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A follow-up study of peri-implantitis cases after treatment

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Abstract

Aim: The aim of this retrospective study was to follow patient cases in a longitudinal manner after peri-implantitis treatment.

Materials and Methods: Two hundred and eighty-one patient cases were selected consecutively from the archives of the Oral Microbiological Diagnostic Laboratory, Gothenburg, Sweden based on microbial analysis of bacterial samples taken from diseased implants. It was feasible to follow-up 245 patients after treatment for a period ranging from 9 months to 13 years.

Results: In 54.7% of the patients it was not feasible to arrest progression of peri-implantitis. Smoking and smoking dose were found to be significantly correlated to failure of peri-implantitis treatment ($p < 0.05$). Early disease development was also significantly associated with failure ($p < 0.05$). Bone plasty in conjunction to antibiotics during surgery was significantly associated with arrested lesions ($p < 0.05$). In a multiple regression model disease development was the only independent variable to significantly predict the likelihood of treatment success.

Conclusions: Peri-implant health may not be easy to establish, especially in cases that develop disease early. Homogenous treatment protocols rather than empirical treatment attempts should be adopted.

Key words: antibiotics; failure; implant loss; osseointegration; peri-implantitis; success; treatment

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Peri-implantitis is a biological complication around dental implants due to the inability of the implant in function to maintain osseointegration (Berglundh et al. 2002, Alsaadi et al. 2008, Pye et al. 2009). Progressive marginal bone loss is synonymous to a failing implant and without diagnostic and therapeutic interventions we may have to deal with a failed implant (implant loss). Systematic long-term scientific documentation of peri-implant marginal bone level changes should be presented by all dental implant systems appearing on the market. However, according to a recent meta-analysis, a 5-year prospective documentation was available only for three dental systems (Laurell & Lundgren 2011). Early diagnosis of peri-implantitis is considered to be of critical importance to arrest progression of the disease, before it reaches a terminal stage (Klinge et al. 2005, Renvert et al. 2008b). Clinicians are encouraged to probe around dental implants at follow-up visits and take follow-up periapical X-rays so as to record marginal bone level changes of the implants in function.

Peri-implantitis is an infectious disease in nature (Mombelli et al. 1987, Leonhardt et al. 1999, Shibli et al. 2008) and the rationale behind treatment is to reduce the bacterial load below the individual threshold for disease so as to re-establish a clinically healthy condition. The main goal of treatment of patients with peri-implantitis is to establish peri-implant health, i.e., arrest the progression of peri-implantitis. Surrogate endpoints of peri-implant treatment are similar to the case of periodontitis and include ''pocket closure'' and absence of suppuration and/or bleeding on probing. Both clinical markers are associated with periodontal and peri-implant stability (Mombelli & Lang 1998, Leonhardt et al. 2003).

It is realized that therapies proposed for the management of peri-implant diseases appear to be largely based on the evidence available for the treatment of periodontitis. Peri-implant mucositis and mild incipient peri-implantitis lesions may be resolved using the cause related measures and non-surgical approach (Lang et al. 2011). Non-surgical therapy alone does not seem to be effective in moderate/severe peri-implantitis lesions. However, this treatment modality should be the preliminary step in the treatment strategy of all peri-implantitis cases, so as to create

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appropriate soft tissue conditions and establish optimal self-performed infection control before taking further decision for surgery. At the re-examination and after having been convinced about the patient's compliance, we decide further surgical therapy if the disease is not arrested, i.e. bleeding on probing/suppuration in combination with deep probing measurements at the sites of pathology.

Most studies on the treatment of peri-implantitis have used systemic antibiotics as an adjunct to surgical interventions (Mombelli & Lang 1992, Leonhardt et al. 2003, Roos-Jansaker et al. 2003). The rationale is the infectious nature of peri-implant disease – established in the literature (Salcetti et al. 1997, Mombelli & Lang 1998, Leonhardt et al. 1999, Quirynen et al. 2002, Heydenrijk et al. 2002) – as well as the inherent difficulty in the mechanical cleansing of the implant surface (Renvert et al. 2008b). The design of the implant (presence of threads coupled with a rough surface structure, as often encountered), does not allow a suppression of the microflora to a level compatible to health by mechanical means alone. Thus, one local antibiotic (minocycline, Arestin, OraPharma Inc., Warminster, PA, USA) has also been applied together with non-surgical mechanical debridement and proved to show improved clinical (Renvert et al. 2006, Salvi et al. 2007, Renvert et al. 2008a) and radiographical (Salvi et al. 2007) parameters over 1 year period. However, no local antibiotics have been tested as adjunct to surgical therapy in prospective clinical trials.

To date, the experience accumulated on peri-implantitis treatment is mostly empirical (Claffey et al. 2008). Although diagnosis of the disease has recently reached a clear consensus (Lindhe & Meyle 2008), universal criteria for success and failure of peri-implantitis treatment have not yet been established. At present, there is no reliable evidence for the most successful method of treating peri-implantitis.

