Peri-implantitis: from diagnosis to therapeutics

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Introduction
Currently, dental implants and supra-implant prosthetics are widely used alternately with conventional removable and fixed dentures. In a consensus report from the Third European Workshop on Periodontology (EWOP) in 1999, according to suggested success criteria for integrated and healthy implants, marginal bone loss should not exceed 2 mm between prosthesis installation and 5 years of follow-up should be given.1 Although implant treatment is very successful, infections around implants such as peri-implant mucositis or peri-implantitis are also increasing considerably. The Sixth EWOP (2008) defined peri-implant mucositis and peri-implantitis as “infectious diseases. Peri-implant mucositis describes an inflammatory lesion that resides in the mucosa, while peri-implantitis also affects the supporting bone”.2

A recent study by Koldsland et al. on 109 patients with implant treatment showed that the prevalence of peri-implantitis ranged from 11 to 47%.3 A series of studies on the prevalence, extent and severity of peri-implantitis undertaken by Fransson et al. on 662 patients with implant treatments from 5–23 years, revealed 184 cases (27.8%) having at least one implant affected by peri-implantitis.4 Among 1070 implants examined, there were 419 (40%) with bone loss associated with peri-implantitis, and the mandibular anterior region was the most affected.5 After the first year of function, there were bone losses of ≥2 mm (32%) and ≥3 mm (10%) around infected implants.6 The severity of peri-implantitis associated with bone loss increases in proportion to the function time of the implant.

The main purpose of this review is to guide clinicians on how to diagnose peri-implantitis, evaluate risk factors and choose appropriate treatments.

Etiology
The Seventh EWOP (2011) assumed that “bone loss occurring after initial remodeling is mainly due to
bacterial infection”. An accumulation of microbes in plaque at the peri-implant or mucosal margin causes a local inflammation, which is a complex reaction of the body in response to infectious agents. Inflammatory cells such as macrophages, neutrophil granulocytes, lymphocytes and plasma cells, provoke considerable tissue damage. The degradation of connective tissue is followed by bone destruction, which marks the borderline between peri-implant mucositis and peri-implantitis. Bacterial contamination of the microgap in two-stage implant systems may play an important role in the development of peri-implantitis. Microbiota associated with peri-implantitis is more complex than that found under healthy peri-implant conditions as well as periodontally healthy teeth or periodontitis. The main flora consist of Gram-negative anaerobic bacteria. Observation by microscope shows that microbial sampling from healthy implants contained only cocci and a few bacilli, while samples from lesions of peri-implantitis reveal an abundance of motile rods, fusiform bacteria and spirochetes. Controlled clinical studies indicate that Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens, Tannerella forsythia, Treponema denticola and Fusobacterium nucleatum were most frequently found in peri-implantitis lesions. Likewise, controlled studies of bacteria frequently associated with periodontitis showed that peri-implantitis lesions had a high rate of periodontal pathogens (Table 1).

Staphylococcus aureus was also frequently found (44–70%) in periodontal pockets and peri-implant lesions. Several studies suggested that S. aureus could play an important role in peri-implantitis. In a recent study of peri-implantitis, a high rate of Pseudomonas aeruginosa was detected. The symbiosis between Bacteroides spp. and P. aeruginosa could promote the persistence of this pathogen in subgingival lesions if infectious tissues were not eliminated by surgery. Moreover, the high prevalence of human cytomegalovirus and Epstein–Barr virus in subgingival plaque as well as an increased prevalence of Methanobrevibacter oralis and Methanobacterium congelense/curvum in peri-implantitis sites suggest that viruses and archaea have a pathogenic role in peri-implantitis.

### Table 1. Pathogenic bacteria most frequently detected in periodontitis and peri-implantitis lesions

<table>
<thead>
<tr>
<th>Pathogenic Bacteria</th>
<th>Periodontitis</th>
<th>Peri-implantitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregatibacter actinomycetemcomitans</td>
<td>≥0.05**</td>
<td>≥0.05**</td>
</tr>
<tr>
<td>Campylobacter rectus</td>
<td>≥0.05†</td>
<td>≥0.05†</td>
</tr>
<tr>
<td>Dialister pneumosintes</td>
<td>&lt;0.05*</td>
<td>≥0.05†</td>
</tr>
<tr>
<td>Eubacterium saphenum</td>
<td>&lt;0.05*</td>
<td>≥0.05†</td>
</tr>
<tr>
<td>Filifactor alocis</td>
<td>&lt;0.05*</td>
<td>≥0.05†</td>
</tr>
<tr>
<td>Fusobacterium nucleatum</td>
<td>≥0.05†</td>
<td>≥0.05†</td>
</tr>
<tr>
<td>Micromonas micros</td>
<td>≥0.05†</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Mogibacterium timidum</td>
<td>&lt;0.01**</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Porphyromonas gingivalis</td>
<td>&lt;0.001***</td>
<td>&lt;0.001***</td>
</tr>
<tr>
<td>Prevotella intermedia</td>
<td>&lt;0.05*</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Prevotella nigrescens</td>
<td>≥0.05†</td>
<td>≥0.05†</td>
</tr>
<tr>
<td>Prevotella tannerae</td>
<td>&lt;0.05*</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Selenomonas spuitigena</td>
<td>≤0.01**</td>
<td>≥0.05†</td>
</tr>
<tr>
<td>Tannerella forsythia</td>
<td>≥0.05†</td>
<td>≥0.05†</td>
</tr>
<tr>
<td>Treponema denticola</td>
<td>&lt;0.05*</td>
<td>≥0.05†</td>
</tr>
<tr>
<td>Treponema medium</td>
<td>&lt;0.05*</td>
<td>≥0.05†</td>
</tr>
<tr>
<td>Treponema socranskii</td>
<td>&lt;0.05*</td>
<td>≥0.05†</td>
</tr>
</tbody>
</table>

Statistically significant difference: *** (P < 0.001) very high frequency, ** (P < 0.01) high frequency, * (P < 0.05) frequent. No statistically significant difference: † (P ≥ 0.05). PCR, polymerase chain reaction.
Nevertheless, no clear criteria of microbiota associated with peri-implantitis have been identified to date for the diagnosis and treatment of this disease.\textsuperscript{10}

**Risk factors of peri-implantitis**

Risk factors which have strong evidence for an association with peri-implantitis are listed below.

