestal portion of the implant, along with an unfavourable distribution of occlusal forces on the implant will result[120]. In addition, these narrow diameter implants will be at increased risk of implant body and abutment screw fracture[121].

Modifications to the implant design have also been applied to counteract their reduced length. These modifications include modified body shapes, new thread designs, and surface

modifications[122]. New developments in surface micro-topography and chemistry, such as acid-etching, grit blasting and titanium plasma spraying, have altered micro-topography of the implant surfaces, increasing their roughness and surface area. Short implants with a roughened surface have demonstrated a significantly lower failure rate, compared with that of machined surfaces, with an odds ratio of 3.6[117]. When rough surface dental implants were analysed, there were no significant differences regarding the cumulative survival rate between wider and narrower implants[123]. A similar conclusion was drawn in a meta-analysis[117], where short narrow-diameter implants did not demonstrate any higher failure rates when compared to their regular diameter counterparts, with rough-surfaced implants with a minimal length of 7 mm representing no risk factor for implant failure, provided they were not placed in the anterior maxilla.

Excessive crown-to-implant ratios (i.e. a ratio greater than 1:1) have been reported to be detrimental to implant survival[124]. Crown-to-implant ratios between 0.5 and 1 were proposed to prevent peri-implant bone stress, crestal bone loss, and eventually implant failure[125]. A recent systematic review which included only 2 studies has refuted this claim however[126].

Bone quality has been hypothesised as being a strong predictor of treatment outcome, given that the lowest survival rates are reported in the posterior maxilla for short implants[127, 128]. Greater survival rates are reported in other anatomical sites, and this may be the result of the increased bone density found at these other anatomical areas (the mandible for instance), the improved mechanical properties of the implant-bone interface, and the reduced stress concentration in bone. Different healing potentials between the maxilla and mandible have been demonstrated, with maxillary bone demonstrating peri-implant cancellous bone that includes rapid formation of new trabeculae by the recruitment of new populations of osteogenic cells within the adjacent healing compartment in unison with remodelling of the pre-existing lamella trabeculae. While in cortical bone, peri-implant bone regeneration relies exclusively on lamellar bone remodelling[129]. All of these aforementioned factors facilitate primary stability and early osseointegration[128].

Low bone density and poor bone quality within the implant site has been hypothesised to be the cause of many short implant failures. Short implants placed in type IV bone resulted in significantly more failures than those placed in type III bone[95, 130]. Moreover, the highest failure rates for short implants were reported in older studies that were performed under routine surgical procedures irrespective of the bone quality, with machined-surface implants, and in anatomic sites with poor bone density[95]. Therefore, a reduction in bone density may lead to early implant failure due to peri-implant strains[116].

Differing survival outcomes of short implants have been hypothesised to be the result of the operator's learning curves. In their review article, Renouard and Nisand[95] noted lower survival rates for implants that were placed utilising a standard surgical protocol, which may have reduced primary stability of the implant at insertion. Some of the more recent publications on short implants though, have instead employed an adapted surgical protocol that facilitates primary stability. In these instances, osteotomy preparation was altered in sites of poor bone density, through either the use of osteotomes, not tapping and/or not countersinking.

6. PERI-IMPLANT DISEASES

Whilst long-term success[1, 131, 132] has been documented with dental implants, they are not immune to complications, which include biological complications involving the hard and soft peri-implant tissues. Such biological complications include peri-implant mucositis and peri-implantitis – both of which pose significant challenges for the clinician and the patient[133].

6.1. DEFINITIONS AND PREVALENCE OF PERI-IMPLANT DISEASES

Peri-implantitis and *peri-implant mucositis* are inflammatory lesions affecting the tissues surrounding an implant[134]. Peri-implant mucositis is defined as an inflammatory lesion confined to the soft tissues surrounding an implant, in the absence of bone loss proceeding the initial bone remodelling that occurs during healing. Peri-implantitis on the other hand, is an inflammatory lesion that also affects supporting bone beyond biological bone remodelling[135]. It must be noted that bone loss due to bacterial infection is to be discriminated from bone loss due to remodelling, such as in instances where implants are placed too deep[136], or in too close proximity to neighbouring structures[26].

Diagnosis of peri-implant mucositis requires bleeding and/or suppuration on probing and no evidence of radiographic bone loss beyond that seen following biological bone remodelling. Bone loss can only be determined by comparison against a baseline radiograph that was taken at the time of suprastructure placement. Where such a baseline radiograph does not exist, it has been recommended that a vertical distance threshold of 2 mm from the expected marginal bone level following remodelling post-implant insertion be adopted instead[135]. A differential diagnosis of peri-implantitis must also include the investigation and identification of any other possible contributing underlying problem(s), such as fracture of a component, or the presence of a foreign body.

The prevalence of peri-implant mucositis is a common occurrence[137], and has been reported to be present in 48% of implants followed for a period between 9-14 years. On the other hand, a variance of incidences for peri-implantitis has been reported in the literature. This is due in part to the lack of consensus used to define the radiographic bone loss threshold in describing the disease criteria. Furthermore, the diversity of implant brands and designs also hampers this process in reaching a consensus. The 1st European Workshop on Periodontology for instance, suggested that the '*criteria of success demand an average marginal bone loss of less than 1.5 mm during the first year after the insertion of the prosthesis and thereafter less than 0.2 mm annual bone loss.*'[138] Berglundh on the other hand proposed the following criteria for peri-implantitis; 2.5 mm peri-implant bone loss; probing depths greater than 6 mm; and the presence of BOP or suppuration on probing[1]. While other studies have diagnosed peri-implant diseases on the basis of exposed implant threads following over 1 year in functional loading[4, 137]. Thus, incidences of peri-implantitis in the literature have ranged from 6.61%[137] to 36.6%[139] over an average observation period of 10 years.

6.2. PATHOGENESIS

The inflammatory process of peri-implant mucositis surrounding a dental implant is very much analogous to that of gingivitis surrounding a natural tooth. Following implant placement, glycoproteins from saliva adhere to the exposed titanium surfaces, giving rise to microbiological colonisation and biofilm formation[140]. Experimental gingivitis models as originally described by Löe[141] have been used to outline the cause-effect relationship that exists between biofilm formation and peri-implant mucositis[142]. The tissue response to plaque has also been observed in a dog model, demonstrating that the size of the inflammatory infiltrate in response to the bacterial challenge created by de novo plaque formation was identical to that of adjacent natural teeth[143]. The clinical and microbiological response to the development of experimental gingivitis

and experimental peri-implant mucositis has also been studied by Pontoriero and co-workers[142], with no significant differences between both lesions.

The epithelial sealing around implants has been reported to be similar in function to that adjacent to natural teeth[144]. In fact, it is concluded that there is no evidence that any structural differences between teeth and implants exist that would significantly alter the host response to the bacterial challenge[142, 145]. Thus, the hypothesis of biofilm formation on implant surfaces causing peri-implant mucositis, and that subsequent removal of this biofilm will resolve this condition, is in fact an extrapolation of these findings.

To this effect, experimental peri-implantitis has also been replicated in ligature-induced animal models. Lindhe[146] found that peri-implant lesions developed directly into the surrounding supporting bone. This is in contrast to periodontitis lesions of natural teeth, where the lesion was contained by the periodontal fibres. Similar histological observations were also reported by Lang[147] in his ligature-induced peri-implantitis and periodontitis lesions in monkeys.

Treatment aimed at eliminating the biofilm by mechanical debridement of the peri-implant pocket and systemic antibiotics seem to improve clinical conditions[148]. In a dog model, mechanical debridement in conjunction with systemic Amoxicillin and Metronidazole yielded in resolution of the experimentally induced peri-implantitis lesions[149].

Peri-implant diseases are also associated with gram-negative anaerobic bacteria similar to those found around periodontally affected teeth. The composition of associated microflora is vastly different between failing and successful implants. Successful implants were colonised by gram-positive cocci, whilst large amounts of gram-negative bacteria were found surrounding failing implants. Fusobacteria, spirochetes, and black pigmenting organisms, such as *P. intermedia* were often found in diseased sites[140, 150-152].

It has been hypothesised that the implant surface roughness as well as its chemical composition may have an impact on both the quantity and quality of plaque formation. Contamination of the titanium oxide layer has been linked to failure of osseointegration through peri-implantitis pathogenesis. Teughels and co-workers[153] noted that rougher surfaces as well as those surfaces with high surface free energy (a natural characteristic of titanium), will accumulate and retain more plaque. The author also added that initial adhesion of bacteria often begins in locations with high wetability (also another natural characteristic of titanium), and where bacteria are protected from shear forces – such as in grooves, pits and implant threads.

In a similar manner to gingivitis being a precursor to periodontitis, peri-implant mucositis is also the precursor to peri-implantitis. However, like the causal relationship between gingivitis and periodontitis, peri-implant mucositis does not necessarily always progress to peri-implantitis. Additionally, evidence exists to suggest that implant mucositis, like gingivitis, is reversible when effectively treated[152].

Similar to periodontitis, peri-implantitis is the result of a host-modulated immune response to the overwhelming bacterial insult. Similarities between microorganisms associated with both periodontal disease and peri-implantitis have been reported in the literature. High proportions of putative periodontal pathogens, such as *P. gingivalis*, *P. intermedia*, *T. forsythia*, and *T. denticola* have been sampled from the implant surfaces within peri-implantitis lesions[151, 154]. Additionally, *S. aureus* and *Enterococci spp.* may also be important pathogens in the initiation of peri-implantitis lesions[155, 156]. In contrast, healthy peri-implant microbiota are associated with gram-positive facultative cocci and rods[157].

Human biopsies of peri-implantitis and periodontitis lesions have demonstrated that these two lesions share many common features. In both lesions, the connective tissue adjacent to the epithelium is infiltrated by inflammatory cells, with B-lymphocytes and plasma cells being the predominating cell types. Upregulation of pro-inflammatory cytokines is also another common

feature shared between these two lesions, with such cytokines as interleukin (IL)-1, IL-6, IL-8, IL-12, and tumour necrosis factor-alpha (TNF-α)[158].

Despite the similarities between peri-implantitis and periodontitis lesions in terms of the pathogenic bacteria and the immunological components, the rate of disease progression and tissue destruction appears to be more rapid in peri-implantitis lesions. In experimental dog studies, undisturbed plaque accumulation on implants and natural teeth over 3 months was investigated[159]. Clinical findings after 3 months demonstrated the formation of large plaque masses, inflamed soft tissues surrounding the implants and teeth, as well as bleeding on probing. Histological examination revealed that both the gingiva and peri-implant mucosa showed an inflammatory cell infiltrate contained within the apical extensions of the junctional epithelium. The composition of these infiltrates was similar, with extensive loss of collagen coupled with a significant increase in the number of inflammatory cells. It was however noted that the inflammatory lesion was almost 3-fold higher, and the apical extensions of the lesion was greater in the peri-implant mucosa compared to the gingiva. This host response has been demonstrated irrespective of the implant system employed[160].

In another monkey study, the inflammatory response of ligature-induced peri-implantitis and ligature-induced periodontitis was investigated in both ankylosed and normal teeth[161]. Histological examination of the teeth and implants revealed a greater extent of bone loss and inflammatory infiltrate around implants and ankylosed teeth. The authors speculated that the increased susceptibility to inflammation and bone loss may be related to the absence of inserting collagen fibres in both the implants and ankylosed teeth.

It has been noted that following ligature removal, some of these lesions will go into remission, while the majority of sites will experience further bone loss. Studies have demonstrated that around 25% of cases will display further rapid bone loss within a 1 year period following ligature removal[162]. This implies that once a peri-implantitis lesion has been established, spontaneous

progression of the disease with additional bone loss will probably ensue. Similar observations were also made by Berglundh et al.[163] comparing peri-implantitis lesions with periodontitis lesions. They noted that a 'self-limiting' process seems to exist in the tissues surrounding natural teeth due to a protective connective tissue capsule of the supracrestal gingival fibres. This connective tissue capsule seems to separate the lesion from the alveolar bone. In contrast to natural teeth, this self-limitation could not be observed in peri-implant tissues, where the lesion extended to the bony crest. Consequently, this lesion has also been observed to progress into bone marrow in some instances[164, 165]. Based upon the tissue anatomy surrounding implants it seems that all implants appear to be susceptible to peri-implantitis[166]. Thus it can be expected that some peri-implantitis lesions would progress quite rapidly and therefore the diagnosis and treatment should be completed in a timely manner.

6.3. RISK FACTORS

Human clinical longitudinal studies of a prospective nature are required to accurately identify true risk factors[155]. The following risk factors that may lead to the establishment and progression of peri-implant diseases[167] have been identified.

6.3.1. Poor plaque control

Given the microbial aetiology of peri-implant diseases, the daily removal of the biofilm on implant surfaces is essential in the prevention of these diseases. The prosthetic design should facilitate mechanical cleaning by the patient with appropriate oral hygiene aids, and also allows clinical evaluation and probing by the dentist. The literature supports this assertion with Lindquist[168] reporting an association between poor oral hygiene and peri-implant bone loss after a period of 10 years. Similarly, Ferreira and co-workers[169] also reported a dose-dependent association between full plaque scores and peri-implant diseases, where very poor oral hygiene was highly

associated with peri-implantitis, with an odds ratio of 14.3; 95% CI 2.0-4.1. Another study performing site level analysis of implants found that a diagnosis of peri-implantitis is frequently associated with limited accessibility or capability for appropriate oral hygiene measures in contrast to accessible sites where peri-implantitis was rarely encountered[170]. Thus the establishment of a regular periodontal maintenance program would help to assess the adequacy of plaque removal efforts and to allow intervention at the earliest convenience when problems are detected.

6.3.2. Previous periodontal disease

Although systematic reviews have indicated that implant survival rates may not be affected by previous periodontal history, peri-implantitis was found to be a frequent occurrence in patients with a history of treated periodontitis, as compared to those without a history of periodontitis[42, 169, 171, 172]. It must be noted that despite showing a positive correlation, these systematic reviews still display a fair degree of heterogeneity in the patient profile and designs, outcome measures, and Supportive Periodontal Therapy regimes. Furthermore, there was also a failure to mention any confounding factors within the included studies, and thus definitive correlations cannot be made[3].

6.3.3. Smoking

Smoking has been identified as the second most important risk factor for both periodontitis and peri-implantitis after poor plaque control[155]. The association between smoking and peri-implantitis has been observed in cohort studies and in systematic reviews[173-176]. A higher risk was associated with smokers, with reported odds-ratios ranging between 3.8 to 31.6[177].

6.3.4. Diabetes

There is limited evidence suggesting an association between diabetes and peri-implantitis. Systematic reviews have suggested that the current evidence does not draw a definitive conclusion of diabetics suffering from a higher incidence of peri-implantitis[169, 175, 176]. These reviews however, do highlight that glycaemic control is an important factor when assessing this relationship. Hyperglycaemia can impact tissue repair and host defence mechanisms with the formation of advanced glycation end products, which affects both neutrophil function and collagen homeostasis[178]. Consequently, the tissue repair ability and defensive mechanisms within diabetic patients is impaired against the bacterial insult presented by plaque.

6.3.5. Genetic traits

Genetic variations have been referenced as a risk factor for peri-implantitis, however, there are conflicting results that draw no definitive conclusion between IL-1 gene polymorphism and peri-implantitis. A recent systematic review[179] which included 27 articles found no consensus amongst those studies. Gruica and co-workers[180] though, reported that IL-1 genotype positive smokers had a significantly greater risk of developing biological complications and/or peri-implant bone loss.

6.3.6. Occlusal overload

Occlusal overload has been hypothesised in the literature as being a possible contributor to peri-implant bone loss. Although clinical studies have mentioned that occlusal factors may be associated with the loss of oral implants, this causative relationship has never been convincingly demonstrated. The combination of small cohort sizes with an even smaller frequency of implant failures together with the difficulty in quantifying the magnitude, direction, duration and frequency of the applied occlusal force and the tolerance threshold of the host, make reporting such a correlation rather difficult[181]. Much of the knowledge from this field has been extrapolated

from a small number of experimental animal studies, where it has been difficult to draw conclusions.

Implants have also been demonstrated to be less tolerable to non-axial occlusal loading, with more dynamic remodelling being demonstrated surrounding the cortical, and especially trabecular bone tissue in a dog model[182]. Forces affect different bones or bone tissues rather differently, with a degree of adaptation. When a mild force (1500-3000 microstrain) is subjected to a dental implant, the resultant biological reaction is one of bone apposition. A force beyond this range will result in bone resorption and eventually even lead to fracture[183]. A recent systematic review has also suggested a positive correlation between peri-implant bone loss and occlusal overload[184].

6.3.7. Residual cement

Cemented prostheses are commonly used in practice today owing to their relative simplicity, elimination of prosthesis screw loosening, improved aesthetics, and economy when compared to a screw-retained prosthesis. However, the cementation may result in the possibility of leaving behind traces of excess cement on the implant or in the surrounding soft tissues, resulting in peri-implant diseases[185, 186]. Furthermore, this excess cement may also impinge on access for mechanical debridement of the subgingival space[187]. The identification of excess cement may be difficult in a radiographic survey due to most commonly used cements having poor radiodensities[188]. The role of residual cement in the aetiology of peri-implantitis is still unclear. It has been proposed that the cement may act as an irritant to the peri-implant mucosa, similar in nature to the effect of calculus around the roots of periodontally involved teeth[189]. Furthermore, the surface of the cement remnants may facilitate bacterial or biofilm attachment. Consequently, the residual cement may facilitate microbial contamination[190] or it may contribute to a toxic reaction by the peri-implant tissues[191].

6.4. DIAGNOSIS

Early detection of peri-implant diseases along with early intervention is essential, given that the treatment of peri-implantitis is not predictable and also difficult to perform. The diagnostic process is focused on diligent evaluation of the peri-implant soft and hard tissues and involves a combination of clinical and radiographical parameters – including the inflammatory status of the peri-implant mucosa, gingival recession, bleeding on probing, probing pocket depths and radiographic bone level changes over time.

The first comprehensive clinical and radiographical diagnosis and assessment of the implant should be completed following final prosthesis installation. These measurements are recorded as baseline measurements and used for comparison to detect any pathological changes in the future.

6.4.1. Probing

Probing is performed around the entire circumference of the implant, similar to that of a natural tooth. It is usually completed with a traditional manual periodontal probe using a probing force of between 0.2-0.3N[192, 193]. Removal of the prosthesis can help facilitate probing around the entire circumference of the implant[194]. It has been demonstrated that any disruption of the soft tissue-implant interface caused by probing will result in the formation of new epithelial attachment within 5 days[193]. Probing is to be performed to the base of the implant sulcus, and the probing depth recorded as the measurement between this reference point to the crest of the peri-implant mucosa. Clinical attachment levels can be measured against a fixed reference point on the suprastructure.

It is important to note that changes in these parameters over time compared to the baseline measurements mentioned above are indispensable to diagnose the incidence of pathological

changes in the peri-implant tissues. Without accurate baseline measurements, early pathological changes cannot be detected. Factors including the surgical technique employed, implant design, implant positioning, or the design and quality of the suprastructure will impact upon peri-implant tissues and are able to initiate non-pathological remodelling processes.

Bleeding on probing alone is indicative of soft tissue inflammation, while increasing probing depth and bleeding indicates the need for additional radiographic examination[195]. In peri-implantitis, the probe may penetrate beyond the connective tissue onto the alveolar bone. The presence of suppuration is indicative of acute pathological changes[137, 196] and warrants further evaluation.

6.4.2. Radiographs

While peri-implant mucositis is an inflammatory lesion that is confined to the peri-implant mucosa, peri-implantitis also encompasses bone loss. Therefore, radiographic examination is an important diagnostic aid to diagnose and to determine the extent and pattern of peri-implant bone loss. Radiographs must be taken at both the time of implant placement and particularly at the time of suprastructure insertion. These radiographs are considered the baseline and are used to compare all future radiographs against. It must also be stressed that not all peri-implantitis lesions may be radiographically detectable. The radiographs should be taken perpendicular to the implant body and must be able to clearly demarcate the implant threads. In cases where there has been an increase in probing depths coupled with positive bleeding scores, supplementary radiographs may reveal an implant-specific saucer-shaped intraosseous lesion.

Unlike periodontitis, peri-implantitis lesions can be localised to just the facial and/or lingual aspects of the implant, and thus may be masked with routine dental radiography. To overcome this, cone beam computed tomography (CBCT) is now increasingly being employed to visualise the extent of these lesions in a three-dimensional plane[197]. It must be noted however that there are limitations to the accuracy of CBCT when assessing peri-implant defects of horizontal bone width

of <0.5mm, where it has been reported that there was a significant discrepancy between the radiological and the histological evaluations (1.93 ± 1.59mm) of peri-implant defects <0.5mm[198].

6.4.3. Mobility

Implant mobility is a useless parameter for the diagnosis of peri-implant diseases. Implant mobility is only found where integration has been completely lost, and indicates the need for explantation[140]. Even with significant bone loss, an implant with remaining osseointegration in the apical portion may not demonstrate mobility[199]. Mobility of the restoration and/or abutment however is indicative of loose or broken components. This can promote plaque accumulation within or surrounding the mobile components and thus may facilitate the development of peri-implant diseases.