The aim of this retrospective study was to follow patient cases in a longitudinal manner after peri-implantitis treatment. Factors associated to the treatment result were also investigated.

Materials and Methods

All patients were selected consecutively from the archives of the Oral Microbiological Diagnostic Laboratory, Gothenburg, Sweden between January 2005 and January 2009. The patients originate from various public and private dental clinics of Sweden, as reported in a previous study (Charalampakis et al. 2011).

The baseline recordings for this investigation were set at the time clinicians recorded pathology and decided to proceed with microbial sampling around diseased dental implants. One of the authors (C. G.), who had no affiliation to any of the centres, visited the centres with the greatest representation. Permission was given by the head of each clinic to get access to the patient files at appropriate working hours. A form was designed and filled in separately for each patient case including data on type of treatment of peri-implant disease, treatment result and follow-up period. Various definitions with clinical and radiographical thresholds were decided for reasons of consistency before the investigation was initiated. Peri-implantitis was defined as follows: presence of suppuration and/or bleeding on probing with probing pocket depth (PPD) $\geqslant 5$ mm and radiographic images of marginal bone loss $\geqslant 1.8$ mm (or three threads of implants with implant pitch 0.6 mm) after 1 year of implants in function. Presence of pus and/or bleeding on probing with PPD $\geqslant 7$ mm on at least one aspect of the implant was characterized severe peri-implantitis. If probing measurement had not been recorded, radiographic images had been considered and marginal bone loss $>1/3$ implant length after 1 year of implants in function was the cut-off point for severe peri-implantitis. Any other case with lower threshold was assigned as mild peri-implantitis. Disease development was defined as the time span for disease to occur. Early disease development was synonymous to having implants in function <4 years and late disease development to having implants in function for >6 years before disease was developed. Number of implants means the number of implants that had been installed in each patient in both jaws and were in function at the time of our baseline recordings.

Baseline patient characteristics, dental status and periodontal conditions, implant treatment as well as peri-implant disease characteristics at the time of disease diagnosis have been presented elsewhere (Charalampakis et al. 2011). Briefly, 61.6% of the patients were women and the prevailing age interval was 60–79 years old (70.5%). 38.4% were current cigarette smokers and 41.3% never smoked. Out of 108 cigarette smokers, smoking dose was recorded for 93 patients. 25.9% were heavy smokers (>15 cigarettes a day), 23.2% were moderate smokers (10–15 cigarettes a day) and 37% were light smokers (<10 cigarettes a day). Severe peri-implantitis was diagnosed in 91.4% and mild peri-implantitis in 6.8% of the patient cases. In 41.3% of patients peri-implantitis was developed early, already after having implants in function for <4 years. In 27% of the cases peri-implantitis was developed after 6 years and in 25% between 4 and 6 years of implants in function.

The clinicians took bacterial samples around the diseased implants with the intention of identifying the associated pathogens. Microbial testing would allow them to choose the most effective antibiotic regimen for every case. The baseline microbial results from both culture and checkerboard analyses have been published previously in detail (Charalampakis et al. 2011) and summarised in Table 1. Having the above clinical and microbiological baseline information, we intended to follow-up the cases after peri-implant disease was diagnosed so as to know the endpoint of the disease and associated therapeutic interventions.

Treatment success and failure criteria

Peri-implantitis treatment success criteria were absence of repeated bleeding on probing and/or suppuration in conjunction to PPD <5 mm. Radiographically, increased or stable marginal bone levels compared with the baseline periapical x-rays were synonymous to treatment success. Any clinical measurements different from the above thresholds or obvious progressive bone loss radiographically were synonymous to treatment failure.

Postoperative recall sessions/oral hygiene procedures

Following surgery, the patients rinsed twice a day for 1 min. with chlorhexidine 0.12% for a period of 2–3 weeks. The sutures were removed 10 days to 2 weeks after the surgery. One week following suture removal, the patients received new oral hygiene instructions

Table 1. Baseline presence and counts of bacteria at moderately heavy/heavy amounts

Scale bacteria	Moderately heavy/heavy (culture)	Score ⩾3 (checkerboard)
	percentage of subjects (%)	
Prevotella intermedia/Prevotella nigrescens	27.3	
AGNB	18.6	
Aggregatibacter actinomycetemcomitans	6	4.2
Tannerella forsythia		37.3
Treponema denticola		31
Prevotella nigrescens		28.9
Prophyromonas endodontalis		28.6
P. intermedia		25.4

AGNB, aerobic Gram-negative bacilli.

tailored to their needs and the individualized sequence of healing events, aiming at optimal plaque control. The patients were recalled at 3, 6, 9 months and once a year thereafter for re-evaluation and maintenance care. The maintenance care included patient motivation and oral hygiene instructions, supragingival plaque control at sites with mucosal inflammation and subgingival scaling at implant sites presenting residual bleeding pockets. Implants with remaining pathology and progressive bone loss, causing symptoms and discomfort to the patients were removed.