**History of periodontitis**

The frequency of implant failure in a partial loss of teeth was significantly higher than in a total loss.\textsuperscript{9} However, study by Renvert et al. indicates that while peri-implantitis is not dependent on the partial or total loss of teeth, a history of periodontitis was a crucial risk for peri-implant mucositis and peri-implantitis.\textsuperscript{23} Patients with a history of chronic periodontitis have a higher prevalence of peri-implantitis (28.6%) than healthy patients (5.8%).\textsuperscript{24} A recent study by Koldsland et al. also indicates that individuals with a history of periodontitis are prone to peri-implantitis if they had peri-implant bone loss ≥2 mm.\textsuperscript{25} Likewise, a systematic review by Renvert et al. concluded that patients with treated periodontitis may be at greater risk for peri-implant infections than those without.\textsuperscript{26} Because the pathogenic flora in peri-implantitis are similar to that found in periodontitis,\textsuperscript{12} periodontal pockets are probably a reservoir of microorganisms colonizing implant surfaces.

**Dental plaque and poor oral hygiene**

In a study by Ferreira et al., higher total plaque scores were statistically associated with peri-implant disease and a very poor oral hygiene status, as described by median scores of full-mouth plaque ≥2, was highly associated with peri-implantitis.\textsuperscript{27} In another study, most patients had relatively good plaque control in their residual teeth but not at implant sites, and inadequate plaque control was detected in around 74% of the implants. Implant sites less accessible by oral hygiene measures showed more peri-implant infectious lesions (48%) than other favorable sites (4%).\textsuperscript{28} This observation suggested that local factors such as poor oral hygiene and the presence of dental plaque play an important role in the development of peri-implantitis. Thus, the control of oral hygiene and periodontal status should be monitored before and after the implant insertion to prevent or at least to minimize the risk of developing peri-implantitis. Furthermore, plaque retention is also influenced by the form of implant-supported prostheses, which must be determined before establishing a treatment plan as well as choosing the number and type of implants.

**Smoking**

Smoke was identified as a major risk factor of both periodontitis and peri-implantitis.\textsuperscript{29} A recent study by Rodriguez-Argueta et al. showed that smokers had an increased risk of infection, implant loss, mucositis and peri-implantitis than non-smoking patients. The pathogenic mechanisms of smoking may be explained by the toxic effects of the more than 4000 toxins present in cigarettes. Nicotine is a potent vasoconstrictor that reduces blood flow and nutrient delivery to healing sites. Some compounds of tobacco also act as chemotactic substances that enhance tissue destruction by enzymes released by neutrophils and macrophages. Peri-implantitis was more frequent in smokers (9.2%) than non-smokers (5.3%).\textsuperscript{30} Smokers had more severe inflammatory signs, deeper peri-implant pockets and larger peri-implant bone loss than non-smokers. The influence of smoking on peri-implant tissue was greater in the maxilla than the mandible.\textsuperscript{8,31} Several retrospective studies over 8 years have also shown that smokers had a high risk of developing peri-implantitis and bone loss.\textsuperscript{32,33} A systematic review of smoking as a risk for implant therapy concluded that there was an increased risk of peri-implantitis in smokers than non-smokers, with odds ratios ranging from 3.6 to 4.6.\textsuperscript{34} Although implant therapy is not contraindicated in smokers, these patients should be encouraged to cease this habit or reduce its intensity; otherwise mucositis and then peri-implantitis could occur.

Risk factors which have a limited evidence of an association with peri-implantitis are listed below.

**Alcohol consumption**

Individuals who use alcohol may have a vitamin K deficit disrupting the production of prothrombin, thus affecting coagulation mechanisms. Alcohol consumption is associated with deficiencies of the complement system, alteration of the neutrophil function and modulating T lymphocyte activity. Moreover, some substances contained in alcoholic drinks such as fusel oil, nitrosamines and ethanol, can cause bone destruction and block the stimulation of bone neoformation. Only one study by Galindo-Moreno et al. concluded that peri-implant marginal bone loss was statistically linked to alcohol consumption >10 g per day and that alcohol induced more serious peri-implantitis than cigarelettes.\textsuperscript{25}

**Diabetes**

A study by Ferreira et al. showed that patients with diabetes (diagnosed by fasting blood sugar ≥126 mg/dL or
taking anti-diabetic medicine over the previous 2 weeks) were more prone than those without diabetes to develop peri-implantitis. Furthermore, the presence of diabetes was statistically associated with an increased risk of peri-implantitis.²⁷ It seems that poor metabolic control in diabetics made patients more susceptible to infection and implant loss. The clinician should inform diabetic patients of their possible increased risk for peri-implantitis.

Risk factors which have conflicting or non-confirmed evidence for an association with peri-implantitis are listed below.

**Genetic traits**

A study by Cornelini et al. showed a significant increase in the density of blood microvessels in peri-implantitis sites, but the expression of vascular endothelial growth factor (VEGF) was statistically low. Thus, VEGF could play a protective role in peri-implantitis.³⁶ There was a correlation between the polymorphisms of the interleukin (IL)-1-specific gene and peri-implant bone loss in smokers.³⁷ Jansson et al. showed that the IL-1 genotype was a risk indicator of peri-implantitis and there was a synergistic effect between the IL-1 genotype and smoke.³⁸ However, two other studies failed to find an association between the IL-1 genotype and peri-implantitis or of implant failure or bone loss.³⁹,⁴⁰ Therefore, future prospective studies with large numbers of patients are necessary to confirm this association.