Studies have demonstrated that bacteria are able to reside within the internal components of implants, where they are also sheltered from host defences. Bacteria have also been found within the implant-abutment and at the abutment-prosthesis interface[200, 201].

6.4.4. Secondary diagnostics

Bacterial culturing, inflammatory markers, and genetic diagnostics have been proposed as additional methods for evaluating the condition of peri-implant tissues. The efficacy of these tests, however, remains to be validated[140].

Non-invasive diagnostic tools, such as resonance frequency analysis (RFA)[202], have been advocated to monitor implant stability. RFA quantifies the degree of bone-implant contact during the early phases of healing and has been used to study jaw bone healing following implant installation. Implant stability is assumed when the RFA quotient is within the range of 57-70. However, no RFA predictive value for loss of implant stability has ever been evaluated. Therefore, the use of this diagnostic method in the diagnosis of peri-implantitis is still questioned[203].

7. TREATMENT

7.1. Peri-implant mucositis

Therapies proposed for the management of peri-implant mucositis appear largely based upon the evidence available for the treatment of gingivitis. Hence, the mechanical removal of the biofilm constitutes the basic element for treatment. Only few studies are available evaluating the various anti-infective protocols for treating peri-implant mucositis. However, both animal and human clinical studies confirm that peri-implant mucositis is reversible by mechanical cleaning alone[204]. In a monkey study[205], experimentally induced peri-implant mucositis lesions were treated with either; mechanical cleaning only; mechanical cleaning with adjunctive 0.2% chlorhexidine gel and 0.12% chlorhexidine mouth rinse; or no treatment at all. No significant differences were found between the two treatment groups in terms of plaque indices, gingival inflammation and histological appearance after 2 months of treatment. Given the similar outcomes achieved from both treatment modalities, the authors concluded that mechanical cleaning alone was sufficient in achieving clinical and histological resolution of the peri-mucositis lesions.

Similarly, in a recent randomised clinical trail[206], 29 patients with one implant diagnosed with peri-implant mucositis were assigned to either test treatment (consisting of tooth brushing instruction together with 0.5% chlorhexidine gel), or control treatment (consisting of tooth brushing instruction with a placebo home-applied gel). At baseline, all implants also received non-surgical mechanical debridement before the patient was allocated to their respective treatment. After 3 months, no statistical significant differences in peri-mucosa inflammation (as assessed by bleeding scores and mean probing depth) were noted between the two treatment modalities. The authors also noted that complete resolution of bleeding was only achieved in 38% of the implants. It was concluded that the adjunctive use of chlorhexidine gel did not provide any additional benefit compared to mechanical cleaning alone.

7.2. Peri-implantitis

There is currently no accepted standard for the treatment of peri-implantitis[207]. Given the similarities in aetiology between periodontitis and peri-implantitis, anti-infective measures similar to those used to treat periodontitis have been adopted to treat peri-implantitis[208]. Thus four main strategies are currently employed: mechanical debridement, pharmacological therapy, surgical therapy, and laser therapy. The treatment of peri-implantitis can also be staged into a non-surgical phase (mechanical debridement with or without antimicrobial therapy) followed by a surgical phase (resective or regenerative therapy)[207].

Mechanical debridement of the contaminated implant surfaces must always be preceded by detailed oral hygiene instructions. Given the importance of plaque control as a risk factor in the development of peri-implant diseases, the patient's supragingival plaque control is paramount in retarding the recontamination and recolonisation of the subgingival environment with periodontal pathogens. Furthermore, existing periodontal disease should ideally be treated prior to implant placement as periodontal pockets are a potential niche for peri-implant pathogens. If peri-implantitis is found in patients with untreated periodontitis, periodontal treatment must also be concurrently delivered when treating the peri-implantitis.

Various modalities to treat infected implants have been described and tested in animal and human studies. The primary treatment goal is to clean and disinfect the implant surface to render it biocompatible to allow healing of the inflammatory lesion, and even possibly facilitate re-osseointegration.

Mechanical debridement should be carried out by non-metal instruments made from carbon fibre, plastic or titanium, as common metal instruments may damage or roughen the implant surface[209]. It has been proposed that this induced roughness may promote plaque accumulation, although there is no direct evidence to support this[209]. Damage to the implant surface induces

changes in the chemical oxide layer that may increase the amount of corrosion. This process consequently impairs fibroblast adhesion and thus biocompatibility of the implant[210].

Thorough mechanical debridement can be impaired where limitations exist in terms of access and visibility and/or the availability of instruments. In such instances, pharmacological intervention – encompassing systemic and local antibiotics and chemotherapeutic agents – may be indicated as adjuncts to mechanical therapy and/or surgery. These agents may be delivered directly into the peri-implant sulci or as a mouthrinse to deplete these residual plaque reservoirs. Limited clinically controlled trials have evaluated the efficacy of such adjunctive therapy. Ciancio and co-workers[211] reported statistically significant reductions in plaque, gingival and bleeding indices compared to the placebo control group following the administration of Listerine in conjunction with mechanical debridement. Porras et al.[212] reported the additional application of 0.12% chlorhexidine gel along with local irrigation of 0.12% chlorhexidine solution with mechanical debridement did not enhance the clinical results when compared to the mechanical debridement-only cohort. Decontamination procedures including the use of sterile saline, chlorhexidine, citric acid, hydrogen peroxide, and CO_2 laser have been evaluated in animal studies. No significant differences were observed between these different decontamination agents[213]. Similar findings were also found with the use of abrasive air-powder in an animal model, where predictable and complete resolution of the experimental peri-implantitis lesions was not accomplished[214]. However in a randomised controlled clinical trial[215] involving 30 patients with at least one implant affected by peri-implantitis, the use of an air-abrasive device with glycine powder resulted in a significantly greater reduction in bleeding on probing (43.5 ± 27.7% vs. 11.0 ± 15.7% [$P < 0.05$]), as compared with mechanical debridement combined with antiseptics (chlorhexidine digluconate).

The clinical and microbiological effects following mechanical therapy have also been examined, with levels of *T. denticola*, *T. forsythia*, *P. micra*, and of *F. nucleatum* being significantly reduced[216].

The use of antibiotics as an adjunct to mechanical debridement of peri-implantitis lesions remains controversial, given the lack of randomised controlled trials. Differing antibiotic regimes, dosage, delivery systems, timing, and duration make such comparisons difficult[217]. Leonhardt and co-workers[218] reported a 58% success rate following surgical treatment in conjunction with systemic antibiotics (Amoxicillin and Metronidazole) on their cohort of 9 patients with 26 implants. Despite their interventions, 7 implants in four of the patients were lost. Büchter et al.[219] reported favourable clinical outcomes with the use of local antibiotics (Doxycycline) in his cohort of 28 patients being treated for peri-implantitis following mechanical debridement of the implants. He reported significant improvements in bleeding scores along with a significant difference in mean probing attachment levels of 0.6 mm. Mombelli and co-workers[148] also reported favourable improvements after 1 year in both the mean probing depths, and quantitative as well as qualitative changes in microbial parameters following the administration of systemic antimicrobials (Ornidazole) in conjunction with mechanical debridement.

In a randomised clinical trial[220] comparing the efficacy of an adjunctive local antibiotics (minocycline microspheres) with a local antimicrobial (1% chlorhexidine gel), demonstrated that the use of the microspheres resulted in a significantly greater reduction of mean probing depths of 0.3 mm after 12 months. The adjunctive use of chlorhexidine resulted in a limited reduction in bleeding scores only. Similar favourable clinical outcomes of minocycline microspheres in conjunction with mechanical therapy were also reported by Salvi et al.[221].

Surgical access to the contaminated implant surface may be indicated in a number of situations. The consensus report of the 6th European Workshop on Periodontology concluded that non-surgical therapy of peri-implantitis was not found to be effective[134, 222]. This statement has also been supported by subsequent randomised controlled clinical trials aimed at investigating the outcomes following different approaches for non-surgical debridement and decontamination with either chlorhexidine digluconate, an erbium-doped laser (Er:YAG), an air abrasive, or an ultrasonic

device. These studies concluded that all treatment procedures investigated resulted in only limited clinical[223] and almost no microbiological improvements at 6 months[224]. Thus, advanced peri-implantitis lesions with the characteristic saucer-shaped bony defects can only be effectively treated/decontaminated using a surgical approach. This view was also supported by Karring and co-workers[225] who reported that a peri-implant lesion exceeding 5 mm with exposed implant threads cannot be decontaminated by submucosal debridement alone. However, there are no randomised controlled trials to date comparing the clinical outcomes of access surgery as a monotherapy in the treatment of peri-implantitis[207].

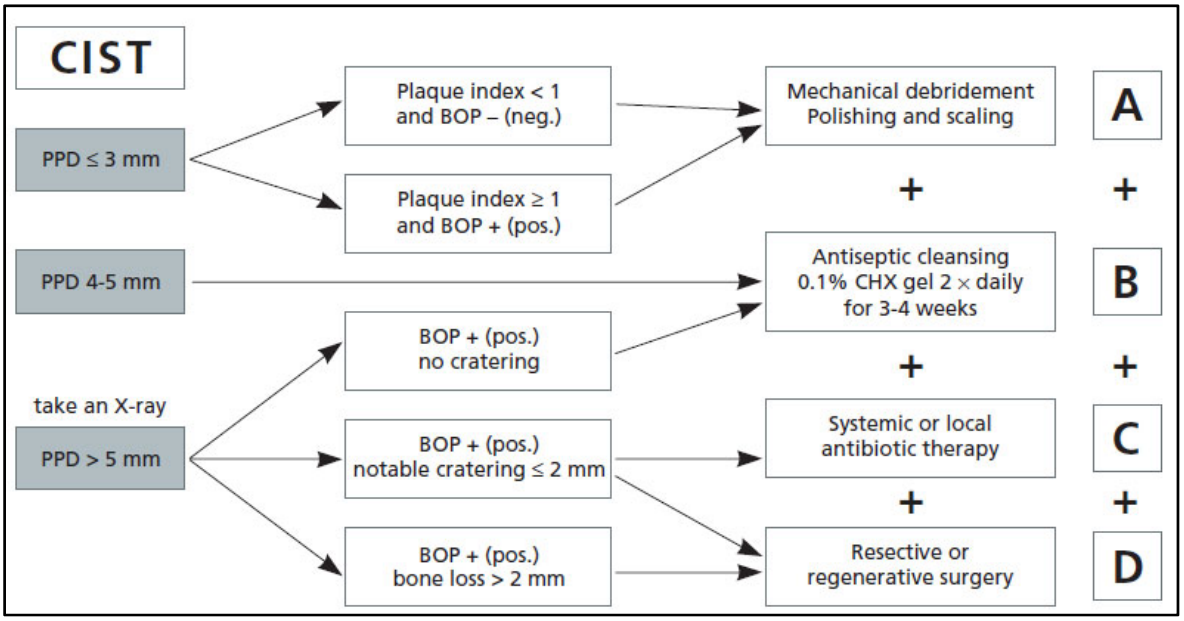
Some studies have indicated that resective surgical procedures involving implantoplasty (with diamond burs, Arkansas stone and silicone polishers) to reduce the surface roughness, and thus supposedly decrease de novo plaque formation, may have a positive effect on the survival rates of rough-surfaced implants affected by peri-implantitis[226, 227]. The authors noted significant improvements in peri-implant probing depths, suppuration and bleeding scores over 3 years. This treatment modality however may result in overheating of the fixture as well as possible embedding of titanium particles into the surrounding tissues, which may initiate an additional inflammatory response.

Regenerative procedures following the decontamination of implant surfaces have also been advocated. However, there is thus far, no evidence indicating GBR procedures provide any additional benefit in achieving good long-term treatment outcomes[155].

Preclinical and clinical studies have used erbium-doped yttrium aluminium garnet (Er:YAG) laser to decontaminate and debride infected implant surfaces[228, 229]. Dental lasers were assumed to be efficient in decontaminating implant surfaces due to their use of a uni-directional light beam, which seemed to provide better access to the implant surface compared to manual instruments[230]. Additionally, Er:YAG laser used at low energy densities have a high bactericidal potential without causing morphological changes to the implant surface by inducing excessive

heat[231]. Favourable formation of new bone has also been demonstrated in animal experimental peri-implantitis studies, where the laser-treated implant surface tended to produce a greater bone-implant contact compared to the curetted controls[232]. Several studies have shown promising short term outcomes following the use of Er:YAG laser therapy in conjunction with both non-surgical and surgical access[224, 228, 233, 234], with notable improvements in clinical and microbiological parameters. However, after 12 months, Schwarz[228] reported that the entire patient cohort had to be retreated due to deterioration in attachment levels and high bleeding scores, despite the patients maintaining good levels of oral hygiene. Although minor beneficial effects of laser therapy on peri-implantitis have been shown, the research in this area is still limited with rather short observation periods (less than 12 months), and thus further long-term studies are required to validate its effectiveness[134].

The *Cumulative Interceptive Supportive Therapy (CIST)* protocol as proposed by Mombelli and Lang in 1998[140], is a decision tree employed for both implant maintenance and in treating peri-implant diseases. This protocol requires the assessment of key clinical parameters: the presence of biofilm, the presence or absence of bleeding on probing, the presence or absence of suppuration, increased peri-implant probing depth and evidence of radiographic alveolar bone loss that consequently dictates the nature of the treatment applied. A key feature of this strategy lies in the fact that each consecutive treatment step builds upon the former. This results in a treatment strategy that is cumulative in nature with increasing anti-infective potential, in light of the worsening clinical parameters. The CIST protocol is as displayed below in **Error! Reference source not found.**. Whilst this strategy is commonly employed, there is little evidence to support rigid adherence to this protocol.



Depending upon the mucosal condition and probing depth, either regime A, or regime A+B, or regime A+B+C or regime A+B+C+D are performed (A = mechanical debridement; B = antiseptic cleansing; C = antibiotic therapy; D = resective or regenerative surgery)

Figure 7.2-A: Decision tree for CIST

8. CONCLUSION

Dental implants are a well established treatment modality for the replacement of missing teeth. Good long-term success rates have been reported for implants being placed in favourable anatomical positions in healthy patients with good oral hygiene. Studies have demonstrated that the success and failure of dental implants can be influenced to varying degrees by local and systemic factors. Technical and biological considerations are also crucial in increasing the clinical success rate of dental implants. However, in clinical practice, the possibility of implant rehabilitation is often favoured as an alternative to therapies aimed at the preservation of the natural dentition, despite the long term success being at least as good – with lower treatment costs, time and morbidity. Given the associated difficulty in diagnosing and treating the biological and technical complications of implant therapy, greater caution should be exercised by the clinician when considering this as a treatment modality.

Part B: Scientific paper

The Long Term Stability of Soft and Hard Tissues Surrounding Brånemark Dental Implants

9. AIMS

i. To examine the long term outcomes of implant therapy in relation to peri-implant clinical parameters (probing depths, bone loss, mucosal recession and mucosal inflammation).

ii. To investigate the effect of contributory factors in the patient's medical history at the time of examination on the outcome of their implant therapy.

iii. To investigate the effect of the prosthetic suprastructure on the extent of peri-implant bone loss and the development of peri-implant disease.

iv. To examine the effect of implant location on peri-implant bone loss.

10. MATERIALS AND METHODS

10.1. Patient selection

Patients for this retrospective cohort study were recruited from Sydney Dental Hospital, a university clinic, for clinical and radiographic evaluation. These patients formed a unique patient pool, all possessing the following common characteristics:

a. They were all recipients of either single or multiple turned-surface Brånemark implants® (the only implant system offered at the time) that were inserted at least 20 years ago
b. They were among the earliest recipients of dental implants in Australia, having also been a mixture of both public and private patients
c. They have all been treated by the same group of clinicians (surgeons and restoring dentists), all of whom were employed at Sydney Dental Hospital at the time

The total patient pool comprised of 278 patients, all of whom had undergone dental implant therapy between the period of January 1981 and May 1994. Utilising this pool, patients were meticulously tracked through a number of various avenues, including:

a. Previous dental record searches
b. Contacting their next of kin
c. Contacting their restoring dentist
d. Various Government database searches
e. An electoral roll search

Where patients were successfully tracked, they were then contacted by mail or e-mail and/or telephone, with a letter detailing the nature of this research project being issued along with an

invitation to participate. This invitation however required the patient's voluntary attendance to Sydney Dental Hospital in order to perform the clinical assessment.

Thus the cohort consisted of patients that met the following inclusion criteria:

a. There was a minimum period of 20 years since implant placement at the time of their re-examination
b. They were able to be tracked and contacted
c. They were willing to participate and able to physically present to Sydney Dental Hospital for re-examination

Eventually, 22 patients were available for examination at the time of this study, with a total of 97 implants being examined. The mean follow up period was 22.6 years, with a range of 6 years.

10.2. Ethics approval

This research protocol was approved by the *Sydney South West Area Health Service Human Research Ethic Committee, Australia* (protocol number X12-0023 & HREC/12/RPAH/33). Patients were informed that their data would be used for statistical analysis and provided their written consent to participate in the study following the issue of written and verbal advice. This research project was conducted in accordance with the *World Medical Association Declaration of Helsinki 2008*[*].

10.3. Implant placement and prosthesis reconstruction

All implants included in this study were turned-surface Brånemark implants® with a diameter of 3.75mm and of varying lengths of either 7mm, 10mm, 13mm, 15mm, 18mm, and 20mm. These

[*] http://www.wma.net/en/30publications/10policies/b3/index.html

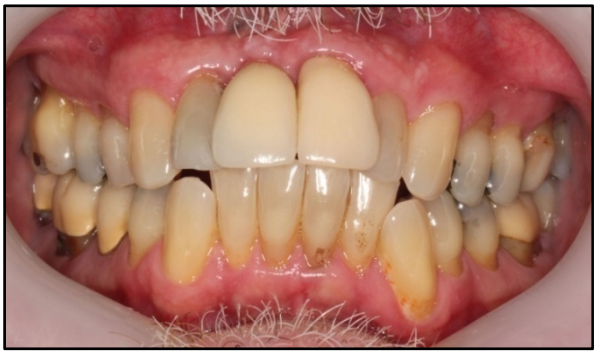
implants were all surgically placed between January 1981 and May 1992 by one of three Oral Surgeons employed at Sydney Dental Hospital at the time.

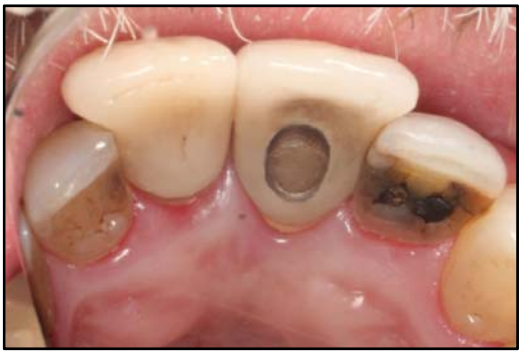
All implant installations were placed under local anaesthesia in all patients, in accordance with the manufacturer's guidelines following a two-staged protocol. After an initial healing period of 4 months in the mandible and 6 months in the maxilla, abutment connection was then completed in a second stage surgery. Following another healing period of 3 months, the suprastructures were fabricated using the system's components. The four groups of reconstructions (some examples are shown in Figure 10.3-A) included:

- Single crowns (screw-retained)
- Implant-borne fixed acrylic partial dentures (screw-retained)
- Implant-borne fixed acrylic full dentures (screw-retained)
- Implant-borne bar-retained removable acrylic full upper and/or lower dentures

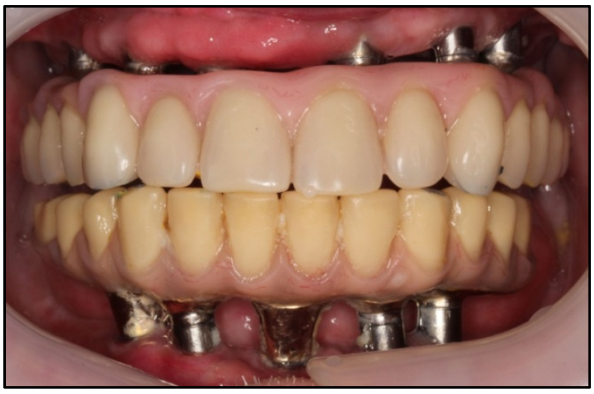
Prosthetic reconstructions were performed by either a senior Prosthodontist or a Prosthodontics Registrar at Sydney Dental Hospital at the time.

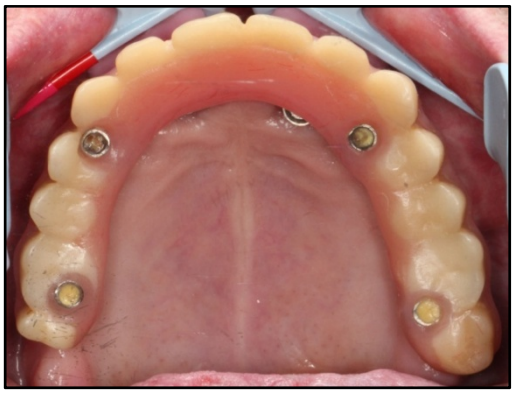
None of the examined patients were consequently prescribed or enrolled into any supportive periodontal therapy program following crown insertion over the last 20+ years, though some patients had voluntarily presented to Sydney Dental Hospital for suprastructure repairs.



