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Peri-implantitis

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At the turn of the millennium, marketing estimates indicated that over 2 million dental implants are installed annually, and this number is expected to rise further over the next few years. It is evident that the installation of oral implants is a routine procedure in the reconstruction of fully or partially edentulous individuals. Like natural teeth, the artificial abutments penetrate the oral mucosa and reach the contaminated oral cavity. When challenged by bacteria within the biofilms formed on implant surfaces, the peri-implant tissue response seems to follow patterns similar to those of the periodontal tissues in a susceptible host [1–3]. Documentation of implant therapy has so far included only exceptional reports on the destructive lesions around implants [4–6]. A systematic review of the incidence of biologic implant complications reported that data on peri-implantitis were provided in only 35% to 45% of the included studies on overdentures, fixed complete dentures, and fixed partial dentures [7]. One factor that may have influenced the detection of peri-implantitis is the historical dogma that probing around implants should be avoided. Another possible reason may be the rare occurrence of peri-implantitis in studies of short-term duration; observation periods exceeding 5 years may be required to detect tissue destruction around implants [8].

Peri-implantitis is defined as an inflammatory reaction with the loss of supporting bone in the tissues surrounding a functioning implant [9]. The overall frequency of peri-implantitis was reported to be 5% to 8% for selected implant systems [7]. A site-specific infection comparable to chronic

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periodontitis, possibly related to implant design and surface characteristics, may have caused the difference in prevalence of peri-implantitis in the various implant systems. Data on the transmission of periopathogenic microorganisms from the periodontal pocket to the peri-implant region have been presented [10]. In a study of partially edentulous patients, van Steenberghe et al [11] found a higher number of late fixture losses in patients with larger amounts of plaque accumulation.

In some studies, implant loss has clustered in a small subset of patients, which may indicate the existence of a high-risk group for implant failure. Other studies, however, have taken the opposite view. Prospective longitudinal data show that the incidence and the prevalence of radiographic bone loss vary among patients. An association between periodontal and peri-implant conditions has been reported. The higher the full-mouth clinical probing pocket depth and the greater the full-mouth attachment loss, the higher the attachment loss is to be expected around implants in the susceptible patient. In individuals with a history of chronic periodontitis, the incidence of peri-implantitis was four to five times higher than in individuals with no history of periodontitis [1]. Longitudinal bone loss around implants was correlated to previous experience of reduced periodontal bone support. Thus, periodontitis-susceptible subjects may show increased implant failure rate and marginal bone loss [12]. Smoking has also been reported to significantly correlate to marginal bone loss around implants [1].

Soft tissue around implants

The soft tissue surrounding healthy osseointegrated dental implants shares anatomic and functional features with the gingiva around teeth. The microstructure has been described in dog models and in human tissues. The outer surface of the peri-implant mucosa is lined by a stratified keratinized oral epithelium that is continuous with a junctional epithelium attached to the titanium surface by a basal lamina and by hemidesmosomes. The 2-mm long nonkeratinized junctional epithelium is only a few cell layers thick in the apical portion and separated from the alveolar bone by 1 to 2 mm of collagen-rich connective tissue. This 3- to 4-mm "biological barrier," formed irrespective of the original mucosal thickness, protects the zone of osseointegration from factors released from plaque and the oral cavity [13] (Fig. 1).

Unlike the gingiva around teeth, the connective tissue compartment between the junctional epithelium and the alveolar bone consists of a scarlike connective tissue, almost devoid of vascular structures, with greater amounts of collagen and fewer fibroblasts [14]. The fibroblast-rich barrier next to the titanium surface has a high cell turnover, and fibroblasts may play an important role in establishing and maintaining the mucosal seal.

