

Prevalence, extent and severity of peri-implantitis

Christer Fransson

Department of Periodontology
Institute of Odontology
Sahlgrenska Academy
University of Gothenburg
Sweden



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Abstract

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Christer Fransson

Department of Periodontology, Institute of Odontology, the Sahlgrenska Academy at University of Gothenburg, Box 450, 405 30 Göteborg, Sweden.

Peri-implantitis is a disorder that affects the tissues surrounding a functional implant. Peri-implantitis can lead to implant loss and impaired function. There is limited information regarding the prevalence of peri-implantitis. In addition the extent of the disease and pattern of bone loss are poorly described.

The objective of the present series of studies was to assess the prevalence of subjects exhibiting progressive bone loss at implants supporting fixed prosthesis (Study I) and to examine the clinical characteristics at implants with radiographic evidence of progressive bone loss (Study II). Furthermore, the extent, severity and pattern of peri-implantitis-associated bone loss were evaluated (Study III and Study IV).

Bone-level assessments were performed in intra-oral radiographs and the clinical conditions of the peri-implant tissues were examined. A multilevel *growth curve* model was used to analyze the pattern of bone loss.

It was demonstrated that 28% of subjects had one or more implants with progressive bone loss. The individuals in this group carried a significantly larger number of implants than the subjects in whom no implants with progressive loss were detected (6.0 vs. 4.8). Out of the total 3413 implants included in the study 12.4 percent demonstrated progressive bone loss (Study I).

Clinical signs of pathology were more frequent at implants with than without progressive bone loss. Smokers had larger numbers of affected implants than non-smokers and the proportion of affected implants that exhibited pus and PPD ≥ 6 mm was higher in smokers than in non-smokers. The findings of pus, recession and PPD ≥ 6 mm at an implant in a smoking subject had a 69% accuracy in identifying history of progressive bone loss (Study II).

About 40% of the implants in each affected subject had peri-implantitis. The proportion of such implants varied between 30 and 52% in different jaw positions. The most common position was the lower front region. (Study III).

The average bone loss after the first year of function at the affected implants was 1.65 mm and 32% of the implants demonstrated bone loss ≥ 2 mm. The bone loss showed a non-linear pattern and the rate of bone loss increased over time (Study IV).

Key words: bone loss, complications, dental implants, implant position, human, multilevel analyses, peri-implantitis, radiographs, smoking.

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Appendix

Study I-IV

Preface

The present thesis is based on the following studies, which is referred to in the text by their Roma numerals:

- I. Fransson, C., Lekholm, U., Jemt, T., Berglundh, T. (2005) Prevalence of subjects with progressive bone loss at implants. *Clinical Oral Implants Research* **16**: 440-446.

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

- III. Fransson, C., Wennström, J., Tomasi, C., Berglundh, T. (2009) Extent of peri-implantitis-associated bone loss. *Journal of Clinical Periodontology* **36**: 357-363.

- IV. Fransson, C., Tomasi, C., Sundén Pikner, S., Gröndahl, K., Wennström, J., Leyland, A.H., Berglundh, T. Severity and pattern of peri-implantitis-associated bone loss. Submitted to *Journal of Clinical Periodontology*.

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Introduction

In 1977, Brånemark and coworkers published an article entitled "Osseointegrated implants in the treatment of the edentulous jaw. Experience from a 10-year period". The study demonstrated that it was possible to use titanium implants to replace lost teeth. This technique has revolutionized clinical dentistry and is a today routine procedure. Several clinical studies have demonstrated that implant-supported prosthesis can be maintained on long-term basis (Adell et al. 1981, Ekelund et al. 2003, Pjetursson et al. 2005, Rasmusson et al. 2005, Lekholm et al. 2006, Jemt & Johansson 2006, Kim et al. 2008, Åstrand et al. 2008).

Technical and biological complications may occur at both tooth- and implant-supported reconstructions (Berglundh et al. 2002, Pjetursson et al. 2007). Biological complications at teeth and implants include processes such as inflammation in the soft tissues and loss of supporting bone. Microorganisms in the oral cavity colonize the surface of a tooth or an implant and form an oral biofilm (Socransky & Haffajee 2002, Marsh et al. 2005) and the microbial challenge induces inflammatory reactions in the surrounding tissues (Löe et al. 1965, Berglundh et al. 1992, Ponteriero et al. 1994). At teeth, inflammation in the gingiva is termed gingivitis, while the term periodontitis in addition to gingival inflammation also includes loss of supporting tissues (Caton et al. 1999, Lindhe et al. 1999). The corresponding conditions at implants are peri-implant mucositis and peri-implantitis. This thesis will focus on the prevalence, extent and severity of peri-implantitis.

Definitions

The term peri-implantitis was introduced by Mombelli et al. (1987), who in a study on the microbiota at implants with and without bone loss concluded that "peri-implantitis can be regarded as a site specific infection which yields many features in common with chronic periodontitis".

Peri-implant diseases, i.e. mucositis and peri-implantitis, were subsequently defined in consensus reports from the 1st (Albrektsson & Isidor 1994) and the 6th European Workshop on Periodontology (Lindhe & Meyle 2008, Zitzmann & Berglundh 2008). The term peri-implant mucositis was according to the definition by Albrektsson & Isidor (1994) “reversible inflammatory reactions in the soft tissues surrounding a functioning implant” and peri-implantitis was “inflammatory reactions with loss of supporting bone in the tissues surrounding a functioning implant”.

In the consensus report from the 6th European Workshop on Periodontology, minor modifications of the definitions of peri-implant diseases entities were suggested. The terms reversible and irreversible were removed and it was also stated that peri-implant diseases are infectious diseases and “peri-implant mucositis was an inflammatory lesion that resides in the mucosa, while peri-implantitis also affects the supporting bone”. (Lindhe & Meyle 2008, Zitzmann & Berglundh 2008).

Diagnosis

The definitions of a disease influence the selection of parameters used for disease assessments (Mombelli et al. 1994). Thus, peri-implant diagnoses require clinical and radiographic assessments of the tissues surrounding an implant.

Clinical examination

Probing periodontal tissues is an established method to evaluate presence of pathology and disease progression at teeth (Listgarten 1976, Armitage et al. 1977, Magnusson & Listgarten 1980, Fowler et al. 1982, Lang & Brägger 1991). Bleeding on probing (BoP) is a finding that indicates inflammation in the gingival tissues (Fowler et al. 1982, Greenstein et al. 1981) and absence of BoP is a reliable predictor for the maintenance of periodontal tissue support (Lang et al. 1986, 1990).

Early studies assessing the outcome of implant therapy questioned the validity to use periodontal examination methods in the evaluation of peri-implant tissue conditions (Adell et al. 1986, Lekholm et al. 1986, Apse et al. 1991).

Peri-implant probing

The validity of probing peri-implant tissues has been evaluated in animal experiments and in clinical studies (Table 1). From experimental studies it is evident that probing healthy tissues at implants and teeth is similar. Thus, the probe tip identifies the apical extension of the barrier epithelium of healthy peri-implant mucosa and gingiva when light probing forces (0.2-0.3 N) are used (Lang et al. 1994, Schou et al. 2002, Abrahamsson & Soldini 2006). It was also reported that the probe penetration increased with increasing degree of inflammation at both implants and teeth (Schou et al. 2002). At sites with inflammation, the probe tip was identified in a more apical position at implants than at teeth. Probing the peri-implant mucosa can be performed without causing permanent damage to the transmucosal attachment (Etter et al. 2002).

Clinical studies have evaluated different aspects of peri-implant probing. DeAngelo et al. (2007) studied early soft tissue healing around implants after one stage surgery and reported that the mean PPD was 2 mm four weeks after surgery and the PPD remained stable over the 12 weeks of observation time. They concluded “peri-implant soft tissue clinical maturity may be established as early as 4 weeks following implant placement”. Nishimura et al. (1997) evaluated the use of periodontal parameters in a group of subjects with healthy peri-implant conditions. All subjects were recalled once every month for prophylaxis during 4 years. Repeated clinical and radiographic examinations were performed and the results indicated that shallow pockets and unchanged PAL accompanied stable peri-implant bone levels.

Brägger et al. (1996) and Quirynen et al. (1991) examined the relationship between probing attachment level and radiographic bone level measurements. Brägger et al. (1996), in a 2-year prospective investigation, demonstrated that the bone level change

at the 2-year examination was best explained by early changes in PAL and radiographic density. Quirynen et al. (1991) found a correlation between PAL and radiographic bone levels. As a mean, the bone level was scored 1.4 mm apically of PAL and 77% of the observations were within a difference of 1 mm.

The association between peri-implant probing depth and bone loss was illustrated by Hultin et al. (2002) who examined patients with and without signs of peri-implantitis. It was observed that the mean PPD was significantly larger at implants with marginal bone loss compared to implants with normal bone height (4.3 mm vs. 2.2 mm). In addition, probing peri-implant tissues is more sensitive to force variation than probing periodontal tissues at teeth (Mombelli et al. 1997).

Bleeding on probing

Studies evaluating the validity of BoP as a diagnostic measure are listed in Table 2. Bleeding following probing peri-implant tissues indicates the presence of an inflammatory lesion in the mucosa (Zitzmann et al. 2001). The BoP frequencies increase with disease severity both at teeth and implants when using a standardized force of 0.2 N (Lang et al. 1994). Furthermore, studies have demonstrated that the propensity to exhibit BoP was higher in peri-implant mucosa than in gingiva in particular with increasing probing forces (Brägger et al. 1997, Gerber et al. 2009). In addition, bleeding following probing peri-implant tissues has a high predictive value for disease progression while the absence of BoP is a reliable predictor for stable and healthy peri-implant conditions (Jepsen et al. 1996, Luterbacher et al. 2000).

Radiographic examination

Intra-oral radiographs of high quality are an important part in periodontal diagnosis but the assessments have limitations. Bone level measurements are limited to interproximal areas and early bone resorption is difficult to detect in wide alveolar ridges (Ramadan & Mitchell 1962, Dunning et al. 1968, Ainamo & Tammissalo 1973, Lang et

al. 1977). Benn et al. (1990) estimated that radiographic bone measurements were unable to detect true bone loss until at least 1 mm had occurred. Furthermore, Zybutz et al (2000) demonstrated that radiographic measurements obtained in standardized intra-oral radiographs underestimated the bone level around teeth by approximately 1.4 mm compared to direct bone measurements performed during surgery.

Marginal bone loss over time assessed in intra-oral radiographs has been regarded as a critical examination variable in many long-term studies on implants (Fourmouzis & Brägger 1999, Wennström & Palmer 1999, Albreksson et al. 1986).

The reliability of radiographic methods for the assessment of the marginal bone level around oral implants has been evaluated in several studies. Hollender & Rockler (1980) studied the influence of the radiographic technique on bone level measurements. It was demonstrated that the interpretation of the peri-implant bone around an implant of the Brånemark System[®] depends on the x-ray beam angulations in relation to the long axis of the implant body. A deviation from a line perpendicular to the long axis of the implant that was $< 9^\circ$ enabled a correct interpretation of the peri-implant bone level. The authors further reported that the experimental ridge into which the implants were placed also influenced the accuracy of the bone level measurement. Thus, the wider the ridge, the more inaccurate bone level readings. Similar results were obtained in an experimental study by Sewerin (1990). The results showed that a strict parallelism between the implant axes and the film plane is essential to obtain valid results using single films and that distortion of buccal and lingual bone margins may result in overestimation of the bone heights.

De Smet et al. (2002) used an experimental model to evaluate the accuracy of radiographic marginal bone level assessments. Implants of the Brånemark System[®] were installed in human cadavers and bone level measurements were performed using different radiographic techniques. No statistically significant differences were observed between the real and radiographic measurements for any of the techniques applied.

The intra-oral paralleling technique yielded an absolute mean difference of 0.18 mm between the real and radiographic measurements. Similar results were obtained by Hermann et al. (2001) who compared linear radiographic measurements with histometric assessments in dogs. The data demonstrated that the differences between bone level measurements performed in standardized peri-apical radiographs and assessments made in histological sections were within 0.2 mm in 89% of cases. These findings were not in agreement with data presented in an animal experiment by Caulier et al. (1997). They installed screw-shaped implants in the maxilla of Dutch goats and compared radiographic bone level assessments to measurements performed in histological sections. The results indicated that the radiographic evaluation significantly underestimated the real bone level by on average 0.85 mm. Gröndahl et al. (1998) determined the inter- and intra variability in radiographic bone level measurement at Brånemark System® implants. Bone level measurement was performed at the time of bridge connection and at year-1 and 3 years of follow-up. The results demonstrated an inter- and intra observer variability of 0.08 mm and 0.14 mm, respectively. The mean bone loss between BL and 3-year follow-up examination varied for the 6 observers between 0.24 mm and 0.74 mm. The radiographic density and the degree of bone loss were factors that influenced the inter-observer variability. Ahlquist et al. (1990) in a study based on repeated radiographic measurements estimated that a change in bone level must exceed 0.47mm to be detectable.

Conclusion

Probing peri-implant mucosa is a reliable measure for diagnosis and the detection of changes in the peri-implant tissue conditions.

The accuracy and precision of radiographic bone level measurements around implants are relatively high provided that a correct technique is applied. Features of the peri-implant bone, such as the width of the alveolar ridge and the amount of bone loss, may reduce the accuracy and precision when estimating bone levels in intra-oral radiographs

Composition of microflora at implant sites (Table 3)

Quirynen et al. (2006), studied early microbial colonization of the “pristine” peri-implant pocket and reported that a complex microbiota was established within a week after abutment insertion. After 7 days of undisturbed plaque accumulation, the detection frequency for most species was nearly identical in plaque samples from the fresh peri-implant pockets compared with samples from reference teeth (Quirynen et al. 2006). Biofilm development at implants and teeth was compared during a 3-week experimental study in human volunteers (Ponteriero et al. 1994). The analyses of the plaque samples showed similar proportions of coccoid cells, motile rods and spirochetes at both teeth and implants at baseline and after 3 weeks of plaque accumulation.

The composition of the biofilm at the implant surface becomes more complex with time (George et al. 1994, Augthun & Conrads 1997, Renvert et al. 2007). George et al. (1994) evaluated the microbiological status in submucosal plaque samples at implants during 4-year period. Analyses of the samples revealed that implants present in the oral cavity for 3 to 4 years were significantly more frequently colonized by *Porphorymonas gingivalis* (P.g.), *Prevotella intermedia* (P.i.) than implants with 1 to 2 years in function (44% vs. 2.6% of sites). The composition of the microflora in deep peri-implant pockets (≥ 6 mm) was analyzed by Augthun & Conrads (1997). The mean function time of the implants was 6 years and the results indicated that Gram-negative bacteria dominated and species such as *Aggregatibacter actinomycetemcomitans* (A.a.), *Bacteroidaceae* spp, *Fusobacterium nucleatum* (F.n.), *Capnocytophaga* spp and *Eikenella corrodens* were frequently found. The complexity of the microflora at implants was also demonstrated in a group of subjects with implants in function for 9-14 years (Renvert et al. 2007). The submucosal microflora was dominated by *Neisseria mucosa*, F.n. spp and *Capnocytophaga sputigena* irrespective of conditions of peri-implant tissues or if subjects had remaining teeth or not.

The composition of the microbiota in plaque samples obtained from implants with peri-implantitis and implants with healthy peri-implant tissues has been compared in several clinical studies. Mombelli et al. (1987) detected an abundance of motile rods, fusiform bacteria and spirochetes in the microbiota at implants with peri-implantitis. 41% of the organisms were G-negative anaerobic rods i.e. *Fusobacterium spp* and *P.i.* Low cultivable counts, small number of G-positive bacteria and few rods characterized the samples from healthy peri-implant mucosa (Mombelli et al. 1987). Leonhardt et al (1999) found a significantly different composition of the microbiota at healthy than in diseased implant sites both in subjects with and without teeth. It was reported that *P.g.*, *P.i.*, *Prevotella nigrescens* and *A.a.* was identified in 60% of the subjects in the peri-implantitis group, while none of the species was detected in the edentulous subjects with healthy peri-implant tissues. Furthermore, *Staphylococcus spp.* enterics and *Candida spp* were found in 55% of the implant sites exhibiting peri-implantitis. Shibli et al. (2007) assessed the composition of supra-and submucosal biofilm of subjects with healthy and diseased implants. They found marked differences in the composition of supra-and submucosal biofilms of healthy and diseased sites. Significantly higher mean counts of *Tanerella forsythia P.g.*, *Treponema denticola*, *F.n. spp*, *P.i.* were found in both supra and submucosal biofilms at diseased than in healthy implants sites.