Follow-up microbiological analysis

Additional microbial samples were taken at a follow-up appointment, at some time point after peri-implantitis treatment. The sample sites around the diseased implants were isolated with cotton rolls and supragingival plaque was removed with sterile cotton pellets. One to three sterile paper points/site (Johnson & Johnson, East Windsor, NJ, USA) were inserted to the depth of the peri-implant pocket and kept in place for 15 s. The microbial samples were sent to the Oral Microbiological Diagnostic Laboratory and processed for culture analysis. They were transferred aseptically to vials, containing 3.3 ml VMGA III (Dahlen et al. 1993) and processed in the laboratory. After mixing a volume of 0.1 ml of the concentrated transport medium to 1:100 and 1:10,000 times dilution in VMGA III, bacteria were plated onto the surface of an enriched Brucella blood agar plate (BBL, Microbiological System, Cockeysville, MD, USA). The agar plates were incubated anaerobically in jars using the hydrogen combustion method (Möller & Möller 1961) at 37°C during 6–8 days for calculating the total viable count (TVC). *Porphyromonas gingivalis* was distinguished from *Prevotella intermedia/Prevotella nigrescens* by its haemagglutinating activity and lack of auto-fluorescence in UV-light (Slots & Genco 1979, Slots & Reynolds 1982). Blood agar (Difco), Staphylococcus agar (Difco), Enterococcus agar (BBL) and TSBV agar plates (BBL) were inoculated and incubated for 2 and 5 days, respectively, at 37°C in air with 10% CO_2. Special attention was given to *Staphylococcus aureus*, *Staphylococcus epidermidis*, enterococci and aerobic Gram-negative bacilli (AGNB). *S. aureus* was distinguished from *S. epidermidis* by performing DNase test on special DNA agar plate (Difco). The plates were examined for typical colony morphology and the specific bacteria were registered as percentage of TVC. We used five different scales to frame the magnitude of bacteria as proportions of TVC, in a fashion similar to the baseline microbiological results (Charalampakis et al. 2011).

Statistical analysis

Both descriptive statistics and statistical analyses were performed with the statistical package PASW Statistics 18.0 (SPSS Inc., Chicago, IL, USA). Variables are presented as absolute and relative frequencies (%). The statistical computational unit was at subject level. In most cases it was more than one implant that was diseased in the same patient. Clinical recordings and microbial samples taken at site level – and most often at multiple sites – were pooled to a mean value per patient. Chi-square tests were applied to study correlations of various independent variables to a binary dependent variable, i.e., treatment result. Multiple logistic regression analysis was also performed stepwise and a final model was constructed. Results were regarded statistically significant at p-value < 0.05.

Results

Peri-implantitis treatment-related characteristics (Table 2)

Two hundred and twenty-eight patients (83.2%) were treated surgically, whereas the remaining 46 patients (16.8%) were treated only non-surgically. Six different surgical approaches could be identified. Access flap and surgical cleaning together with systemic antibiotics therapy was the most prevalent approach (40.5%), followed by access flap and surgical cleaning without systemic antibiotics (17.5%). Apically repositioned flaps with bone plasty and reconstructive surgical therapy with or without systemic antibiotics were less frequently performed.

Treatment protocols varied significantly among clinicians and clinics. Non-surgical mechanical debridement was performed in most cases by means of titanium or carbon-fibre curettes and seldom by ultrasonic instrument. In all centres, deep peri-implant pockets were finally rinsed with various antiseptics (NaCl, chlorhexidine, iodine).

With regard to antibiotics, the choice during surgery was based on the results of the baseline microbial testing (Table 1). The most frequent antibiotic regimen was the combination of amoxicillin and metronidazole, as used in 47.1% of the patients. In one case that the patient was allergic to amoxicillin, the combination of clindamycin and metronidazole was chosen. Metronidazole was used in 20% of the patients, aiming at Gram-negative anaerobic bacteria, whereas ciprofloxacin in 11.2%. Ciprofloxacin was chosen in the presence of increased numbers of AGNB. Other antibiotic regimens against anaerobic pathogens, less commonly used, were: tetracycline, tetracycline in conjunction to amoxicillin, penicillin V, amoxicillin alone, clindamycin, amoxicillin with clavulanic acid and azithromycin. All the above antibiotics were administered per os in doses and duration (days/week) that varied among clinicians. Compliance with antibiotics was not reported in most cases but in two cases lack of

compliance was recorded. Table 3 depicts the types of antibiotics chosen during surgery, based on the results of the baseline microbial testing.

The antiseptics used during surgery varied in concentrations and were either single or in combinations (NaCl, H_2O_2, chlorhexidine, iodine) dependent on the protocol of the individual clinic. The protocol used in all cases from one centre was somewhat special and included a combination of 3% H_2O_2, 0.04% iodine, 0.2% chlorhexidine and final rinses with NaCl. With regard to local antibiotics, Atridox gel (doxycycline hyclate 10%) (Atrix Laboratories, Fort Collins, CO, USA) and Elyzol gel (25% metronidazole) (Colgate-Palmolive Company, New York, NY, USA) were used in nine and five cases, respectively. Periochip (chlorhexidine gluconate 2.5 mg) (Adrian Pharmaceuticals, LLC, Spring Hill, FL, USA) was also used in one patient.