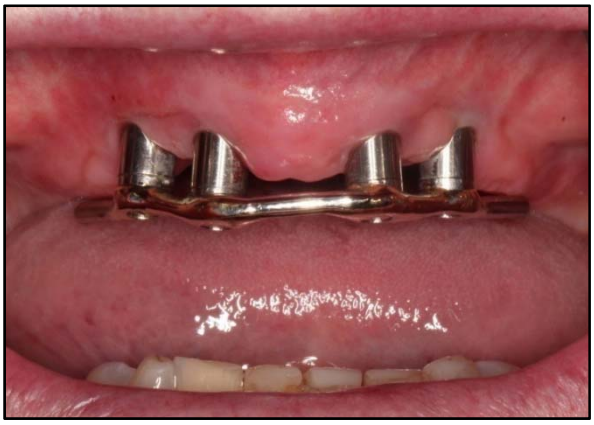


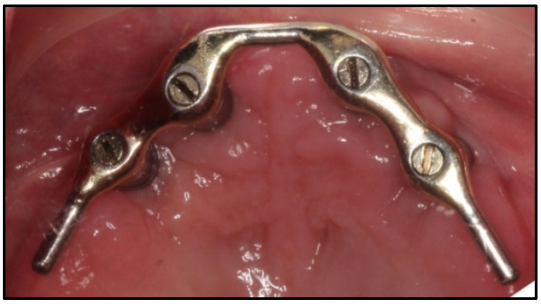
21 single crown (screw-retained)





Implant-borne fixed partial dentures (screw-retained)





Implant-borne bar-retained removable acrylic full upper denture

Figure 10.3-A: Prosthetic reconstructions as seen at re-evaluation

10.4. Clinical examination

Prior to clinical and radiographic examination, a thorough medical history was elicited from each patient. Information pertaining to the patient's medical history and general health is as outlined in

Table 10.4-A below.

Table 10.4-A: Medical and general health history gathered

Cardiovascular issues	Rheumatic fever
Hypertension	Bleeding disorders
Respiratory issues	Central nervous system issues
Diabetes and glycaemic control (HbA1c)	Thyroid issues
Infectious diseases	Musculoskeletal issues
Immune disorders	Gastro-intestinal issues
Hepatic issues	Cancer
Medications	Allergies
Hospital admissions/operations	Smoking habits

Peri-implant soft tissues were evaluated clinically by a single examiner. The following clinical parameters were assessed:

- Modified plaque index (mPI) for all implants[7]
- Modified bleeding index (mBI) for all implants[7]
- Peri-implant probing depths (PD) in millimetres at 6 sites around the implant
- Distance between the implant shoulder and the mucosal margin (DIM) in millimetres

- Probing attachment level (PAL) in millimetres calculated by adding PPD to DIM
- Bleeding on probing (BOP) after 30 seconds at 6 sites around the implant

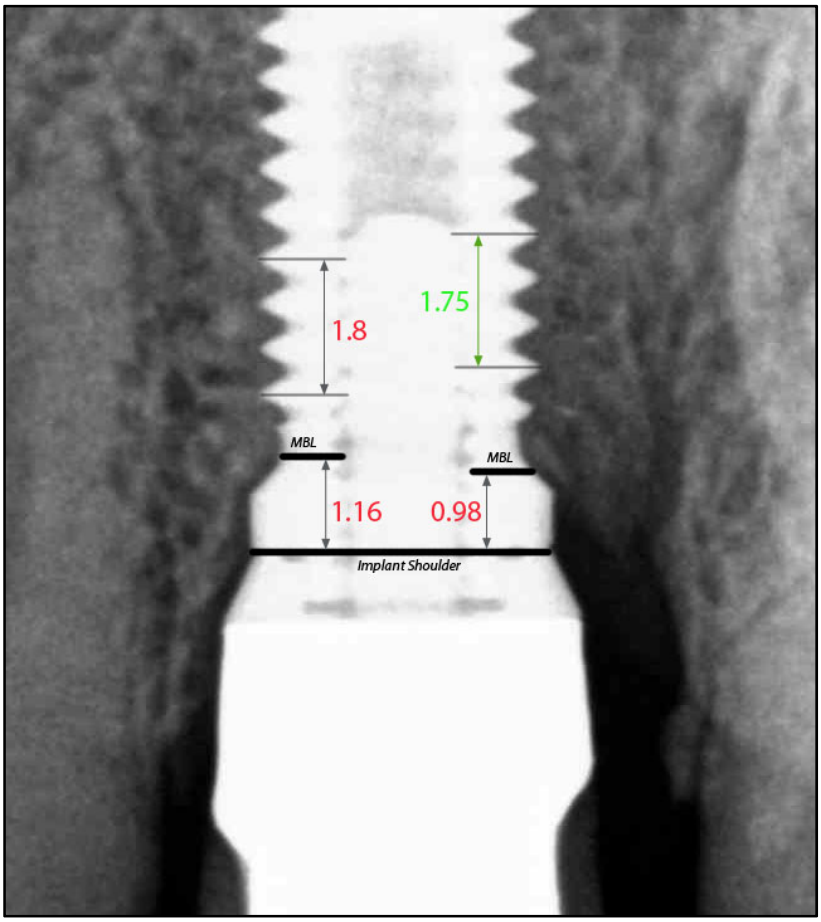
All clinical measurements were recorded utilising an automated probe (Florida Probe®, Florida Probe Corporation, Gainesville, FL, USA). The Florida Probe® is advantageous in its application of a constant force, electronic measurement to 0.1mm, along with the electronic storage of clinical data. The probe tip has a diameter of 0.4mm, and the probing force is pre-set to a constant force of 25g.

During the clinical examination, any incidences of biological and/or technical complications were identified and treated. In the case of a biological complication, a cumulative interceptive anti-infective treatment protocol as suggested by Mombelli & Lang[140] (**Error! Reference source not found.**) was instituted. In the event of technical complications that required repair or where there were failures that required further treatment planning, additional appointments were subsequently arranged with the Prosthodontist.

10.5. Radiographic measurements

For evaluation of the marginal bone levels (MBL), digital periapical radiographs were taken of each of the implants at the time of clinical examination. All radiographs were taken using a long cone Rinn holder (Dentsply, York, PA, USA) paralleling device[235]. Radiographic machinery used were Pro X Planmeca (PlanmecaOy, Helsinki, Finland) with Scan-X Phosphor plates (Air Techniques, Melville, NY, USA) set at 70 kV 8mA with an exposure of 200mGy. The measured distance between 3 implant threads was used as the basis for calibration and to account for any magnification and distortion of the images[236]. The MBL was determined to be the distance between the top of the implant shoulder (implant-abutment interface) and the first visible bone-implant contact, measured on the mesial and distal aspect of each implant using a x10-15 magnification[237] (as demonstrated in Figure 10.5-A). These 2 values of the radiographic

assessment of the bone levels mesially and distally were then averaged to one value each per implant for data analysis.



Measurements in red represent actual measurements in millimetres and the green measurement represent the actual measurement on the image, which is then used for scaling and calibrating the measurements.

Figure 10.5-A: Assessment of the distance from the shoulder to the first bone-to-implant contact on the digitised radiographs

Before radiographic analysis was performed, intra-examiner calibration was conducted utilising 10 radiographs chosen at random and re-measured 48 hours apart. The intra-examiner repeatability was 0.90 (Pearson correlation, $p < 0.01$).

All radiographic measurements were performed by the one examiner, with measurements being recorded on two separate passes, one hour apart. The agreement between measurements yielded a κ statistic of 0.83.

The recently acquired radiographs taken at the time of clinical examination were then subsequently used for comparison against any pre-existing radiographs that were taken at the time of prosthetic reconstruction, or at the time of implant placement. These radiographs that were successfully obtained were then digitised, and measurements were obtained with the use of a computer software program (ImageJ, National Institute of Health, USA). The aforementioned process was also used for the radiographic analyses of these radiographs.

The radiographic crestal bone change was then calculated by subtracting the MBL at baseline from the MBL measured at the time of re-examination.

The radiographic bone loss was calculated for the time points between restoration and the follow-up examination. Bone loss of 1.0mm in the first year of service, and 0.2mm per year thereafter was used as a radiographic threshold for peri-implantitis[238].

10.6. Statistical analysis

Data were available for 97 implants in 22 patients. Data were summarised by mean (standard deviations). Comparisons between groups were made by *t* tests at the patient and implant levels.

The suprastructures were re-categorised into the following 4 categories for analysis, in keeping with a previous study of this same cohort:

1. Overdenture (implant-borne bar-retained removable acrylic full upper and/or lower dentures)
2. Full fixed denture (implant-borne fixed acrylic full upper and/or lower dentures)
3. Partial fixed denture (implant-borne fixed acrylic partial upper and/or lower dentures)
4. Single crown.

Relative risks were calculated using Yates continuity correction, with mid-*P* exact *P* values and small-sample adjusted confidence intervals. *P* values less than 0.05 were regarded as significant. R 3.1.1[†] was used for all analyses.

[†]R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. (http://www.R-project.org/)

11. RESULTS

11.1. Patient cohort

Twenty-two patients from an initial patient pool of 278 patients were enrolled in this study. From this initial pool of implant patients who had undergone dental implant therapy at Sydney Dental Hospital at least 20 years ago, 51 patients (18.3%) were deceased, 12 (4.3%) had insufficient records to facilitate the tracking of these patients, and 147 (52.9%) patients could not be located despite our exhaustive search methods. Patient drop outs are illustrated in Figure 11.1-A.

Of the remaining 68 patients who could be contacted, 22 volunteered to present to Sydney Dental Hospital for clinical re-examination, thus forming the participant cohort. The remaining 46 patients formed the non-participant cohort. Within the non-participant cohort, 3 patients provided conflicting information and were adamant that they had never received implants, and another 3 patients were in such poor health that their next of kin recommended against their participation. A further 40 patients declined the invitation to present to the hospital for clinical re-evaluation, citing distance, mobility issues, and/or personal reasons. The ethnicity of the patients varied between European descent, East-Asian, Indian, Indigenous Australian and Australian-born.

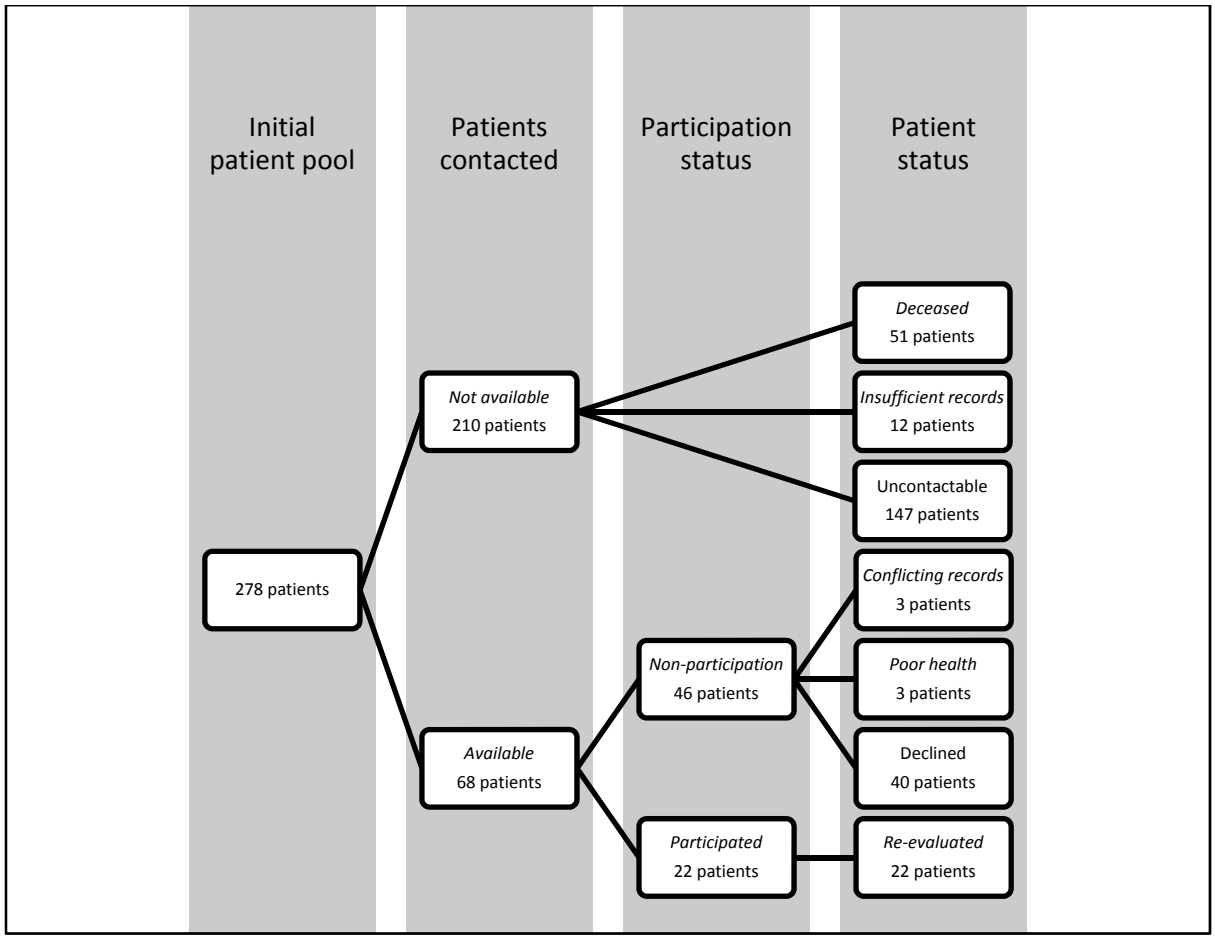


Figure 11.1-A: Patient contacts and dropouts

11.2. Patient demographics

The patient demographic data is presented in Table 11.2-A. There was an even distribution of males and female participants, with implants being placed at the median age of 48.5 years. For the non-participants, there were a higher proportion of females (72%) than males (28%) and their median age of placement was also higher at 58.5 years old. The present clinical examination of the patients occurred at the median age of 73 years. Thus, at the time of this examination, the implants of the participant cohort had a median of 22 years of service. Within the participant patient cohort at the time of examination, there were 4 diabetics (18%), 7 never-smokers (32%), 14 ex-smokers (32%) and only 1 smoker (5%). The year of implant placement within the

participant patient cohort ranged from 1986 to 1992, whilst in the non-participants, the range was greater, extending from 1981 to 1992. During the follow-up, 7 of the implants (representing 7% of the total implants analysed) in 3 participants (14% of the patient cohort) were lost. In the participant patient cohort, a slightly greater number of implants were placed in the maxilla (51%) compared with the mandible (49%). In the non-participants, this trend was reversed, with more implants located in the mandible (69%) than in the maxilla (31%).

The suprastructures were categorised into 4 categories: overdenture, full fixed denture, partial fixed denture, and single crowns. Within the participant cohort, when analysed at a patient level, overdentures comprised the largest proportion of suprastructures (*n* = 16, 70%), followed by single crowns (*n* = 4, 17%), full fixed dentures (*n* = 2, 9%), and partial fixed dentures (*n* = 1, 4%). When analysed at an implant level, overdentures also comprised the largest proportion of suprastructures (*n* = 74, 76%), followed by full fixed dentures (*n* = 13, 13%), single crowns (*n* = 6, 6%), and partial fixed dentures (*n* = 4, 4%). For the non-participant cohort, when analysed at a patient level, the overdentures also comprised the largest proportion (*n* = 34, 76%), followed by single crowns (*n* = 9, 20%), and then full fixed dentures (*n* = 1, 2%). There were no partial fixed dentures in this cohort. When this cohort was then analysed at an implant level, overdentures comprised 86% (*n* = 125) of the suprastructures, followed by single crowns (*n* = 11, 8%), with both full fixed dentures (*n* = 5) and partial fixed dentures (*n* = 4) having the same distribution (3% each).

The vast majority of the examined cohort received regular length implants (*n* = 92, 95%), with only 5% (*n* = 5) of the cohort receiving short implants (7mm). Conversely, there were more recipients of short implants (< 10mm) within the non-participant cohort (*n* = 23, 16%), with the remaining majority of these patients receiving regular length implants of either 10mm, 13mm, 15mm, 18mm, or 20mm lengths (*n* = 122, 84%).

Table 11.2-A Demographic data of the patient cohort

	Patient level				Implant level			
	Participant (*N* = 22)		Non-participant (*N* = 46)		Participant (*N* = 97)		Non-participant (*N* = 145)	
	n	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Sex								
Male	11	50	13	28	—			
Female	11	50	33	72	—			
Age at implant placement: *median, interquartile range*	48.5	41.8–57.5	58.5	42.8–64.0	—			
Age at examination: *median, interquartile range*	73.0	66.0–79.3	—		—		—	
Diabetes	4	18	—					
Smoker								
Never-smoker	7	32	—					
Ex-smoker	14	64	—					
Smoker	1	5	—					
Year of placement								
1981			2	4			12	8
1982			0	0			0	0
1983			0	0			0	0
1984			1	2			6	4
1985			1	2			2	1
1986	1	5	6	13	8	8	16	11
1987	0	0	1	2	0	0	1	1
1988	2	9	1	2	6	6	6	4
1989	5	23	4	9	20	21	11	8
1990	4	18	6	13	25	26	18	12
1991	3	14	19	41	15	15	58	40
1992	7	32	5	11	23	24	15	10
Years of service: *median, interquartile range*	22	21–24			22	21–24		
Lost	3	14			7	7		
Location								
Mandible	13	59	27	59	48	49	100	69
Maxilla	12	55	19	41	49	51	45	31
Suprastructure								
Overdenture	16	70	34	76	74	76	125	86
Full fixed denture	2	9	1	3	13	13	5	3
Partial fixed denture	1	4	0	0	4	4	4	3
Single crown	4	17	9	21	6	6	11	8
Length (mm)								
7					5	5	19	13
8					0	0	4	3
10					20	21	40	28
13					38	39	24	17
15					19	20	28	19
18					6	6	10	7
20					9	9	3	2

11.3. Clinical findings

Table 11.3-A: Summary of clinical findings

	Patient level (*n* = 22)		**Implant level** (*n* = 97)	
	Mean	**SD**	**Mean**	**SD**
Modified plaque index (mPl)	1.9	0.8	2.0	0.8
Modified bleeding index (mBl)	1.6	1.0	1.8	0.9
Probing depth (mm)	3.2	0.9	3.3	1.0
Probing attachment level (mm)	3.3	1.1	3.5	1.3
Bleeding on probing (%)	42	20	39	30
Marginal bone level difference (mm)	1.0	0.7	1.1	0.9
Marginal bone level loss (%)	6.8	4.6	7.2	5.9

The clinical findings within the participant cohort are presented in Table 11.3-A. When analysed at a patient level, patients showed a mean modified plaque index of 1.9 and a mean modified bleeding index of 1.6. The mean probing depth was 3.2mm, the mean probing attachment level (PAL) was calculated to be 3.3mm and bleeding on probing (BOP) was observed at 42% of probing sites. When the radiographic crestal bone levels were analysed, the mean marginal bone level (MBL) difference/mean marginal bone loss compared to baseline was calculated to be 1.0mm. This equates to a mean MBL loss of 6.8% of the total implant length.

When analysed at an implant level, patients exhibited a mean modified plaque index and mean modified bleeding index of 2.0 and 1.8 respectively. The mean probing depth and mean probing attachment levels were calculated to be 3.3mm and 3.5mm respectively. BOP was observed at 39% of the probing sites. The mean MBL was 1.1mm, which equates to a mean MBL loss of 7.2% of the total implant length.

Ten implants in 4 patients (4 prostheses) showed peri-implantitis (probing depth > 5mm and bleeding on probing at any site). All these implants were located in the maxilla and all supported overdentures.

Figure 11.3-A illustrates the frequency distribution of different probing depths measured during the clinical re-evaluation within the participant cohort. The frequency for each of the probing depths as a proportion of the total 582 probing sites is listed as a percentage above each of the bars. Most of the probing depths recorded were shallow, being either 2mm (32.1% of total sites measured), 3mm (34.4% of total sites measured) or 4mm (17.7% of total sites measured) and 15% of depths being greater than 4 mm.