Conclusion

The development of the oral biofilm is similar at teeth and implants. Furthermore, no marked differences in the microbial profile were observed between implants and teeth irrespective of clinical conditions. Thus, implants with per-implantitis have a composition of microorganisms resembling that at teeth with periodontitis.

Tissue response to microbial challenge

Tissue response to microbial challenge at teeth and implants has been studied in animal experiments and clinical trials (Table 4). Berglundh et al. (1992) and Ericsson et al. (1992) studied the reaction of the gingiva and the peri-implant mucosa to *de novo* plaque formation. Clinical examinations and biopsy were carried out after 3 weeks (Berglundh et al. 1992) and 3 months (Ericsson et al. 1992). It was demonstrated that 3 weeks of plaque formation resulted in the establishment of inflammatory lesions in the gingiva and the peri-implant mucosa that had similar location, composition, size and apical extension. Also the lesions formed following 3 months of plaque accumulation had a similar composition but differed with respect to their apical extension. Thus, the ICT formed in the peri-implant mucosa following 3 months of plaque accumulation extended further apically than that in the gingiva.

Abrahamsson et al. (1998) described the soft tissue reaction to longstanding plaque on different implant systems in dogs. Following one month of post-surgical plaque control implants of the Astra Tech Implants[®] Dental System, Brånemark System[®] and ITI[®] Dental Implant System were exposed to plaque accumulation for 5 months. The inflammatory infiltrate (ICT) that formed in the peri-implant mucosa around the implants did not differ with respect to location and composition between the three systems.

Pontoriero et al. (1994) used the classical "experimental gingivitis design" (Løe et al. 1965) to determine the clinical soft tissue response to plaque formation on implants and teeth. A similar degree of plaque formation and resulting soft tissue inflammation was observed at teeth and implants. The findings by Pontoriero et al. (1994) confirmed observations made in the previous experiments in the dogs (Berglundh et al. 1992). Zitzmann et al. (2001) examined the tissue reaction to *de novo* plaque formation at implants and teeth in humans using immunohistochemical techniques. The authors also applied the "experimental gingivitis design" (Løe et al. 1965) and collected soft tissue biopsies on day 0 and day 21 of plaque formation. It was demonstrated that

plaque formation was associated with clinical signs of inflammation including an increase of the size of the soft tissue lesion. The inflammatory response was characterized by increased proportions of T- and B-cells in the ICT of both gingiva and the peri-implant mucosa.

Liljenberg et al. (1997) reported some characteristics of plaque-associated lesions in the gingiva and the peri-implant mucosa sampled from the same subjects. Small inflammatory infiltrates (ICT) were found in the connective tissue lateral to the junctional epithelium in both types of tissues. 0.17 mm² of the peri-implant mucosa was occupied of an ICT, while the size of the corresponding lesion in the gingiva was 0.25 mm². The density of B cells (CD19) was 7 times higher in the gingiva than in the peri-implant mucosa (3.7 % vs. 0.5 %) while the densities of T cells (CD3) were 7.5% (gingiva) and 4.7% (peri-implant mucosa). The density of PMN elastase positive cells was about 3 times higher in the gingiva than in the peri-implant mucosa. The ratio between memory (CD45RO) and naive (CD45RA) phenotypes were almost similar in the two types of tissues.

Biopsies from human material have been used to describe histopathological characteristics of peri-implant tissues (Table 5). Sanz et al (1991) collected interproximal biopsies at implants with and without peri-implant infection and found significant differences between the two groups of tissues regarding size and cellular components of the ICT's. The specimens in the peri-implant infection group demonstrated higher transmigration of PMN cells in the pocket epithelium, larger % ICT in the connective tissue with higher numbers of plasma cells and mononuclear cells than biopsies in the healthy tissue samples. Berglundh et al. (2004) obtained soft tissue biopsies from implants with advanced bone loss and signs of severe inflammation. The histometric and morphometric analyses demonstrated that all soft tissue units harbored large ICT's that extended apical of the pocket epithelium and inflammatory cells, dominated by plasma cells, occupied 60% of the ICT area. Furthermore, PMN cells were present not only in the pocket epithelium but also in

peri-vascular compartments in central areas of the ICT. Similar results were described by Gualini & Berglundh (2003) who analyzed the proportion of various inflammatory cells in soft tissue biopsies from mucositis and peri-implantitis sites. The size of the ICT from peri-implantitis sites was larger and contained higher proportion of plasma and PMN cells than the lesions from mucositis sites. In addition, PMN cells were consistently found in the central portion of the inflammatory lesions at sites exhibiting peri-implantitis.

Duarte et al. (2009) evaluated inflammatory cytokines and osteoclastogenesis-related factors in sites exhibiting different clinical and radiographic severity of peri-implant disease. Soft tissue biopsies were obtained from sites with healthy mucosa and mucositis and from sites with initial and severe peri-implantitis. The results indicated that the expression of IL-12, TNF- α and RANK-L increased with increasing disease severity. Furthermore, the highest OPG/RANK-L ratio was observed in healthy peri-implant tissues and the lowest ratio was found in severe peri-implantitis sites.

Experimental peri-implantitis studies in animals have used ligature models to promote tissue breakdown (e.g. Lindhe et al. 1992, Lang et al. 1993, Schou et al. 1993, Marinello et al. 1995, Albouy et al. 2008, 2009) and the lesion obtained had many features in common with those analyzed from human biopsy material.

Conclusion

Findings from clinical studies and animal experiments have demonstrated that the response to microbial challenge is similar at teeth and implants but the peri-implant mucosa seems to be less effective in limiting the extension of the inflammatory process than the gingiva.

Effect of load on marginal bone loss

The influence of static and dynamic load on bone loss at implants has been evaluated in several animal experiments (Table 6 and Table 7). The effect of static load of different magnitudes and duration in time was tested in a Beagle dog model (Gotfredsen et al. 2001a, b, c). It was demonstrated that orthodontic type forces in a lateral direction did not induce marginal bone loss. On the contrary, the bone density and the degree of mineralized bone-to-implant contact were higher around test implants than around controls. Similar results were obtained in a monkey model by Melsen & Lang (2001). Orthodontic type forces was applied to implants using Ni-Ti coil springs and it was reported that the bone tissue turnover as well as the density of the alveolar bone were higher adjacent to loaded compared to unloaded implants. Furthermore, the remodeling of the bone increased with increasing strain. The influence of static load on implants with mucositis and peri-implantitis was studied by Gotfredsen et al. (2002). It was concluded that “lateral static load failed to induce marginal bone loss at implants with mucositis and failed to enhance bone loss at implants with experimental peri-implantitis”.

A complete loss of osseointegration was demonstrated at implants exposed to excessive occlusal load in a lateral direction (Isidor et al. 1996, 1997, Miyata 2000). On the other hand, Miyata et al (1998) and Heitz-Mayfield et al. (2004), in a monkey and dog model, respectively, reported that similar degree of bone loss occurred around implants in supra occlusion as around unloaded controls. Berglundh et al. (2005) addressed the question whether functionally load to implant-supported prosthesis can induce marginal bone loss. Implant supported fixed partial dentures were installed in the mandible of six Beagle dogs. The occlusion was carefully adjusted so that the bridgework had a normal function. The radiographic and histological analyses indicated that (i) the largest amount of bone loss occurred before the implants were loaded (ii) no differences in marginal bone loss were observed between functional loaded implants and unloaded controls (iii) implants exposed to functional load exhibited a higher degree of bone-to-implant contact than control implants.

Kozlowsky et al. (2007) assessed the effect of loading on peri-implant bone level in the presence of healthy and inflamed peri-implant tissues. While it was suggested that excessive supra-occlusal contacts aggravated the ligature/plaque induced bone resorption, the absence of longitudinal assessments makes it difficult to interpret data.

Extra oral models evaluating the effect on static and dynamic forces on marginal bone loss at implants indicate that excessive load on single implants may result in decreased bone density around the marginal part of the implant (Hoshaw et al. 1994, Duyck et al. 2001).

Bone loss analyses performed in short and long-term prospective clinical studies indicate that early bone loss may not be related to functional load (Table 8). Thus, the investigations demonstrated that the major changes in the marginal bone level took place between implant insertion and loading of the implants. Cochran and co-workers (2009) in a 5-year prospective multi-center study reported that 86% of the total mean bone loss occurred before loading of the implants. Furthermore, the influence of occlusal loading factors on peri-implant bone loss was elucidated in a 12-15 years prospective study (Lindquist et al. 1996). The authors evaluated different factors related to the presence of peri-implant bone loss such as oral hygiene, smoking habits, maximum bite force, tooth cleansing and lengths of cantilevers. They found a significant correlation between bone loss and poor oral hygiene and smoking habits while occlusal loading factors was of minor importance.

Conclusion

Results from animal experiments using static and occlusal load models and clinical studies do not support the hypothesis that load causes marginal bone loss at implants.

Factors influencing early bone loss at implants

Results from clinical studies have demonstrated that bone loss occur during initial healing and before loading of the implants (Åstrand et al. 2002, 2004, Cochran et al. 2009). Factors influencing early bone loss, besides remodeling of bone after implant surgery as described above, have been investigated in animal experiments. Berglundh & Lindhe (1996) performed a study in the Beagle dog to evaluate the influence of soft tissue dimensions (“biological width”) on early bone loss at implants. It was reported that the healing following abutment connection consistently resulted in bone resorption at implant sites with thin (≤ 2 mm) ridge mucosa. The authors suggested that, “a mucosal attachment of a certain minimum dimension (biological width) is required to protect osseointegration”. The position of the micro-gap in 2-part implants in relation to early bone loss has been discussed in several papers. It was suggested that the placement of the abutment implant junction below the bone crest will result in marginal bone loss (Cochran et al. 1997, Hermann et al. 1997, 2000, 2001a, b). Other studies suggest that the marginal bone level will be established at a position close to the abutment-implant interface irrespective of the implant is positioned at or below the bone crest (Abrahamsson 1996, 1999, Pontes et al. 2008, Welander et al. 2009). Periosteal reflection at implant installation and abutment connection has also been suggested to cause remodeling of the bone support around implants. (Oh et al. 2002, Cardaropoli et al. 2006).

Risk for peri-implantitis

Effect of smoking

An association between smoking and periodontal disease was found in a systematic review on 70 cross-sectional studies and 14 case-control studies (Bergström 2006). Furthermore, in two recent studies (Okamoto et al. 2006, Thomson et al 2007) it was reported that the 4-year and the 6-year cumulative incident risk for periodontal disease was 1.7 and 5.2 times higher in smokers compared to non-smokers. It was also reported that smokers developed periodontal disease earlier than non-smokers. Other studies indicated that the number of cigarettes and time of exposure influenced the severity of periodontal disease in smokers (Grossi et al. 1995, Martinez-Canut et al. 1995). Several mechanisms may contribute to the different periodontal disease development in smokers in relation to non-smokers (Heasman et al. 2006).

The influence of smoking habits on the short- and long-term outcome of implant therapy was addressed in a systematic review (Strietzel et al. 2007). Studies were analyzed both at subject and implant levels and the outcome variables included implant loss, bone loss > 50%, implant mobility, persistent pain or peri-implantitis. Based on information from 10 studies providing data on a subject level, smokers showed an overall OR of 2.64 (95% CI 1.70-4.09) to experience implant complications according to the outcome variables. The corresponding OR on the implant level (18 studies included) was 2.17 (95% CI 1.67-2.83).

Studies evaluating the influence of smoking on peri-implant bone loss and clinical signs of pathology are reported in Table 9. A significant increase in bone loss in smokers compared to non-smokers was found in both prospective (Lindqvist et al. 1997, Nitzan et al 2005), and retrospective studies (Haas et al. 1996, Feloutzis et al. 2003, Roos-Jansåker 2006c). Haas and co-workers reported that smokers had significantly more bone loss in the maxilla (3.95 mm vs. 1.64 mm) compared to non-smokers, while no differences were found in the mandible. Lindqvist et al. (1997) in a

10-year study prospective study showed that smokers had greater bone loss at all implant positions in the mandible and that the tobacco exposure influenced the severity of bone loss. Thus, smokers who consumed ≥ 14 cigarettes/day had significantly more bone loss than smokers who smoked < 14 cigarettes/day. A marked and significant different peri-implant marginal bone loss was also demonstrated in a retrospective survey (Feloutzis et al. 2003). The median annual bone loss rate was 8-fold higher in smokers compared to non-smokers (0.04 mm vs. 0.32 mm). Similar results were presented in a 1-7 years prospective study (Nitzan et al. 2005). They reported that the mean bone loss in smokers was 0.153 mm compared to 0.047 mm in the non-smoking group of subjects. The influence of smoking on peri-implant bone loss was assessed in a long-term retrospective study by Roos-Jansåker et al. (2006c). The results from the multivariate analysis indicated that smoking was significantly associated with peri-implant bone level of ≥ 3 threads OR 10 (95% CI 4.1-26).

There is limited information in the literature with respect to the influence of smoking habits on the presence of peri-implantitis (Table 10). Haas et al. (1996) examined the association between smoking and peri-implantitis in 107 smokers and 314 non-smokers. Smokers had higher bleeding scores, more signs of clinical inflammation, deeper probing pocket depths and more radiographic bone loss around implants than non-smokers. McDermott et al. (2003) in a 13-months retrospective study found that smokers had an increased risk for inflammatory complications such as infection, bone loss, pain, mobility, impaired wound healing and gingival recession (OR 3.26 CI_{95%} 1.74-6.10). Grucia et al. (2004) reported that biological complications such as suppuration, fistula and peri-implantitis were significantly associated with smoking status. Furthermore, the long-term retrospective study by Roos-Jansåker et al. (2006c) demonstrated that smoking were significantly associated with both mucositis (OR 2.8 CI_{95%} 1.2-6.2) and peri-implantitis (OR 4.6 CI_{95%} 4.1-19).

Conclusion

Bone loss and clinical signs of pathology are more common among smokers than non-smokers. A general problem in the analysis of the literature regarding the influence of smoking on the short- and long-term outcome of implant therapy is that the majority of the studies include evaluation assessed only on the implant level. Smoking is a subject-related factor and analysis of the effect of smoking habits on the outcome of implant therapy should ideally be performed on a subject level. Further, in most studies the data have been collected retrospectively and usually analyzed using bivariate statistical methods without considering potential confounding factors (e.g. periodontal disease experience, standard of oral hygiene, maxillary/mandibular jaw, implant surface roughness).

History of periodontitis

Periodontitis has been reported to affect about 40-60% of an adult population and approximately 10% of the subjects exhibit severe disease (Papapanou & Lindhe 2008, Hugoson et al. 2008 a, b). Michalowicz et al. (1991, 1994, 2000) estimated that genetic factors might account for 50% of the variation seen in periodontal disease expression. Thus, it is suggested that individuals with a history of periodontitis that are treated with implant-supported prosthesis have an increased risk to develop peri-implant disease (Heitz-Mayfield 2008). This question has been addressed in several systematic reviews (Van der Weijden et al. 2005, Schou et al. 2006, 2008, Karoussis et al. 2007, Ong et al. 2008, Renvert & Persson 2009). All the reviews concluded that peri-implantitis was more common among implants in subjects with than without a history of periodontitis. The review by Schou et al. (2006) included 2 studies with a 5 and 10-year follow up, respectively (Hardt et al. 2002, Karoussis et al. 2003). A significant association between history of periodontitis and peri-implantitis was found (Risk ratio 9 CI_{95%} 3.9-20.6).