Reconstructive surgery performed in 33 patients varied also significantly in terms of reconstructive material. The porous fluorohydroxyapatitic biomaterial FRIOS Algipore (Dentsply Friadent, Mannheim, Germany) was used in 11 cases, the enamel matrix derivative (Emdogain) (Straumann, Basel, Switzerland) was used in 20 cases, in one case Emdogain was combined with synthetic bone graft material (Bone ceramic, Straumann, Basel, Switzerland) in the same peri-implant site, whereas in one patient Emdogain and Bio-Oss (Geistlich Biomaterials, Wolhuser, Switzerland) were used in two different peri-implant sites.

The follow-up period after treatment could be recorded for 245 patient cases. 98% of these patients were followed for up to 6 years after treatment. One case could be followed for 13 years after treatment. Having in mind the thresholds for success and failure of treatment, as set above, we found out that success of treatment was associated with 45.3% of all 245 cases, whereas the rest 54.7% were associated with failure and inability to arrest the progression of peri-implantitis. Notably, in 30 patients (11%) at least one implant had to be removed during surgery or at some time point after surgery because peri-implantitis reached its terminal stage and implant loss was unavoidable.

We investigated factors which proved to be associated with the treatment result. The effect of smoking on the treatment result was further analysed.

Table 2. Peri-implantitis treatment-related characteristics

Variables	Subcategory	N^*	$\%^\dagger$
Type of treatment ($N = 274$)	Non-surgical	46	16.8
	Surgical	228	83.2
Surgical treatment	Access flap without antibiotics	48	17.5
	Access flap with antibiotics	111	40.5
	Apical repositioned flap without antibiotics	9	3.3
	Apical repositioned flap with antibiotics	27	9.9
	Reconstructive surgery without antibiotics	1	0.4
	Reconstructive surgery with antibiotics	32	11.7
Follow-up after treatment ($N = 245$)	9 months–1 year	96	39.2
	2–3 years	104	42.4
	4–6 years	40	16.3
	>6 years	5	2
Treatment result ($N = 245$)	Success	111	45.3
	Failure	134	54.7

*Number of subjects in absolute count.
†Percentage of subjects.

Table 3. Antibiotic regimen chosen based on baseline microbial analysis

Variables	Subcategory	N^*	$\%^\dagger$
Type of antibiotic during surgery	Amoxicillin+metronidazole	80	47.1
	Metronidazole	34	20
	Ciprofloxacin	19	11.2
	Tetracycline	11	6.5
	Amoxicillin+tetracycline	7	4.1
	Penicillin V	6	3.5
	Amoxicillin	5	2.9
	Clindamycin	5	2.9
	Clindamycin+metronidazole	1	0.6
	Amoxicillin + clavulanic acid	1	0.6
	Azithromycin	1	0.6

*Number of subjects in absolute count.
†Percentage of subjects.

We performed separate χ^2-tests for cigarette smokers and non-smokers. We found that non-smokers were associated statistically significantly with success compared with smokers ($p = 0.002$). Cigarette smokers were also statistically significantly correlated with failure ($p = 0.002$). Moreover, in the present study the dose of smoking was strongly associated with the treatment result, showing a clear statistical significant difference ($p = 0.011$). Fewer moderate and heavy smokers were associated with success compared with non-smokers.

We performed χ^2-tests to investigate a potential statistical significant association of disease development on the treatment result. We found that early disease development was significantly associated with failure ($p = 0.007$), whereas late disease development, i.e. >6 years was significantly associated with success ($p = 0.047$). Disease development between 4 and 6 years was not associated with the treatment result ($p = 0.328$).

We performed χ^2-tests separately for every treatment modality to find potential correlations to the treatment result. Apical repositioned flap with bone recontouring and antibiotics was statistically significantly associated with success ($p = 0.018$). Reconstructive surgery with antibiotics was also associated with success but did not reach a statistical significant difference ($p = 0.082$). Access flap alone with antibiotics proved to be associated to failure but the difference was also not statistically significant ($p = 0.858$).

In addition, we performed multiple logistic regression analysis stepwise to assess the impact of a number of factors on the likelihood that the subjects would experience success of peri-implantitis treatment. All potential factors [type of centre (public/private), centre per se, age, sex, health, specific diseases, medication, edentulism, oral hygiene,

cigarette smoking, previous periodontitis, periodontitis, type and position of the implant, number of implants, extent of disease, disease severity, disease development, non-surgical/surgical treatment, all types of surgical treatment, type of bacteria per se, magnitude of bacteria] have been tested separately with χ^2-tests for potential statistical significant correlations with the categorical dependent variable, i.e. treatment result. Type of centre (public/private), sex, health, specific diseases or medication, edentulism, oral hygiene, previous periodontitis, periodontitis, type and position of the implant and extent of disease were not found to be correlated to the treatment result and were not included in the final model (data not shown). The model contained 12 independent variables, including all seven treatment interventions and correctly classified 69.2% of the cases. Only one independent variable (disease development) made a unique statistically significant contribution to the model, as shown in Table 4. This implies that timing of disease development was able to surely predict the treatment result, whereas the rest eleven variables (age, smoking, number of implants, disease severity and all seven treatment modalities) did not contribute statistically significantly to the likelihood of treatment success.