**Lacking keratinized mucosa**

A study by Block et al. suggested that the presence of keratinized gingiva around implants was correlated with the health of both soft and hard tissue as well as implant survival.⁴¹ However, an analysis of multiple potential factors of peri-implant mucositis and peri-implantitis was performed, but no association between the absence of keratinized gingiva and peri-implant infection was found.²⁵,⁴² Therefore, lacking keratinized mucosa has not currently been confirmed as risk factor of peri-implantitis.⁴³

**Implant surface characteristics**

Most recent titanium implants with a rough surface showed more favorable osseointegration than those with smooth surfaces.⁴⁴,⁴⁵ However, a rough surface also favored the formation and retention of dental plaque. Roughness increased both the adhesive surface of bacteria and the difficulty in cleaning the implant.⁴⁶ In a study by Astrand et al. in 2004, ITI Dental Implant System⁴⁶ implants (Straumann AG, Waldenburg, Switzerland) with a plasma-sprayed surface had a statistically higher incidence of peri-implantitis than Branemark System⁴⁷ implants (Nobel Biocare AB, Gothenburg, Sweden) with a smooth surface.⁴⁷ Conversely, a systematic review by Esposito et al. showed that there was no statistically significant difference in the incidence of peri-implantitis between smooth and rough implant surfaces.⁴⁸ Likewise, in a recent review by Renvert et al., there was no evidence that implant surface characteristics can have a significant effect on the initiation of peri-implantitis.⁴⁹

**Other non-confirmed risks**

Xerotonia could be a risk factor for peri-implantitis. In fact, a decrease of salivary flow was often accompanied by a change in its composition and reducing bacterial clearance in the oral cavity. More viscous saliva with a reduction of antibacterial activity promoted the formation of dental plaque and bacterial growth.⁵⁰ Likewise, postmenopausal osteoporosis is a metabolic disease in which an imbalanced bone status resulting from estrogen deficiency may have a relationship with oral infectious disease, possibly by providing a more susceptible environment for bacteria. However, a study by Dvorak et al. found no relation between osteoporosis and peri-implantitis in adult women.⁵¹ Moreover, implants inserted in the maxilla were more likely to be registered with inflammation than those in the mandible. A study by Koldsland et al. identified the location in the maxilla as risk indicator of peri-implantitis.²⁵ Furthermore, in the anterior region of maxilla, especially in cases where a single tooth is missing, excessive insertion of an implant into alveolar bone is often performed to optimize the esthetic aspect. This approach increased peri-implant pocket depth and infection risks.⁵²

**Diagnosis of peri-implantitis**

**Clinical diagnosis**

A periodontal probe is an essential tool for the clinical diagnosis of peri-implantitis. Probing with a light force of 0.25 N does not cause peri-implant tissue damage and it is recommended for evaluating peri-implant disease. Clinical signs of peri-implantitis are bleeding on probing in conjunction with peri-implant pockets ≥ 5 mm with or without suppuration. In fact, bleeding on probing and suppuration indicate the presence of inflammation and infection. Because healthy implants generally have probing depths that are less than 4 mm, peri-implant pockets of 5 mm or more should be regarded as an indicator of bone loss⁹ and hence, a radiographic evaluation is required. A peri-implant pseudopocket could be present as soft tissues that are positioned above the implant.
shoulder intentionally for esthetic reasons. Also, peri-
implant hyperplasia is often found in an area of absence
of keratinized gingiva or the overflow of supra-implant
structures. Contrariwise, platform-switched or abutment
designs could also provoke difficult probing and the
probing depth may hence underestimate the extent of
the lesion. Implant mobility is not used to diagnose
peri-implantitis because it indicates the complete loss of
osseointegration and the failure of the implant. Moreover,
pain is not a typical sign of peri-implantitis.

Radiographic assessment
In the First EWOP (1994) it was proposed that marginal
bone loss of less than 1.5 mm during the first year in
function and less than 0.2 mm per year thereafter to be
one of the major criteria for success. Baseline radiographs
should be taken to determine alveolar bone levels
after physiological remodeling and when clinical signs
suggest peri-implantitis, a radiograph of the site is
required to confirm the diagnosis. In two recent studies
by Koldsland et al. it was proposed that a radiographic
peri-implant bone loss ≥2 mm was a possible risk indi-
cator of peri-implantitis. In terms of dental radiographic
techniques, panoramic radiography gives a complete visualization of anatomical structures around
implants but its use is limited because of its low resolu-
tion and image distortion. Periapical radiography is
often used to verify marginal bone level or interproximal
bone loss in peri-implantitis. However, our inability to
assess facial and lingual or palate bone tables and the
underestimation of intraosseous lesions are still limiting
conventional radiography. For minimizing the eventual
error of a radiographic assessment of bone loss, the utili-
ization of individual or fixed angulators could be useful
to prevent image deformation. Currently, multi-slice
computer tomography and cone beam volume imaging
offer implant dentistry certain advantages, such as repres-
enting infrabony lesions in three planes, true to scale
and without any overlay or distortion. Furthermore,
computer-assisted image analysis, such as subtraction
radiography, permits the detection of small changes in
bone density.

Differential diagnosis
Peri-implant mucositis
Peri-implant mucositis may be identified clinically by red-
ness, swelling of the soft tissue without loss of supporting
bone (probing depth <5 mm) and bleeding on probing
are currently considered to be important indicators. The
treatment of peri-implant mucositis includes the removal
of dental plaque and calculus by using appropriate instru-
ments and oral hygiene instruction without antiseptic or
combined with antiseptic. Likewise, the literature review
of Renvert et al. confirmed that mechanical non-surgical
therapy could be effective in the treatment of peri-
implant mucositis and the adjunctive use of antimicrobial
mouth rinses enhanced the outcome of such therapy. However, two later studies indicated that an adjunctive
application of chlorhexidine did not enhance results in
comparison with mechanical cleansing alone. Furthermore,
the treatment of peri-implant mucositis is useful
for the prevention of peri-implantitis because mucositis
represents an obvious precursor of peri-implantitis.