Table 11 summarizes some of the studies included in the various reviews. In the study by Karoussis et al. (2003), subjects with tooth loss caused by periodontitis had a significantly higher incidence of peri-implantitis than subjects who had lost their teeth due to other reasons (28.6% vs. 5.4%). Roos-Jansåker et al. (2006c) analyzed the influence of history of periodontitis on the prevalence of peri-implantitis. The results of the multivariate analyses indicated that subjects with history of periodontitis had an increased risk to exhibit implants with peri-implantitis (OR 4.7 CI_{95%}1.0-22).

Conclusion

Studies indicate that subjects with a history of periodontal disease have an increased risk to develop peri-implantitis. However, the evidence is based on few studies with a large variation in design. Furthermore, different definitions for periodontitis were used and confounding factors, such as smoking are usually not taken into consideration.

Oral hygiene (Table 12)

An association between oral hygiene and peri-implant bone loss was demonstrated in a 10-year prospective study (Lindquist et al. 1997). The authors evaluated different factors related to peri-implant bone loss such as oral hygiene, smoking habits, maximum bite force, tooth cleansing and extension of cantilevers. While smoking demonstrated the strongest association to peri-implant bone loss, subjects with a combination of poor oral hygiene and smoking had significantly greater mean marginal bone loss than smokers with good oral hygiene (1.61 mm vs. 0.99 mm; $p < 0.001$).

Ferreira et al. (2006) in a cross-sectional study evaluated possible risk variables associated with peri-implantitis. They reported that the risk for the subjects to experience peri-implantitis was associated with the level of oral hygiene. Thus, the OR for subjects exhibiting poor oral hygiene was 3.8 (95% CI 2.1-6.8) while individuals with very poor hygiene (PII ≥ 2) had an OR of 14.3 (95% CI 9.1-28.7). The authors concluded that “the association between plaque scores and peri-implantitis seems to

be dose dependent”. The influence of the level of oral hygiene on peri-implant bone loss was also analyzed in a 6 months prospective study by Jepsen et al. (1996). The authors reported significantly higher mean plaque scores in subjects exhibiting disease progression than in subjects with stable conditions (73% vs. 45%).

The association between accessibility for oral hygiene and peri-implantitis was recently examined in a group of subjects referred for treatment of peri-implantitis (Serino et al. 2009). The positive and negative predictive value for accessibility for oral hygiene and peri-implantitis was 65% and 82%, respectively. Thus, implants with appropriate accessibility for cleaning were rarely associated with peri-implantitis.

Interestingly, other studies have failed to find an association between level of oral hygiene and presence of peri-implantitis i.e. Roos-Jansåker et al. (2006b), Chung et al. (2007), Kim et al. (2008).

Conclusion

Several studies have demonstrated an association between oral hygiene and peri-implantitis. Different levels of oral hygiene in the various subject samples may explain why some studies have failed to find such an association.

Prevalence of peri-implantitis

The prevalence of a disease describes “the number of cases of a disease that is present in a population at one point in time“ (Newman Dorland 1994). Disease incidence is defined as “the rate at which a certain event occurs e.g. the number of new cases of a specific disease occurs during a certain period (Newman Dorland 1994). Thus, information on the prevalence of peri-implantitis must be generated from data assessed in studies with a cross-sectional design, while information on disease incidence can be provided from longitudinal studies.

In a systematic review summarized in Table 13, Berglundh et al. (2002) reported on the incidence of biological and technical complications in implant therapy in prospective longitudinal studies of at least 5 years. The review evaluated biological complications such as implant loss, sensory disturbances, soft tissue complications, peri-implantitis, bone loss ≥ 2.5 mm and implant fractures. Implant loss was the most frequently reported type of complication in the evaluated studies, while information regarding other categories, such as bone loss ≥ 2.5 mm, was provided in 20-50% of the studies. The proportion of implants with radiographic bone loss ≥ 2.5 mm varied from 1.01% (FPD's) to 4.76% at implants supporting overdentures. In addition, the available information regarding crestal bone loss in the studies analyzed was in most cases presented as implant-based mean values, while frequency distribution data on (i) clinical probing assessment and (i) radiographic bone loss were less frequently reported. Thus, data on the incidence of peri-implantitis were provided in 35-45% of the studies. The percentage of implants with peri-implantitis varied from 0.31% at single implants to 6.47% at FPD's. No subject-based data i.e. the prevalence of subjects exhibiting peri-implantitis were available in the studies reviewed by Berglundh et al. (2002).

Different criteria on peri-implantitis

The proportions of implants/subjects that exhibit peri-implant diseases are influenced by used disease criteria. Table 14 summarizes the % of peri-implant mucositis and peri-implantitis with respect to various definitions. The occurrence of peri-implantitis analyzed on the implant level varied between 1 and 24.8%. The corresponding figures for subject-based analyses were few. Ekelund et al. (2003) described peri-implantitis as a combination of inflammation, pain and continuous bone loss. The authors reported that between 1-3% of the implants were affected by peri-implantitis. When peri-implantitis was defined as crater formed bone loss and BoP, 2.4% of the implants were affected (Åstrand et al. 2008). In the study sample analyzed by Keller et al. (2009), 27.4% of the implants exhibited peri-implantitis defined as bone loss ≥ 2.5 mm after prosthesis insertion, PPD ≥ 4 mm and BoP. Roos-Jansåker and co-workers (2006b) reported that about 7% of the implants exhibited peri-implantitis according to the criteria (i) bone loss ≥ 1.8 mm after year-1 and (ii) BoP. Considering the large variation in disease criteria it is important to apply uniform measures to obtain comparable data and to provide results based on subjects, rather than implants. Thus, in a recent review by Zitzmann & Berglundh (2008) the criteria for peri-implantitis were BoP + bone loss. The recalculation of the data presented by Roos-Jansåker et al. (2006b) yielded that 25% of the implants and $> 56\%$ of the subjects had peri-implantitis in the study by Roos-Jansåker et al. (2006b).

New studies on the prevalence of peri-implantitis

Table 15 summarizes clinical studies on prevalence of peri-implantitis (BoP + bone loss after year-1) published after 2002. The majority (80%) of the selected cohort studies had a prospective design. One of the studies with a cross sectional design reported data from both radiographic and clinical assessments (Roos-Jansåker et al. 2006b). Frequency distribution data on radiographic bone loss were more frequently reported in studies after 2001 (7/10) compared to the review by Berglundh et al. (2002). The prevalence of peri-implantitis according to the definition in the consensus

reports (Albrektsson & Isidor 1994, Lindhe & Meyle 2008, Zitzmann & Berglundh 2008) was not presented in any of the studies. The % of implants with peri-implantitis based on other disease criteria is provided in < 50% of the long-term studies evaluating implant-supported therapy (Table 14). Only one of the studies analyzed the prevalence of subjects exhibiting peri-implant diseases (Roos-Jansåker et al. 2006b).

Conclusion

The majority of studies evaluating implant therapy have a longitudinal design. Thus, there is limited information in the literature with respect to the prevalence of peri-implantitis in subjects restored with fixed implant-supported prostheses as based on cross-sectional analyses. The aim of the **Study I** of the present series was to assess the prevalence of subjects with progressive bone loss at implants with a function time of at least 5 years. The aim of **Study II** was to examine the clinical characteristics at implants in relation to radiographic evidence of a history of bone loss. While the prevalence of the disease reveals the proportion of subjects that are affected, the *extent* of the disease describes the number or proportion of affected implants for each subject. The aim of **study III** was to analyze the extent of peri-implantitis-associated bone loss. An appropriate epidemiological description of peri-implantitis must also include the *severity* of the disease, i.e. the amount of bone loss that occurred around the affected implants. One aim of **Study IV** was to assess the severity of peri-implantitis associated bone loss. A second aim was to analyze the pattern of bone loss around implants in this group of subjects.

Table 1. The validity of probing as diagnostic measure

Authors/Title	Material	Methods	Main findings
Quirynen et al. 1991 "The reliability of pocket probing around screw-type implants"	108 subjects/ Brånemark system Overdenture	Clinical examination PPD, "Recession" (top of abutment – marginal border of the soft tissue). Calculated PAL Manual and constant force probe (0.25N). Radiographic examination Distance from Abutment Implant Junction to bone crest Examined the relationship between bone and PAL measurements.	Manual probing Mean bone level was scored 1.4 mm apically of PAL. 77 % of the observations were within 1 mm. Pearson Correlation coefficient for bone level and PAL at mesial and distal sites; 0.67 and 0.61 respectively. Intra-examiner variation; more than 90 % of the variation was within 0.5 mm. Conclusion: "clinical attachment level determination is a reliable indicator for bone level around implants with moderate healthy gingiva"
Lang et al. 1994 "Histologic probe penetration in healthy and inflamed peri-implant tissues"	5 Beagle dogs. 6 ITI® Dental Implant System implants in the mandible of each dog. 6 molar - control teeth.	3 different clinical conditions 1. Clinically healthy mucosa/gingiva. 2. Mucositis/gingivitis 3. Ligature induced peri-implantitis / periodontitis. Clinical variables; PI, GI, BoP, PPD, CAL. Probes with standardized force 0.2N placed m, d aspects of each implant/control-teeth. Histological analyses; Histologic Probing Depth (HPD) Histologic Distance Alveolar bone to Probe tip (DBP). Histologic Attachment Level - distance marginal mucosa to apical level of junctional epithelium (HAL).	healthy mucosa 2.1 mm 1.7 mm 1.7 mm 0.6 mm mucositis 1.9 mm 1.6 mm 1.6 mm 0.8 mm peri-implantitis 4.3 mm 3.8 mm 3.3 mm 0.3 mm gingiva NR 1.3 mm 1.5 mm 1.1 mm gingivitis NR 1.7 mm 1.6 mm 1.2 mm periodontitis NR 2.7 mm 2.2 mm 0.2 mm

Authors/Title	Material	Methods	Main findings
Brägger et al. 1996 “Correlations between radiographic, clinical and mobility parameters after loading of oral implants with fixed partial dentures”	11 subjects/ 18 implants ITI® Dental Implant System FPD	Clinical and radiographic examination at BL (loading) 1, 3, 6, 12 and 24 months. Manual probing. Radiographic examination; distance between implant shoulder and bone-to-implant contact. Clinical parameters; mPII, mBI, Recession, PPD, Calculated PAL. Multiple stepwise regression analyses.	No differences in PPD between 1-24 months Significant increase in PAL between 1-24 months The expected bone level change over 2-years was best explained by early changes in density and PAL measurements
Nishimura et al. 1997 “ Periodontal parameters of osseointegrated dental implants” A four-year controlled follow-up study”	12 subjects 32 ITI® Dental Implant System	Recalled once every month for prophylaxis over 4 years Clinical examination; PII, BoP, mobility, PPD, PAL. Conventional probing at 6 sites/implant. Radiographic examination; distance between implant shoulder and bone-to-implant contact (DIB). Clinical and radiographic examination at 6, 12, 36 and 48 months.	PLI score 0 at 74 % of all sites BoP < 20 % of sites PPD 97 % of the total sites ≤ 3 mm. mean PII = 0.31±0.51 mean BoP = 0.2±0.4 Mean PPD mean PAL 6 months 2.2 mm 1-year 2.3 mm 2-year 2.0 mm 4-year 2.0 mm mean PPD 2.0 ± 0.75 mm mean PAL 2.6 ± 1.01 mm mean DIB 3.5 ± 0.6 mm DIB increased during the first 3 months – stable between 3 months and 4 years.

Authors/Title	Material	Methods	Main findings
Mombelli et al. 1997 "Comparison of periodontal and peri-implant probing by depth-force pattern analysis"	11 subjects 1 ITT® Dental Implant System Function time ≥ 5 years. 1 tooth.	Special periodontal probing device; standardized alignment for probing measurements and radiographs. Continuous probing force at implants and teeth; 0.25N, 0.50N, 0.75N, 1.00N, 1.25N. Clinical examination: conventional probing, BoP, PII. Radiographic examination.	Implants Teeth PII 0.36. 0.32. BoP 9 % 7 % PPD 0.25N 3.4 mm PPD 1.25N 5 mm 4 mm Gradually deeper mean PPD at implants compared to teeth with increasing probing force. Mean distance probe tip to bone crest at 0.25N; Implants 0.75 mm Teeth 0.43 mm Conclusion: "peri-implant pocket probing is more sensitive to force variation than pocket probing at teeth".
Eitter et al. 2002 "Healing after standardized clinical probing of the peri-implant soft tissue seal"	3 Foxhounds 6 ITT® Dental Implant System /dog 3 month healing. Plaque control 1 times/day Absence of BoP.	Clinical probing Day 1, 2, 3, 5, 7. 1 implant was probed at m, d site each examination day. Pressure sensitive probe 0.25N. Tip diameter 0.45mm. Un probed control implant. Histomorphometric analyses Distance from alveolar crest to coronal border of connective tissue adaptation. Length of JE.	The probe caused a separation between the surface of the implant and the junctional epithelium but not within the connective tissue adaptation. A new epithelium attachment to the implant surface was completed after 5 days. No signs of inflammation in the connective tissue due to trauma after probing.
Hultin et al. 2002 "Microbiological findings and host response in patients with peri-implantitis"	17 subjects/98 implants Brånemark System. ITT® Dental Implant System	Clinical examinations; Plaque, GI, PPD standardized force 0.20N. Comparison PPD between implants with stable bone level (n=53) and implants with marginal bone loss ≥ 1.8 mm after year 1 (n=45) and teeth (n=133). 17 control subjects with stable implants and teeth.	Mean PPD Stable implants = 2.6 mm Peri-implantitis = 4.3 mm Teeth = 2.1 mm Control subjects Stable implants (n=114)= 2.2 mm Teeth (n=109)= 1.8 mm

Authors/Title	Material	Methods	Main findings
<p>Schou et al. 2002</p> <p>“Probing around implants and teeth with healthy or inflamed peri-implant mucosa/gingiva. A histologic comparison in cynomolgus monkeys (Macaca fascicularis)”</p>	<p>8 monkeys</p> <p>4 implants Astra Tech machined surface in each monkey</p>	<p>4 different clinical conditions around teeth and implants</p> <ol style="list-style-type: none"> 1. Healthy peri-implant mucosa/gingiva. 2. Mild mucositis/gingivitis 3. Severe mucositis/gingivitis. 4. Ligature induced peri-implantitis/periodontitis (Bone loss 2-4 mm). <p>Clinical examination; Plaque and gingival scores, PPD, PAl.</p> <p>Standardized probe force 30-40 g (0.3-0.4 N)</p> <p>Radiographic examination</p> <p>Pert-probes attached to implants and teeth</p> <p>Histomorphometri;</p> <p>probing depth</p> <p>distance between probe tip and alveolar bone.</p>	<p>Clinical probing depth;</p> <ol style="list-style-type: none"> 1 o 2.: PPD 0.5 mm-2 mm 3: PPD 1-4 mm 4: PPD 2-6 mm <p>Distance between probe tip and alveolar bone; no difference between implant and teeth at healthy mucosa/teeth (0.5-1.5 mm).</p> <p>All other clinical conditions;</p> <p>the probe tip significantly closer to the bone around implants (< 0.5 mm) than around teeth (0.5-1.5 mm).</p> <p>All clinical conditions;</p> <p>correspondence between clinical and histological probing depth (difference less than 0.5 mm).</p> <p>“No difference between maxilla and mandible”</p>
<p>Abrahamsson & Soldini 2006</p> <p>“Probe penetration in periodontal and peri-implant tissues</p> <p>A experimental study in the beagle dog”</p>	<p>4 beagle dogs</p> <p>4 experimental non-submerged implants.</p>	<p>Clinically healthy conditions.</p> <p>PPID at implants and first molars, buccal aspects.</p> <p>Pressure sensitive probe / Ø 0.4 mm/ 0.2 N.</p> <p>Block biopsies.</p> <p>Histometric examination.</p>	<p>Probing resulted in similar probe extension at implants and teeth.</p> <p>Probe extension corresponded to the extension of the barrier epithelium.</p> <p>Distance probe tip to bone about 1 mm in both peri-implant and periodontal tissues.</p>

Authors/Title	Material	Methods	Main findings
<p>DeAngelo et al. 2007</p> <p>”Early soft tissue healing around one-stage dental implants: clinical and microbiologic parameters”</p>	<p>21 subjects Astra Tech implants Single implants</p>	<p>Each patient contributed with 1 implant. One stage surgery, healing abutment. Clinical examination 2, 4, 8, 12 weeks postoperatively. PII, GI, PPD, width of keratinized gingiva, Flap thickness, Papilla height, BoP. Manual probing.</p>	<p>Mean PPD ranged from 2 mm - 2.6 mm from postop week 4 to postop week 12.</p> <p>No significant difference between 4 and 12 weeks.</p> <p>No association between pre-existing flap thickness and peri-implant sulcus depth</p> <p>Conclusion “Peri-implant soft tissue clinical maturity may be established as early as 4 weeks following implant placement”</p>

Table 2. The validity of BoP as diagnostic measure

Authors/Title	Material	Methods	Main findings
Lang et al. 1994 "Histologic probe penetration in healthy and inflamed peri-implant tissues"	5 Beagle dogs. 6 III implants in the mandible of each dog 6 molar - control teeth.	3 different clinical conditions 1. Clinically healthy mucosa/gingiva 2. Mucositis/gingivitis 3. Ligature induced peri-implantitis / periodontitis Clinical variables; PII, GI, BoP, PPD, P,AL Standardized force 0.2N	Healthy mucosa Teeth Mean PII 0.47 Mean GI 0.06 BoP 0 % Mucositis Gingivitis Mean PII 1.61 Mean GI 1.61 BoP 66 % Periodontitis Mean PII 1.96 Mean GI 2.05 BoP 90.9 % 6 % of sites, 19 % of implants and 28 % of subjects demonstrated disease progression. BoP Pos. Predictive Value: implant site 10 %, implant 19 % Neg. Predictive Value: implant site 97 %, implant 82 % Significantly higher plaque scores at implant with progression (73 % vs. 45 %). Absence of BoP indicates stable peri-implant conditions
Jepsen et al. 1996 "Progressive peri-implantitis. Incidence and prediction of peri-implant attachment loss"	25 subjects 54 IMZ implants Overdentures	Clinical examination Plaque, BoP, PPD, CAL Probing force 0.15 – 0.35N Baseline and after 6 months Disease progression defined as CAL change of ≥ 1 mm in 6 months.	