Microbiological characteristics (Table 5)

Microbial samples around implants of 27 patients were taken at a follow-up appointment after peri-implantitis treatment and processed for culture analysis. The main concern for the clinician in 23 cases was to identify the pathogens associated with ongoing peri-implant infection so as to choose the most effective antibiotic regimen. In three cases the clinician wanted to verify the low number of periodontal pathogens, associated with treatment success. In one patient the treatment result was not known, thus we were unable to understand the rationale behind additional microbial sampling.

Culture analysis showed that *P. gingivalis* and *P. intermedia/P. nigrescens* were the most representative bacteria in magnitude as found in moderately heavy and heavy growth in 25.9% and 22.2% of all cases, respectively. AGNB also had significant representation, as found at moderately heavy growth in 25.9% of the cases respectively. *S. aureus* and fungi were not detected in 100% of the patients, whereas *Aggregatibacter actinomycetemcommitans* in 88%. Enterococci and AGNB were equally not detected in 85.2% of the cases.

Table 4. Logistic regression model predicting likelihood of treatment success

Final independent variables	Odds ratio	95% CI for odds ratio		*p*-value
		lower	upper	
Age	1.016	0.986	1.046	0.308
Smoking	1.890	0.990	3.606	0.054
Number of implants	0.791	0.533	1.173	0.243
Disease severity	0.273	0.073	1.023	0.054
Non-surgical treatment	1.989	0.566	6.985	0.284
Access flap without antibiotics	0.664	0.201	2.195	0.502
Access flap with antibiotics	1.141	0.451	2.885	0.780
Apical repositioned flap without antibiotics	0.876	0.147	5.217	0.884
Apical repositioned flap with antibiotics	3.073	0.898	10.513	0.074
Reconstructive surgery without antibiotics	1.989	0.566	6.985	0.284
Reconstructive surgery with antibiotics	9.833	0.000	–	1.000
Disease development	1.702	1.173	2.469	0.005

Discussion

This retrospective study investigates patient cases in a longitudinal manner after peri-implantitis treatment. Baseline characteristics of this material at the time of diagnosis have been described in detail in a previous study (Charalampakis et al. 2011) but certain patient, implant and peri-implant disease characteristics have been summarised again as found to be correlated to the treatment result. Thus, we were able to map out the course of peri-implant disease and associate potential contributing factors to the treatment result. However, due to the retrospective design of the study no cause-effect relationships can be determined and results should be interpreted with caution.

On the one hand, the extremely prolonged period of follow-up until peri-implantitis development, treatment and some years after treatment is striking, as it would be almost impossible to design a prospective controlled clinical trial with such an extended follow-up period. On the other hand, this study lacks uniformity as it provides cases from different clinics with various protocols and unstandardized follow-up periods, making comparison between cases impossible.

The multicentre design of this study depicts the great variation in the treatment modalities performed in different centres in an attempt to arrest progression of peri-implant disease. It verifies more or less the conclusion of the recent consensus (Claffey et al. 2008) that there is currently no evidence-based

Table 5. Presence and counts of bacteria after peri-implantitis treatment as detected by culture analysis for 27 patients

Scale Bacteria	Non-detected	Very sparse	Sparse	Moderately heavy	Heavy
			percentage of subjects (%)		
Aggregatibacter actinomycetemcomitans	88	4	4	4	0
Porphyromonas gingivalis	70.4	0	3.7	18.5	7.4
Prevotella intermedia/Prevotella nigrescens	51.9	3.7	22.2	7.4	14.8
Staphylococcus aureus	100	0	0	0	0
Staphylococcus epidermidis	77.8	22.2	0	0	0
Enterococci	85.2	7.4	0	3.7	3.7
AGNB	85.2	3.7	0	25.9	0
Fungi	100	0	0	0	0

AGNB, aerobic Gram-negative bacilli.

peri-implantitis treatment to offer. A recent meta-analysis of peri-implantitis treatment (Kotsovilis et al. 2008) included five randomized controlled and/or comparative trials. However, they were not optimally designed (small sample size, short follow-up period) making it impossible to draw clear conclusions with regard to the most effective therapeutic interventions. Although this study presents a significant amount of patient cases, we still cannot draw clear conclusions because it is retrospective and heterogenous to a large extent. It has a descriptive character of treatment patterns among clinicians and was not aiming at comparing different treatment modalities.