Occlusal overload
Occlusal overload together with peri-implantitis are the
major causes of implant loss. Factors associated with
occlusal overload or occlusal trauma probably consist of
an excessive expansion of a prosthesis in the posterior
region, implant alignments, a significant deviation of the
implant axis from the function axis, an important ratio of
crown height/implant length, a discrepancy in dimensions
between the implant head and occlusal table. An occlu-
sal overload can cause the complete bone loss of an
osteointegrated implant. Bone destruction is accelerated if
occlusal trauma is combined with peri-implant infection.
In fact, the marginal bone loss due to overload is often
accompanied by attachment loss and deepening of the
pockets. After some time the newly created anaerobic
environment will inevitably harbor periopathogenic flora.
Therefore, the presence of pathogenic subgingival flora
after occlusal overload may reflect a secondary infection
of a favorable environment which can contribute to fur-
ther loss of marginal bone. Occlusal correction is neces-
sary to stop the progress of bone destruction. Control of
occlusion by progressive loading depending on bone den-
sity can reduce peri-implant bone loss in a healing
phase. A case report of occlusal overload associated with
peri-implantitis used combined treatment methods
including occlusal adjustment, the surgical removal of
contaminated tissue and an autogenous bone graft. After
12 months, a radiograph revealed marginal bone regener-
atation and a normal clinical aspect was observed.

Retrograde peri-implantitis
Retrograde peri-implantitis is defined as a clinically symp-
tomatic periapical lesion (diagnosed as a radiolucency)
that develops shortly after implant insertion while the
coronal portion of the implant becomes a healthy bone at
the implant interface. Clinical symptoms include pain,
tenderness, swelling or presence of a fistulous tract.
The etiology of retrograde peri-implantitis may be
bacterial contamination during the implant insertion or pre-existing bone inflammation (such as bacteria, a cyst or granuloma after tooth extraction). Compared with successful implants, these periapical lesions appear on extracted tooth sites that have a history of endodontic pathology. The lesion forms at the apex of the implant but it does not extend to the coronal, proximal or facial area. Quirynen et al. suggested the treatment method of retrograde lesions, including the complete removal of granulation tissue, curettage of bony cavity walls and filling substitute bone (Bio-Oss®, Geistlich, Schlieren, Switzerland). The surgery was performed under the antibiotic coverage of forms of β-lactamase-resistant penicillin. This method was more successful on the maxilla than the mandible. In a report of four cases of retrograde peri-implantitis, Mohamed et al. concluded that careful preoperative assessment of the site, adjacent teeth and postoperative observation and conservative management.66

**Inflammatory implant periapical lesion**

Clinical manifestations consisted of pain after implant placement and the absence of implant mobility with or without periapical radiolucent area. No response to antibiotic treatment indicated that bacteria were not the only cause. Poor vascularization or vascular ischemia could cause bone loss around the apex of the implant. Other causative factors included insufficient insertion of the implant in terms of drilling depth and overheating during drilling, inducing aseptic necrosis of the alveolar bone. Therefore, surgery removing periapical inflammatory tissues combined with chlorhexidine irrigation was an effective treatment. As well as occlusal overload and retrograde peri-implantitis, inflammatory implant periapical lesions occur if the therapist is incompetent or because of inappropriate treatment planning due to a lack of knowledge. Thus, prevention is the optimal strategy to manage such complications. Strict adherence to hygienic rules and manufacturers’ guidelines during implant insertion are of particular importance.

**Non-surgical treatment of peri-implantitis**

**Microbiological test**

A microbiological test of subgingival microflora using a bacteria culture, checkerboard DNA–DNA hybridization, polymerase chain reaction (PCR), monoclonal antibody and enzyme assays could suggest antibiotic therapy. In fact, peri-implantitis is associated in most cases with a mixed anaerobic flora, including *Fusobacterium* spp. and *P. intermedia* in high numbers. Antimicrobial agents such as metronidazole and ornidazole, which act specifically against strict anaerobes, seem to be an excellent choice for this type of infection. However, a limited number of patients may have peri-implantitis lesions that are dominated by *Staphylococcus* spp. or metronidazole-resistant *Aggregatibacter actinomycetemcomitans* or enteric bacteria and yeasts. Moreover, certain cases of peri-implantitis are characterized by periods of rapid and marked destruction compared with periodontitis. This progression may be explained by the host response to specific infectious agents.

**Mechanical therapy alone**

The formation of dental plaque was crucial to the development of the peri-implant infections (such as peri-implant mucositis and peri-implantitis) that altered the biocompatibility of the implant surface. Treatment of infected implant surface and the reduction of pathogenic bacterial flora around the implant are the main goals of peri-implantitis treatment. The specific morphology of implant thread combined with a modified surface facilitated bacterial colonization but limited the efficiency of conventional cleaning instruments. In addition, debridement using metal instruments harder than titanium could alter the implant surface, therefore curettes or inserts in plastic or carbon fiber were recommended. A study by Karring et al. showed that non-surgical mechanical treatment alone was insufficient to eliminate peri-implant lesions. Although bleeding on probing had improved after 6 months, the peri-implant pocket depth was unchanged (Table 2). Another study compared the efficiency of two mechanical non-surgical methods using a titanium curette and the vector-ultrasonic system for peri-implantitis treatment. No difference in results between the two methods was found. There was the reduction of bleeding on probing and dental plaque index after 6 months but no change in pocket depth and peri-implant bacterial composition (Table 2).

**Mechanical therapy with an adjunct of an antiseptic agent**

The mechanical non-surgical debridement alone was not effective in reducing bacterial flora around infected implants. The addition of antimicrobial treatment therefore seems necessary to improve clinical results. The antimicrobial treatment using a topical application of chlorhexidine was proposed to complete the mechanical treatment. However, a local irrigation of 0.12% chlorhexidine combined with a local application of 0.12% chlorhexidine gel and a mouthwash containing...
0.12% chlorhexidine for 10 days gave a no better result.\textsuperscript{71} Peri-implantitis was treated using a plastic curette associated with an antiseptic (chlorhexidine 0.2%) and improved clinical parameters such as the reduction of bleeding on probing and of the pocket depth after 6 months, but residual defects still persisted.\textsuperscript{72} These results suggested that chlorhexidine has a limited antimicrobial effect in infectious peri-implant lesions.