In animal models and in humans, the inflammatory infiltrate in peri-implant tissue and the response to plaque accumulation have been described. As in gingivitis around natural teeth, an inflammatory infiltrate forms in the

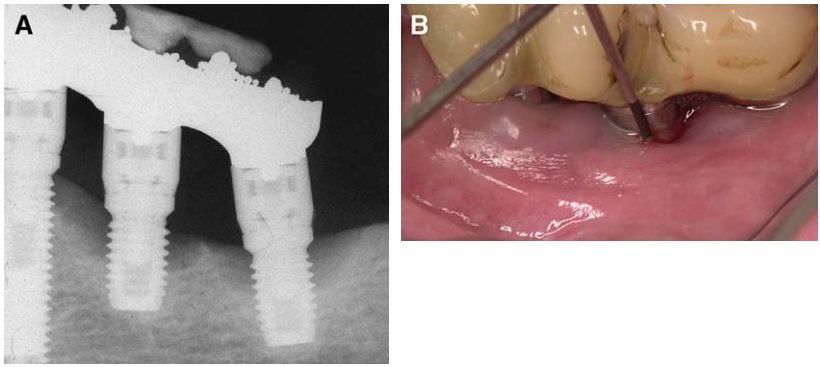

Fig. 1. (*A*) Radiograph from two implants exhibiting peri-implantitis, with crater- or saucer-shaped defects formed in the left side of the mandible. (*B*) Probing assessment (8 mm) at one of the implants with peri-implantitis. Note the bleeding and suppuration following probing.

connective tissue in response to microbial colonization of the titanium surface [15]. The infiltrate represents the local host response to bacterial accumulation and proliferates in an apical direction when the time for plaque accumulation is prolonged. The peri-implant mucosa is similar to the gingiva around teeth as regards function and host response to infection [16]. An inflammatory cell infiltrate of equal size and composition has been found in clinically healthy tissues of gingiva and in peri-implant mucosa [17]. Results from immunohistochemical and morphologic analyses show that inflammatory cells (eg, neutrophils, lymphocytes, macrophages, and plasma cells) are present. Functional adaptation of the junctional epithelium occurs, although its origin differs from that around the teeth (Fig. 2).

Periodontitis and tooth loss

Epidemiologic studies show that although the incidence of periodontitis increases with age, only a limited number of persons develop the more severe forms. Several studies report that 5% to 10% of the adult population has severe disease, which is unaffected by oral hygiene habits. This prevalence is similar in various parts of the world. In addition, the number of persons developing severe periodontitis appears to be consistent over time [18].

Periodontitis and other reasons for tooth extraction have been studied in various populations. Caries is the main reason for tooth extractions in persons up to 40 years of age. Above the age of 40 years, periodontitis accounts for about 30% to 35% of tooth extractions and caries and caries-related reasons account for 50% of tooth extractions. In older age groups, however, tooth extractions are performed equally due to periodontitis and caries. In general, the main risk factors for tooth loss include age, smoking, socioeconomic behavioral traits, and periodontitis scores. It therefore seems