Non-surgical treatment alone was performed in 16.8% of the subjects. It refers mainly to patients with incipient peri-implant lesions or patients who either were unwilling to proceed with surgery or had suboptimal oral hygiene. This first phase of therapy comprised of both mechanical (carbon fibre or titanium curettes/ultrasonic device) and chemical means (rinses with antiseptic agent). In randomized controlled trials no significant difference was found over a 6-month period between an ultrasonic device and carbon fibre curettes (Karring et al. 2005) or an ultrasonic device and titanium hand instruments (Renvert et al. 2009). No laser therapy was applied in any of the centres. Existing evidence from randomized controlled trials of 6 (Renvert et al. 2011) or 12 months (Schwarz et al. 2006a) does not favour the use of the Er:YAG laser over mechanical debridement.

The most prevalent surgical intervention in our study was access flap debridement in conjunction to systemic antibiotics. A previous study (Leonhardt et al. 2003) based on nine patients and 26 implants reported the use of systemic antibiotic therapy in combination to surgical debridement. In our material antibiotics were used in most cases and the type of systemic antibiotic was also decided after the result of microbial analysis. Amoxicillin together with metronidazole was the prevalent ''cocktail'' against periodontal pathogens, as in the case of chronic periodontitis. This dual antibiotic regimen originally was used in *A. actinomycetemcommitans* associated periodontitis and proved to eradicate this specific bacterium (van Winkelhoff et al. 1992). A later double blind placebo study (Winkel et al. 2001) with favourable results set the pace for use of amoxicillin and metronidazole for all cases of chronic periodontitis. However, we should bear in mind the short-term (6 month) duration of the study. No detection of *A. actinomycetemcommitans* in the majority of peri-implantitis cases (Tables 1 and 5) may imply the unnecessary use of a ''cocktail'' in the treatment of peri-implantitis. Peri-implantitis is defined as a polymicrobial anaerobic infection and metronidazole alone should be effective as a broad-spectrum antibiotic against anaerobic bacteria.

The goal of therapy, i.e. establishment of peri-implant health was not achieved in more than half of the patients. The criteria for success were rather harsh as set on a subject level with no pockets $\geqslant 5$ mm associated with bleeding/suppuration. It does not make sense to name goal of therapy the ''control'' of infection at one implant site but not at others in the same mouth. In a recent 2-year prospective single centre clinical trial (Serino & Turri 2011) peri-implantitis treatment was successful in 77% of the patients. However, the thresholds for success were higher (no pockets $\geqslant 6$ mm) compared with our study and if lowered to $\geqslant 4$ mm, the percentage of successful patient cases dropped down to 48%. Failed patient cases with peri-implantitis in our study were significantly correlated to disease severity, which makes absolute sense. The vast majority of our patients were suffering from severe peri-implantitis (91.4%).

Smoking was also found to be significantly associated to the treatment result. The only available relevant study on a subject level (Leonhardt et al. 2003) showed that smokers with severe peri-implantitis had a less favourable treatment outcome. In a recent study (Serino & Turri 2011), no statistical significant difference was noted in the number of healthy implants after treatment between smokers and non-smokers but the statistical analysis was at implant level. In the present study, the dose of smoking was strongly associated with an impaired healing outcome. Moderate and heavy smokers were significantly correlated to failure compared with non-smokers. These findings are in line with the knowledge from periodontitis that smokers are associated with impaired healing response to periodontal therapy compared with non-smokers (Ah et al. 1994, Tonetti et al. 1995, Rosen et al. 1996, Trombelli et al. 1997, Bergstrom 2006) as well as that the effect of smoking on the outcome of periodontal treatment is dose dependent (Kaldahl et al. 1996, Tonetti 1998).

Disease development was also found to be significantly associated with the treatment result. Interestingly, early disease development was significantly correlated to failure. These results could be explained better, if combined with the additional knowledge from the previous study (Charalampakis et al. 2011), that moderately rough surfaces, i.e. Nobel TiUnite (Nobel Biocare, Gothenburg, Sweden) and Astra Osseospeed (Astra, Mölndal, Sweden) surfaces were associated with early disease development, whereas smooth surfaces, i.e., Nobel turned surface with late disease development. The implant rough surface structure may provide the bacteria with ''protected areas'' inaccessible to conventional mechanical removal. Moreover, bacteria may express a more virulent and resistant profile in this ''protected'' ecological niche mimicking an acute infection at early stage and their reduction to levels compatible to health may not be an easy task with the current chemomechanical means. However, this is a plausible scenario that needs further investigation.