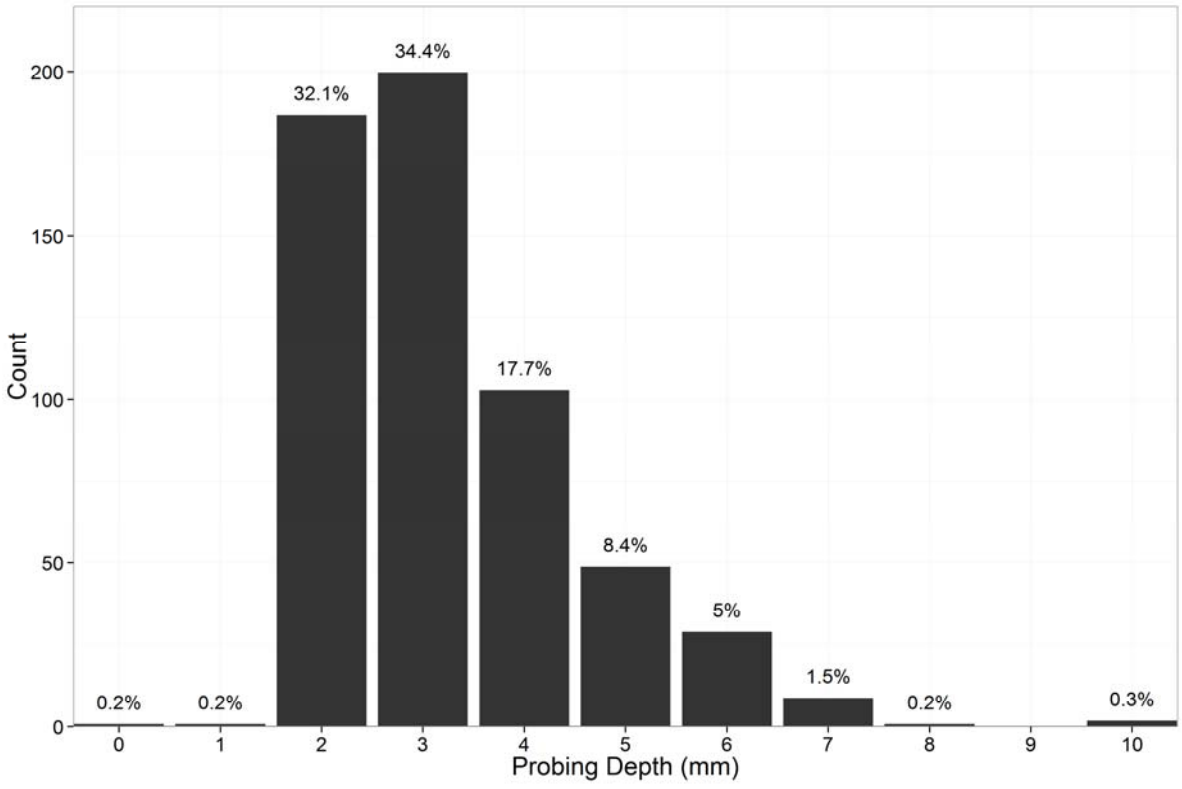


Figure 11.3-A: Histogram of the probing depths at the 582 probing sites

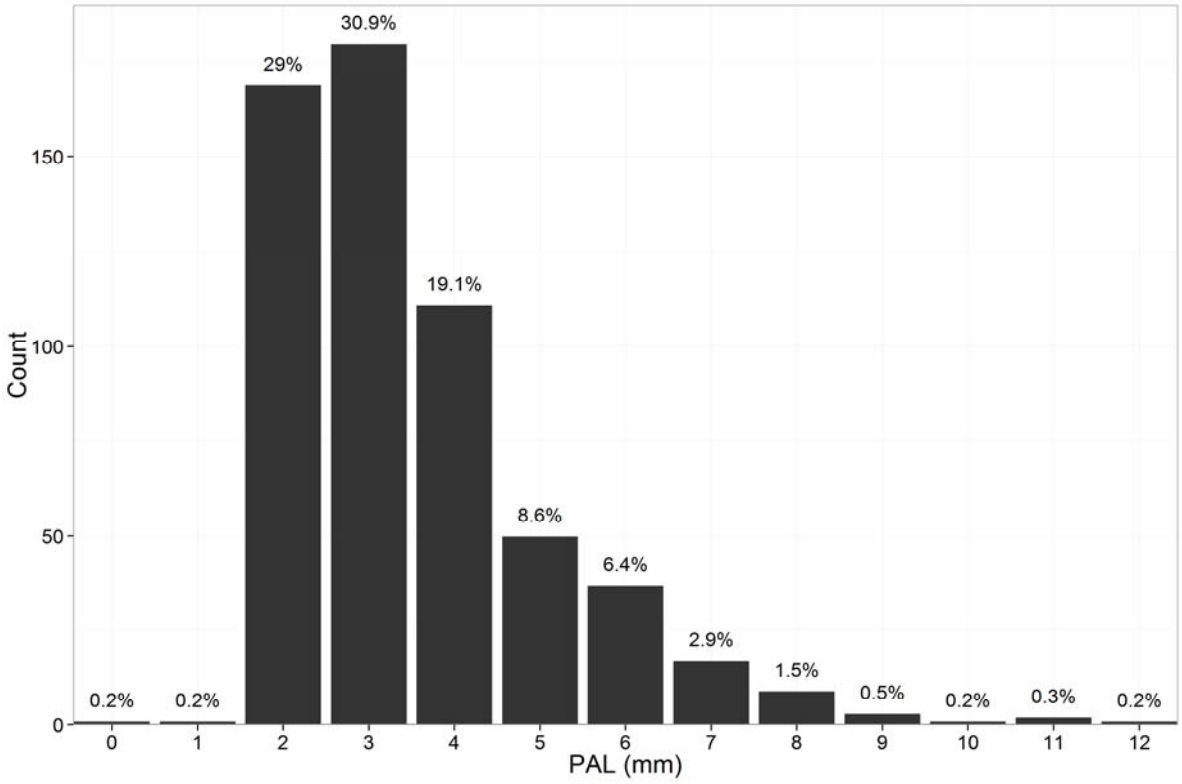


Figure 11.3-B: Frequency histogram of the probing attachment levels (PAL) as calculated at each of the 582 probing sites

Figure 11.3-B illustrates the frequency distribution of the calculated probing attachment levels (PAL) as measured at each of the probing sites during the clinical re-evaluation within the participant cohort. The frequency for each of the probing attachment levels as a proportion of the total 582 probing sites is listed as a percentage above each of the bars. The highest frequency of PAL was calculated to be either 2mm (29% of all sites measured), 3mm (30.9% of all sites measured), or 4mm (19.1% of all sites measured) – representing a trend for loss of attachment over the 20+ year observation period.

Table 11.3-B: Clinical parameters by suprastructure at a patient level

	Overdenture (*n* = 16)	**Full fixed denture** (*n* = 2)	**Partial fixed denture** (*n* = 1)	**Single crown** (*n* = 4)	***P***[¤]
Modified plaque index (mPI)	1.9 (0.9)	2.5 (0.7)	3.0	1.5 (0.6)	0.26
Modified bleeding index (mBl)	1.5 (0.7)	3.0 (0)	3.0	1.3 (1.5)	0.08
Probing depth (PD)	3.2 (1.0)	3.0 (0.3)	3.8	3.2 (1.0)	0.84
Bleeding on probing (BOP)	41 (22)	54 (26)	33	46 (16)	0.77
Probing attachment level (PAL)	3.4 (1.3)	3.1 (0.5)	3.8	3.2 (1.0)	0.90
MBL[§] difference (mm)	1.2 (0.8)	0.9 (0.2)	0.7	0.6 (0.7)	0.84
MBL[§] difference (%)	8.2 (5.5)	6.1 (0.6)	4.9	3.0 (3.6)	0.56

[¤]*P values from Kruskal-Wallis test,* [§]*Marginal bone level.*

The results of the clinical parameters investigated by suprastructure at a patient level are shown in Table 11.3-B.

However, the low number of full fixed dentures (*n* = 2), partial fixed dentures (*n* = 1), and single crowns (*n* = 4) compared to overdentures (*n* = 16) does not allow for a meaningful analysis regarding significant statistical differences.

Table 11.3-C: Clinical parameters by suprastructure at an implant level

	Overdenture (*n* = 74)	**Full fixed denture** (*n* = 13)	**Partial fixed denture** (*n* = 4)	**Single crown** (*n* = 6)	***P*[¤]**
Modified plaque index (mPl)	1.9 (0.8)	2.5 (0.5)	3.0 (0.0)	1.8 (0.4)	0.005*
Modified bleeding index (mBl)	1.6 (0.7)	2.8 (0.4)	3.0 (0.0)	2.0 (1.2)	<0.001*
Probing depth (PD)	3.3 (1.0)	3.0 (0.4)	3.8 (0.3)	3.3 (1.0)	0.40
Bleeding on probing (BOP)	36 (31)	53 (33)	33 (14)	44 (17)	0.27
Probing attachment level (PAL)	3.6 (1.5)	3.1 (0.6)	3.8 (0.3)	3.3 (1.0)	0.63
MBL[§] difference (mm)	1.2 (1.1)	1.0 (0.8)	0.7 (0.9)	0.4 (0.6)	0.33
MBL[§] difference (%)	8.5 (7.4)	6.1 (4.9)	4.9 (6.3)	2.1 (3.0)	0.20

[¤]*P values from Kruskal-Walis test, P values from ANOVA, *P < 0.05,* [§]*Marginal bone level.*

When analysed at an implant level, the modified plaque and modified bleeding indices both showed significant differences (p <0.05) based on the type of suprastructure. Full fixed dentures and partial fixed dentures displayed significantly higher index values than overdentures and single crowns. There were no significant differences by type of suprastructure for any of the other clinical parameters investigated (Table 11.3-C).

Figure 11.3-C through to Figure 11.3-I illustrate the different clinical parameters measured at implants in relation to the respective type of suprastructure. These results are presented as box plots. For the box plots, the middle line across the box indicates the median value, the box limits show the interquartile range (25th and 75th centiles), the whiskers extend to the extreme points within 1.5 times the interquartile range from the upper or lower quartile, and any points further from the quartiles are shown individually. Owing to the small numbers, the box and whisker structure is not fully present for some figures.

Figure 11.3-C: Box plots of the modified plaque index (mPl) based upon the suprastructure type

Figure 11.3-D: Box plots of the modified bleeding index (mBI) based upon the suprastructure type

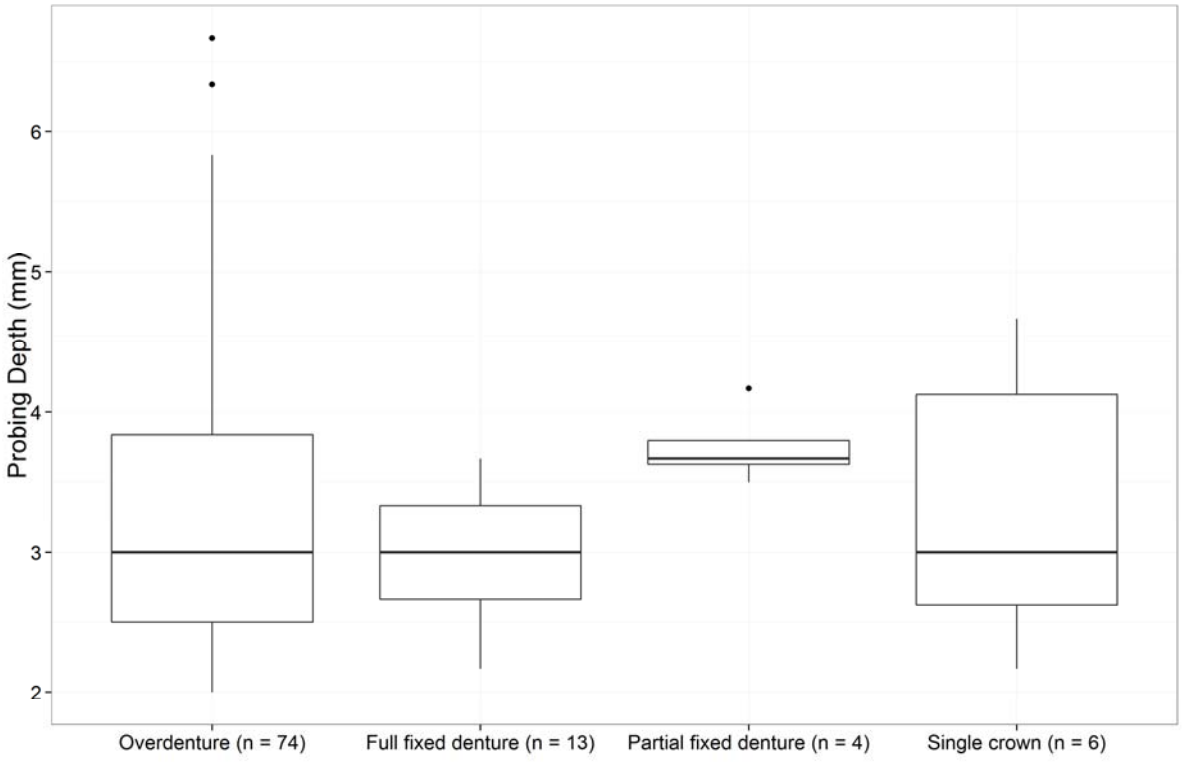


Figure 11.3-E: Box plots of the probing depths (mm) based upon the suprastructure type

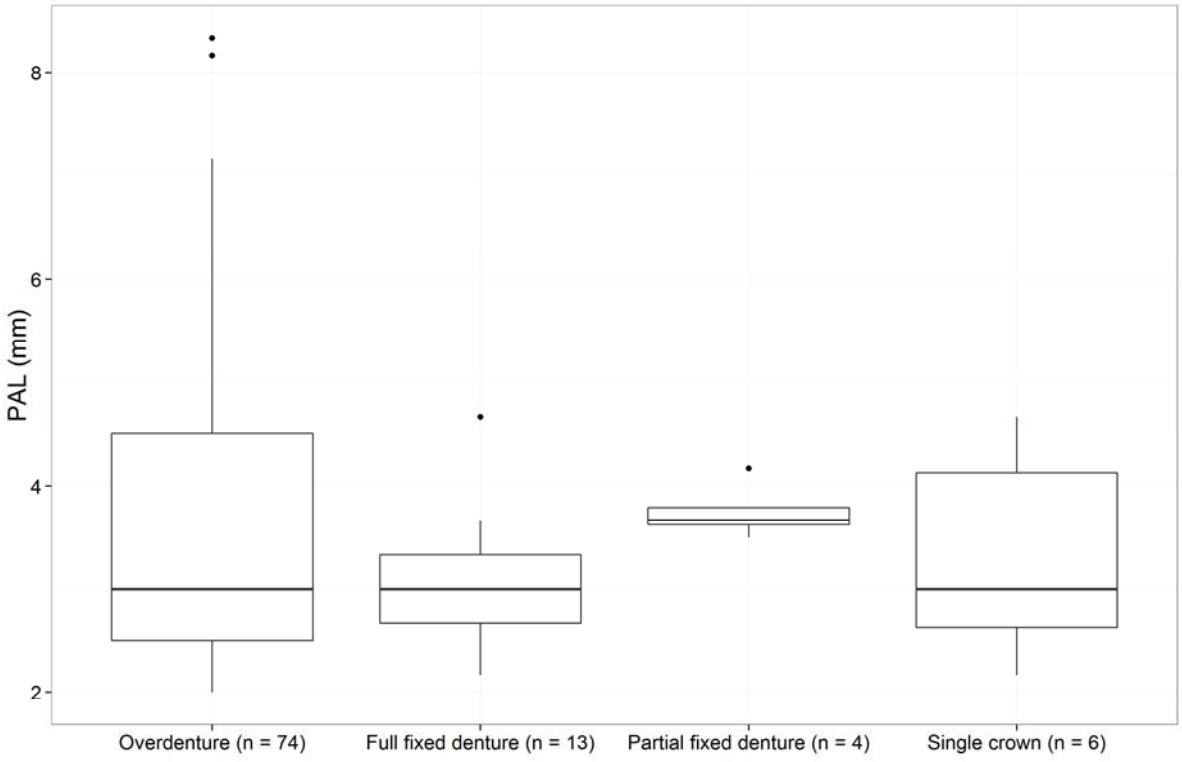


Figure 11.3-F: Box plots of the probing attachment level (PAL) based upon the suprastructure type

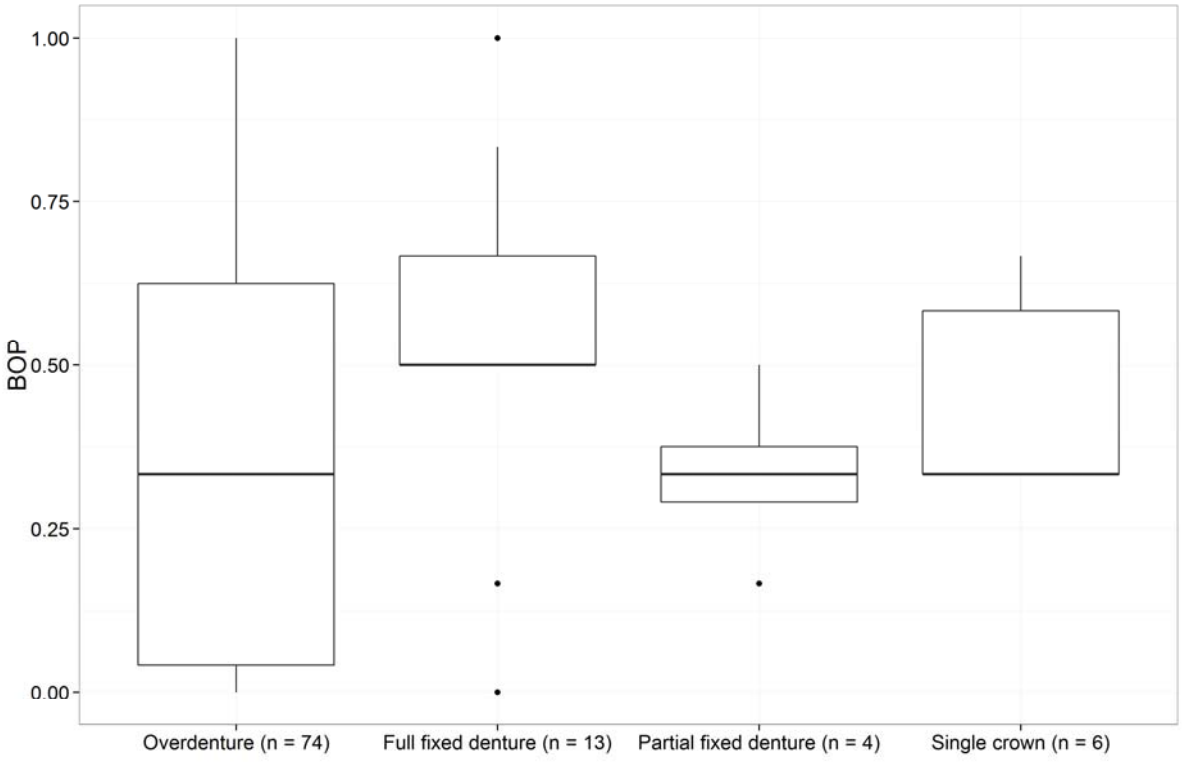


Figure 11.3-G: Box plots of the bleeding on probing (BOP) compared between the suprastructures

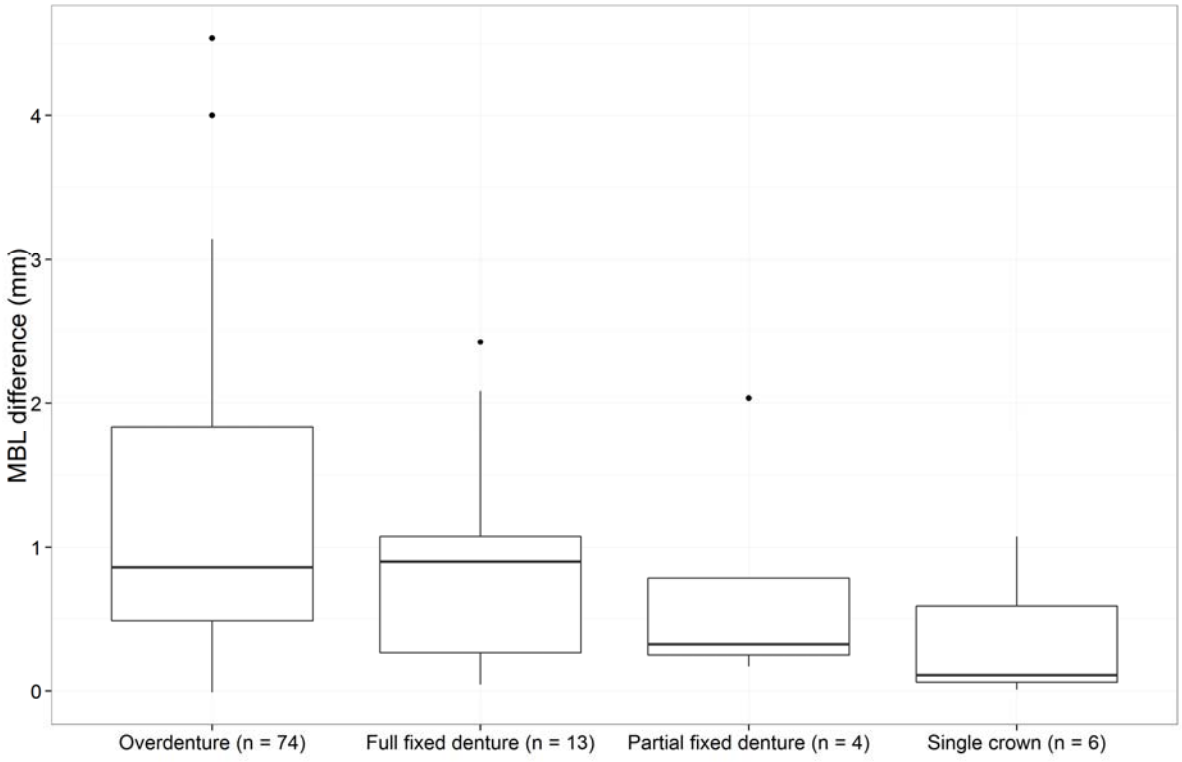


Figure 11.3-H: Box plots of the marginal bone level (MBL) difference as measured in mm as compared between the suprastructures