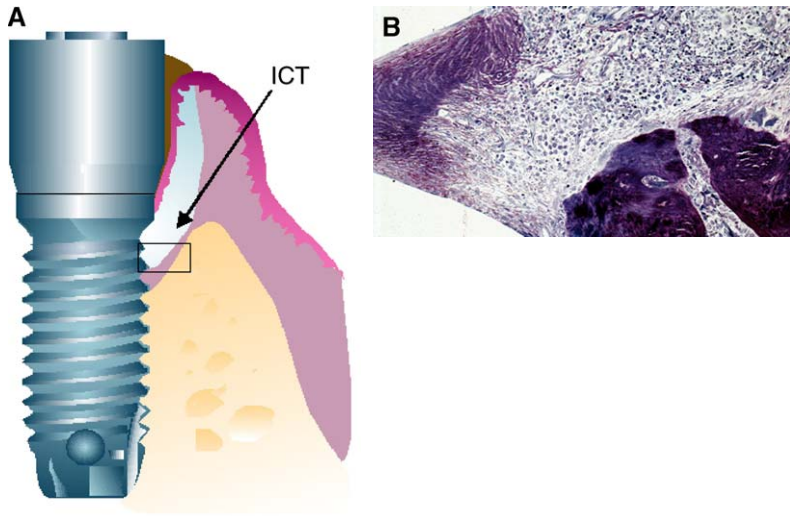

Fig. 2. (*A*) Schematic illustration of a peri-implantitis lesion. Note the apical extension of the inflammatory cell infiltrate (ICT). (*B*) Histologic section from an experimental peri-implantitis lesion illustrating the outlined area in *A*. Note the inflammatory cells close to the bone and the osteoclasts on the bone surface.

reasonable to assume that in partially edentulous patients, 30% to 40% of those given dental implants have lost their teeth due to periodontitis.

Microbiology of the peri-implant area

The transmucosal abutment of osseointegrated dental implants serves as a surface for bacterial colonization of microbial biofilms. Like the gingival crevice around the natural tooth, the peri-implant mucosa, which covers the alveolar bone, is closely adapted to the implant. Microbial colonization and the ensuing inflammatory reactions in the peri-implant tissues might be analogous to key events in the pathogenesis of periodontitis. In partially edentulous subjects, the developing microbiota around implants closely resembles the microflora of naturally remaining teeth [19,20]. A history of periodontitis and the presence of putative periodontal pathogens are factors that can influence the condition of peri-implant tissues in partially edentulous subjects. Quirynen and Listgarten [21] used phase-contrast microscopy to evaluate the impact of periodontitis around remaining teeth and probing depth around the implants on the composition of the peri-implant subgingival flora in partially edentulous subjects. The investigators found that the subgingival microflora around implants harbored increased spirochetes and motile rods compared with teeth present in the same jaw. Samples from deep peri-implant pockets ($\geq$4 mm) in the residual dentition of patients with chronic or refractory periodontitis showed significantly higher proportions of

spirochetes and motile rods than samples from periodontally healthy patients with comparable probing pocket depths.

Papaioannou et al [22], also using phase-contrast microscopy and DNA probes, determined the prevalence of putative periodontal pathogens in partially edentulous and edentulous patients with a history of periodontal disease. The microbiologic profiles were similar around teeth and dental implants of equal pocket depth, which may indicate that pockets around teeth can serve as a reservoir for putative periodontal pathogens. This finding was confirmed in several studies on partially edentulous patients [23]. As early as 1 month after implantation, putative periodontal pathogens were detected around the implants of partially edentulous patients [19].

Implant failures due to infection are characterized by a complex peri-implant microbiota resembling that of adult periodontitis. In edentulous subjects, *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* are not as frequently associated with peri-implant infection as in dentate subjects [4]. Danser et al [24] reported that after total extraction in patients with severe periodontitis, *Porphyromonas gingivalis* could no longer be detected on the mucosal surface of edentulous patients. Furthermore, *A actinomycetemcomitans* and *Porphyromonas gingivalis* could not be isolated at the peri-implant pockets in these patients after insertion of implants [25].

In addition to the dark-pigmented, gram-negative anaerobic rods, other bacterial species are associated with peri-implant infections (eg, *Bacteroides forsythus, Fusobacterium nucleatum, Campylobacter, Peptostreptococcus micros* and *Prevotella intermedia*) [26]. Organisms that are less frequently associated with periodontitis, such as *Staphylococcus* spp, enterics, and *Candida* spp, have also been found in peri-implant infections [27,28]. Longitudinal data on implants in partially edentulous persons with a history of periodontal disease, however, have shown no association between periodontal pathogens and loss of attachment at implants after 36 months of function [19,29]. This finding corresponds to the situation observed in periodontitis: putative periodontal pathogens can also be detected in apparently healthy periodontal pockets and at sites with no periodontal progression. Thus, it has been suggested that the pathogens in peri-implant infections propagate from the periodontopathic bacteria of natural teeth into the saliva and become transmitted to the vicinity of implants [10].