Authors/Title	Material	Methods	Main findings
Brägger et al. 1997 "Associations between clinical parameters assessed around implants and teeth"	127 subjects 258 ITI implants FPD 253 contra-lateral teeth	Clinical evaluation after 1 year in function PII, GI, PPD, BoP, PAL, Recession Manual probing Comparisons between implants and contra-lateral teeth.	% BoP implants 24 % Teeth 12 % (p<0,01) No difference between implants/teeth with respect to mean PII (0.22/0.30) Mean GI (0.35/0.44)
Luterbacher et al. 2000 "Diagnostic characteristics of clinical and microbiological tests for monitoring periodontal and peri-implant mucosal tissue conditions during supportive periodontal therapy (SPT)"	19 subjects. Treated for moderate to advanced periodontal disease Implant supported prosthesis-function time 3 years SPT program for 5 years (recall interval 3 to 5 months)	1 implant (test) 1 contra-lateral tooth (control) Standardized probing (0.25N) Presence or absence of BoP Calculated number of recall visits with positive BoP during the last 2 years of supportive therapy. Disease progression defined as PAL change of 2.5 mm in 5 years (0.5 mm annually) or - 3.5 CADIA values (digital radiographic analyses) in 5 years (-0.7 mm/year). Diagnostic test (two-by-two tables)	8/19 tooth sites and 10/19 implant sites lost support. BoP frequency of ≥ 50% Sensitivity 50 % Specificity 100 % Positive predictive value 100 % Negative predictive value for implants 100 % Conclusion BoP is a useful clinical parameter for predicting peri-implant "attachment loss".

Authors/Title	Material	Methods	Main findings
Zitzmann et al. 2001 “Experimental peri-implant mucositis in man”	12 partially edentulous subjects restored with Brånemark implants in function at least 7 months.	3 weeks plaque control program. Baseline examination; PII, modified gingival index (MGI). Soft tissue biopsy from gingiva and peri-implant mucosa (PiM). 3 weeks of plaque accumulation. Clinical examination and soft tissue biopsy from gingiva and peri-implant mucosa (PiM). Morphometric and immunohistochemical analyses.	Baseline - 3 weeks plaque accumulation; Implants Teeth Mean PII Baseline 0.17 3 weeks plaque 2.08 Mean MGI Baseline 0.13 3 weeks plaque 1.92 Histological analyses Size of infiltrate Baseline 0.03 mm ² 3 weeks plaque 0.14 mm ² 0.03 mm ² 0.26 mm ²
Gerber et al. 2009 ”Bleeding on probing and pocket probing depth in relation to probing pressure and mucosal health around oral implants”	17 subjects Implants and teeth with healthy clinical conditions; PPD ≤3mm, PII <1, modified Sulcus Bleeding Index =0 at implants SPT 3-6 months	Evaluation of PPD and BoP at implants and contra-lateral teeth 2 different probing forces 0.15N and 0.25N	Increasing probing pressure from 0.15N and 0.25N resulted in increase in BoP% - 13.7% at implants and 6.6% at teeth. Significantly larger BoP % at implants compared to teeth with a probing force of 0.25N. No difference with probing force 0.15N

Table 3. Composition of microflora at implant sites

Authors/Title	Material	Methods	Main findings
Mombelli et al. 1987	5 subjects with successful implants ITI; no bone loss, PPD ≤ 5 mm, (probing force 0.5N), no suppuration. 7 subjects with failing ITI implants; bone loss, PPD ≥ 6mm, suppuration.	Submucosal plaque samples from “successful” and “failing” implants. Microbiological analyses; dark field microscopy, immunohistochemical and cultural methods.	Peri-implantitis (failing) implants; abundance of motile rods, fusiform bacteria and spirochetes. 41% of organisms were G-negative anaerobic rods i.e. <i>Finobacterium spp</i> and <i>Prevotella intermedia</i> . Healthy peri-implant mucosa; small number of coccoid cells and few rods. Low cultivable counts, most bacteria G-positive cocci.
George et al. 1994	24 subjects/98 implants. Periodic maintenance care twice a year.	Clinical examination; PII, Gingival bleeding Index. Microbiological examination; Submucosal plaque samples. <i>Porphyrromonas gingivalis</i> , <i>Prevotella intermedia</i> and <i>A. actinomycetemcomitans</i> were identified by latex agglutination test.	“Peri-implantitis is a site specific infection with many features in common with chronic periodontitis” . 62.5% of the subjects had ≥1 implant colonized by the test bacteria. The bacteria occurred both in partially edentulous and edentulous subjects. Sub-mucosal sites that harboring 1 of test microorganisms had significantly greater PPD and GBI than non-colonized sites. Implant in function for 3 to 4 years had significantly greater frequency of test microorganisms than implants in function 1 to 2 years. (44% vs. 2.6%, p<0.001)
Ponteriero et al. 1994	20 partially edentulous subjects. Periodontal therapy, SPT. IMZ implants, (test). Adjacent natural tooth (control).	Baseline examination at test and control PII, GI, SBI, PPD, Submucosal/subgingival plaque samples Phase-contrast microscopy. 3 weeks of undisturbed plaque accumulation. Repeated examination procedures at test and control.	Baseline - 3 weeks plaque accumulation No significant differences between implant and teeth in any clinical variables or in the composition of the submucosal/subgingival microbiota at any of the observation times.
“Experimentally induced peri-implant mucositis A clinical study in humans”			

Authors/Title	Material	Methods	Main findings
<p>Augthun & Conrads 1997</p> <p>“Microbial findings of deep peri-implant bone defects”</p>	<p>12 subjects/18 IMZ implants mean function time 74.7 months.</p> <p>Bar supported mandibular prosthesis.</p> <p>Each implant had ≥ 6 mm vertical peri-implant bone loss.</p>	<p>Mucoperiosteal flaps.</p> <p>Removal of the peri-implant inflammatory tissue within the bone defect.</p> <p>Microbiological analyses – cultural methods.</p>	<p>Gram-negative bacteria dominated the samples. High incidence of <i>A. actinomycetemcomitans</i> and <i>Bacteroidaceae</i> species in 16 of 18 samples. Other species frequently found was <i>F. nucleatum</i>, <i>Capnocytophaga</i> spp and <i>Eikenella corrodens</i>.</p>
<p>Leonhardt et al. 1999</p> <p>“Microbial findings at failing implants”</p>	<p>37 subjects exhibiting 1-4 implants with peri-implantitis (crater like bony destruction, bone loss ≥ 1.8 mm compared to year 1, BoP and/or pus.)</p> <p>51 subjects without clinical and signs of disease and no bone loss. Brånemark system implants.</p> <p>Function time ≥ 5 years.</p>	<p>Sub-mucosal plaque samples from 1-4 diseased sites/subjects and 2-3 sites/subjects in the control group. Paper points.</p> <p>Microbiological analyses by culture methods.</p> <p>Comparison between diseased dentate or edentulous and healthy dentate or edentulous subjects.</p>	<p>Significant different microbiota at healthy and diseased implants in both dentate and edentulous subjects.</p> <p><i>Porphyromonas gingivalis</i>, <i>Prevotella intermedia/Prevotella nigrescens</i> and <i>A. actinomycetemcomitans</i> was found in 60% of the subjects in the peri-implantitis group. None of the analyzed bacteria was detected in the edentulous subjects with healthy implants.</p> <p><i>Porphyromonas gingivalis</i> and <i>A. actinomycetemcomitans</i> were detected in peri-implant lesions both in dentate and edentulous subjects.</p> <p><i>Staphylococcus</i> spp. enterics and <i>Candida</i> spp were found in 55% of the implants with peri-implantitis.</p>

Authors/Title	Material	Methods	Main findings
Quirynen et al. 2006 “Dynamics of initial subgingival colonization of “pristine” peri-implant pockets”	42 partially edentulous subjects restored with Brånemark system. Control teeth.	Healing abutments 2-3 months plaque control. Final abutments and crown/bridges installation. 4 sub-gingival plaque samples from shallow and medium deep pocket around implants and teeth at week 1, 2, 4, 13, 26, and 78 weeks of undisturbed plaque accumulation. Checkerboard DNA-DNA hybridization, culture techniques, PCR.	A complex subgingival microbiota is established in a “pristine” peri-implant pocket within 1 week. After 7 days the detection frequency for most species (including red and orange complex) was nearly identical in samples from the fresh peri-implant pockets compared with samples from reference teeth.
Renvert et al. 2007 “Infection at titanium implants with or without a clinical diagnosis of inflammation”	213 subjects/976 Brånemark system implants in function years 9-14 years (mean 10.8 years).	4 subgingival and 4 submucosal plaque samples from the deepest PPD (0.25N) at teeth and implant. Paper points. Pooled separately for implants and teeth. 40 species identified by checkerboard DNA-DNA hybridization. Comparisons of the microbiota in relation to; - implant status (healthy, mucositis (PPD \geq 4 mm, BoP, $<$ 3 threads bone loss), peri-implantitis (bone loss \geq 1.8 mm after year 1, BoP). - teeth vs. implants. - subjects with or without teeth.	No uniform SPT. Patient characteristics; Plaque mean implant 41.8%. BoP mean implant 84.6%. PPD mean implant; healthy sites 2.3 mm, mucositis 4.7 mm, peri-implantitis 5.3 mm No differences in microbial profile with respect to; conditions of peri-implant tissues, teeth and implants or if subjects had teeth or not. <i>Neisseria mucosa</i> , <i>Fusobacterium nucleatum</i> sp. <i>Nucleatum</i> , <i>F. nucleatum</i> sp. <i>polymorphum</i> , <i>Capnocytophaga sputigena</i> dominated the sub-mucosal and sub-gingival microbiota.

Authors/Title	Material	Methods	Main findings
<p>Shibli et al. 2007</p> <p>“Composition of supra-and subgingival biofilm of subjects with healthy and diseased implants”</p>	<p>44 subjects restored with implants in function for at least 2 years.</p> <p>22 subjects \geq 1 healthy implant.</p> <p>22 subjects \geq 1 implant with peri-implantitis (\geq3 mm bone defect, BoP).</p>	<p>Clinical examination; Plaque, gingival bleeding, BoP, PPD. CAL.</p> <p>Sample site; peri-implant site with deepest pocket. Plastic cyrette.</p> <p>Supra mucosal and submucosal plaque samples from the same site.</p> <p>Microbiological analyses; checkerboard DNA-DNA hybridization.</p>	<p>All clinical parameters, (except plaque) were statistically higher in peri-implantitis group.</p> <p>Higher mean count of <i>T. forsythia</i>, <i>P. gingivalis</i>, <i>T. denticola</i>, <i>F. nucleatum</i> <i>ss nucleatum</i>, <i>F. nucleatum</i> <i>ss vincentii</i>, <i>P. intermedia</i> in both supra and submucosal biofilm at diseased compared to healthy implants sites ($p < 0.05$).</p> <p>Conclusion: Marked differences in the composition of supra-and submucosal biofilm between healthy and diseased sites.</p>

Table 4. Tissue response to microbial challenge

Authors/Title	Material	Methods	Main findings
Berglundh et al. 1992 “Soft tissue reaction to the novo plaque formation on implants and teeth”	5 Beagle dogs Brånemark implants Control teeth	2 months daily plaque control Clinically healthy conditions Biopsies from implant and tooth sites. 3 weeks plaque accumulation. Clinical evaluation; plaque and soft tissue inflammation. Biopsies from implant and tooth sites. Histometric and morphometric analyses.	Clinical evaluation; large amounts of plaque and BoP at implant and tooth sites. Histological analyses; Presence of subgingival plaque. The mucosa around implants and teeth had a similar reaction to plaque accumulation with respect to leukocyte transmigration, extension (0.9 mm) and size and composition of the inflammatory cell infiltrate (ICT).
Ericsson et al. 1992 “Long-standing plaque and gingivitis at implants and teeth in the dog”	5 Beagle dogs Brånemark Implants Control teeth	4 months daily plaque control Clinical evaluation; plaque and gingivitis. 3 months of plaque accumulation. Clinical evaluation; plaque and gingivitis. Biopsies from implant and contra-lateral tooth. Histometric and morphometric analyses.	The histological examination demonstrated; (i) both tissues contained ICT, (ii) apical extension of ICT was more pronounced in the peri-implant mucosa than in the gingival (0.9 mm vs. 1.3 mm, $p < 0.05$) (iii) the composition of the 2 lesions had many features in common.