**Mechanical therapy with an adjunct of antibiotic therapy**

Mombelli and Lang conducted a study for the treatment of peri-implant infections by combining mechanical debridement with systemic antimicrobial therapy. The bleeding on probing index immediately decreased after systemic antibiotic therapy and there were also quantitative and qualitative changes of pathogenic flora. However, these parameters were reversible after the treatment period.\textsuperscript{73} A local application releasing a high dose of antibiotic in infected sites for several days effectively cleared bacteria that were not eliminated by mechanical treatments. In fact, debridement followed by an insertion of non-resorbable fibers containing tetracycline (Actisite\textsuperscript{8}, ALZA Corporation, Palo Alto, CA, USA) in peri-implant pockets for 10 days showed a significant reduction of pocket depth after 12 months.\textsuperscript{74} Buchtet et al. compared the efficiency of mechanical treatment alone using a plastic curette with mechanical treatment combined with a local application of bioreabsorbable polymer-releasing doxycycline (Atridox\textsuperscript{TM}, Block Drug Corporation, Jersey City, NJ, USA). The results after 4 months showed that patients treated with Atridox had a higher clinical attachment gain than those treated by debridement alone. The reduction of bleeding on probing and peri-implant pockets was statistically significant only among patients in the Atridox treatment group\textsuperscript{75} (Table 2). A recent study combining mechanical treatment with a repeated local application of minocycline microspheres (Arestin\textsuperscript{®}, OraPharma, Warminster, PA, USA) after 30 and 90 days showed benefits in the therapy of peri-implantitis. This study also indicated that mechanical treatment combined with the local application of an antibiotic\textsuperscript{76} achieved a better result (Table 2). A limitation of the local application of the antibiotic was the difficulty in introducing this antimicrobial agent in the bottom of the pocket.\textsuperscript{12} As poor oral hygiene is a major risk factor directly affecting results of peri-implantitis treatment, careful instruction on oral hygiene plays a crucial role in the success of non-surgical treatment.\textsuperscript{29}

\textbf{Table 2. Clinical studies of non-surgical treatment of peri-implantitis}

<table>
<thead>
<tr>
<th>Authors and study design</th>
<th>Number of patients (implants)</th>
<th>Treatment</th>
<th>Evaluation period (months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchter et al.\textsuperscript{75}</td>
<td>48 Group (a) 14 Group (b) 14</td>
<td>Irrigation with 0.2% chlorhexidine + debridement using plastic curettes + (a) Bioreabsorbable polymer releasing 8.5% doxycycline (Atridox) (b) No adjunctive treatment</td>
<td>4</td>
<td>Patients in group (a) showed a significantly greater gain of CAL than those in group (b) Reduction of BOP and PD was statistically significant only in group (a)</td>
</tr>
<tr>
<td>Karring et al.\textsuperscript{68}</td>
<td>11 (22)</td>
<td>(a) Vector ultrasonic system using carbon fiber inserts (b) Carbon fiber curettes</td>
<td>6</td>
<td>Reduction of PI, improvement of BOP, no change of PD, no statistical difference between two treatment methods (a) and (b)</td>
</tr>
<tr>
<td>Renvert et al.\textsuperscript{76}</td>
<td>Group (a) 17 (57) Group (b) 15 (38)</td>
<td>Debridement + subgingival application: (a) Minocycline microspheres (Arestin) (b) 1 mL of 1% chlorhexidine gel → repeated antimicrobial therapy after 1 month and 3 months</td>
<td>12</td>
<td>Statistically significant improvement of PI, BOP and PD in both groups (a) and (b) Reduction of BOP (12 months) and PD (6 months) in group (a) was statistically higher than that in group (b); ( P &lt; 0.001 ) and ( P &lt; 0.05 ) respectively</td>
</tr>
<tr>
<td>Renvert et al.\textsuperscript{69}</td>
<td>Group (a) 17 (17) Group (b) 14 (14)</td>
<td>(a) Mechanical debridement using titanium curettes (b) Mechanical debridement using vector ultrasonic system → rubber cup polishing</td>
<td>6</td>
<td>Improvement of PD, statistically significant reduction of PI ( (P &lt; 0.01) ) and BOP ( (P &lt; 0.01) ) in both groups (a) and (b) No statistical difference between two groups (a) and (b)</td>
</tr>
</tbody>
</table>

BOP, bleeding on probing; CAL, clinical attachment level; PD, pocket depth; PI, plaque index.
Surgical treatment of peri-implantitis

Classification of peri-implant bone defects

Classification of the morphology of peri-implant lesions was important for choosing a reliable type of bone regeneration and for prognosis of surgical therapy of peri-implantitis. According to the classification of Schwarz et al. in 2007, class I consisted of infrabony destruction while class II was characterized by horizontal bone loss. Class I was subdivided into class Ia (buccal dehiscence), class Ib (buccal dehiscence + semicircular bone resorption to the middle of the implant body), class Ic (buccal dehiscence + circular bone resorption under maintenance of the lingual compacta), class Id (buccal dehiscence + circular bone resorption under loss of the lingual compacta) and class Ie (circular bone resorption under maintenance of the buccal and oral compacta). The bone defects most frequently found in peri-implantitis were class Ie (55.3%) followed by class Ib (15.8%), class Ic (13.3%), class Id (10.2%) and class Ia (5.4%). The application of bone regeneration seems to be more favorable in class I bone destruction, but it is very limited in class II defects. The best results for reducing pocket and clinical attachment gain were found in class Ie defects.

Resective surgery

In particular clinical conditions such as peri-implantitis with suprabony destruction, one-wall infrabony defects or buccal dehiscences in non-esthetic regions, the application of resective surgery including osteotomy or osteoplasty associated with the polishing of the transmucosal implant part and apically positioned flap has been suggested. The goals of resective surgery were the reduction of the peri-implant pocket and the morphological reconstruction of soft tissue to promote patients’ oral-implant hygiene. A clinical study by Romeo et al. demonstrated that resective therapy associated with implantoplasty improved the survival of infected implants (Table 3).