At present, there is no reliable evidence for the most successful method of treating peri-implantitis. However, in our study apical repositioned flap with bone plasty in conjunction to antibiotics was statistically significantly associated with success. Resective surgery was not combined with alteration of the topography of the implant surface (implantoplasty) in any of the cases. However, implantoplasty has been suggested in the literature with improved clinical outcomes (Romeo et al. 2005, Schwarz et al. 2011). Another recent study (Serino & Turri 2011) concluded that apical repositioned flap with bone recontouring alone was an effective means to treat peri-implantitis for the majority of the patients over a 2-year period. Reconstructive surgery with antibiotics was also associated with arrested lesions in our study but did not reach a statistical significant difference. A randomized controlled trial proved to show clinical attachment level gains for two reconstructive approaches over a 6-month period (Schwarz et al. 2006b). Centres consistently following one of the above treatment regimens, either resection or reconstruction, towards an alteration of the deepened and diseased pocket, had

more success in their treatment outcome (data not shown). Access flap alone with antibiotics proved to be associated to more failure than success but the difference was also not statistically significant. These associations should be interpreted with caution because of the retrospective and heterogenous design of the study. In contrast to our results, a short-term (3 months) prospective trial with few subjects (Maximo et al. 2009) suggests that open flap debridement could be used as a standard procedure in the treatment of peri-implantitis.

Baseline microbial findings were not correlated to the treatment result neither in terms of name nor magnitude. Not a single specific bacterium was correlated to more success than failure. We would expect this result because peri-implantitis is a polymicrobial rather than a specific infection. Severity of the disease in the multiple regression analysis was correlated to the treatment result but not the magnitude of bacteria. However, we would expect more bacteria to survive and thrive in the deepest pockets and thus less chance to succeed in therapy. This paradox result is probably explained by the inabilities of the current sampling methods to fully disclose the magnitude and virulence patterns of the associated microbiota.

The microbiological results after peri-implantitis treatment stem from culture analysis of samples harvested from 27 patients. The rationale behind further microbiological analysis in the majority of the cases was the inability to arrest further progression of peri-implantitis and the concomitant dilemma about the type of antibiotic to choose. We used different thresholds of magnitude so as to describe not just the presence/absence of the associated peri-implant pathogens but also a measure of growth and increased number. Similarly, we would expect bacteria to be a lot more representative in terms of magnitude in the sites with progression of peri-implant disease but we did not observe optimal correlations to the clinical results. Underpowered results may again imply that we face a clear inability to ''frame'' the associated microbiota. However, AGNB were still detected at moderately heavy growth in increased number of the patients (25.9%), despite the previous use of systemic antibiotic (ciprofloxacin). AGNB consist of enteric rods and non-lactose fermenting Gram-negative rods (e.g. *Pseudomonas* spp., *Klebsiella* spp.), which have proven to be multi-resistant and difficult to eradicate (Goncalves et al. 2007). *P. gingivalis* and *P. intermedia* were also detected at moderately heavy/heavy growth in about 1/4 of the patients, respectively. Culture detected at least one species at moderately heavy/heavy growth in 60.9% of patients with unarrested infection. Thus, culture was able to ''identify'' peri-implant disease after failed treatment in more than half of the subjects, similarly to peri-implant cases before treatment (Charalampakis et al. 2011).

Coming to a conclusion, clinicians are bound to run into cases of peri-implantitis more and more often and should be alert to diagnose them before the disease reaches its terminal stage. Peri-implantitis is probably hard to eradicate. Nowadays, treatment of peri-implantitis is directed towards divergent orientations without a single optimal treatment regimen, mainly due to the fact that pathogenesis of peri-implantitis has not yet been fully elucidated. Homogenous evidence-based treatment protocols rather than empirical treatment attempts should be adopted so that comparative analysis of treatment strategies could be investigated. The present study represents the largest clinical analysis of patients with peri-implantitis with the most extended follow-up to date but has limitations due to its retrospective design. Ideally, it will stimulate carefully designed prospective trials to optimise peri-implantitis treatment in the future.

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References

Ah, M. K., Johnson, G. K., Kaldahl, W. B., Patil, K. D. & Kalkwarf, K. L. (1994) The effect of smoking on the response to periodontal therapy. *Journal of Clinical Periodontology* **21**, 91–97.

Alsaadi, G., Quirynen, M., Komarek, A. & van Steenberghe, D. (2008) Impact of local and systemic factors on the incidence of late oral implant loss. *Clinical Oral Implants Research* **19**, 670–676.

Berglundh, T., Persson, L. & Klinge, B. (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. *Journal of Clinical Periodontology* **29** (Suppl. 3), 197–212; discussion 232-193.

Bergstrom, J. (2006) Periodontitis and smoking: an evidence-based appraisal. *The Journal of Evidence Based Dental Practice* **6**, 33–41.

Charalampakis, G., Leonhardt, Å., Rabe, P. & Dahlén, G. (2011) Clinical and microbiological characteristics of peri-implantitis cases: a retrospective multicenter study. *Clinical Oral Implants Research* doi: 10.1111/j.1600-0501.2011.02258.x.

Claffey, N., Clarke, E., Polyzois, I. & Renvert, S. (2008) Surgical treatment of peri-implantitis. *Journal of Clinical Periodontology* **35**, 316–332.

Dahlen, G., Pipattanagovit, P., Rosling, B. & Moller, A. J. (1993) A comparison of two transport media for saliva and subgingival samples. *Oral Microbiology and Immunology* **8**, 375–382.