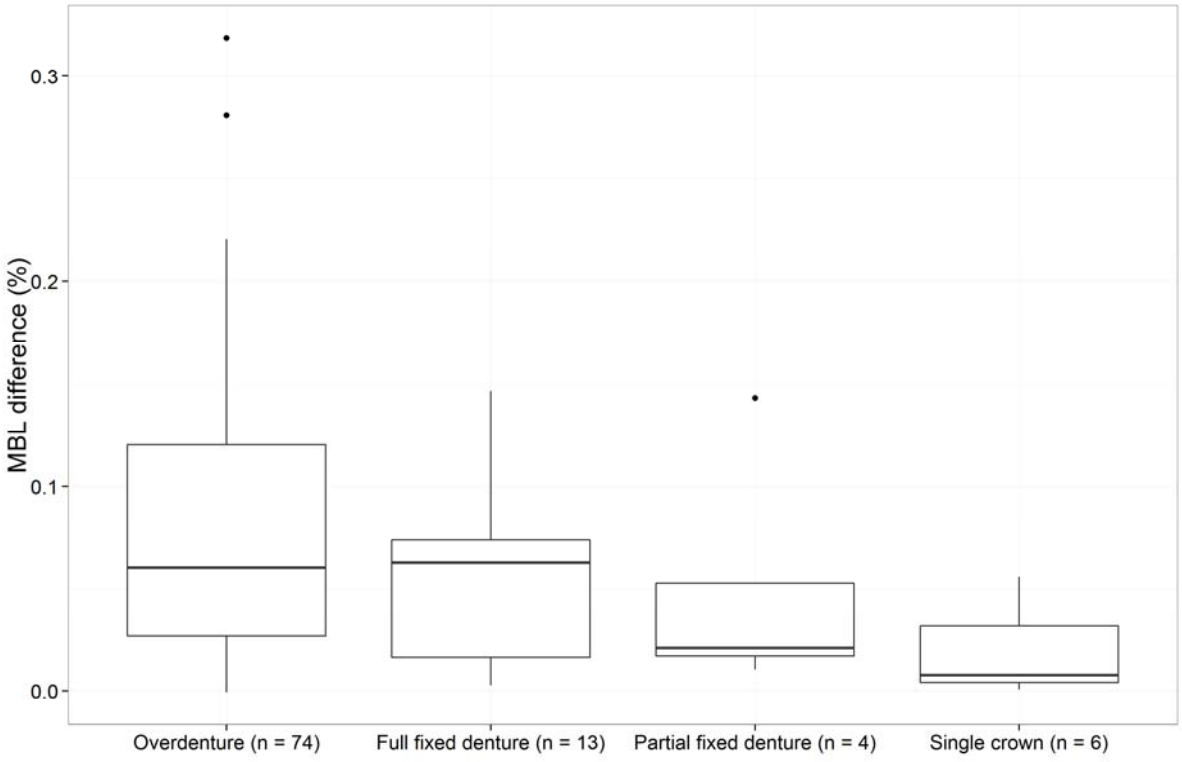


Figure 11.3-I: Box plots of the marginal bone level (MBL) difference as a percentage of implant length as compared between the suprastructures

11.4. Contributory factors

Table 11.4-A: Effects of patient contributory factors on clinical outcome measures at a patient level

	Smoking status				Diabetes			
	Never-smoker (*n* = 7)	**Ex- or current smoker** (*n* = 15)	**Difference**	***P***¨	**Non-diabetic** (*n* = 18)	**Diabetic** (*n* = 4)	**Difference**	***P***¨
mPl~	1.5	2.0	0.5 (-0.1 to 1.2)	0.084	1.8	2.3	0.5 (-0.8 to 1.8)	0.21
mBl[ç]	1.3	1.8	0.5 (-0.3 to 1.3)	0.287	1.5	2.2	0.7 (-0.6 to 2.0)	0.25
PD[¯] (mm)	3.3	3.1	-0.2 (-1.0 to 0.5)	0.27	3.2	2.9	-0.3 (-1.5 to 0.8)	0.35
BOP[«] (%)	48	39	-9 (-31 to 13)	0.36	40	50	10 (-8 to 27)	0.28
PAL[i] (mm)	3.3	3.3	0.0 (-0.9 to 0.8)	0.46	3.4	3.0	-0.4 (-1.9 to 1.1)	0.39
MBL[§] difference (mm)	0.3	1.1	0.8 (-0.1 to 1.8)	0.04*	1.0	1.1	0.1 (-0.6 to 0.8)	0.66
MBL[§] difference (%)	2.1	7.5	5.4 (-2.9 to 14)	0.11	6.8	7.0	0.2 (-4.9 to 5.3)	0.85

*¨P values from Wilcoxon rank sum tests, *P< 0.05, ~Modified plaque index, [ç]Modified bleeding index, [¯]Probing depth, [«]Bleeding on probing, [i]Probing attachment levels, [§]Marginal bone level.*

As there was only 1 smoker, this person was combined with the ex-smokers for the data analyses. There were no significant differences by smoking status or diabetes status when clinical outcomes were examined at the patient level, except for MBL difference when measured in mm for smokers (Table 11.4-A). Ex- or current smokers showed significantly more bone loss around the implants than never-smokers.

Table 11.4-B: Effects of patient contributory factors on clinical outcome measures at an implant level

	Smoking status				Diabetes			
	Never-smoker (*n* = 27)	**Ex- or current smoker** (*n* = 70)	**Difference**	***P*¨**	**Non-diabetic** (*n* = 74)	**Diabetic** (*n* = 23)	**Difference**	***P*¨**
mPl~	1.4	2.3	0.9 (0.6 to 1.2)	<0.001*	1.9	2.5	0.6 (0.3 to 0.9	0.001*
mBl[c]	1.4	2.0	0.6 (0.3 to 0.9)	0.001*	1.6	2.6	1.0 (0.7 to 1.4)	<0.001*
PD¯ (mm)	3.2	3.3	0.1 (-0.3 to 0.4)	0.71	3.2	3.3	0.1 (-0.4to 0.6)	0.69
BOP« (%)	34	40	6 (-7 to 20)	0.41	34	53	19 (-4 to 34)	0.011*
PAL[i] (mm)	3.2	3.7	0.5 (0.0 to 0.9)	0.61	3.5	3.6	0.1 (-0.6 to 0.7)	0.90
MBL[§] difference (mm)	0.4	1.2	0.8 (0.5 to 1.2)	<0.002*	1.0	1.3	0.3 (0.2 to 0.8)	0.22
MBL[§] difference (%)	3.2	8.5	5.3 (2.3 to 8.2)	0.007*	7.1	8.6	1.5 (-2.2 to 5.3)	0.38

*¨P values from Wilcoxon rank sum tests, *P< 0.05, ~Modified plaque index, [c]Modified bleeding index, ¯Probing depth, «Bleeding on probing, [i]Probing attachment levels, [§]Marginal bone level.*

As there was only 1 smoker, this person was combined with the ex-smokers for the data analyses. When examined at the implant level, the marginal bone loss (MBL difference in mm and as a percentage) was significantly greater in smokers and ex-smokers compared to never-smokers (p <0.001). Modified plaque and modified bleeding indices were also significantly higher in smokers than in never-smokers (p <0.001 and p = 0.001 respectively). Probing depth, bleeding on probing (BOP) and probing attachment levels (PAL) did not differ by smoking status (Table 11.4-B).

BOP was significantly more frequent among diabetic patients than non-diabetic patients (p = 0.016). Modified plaque and modified bleeding indices were also significantly higher in diabetic patients compared to non-diabetics (p = 0.001 and p <0.001 respectively). However, no other clinical parameter differed based on the diabetes status.

11.5. Radiographic findings

Table 11.5-A: Marginal bone level (MBL) difference by location

	Mandible (*n* = 48)	**Maxilla** (*n* = 49)	**Difference**	***P***
MBL difference (mm)	0.93	1.29	0.36 (-0.12 to 0.85)	0.24
MBL difference (%)	5.7	9.6	3.9 (0.6 to 7.2)	0.04

Table 11.5-A reveals that the marginal bone level (MBL) difference as a percentage of the implant length was significantly greater in the maxilla than in the mandible ($p = 0.04$), but when measured in mm, this difference was not significantly different ($p = 0.24$).

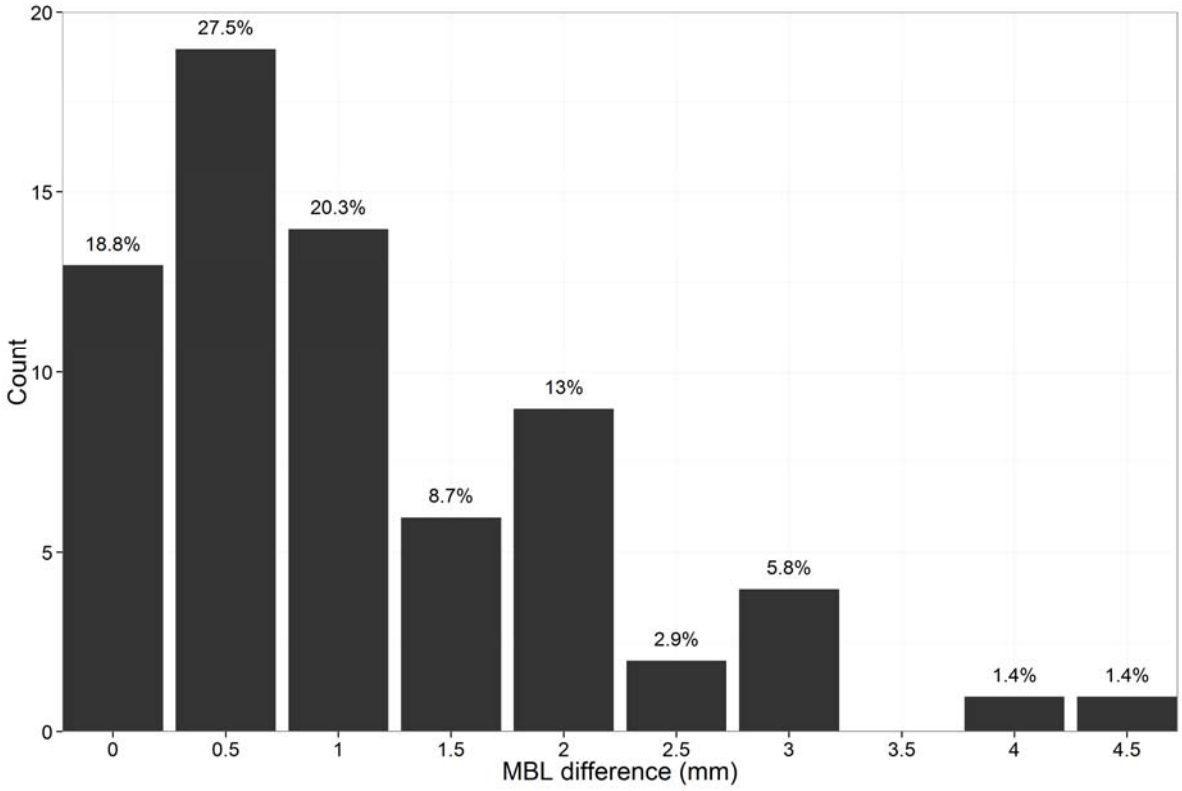


Figure 11.5-A: Histogram of the marginal bone level (MBL) difference for the implants

Figure 11.5-A illustrates the frequency distribution of the marginal bone level (MBL) difference as measured in mm for each of the implants as calculated from the radiographic analyses for the participant cohort. The frequency of each of the calculated MBL difference measurements as a proportion of the total number of analysed implants is listed as a percentage above each of the bars. 69 of the 97 implants (71.1%) had baseline radiographs available for analysis. Most MBL differences were 0-1 mm, and the frequency of larger differences appeared to decrease following an exponential distribution.

11.6. Relative risk for bone loss by suprastructure

Table 11.6-A: Risk ratios for bone loss by suprastructure

	Bone loss ≤ 1mm		Bone loss > 1mm		Risk ratio	95% CI	*P*
	n	**%**	***n***	**%**			
Overdenture	27	55	22	45	0.90	0.18-4.58	0.75
Full fixed denture	7	54	6	46	0.92	0.17-5.08	0.75
Partial fixed denture	3	75	1	25	0.50	0.05-5.15	0.86
Single crown *(reference)*	2	67	1	33	1.00		

The clinical findings showed that the greatest prevalence of bone loss was associated with overdentures or full fixed dentures. The risk ratio for bone loss, however, showed no difference between these 2 suprastructures. The likelihood of bone loss where partial fixed dentures were used was less in comparison [0.50 (95% CI = 0.05-5.15)] to that of overdentures or full fixed dentures (Table 11.6-A), but the differences were not significant.

12. DISCUSSION

It has been suggested that when more than 20–25% of patients within a study patient cohort are lost to follow-up, a study will not provide reliable data[239]. This current study had a loss to follow-up rate of 79.9%, compared with 36%[12], 37%[13], and 56%[11] published in similar studies. However, none of these aforementioned studies had a dropout rate below 25% either, because the nature of such long term studies naturally involves a high attrition rate of participants. In the present study, more than half (52.9%) of the 278 original patients could not be located anymore. Some possible reasons for the failure to locate these patients included the patients being deceased, living in either another country or in an elderly-care facility, or having changed names or addresses. Given these challenges, it would be difficult for any study with an observation period of more than 20 years to achieve a dropout rate below 25% and certainly none of the aforementioned, including this study, have managed to do so. Even though the loss to follow-up was high, the participants in the study did have some similarities with the larger cohort (Table 11.2-A Demographic data of the patient cohortTable 11.2-A).

Given the retrospective nature of the present study, the potential for bias certainly remains high. If this study could be redesigned, a prospective study would have been preferable. Edentulous patients may have been randomised to receive either a full fixed prosthesis or an implant-retained overdenture. Patients could have been followed more carefully until they dropped out. Most of the patients in the present study were of European or Australian-born, one from India, one from the Middle-East, two patients were Chinese, and one was an Aboriginal. This study shows that there is an external applicability of the data from the Swedish studies to other populations. The average age of participants was 48.5 years at the time of implant placement which is similar to that found in other comparable long-term studies[11-13], where the average age ranged between 48 to 54 years. The follow-up time of our study was 21–24 years. There are only three other studies with a minimum follow-up time of 20 years. A further two articles have

reported follow up periods of 5–25 years[240] and 10–24 years[241]. Our study nonetheless contributes to the body of evidence on 20-year implant data.

An important consideration for any clinician and patient is the expected longevity and possible complications associated with implant therapy, along with its associated prosthetic reconstruction. This is critical as implant therapy involves an invasive surgical procedure of varying degrees of complexity. However, long-term follow-up studies are scarce, involve only a small number of patients and generally report on only one type of restorative prosthesis. To date, there are only limited studies that report on the clinical outcomes of implants following at least 20 years of service with fixed full prostheses, fixed partial prostheses, and overdentures using the turned Brånemark implant®[11-13]. However, no study has compared or reported on all of these prostheses in one cohort together, including the addition of single crowns. Furthermore, to our knowledge, there is no study with an observation period of more than 20 years investigating the impact of prosthetic suprastructure on the marginal bone loss of the supporting implant.

The outcomes of the present 20-year study showed that the radiographic crestal bone levels were more or less maintained around turned-surface Brånemark implants®, with only minimal changes/bone loss being observed. These results were observed in all subjects within the patient cohort and seemed to be independent of the suprastructures.

Although the use of titanium oral implants has become a routine clinical procedure in the clinical practice for the rehabilitation of partially edentulous patients[242], several factors have been shown to affect the short[238, 243] and long term[244-246] outcomes. Among them, tobacco smoking has been demonstrated to represent a risk factor for early and late implant loss[176, 247, 248], biological complications (peri-implant diseases), and marginal bone loss[3, 42, 173, 249]. Cigarette smoking has various local and systemic effects on the human body. The local effects are regulated by cytotoxic and vasoactive substances within tobacco smoke, such as nicotine. Systemically, cigarette smoking adversely affects the immunologic response with disturbances in peripheral neutrophil

granulocytic function[250], a decrease in the prostacyclin in urine[251] that results in vasodilation, direct vasoconstriction[252], limited antibodies[253], and an effect on peripheral immunoregulatory T-cells[254]. In the present study, implants in current and ex-smokers showed higher marginal bone loss compared to implants placed in never-smoking patients. The bone loss around implants correlates well with the patient's smoking status. This is in agreement with other studies where a smoking habit negatively affected the long-term outcomes of implant therapy[173, 176, 180, 255-260].

The higher marginal bone loss could be partially explained through the findings of Oates and co-workers[261], who demonstrated that pyridinoline levels are specifically elevated in the crevicular fluid of smoking implant patients, which may affect the implant success in part through alterations in the level of bone resorption. Lambert and co-workers[262] suggested that increased implant failures in smokers are not the result of poor healing or osseointegration, but rather due to the exposure of peri-implant tissues to tobacco smoke.

Smoking also influences the bone. Studies demonstrate a lower mineral bone content within smokers. In an experimental study in rats in which subperiosteal bone formation was stimulated, Boyne and Herford found those rats exposed to cigarette smoke produced less bone than in the control rats[263]. Rats that were not exposed to cigarette smoke and received 1.0mg of nicotine via a patch applied to their backs exhibited 35% less bone growth than those exposed to smoke, and 50% less bone growth than the control group. The fact that tobacco smokers display higher proportions of implant failures and marginal bone loss compared with non-smokers has now been well documented[247, 264, 265].

In the present study, 53% of diabetics presented with peri-implant BOP, which is lower than that reported in the literature[266, 267]. The presence of bleeding on gentle probing is a useful parameter for the diagnosis of mucosal inflammation[3]. Lang and co-workers[268] have demonstrated that healthy peri-implant sites had an absence of BOP, while there was increased BOP at peri-implant mucositis sites (67%), and at peri-implantitis sites (91%). A possible explanation for the lower BOP

scores in this study could be due to the low probing force used [269]. The Florida Probe® system used in the present study utilises a constant probing force of 25g. Similar findings were also found by Luterbacher and co-workers[270] who evaluated the prognostic value of BOP in monitoring peri-implant mucosal conditions within a periodontally maintained group. Here, it was concluded that the positive predictive value for worsening peri-implant tissue conditions was 100% where there was greater than 50% BOP in subjects showing any bleeding site at more than half of their recall visits over a 2 year period.

In the present study, when analysed at the implant level, diabetic patients had significantly greater BOP and greater modified plaque and bleeding indices. No other clinical outcomes were affected by the diabetic status of the patients. Of the 4 diabetic patients, 2 of these patients had poor glycaemic control (HbA1c > 8%). Diabetes is a systemic disease that may be responsible for a wide range of mechanisms that result in delayed wound healing and increase the patient's susceptibility to infection or implant loss[271]. There has only been one cross-sectional study describing the link between diabetes and peri-implantitis. Ferreira and co-workers[267] reported a prevalence of 64.6% peri-implant mucositis and 8.9% peri-implantitis in 212 non-smoking Brazilians. The diabetic status of each of these patients was evaluated at the time of surgery, as well as at the time of re-evaluation. Following a multivariate analysis, the risk variables associated with increased odds for having peri-implant disease were identified as: gender, plaque scores, and periodontal BOP. Furthermore, the presence of periodontitis and diabetes were statistically associated with greater risk of peri-implantitis (OR 1.9 [CI 2.1-5.6]) – especially in those subjects with poor metabolic control.

The relatively minimal marginal bone loss observed over the 20 year observation period in the present study may be related to the turned surface of the implants with minimal roughness. Increases in surface roughness and surface free energy have been shown to facilitate microbial biofilm formation on dental implant and abutment surfaces[153, 272]. Experimental dog studies have

suggested that the progression of untreated peri-implantitis lesions varied among different types of implants[164, 165], being more pronounced at implants with a moderately rough surface (e.g. sand-blasted and acid-etched) as opposed to those with a turned surface[273]. Clinical studies in partially edentulous patients have also shown that implants with a rough surface display higher rates of peri-implantitis and late failures than those implants with moderately roughened or turned surfaces[274, 275].

Another drawback in this study lies upon its reliance upon initial radiographic records taken at the time of implant placement. Twenty-eight out of 97 (28.9%) implants did not have baseline radiographs available for analysis. Furthermore, the vast majority of radiographic records used for analysis were panoramic tomography. Although radiographic techniques including panoramic tomography and long cone paralleling techniques have been used to monitor marginal bone levels at implants and to diagnose interproximal bone loss[276], their limitations in image resolution and distortion are also well documented[277, 278]. Another drawback of conventional radiography includes its inability to monitor facial and lingual or palatal bone levels; a low sensitivity in the detection of early bone changes; along the with underestimation of bone loss[278, 279]. Alternatives to conventional radiographic techniques in detecting changes in bone density include subtraction radiography[280], multi-slice computer tomography (CT) and cone beam volume imaging. CT and cone beam allow evaluation of the osseous structures in 3 planes without overlay or distortion[281]. Unfortunately, these techniques were not available when the implants being investigated in the present study were inserted.