Bone regeneration

A study of autogenous bone graft on 17 patients with 25 treated implants showed a reduction of the peri-implant pocket from 6.9 to 0.7 mm \((P = 0.001)\), corresponding to 90% bone reconstruction and improvement of marginal bone level from 6.2 to 2.3 mm after 2–3 years. Vertical bone resorption under 4.5 mm was completely regenerated. The application of a membrane barrier gave protection from blood clots and created a space around peri-implant defects to promote bone regeneration as well as to avoid competition from other tissues. Recently, collagen membranes were recommended for their convenient properties, namely, their hemostatic function, early stabilization, chemotactic activity attracting fibroblasts and semi-permeability. In studies by Schwarz et al., nanocrystalline hydroxyapatite (Ostim™, Heraeus Kulzer, Hanau, Germany) alone or bovine biological apatite (Bio-Oss) combined with a collagen membrane (Bio-Gide®, Geistlich, Schlieren, Switzerland) were applied for the treatment of peri-implantitis. The results indicated that these methods made a significant reduction of the peri-implant pocket depth and a great clinical attachment gain after 6 months. Surveillance after 2 years showed 1.5–2.4 mm reduction of peri-implant pockets and 1–2 mm clinical attachment gain. Radiographic observation after 4 years confirmed better results in a group using natural mineral bone (Bio-Oss) than in a group using nanocrystalline hydroxyapatite (Ostim) (Table 3). A case report from Ross-Jansaker et al. in 2007 using substitutive material (Algipore®, Friadent, Malmo, Sweden) combined with a resorbable membrane (Osseoquest®, W.L. Gore & Associates Inc., Flagstaff, Arizona, USA) also showed a reduction of the peri-implant pocket (4.2 mm) and an improvement of marginal bone level (2.3 mm) after 1 year. Membrane exposition was the most frequent complication (31.3%) (Table 3). Three surgical methods including a bone graft without a membrane, an autogenous bone graft combined with non-resorbable membrane e-PTEF (expanded polytetrafluoroethylene) and autogenous bone graft combined with bioresorbable membrane Bio-Gide were compared in the treatment of peri-implantitis. However, this study showed that the addition of a membrane did not improve treatment results. Ross-Jansaker et al. also compared two bone regeneration techniques using substitutive material (Algipore® combined with or without a bioresorbable membrane (Osseoquest) for peri-implantitis treatment. There was no statistically significant difference in clinical parameters between the two techniques (Table 3).

Laser-assisted treatment of peri-implantitis

Non-surgical therapy

Different laser systems with bactericidal effects, tissue ablation and detoxification were proposed for peri-implantitis therapy. Erbium-doped yttrium, aluminum and garnet (Er:YAG) laser has the ability to remove dental plaque and calculus on the smooth or porous surface of implants without causing alterations. A study by Schwarz et al. on the efficiency of the Er,YAG laser showed the improvement of bleeding on probing was greater than that using a mechanical treatment (plastic curettes) combined with an antiseptic agent (0.2% chlorhexidine digluconate) in the non-surgical therapy of peri-implantitis. The Er:YAG laser also showed a
reduction of the peri-implant pocket and attachment gain after 6 months. However, there was no statistical difference in the results after 12 months in each group or between two groups of laser-assisted therapy and mechanical therapy88 (Table 4).

Surgical therapy

Bone regeneration was often recommended for peri-implantitis treatment; however, contamination of the implant surface limited the success of this procedure. The efficiency of bacterial reduction by lasers has been confirmed by several studies.87,89,90 The clinical cases report by Haas et al. using associated methods (curettage + laser-assisted decontamination of implant surfaces + autogenous bone graft + e-PTFE membrane + systemic antibiotic therapy for 5 days) showed great results for peri-implantitis treatment with a 36.4% bone gain after 10 months.91

Deppe et al. conducted a study to compare the effectiveness of two methods of decontaminating implant surfaces in the surgical therapy of peri-implantitis. After 4 months, radiographic and clinical parameters indicated that laser decontamination could stop bone resorption better than conventional treatment but results after 5 years showed no difference of bone level between the two groups. Nevertheless, this study did not demonstrate the independent effects of laser in peri-implantitis therapy92 (Table 4). CO2 laser irradiation combined with an autograft or xenograft (Bio-Oss) and a non-resorbable membrane (Bio-Gide) without the preoperative and postoperative addition of systemic antibiotics regenerated peri-implant bone completely after 27 months93 (Table 4). The effect of coagulation by laser permitting good stabilization of blood clots and good contact of substitutive materials with the implant surface promoted re-osteointegration. Application of the erbium, chromium-doped: yttrium, scandium, gallium and garnet

Table 3. Clinical studies of surgical treatment of peri-implantitis

<table>
<thead>
<tr>
<th>Authors and study design</th>
<th>Number of patients (implants)</th>
<th>Treatment</th>
<th>Evaluation period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romeo et al.79</td>
<td>Group (a) 10 (19) Group (b) 7 (16)</td>
<td>Antibiotic therapy (amoxicillin × 8 days) + debridement using plastic curettes + (a) Resective surgery + topographic modification of implant surface (b) Resective surgery alone</td>
<td>3 years</td>
<td>Implant survival rate was 100% in group (a) and 87.5% in group (b) Statistically significant reduction of BOP, PD and gingival recession during 3 years in group (a) and 2 years in group (b)</td>
</tr>
<tr>
<td>Ross-Jansaker et al.84</td>
<td>12 (16)</td>
<td>Antibiotic therapy (amoxicillin + metronidazole × 10 days) + debridement and suppression of granulation tissue using titanium curettes + irrigation with 3% hydrogen peroxide and saline solution + substitutive material (Algipore) and resorbable membrane (Osseoquest)</td>
<td>12 months</td>
<td>Reduction of PD = 4.2 ± 1.5 mm Gain of CAL = 1.4 ± 1.7 mm Gingival recession = −2.8 ± 1.4 mm Defect fill = 2.3 ± 1.2 mm</td>
</tr>
<tr>
<td>Ross-Jansaker et al.96</td>
<td>Group (a) 17 (29) Group (b) 19 (36)</td>
<td>Antibiotic therapy (amoxicillin + metronidazole × 10 days) + debridement and suppression of granulation tissue using titanium curettes + irrigation with 3% hydrogen peroxide and saline solution + (a) Substitutive material (Algipore) and resorbable membrane (Osseoquest) (b) Substitutive material (Algipore) alone</td>
<td>12 months</td>
<td>(a) Reduction of PD = 2.9 ± 2 mm, Gain of CAL = 1.6 ± 2 mm, Gingival recession = −1.3 ± 1.5 mm (b) Reduction of PD = 3.4 ± 1.6 mm Gain of CAL = 1.8 ± 1.4 mm Gingival recession = −1.6 ± 1.6 No statistical difference between two groups (a) and (b)</td>
</tr>
<tr>
<td>Schwarz et al.81–83</td>
<td>Group (a) 11 (11) Group (b) 11 (11)</td>
<td>Suppression of granulation tissue using plastic curettes + irrigation with saline solution + (a) Nanocrystalline hydroxyapatite (Ostim) (b) Bovine-derived bone mineral (Bio-Oss) + collagen membrane (Bio-Gide)</td>
<td>6 months 2 years 4 years</td>
<td>(a) 6 months: Reduction of PD = 2.1 ± 0.5 mm and gain of CAL = 1.8 ± 0.6 mm (b) 6 months: Reduction of PD = 2.6 ± 0.4 mm and gain of CAL = 2.3 ± 0.6 mm (a) 2 years: Reduction of PD = 1.5 ± 0.6 mm and gain of CAL = 1.0 ± 0.4 mm (b) 2 years: Reduction of PD = 2.4 ± 0.8 mm and gain of CAL = 2.0 ± 0.8 mm (a) 4 years: Reduction of PD = 1.1 ± 0.3 mm and gain of CAL = 0.6 ± 0.5 mm (b) 4 years: Reduction of PD = 2.5 ± 0.9 mm and gain of CAL = 2.0 ± 1.0 mm</td>
</tr>
</tbody>
</table>