Inflammation leading to tissue destruction

Inflammation is a complex reaction of the body in response to an infectious agent, antigen challenge, or injury. An accumulation of microbes at the peri-implant/mucosal margin is followed by a local inflammatory response. Within 10 to 20 days of plaque accumulation on teeth, clinical signs of inflammation can be seen. Even during early stages of inflammation, considerable tissue damage occurs. As reported in dogs, the collagen content of the inflammatory lesion in the gingival of teeth decreases by approximately

30% after 28 days of undisturbed plaque accumulation [30]. Thus, the cells in the inflammatory lesion cause considerable tissue damage in their effort to combat the invading microorganisms. Accumulation of plaque in the gingival crevice aggravates the inflammatory reaction over time, and consequently, irreversible tissue destruction occurs. Degradation of connective tissue is followed by epithelial migration and bone resorption, which marks the borderline between gingivitis/mucositis and periodontitis/peri-implantitis.

Periodontitis–peri-implantitis relation

Periodontitis is one of the main causes of tooth loss in adults. It can therefore be assumed that a great number of patients receiving dental implants have a history of periodontal disease. When replacing lost teeth with implants, it is important and necessary to determine whether a history of periodontitis will affect the prognosis and maintenance of implants. First, do patients with periodontal disease lose more implants in the early healing period, and second, is the long-term prognosis and maintenance of implants affected?

In the available literature concerning implant treatment of periodontally compromised patients, case reports show that implants are lost in those with severe forms of periodontitis [5,6]. Clustering of implant losses in certain individuals has been suggested to indicate systemic or host-related factors of importance for fixture losses [31]; however, early failure rates of implants in patients treated for periodontitis are similar to those in partly edentulous patients in general [29,32].

Few studies have evaluated attachment loss and marginal bone loss around implants in patients treated for periodontitis. In a retrospective study of periodontally treated patients receiving implants, Ellegaard et al [32] reported that the incidence of bone loss during the 5 years after implantation increased in 45% of all implants displaying marginal bone loss of 1.5 mm or more.

In another 5-year retrospective radiographic study, the outcome of implant therapy in relation to experience of periodontal tissue destruction was evaluated in 97 partially edentulous subjects. Hardt et al [12] defined two groups of subjects (''Perio'' and ''Non-Perio'') with regard to an age-related bone loss score at teeth. The study reported that early failures of implants were more frequent in the Perio group than in the Non-Perio group. Furthermore, the proportion of subjects who had >2 mm bone loss at implant sites during the 5-year study period was significantly larger in the Perio group than in the Non-Perio group. It was concluded that longitudinal bone loss around implants was correlated with previous experience of periodontal bone loss.

In contrast, Wennström et al [33] performed a 5-year prospective study and reported the existence of few implant losses and relatively small amounts of marginal bone loss in a group of periodontally susceptive subjects. The conflicting outcomes of implant therapy in periodontally compromised subjects reported in the studies by Wennström et al [33] compared with

Ellegaard et al [32] and Hardt et al [12] may be related to differences in maintenance programs (such as the frequency of recall visits).

In a recent study, Karoussis et al [1] compared the failure, success, and complication rates of patients who lost their teeth due to periodontitis or other reasons. The group with a history of chronic periodontitis had a significantly higher incidence of peri-implantitis (28.6%) than the group with no history of periodontitis (5.8%).

Peri-implantitis

Peri-implantitis is defined as an inflammatory reaction, with the loss of supporting bone in the tissues surrounding a functioning implant [9]. It has also been described as "a site-specific infection yielding many features in common with chronic adult periodontitis" [4] or "an inflammatory, bacterial-driven destruction of the implant-supporting apparatus" [34]. The view that microorganisms play a major role in the development of peri-implantitis is supported by several clinical findings. A cause-related effect between plaque accumulation and peri-implant mucositis has been shown in animals and humans [15,35]. Moreover, the microbial colonization of implants follows the same pattern as that described around teeth [19,36]. During peri-implant breakdown, a complex microbiota is established, closely resembling that found in adult periodontitis [4]. When peri-implant tissue breakdown is induced by placing plaque-retentive ligatures submarginally in animals, a shift in the microflora occurs [36,37].