The mean change in marginal bone levels over the 20+ year observation was very small. A frequency distribution analysis of the different bone loss categories revealed that the majority (47.4%) of implants showed small bone level alterations (≤ 1mm), while 15.5% of the implants exhibited between 1.1 and 2mm and 8.2% of the implants had bone loss exceeding 2mm. The mean change was 1.1mm when analysed at an implant level, which equates to a mean annual

bone loss 0.05mm. When compared against other long-term studies also of the same implant system, this result is identical to that reported by Lindquist and colleagues over an observation period of 15 years[255] and by Lekholm et al. observed over 20 years[13]; but lower than that found by Ekelund and co-workers[12] (0.08mm over 20 years); and higher than that reported by Astrand and co-workers[11] (0.03mm observed over 20 years).

When analysed by suprastructure, all 10 implants (10.3% of the total implants analysed) of the present study affected with peri-implantitis supported overdentures (PPD >5mm, BOP positive at any site, and evidence of radiographic marginal bone loss). Figures on the prevalence of peri-implantitis vary considerably in the literature, from 0.31% for single tooth replacements to 6.47% for implants involved in fixed partial dentures after at least 5 years of follow-up[1], and 12-43% of implants after at least 5 years of follow-up[4]. It is worth noting that these figures are based on a small number of studies that show large variations in study design, patients and implants included, and the definitions used to define peri-implantitis.

Statistical analysis of the data from the present study revealed that although the greatest prevalence of bone loss was associated with overdentures or full fixed dentures, there were no statistically significant differences between these 2 suprastructures and partial fixed dentures or single crowns. However, analysis of the marginal bone loss by suprastructure at both the patient and implants levels indicated a trend: implants supporting overdentures showed the highest bone loss, followed by implants supporting full fixed dentures, partial fixed dentures, and single crowns. The prosthetic estimated cumulative survival rate in a previous study of the same population cohort also exhibited a similar trend, with the lowest cumulative survival rate of 22% being reported for overdentures, 50% for full fixed prostheses, 80% for fixed partial prostheses and 84% for single crowns[14]. This marginal bone loss observation is also consistent with a review by Berglund and co-worker's[1], where implant-supported overdentures and fixed complete dentures showed greater bone loss (beyond 2.5mm) than implants restored with fixed partial dentures and

single tooth replacements (4.76% and 3.78% vs. 1.01% and 1.28%). The authors also reported that peri-implant tissue complications (such as excessive swelling, hyperplasia requiring surgical therapy, fistula or suppuration) were higher for implants supporting overdentures compared to those supporting fixed reconstructions (0.27 vs. 0.19 [complete] and 0.15 [partial] incidences per patient over a 5 year period).

One hypothesis for the increased bone loss seen in overdentures is that high occlusal forces and loading on distal cantilever bar extensions (a common restorative suprastructure in the present study cohort) are responsible for the excessive bone loss around implants, leading to loss of osseointegration, and potentially implant failure. There is still controversy regarding the ideal design of an overdenture attachment that provides optimum force distribution around its supporting implants to allow bone loading within physiologic levels. In-vitro experiments and numeric analyses have suggested that overdenture attachment design may influence stress/strain magnitudes around implants and that lower stresses occur around unsplinted implants[282-284]. In-vivo however, it has been shown that bar retainers contribute to force partitioning (load sharing) between implants; that higher forces are exerted on unsplinted implants; and that loading on distal cantilever bar extensions does not lead to excessive bone loss around implants[285, 286].

During this long follow up period, a small number of the implants suffered from a significant amount of bone loss. According to Albrektsson et al.[17], a successful implant should not lose more than 0.2mm of bone after the first year of function. In keeping with this suggested criteria, implants with more than 4.0mm of bone loss after 20 years should be defined as failures. Applying this criteria for successful implants, 2 of the implants in this study would have been defined as failures, despite them still well-supporting the various suprastructures, with the majority of them also not causing any clinical problems. In light of this, neither the patients nor the clinicians judged these implants a failure, and thus, it may be time to redefine the aspect of bone loss within these criteria in relation to the long term success of implants.

The clinical implant parameters examined in the present study (mPl, mBl, BOP, PD, and radiographic MBL) are important indicators of peri-implant diseases that may lead to loss of an implant. Today peri-implant diseases are considered the result of the imbalance between bacterial overload and host defences[3]. In this study, the majority of the overdentures were cast bar-retained dentures which have been reported to be difficult for patients to clean[287, 288] – particularly for older patients who have limited manual dexterity and vision. Similarly, many of the full and partial fixed denture designs did not facilitate hygiene access and were also challenging for the patient to clean, as evidenced by the higher mPl and mBl scores recorded. Despite this, probing depths around the implants were predominately shallow (84.2% of implant probing sties were between 2-4mm; mean probing depth was 3.3mm) and BOP was present on only 39% of the 97 implants examined. It is also worth noting that the vast majority of these patients were not enrolled in any regular maintenance program over the past 20 years.

It also has to be mentioned that the small sample size of this cohort led to a low power for the comparative analyses. A larger sample size would have thus increased the power of the statistical analyses.

In conclusion, the treatment of both complete and partially edentulous patients with turned titanium implants seems to function well over 2 decades, providing patients with good support for fixed and removable constructions with no major complications. Minimal soft tissue inflammation and minimal radiographic bone loss was observed, despite the vast majority of the patients not being enrolled in a regular maintenance program.

13. REFERENCES

1. Berglundh T, Persson L, Klinge B. A systematic review of the incidence of biological and technical complications in implant dentistry reported in prospective longitudinal studies of at least 5 years. Journal of Clinical Periodontology 2002;29:197-212.
2. Goodacre CJ, Bernal G, Rungcharassaeng K, Kan JYK. Clinical complications with implants and implant prostheses. The Journal of Prosthetic Dentistry 2003;90:121-132.
3. Heitz-Mayfield LJA. Peri-implant diseases: diagnosis and risk indicators. Journal of Clinical Periodontology 2008;35:292-304.
4. Zitzmann NU, Berglundh T. Definition and prevalence of peri-implant diseases. Journal of Clinical Periodontology 2008;35:286-291.
5. Tonetti M, Palmer R, on behalf of Working Group 2 of the VEWoP. Clinical research in implant dentistry: study design, reporting and outcome measurements: consensus report of Working Group 2 of the VIII European Workshop on Periodontology. Journal of Clinical Periodontology 2012;39:73-80.
6. McGrath C, Lam O, Lang N. An evidence-based review of patient-reported outcome measures in dental implant research among dentate subjects. Journal of Clinical Periodontology 2012;39:193-201.
7. Tomasi C, Derks J. Clinical research of peri-implant diseases – quality of reporting, case definitions and methods to study incidence, prevalence and risk factors of peri-implant diseases. Journal of Clinical Periodontology 2012;39:207-223.
8. Graziani F, Figuero E, Herrera D. Systematic review of quality of reporting, outcome measurements and methods to study efficacy of preventive and therapeutic approaches to peri-implant diseases. Journal of Clinical Periodontology 2012;39:224-244.

9. Lang NP, Zitzmann NU, on behalf of Working Group 3 of the VEWoP. Clinical research in implant dentistry: evaluation of implant-supported restorations, aesthetic and patient-reported outcomes. Journal of Clinical Periodontology 2012;39:133-138.

10. Fiorellini JP, Martuscelli G, Weber HP. Longitudinal studies of implant systems. Periodontology 2000 1998;17:125-131.

11. Astrand P, Ahlqvist J, Gunne J, Nilson H. Implant treatment of patients with edentulous jaws: a 20-year follow-up. Clinical Implant Dentistry & Related Research 2008;10:207-217.

12. Ekelund J-A, Lindquist LW, Carlsson GE, Jemt T. Implant treatment in the edentulous mandible: a prospective study on Branemark system implants over more than 20 years. International Journal of Prosthodontics 2003;16:602-608.

13. Lekholm U, Grondahl K, Jemt T. Outcome of oral implant treatment in partially edentulous jaws followed 20 years in clinical function. Clinical Implant Dentistry & Related Research 2006;8:178-186.

14. Tran DC. Long-term survival of dental implants and prosthetic suprastructures: a 20 year follow-up study. University of Sydney, 2013.

15. Branemark PI. Vital microscopy of bone marrow in rabbit. Scand J Clin Lab Invest 1959;11 Supp 38:1-82.

16. Esposito M, Hirsch J-M, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants, (I). Success criteria and epidemiology. European Journal of Oral Sciences 1998;106:527-551.

17. Albrektsson T. The long-term efficacy of currently used dental implants: a review and proposed criteria of success. The International journal of oral and maxillofacial implants 1986;1:11-25.

18. Brägger U, Aeschlimann S, Bürgin W, Hämmerle CHF, Lang NP. Biological and technical complications and failures with fixed partial dentures (FPD) on implants and teeth after four to five years of function. Clinical Oral Implants Research 2001;12:26-34.

19. Scurria MS. Prognostic variables associated with implant failure: a retrospective effectiveness study. The International journal of oral and maxillofacial implants 1998;13:400-406.

20. Vilhjálmsson VH, Klock KS, Størksen K, Bårdsen A. Aesthetics of implant-supported single anterior maxillary crowns evaluated by objective indices and participants' perceptions. Clinical Oral Implants Research 2011;22:1399-1403.

21. Bornstein MM, Cionca N, Mombelli A. Systemic conditions and treatments as risks for implant therapy. International Journal of Oral & Maxillofacial Implants 2009;24 Suppl:12-27.

22. Martin W. Local risk factors for implant therapy. The International journal of oral and maxillofacial implants 2009;24 Suppl:28-38.

23. A M. Criteria for success: Monitoring. Proceedings of the 1st European Workshop on Periodontology 1994;317–325.

24. Mombelli A, Lang NP. Clinical parameters for the evaluation of dental implants. Periodontology 2000 1994;4:81-86.

25. Esposito M, Thomsen P, Ericson LE, Lekholm U. Histopathologic observations on early oral implant failures. International Journal of Oral & Maxillofacial Implants 1999;14:798-810.

26. Tarnow DP. The effect of inter-implant distance on the height of inter-implant bone crest. Journal of periodontology (1970) 2000;71:546-549.

27. Esposito M, Ekestubbe A, Gröndahl K. Radiological evaluation of marginal bone loss at tooth surfaces facing single Brånemark implants. Clinical Oral Implants Research 1993;4:151-157.

28. Cardaropoli G, Lekholm U, Wennstrom JL. Tissue alterations at implant-supported single-tooth replacements: a 1-year prospective clinical study. Clin Oral Implants Res 2006;17:165-171.

29. Buser D, Martin W, Belser UC. Optimizing esthetics for implant restorations in the anterior maxilla: anatomic and surgical considerations. International Journal of Oral & Maxillofacial Implants 2004;19 Suppl:43-61.

30. Schwartz-Arad D, Chaushu G. Placement of implants into fresh extraction sites: 4 to 7 years retrospective evaluation of 95 immediate implants. Journal of Periodontology 1997;68:1110-1116.

31. Lang NP, Bragger U, Hammerle CH, Sutter F. Immediate transmucosal implants using the principle of guided tissue regeneration. I. Rationale, clinical procedures and 30-month results. Clinical Oral Implants Research 1994;5:154-163.

32. Truninger TC, Philipp AOH, Siegenthaler DW, Roos M, Hämmerle CHF, Jung RE. A prospective, controlled clinical trial evaluating the clinical and radiological outcome after 3 years of immediately placed implants in sockets exhibiting periapical pathology. Clinical Oral Implants Research 2011;22:20-27.

33. Villa R, Rangert B. Immediate and early function of implants placed in extraction sockets of maxillary infected teeth: a pilot study. Journal of Prosthetic Dentistry 2007;97:S96-S108.

34. Lindeboom JAH, Tjiook Y, Kroon FHM. Immediate placement of implants in periapical infected sites: a prospective randomized study in 50 patients. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics 2006;101:705-710.

35. Novaes AB, Jr., Vidigal Junior GM, Novaes AB, Grisi MF, Polloni S, Rosa A. Immediate implants placed into infected sites: a histomorphometric study in dogs. International Journal of Oral & Maxillofacial Implants 1998;13:422-427.

36. Esposito M, Hirsch J-M, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants, (II). Etiopathogenesis. European Journal of Oral Sciences 1998;106:721-764.

37. Esposito M, Grusovin MG, Worthington HV. Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications. Cochrane Database of Systematic Reviews 2013;7:CD004152.

38. Evans CDJ, Chen ST. Esthetic outcomes of immediate implant placements. Clinical Oral Implants Research 2008;19:73-80.

39. Lang NP, Loe H. The relationship between the width of keratinized gingiva and gingival health. J Periodontol 1972;43:623-627.

40. Bouri A, Jr., Bissada N, Al-Zahrani MS, Faddoul F, Nouneh I. Width of keratinized gingiva and the health status of the supporting tissues around dental implants. International Journal of Oral & Maxillofacial Implants 2008;23:323-326.

41. Chung DM, Oh T-J, Shotwell JL, Misch CE, Wang H-L. Significance of keratinized mucosa in maintenance of dental implants with different surfaces. Journal of Periodontology 2006;77:1410-1420.

42. Roos-Jansåker A-M, Renvert H, Lindahl C, Renvert S. Nine- to fourteen-year follow-up of implant treatment. Part III: factors associated with peri-implant lesions. Journal of Clinical Periodontology 2006;33:296-301.

43. Wennström JL, Bengazi F, Lekholm U. The influence of the masticatory mucosa on the peri-implant soft tissue condition. Clinical Oral Implants Research 1994;5:1-8.

44. Esposito M. Different loading strategies of dental implants: a Cochrane systematic review of randomised controlled clinical trials. European journal of oral implantology 2008;1:259-276.

45. Orenstein IH, Tarnow DP, Morris HF, Ochi S. Three-year post-placement survival of implants mobile at placement. Annals of Periodontology 5:32-41.

46. Molly L. Bone density and primary stability in implant therapy. Clinical Oral Implants Research 2006;17:124-135.

47. Oczakir C, Balmer S, Mericske-Stern R. Implant-prosthodontic treatment for special care patients: a case series study. International Journal of Prosthodontics 2005;18:383-389.

48. Haas SE. Implant-supported, long-span fixed partial denture for a scleroderma patient: a clinical report. Journal of Prosthetic Dentistry 2002;87:136-139.

49. Czerninski R, Kaplan I, Almoznino G, Maly A, Regev E. Oral squamous cell carcinoma around dental implants. Quintessence International 2006;37:707-711.

50. Garagiola U, Maiorana C, Ghiglione V, Marzo G, Santoro F, Szabo G. Osseointegration and guided bone regeneration in ectodermal dysplasia patients. Journal of Craniofacial Surgery 2007;18:1296-1304.

51. Sweeney IP, Ferguson JW, Heggie AA, Lucas JO. Treatment outcomes for adolescent ectodermal dysplasia patients treated with dental implants. International Journal of Paediatric Dentistry 2005;15:241-248.

52. Isidor F, Brondum K, Hansen HJ, Jensen J, Sindet-Pedersen S. Outcome of treatment with implant-retained dental prostheses in patients with Sjogren syndrome. International Journal of Oral & Maxillofacial Implants 1999;14:736-743.

53. Lustig JP, Yanko R, Zilberman U. Use of dental implants in patients with Down syndrome: a case report. Special Care in Dentistry 2002;22:201-204.

54. Ekfeldt A. Early experience of implant-supported prostheses in patients with neurologic disabilities. International Journal of Prosthodontics 2005;18:132-138.

55. Addy L, Korszun A, Jagger RG. Dental implant treatment for patients with psychiatric disorders. European Journal of Prosthodontics & Restorative Dentistry 2006;14:90-92.

56. Strietzel FP, Rothe S, Reichart PA, Schmidt-Westhausen A-M. Implant-prosthetic treatment in HIV-infected patients receiving highly active antiretroviral therapy: report of cases. International Journal of Oral & Maxillofacial Implants 2006;21:951-956.

57. Sakakura CE, Margonar R, Sartori R, Morais JAND, Marcantonio E, Jr. The influence of cyclosporin a on mechanical retention of dental implants previously integrated to the bone: a study in rabbits. Journal of Periodontology 2006;77:2059-2062.

58. Sakakura CE, Marcantonio E, Jr., Wenzel A, Scaf G. Influence of cyclosporin A on quality of bone around integrated dental implants: a radiographic study in rabbits. Clinical Oral Implants Research 2007;18:34-39.

59. Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ. Epidemiology of osteoporosis and osteoporotic fractures. Epidemiologic Reviews 1985;7:178-208.

60. Friberg B, Ekestubbe A, Mellstrom D, Sennerby L. Branemark implants and osteoporosis: a clinical exploratory study. Clinical Implant Dentistry & Related Research 2001;3:50-56.

61. Steiner M, Ramp WK. Endosseous dental implants and the glucocorticoid-dependent patient. Journal of Oral Implantology 1990;16:211-217.

62. Cranin AN. Endosteal implants in a patient with corticosteroid dependence. Journal of Oral Implantology 1991;17:414-417.

63. Friberg B. Treatment with dental implants in patients with severe osteoporosis: a case report. International Journal of Periodontics & Restorative Dentistry 1994;14:348-353.

64. von Wowern N, Gotfredsen K. Implant-supported overdentures, a prevention of bone loss in edentulous mandibles? A 5-year follow-up study. Clinical Oral Implants Research 2001;12:19-25.

65. Becker W, Hujoel PP, Becker BE, Willingham H. Osteoporosis and implant failure: an exploratory case-control study. Journal of Periodontology 2000;71:625-631.

66. Dello Russo NM, Jeffcoat MK, Marx RE, Fugazzotto P. Osteonecrosis in the jaws of patients who are using oral biphosphonates to treat osteoporosis. International Journal of Oral & Maxillofacial Implants 2007;22:146-153.

67. Wang H-L, Weber D, McCauley LK. Effect of long-term oral bisphosphonates on implant wound healing: literature review and a case report. Journal of Periodontology 2007;78:584-594.

68. Marx RE. Bisphosphonate-induced osteonecrosis of the jaws: a challenge, a responsibility, and an opportunity. International Journal of Periodontics & Restorative Dentistry 2008;28:5-6.

69. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. International Journal of Oral & Maxillofacial Implants 2006;21:349-353.

70. Grant B-T, Amenedo C, Freeman K, Kraut RA. Outcomes of placing dental implants in patients taking oral bisphosphonates: a review of 115 cases. Journal of Oral & Maxillofacial Surgery 2008;66:223-230.

71. Granstrom G. Radiotherapy, osseointegration and hyperbaric oxygen therapy. Periodontology 2000 2003;33:145-162.

72. Colella G, Cannavale R, Pentenero M, Gandolfo S. Oral implants in radiated patients: a systematic review. International Journal of Oral & Maxillofacial Implants 2007;22:616-622.

73. Granstrom G. Osseointegration in irradiated cancer patients: an analysis with respect to implant failures. Journal of Oral & Maxillofacial Surgery 2005;63:579-585.

74. Esser E, Wagner W. Dental implants following radical oral cancer surgery and adjuvant radiotherapy. International Journal of Oral & Maxillofacial Implants 1997;12:552-557.

75. Granstrom G. Placement of dental implants in irradiated bone: the case for using hyperbaric oxygen. Journal of Oral & Maxillofacial Surgery 2006;64:812-818.

76. Esposito M, Grusovin MG, Patel S, Worthington HV, Coulthard P. Interventions for replacing missing teeth: hyperbaric oxygen therapy for irradiated patients who require dental implants. Cochrane Database of Systematic Reviews 2008;

77. Papaspyridakos P. A systematic review of biologic and technical complications with fixed implant rehabilitations for edentulous patients. The International journal of oral and maxillofacial implants 2012;27:102-110.

78. Bozini T. A meta-analysis of prosthodontic complication rates of implant-supported fixed dental prostheses in edentulous patients after an observation period of at least 5 years. The International journal of oral and maxillofacial implants 2011;26:304-318.

79. Dudic A, Mericske-Stern R. Retention mechanisms and prosthetic complications of implant-supported mandibular overdentures: long-term results. Clinical Implant Dentistry & Related Research 2002;4:212-219.

80. Bell AM, Kurzeja R, Gamberg MG. Ceramometal crowns and bridges. Focus on failures. Dental Clinics of North America 1985;29:763-778.

81. Sahin S, Cehreli MC, Yalcin E. The influence of functional forces on the biomechanics of implant-supported prostheses--a review. Journal of Dentistry 2002;30:271-282.

82. Duyck J, Van Oosterwyck H, Vander Sloten J, De Cooman M, Puers R, Naert I. Magnitude and distribution of occlusal forces on oral implants supporting fixed prostheses: an in vivo study. Clinical Oral Implants Research 2000;11:465-475.

83. Attard NJ, Zarb GA. Long-term treatment outcomes in edentulous patients with implant-fixed prostheses: the Toronto study. International Journal of Prosthodontics 2004;17:417-424.

84. Davis DM, Packer ME, Watson RM. Maintenance requirements of implant-supported fixed prostheses opposed by implant-supported fixed prostheses, natural teeth, or complete dentures: a 5-year retrospective study. International Journal of Prosthodontics 2003;16:521-523.