Authors/Title	Material	Methods	Main findings
Pontiero et al. 1994 "Experimentally induced peri-implant mucositis A clinical study in humans"	20 partially edentulous subjects. Periodontal therapy, SPT. IMZ implants, (test). Adjacent natural tooth (control).	Baseline examination at test and control PII, Gingival Index (GI), Sulcus bleeding Index (SBI), PPD, Plaque samples Phase-contrast microscopy. 3 weeks of undisturbed plaque accumulation. Repeated examination procedures at test and control.	Baseline - 3 weeks plaque accumulation; Implants Teeth Mean PI 0.8 Baseline 0.4 3 weeks plaque 2.4 Mean GI 0.4 Baseline 1.6 3 weeks plaque 0.4 Mean SBI 1.4 Baseline 0.3 3 weeks plaque 1.6 Mean PPD 2.8 mm Baseline 3.7 mm 3 weeks plaque 2.6mm 3.1 mm No significant differences between implant and teeth in any clinical variables or in the composition of the submucosal/subgingival microbiota at any of the observation times.
Liljenberg et al. 1997 "Composition of plaque-associated lesions in the gingiva and peri-implant mucosa in partially edentulous subjects"	20 partially edentulous patients. Treated for moderate to advanced periodontal disease. Implant supported therapy was completed 6 - 24 months prior to soft tissue biopsy.	Samples of gingival tissue and peri-implant mucosa from one tooth and one implant site of the same jaw. Morphometric assessments.	Peri-implant mucosa Gingiva Size ICT (mm ²) 0.17 0.25 CD3 4.47 CD4 2.81 CD8 2.08 CD19 0.49 CD45RA 2.04 CD45RO 6.07 CD68 3.09 PMN elastase 1.16 *p<0.05 7.54 * 4.51 * 2.53 3.70 * 3.99 * 8.43 * 2.71 3.65 *

Authors/Title	Material	Methods	Main findings
<p>Abrahamsson et al. 1998</p> <p>“Soft tissue response to plaque formation at different implant systems. A comparative study in the dog”</p>	<p>5 Beagle dogs Brånemark, Astra Tech, ITI implants.</p>	<p>1 months daily plaque control Clinically healthy conditions 5 months of plaque accumulation. Biopsies. Histometric and morphometric analyses.</p>	<p>Plaque formation resulted in the establishment of an ICT lateral to a pocket epithelium. The extension and composition of the ICT was similar in the 3 implants systems tested.</p>
<p>Zitzmann et al. 2001</p> <p>“Experimental peri-implant mucositis in man”</p>	<p>12 partially edentulous subjects restored with Brånemark implants in function at least 7 months.</p>	<p>3 weeks plaque control program. Baseline examination; PII, modified gingival index (MGI). Soft tissue biopsy from gingiva and peri-implant mucosa (PiM). 3 weeks of plaque accumulation. Clinical examination and soft tissue biopsy from gingiva and peri-implant mucosa (PiM). Morphometric and immunohistochemical analyses.</p>	<p>Baseline - 3 weeks plaque accumulation; Implants</p> <p>Teeth</p> <p>Mean PI Baseline 0.17 3 weeks plaque 2.08</p> <p>Mean MGI Baseline 0.13 3 weeks plaque 1.92</p> <p>Histological analyses Size of infiltrate Baseline 0.03 mm² 3 weeks plaque 0.14 mm²</p> <p>Inflammatory response characterized by increased proportions of T- and B-cells in the ICT of both gingiva and PiM.</p>

Table 5. Histopathological characteristics of mucositis and peri-implantitis

Authors/Title	Material	Methods	Main findings																					
Sanz et al. 1991 “Histopathologic characteristics of peri-implant soft tissues in Brånemark implants with 2 distinct clinical and radiological patterns. A histometric and ultrastructural study”	12 subjects Partially edentulous restored with Brånemark System implants. Divided in; (i) Peri-implant infection group (PPD ≥ 3 mm, BoP, Bone loss > 3 mm). (ii) non peri-implant infection group (PPD < 3 mm, Bone loss < 3 mm).	Interproximal biopsies of supracrestal peri-implant tissues of each subject groups. Histometric and ultra structural analyses (electron microscopy).	The biopsies in the Peri-implant infection group demonstrated significantly; (i) higher transmigration of PMN cells in the epithelium, (ii) higher % ICT in the connective tissue, (iii) higher numbers of plasma cells and mononuclear cells, than biopsies in the non peri-implant group. Conclusion: submucosa around implants reacts to plaque bacteria by chronic inflammation.																					
Gualini & Berglundh 2003 “Immuno-histochemical characteristics of inflammatory lesions at implants”	2 groups of subjects. Group A 10 partially edentulous subjects with peri-implant mucositis. Group B 6 subjects ≥ 1 implant site with peri-implantitis i.e. (i) history of continuous bone loss (ii) BoP, pus (iii) no implant mobility.	Soft tissue biopsies from mucositis and peri-implantitis sites. Immunohistochemical analyses regarding the proportion of cells positive for CD3, CD4, CD8, CD19, and elastase markers.	<table border="1"> <thead> <tr> <th>Size ICT (mm²)</th> <th>Peri-implant mucositis</th> <th>Peri-implantitis</th> </tr> </thead> <tbody> <tr> <td>CD3</td> <td>0.36</td> <td>1.26*</td> </tr> <tr> <td>CD4</td> <td>7.3</td> <td>9.8</td> </tr> <tr> <td>CD8</td> <td>5.4</td> <td>8.0</td> </tr> <tr> <td>CD19</td> <td>5.3</td> <td>5.7</td> </tr> <tr> <td>PMN elastase</td> <td>4.1</td> <td>13.3 *</td> </tr> <tr> <td></td> <td>2.2</td> <td>4.0*</td> </tr> </tbody> </table> <p>*p<0.05 Peri-implantitis sites, in contrast to sites with mucositis, displayed elastase positive cells in the central portion of the infiltrate.</p>	Size ICT (mm ²)	Peri-implant mucositis	Peri-implantitis	CD3	0.36	1.26*	CD4	7.3	9.8	CD8	5.4	8.0	CD19	5.3	5.7	PMN elastase	4.1	13.3 *		2.2	4.0*
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PMN elastase	4.1	13.3 *																						
	2.2	4.0*																						

Authors/Title	Material	Methods	Main findings
Berglundh et al. 2004 “Histopathological observations of human peri-implant lesions”	Soft tissue biopsies from 12 implant sites in 6 subjects. Implants in function between 4 and 21 years. All sites exhibited advanced bone loss. Clinical signs of severe inflammation in majority of sites. 7/12 implants mobile	Soft tissue biopsies. Histometric and morphometric analyses.	(i) Large ICT's (mean 3.61 mm ²) that extended apical of the pocket epithelium (ii) 60% of ICT occupied by inflammatory cells, dominated by plasma cells (iii) Numerous PMN cells not only in the pocket epithelium but also present in peri-vascular more central areas of ICT
Duarte et al. 2009 “Differential cytokine expression affects the severity of peri-implant disease.	48 subjects/1 implant in each subject (3i implant innovations)	3 different peri-implant conditions 1. Healthy (n=11); PPD ≤ 4 mm, absence of MB, BoP, Pus and no radiographic evidence of bone loss. 2. Mucositis (n=15); MB and/or BoP, no radiographic evidence of bone loss. 3. Initial peri-implantitis (n=10); PPD ≥ 5mm, BoP and/or pus and 4 threads of bone loss 4. Severe peri-implantitis (n=12); PPD ≥ 5 mm, BoP and/or pus and bone loss > 5 threads. Soft tissue biopsies Assessments of gene expression of IL-12, TNF- α , IL-10, IL-4, RANK-L, OPG. Correlation analyses between levels of inflammatory and osteoclastogenesis-related factors and peri-implant conditions.	IL-12 and TNF- α , levels were significantly higher in severe peri-implantitis followed by initial peri-implantitis and mucositis (p<0.05). The lowest levels were observed in healthy peri-implant tissue (p<0.05). The expression of RANK-L progressively increased as the peri-implantitis severity increased (p<0.05). The highest OPG/RANK-L ratio was observed in healthy peri-implant tissue and the lowest in severe peri-implantitis (P<0.01). Conclusion “Inflammatory and osteoclastogenesis-related factors may play an important role in the onset and severity of peri-implant disease”

Table 6. Effect of load on marginal bone loss - Static load models

Authors/ title	Material	Methods	Main findings
<p>Gotfredsen et al. 2001a</p> <p>"Bone reactions adjacent to titanium implants subjected to static load. A study in the dog (I)"</p>	<p>3 Beagle dogs 8 ITI®Dental Implant System</p>	<p>Crowns in pairs connected with orthodontic expansion screw. 4 loading units in each dog 1) no expansion, 2) 0.2 mm expansion 3) 0.4 mm expansion and 4) 0.6 mm expansion 24 weeks Plaque control 1/day Clinical registrations, standardized radiographs and flourochrome labeling Histological analyses</p>	<p>No evident marginal bone loss was observed either at test or control implants.</p> <p>The bone density and the mineralized bone-to-implant contact were higher adjacent to the lateral loaded implants than at the unactivated control sites.</p>
<p>Gotfredsen et al. 2001b</p> <p>"Bone reactions adjacent to titanium implants with different surface characteristics subjected to static load. A study in the dog (II)"</p>	<p>3 Beagle dogs 2 implants TPS 2 implants machined surface.</p>	<p>Crowns in pairs connected with orthodontic expansion screw. 2 loading units in each dog 0.6 mm expansion 24 weeks Plaque control 1/day Clinical registrations, standardized radiographs and flourochrome labeling Histological analyses</p>	<p>A higher marginal bone level was observed around implants with a TPS surface compared to machined implants.</p> <p>Bone-to-implant contact at the bone/implant interface as well as the density of the peri-implant bone were lower at the machined than at the TPS implants.</p>
<p>Gotfredsen et al. 2001c</p> <p>"Bone reactions adjacent to titanium implants subjected to static load of different duration. A study in the dog (III)"</p>	<p>3 Beagle dogs 6 ITI®Dental Implant System</p>	<p>2 crowns fused together and connected to the 3 third implant with a orthodontic expansion screw. 2 loading units in each dog. Gradually activated expansion screw (once every 2 weeks) up to 1.6 mm. 10 weeks or 46 weeks Plaque control 1/day Flourochrome labeling Histological analyses</p>	<p>10 weeks or 46 weeks of lateral load had a similar (i) distribution of bone markers (ii) proportion of bone density and (iii) degree of bone-to-implant contact. No differences in marginal bone loss (0.1 mm).</p>

Authors/ title	Material	Methods	Main findings
Melsen & Lang 2001 "Biological reactions of alveolar bone to orthodontic loading of oral implants"	6 monkeys Specially design screw implants	Orthodontic forces 100cN-300cN applied to implants with a Ni-Ti coil springs 11 weeks. Plaque control 1 monkey control. Histological analyses.	None of the implants lost osseointegration. The bone tissue turnover as well as the density of the alveolar bone was higher adjacent to loaded compared to unloaded implants. Bone remodeling increased with increasing strain.
Gotfredsen et al. 2002 "Bone reactions at implants subjected to experimental peri-implantitis and static load. A study in the dog."	5 Beagle dogs ITT®Dental Implant System 3 implants SLA 3 implants machined surface.	Crowns without occlusion contact. Central and posterior implants connected with a bar containing orthodontic expansion screw. Anterior and posterior implants ligature-induced breakdown. Gradually activated expansion screw (once every 2 weeks) up to 1.6 mm. Three different experimental categories 1. Mucositis + load 2. Peri-implantitis – no load 3. Peri-implantitis – lateral static load Fluorochrome labeling Radiographic and histological analyses	Lateral static load failed to induce marginal bone loss at implants with mucositis and failed to enhance bone loss at implants with experimental peri-implantitis. Static load resulted in bone modeling and higher bone density lateral to the implants. No differences between the implant types.

Table 7. Effect of load on marginal bone loss - Occlusal load models

Authors/Title	Material	Methods	Main findings
Isidor et al. 1996, 1997 “Histological evaluation of peri-implant bone at implants subjected to occlusal overload or plaque accumulation”	4 monkeys 5 screw-type implants Astra Tech AB, 8 mm. Each lateral mand jaw segment 1 TiO ₂ , 1 machined surface Anterior segment; 1 TiO ₂	Max jaw; 2 splints covering premolars and molars. Mand jaw; FPD on 2 implants in one lateral segment in supra occlusal contact with Max. splint. <i>Excessive load in lateral direction.</i> FPD replaced 1 or 2 times. Plaque control 1/day Remaining implants, ligature induced breakdown 18 months Clinical and radiographic examinations including mobility test (1996). Histological analyses (1997)	5 out of 8 implants with excessive load lost osseointegration after 4.5 to 15.5 months. Monkey 1: 2 mobile implants after 4 1/2 and 5 1/2 month. Monkey 2: 1 mobile implant after 15 months. Monkey 3: 2 mobile implants after 15 1/2 months. Monkey 4: no mobile implants. Implants with plaque accumulation: increasing bone loss (mean 1.8 mm after 18 months) No differences between implant type.
Miyata et al. 1998 “The influence of controlled occlusal overload on peri-implant tissue: a histologic study in monkeys”	5 monkeys 2 experimental IMZ implants	Crowns in 100µm supra-occlusion. <i>Excessive lateral force lingual to buccal.</i> Plaque control. 1, 2, 3, 4 weeks. 1 monkey/2 implants each time period. Unloaded control Histological analyses	Similar degree of bone loss at test and control.
Miyata et al. 2000 “The influence of controlled occlusal overload on peri-implant tissue. Part 3: A histologic study in monkeys”	4 monkeys 2 experimental IMZ implants	Crowns in supra-occlusion 100µm, 180µm, 250µm <i>Excessive lateral force lingual to buccal.</i> Plaque control. 4 weeks. 1 monkey/2 implants each occlusal height. Unloaded control Clinical examinations Histological analyses	250µm excessive-occlusal height (1 monkey 2 implants) resulted in complete loss of osseointegration.

Authors/Title	Material	Methods	Main findings
<p>Hertz-Mayfield et al. 2004</p> <p>"Does excessive occlusal load affect osseointegration? An experimental study in the dog"</p>	<p>6 Labrador dogs 2 TPS and 2 SLA implants. 45 implants</p>	<p>Gold crowns in supra-occlusal contacts. <i>Excessive load</i> Unloaded control Plaque control 8 months Clinical, radiographic and histological analyses.</p>	<p>No difference in the clinical, radiographic and histological parameters between loaded and non-loaded implants.</p>
<p>Berglundh et al. 2005</p> <p>"Bone reactions to longstanding functional load at implants: an experimental study in dogs"</p>	<p>6 Beagle dogs AstraTech® and Bränemark System® implants</p>	<p>Fixed partial denture mandibular jaw 10 month <i>Functional load</i> Plaque control/1/day. Unloaded control Radiographic and Histological analyses</p>	<p>Largest amount of bone loss occurred following implant installation and abutment connection.</p> <p>No differences in marginal bone loss between functional loaded implants and unloaded control.</p> <p>Implants exposed to functional load exhibited a higher degree of bone-to-implant contact than control implants in both implant systems.</p>
<p>Kozlovsky et al. 2007</p> <p>"Impact of implant overloading on the peri-implant bone in inflamed and non-inflamed peri-implant mucosa"</p>	<p>4 Beagle dogs 8 screw-type implants (Hi Tec Implant Ltd)</p>	<p>4 implants plaque control 4 implants ligature induced breakdown. <i>Excessive load</i> Four different experimental categories 1) Loaded non-inflamed. 2) Loaded inflamed. 3) Unloaded non-inflamed. 4) Unloaded inflamed. 12 months. Clinical and radiographic examinations. Histological analyses</p>	<p>Overloading of implants with non-inflamed mucosa resulted in increased bone to implant contact.</p> <p>"Overloading aggravated the ligature/plaque induced bone resorption".</p> <p>No longitudinal assessments of radiographic bone level changes were made. Only data from histology, no longitudinal assessments.</p>

Authors/Title	Material	Methods	Main findings
<p>Hoshow et al. 1994</p> <p>“Mechanical loading of Brånemark implants affects interfacial bone modeling and remodeling”</p>	<p>Ten coon dogs 20 tibiae 2 Brånemark System® implants in each tibiae.</p>	<p><i>Extra-oral model</i></p> <p>Dynamic load Axial tension with a triangular waveform (300N maximum, 10N minimum, 330 N/s) for 500 cycles/day 5 consecutive days. Unloaded controls Fluorochrome labeling Light and scanning microscopy</p>	<p>Increased bone resorption around the neck of loaded implants. A decreased percentage of mineral tissue in the cortex within 350 micrometer of the implant 12 weeks after the applied loading protocol.</p>
<p>Duyck et al. 2001</p> <p>“The influence of static and dynamic loading on marginal bone reactions around osseointegrated implants: an animal experiment”</p>	<p>10 New Zealand rabbits 3 and 2 Brånemark System® implants in the right and left tibia.</p>	<p><i>Extra-oral model</i></p> <p>Static load Continuous horizontal force of 3kg – 2 weeks. Dynamic load Cyclic load of 1.5kg on a distance of 50 mm from the implant top 90 cycles/day during first week, 270 cycles/day during second week Total 2520 loading cycles Unloaded control Radiographic analyses Histological analyses</p>	<p>Static load No differences between loaded and unloaded implants Dynamic load No differences in bone to implant contact between loaded and unloaded implants. Significantly less bone density of the marginal part of the dynamically loaded implants compared to controls.</p>

Authors/Title	Subjects /implants	Follow-up /years	Methods	Main findings
Astrand et al. 2004 “Astra Tech and Brånemark system implants: a 5-year prospective study of marginal bone reactions”	66/ 31 Astra Tech implants 33 Brånemark System®	5	Prospective study Radiographic and clinical examination Bone level assessments at abutment connection, baseline and year 1, 3 and 5. Bone level at reference point implant insertion at the time of surgery.	Mean bone level relative to reference points. At Loading (Baseline) Upper Jaw Lower Jaw 1.47 mm 0.96 mm 2.10 mm 1.59 mm 5 years Upper Jaw Lower Jaw 1.91 mm 1.09 mm 2.20 mm 1.88 mm Brånemark Plaque 0-19% surfaces, BoP 0-5% surfaces The major postoperative changes of the marginal bone level took place between implant insertion and loading of the implants
Astrand et al. 2008 “Implant treatment of patients with edentulous jaws: a 20-year follow-up”	21/123 Brånemark System®	20	Prospective study Radiographic and clinical examination.	Plaque 22% BoP 20% Mean PPD 3.4 mm Mean bone loss; before 1 year 1.84 mm 1-20 years 0.53 mm
Cochran et al. 2009 “A prospective multicenter 5-year radiographic evaluation of crestal bone levels over time in 596 dental implants placed in 192 patients”	192/569 Solid screw or hollow-cylinder implants.	5	Prospective multi-center study Smokers ≥10 cigarettes not included. Radiographic and clinical examination Bone level assessments.	86% of the total mean bone loss occurred before loading of the implants.