Rosenberg et al [38] divided patients with failing implants into two groups: suspected infection and trauma (overload). In the trauma group, patients had no pain or suppuration and the failed implants had a microbiologic profile similar to that found at healthy implant sites. In the infected group, however, implants were colonized by microbiota similar to that found in periodontitis.

Most information on the histopathologic features of peri-implantitis lesions has been obtained from experimental studies in dogs and monkeys [39–42]. In the experimental models used, plaque formation was allowed and ligatures were placed in a submarginal position around the neck of implants. The ligatures were removed when the ensuing inflammatory response in the peri-implant tissues had mediated advanced bone destruction. Histologic analysis of the biopsy material revealed the presence of large inflammatory lesions in the peri-implant mucosa and that these lesions extended to the alveolar bone. Lindhe et al [39] suggested that peri-implant tissues, in contrast to periodontal tissues, have a limited capacity to resolve progressive, plaque-associated lesions. Few reports exist on peri-implant tissues at failed implant sites in humans. Although some documentation reveals the presence of inflammatory lesions in the peri-implant mucosa [43,44], other reports claim that inflammatory cell infiltrates were virtually absent [45]. In a recent study on the histopathologic features of human peri-implantitis [46], it was reported

that harvested soft tissue specimens harbored large inflammatory cell infiltrates that extended to a position apical of a pocket epithelium. Furthermore, about 60% of the lesions were occupied by inflammatory cells, among which plasma cells dominated. The investigators also reported that there were numerous polymorphonuclear cells in the connective tissue areas adjacent to the pocket epithelium and in the perivascular compartments in more central areas of the inflammatory cell infiltrate. Similar observations were made in a study on the immunohistochemical characteristics of human peri-implantitis lesions [47]. This study reported that peri-implantitis lesions consistently exhibited elastase-positive cells (ie, polymorphonuclear cells) in the central portions of the infiltrate. The findings concerning polymorphonuclear cells in human peri-implantitis lesions are also consistent with results from studies on crevicular fluid at implants with peri-implantitis [8,48].

Smoking

Several epidemiologic studies have shown the negative influence of smoking on periodontal status [49]. Its role as a risk factor for periodontal disease progression has recently been confirmed [50], and current data suggest that smokers have at least a threefold increased risk of developing periodontitis [51].

The possible relationship between smoking and implant failures has been evaluated in several retrospective and prospective clinical studies [52]. In a retrospective analysis of the outcome of 2194 implants placed in 540 subjects, Bain and Moy [53] reported that a significantly greater percentage of implant failures occurred in smokers than in nonsmokers. Smokers had an overall failure rate of 11.3%, whereas only 4.8% of the implants placed in nonsmokers failed. Gorman et al [54] found that implant failures were twice as common in smokers as in nonsmokers at second-stage surgery. In general, it can be concluded that smoking has a negative effect on implant survival, especially during the early healing period after implant installation.

The effect of smoking on marginal bone loss has also been evaluated. Cigarette smoking was associated with significantly greater marginal bone loss at implants used in the treatment of edentulous mandibles [55]. The 10- and 15-year follow-up reports on this group of edentulous patients showed that bone loss, although limited, was related to several factors, among which smoking and oral hygiene were the most important.

Haas et al [56] compared the association between smoking and peri-implantitis in 107 smokers compared with 314 nonsmokers. Smokers had higher bleeding scores, more signs of clinical inflammation, deeper probing pocket depth, and more radiographic bone loss around implants than nonsmokers. The investigators further stated that the effect of smoking on the condition of peri-implant tissues was more pronounced in the maxilla than in the mandible.