85. Stewart RB, Desjardins RP, Laney WR, Chao EY. Fatigue strength of cantilevered metal frameworks for tissue-integrated prostheses. Journal of Prosthetic Dentistry 1992;68:83-92.

86. Araujo MG, Lindhe J. Dimensional ridge alterations following tooth extraction. An experimental study in the dog. J Clin Periodontol 2005;32:212-218.

87. Hämmerle CHF, Jung RE, Feloutzis A. A systematic review of the survival of implants in bone sites augmented with barrier membranes (guided bone regeneration) in partially edentulous patients. Journal of Clinical Periodontology 2002;29:226-231.

88. McAllister BS, Haghighat K. Bone Augmentation Techniques. Journal of Periodontology 2007;78:377-396.

89. Esposito M, Felice P, Worthington Helen V. Interventions for replacing missing teeth: augmentation procedures of the maxillary sinus. Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, 2014. 5.

90. Chiapasco M, Zaniboni M, Rimondini L. Autogenous onlay bone grafts vs. alveolar distraction osteogenesis for the correction of vertically deficient edentulous ridges: a 2–4-year prospective study on humans. Clinical Oral Implants Research 2007;18:432-440.

91. Monje A, Fu J-H, Chan H-L, et al. Do Implant Length and Width Matter for Short Dental Implants (<10 mm)? A Meta-Analysis of Prospective Studies. Journal of Periodontology 2013;84:1783-1791.

92. Esposito M, Cannizzaro G, Soardi E, et al. Posterior atrophic jaws rehabilitated with prostheses supported by 6 mm-long, 4 mm-wide implants or by longer implants in augmented bone. Preliminary results from a pilot randomised controlled trial. European journal of oral implantology 2012;5:19-33.

93. das Neves FD, Fones D, Bernardes SR, do Prado CJ, Neto AJ. Short implants - an analysis of longitudinal studies. International Journal of Oral & Maxillofacial Implants 2006;21:86-93.

94. Morand M, Irinakis T. The challenge of implant therapy in the posterior maxilla: providing a rationale for the use of short implants. Journal of Oral Implantology 2007;33:257-266.

95. Renouard F, Nisand D. Impact of implant length and diameter on survival rates. Clinical Oral Implants Research 2006;17:35-51.

96. Telleman G, Raghoebar GM, Vissink A, den Hartog L, Huddleston Slater JJR, Meijer HJA. A systematic review of the prognosis of short (<10 mm) dental implants placed in the partially edentulous patient. Journal of Clinical Periodontology 2011;38:667-676.

97. Annibali S, Cristalli MP, Dell'Aquila D, Bignozzi I, La Monaca G, Pilloni A. Short Dental Implants: A Systematic Review. Journal of Dental Research 2012;91:25-32.

98. Maló P, De Araújo Nobre M, Rangert B. Short Implants Placed One-Stage in Maxillae and Mandibles: A Retrospective Clinical Study with 1 to 9 Years of Follow-Up. Clinical Implant Dentistry and Related Research 2007;9:15-21.

99. Tawil G, Younan R. Clinical evaluation of short, machined-surface implants followed for 12 to 92 months. International Journal of Oral & Maxillofacial Implants 2003;18:894-901.

100. Jokstad A. The evidence for endorsing the use of short dental implants remains inconclusive. Evid Based Dent 2011;12:99-101.

101. Chuang S-K, Cai T. Predicting Clustered Dental Implant Survival Using Frailty Methods. Journal of Dental Research 2006;85:1147-1151.

102. Feldman S, Boitel N, Weng D, Kohles SS, Stach RM. Five-Year Survival Distributions of Short-Length (10 mm or less) Machined-Surfaced and Osseotite® Implants. Clinical Implant Dentistry and Related Research 2004;6:16-23.

103. Friberg B. Clinical outcome of Brånemark System implants of various diameters: a retrospective study. The International journal of oral and maxillofacial implants 2002;17:671-677.

104. Rocchietta I, Fontana F, Simion M. Clinical outcomes of vertical bone augmentation to enable dental implant placement: a systematic review. J Clin Periodontol 2008;35:203-215.

105. Lai HC, Zhuang LF, Lv XF, Zhang ZY, Zhang YX. Osteotome sinus floor elevation with or without grafting: a preliminary clinical trial. Clin Oral Implants Res 2010;21:520-526.

106. Tonetti MS, Hammerle CH. Advances in bone augmentation to enable dental implant placement: Consensus Report of the Sixth European Workshop on Periodontology. J Clin Periodontol 2008;35:168-172.

107. Pierrisnard L, Renouard F, Renault P, Barquins M. Influence of Implant Length and Bicortical Anchorage on Implant Stress Distribution. Clinical Implant Dentistry and Related Research 2003;5:254-262.

108. Rangert B, Krogh PH, Langer B, Van Roekel N. Bending overload and implant fracture: a retrospective clinical analysis. International Journal of Oral & Maxillofacial Implants 1995;10:326-334.

109. Lum LB. A biomechanical rationale for the use of short implants. Journal of Oral Implantology 1991;17:126-131.

110. Bernard JP, Szmukler-Moncler S, Pessotto S, Vazquez L, Belser UC. The anchorage of Branemark and ITI implants of different lengths. I. An experimental study in the canine mandible. Clin Oral Implants Res 2003;14:593-600.

111. Vigolo P, Givani A. Clinical evaluation of single-tooth mini-implant restorations: a five-year retrospective study. Journal of Prosthetic Dentistry 2000;84:50-54.

112. Vigolo P, Givani A, Majzoub Z, Cordioli G. Clinical evaluation of small-diameter implants in single-tooth and multiple-implant restorations: a 7-year retrospective study. International Journal of Oral & Maxillofacial Implants 2004;19:703-709.

113. Zinsli B, Sagesser T, Mericske E, Mericske-Stern R. Clinical evaluation of small-diameter ITI implants: a prospective study. International Journal of Oral & Maxillofacial Implants 2004;19:92-99.

114. Chang SH, Lin CL, Hsue SS, Lin YS, Huang SR. Biomechanical analysis of the effects of implant diameter and bone quality in short implants placed in the atrophic posterior maxilla. Med Eng Phys 2012;34:153-160.

115. Ivanoff CJ. Influence of variations in implant diameters: a 3- to 5-year retrospective clinical report. The International journal of oral and maxillofacial implants 1999;14:173-180.

116. Petrie CS, Williams JL. Comparative evaluation of implant designs: influence of diameter, length, and taper on strains in the alveolar crest. Clinical Oral Implants Research 2005;16:486-494.

117. Pommer B, Frantal S, Willer J, Posch M, Watzek G, Tepper G. Impact of dental implant length on early failure rates: a meta-analysis of observational studies. Journal of Clinical Periodontology 2011;38:856-863.

118. Degidi M, Piattelli A, Iezzi G, Carinci F. Wide-diameter implants: analysis of clinical outcome of 304 fixtures. J Periodontol 2007;78:52-58.

119. Ormianer Z, Palti A, Demiralp B, Heller G, Lewinstein I, Khayat PG. Implant-supported first molar restorations: correlation of finite element analysis with clinical outcomes. International Journal of Oral & Maxillofacial Implants 2012;27:e1-12.

120. Quek CE, Tan KB, Nicholls JI. Load fatigue performance of a single-tooth implant abutment system: effect of diameter. International Journal of Oral & Maxillofacial Implants 2006;21:929-936.

121. Lee JH, Frias V, Lee KW, Wright RF. Effect of implant size and shape on implant success rates: a literature review. Journal of Prosthetic Dentistry 2005;94:377-381.

122. Vandeweghe S, Ackermann A, Bronner J, Hattingh A, Tschakaloff A, De Bruyn H. A Retrospective, Multicenter Study on a Novo Wide-Body Implant for Posterior Regions. Clinical Implant Dentistry and Related Research 2012;14:281-292.

123. Esposito M, Coulthard P, Thomsen P, Worthington HV. The role of implant surface modifications, shape and material on the success of osseointegrated dental implants. A Cochrane systematic review. European Journal of Prosthodontics & Restorative Dentistry 2005;13:15-31.

124. Schulte J, Flores AM, Weed M. Crown-to-implant ratios of single tooth implant-supported restorations. The Journal of Prosthetic Dentistry 2007;98:1-5.

125. Haas R, Mensdorff-Pouilly N, Mailath G, Watzek G. Branemark single tooth implants: a preliminary report of 76 implants. Journal of Prosthetic Dentistry 1995;73:274-279.

126. Blanes RJ. To what extent does the crown-implant ratio affect the survival and complications of implant-supported reconstructions? A systematic review. Clin Oral Implants Res 2009;20 Suppl 4:67-72.

127. Sun HL. Failure rates of short (≤ 10 mm) dental implants and factors influencing their failure: a systematic review. The International journal of oral and maxillofacial implants 2011;26:816-825.

128. Renouard F. Short implants in the severely resorbed maxilla: a 2-year retrospective clinical study. Clinical Implant Dentistry and Related Research 2005;7 Suppl 1:S104-110.

129. Davies JE. Understanding peri-implant endosseous healing. J Dent Educ 2003;67:932-949.

130. Lai H-C, Si M-S, Zhuang L-F, Shen H, Liu Y-l, Wismeijer D. Long-term outcomes of short dental implants supporting single crowns in posterior region: a clinical retrospective study of 5–10 years. Clinical Oral Implants Research 2013;24:230-237.

131. Pjetursson BE, Tan K, Lang NP, Brägger U, Egger M, Zwahlen M. A systematic review of the survival and complication rates of fixed partial dentures (FPDs) after an observation period of at least 5 years. Clinical Oral Implants Research 2004;15:625-642.

132. Jung RE, Pjetursson BE, Glauser R, Zembic A, Zwahlen M, Lang NP. A systematic review of the 5-year survival and complication rates of implant-supported single crowns. Clinical Oral Implants Research 2008;19:119-130.

133. Mardinger O, Oubaid S, Manor Y, Nissan J, Chaushu G. Factors Affecting the Decision to Replace Failed Implants: A Retrospective Study. Journal of Periodontology 2008;79:2262-2266.

134. Lindhe J, Meyle J, on behalf of Group DotEWoP. Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology. Journal of Clinical Periodontology 2008;35:282-285.

135. Sanz M, Chapple IL, on behalf of Working Group 4 of the VEWoP. Clinical research on peri-implant diseases: consensus report of Working Group 4. Journal of Clinical Periodontology 2012;39:202-206.

136. Hämmerle CHF, Brägger U, Bürgin W, Lang NP. The effect of subcrestal placement of the polished surface of ITI® implants on marginal soft and hard tissues. Clinical Oral Implants Research 1996;7:111-119.

137. Roos-Jansåker A-M, Lindahl C, Renvert H, Renvert S. Nine- to fourteen-year follow-up of implant treatment. Part II: presence of peri-implant lesions. Journal of Clinical Periodontology 2006;33:290-295.

138. Albrektsson T IF. Consensus report of session IV. London: Quintessence Publishing, 1994.

139. Koldsland OC, Scheie AA, Aass AM. Prevalence of Peri-Implantitis Related to Severity of the Disease With Different Degrees of Bone Loss. Journal of Periodontology 2009;81:231-238.

140. Mombelli A, Lang NP. The diagnosis and treatment of peri-implantitis. Periodontology 2000 1998;17:63-76.

141. Löe H, Theilade E, Jensen SB. Experimental Gingivitis in Man. Journal of Periodontology 1965;36:177-187.

142. Pontoriero R, Tonelli MP, Carnevale G, Mombelli A, Nyman SR, Lang NP. Experimentally induced peri-implant mucositis. A clinical study in humans. Clinical Oral Implants Research 1994;5:254-259.

143. Berglundh T, Lindhe J, Marinell C, Ericsson I, Liljenberg B. Soft tissue reaction to de novo plaque formation on implants and teeth. An experimental study in the dog. Clinical Oral Implants Research 1992;3:1-8.

144. Gould TRL, Westbury L, Brunette DM. Ultrastructural study of the attachment of human gingiva to titanium in vivo. The Journal of Prosthetic Dentistry 1984;52:418-420.

145. Zitzmann NU, Berglundh T, Marinello CP, Lindhe J. Experimental peri-implant mucositis in man. Journal of Clinical Periodontology 2001;28:517-523.

146. Lindhe J, Berglundh T, Ericsson I, Liljenberg B, Marinello C. Experimental breakdown of peri-implant and periodontal tissues. A study in the beagle dog. Clinical Oral Implants Research 1992;3:9-16.

147. Lang NP, Brägger U, Walther D, Bearner B, Kornman KS. Ligature-induced peri-implant infection in cynomolgus monkeys.Clinical and radiographic findings. Clinical Oral Implants Research 1993;4:2-11.

148. Mombelli A, Lang NP. Antimicrobial treatment of peri-implant infections. Clinical Oral Implants Research 1992;3:162-168.

149. Ericsson I, Persson LG, Berglundh T, Edlund T, Lindhe J. The effect of antimicrobial theram on peri-implantitis lesions. An experimental study in the dog. Clinical Oral Implants Research 1996;7:320-328.

150. Mombelli A, Mericske-ster R. Microbiological features of stable osseointegrated implants used as abutments for overdentures. Clinical Oral Implants Research 1990;1:1-7.

151. Mombelli A, Buser D, Lang NP. Colonization of osseointegrated titanium implants in edentulous patients. Early results. Oral Microbiology and Immunology 1988;3:113-120.

152. Salvi GE, Aglietta M, Eick S, Sculean A, Lang NP, Ramseier CA. Reversibility of experimental peri-implant mucositis compared with experimental gingivitis in humans. Clinical Oral Implants Research 2012;23:182-190.

153. Teughels W, Van Assche N, Sliepen I, Quirynen M. Effect of material characteristics and/or surface topography on biofilm development. Clinical Oral Implants Research 2006;17:68-81.

154. Leonhardt Å, Berglundh T, Ericsson I, Dahlen G. Putative periodontal and teeth in pathogens on titanium implants and teeth in experimental gingivitis and periodontitis in beagle dogs. Clinical Oral Implants Research 1992;3:112-119.

155. Heitz-Mayfield LJA, Lang NP. Comparative biology of chronic and aggressive periodontitis vs. peri-implantitis. Periodontology 2000 2010;53:167-181.

156. Renvert S, Lindahl C, Renvert H, Persson GR. Clinical and microbiological analysis of subjects treated with Brånemark or AstraTech implants: a 7-year follow-up study. Clinical Oral Implants Research 2008;19:342-347.

157. Leonhardt Å, Renvert S, Dahlén G. Microbial findings at failing implants. Clinical Oral Implants Research 1999;10:339-345.

158. Duarte PM, De Mendonça AC, Máximo MBB, Santos VR, Bastos MF, Nociti Júnior FH. Differential cytokine expressions affect the severity of peri-implant disease. Clinical Oral Implants Research 2009;20:514-520.

159. Ericsson I, Berglundh T, Marinello C, Liljenberg B, Lindhe J. Long-standing plaque and gingivitis at implants and teeth in the dog. Clinical Oral Implants Research 1992;3:99-103.

160. Abrahamsson L, Berglundh T, Lindhe J. Soft tissue response to plaque formation at different implant systems. A comparative study in the dog. Clinical Oral Implants Research 1998;9:73-79.

161. Schou S, Holmstrup P, Reibel J, Juhl M, Hjørting-Hansen E, Kornman KS. Ligature-Induced Marginal Inflammation Around Osseointegrated Implants and Ankylosed Teeth: Stereologic and Histologic Observations in Cynomolgus Monkeys (Macaca Fascicularis). Journal of Periodontology 1993;64:529-537.

162. Zitzmann NU, Berglundh T, Ericsson I, Lindhe J. Spontaneous progression of experimentally induced periimplantitis. Journal of Clinical Periodontology 2004;31:845-849.

163. Berglundh T, Zitzmann NU, Donati M. Are peri-implantitis lesions different from periodontitis lesions? Journal of Clinical Periodontology 2011;38:188-202.

164. Albouy J-P, Abrahamsson I, Persson LG, Berglundh T. Spontaneous progression of peri-implantitis at different types of implants. An experimental study in dogs. I: clinical and radiographic observations. Clinical Oral Implants Research 2008;19:997-1002.

165. Albouy J-P, Abrahamsson I, Persson LG, Berglundh T. Spontaneous progression of ligatured induced peri-implantitis at implants with different surface characteristics. An experimental study in dogs II: histological observations. Clinical Oral Implants Research 2009;20:366-371.

166. Albouy J-P, Abrahamsson I, Berglundh T. Spontaneous progression of experimental peri-implantitis at implants with different surface characteristics: An experimental study in dogs. Journal of Clinical Periodontology 2012;39:182-187.

167. Rocchietta I, Nisand D. A review assessing the quality of reporting of risk factor research in implant dentistry using smoking, diabetes and periodontitis and implant loss as an outcome: critical aspects in design and outcome assessment. Journal of Clinical Periodontology 2012;39:114-121.

168. Lindquist LW, Carlsson GE, Jemt T. Association between marginal bone loss around osseointegrated mandibular implants and smoking habits: A 10-year follow-up study. Journal of Dental Research 1997;76:1667-1674.

169. Ferreira SD, Silva GLM, Cortelli JR, Costa JE, Costa FO. Prevalence and risk variables for peri-implant disease in Brazilian subjects. Journal of Clinical Periodontology 2006;33:929-935.

170. Serino G, Ström C. Peri-implantitis in partially edentulous patients: association with inadequate plaque control. Clinical Oral Implants Research 2009;20:169-174.

171. Van der Weijden GA, Van Bemmel KM, Renvert S. Implant therapy in partially edentulous, periodontally compromised patients: a review. Journal of Clinical Periodontology 2005;32:506-511.

172. Karoussis IK, Kotsovilis S, Fourmousis I. A comprehensive and critical review of dental implant prognosis in periodontally compromised partially edentulous patients. Clinical Oral Implants Research 2007;18:669-679.

173. Haas R, Haimböck W, Mailath G, Watzek G. The relationship of smoking on peri-implant tissue: A retrospective study. The Journal of Prosthetic Dentistry 1996;76:592-596.

174. Laine ML, Leonhardt Å, Roos-Jansåker A-M, et al. IL-1RN gene polymorphism is associated with peri-implantitis. Clinical Oral Implants Research 2006;17:380-385.

175. Hinode D, Tanabe S-i, Yokoyama M, Fujisawa K, Yamauchi E, Miyamoto Y. Influence of smoking on osseointegrated implant failure: a meta-analysis. Clinical Oral Implants Research 2006;17:473-478.

176. Strietzel FP, Reichart PA, Kale A, Kulkarni M, Wegner B, Küchler I. Smoking interferes with the prognosis of dental implant treatment: a systematic review and meta-analysis. Journal of Clinical Periodontology 2007;34:523-544.

177. Rinke S, Ohl S, Ziebolz D, Lange K, Eickholz P. Prevalence of periimplant disease in partially edentulous patients: a practice-based cross-sectional study. Clinical Oral Implants Research 2011;22:826-833.

178. Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. Periodontology 2000 2007;44:127-153.

179. Bormann K-H, Stuhmer C, Z'Graggen M, Kokemoller H, Rucker M, Gellrich N-C. IL-1 polymorphism and periimplantitis. A literature review. Schweizer Monatsschrift fur Zahnmedizin 2010;120:510-520.

180. Gruica B, Wang H-Y, Lang NP, Buser D. Impact of IL-1 genotype and smoking status on the prognosis of osseointegrated implants. Clinical Oral Implants Research 2004;15:393-400.

181. Isidor F. Influence of forces on peri-implant bone. Clinical Oral Implants Research 2006;17:8-18.

182. Barbier L, Schepers E. Adaptive bone remodeling around oral implants under axial and nonaxial loading conditions in the dog mandible. International Journal of Oral & Maxillofacial Implants 1997;12:215-223.

183. Stanford CM, Brand RA. Toward an understanding of implant occlusion and strain adaptive bone modeling and remodeling. The Journal of Prosthetic Dentistry 1999;81:553-561.

184. Fu J-H, Hsu Y-T, Wang H-L. Identifying occlusal overload and how to deal with it to avoid marginal bone loss around implants. European journal of oral implantology 2012;5 Suppl:S91-103.

185. Pauletto N, Lahiffe BJ, Walton JN. Complications associated with excess cement around crowns on osseointegrated implants: a clinical report. International Journal of Oral & Maxillofacial Implants 1999;14:865-868.

186. Wilson Jr TG. The Positive Relationship Between Excess Cement and Peri-Implant Disease: A Prospective Clinical Endoscopic Study. Journal of Periodontology 2009;80:1388-1392.

187. Agar JR, Cameron SM, Hughbanks JC, Parker MH. Cement removal from restorations luted to titanium abutments with simulated subgingival margins. The Journal of Prosthetic Dentistry 1997;78:43-47.

188. Wadhwani C, Hess T, Faber T, Piñeyro A, Chen CSK. A descriptive study of the radiographic density of implant restorative cements. The Journal of Prosthetic Dentistry 2010;103:295-302.

189. White DJ. Dental calculus: recent insights into occurrence, formation, prevention, removal and oral health effects of supragingival and subgingival deposits. European Journal of Oral Sciences 1997;105:508-522.