Table 9. Bone loss at implants in smokers and non-smokers

Authors/ Year	Study design	Subjects	Main findings
Haas et al. 1996	Retrospective 22 months	107 smokers 314 non-smokers	Smokers had significantly more bone loss in the maxilla (3.95 mm vs. 1.64 mm) No differences in the mandible.
Lindqvist et al. 1997	Prospective 10 years	21 smokers 24 non-smokers	Smoking was significantly associated with implant bone loss. Smokers had greater bone loss at all implant positions (Mandible). Smokers ≥ 14 cigarettes/day had significantly more bone loss than smokers < 14 cigarettes. Smokers with poor oral hygiene had significantly greater bone loss than smokers with good oral hygiene.
Feloutzis et al. 2003	Retrospective 2-12 years, mean 5.6 years	14 smokers ≥ 20 cigarettes/day 39 non-smokers	Median annual bone loss rate Non-smokers 0.04 mm 0.18 mm Median absolute bone loss; Smokers ≥ 20 cigarettes/day 0.32 mm 1.98 mm ($p < 0.02$) ($p < 0.02$)
Nirizan et al. 2005	Prospective cohort 1-7 years (mean 3.8yrs)	59 smokers 102 non-smokers	Mean marginal bone loss Non-smokers 0.047 mm Smokers 0.153 mm ($p < 0.001$)
Roos- Jansäker et al. 2006c	Retrospective 9-14 years	57 smokers 80 non-smokers 81 ex-smokers	Smoking was significantly associated with peri-implant bone level ≥ 3 mm OR 10 (95% CI, 4.1-26)
Levin et al. 2008	Prospective 5-14 years Mean 6.14 Single implants	6 smokers 49 non-smokers 5 ex-smokers	Current and former smokers demonstrated significantly higher bone loss compared to non-smokers

Table 10. Peri-implant disease in smokers and non-smokers

Authors Year	Study design	Subjects	Main findings
Haas et al. 1996	Retrospective 22 months	107 smokers 314 non-smokers	Smokers had significantly higher BoP, PPD, mucosal inflammation in the maxilla. No differences in the mandible.
Mc Dermott et al. 2003	Retrospective 13 months	57 smokers 496 non-smokers	Smokers had an increased risk for inflammatory complications OR 3.26 (95% CI, 1.74-6.10) (infection, bone loss, pain, mobility, impaired wound healing, gingival recession).
Gruica et al. 2004	Retrospective 8-15 years	53 smokers 127 non-smokers	Smoking status was significantly associated with biological implant complications (suppuration, fistula and peri-implantitis).
Roos- Jansåker et al. 2006c	Retrospective 9-14 years	57 smokers 80 non-smokers 81 ex-smokers	Smoking was significantly associated with both mucositis OR 2.8 (95% CI 1.2-6.2) and peri-implantitis (BoP+bone loss \geq 1.8 mm after year-1) OR 4.6 (95% CI, 1.1-19).

Table 11. Peri-implantitis in subjects with a history of periodontitis

Authors	Study design Years	Subjects	Main findings
Hardt et al. 2002	Retrospective 5	25 Perio 25 Non-Perio	Perio: 64% peri-implant bone loss >2 mm Non-Perio: 24% peri-implant bone loss >2 mm Significant relationship between periodontitis experience and peri-implant bone level change. ($p < 0.05$)
Karoussis et al. 2003	Prospective 10	8 Perio 45 Non-Perio	Incidence of peri-implantitis (PPD ≥ 5 mm + BoP and radiographic signs of bone loss after year-1) Perio: 28.6% of implants Non-Perio: 5.8% of implants ($p < 0.0001$)
Rosenberg et al. 2004	Retrospective Up to 13	150 Perio 183 Non-Perio	“Peri-implantitis-related failures” Perio: 25.6% of implants Non-Perio: 5.4% of implants
Evian et al. 2004	Retrospective case series	77 Perio 72 Non-Perio	Implant failure – advanced bone loss infection, pain Perio: 21% of implants Non-Perio: 8% of implants Peri-implantitis significantly associated with a history of periodontitis
Roos-Jansäker et al. 2006b	Retrospective 9-14	94 Perio 62 Non-Perio	Perio = >30% teeth ≥ 4 mm bone loss Non-Perio $\leq 30\%$ teeth ≥ 4 mm bone loss. Peri-implantitis significantly associated with a history of periodontitis (OR 4.7 CI _{95%} 1.0–22)

Perio = Subjects with a history of periodontitis

Non-Perio = Subjects without a history of periodontitis

Table 12. The role of oral hygiene on peri-implant diseases

Author/Title	Patients /implants	Follow-up /years	Methods	Main findings
Jepsen et al. 1996 “Progressive peri-implantitis. Incidence and prediction of peri-implant attachment loss”	25 subjects 54 IMZ Overdentures	6 months	Clinical examination Plaque, BoP, PPD, CAL Probing force 0.15 – 0.35N Baseline and after 6 months Disease progression defined as CAL change of ≥ 1 mm in 6 months.	6% of sites, 19% of implants and 28% of subjects demonstrated disease progression. Significantly higher mean plaque scores in subjects exhibiting disease progression than in subjects with stable conditions (73% vs. 45%).
Lindqvist et al. 1997 “Association between marginal bone loss around osseointegrated mandibular implants and smoking habits: a 10-year follow-up study”	21 smokers 24 non-smokers	Prospective 10	Radiographic and clinical examination including: Level of oral hygiene 3 point scale 0=no plaque 1= local plaque (<25% of visible abutment area) 2= general plaque ($\geq 25\%$ of visible abutment area) 0= good, 2 = poor oral hygiene.	Mean bone loss (mm) BL-10 years smokers non-smokers Good oral hygiene 0.99 0.69 Poor oral hygiene 1.61 0.65 Smokers with poor oral hygiene had significantly greater bone loss than smokers with good oral hygiene ($p < 0.001$).

Author/Title	Patients /implants	Follow-up /years	Methods	Main findings
Ferreira et al. 2006 "Prevalence and risk variables for peri-implant disease in Brazilian subjects"	212/578 Brånemark System Implant Innovation Intra-lock	6 months- 5 years Retrospektive	Radiographic and clinical examination Peri-implantitis ("Vertical bone loss", PPD \geq 5 mm and BoP or pus) mPII median full mouth Plaque scores \leq 1 good $>$ 1- $<$ 2 poor \geq 2 very poor	Logistic regression analyses for the risk of peri-implantitis (OR 95% CI) Poor oral hygiene 3.8 (95% CI 2.1-6.8) Very poor oral hygiene 14.3 (95% CI 9.1-28.7) "The association between plaque scores and peri-implantitis seems to be dose dependent".
Serino et al. 2009 "Peri-implantitis in partially edentulous patients: association with inadequate plaque control"	23 consecutive patients referred for treatment of peri-implantitis	NA	Radiographic and clinical examination. PII Access to oral hygiene (OH). Peri-implantitis PPD \geq 6 mm, BoP and bone loss to \geq 3 threads.	peri-implantitis no peri-implantitis Number of implants No access to OH 53 28 Access to OH 5 23 Access to oral hygiene had a 65% positive predictive value and 82% negative predictive value for peri-implantitis. Conclusion: Accessibility for oral hygiene is related to presence or absence of peri-implantitis.

Table 13. Systematic review on the incidence of peri-implantitis

Authors/Title	Study design	Inclusion/exclusion criteria	Number of studies	Peri-implantitis definitions	Results/comments
Berglundh et al. 2002 "A systematic review of the incidence of biological and technical complications in implant dentistry reported in prospective longitudinal studies of at least 5 years"	Systematic review	Prospective longitudinal studies with follow-up ≥ 5 years. Prospective studies reporting life tables were included if 80% of initial subject sample was examined at 5 years.	Paper published until Dec 2001. 1310 screened 159 full-text analysis 51 selected 14 studies reported data on FCD's, 14 FPD's, 15 overdentures and 8 single tooth replacement. Number of patients/implants included 5-269/ 7-618.	Implants exhibiting; Radiographic bone loss, BoP and or pus according to Albetksson & Isidor (1994). Or PPD > 6 mm BoP Attachment loss/ Radiographic bone loss ≥ 2.5 mm.	Weighted means and 95% (C.I.) % implants with Peri-implantitis; FCD 0.71 (0.44-0.98) FPD 6.47 (5.26-7.69) Single tooth 0.31 (0.06-0.56) Overdentures 0.66 (0.55-0.77) % implants with bone loss ≥ 2.5 mm; FCD 3.78 (2.41-5.14) FPD 1.01 (0.79-1.23) Single tooth 1.28 (0.78-1.78) Overdentures 4.76 (0.55-0.77) Data on peri-implantitis were provided in 35-45% of studies. Data on crestal bone loss ≥ 2.5 mm were found in 20-50% of studies. Limited information of data describing frequency distributions of (1) probing assessments and (2) radiographic bone loss. No data describing the incidence of subjects exhibiting peri-implantitis

Table 14. Different criteria on peri-implantitis

Authors	N:o of Subjects/ implants	Implant System	Design/ Follow-up (years)	Diagnostic criteria	Peri-implantitis (%) Implants / Subjects
Ekelund et al. 2003	30/179	Brånemark System®	Prospective 20-23	Continuous bone loss Inflammation Pain	1-3 / NR
Karoussis et al. 2004	89/166	ITI®Dental Implant System (Mixed types)	Prospective 8-12	Radiographic signs of bone loss after year-1 PPD ≥ 5 mm. BoP	15.4 / NR
Roos-Jansäker et al. 2006b	216/987	Brånemark System®	Retrospective 9-14 (Mean 10.8)	Bone loss ≥ 1.8 mm after year-1 Bone level ≥ 3.1 mm from implant shoulder. BoP	6.6 / 16
Ferreira et al. 2006	212/578	Brånemark System® Implant Innovation Intra-lock	Cross-sectional 6months - 5 years (Mean 42,5 months) Prospective 20	“Vertical bone loss” PPD ≥ 5 mm BoP or pus	7.4 / 8.9
Åstrand et al. 2008	21/123	Brånemark System®	Prospective 20	Crater form type of bone loss BoP	2.4 / NR
Keller et al. 2009	39/NR	Brånemark System® Friadent ITI®Dental Implant System	Prospective 5	Bone loss ≥ 2.5 mm from Baseline BoP PPD ≥ 4 mm	27.4 / NR

Table 15. Prevalence of peri-implantitis (BoP + bone loss after year-1). Studies after 2002.

Authors	N:o of Subjects / implants included	N:o of Subjects / implants followed to final exam	Implant System	Design / Follow-up (years)	Mean Implant bone loss from BL	Mean bone loss year 1- final exam (mm)	Mean implant bone level (mm)	Bone loss ≥ 2.0 mm from BL (%) Implants / Subjects	Peri-implantitis (Bone loss+BoP) (%) Implants / Subjects	Comments
Leonardt et al. 2002	19/NR	15/57	Brånemark System®	Prospective / 10	1.7*	NR	1.9	18*	NA / NA	* from abutment connection
Ekelund et al. 2003	47/273	30/179	Brånemark System®	Prospective / 20-23	NA	NA	1.6	NA	NA / NA	Mandibles 14% implants bone level ≥ 3 mm below RP.
Karoussis et al. 2004	127/NR	89/166	ITI® Dental Implant System (Mixed types)	Prospective / 10 (8-12)	NA	NA	NA	NA	15.4 / NA	+ PPD ≥ 5 mm
Rasmusson et al. 2005	36/199/	28/155	Astra Tech TiOblast™	Prospective / 10	1.27	NA	1.27	NA	NA / NA	7 years radiographic data 7 % ≥ 2.8 mm bone loss
Jemt & Johansson 2006	76/450	25/150	Brånemark System®	Prospective / 15	0.5	NA	2.1	2	NA / NA	Maxilla Bone level ≥ 3 mm below RP; 14% implants, 44% subjects ≥ 1 implant.

RP = Reference point = Implant abutment junction

BL (Baseline) = Prosthesis insertion

NR = Not reported

NA = Not analyzed

Authors	N:o of Subjects / implants included	N:o of Subjects / implants followed to final exam	Implant System	Design / Follow-up (years)	Mean Implant bone loss from BL	Mean bone loss year 1-final exam (mm)	Mean implant bone level (mm)	Bone loss ≥ 2.0 mm from BL Implants (%)	Peri-implantitis (Bone loss+BoP) Implants / Subjects (%)	Comments
Ros-Jansäker et al. 2006b	294/	216/987	Brånemark System®	Retrospective / 9-14 (Mean 10.8)	NA	NA	NA	NA	24.8 / >56	“Without systematic supportive treatment”
Lekholm et al. 2006	27/69	17/26	Brånemark System®	Prospective 20	1.0*	NR	NR	NR	NA / NA	* from abutment connection Mean bone loss at teeth 0.7 mm.
Åstrand et al. 2008	47/NR	21/123	Brånemark System®	Prospective 20	1.72	0.53	2.33	10	NR	Radiographic data on 100 implants.
Pikner et al. 2009	640/346 2	NA	Brånemark System®	Retrospective 5-20	NA	NA	3.0	15.9**	NA / NA	** BL-15 years
Cochran et al. 2009	192/569	NR/453	Solid screw or hollow-cylinder implants	Prospective Multicenter 5	NA	0.19	2.84	NA	NA	Smokers ≥ 10 cigarettes not included

RP = Reference point = Implant abutment junction BL (Baseline) = Prosthesis insertion NR = Not reported NA = Not analyzed

Aims

The objectives of this series of investigations were:

- to assess the prevalence of subjects with progressive bone loss at implants with a function time of at least 5 years.
- to examine the clinical characteristics at implants in relation to radiographic evidence of a history of bone loss.
- to analyze the extent of peri-implantitis-associated bone loss with regard to implant position in the jaw and in the reconstruction.
- to analyze the pattern and severity of peri-implantitis-associated bone loss.

Material and methods

Subject sample

Study I

Patient files from 1346 patients who had attended annual follow up visits at the Brånemark Clinic, Public Dental Services, Göteborg, Sweden, during 1999 were analyzed. The subjects to be included were all provided with implant-supported (Brånemark System® Nobel Biocare, Göteborg, Sweden) fixed partial- or complete dentures or single tooth replacements with a documented function time in radiographs of at least 5 years. Subjects restored with removable prosthesis, i.e. overdentures, or who had received implant therapy in conjunction with osseous grafting or other augmentation procedures including the use of barrier membranes, were excluded. The number of individuals who fulfilled the inclusion criteria and the categories of individuals excluded for various reasons are described in Table 1.

Table 1. Number of included and excluded subjects and % distribution of subjects in different exclusion categories.

Total number	1346	
Number of included subjects	662	
Number of excluded subjects	684	
Reasons for exclusion;	No.	% of excluded subjects
Function time documented on radiographs < 5 years	574	83.9
Overdentures	24	3.5
Bone augmentation procedures	23	3.4
Function time < 5years due to loss of implants	15	2.2
Various reasons e.g. inadequate radiographs, initial therapy performed at other clinics.	48	7.0

Thus, radiographs of 662 subjects restored with fixed prosthesis on implants with a function time between 5 and 20 years were included in Study I.