BOP, bleeding on probing; CAL, clinical attachment level; PD, pocket depth.
laser in the surgical treatment of peri-implantitis has given satisfaction to both patients and surgeons. However, this single case report also did not confirm the additive effects of the laser-assisted therapy94 (Table 4).

**Discussion**

Although no study has examined the relationship between peri-implantitis and platform switching, it has been shown statistically that the platform-switched implants result in a lower level of crestal bone loss compared with conventional implants.95,96 However, according to Linkevicius et al., when the mucosa is thin the switching platform implant does not preserve more bone level than implants with a conventional platform.97 In his study, Cappiello et al. showed a vertical bone loss at 12 months of between 0.6 and 1.2 mm (mean: 0.95 ± 0.32 mm) for a switching platform implant while the vertical bone loss was 1.3 and 2.1 mm (mean: 1.67 ± 0.37 mm) for control implants.95 Fickl et al. found similar results in a study of 89 implants. The authors compared 5-mm diameter implants followed by a switching platform placed in a subcrestal position to control implants of a standard diameter with an internal connection placed at the crest. After inserting the definitive prosthesis, the bone level was 0.30 ± 0.07 mm versus 0.68 ± 0.17 mm, P < 0.05 and 1 year after insertion it was 0.39 ± 0.07 mm compared to 1.00 ± 0.22 mm, P < 0.01.98 By extrapolation, if over a period of time, the behavior of the switching platform reduces bone loss, we also can imagine a reduction of peri-implantitis. In a theoretical model analyzed by linearly elastic 3-dimensional finite element simulations, Baggi et al. examined the relationship between different forms of implants, showing that the maximum stress is located at the neck of the implant. Among the tested implants, the implant Ankylos (Dentsply Friadent, Mannheim, Germany) with platform-switched and sub-crestal placement shows less stress and a reduced overload

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Schwarz et al.98 Controlled study</td>
<td>Group (a) 10 (20) Group (b) 10 (20)</td>
<td>Rubber cup polishing + non-surgical treatment: (a) Er:YAG laser-assisted decontamination of infected sites (b) Mechanical debridement using plastic curettes + irrigation with 0.2% chlorhexidine + local application of 0.2% chlorhexidine gel</td>
<td>12 months</td>
<td>After 3 and 6 months, the reduction of BOP in group (a) was statistically greater than that in group (b; P &lt; 0.01 and P &lt; 0.05, respectively) After 3 and 6 months, a gain of CAL was significantly obtained in both groups (a) and (b; P &lt; 0.01) No statistical difference of results after 12 months in each group or between two groups (a) and (b)</td>
</tr>
<tr>
<td>Deppe et al.92 Controlled study</td>
<td>Group (a) 13 (39) Group (b) 19 (34)</td>
<td>Resective surgery removing granulation tissue + (a) CO2 laser irradiation with or without bone graft (autogenic bone: βTCP 50:50) + non-resorbable membrane (Gore-Tex G4) (b) Air-abrasion decontamination with or without bone graft (autogenic bone: βTCP 50:50) + non-resorbable membrane (Gore-Tex G4)</td>
<td>5 years</td>
<td>After 4 months, clinical parameters and radiography showed that laser-assisted decontamination (group a) could stop bone loss better than conventional treatment (group b) but results obtained after 5 years did not show a difference of bone level between the two groups</td>
</tr>
<tr>
<td>Romanos and Nentwig93 Controlled study</td>
<td>Group (a) 8 (10) Group (b) 7 (9)</td>
<td>Suppression of granulation tissue using titanium curettes + CO2 laser irradiation + (a) Bone autograft (b) Substitutive material (Bio-Oss) + collagen membrane (Bio-Gide)</td>
<td>27 months</td>
<td>In 2 groups (a) and (b): absence of BOP and suppuration statistically significant reduction of PD bone reconstruction</td>
</tr>
<tr>
<td>Azzeh94 Case report</td>
<td>1 (1)</td>
<td>Rubber cup polishing + Er, Cr:YSGG laser (full-thickness flap access + suppression of granulation tissue + decontamination) + irrigation with saline solution + substitutive material + collagen membrane → repeated intervention after 12 months</td>
<td>18 months</td>
<td>Absence of BOP and suppuration Reduction of PD from 7 mm to 2 mm Diminution of gingival recession from 2 mm to &lt;1 mm</td>
</tr>
</tbody>
</table>

BOP, bleeding on probing; CAL, clinical attachment level; Er, Cr:YSGG, erbium, chromium-doped: yttrium, scandium, gallium and garnet; PD, pocket depth; TCP, tricalcium phosphate.

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**Table 4. Clinical studies of laser-assisted treatment of peri-implantitis**

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of the bone. These elements are in favor of a reduction in the risk of peri-implantitis.