Clinical appearance of peri-implantitis

Peri-implantitis lesions are often asymptomatic and usually detected at routine recall appointments. Careful probing around teeth and implants should be routine procedures included at these check-up appointments. The validity of probing around implants to properly detect peri-implant lesions has previously been questioned, although this dogma needs to be reassessed. Increased clinical probing pocket depth, often accompanied by bleeding and sometimes suppuration, is an indicator of pathology in peri-implant tissues. A common clinical problem regarding probing at implants is accessibility (ie, the design of the bridgework may interfere with the probing procedure). In this context, it is important to realize that peri-implant defects normally encompass the full circumference of the implant; therefore, it may be sufficient to probe only solitary sites at any given implant when there is obstruction by the prostheses. Based on the findings of the clinical examination, radiographs of the selected areas may be proposed. In peri-implantitis, a bony defect develops around single or multiple implants. The radiographic appearance is often in the shape of a saucer or rounded beaker and, as stated earlier, the lesion most often extends the full circumference of the implant.

Peri-implant lesions may develop after several years. In biomedicine, a "safety zone" of 5 years has often been misinterpreted to denote safe survival or no further risk for disease progression. In periodontitis, tissue destruction seems to be a relatively slow process; consequently, a function time exceeding 5 years for implants may be required to detect destructive peri-implantitis sites. Regular check-up visits and life-long supportive therapy is an absolute necessity for the implant patient.

Treatment of peri-implantitis

According to the best available evidence, traditional periodontal infection control including plaque control regimens and mechanical instrumentation of the affected areas possessing surgical flap access should be performed. It is essential to inform the patient about the need for effective oral hygiene procedures (particularly around implants), and the patient should be carefully instructed in the proper use of necessary additional oral hygiene aids. Oral hygiene procedures should be trained under professional supervision (Figs. 3–8).

A systematic review of the studies done on anti-infective therapy for the treatment of peri-implantitis reported that many different treatment regimens were used [57,58]. Type of antibiotic, dosage, duration, and time for initiation of antibiotic treatment were different for all studies. Leonhardt et al [59] reported 5-year outcomes following the treatment of peri-implantitis in humans. Implants that demonstrated marginal bone loss (>3 threads compared with baseline measurements at 1 year on intraoral radiographs), bleeding on probing, and suppuration from the sulci were

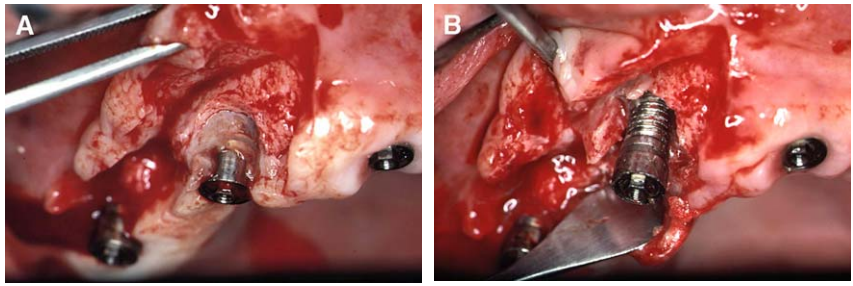

Fig. 3. (*A*) Peri-implant lesion in the anterior maxillary region. A surgical procedure with a full-thickness flap was performed to expose the affected area. (*B*) Mechanical instrumentation was performed to remove inflamed tissues (similar to conventional periodontal surgery). Implant surface was cleaned using EDTA solution.

included. Subgingival bacterial samples were collected for each individual and cultured. Surgical exposure of the lesions was performed, and the affected implants were cleaned using hydrogen peroxide. Systemic antibiotics were administered according to a susceptibility test of target bacteria. The applied surgical and antimicrobial treatment strategy was successful in less than 60% of the treated implants during the 5-year follow-up. Despite treatment and re-treatment of peri-implantitis–affected areas, additional loss of supporting bone was found in up to 40% of the advanced peri-implant lesions.