190. Tan B, Gillam DG, Mordan NJ, Galgut PN. A preliminary investigation into the ultrastructure of dental calculus and associated bacteria. Journal of Clinical Periodontology 2004;31:364-369.

191. Schedle A, Franz A, Rausch-Fan X, et al. Cytotoxic effects of dental composites, adhesive substances, compomers and cements. Dental Materials 1998;14:429-440.

192. Schou S, Holmstrup P, Stoltze K, Hjørting-Hansen E, Fiehn N-E, Skovgaard LT. Probing around implants and teeth with healthy or inflamed peri-implant mucosa/gingiva. Clinical Oral Implants Research 2002;13:113-126.

193. Etter TH, Håkanson I, Lang NP, Trejo PM, Caffesse RG. Healing after standardized clinical probing of the perlimplant soft tissue seal. Clinical Oral Implants Research 2002;13:571-580.

194. Serino G, Turri A, Lang NP. Probing at implants with peri-implantitis and its relation to clinical peri-implant bone loss. Clinical Oral Implants Research 2013;24:91-95.

195. Lang NP, Berglundh T, on Behalf of Working Group 4 of the Seventh European Workshop on P. Periimplant diseases: where are we now? – Consensus of the Seventh European Workshop on Periodontology. Journal of Clinical Periodontology 2011;38:178-181.

196. Fransson C, Wennström J, Berglundh T. Clinical characteristics at implants with a history of progressive bone loss. Clinical Oral Implants Research 2008;19:142-147.

197. Schwarz F, Sahm N, Mihatovic I, Golubovic V, Becker J. Surgical therapy of advanced ligature-induced peri-implantitis defects: cone-beam computed tomographic and histological analysis. Journal of Clinical Periodontology 2011;38:939-949.

198. Fienitz T, Schwarz F, Ritter L, Dreiseidler T, Becker J, Rothamel D. Accuracy of cone beam computed tomography in assessing peri-implant bone defect regeneration: a histologically controlled study in dogs. Clinical Oral Implants Research 2012;23:882-887.

199. Mombelli A. Microbiology and antimicrobial therapy of peri-implantitis. Periodontology 2000 2002;28:177-189.

200. Quirynen M, Bollen CML, Eyssen H, Van Steenberghe D. Microbial penetration along the implant components of the Brånemark system®. An in vitro study. Clinical Oral Implants Research 1994;5:239-244.

201. Quirynen M, Van Steenberghe D. Bacterial colonization of the internal part of two-stage implants. An in vivo study. Clinical Oral Implants Research 1993;4:158-161.

202. Meredith N, Alleyne D, Cawley P. Quantitative determination of the stability of the implant-tissue interface using resonance frequency analysis. Clinical Oral Implants Research 1996;7:261-267.

203. Huwiler MA, Pjetursson BE, Bosshardt DD, Salvi GE, Lang NP. Resonance frequency analysis in relation to jawbone characteristics and during early healing of implant installation. Clinical Oral Implants Research 2007;18:275-280.

204. Renvert S, Roos-Jansåker A-M, Claffey N. Non-surgical treatment of peri-implant mucositis and peri-implantitis: a literature review. Journal of Clinical Periodontology 2008;35:305-315.

205. Trejo PM, Bonaventura G, Weng D, Caffesse RG, Bragger U, Lang NP. Effect of mechanical and antiseptic therapy on peri-implant mucositis: an experimental study in monkeys. Clinical Oral Implants Research 2006;17:294-304.

206. Heitz-Mayfield LJA, Salvi GE, Botticelli D, et al. Anti-infective treatment of peri-implant mucositis: a randomised controlled clinical trial. Clinical Oral Implants Research 2011;22:237-241.

207. Kotsovilis S, Karoussis IK, Trianti M, Fourmousis I. Therapy of peri-implantitis: a systematic review. Journal of Clinical Periodontology 2008;35:621-629.

208. Lang NP, Wilson TG, Corbet EF. Biological complications with dental implants: their prevention, diagnosis and treatment. Clinical Oral Implants Research 2000;11:146-155.

209. Louropoulou A, Slot DE, Van der Weijden FA. Titanium surface alterations following the use of different mechanical instruments: a systematic review. Clinical Oral Implants Research 2012;23:643-658.

210. Dmytiyk JJ, Fox SC, Moriarty JD. The Effects of Scaling Titanium Implant Surfaces With Metal and Plastic Instruments on Cell Attachment. Journal of Periodontology 1990;61:491-496.

211. Ciancio SG, Lauciello F, Shibly O, Vitello M, Mather M. The Effect of an Antiseptic Mouthrinse on Implant Maintenance: Plaque and Peri-Implant Gingival Tissues*. Journal of Periodontology 1995;66:962-965.

212. Porras R, Anderson GB, Caffesse R, Narendran S, Trejo PM. Clinical Response to 2 Different Therapeutic Regimens to Treat Peri-Implant Mucositis. Journal of Periodontology 2002;73:1118-1125.

213. Schou S, Berglundh T, Lang NP. Surgical treatment of peri-implantitis. International Journal of Oral & Maxillofacial Implants 2004;19 Suppl:140-149.

214. Wetzel AC, Vlassis J, Caffesse RG, Hammerle CH, Lang NP. Attempts to obtain re-osseointegration following experimental peri-implantitis in dogs. Clin Oral Implants Res 1999;10:111-119.

215. Sahm N, Becker J, Santel T, Schwarz F. Non-surgical treatment of peri-implantitis using an air-abrasive device or mechanical debridement and local application of chlorhexidine: a prospective, randomized, controlled clinical study. J Clin Periodontol 2011;38:872-878.

216. Máximo MB, De Mendonça AC, Renata Santos V, Figueiredo LC, Feres M, Duarte PM. Short-term clinical and microbiological evaluations of peri-implant diseases before and after mechanical anti-infective therapies. Clinical Oral Implants Research 2009;20:99-108.

217. Heitz-Mayfield LJA. Antimicrobial treatment of peri-implant diseases. The International journal of oral and maxillofacial implants 2004;19 Suppl:128-139.

218. Leonhardt Å, Dahlén G, Renvert S. Five-Year Clinical, Microbiological, and Radiological Outcome Following Treatment of Peri-Implantitis in Man. Journal of Periodontology 2003;74:1415-1422.

219. Büchter A, Meyer U, Kruse-Lösler B, Joos U, Kleinheinz J. Sustained release of doxycycline for the treatment of peri-implantitis: randomised controlled trial. British Journal of Oral and Maxillofacial Surgery 2004;42:439-444.

220. Renvert S, Lessem J, Dahlén G, Lindahl C, Svensson M. Topical minocycline microspheres versus topical chlorhexidine gel as an adjunct to mechanical debridement of incipient peri-implant infections: a randomized clinical trial. Journal of Clinical Periodontology 2006;33:362-369.

221. Salvi GE, Persson GR, Heitz-Mayfield LJA, Frei M, Lang NP. Adjunctive local antibiotic therapy in the treatment of peri-implantitis II: clinical and radiographic outcomes. Clinical Oral Implants Research 2007;18:281-285.

222. Esposito M. Treatment of peri-implantitis: what interventions are effective? A Cochrane systematic review. European journal of oral implantology 2012;5 Suppl:S21 41.

223. Renvert S, Polyzois I, Maguire R. Re-osseointegration on previously contaminated surfaces: a systematic review. Clinical Oral Implants Research 2009;20 Suppl 4:216-227.

224. Persson GR, Roos-Jansåker A-M, Lindahl C, Renvert S. Microbiologic Results After Non-Surgical Erbium-Doped:Yttrium, Aluminum, and Garnet Laser or Air-Abrasive Treatment of Peri-Implantitis: A Randomized Clinical Trial. Journal of Periodontology 2011;82:1267-1278.

225. Karring ES, Stavropoulos A, Ellegaard B, Karring T. Treatment of peri-implantitis by the Vector® system. Clinical Oral Implants Research 2005;16:288-293.

226. Romeo E, Ghisolfi M, Murgolo N, Chiapasco M, Lops D, Vogel G. Therapy of peri-implantitis with resective surgery. Clinical Oral Implants Research 2005;16:9-18.

227. Romeo E, Lops D, Chiapasco M, Ghisolfi M, Vogel G. Therapy of peri-implantitis with resective surgery. A 3-year clinical trial on rough screw-shaped oral implants. Part II: radiographic outcome. Clinical Oral Implants Research 2007;18:179-187.

228. Schwarz F, Sculean A, Rothamel D, Schwenzer K, Georg T, Becker J. Clinical evaluation of an Er:YAG laser for nonsurgical treatment of peri-implantitis: a pilot study. Clinical Oral Implants Research 2005;16:44-52.

229. Sculean A, Schwarz F, Becker J. Anti-infective therapy with an Er:YAG laser: influence on peri-implant healing. Expert Review of Medical Devices 2005;2:267-276.

230. Matsuyama T, Aoki A, Oda S, Yoneyama T, Ishikawa I. Effects of the Er:YAG laser irradiation on titanium implant materials and contaminated implant abutment surfaces. Journal of Clinical Laser Medicine & Surgery 2003;21:7-17.

231. Kreisler M, Kohnen W, Marinello C, et al. Bactericidal Effect of the Er:YAG Laser on Dental Implant Surfaces: An In Vitro Study. Journal of Periodontology 2002;73:1292-1298.

232. Takasaki AA, Aoki A, Mizutani K, Kikuchi S, Oda S, Ishikawa I. Er:YAG laser therapy for peri-implant infection: a histological study. Lasers in Medical Science 2007;22:143-157.

233. Badran Z, Bories C, Struillou X, Saffarzadeh A, Verner C, Soueidan A. Er:YAG laser in the clinical management of severe peri-implantitis: a case report. Journal of Oral Implantology 2011;37 Spec No:212-217.

234. Renvert S, Lindahl C, Roos Jansåker A-M, Persson GR. Treatment of peri-implantitis using an Er:YAG laser or an air-abrasive device: a randomized clinical trial. Journal of Clinical Periodontology 2011;38:65-73.

235. Friberg B, Henningsson C, Jemt T. Rehabilitation of Edentulous Mandibles by Means of Turned Brånemark System® Implants after One-Stage Surgery: A 1-Year Retrospective Study of 152 Patients. Clinical Implant Dentistry and Related Research 2005;7:1-9.

236. Van der Zee E, Vogels M-F, Oosterveld P, Van Waas M. Reproducibility and accuracy of automated probe measurements of gingiva and bone levels on stone casts following guided bone regeneration treatment. Journal of Clinical Periodontology 2004;31:318-323.

237. Marks RG, Low SB, Taylor M, Baggs R, Magnusson I, Clark WB. Reproducibility of attachment level measurements with two models of the Florida Probe®. Journal of Clinical Periodontology 1991;18:780-784.

238. Esposito M, Hirsch JM, Lekholm U, Thomsen P. Biological factors contributing to failures of osseointegrated oral implants. (II). Etiopathogenesis. Eur J Oral Sci 1998;106:721-764.

239. Pjetursson BE, Zwahlen M, Lang NP. Quality of reporting of clinical studies to assess and compare performance of implant-supported restorations. Journal of Clinical Periodontology 2012;39:139-159.

240. Vercruyssen M, Marcelis K, Coucke W, Naert I, Quirynen M. Long-term, retrospective evaluation (implant and patient-centred outcome) of the two-implants-supported overdenture in the mandible. Part 1: survival rate. Clin Oral Implants Res 2010;21:357-365.

241. Ueda T, Kremer U, Katsoulis J, Mericske-Stern R. Long-term results of mandibular implants supporting an overdenture: implant survival, failures, and crestal bone level changes. International Journal of Oral & Maxillofacial Implants 2011;26:365-372.

242. Bornstein MM, Halbritter S, Harnisch H, Weber HP, Buser D. A retrospective analysis of patients referred for implant placement to a specialty clinic: indications, surgical procedures, and early failures. International Journal of Oral & Maxillofacial Implants 2008;23:1109-1116.

243. Martin W, Lewis E, Nicol A. Local risk factors for implant therapy. International Journal of Oral & Maxillofacial Implants 2009;24 Suppl:28-38.

244. Adell R, Eriksson B, Lekholm U, Branemark PI, Jemt T. Long-term follow-up study of osseointegrated implants in the treatment of totally edentulous jaws. International Journal of Oral & Maxillofacial Implants 1990;5:347-359.

245. Branemark PI, Svensson B, van Steenberghe D. Ten-year survival rates of fixed prostheses on four or six implants ad modum Branemark in full edentulism. Clin Oral Implants Res 1995;6:227-231.

246. Buser D, Mericske-Stern R, Bernard JP, et al. Long-term evaluation of non-submerged ITI implants. Part 1: 8-year life table analysis of a prospective multi-center study with 2359 implants. Clin Oral Implants Res 1997;8:161-172.

247. De Bruyn H, Collaert B. The effect of smoking on early implant failure. Clin Oral Implants Res 1994;5:260-264.

248. Heitz-Mayfield LJA. History of treated periodontitis and smoking as risks for implant therapy. The International journal of oral and maxillofacial implants 2009;24 Suppl:39-68.

249. Levin LDMD, Hertzberg RDMD, Har-Nes SDMD, Schwartz-Arad DDMDP. Long-Term Marginal Bone Loss Around Single Dental Implants Affected by Current and Past Smoking Habits. Implant Dentistry 2008;17:422-429.

250. Eichel B, Shahrik HA. Tobacco smoke toxicity: loss of human oral leukocyte function and fluid-cell metabolism. Science 1969;166:1424-1428.

251. Nadler JL, Velasco JS, Horton R. Cigarette smoking inhibits prostacyclin formation. Lancet 1983;1:1248-1250.

252. Reus WF, Robson MC, Zachary L, Heggers JP. Acute effects of tobacco smoking on blood flow in the cutaneous micro-circulation. Br J Plast Surg 1984;37:213-215.

253. Bennet KR, Reade PC. Salivary immunoglobulin A levels in normal subjects, tobacco smokers, and patients with minor aphthous ulceration. Oral Surg Oral Med Oral Pathol 1982;53:461-465.

254. Costabel U, Bross KJ, Reuter C, Ruhle KH, Matthys H. Alterations in immunoregulatory T-cell subsets in cigarette smokers. A phenotypic analysis of bronchoalveolar and blood lymphocytes. Chest 1986;90:39-44.

255. Lindquist LW, Carlsson GE, Jemt T. A prospective 15-year follow-up study of mandibular fixed prostheses supported by osseointegrated implants. Clinical results and marginal bone loss. Clinical Oral Implants Research 1996;7:329-336.

256. Lindquist LW. Association between marginal bone loss around osseointegrated mandibular implants and smoking habits: a 10-year follow-up study. Journal of Dental Research 1997;76:1667-1674.

257. Carlsson GE, Lindquist LW, Jemt T. Long-term marginal periimplant bone loss in edentulous patients. International Journal of Prosthodontics 2000;13:295-302.

258. Feloutzis A, Lang NP, Tonetti MS, et al. IL-1 gene polymorphism and smoking as risk factors for peri-implant bone loss in a well-maintained population. Clinical Oral Implants Research 2003;14:10-17.

259. Karoussis IK, Müller S, Salvi GE, Heitz-Mayfield LJA, Brägger U, Lang NP. Association between periodontal and peri-implant conditions: a 10-year prospective study. Clinical Oral Implants Research 2004;15:1-7.

260. Wennstrom JL, Ekestubbe A, Grondahl K, Karlsson S, Lindhe J. Oral rehabilitation with implant-supported fixed partial dentures in periodontitis-susceptible subjects. A 5-year prospective study. J Clin Periodontol 2004;31:713-724.

261. Oates TW, Caraway D, Jones J. Relation between smoking and biomarkers of bone resorption associated with dental endosseous implants. Implant Dent 2004;13:352-357.

262. Lambert PM, Morris HF, Ochi S. The influence of smoking on 3-year clinical success of osseointegrated dental implants. Ann Periodontol 2000;5:79-89.

263. Boyne JB, Herford AS. Effect of tobacco smoke and transdermal nicotine on bone formation. Palm Springs, California, 1995.

264. Huynh-Ba G. Implant failure predictors in the posterior maxilla: a retrospective study of 273 consecutive implants. Journal of periodontology (1970) 2008;79:2256-2261.

265. Heitz-Mayfield LJ, Huynh-Ba G. History of treated periodontitis and smoking as risks for implant therapy. International Journal of Oral & Maxillofacial Implants 2009;24 Suppl:39-68.

266. Lekholm U, Adell R, Lindhe J, et al. Marginal tissue reactions at osseointegrated titanium fixtures. (II) A cross-sectional retrospective study. Int J Oral Maxillofac Surg 1986;15:53-61.

267. Ferreira SD, Silva GLM, Cortelli JR, Costa JE, Costa FO. Prevalence and risk variables for peri-implant disease in Brazilian subjects. Journal of Clinical Periodontology 2006;33:929-935.

268. Lang NP, Wetzel AC, Stich H, Caffesse RG. Histologic probe penetration in healthy and inflamed peri-implant tissues. Clinical Oral Implants Research 1994;5:191-201.

269. Salvi GE, Lang NP. Diagnostic parameters for monitoring peri-implant conditions. International Journal of Oral & Maxillofacial Implants 2004;19 Suppl:116-127.

270. Luterbacher S, Mayfield L, Brägger U, Lang NP. Diagnostic characteristics of clinical and microbiological tests for monitoring periodontal and peri-implant mucosal tissue

conditions during supportive periodontal therapy (SPT). Clinical Oral Implants Research 2000;11:521-529.

271. Fiorellini JP, Nevins ML. Dental implant considerations in the diabetic patient. Periodontology 2000 2000;23:73-77.

272. Subramani K, Jung RE, Molenberg A, Hammerle CH. Biofilm on dental implants: a review of the literature. International Journal of Oral & Maxillofacial Implants 2009;24:616-626.

273. Berglundh T, Gotfredsen K, Zitzmann NU, Lang NP, Lindhe J. Spontaneous progression of ligature induced peri-implantitis at implants with different surface roughness: an experimental study in dogs. Clin Oral Implants Res 2007;18:655-661.

274. Åstrand P, Engquist B, Anzén B, et al. A Three-Year Follow-Up Report of a Comparative Study of ITI Dental Implants® and Brånemark System® Implants in the Treatment of the Partially Edentulous Maxilla. Clinical Implant Dentistry and Related Research 2004;6:130-141.

275. Quirynen M, Abarca M, Van Assche N, Nevins M, Van Steenberghe D. Impact of supportive periodontal therapy and implant surface roughness on implant outcome in patients with a history of periodontitis. Journal of Clinical Periodontology 2007;34:805-815.

276. Kullman L. Comparison of radiographic bone height assessments in panoramic and intraoral radiographs of implant patients. The International journal of oral and maxillofacial implants 2007;22:96-100.

277. Akesson L, Hakansson J, Rohlin M, Zoger B. An evaluation of image quality for the assessment of the marginal bone level in panoramic radiography. A comparison of radiographs from different dental clinics. Swed Dent J 1993;17:9-21.

278. De Smet E, Jacobs R, Gijbels F, Naert I. The accuracy and reliability of radiographic methods for the assessment of marginal bone level around oral implants. Dentomaxillofac Radiol 2002;31:176-181.

279. Bragger U, Pasquali L, Rylander H, Carnes D, Kornman KS. Computer-assisted densitometric image analysis in periodontal radiography. A methodological study. J Clin Periodontol 1988;15:27-37.

280. Nicopoulou-Karayianni K, Bragger U, Lang NP. Subtraction radiography in oral implantology. International Journal of Periodontics & Restorative Dentistry 1997;17:220-231.

281. Mengel R, Kruse B, Flores-de-Jacoby L. Digital volume tomography in the diagnosis of peri-implant defects: an in vitro study on native pig mandibles. J Periodontol 2006;77:1234-1241.

282. Tokuhisa M, Matsushita Y, Koyano K. In vitro study of a mandibular implant overdenture retained with ball, magnet, or bar attachments: comparison of load transfer and denture stability. International Journal of Prosthodontics 2003;16:128-134.

283. Porter JA, Jr., Petropoulos VC, Brunski JB. Comparison of load distribution for implant overdenture attachments. International Journal of Oral & Maxillofacial Implants 2002;17:651-662.

284. Meijer HJ, Kuiper JH, Starmans FJ, Bosman F. Stress distribution around dental implants: influence of superstructure, length of implants, and height of mandible. Journal of Prosthetic Dentistry 1992;68:96-102.

285. Mericske-stern R, Piotti M, Sirtes G. 3-D in vivo force measurements on mandibular implants supporting overdentures. A comparative study. Clinical Oral Implants Research 1996;7:387-396.

286. Mericske-Stern R. Force distribution on implants supporting overdentures: the effect of distal bar extensions. A 3-D in vivo study. Clin Oral Implants Res 1997;8:142-151.

287. Behneke A, Behneke N, d'Hoedt B. A 5-year longitudinal study of the clinical effectiveness of ITI solid-screw implants in the treatment of mandibular edentulism. International Journal of Oral & Maxillofacial Implants 2002;17:799-810.

288. Lehmann KM, Kammerer PW, Karbach J, Scheller H, Al-Nawas B, Wagner W. Long-term effect of overdenture bar design on peri-implant tissues. International Journal of Oral & Maxillofacial Implants 2013;28:1126-1131.