Study II

Out of the 662 subjects in Study I, 184 had ≥ 1 implant with “progressive” bone loss. At the time for the clinical examination in Study II, 20 subjects were deceased and 4 had moved out of town. Hence, 160 subjects were invited for a clinical follow-up examination. 78 subjects declined the invitation for various reasons.

The final sample in study II comprised 82 subjects, i.e. 45% of the 184 previously identified individuals.

Study III and IV.

Intra oral radiographs from 182 of the 184 previously identified subjects with “progressive bone loss” (Study I) were used. Among the 1070 examined implants in this group of subjects, 419 implants exhibited a history of bone loss and were hence, included in the analyses.

Radiographic examination

Intra-oral radiographs were obtained at the Clinic of Oral & Maxillofacial Radiology, Public Dental Service, Göteborg.

Study I

Using a magnification lens (7x), the marginal bone level at implants being in function for 5 up to 20 years was assessed. Sites that demonstrated a bone level corresponding to the position of, or apical to the third marginal peak of a thread of an implant (threshold level; a position located about 3 mm apical of the abutment-fixture junction) were detected. In such sites, the corresponding radiographic bone level at the time of the one-year follow-up examination was determined. Thus, progressive bone loss at the identified implants was defined as bone level alterations occurring between the one-year examination and the ≥ 5 -year follow-up. Bone loss was recorded at an implant site if at least one surface demonstrated ≥ 1 thread (0.6 mm) bone loss. The

number of subjects who exhibited one or more implants with progressive bone loss to the threshold level was recorded.

Study III

The position of each implant was determined in relation to a preceding tooth position. Thus, the implants in the maxilla were assigned positions extending from 17 to 27 and the implants in the mandible were given positions from 47 to 37.

Study III and IV

The distance between the abutment-fixture junction and the most coronal position of bone to implant contact was assessed at the mesial and distal aspects of each of the 419 identified “affected” implants using a magnifying lens (7x) with a 0.1 mm graded scale. In cases where implants were displayed in different radiographs, the largest value for the distance was used. The measurements were performed on radiographs representing the 1-year follow-up and the end-point examination (5-23 years), respectively.

Examiners and measurement error

Study I

Four experienced clinicians (C.F, T.B, T.J and U.L) evaluated the implant bone levels. Full agreement was made between all 4 examiners regarding the selection of subjects with implants exhibiting progressive bone loss to the defined criteria.

Study III and IV

The bone level assessments were performed by two specialists in radiology at the Clinic of Oral & Maxillofacial Radiology, Public Dental Service, Göteborg (S.S-P, K.G). The inter-examiner variability was determined in results obtained from analyses of intra oral radiographs from 38 randomly chosen subjects (229 implants). The mean inter-examiner measurement error was 0.25mm (SD 0.66, $r= 0.82$) (Pikner et al. 2009).

Clinical examination

Study II

The clinical assessments were performed at the mesial, distal, buccal and lingual aspects of each implant and without removing the bridge constructions. The following variables were included; plaque (modified Plaque Index scores 1-3, Mombelli et al. 1987), probing pocket depth (PPD) measured to the nearest mm with a plastic periodontal probe (#12 Colorvue, Hu-Friedy, Chicago, USA) or a stainless periodontal probe (ZVA-084 #23, Lascod, Florence, Italy), bleeding on probing (BoP), suppuration following probing (Pus), presence of calculus on implants surfaces (Calc), and presence of soft tissue “recession” (exposed implant surface) i.e. the mucosal margin located apical of the fixture/abutment junction.

The clinical examination was performed by one examiner (C.F), who was blinded with respect to the number and position of implants with “progressive” bone loss.

Smoking habits were recorded and subjects were classified to the non-smoker category if they had never smoked or had quit smoking before the implant therapy was initiated.

Data analyses

All statistical analyses were 2-tailed and the null hypothesis was rejected at $p < 0.05$.

Study I.

Subjects were grouped according to presence (Group A) or absence (Group B) of implants exhibiting progressive bone loss. Differences between the groups regarding age, gender distribution, number of implants and function time were analyzed using the Student's *t*-test for unpaired samples and logistic regression analyses. The distribution of gender and construction types, i.e. fixed complete denture (FCD), fixed partial denture (FPD) and single tooth replacement (ST), as well as the jaw distribution

assessed for each group, were compared using Fishers Exact test and Chi-square analysis.

The number of recall visits and follow-up time prior to and including the year 1999 were retrieved from the patient's files. A ratio of follow-up time and number of recall visits was calculated for each subject.

Study II.

Subjects available (n=82) and not available (n=102) for the clinical examination were compared regarding age, number of installed and affected implants as well as function time. Differences between groups were analyzed using the Student's *t*-test for unpaired samples.

For the data description on the implant level, the findings of plaque, BoP, Pus, Calculus or "recession" at any aspect of an implant was used to identify an implant as positive for the various variables. For the PPD assessments the highest recorded value at the different aspects of the implant was used. Frequencies and mean values were calculated and differences between groups of subjects/implants were analyzed using the Student's *t*-test for unpaired samples and Fishers Exact test, respectively. The Student's *t*-test for paired samples was used for the intra-individual analysis of differences between implant categories (In 76 subjects with both categories of implants i.e. implants with and without progressive bone loss).

A dichotomous logistic regression model was formulated to evaluate the influence of various variables on the probability of identifying an implant with "progressive" bone loss. The variables that were significantly associated with a history of bone loss in the bivariate comparisons were entered into the model.

Study III.

The implants were grouped into either front (13-23 or 43-33) or posterior (17-14 or 47-44 and 24-27 or 34-37) position categories. Four groups of positions were hereby created; upper posterior (UP), upper front (UF), lower posterior (LP) and lower front (LF). The implant positions within the fixed reconstructions were also determined. Thus, an implant was defined as a “Mid” abutment if another implant within the reconstruction was positioned in both its mesial and distal aspect. In other cases the implant was classified as an “End” abutment. The percentage distribution of (i) affected (“progressive” bone loss) and non-affected implants and (ii) implant bone loss groups among the different position categories within the jaws and the fixed reconstructions was evaluated using the Fishers Exact test. The number of affected implants was related to the total number of implants in each subject and expressed as percentage. The mean value of bone loss between the 1-year and the end-point assessments of the selected implants was calculated.

A logistic multilevel regression model was applied to evaluate the influence of implant position (within the jaw or within the prosthetic reconstruction) and of type of prosthetic reconstruction on the risk for peri-implantitis-associated bone loss.

The model was applied to the data and the variables were estimated with a 2nd order PQL (penalised quasi-likelihood) procedure implemented in the software, and the significance of each covariate was tested using a Wald test. The covariates were estimated individually by adding them to the null model and testing the significance. The final model included all factors. The intra-class correlation (ICC), i.e. the proportion of the total variance attributed to the subject level, was approximated (Snijders & Bosker 1999).

A statistical package specifically designed for multilevel modeling was used (MLwiN 2.10, ©Multilevel Models Project Institute of Education, London UK).

Study IV

A mean value was calculated from the mesial and distal bone level measurements of each implant and the amount of bone loss that occurred from year 1 was determined. In the absence of radiographs representing the 1-year follow-up, information was obtained from the 2-year examination. In 25 of the 419 implants neither 1 nor 2 – year data were available and these implants were hence excluded from the analyses regarding bone level changes. For the remaining 394 implants the cumulative percentage of implants with different amount of bone loss after year-1 was calculated.

In order to analyze of bone loss patterns a multilevel *growth curve* model was built using the bone level of the implant as the dependent variable. The levels that were identified for the hierarchical analysis were the subject (n=182), the implant (n=419) and the event of the radiographic examination (measurement occasion; n=1785). The lowest level units were the implant bone level data obtained from the radiographic examinations during follow-up and the time-point of each examination was included as an explanatory variable. First, the hypothesis of a linear relation between bone loss and time was tested. Secondly, a curved relation model was built and compared to the linear model. Finally, the multilevel analysis included modeling the complex variance structures at the different levels.

Regression coefficients were estimated using iterative generalized least squares (IGLS) and the significance of each covariate was tested using a Wald test. Nested models were tested for significant improvements in model fit by comparing the reduction in -2LL (-2 log likelihood) with a Chi-squared distribution.

A statistical package designed for multilevel modeling (MLwiN 2.10[©], Centre for Multilevel Modelling, University of Bristol, UK) was used.

Results

Prevalence of progressive bone loss at implants (Study I)

28% (184) of 662 included subjects had one or more implants with progressive bone loss. The individuals in this group A carried a significantly larger number of implants than the subjects in whom no implants with progressive loss were detected (group B) (6.0 vs. 4.8). Neither age, gender, type of reconstruction, function time nor maxillary or mandibular position of the implants influenced the probability for subjects to exhibit bone loss. On the other hand, the number of installed implants per individual had a significant impact on the likelihood to exhibit ≥ 1 implants with progressive bone loss.

The mean ratio of follow-up time and number of recall visits was 1.4 ± 0.35 and 1.3 ± 0.32 in the group A (≥ 1 implants with progressive bone loss) and B respectively ($p > 0.05$).

Out of the total 3413 implants included in the study 423 implants (12.4%) demonstrated progressive bone loss.

Association between bone loss and clinical signs of pathology (Study II)

No statistically significant differences were found regarding age, gender, number of installed and affected implants or function time between the subjects available and not available for the clinical examination.

The intra-individual analyses revealed that the findings of BoP, pus, “recession” and PPD ≥ 6 mm were more common at implants with than without a history of progressive bone loss.

Presence of inflammation (BoP) was detected in 94% of the implants with a history of progressive bone loss. The logistic regression model demonstrated that the probability to detect the clinical variables pus, “recession” and PPD \geq 6 mm was between 2.3-4.6 times higher at implants with than without bone loss to the defined criteria. Furthermore, the findings of pus, “recession” and PPD \geq 6 mm at an implant in a smoking subject had a 69% accuracy in identifying history of progressive bone loss.

Extent of peri-implantitis-associated bone loss (Study I, II and III)

The majority of the 184 subjects in group A (history of progressive bone loss) had one or two affected implants (38.5 and 28.3%, respectively), the remaining 33.2% of the subjects exhibited \geq 3 implants with progressive bone loss to the threshold level. Almost 10% of the subjects demonstrated \geq 5 affected implants. The mean number and proportion of affected implants for each subject were 2.3 and 41.8 % (range 7%-100%), respectively. Smokers had a significantly larger number of affected implants than non-smokers (3.2 vs. 1.7).

Implants with progressive bone loss occurred in all jaw positions. The largest frequency of affected implants was found in the lower front region (52%). The proportions of affected implants in other positions were 39% (Upper Front), 35% (Lower Posterior) and 30% (Upper Posterior). The difference in percentage of affected implants between the lower front position and the other regions was statistically significant.

The number of implants supporting FCDs was about 3 times larger than that in FPDs. No difference in the proportion of affected implants between the two types of prosthesis was observed. The majority of implants in FCDs was in “Mid” positions (512 vs. 283), while in FPDs most implants were classified as “End” abutments (165 vs. 107). The proportion of affected implants was significantly larger among “Mid”

than “End” abutments in both types of reconstructions (FCD; 43% vs. 31% and FPD; 49% vs. 35%).

The stepwise multilevel logistic model with the outcome variable “peri-implantitis-associated bone loss” suggested that neither the implant position within the prosthetic reconstruction, i.e. “Mid” or “End” abutment, nor implants supporting different types of prosthetic reconstruction i.e. FPD or a FCD did affect the occurrence of peri-implantitis-associated bone loss. Only the position of the implant in the lower front region increased significantly the probability for implants to exhibit peri-implantitis-associated bone loss (OR 2.4 CI_{95%} 1.5–3.9). The model also disclosed that 11% of the unexplained variance was attributable to differences between subjects.

Severity of peri-implantitis-associated bone loss

Radiographic observations

About 42% of the affected implants had a bone level corresponding to 3 threads, 24% of the implants had lost bone support to the 4th thread and the remaining 33% of the identified implants exhibited bone levels from 5 threads or more (Study I).

The mean bone loss was 1.68 ± 1.32 mm. Bone loss ≥ 1 mm occurred in 68% of the implants, while 32% of the implants exhibited ≥ 2 mm bone loss after the first year in function. Bone loss of ≥ 3 mm was observed in 10% of the implants (Study IV).

The predicted average bone level (95% CI) was -2.15 mm (-2.06, -2.24) at year 1, -2.95 mm (-2.83, - 3.06) at year 5, -3.60 mm (-3.46, -3.75) at year 10, -4.10 mm (-3.84, -4.35) at year 15 and -4.64 mm (-3.76, -5.52) at year 20. The estimate was reliable up to 17 years of follow up (Study IV).

Clinical findings (Study II)

All examined subjects had at least one implant with BoP, while suppuration after probing at any implant was detected in 33% of the subjects. Probing pocket depth of ≥ 6 mm was observed in 51% and soft tissue “recession” in 59% of the subjects. Few subjects demonstrated calculus on implant surfaces (13%).

The proportion implants with progressive bone loss that demonstrated Pus and PPD ≥ 6 mm was significantly higher in smokers than in non-smokers (25% vs. 6 % and 40% vs. 20 %).

94% of the implants with a history of bone loss had at least one surface with BoP, while suppuration after probing at any surface was detected in 18.8% of the implants. Probing pocket depth of ≥ 6 mm was observed in 34.5% and soft tissue “recession” in 43.2% of the implants. Few implants demonstrated calculus on implant surfaces (7.1%). The mean PPD was 4.8 mm.

Pattern of peri-implantitis-associated bone loss

The multilevel model revealed that (i) bone loss over time showed a non-linear pattern, (ii) the rate of bone loss increased over time and (iii) the variance increased with time for all levels and was after 19 years mostly due to variation between subjects.

Main findings

Study I

- 28% (182) of 662 subjects treated with fixed implant-supported prosthesis had one or more implants with progressive bone loss.
- The individuals in this group carried a significantly larger number of implants than the subjects in whom no implants with progressive loss were detected.
- Out of the total 3413 implants included in the study 12.4% demonstrated progressive bone loss.

Study II

- The frequencies of bleeding on probing, pus, recession and probing pocket depth ≥ 6 mm were significantly higher at implants with than without progressive bone loss.
- Smokers had larger numbers of affected implants than non-smokers and the proportion of affected implants that exhibited pus and PPD ≥ 6 mm was higher in smokers than in non-smokers.
- The findings of pus, recession and PPD ≥ 6 mm at an implant in a smoking subject had a 69% accuracy in identifying history of progressive bone loss.

Study III

- About 40% of the implants in each of the 182 subjects had peri-implantitis-associated bone loss.
- Peri-implantitis occurred in all jaw regions but was more common among implants in the lower front region.

Study IV

- The average bone loss at the affected implants after the first year of function was 1.65 mm and 32% of the implants demonstrated bone loss ≥ 2 mm.
- The bone loss showed a non-linear pattern and the rate of loss increased over time.
- The pattern of peri-implantitis-associated bone loss was similar within the same subject.

Concluding remarks

Study design

Treatment planning involves decision-making and, usually the patient and the dentist discuss different treatment options. In this process it is important to inform the patient regarding technical and biological complications that may occur in relation to different treatment alternatives. To answer the question on how often a patient treated with implant-supported prosthesis will experience either loss of implants or loss of supporting bone around implants requires that data on a subject level are available. In other words, concerning the latter case, the prevalence of subjects with bone loss at implants has to be evaluated.

Cross-sectional random sample

The prevalence of a disease describes the number of diseased cases that is present in a population at one point in time (Newman Dorland 1994). Thus, information on the prevalence of a disorder must be generated from data assessed in studies with a cross-sectional design. The majority of studies evaluating implant therapy have a longitudinal design and, hence, the information retrieved from this kind of studies is limited and describes possible the incidence of new cases over time. Furthermore, the available information regarding crestal bone loss around implants was in most cases presented as implant-based data. (Berglundh et al. 2002, Table 15).