New data support the need for treatment of peri-implant lesions. Spontaneous progression of experimentally induced peri-implantitis was reported by Zitzmann el al [60]. Additional bone loss occurred in most of the implant sites following ligature removal in this experimental model. The reason why some peri-implantitis lesions were associated with extensive bone loss and others with only minor bone loss is currently not understood. Differences between implant sites regarding the subgingival biofilm or the

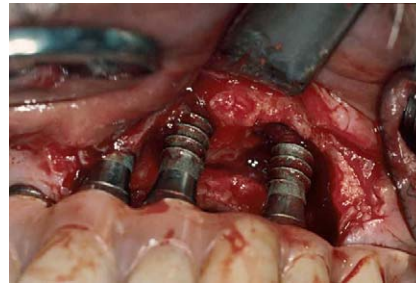

Fig. 4. Peri-implant lesion in the anterior maxillary region 4 years after implant surgery. Inflamed tissue has been removed.

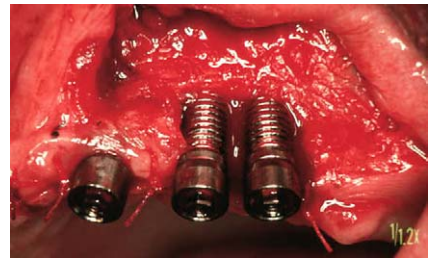

Fig. 5. Peri-implant lesion in the anterior maxillary region 3 years after implant surgery. The area has been instrumented and inflamed tissue removed. Note the circumferential appearance of the bone destruction.

quality of the inflammatory response to the infection may be factors of importance.

In a prospective, randomized controlled clinical trial, Wennström et al [33] studied the outcome of restorative therapy in periodontitis-susceptible patients who, following basic periodontal therapy, had been restored with

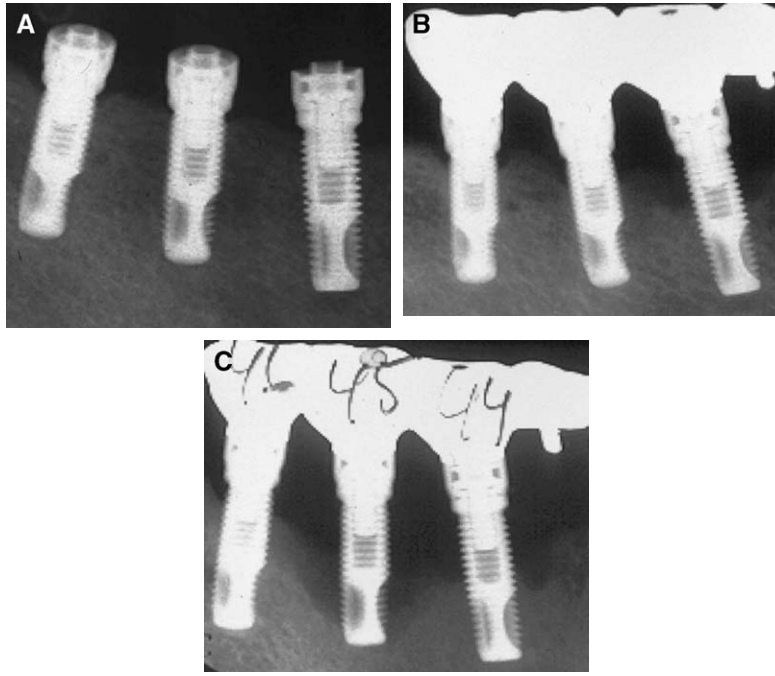

Fig. 6. (*A*) Implants inserted in the lower right mandible. (*B*) In the same patient 9 months later, an early peri-implant lesion can be detected around the right implant. (*C*) In the same patient an additional 22 months later, severe peri-implant tissue destruction can be seen, especially around the middle and right implants.