In comparison with periodontal tissue around natural teeth, peri-implant tissue has a poor vascularization but is rich in collagen fibers. The more rapid and more severe evolution of peri-implantitis could be explained by modifications of these anatomical microstructures which lead to a change in the host response. Progression from peri-implant mucositis to peri-implantitis is similar to that from gingivitis to periodontitis, and peri-implantitis also has accelerated periods of bone destruction. A recent systematic review by Berglungh et al. showed that the apical extension of the inflammatory cell infiltrate was more marked in peri-implantitis than in periodontitis and was in most cases located apically of the pocket epithelium. While plasma cells and lymphocytes dominated in both types of lesions, neutrophil granulocytes and macrophages occurred in larger proportions in peri-implantitis than in periodontitis. Hence, the apical extension of the lesion was more pronounced in peri-implantitis than in periodontitis. Therefore, early detection of mucositis and maintenance of peri-implant soft tissue health can prevent the occurrence of peri-implantitis.

Even if an analysis of peri-implant crevicular fluid (PICF) is not a useful parameter for clinically diagnosing peri-implantitis, several studies have shown increasing levels of proinflammatory cytokines such as IL-1β, IL-6, IL8, IL-17 and tumor necrosis factor-α in the PICF of patients with peri-implantitis. Because such proinflammatory cytokines promote osteoclastic activity that may lead to the bone loss, monitoring cytokine levels in the PICF can help in the early detection of inflammatory conditions that may not be clinically apparent.

The concept that the prevention of biological complications is easier than managing them after they have occurred must be inculcated in both patients and clinicians. Patients with a history of periodontitis, and smokers, alcoholics and diabetic patients must be informed that they are at greater than normal risk of peri-implant disease. The clinician should also inform patients having implant-supported restorations that dental plaque and poor oral hygiene play a crucial role in developing peri-implant infections. Thus, regular maintenance of the device after insertion, including oral hygiene instructions for patients, the removal of dental plaque and calculus, occlusal control, prosthesis adjustment and periodic radiographic control contributes to the prevention of peri-implant diseases. Finally, the clinician should be aware that peri-implantitis is difficult to treat and the outcomes may not be predictable. Hence, prevention and control of these risks are essential.

Mechanical treatment alone shows limitations in decontaminating the rough implant surface. Although plastic instruments do not alter the titanium surface they cause macroscopically visible contamination. Having a broader activity spectrum than antibiotics, antiseptics can reduce bacteria resistance but they are potentially toxic to both infectious agents and host cells. Therefore, citric acid with a capacity for removing endotoxin is often used for detoxification of the implant surfaces. Currently, chlorhexidine shows a broad antibacterial spectrum including Gram-positive and Gram-negative bacteria and it also has the ability to bind hard and soft tissues for late release. Moreover, chlorhexidine gluconate may inhibit plaque formation and improve the gingival situation around teeth and implants. In recent years lasers have been used to decontaminate the implant surfaces. Even if animal studies have shown many promising results for lasers such as their bactericidal effect, promoting bone formation and higher bone reconstruction (44.8%) than mechanical (8.7%) or chemical (14.8%) treatments, the improvement of clinical parameters of laser-assisted treatment was still limited in the short term.

Subgingival debridement alone using plastic curettes or ultrasonic instruments is not sufficient for peri-implantitis treatment. Mechanical treatment combined with an antiseptic agent or the local application of antibiotics may improve clinical parameters in the short term but residual defects still persist. Likewise, non-surgical treatment using lasers also demonstrates their minor beneficial effects on peri-implantitis therapy and on improving clinical parameters within 6 months. Resective surgery can remove the infected tissue and promote healing, but the capacity for tissue reconstruction is still a major limitation of this method. Instead, bone regeneration or the application of substitutive material showed the superiority in peri-implantitis treatment in the long term. The application of a membrane can stabilize blood clots, create space for bone regeneration and prevent the migration of connective and epithelium tissues towards peri-implant defects. Nevertheless, membrane exposition is a frequent complication of this method. A local application of chlorhexidine may reduce plaque formation on the exposed membrane but bacterial penetration is not prevented. Therefore, the immediate removal of the exposed membrane is recommended.

The combination of two phases, non-surgical and surgical, seems necessary for the effective treatment of peri-implantitis. Therefore, an excessive combination of different surgical and non-surgical methods for peri-implantitis treatment has often been performed by dentists hoping for ideal results. However, it is difficult to assess the additive effect of each method. This combination leads to more complicated surgical procedures, longer processing time and an increase in price but may not prove beneficial for patients.
Conclusions

Although bacteria are confirmed as being the etiology of peri-implant infections, no clear criteria of microbiota associated with peri-implantitis have been identified to date for diagnosis and treatment. General risks of peri-implantitis including smoking, alcohol consumption, diabetes and possibly genetic traits, xerotomia and postmenopausal osteoporosis are cited as all biological factors that may influence the inflammatory reaction of the patient and host response to infection. Local risk factors including history of periodontitis, dental plaque, poor oral hygiene and possibly absence of keratinized mucosa, implant surface characteristics, location in maxilla are also classified as morphological and environmental conditions that may influence the elimination of bacterial flora. The presence of such risk factors emphasizes the importance of the prevention concept based on early detection and regular maintenance.

The diagnosis of peri-implantitis must include a clinical examination (showing inflammatory signs such as bleeding on probing, a peri-implant pocket depth \( \geq 5 \) mm with or without suppuration) with radiography (indicating bone loss \( \geq 2 \) mm) and differential diagnosis (with peri-implant mucositis, occlusal overload, retrograde peri-implantitis and inflammatory implant periapical lesion). For each clinical situation of the implant infection, it is important to determine treatment goals based on an accurate diagnosis and choose the most appropriate treatment methods to achieve these goals.

The non-surgical treatment of peri-implantitis, including mechanical treatment alone or combined with anti-septic agents or with antibiotics, can improve clinical parameters in the short term but residual defects still persist. Surgical treatment such as guided bone regeneration results in a gain of clinical attachment level and bone reconstruction in the long term. Laser-assisted treatment shows minor beneficial effects in a short term and needs further evaluation. After the therapy, the prevention concept comes back and continually occupies the principal role (Figure 1).

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