The objective of Study I was to assess the prevalence of subjects that exhibited peri-implant bone loss at ≥ 1 implant. Thus, a cross-sectional study design using a sample of subjects treated with prosthesis on implants was required. The subject sample in Study I comprised patients that had been treated with implant-supported prosthesis and were enrolled in a recall program at the Brånemark clinic, Public Dental Services, Göteborg, Sweden. A data list of 1346 patients that had visited the clinic for a scheduled annual check-up during year 1999 was available and the patient files and radiographs were analyzed according to defined inclusion and exclusion criteria.

Subjects with a history of different complications including of progressive bone loss around implants may have been scheduled for more frequent follow-up examinations than subjects without such a complication. Thus, subjects with progressive bone loss might have been overrepresented in the study sample. To clarify this issue the follow-up frequencies in the two groups with (A) and without (B) progressive bone loss were analyzed. The number of recall visits and the follow-up time prior to and including the year 1999 were retrieved from the patient's files. A ratio of each subject's follow-up time and the number of recalls was formulated and differences between the subjects with (A) and without (B) bone loss were analyzed. No significant difference in the mean ratio between the two groups was observed. The present sample may therefore be regarded as a representative group of subjects treated with fixed dentures on implants.

Exclusion criteria

The consensus report from the 3th European Workshop on Periodontology (1999) recommended that studies evaluating the outcome of implant therapy should have a follow-up time of ≥ 5 years (Wennström & Palmer 1999). Bone loss at teeth associated with periodontitis occurs in the majority of individuals as a slow chronic process (Papapanou et al. 1989, Norderyd et al. 1999, Schätzle et al. 2003). Peri-implantitis has many features in common with periodontitis. Implants exhibiting early (< 5 years) bone loss leading to loss of function may not only be associated with peri-implantitis and were, hence, not included in the analyses. Thus, in Study I only subjects and implants with a function time of ≥ 5 years were included. Subjects restored with removable prosthesis, i.e. overdentures or who had received implant therapy in conjunction with osseous grafting or other augmentation procedures including the use of barrier membranes, were not included due to the expected different outcome regarding implant complications. In the systematic review by (Berglundh et al. 2002), it was demonstrated that implants supporting overdentures exhibited higher frequencies of biological and technical complications than implants used in fixed reconstructions.

Drop-out analyses

The aim of Study II was to describe the clinical characteristics at implants in relation to radiographic evidence of bone loss and the objective was to include all 184 subjects with a history of bone loss identified in Study I. At the time of the clinical examinations 20 subjects were deceased and 4 had moved out of town. Hence, 160 subjects were invited for the clinical follow-up examination. 78 subjects declined the invitation for various reasons and the final sample consequently comprised 82 subjects, i.e. 45% of the 184 previously identified individuals. The drop-out analysis based on data retrieved from Study I revealed no statistically significant differences between subjects available and not available for the clinical examination. Similar analyses performed in other studies have indicated that dropouts have worse conditions with respect to the evaluated variables than those in subjects willing to participate (Roos-Jansåker et al. 2006b, Jemt & Johansson 2006). Thus, the examined subgroup was considered to be a representative sample.

Data analyses

Retrospective analyses of bone level changes around implants pose difficulties due to variability in the study material and thereby a large heterogeneity in the data set. In addition, the data is often hierarchical in structure (subjects/implants/measurement occasions) and there is a variation with respect to the follow-up time between subjects and to the number of and time between radiographic examinations. A complex pattern of variability on the different levels further complicates the analyses.

Multilevel models

Multilevel models are useful for the analyses of complex patterns of variability (Snijders & Bosker 1999). This method has been used in studies analyzing periodontal disease progression. Albandar & Goldstein (1992) in a model paper suggested that multilevel models had several advantages over unilevel methods, such as statistical validity and efficiency. Other suggested advantages were that analyses can be made

also in cases where the study material may be unbalanced. Thus, the number of observations needs not to be equal in all subjects, the observations may be measured at different time points and different sites may have different numbers of observations. The ability to incorporate explanatory variables at different levels in multilevel modeling was also pointed out (Albandar & Goldstein 1992). Gilthorpe et al. (2003) and Tu et al. (2004) applied multilevel modeling in the analysis of periodontal disease progression in a cohort of 100 young males. It was reported that the model provided new information on the dynamic hierarchical system of periodontal disease progression and that both “linear” and “burst” concepts had validity at different levels of this system.

Multilevel *growth curve* models were originally developed to analyze anthropometric data i.e. measurements of the human individual for the purposes of understanding human physical variation (Goldstein 1979). In Study IV a multilevel *growth curve* model was applied to analyze implant bone loss patterns using the bone level obtained from the radiographic examinations during follow-up as the dependent variable (Snijders & Bosker 1999). The time-point of each examination was included as an explanatory variable. First, the hypothesis of a linear relation between bone loss and time was tested. Secondly, a curved relation model was built and compared to the linear model. In addition, the multilevel analysis included modeling of the complex structure of variance at the different levels.

Association between clinical signs of pathology and peri-implant bone loss

The findings in Study II suggest an association between clinical signs of inflammation and bone loss at implants. Association between clinical signs of inflammation and bone loss at implants is supported in the literature (Table 1 and 2). Mombelli et al. (1987) compared probing pocket depth at implants with and without bone loss in patients with implant supported overdentures. It was reported that the probing depth varied between 6 and 12 mm at implants exhibiting bone loss while the probing depth

at “successful” implants was ≤ 4 mm. Hultin et al. (2002) examined patients with and without signs of peri-implantitis and observed that the mean PPD was significantly larger at implants with marginal bone loss compared to implants with normal bone height (4.3 mm vs. 2.2 mm). Lang et al. (1994) determined the histological level of probe penetration in healthy and inflamed tissues around implants inserted in Beagle dogs. Probes were placed with a standardized force of 0.2N and the histological examination revealed that the probe penetration increased with increasing level of inflammation. The authors concluded that, “probing around implants represents a good technique for assessing the status of peri-implant mucosal health and disease”. Similar results were presented in an experiment in monkeys. Schou et al. (2002) who utilized a comparable experimental model as presented by Lang et al. (1994), demonstrated that the probing depth was consistently greater at implants with peri-implantitis than at implants with healthy mucosa or mild mucositis.

The value of using clinical variables in the evaluation of implant therapy was further illustrated in two short-term clinical studies. Brägger et al. (1996) studied the changes in probing attachment level in relation to radiographic evidence of bone loss. It was reported that early changes in probing attachment level predicted future peri-implant bone loss. In the study by Nishimura et al. (1997) the included subjects were recalled for prophylaxis once every month over 4 years. Both the peri-implant bone level and mean PPD and PAL remained stable in this well maintained group of subjects. Hence, the shallow peri-implant pockets over time were associated with stable peri-implant bone levels. Furthermore, studies have indicated that the absence of bleeding following peri-implant probing is a reliable predictor for stable and healthy peri-implant conditions (Jepsen et al. 1996, Luterbacher et al. 2000).

An initial radiographic examination at the time of prosthesis insertion to establish a bone level reference has been recommended (Lang et al. 2004). The association between clinical and radiographic findings suggests that the decision for future radiographic examination should be based on the results from the clinical

examination. Thus, the clinical conditions of the peri-implant tissues should be examined on a regular basis to identify signs of inflammation and clinical findings, such as increased PPD and BoP/pus, indicate the need for radiographic examination. This is in line with the recommendations by the international Commission on Radiation Protection (ICRP 60, 1991) who stated that all radiographic examinations should be justified and optimized. This was further supported by Gröndahl & Gröndahl (2008) who stated that “it is the clinical need of radiographic examination that can make the radiographic examination justified”.

A prerequisite to use clinical parameters when evaluating the condition of the peri-implant tissues is that the design of the prosthetic construction allows accessibility to probe around the implants. van Steenberghe et al. (1993) examined 460 implants supporting 174 bridges over a period of 3 years and reported that 33% of the assessed sites were not accessible to probe. In Study II, 15% (data not shown) of the sites to be probed were excluded due to limited accessibility but all implants could be probed at ≥ 1 site (buccal, lingual or interproximal aspect).

Prevalence of subjects exhibiting peri-implantitis

In Study I, it was reported that about 28% of 662 subjects with implant-supported prosthesis had ≥ 1 implants with progressive bone loss. Study II demonstrated an association between clinical signs of pathology and bone loss at implants. In addition, bleeding on probing was detected in 94% of the implants with a history of bone loss. Thus, according to the definition of peri-implantitis and the findings that implants with a history of bone loss also exhibited BoP suggests that the prevalence of subjects with peri-implantitis within the studied population was about 28%.

There is limited information in the literature with respect to the prevalence of subjects exhibiting peri-implantitis. This statement was supported in a recent review by Zitzmann & Berglundh (2008) who evaluated the literature on the prevalence of peri-

implant disease. They concluded that “cross-sectional studies on implant-treated subject are rare and data from only 2 study samples were available”.

One of the studies included in the review by Zitzmann & Berglundh (2008) analyzed the prevalence of peri-implantitis among 218 subjects at 9-14 years after implant placement (Roos-Jansåker et al. 2006b). Bone-level assessments were performed in intra-oral radiographs and the clinical conditions of the peri-implant tissues were examined using clinical variables. Roos-Jansåker et al. (2006b) reported that 16% of the subjects and 6.6% of the implants had peri-implantitis using different disease criteria than in Study I of the present series. While Roos-Jansåker et al. (2006b) reported on results based on subjects that exhibited ≥ 1 implant with ≥ 1.8 mm (3 threads of a Brånemark implant) bone loss after year-1 (+ BoP) the findings in Study I were based on implants with ≥ 1 thread (≥ 0.6 mm) of bone loss after year-1. In the review by Zitzmann & Berglundh (2008) bone loss + BoP was applied as the criteria for peri-implantitis (as in Study I and II). Recalculation of the data from Roos-Jansåker et al. (2006b) revealed that almost 25% of the implants and $> 56\%$ of the subjects were diagnosed as having peri-implantitis (Zitzmann & Berglundh 2008). In other words, the subject sample in the study by Roos-Jansåker et al. (2006b) presented higher prevalence figures compared to the results in Study I. Differences in the maintenance therapy between the two subject samples may be one explanation to the different outcome. Thus, the majority of subjects in Study I were enrolled in a regular follow-up program at the Brånemark Clinic, while many of the subjects in the study by Roos-Jansåker et al. (2006b) were not included in a follow-up program.

Extent and severity of peri-implantitis

The finding in Study III that peri-implantitis occurred in all jaw regions but was more common among implants in the lower front region is in agreement with previous observations. Thus, Lindquist et al. (1996) evaluated 47 subjects who were treated with mandibular FCDs supported by Brånemark implants. After 12-15 years the implants in

anterior positions had a more pronounced bone loss compared to implants placed in posterior regions. In a 10-year follow-up study on implant-supported FCDs in 13 subjects it was reported that the mean bone loss was similar in the maxilla and the mandible (Carlsson et al. 2000). Anterior implants exhibited more bone loss than posterior ones in the mandible, while no such difference was found in the maxilla.

In the description of extent of peri-implantitis the analogy to periodontitis is evident. Laurell et al. (2003) reported on periodontal bone loss around 998 teeth in 433 subjects. Although all tooth categories demonstrated signs of bone loss at the 17-year follow-up, lower incisors and upper molars exhibited more pronounced bone loss than other sites. In a 10-year prospective study Paulander et al. (2004) evaluated intra-oral pattern of periodontal bone loss. It was reported that mandibular incisors showed larger amount of bone loss than other tooth categories. These observations are in accordance with data presented in Study III and indicate that although destructive disease in the tissues surrounding teeth and implants may occur in all areas of the jaws, anatomical aspects in the lower front region may render an risk for periodontal and peri-implant bone loss.

An interesting observation in study II was that the extent and severity of peri-implantitis was higher in smokers than in non-smokers. Thus, smokers had a higher prevalence of implants exhibiting peri-implantitis and the proportion of affected implants that exhibited pus and PPD ≥ 6 mm was higher in smokers than in non-smokers. Although the reason for these differences are not fully understood, similar results are reported in the literature (Strietzel et al. 2007, Table 9, 10). For example, Haas et al. (1996) examined the association between smoking and the presence of peri-implantitis in 107 smokers and 314 non-smokers. Smokers had higher bleeding scores, more signs of clinical inflammation, deeper probing pocket depths and more radiographic bone loss around implants than non-smokers. Furthermore, Roos-Jansåker et al. (2006c) reported that smoking was significantly associated with peri-

implantitis (OR 4.6 CI_{95%}4.1-19). Thus, smokers should be informed about the association between smoking and increased risk for peri-implantitis.

The severity of peri-implantitis was addressed in the above-mentioned study by Roos-Jansåker et al. (2006b). The relative proportion of implants with peri-implantitis that exhibited bone loss of ≥ 3 peaks of a thread was about 27%. This finding accords with the results in Study IV, in which, 32% of the affected implants had bone loss ≥ 2 mm. Although the prevalence of implants exhibiting peri-implantitis was higher in the study by Roos-Jansåker et al. (2006b) compared to the results in Study I and II, the relative proportion of implants exhibiting pronounced bone loss (≥ 1.8 mm) was similar in the two studies.

Study I demonstrated that 33.2% of the 184 subjects with a history of progressive bone loss (group A) exhibited ≥ 3 implants with progressive bone. This finding suggests that a sub-group of about 10 % of the 662 subjects had ≥ 3 affected implants.

Pattern of peri-implantitis-associated bone loss

An important finding from the multilevel *growth curve* model in Study IV was that the pattern of peri-implantitis associated bone loss was curved and that the rate of bone loss increased over time.

Several success criteria for individual implants or implant systems has been proposed (Schnitmann & Schulmann 1979, Albrektsson et al. 1986, Smith & Zarb 1989, Albrektsson & Zarb 1993, Wennström & Palmer 1999). According to Albrektsson et al. (1986) marginal bone loss should not exceed 1.5 mm during the first year in function and be < 0.2 mm/year thereafter. Success criteria expressed as a minimum amount of annual bone loss implies that the bone loss pattern in linear. Since the findings that peri-implantitis associated bone loss showed a non-linear pattern and that

the rate of bone loss increased over time as suggested in study IV, the commonly used calculation on annual bone loss for the function period of implants becomes misleading.

Furthermore, the general concept of using annual bone loss around implants as a criterion for implant success may be questioned as the suggested values of < 0.2 mm annual bone loss after the first year in function (Albrektsson et al. 1986) may include levels of bone loss that correspond to the progression of rapid and moderate forms of periodontitis (Papapanou et al. 1989, Norderyd et al. 1999, Schätzle et al. 2003). Success criterion that includes a certain minimum amount of annual bone loss entails that continuous bone loss around implants is a normal condition. This issue is not clarified in the literature.

Conclusions and future considerations

There is limited information on the prevalence of subjects that exhibit peri-implantitis. This thesis focused on the prevalence, extent and severity of peri-implantitis and new information has been presented. About 28% of subjects restored with fixed dentures on implants with a mean function time of about 10 years exhibited peri-implantitis ≥ 1 implant. A subgroup of about 10 % of the subjects had ≥ 3 affected implants.

The majority of studies evaluating the long-term outcome of implant therapy are so-called efficacy studies, i.e. studies evaluating implant therapy performed under ideal conditions. Such studies have high internal validity and, hence, the results may not directly be extrapolated to all patients restored with implants. Effectiveness studies, on the other hand, should evaluate implant therapy performed in daily practice, e.g. in dental clinics with a large variation with respect to training, experience, personnel, equipment, support and implant systems (Davies et al. 2005). To further gain information on the outcome of implant therapy, effectiveness studies are needed using a cross-sectional study design with large samples of subjects treated with implants.

Conclusions

This series of studies have demonstrated that:

- (i) prevalence of progressive bone loss at implants assessed from subject-based data is higher than that evaluated from implant-based data,
- (ii) there is an association between clinical signs of pathology and bone loss at implants,
- (iii) peri-implantitis occurs in all jaw positions and that an “end”-abutment position in a fixed reconstruction is not associated with an enhanced risk for peri-implantitis,
- (iv) peri-implantitis-associated bone loss varies between subjects and is in most cases characterized by non-linear progression with increasing rate over time.

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