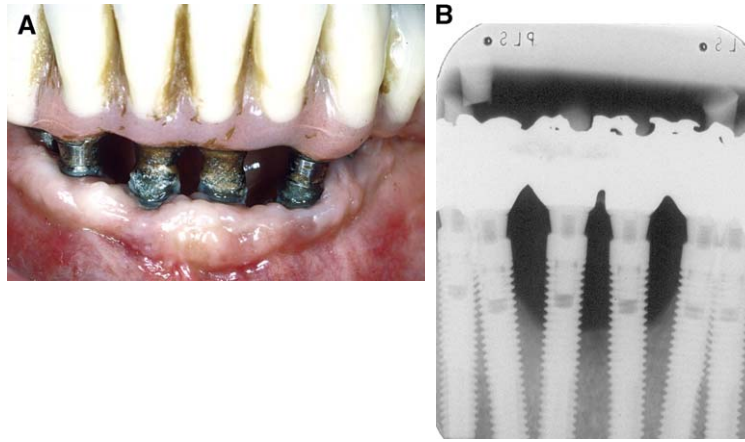

Fig. 7. (*A*) Patient has neglected oral hygiene at anterior mandibular implants for 5 years. (*B*) Radiograph of the anterior region in the same patient.

implants. The amount of peri-implant bone loss that occurred during a 5-year observation period was small in general but more pronounced in the maxilla than in the mandible. A further analysis also revealed that the amount of bone loss that occurred in smokers during the 5-year interval was more pronounced than the corresponding change in nonsmokers.

This finding is also interesting in the light of a recent observation by Airila-Månsson et al [61]. In their study on periodontitis subjects over a 17-year period, it was found that marginal bone loss was most severe in the maxillary molar region. In addition, smokers in this study showed more severe marginal bone loss over time.

Thresholds for peri-implantitis and standardized internationally accepted criteria for the definition of success are lacking. Relying on purely clinical

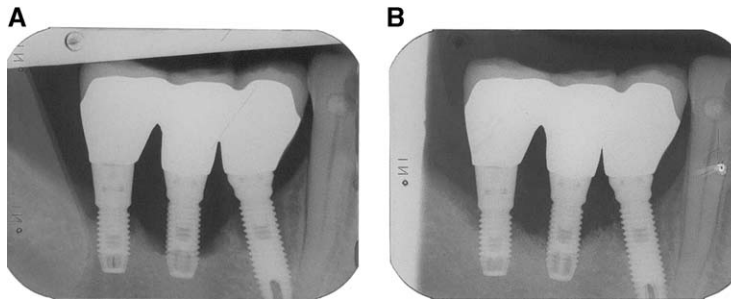

Fig. 8. (*A*) Peri-implant lesion in lower right mandibular region 5 years following placement of implants. Surgical infection control procedures were performed, including flap procedure, mechanical implant instrumentation, and postoperative antibiotics. (*B*) Radiograph of ongoing bone healing 5 months after surgical intervention.

parameters instead of combining clinical and radiographic assessments may over-rate the success [62]. To arrive at an agreement on how to evaluate the outcome of implant treatment in longitudinal studies, complications such as peri-implantitis should always be reported.

Summary

Peri-implant lesions may develop after several years. Patients who have lost their teeth due to periodontal disease seem to be at greater risk. Although several anti-infective treatment strategies have demonstrated beneficial clinical effects in humans (eg, resolution of inflammation, decrease in probing depth, and gain of bone in the defects), there is insufficient evidence to support a specific treatment protocol. Available studies on the treatment of peri-implantitis have included only a small number of subjects, and in general, the study periods have been relatively short. To date, there is no reliable evidence that suggests which interventions could be the most effective for treating peri-implantitis [3,57,58]. This is not to say, however, that currently used interventions are not effective.

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