Goncalves, M. O., Coutinho-Filho, W. P., Pimenta, F. P., Pereira, G. A., Pereira, J. A., Mattos-Guaraldi, A. L. & Hirata, R. Jr. (2007) Periodontal disease as reservoir for multi-resistant and hydrolytic enterobacterial species. *Letters in Applied Microbiology* **44**, 488–494.

Heydenrijk, K., Meijer, H. J., van der Reijden, W. A., Raghoebar, G. M., Vissink, A. & Stegenga, B. (2002) Microbiota around root-form endosseous implants: a review of the literature. *The International Journal of Oral & Maxillofacial Implants* **17**, 829–838.

Kaldahl, W. B., Johnson, G. K., Patil, K. D. & Kalkwarf, K. L. (1996) Levels of cigarette consumption and response to periodontal therapy. *Journal of Periodontology* **67**, 675–681.

Karring, E. S., Stavropoulos, A., Ellegaard, B. & Karring, T. (2005) Treatment of peri-implantitis by the Vector system. *Clinical Oral Implants Research* **16**, 288–293.

Klinge, B., Hultin, M. & Berglundh, T. (2005) Peri-implantitis. *Dental Clinics North America* **49**, 661–676.

Kotsovilis, S., Karoussis, I. K., Trianti, M. & Fourmousis, I. (2008) Therapy of peri-implantitis: a systematic review. *Journal of Clinical Periodontology* **35**, 621–629.

Lang, N. P., Bosshardt, D. D. & Lulic, M. (2011) Do mucositis lesions around implants differ from gingivitis lesions around teeth? *Journal of Clinical Periodontology* **38** (Suppl. 11), 182–187.

Laurell, L. & Lundgren, D. (2011) Marginal bone level changes at dental implants after 5 years in function: a meta-analysis. *Clinical Implant Dentistry and Related Research* **13**, 19–28.

Leonhardt, A., Dahlen, G. & Renvert, S. (2003) Five-year clinical, microbiological, and radiological outcome following treatment of peri-implantitis in man. *Journal of Periodontology* **74**, 1415–1422.

Leonhardt, A., Renvert, S. & Dahlen, G. (1999) Microbial findings at failing implants. *Clinical Oral Implants Research* **10**, 339–345.

Lindhe, J. & Meyle, J. (2008) Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology. *Journal of Clinical Periodontology* **35**, 282–285.

Maximo, M. B., de Mendonca, A. C., Renata Santos, V., Figueiredo, L. C., Feres, M. & Duarte, P. M. (2009) Short-term clinical and microbiological evaluations of peri-implant diseases before and after mechanical anti-infective therapies. *Clinical Oral Implants Research* **20**, 99–108.

Möller, O. & Möller, A. (1961) Some methodological considerations for anaerobic cultivation. *Acta Pathology Microbiology Scandinavica* **51** (Suppl. 144), 245–247.

Mombelli, A. & Lang, N. P. (1992) Antimicrobial treatment of peri-implant infections. *Clinical Oral Implants Research* **3**, 162–168.

Mombelli, A. & Lang, N. P. (1998) The diagnosis and treatment of peri-implantitis. *Periodontology 2000* **17**, 63–76.

Mombelli, A., van Oosten, M. A., Schurch, E. Jr. & Land, N. P. (1987) The microbiota associated with successful or failing osseointegrated titanium implants. *Oral Microbiology Immunology* **2**, 145–151.

Pye, A. D., Lockhart, D. E., Dawson, M. P., Murray, C. A. & Smith, A. J. (2009) A review of dental implants and infection. *The Journal of Hospital Infection* **72**, 104–110.

Quirynen, M., De Soete, M. & van Steenberghe, D. (2002) Infectious risks for oral implants: a review of the literature. *Clinical Oral Implants Research* **13**, 1–19.

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

Renvert, S., Lessem, J., Dahlen, G., Renvert, H. & Lindahl, C. (2008a) Mechanical and repeated antimicrobial therapy using a local drug delivery system in the treatment of peri-implantitis: a randomized clinical trial. *Journal of Periodontology* **79**, 836–844.

Renvert, S., Lindahl, C., Roos Jansaker, A. M. & Persson, G. R. (2011) Treatment of peri-implantitis using an Er: YAG laser or an air-abrasive device: a randomized clinical trial. *Journal of Clinical Periodontology* **38**, 65–73.

Renvert, S., Roos-Jansaker, A. M. & Claffey, N. (2008b) Non-surgical treatment of peri-implant mucositis and peri-implantitis: a literature review. *Journal of Clinical Periodontology* **35**, 305–315.

Renvert, S., Samuelsson, E., Lindahl, C. & Persson, G. R. (2009) Mechanical non-surgical treatment of peri-implantitis: a double-blind randomized longitudinal clinical study. I: clinical results. *Journal of Clinical Periodontology* **36**, 604–609.

Romeo, E., Ghisolfi, M., Murgolo, N., Chiapasco, M., Lops, D. & Vogel, G. (2005) Therapy of peri-implantitis with resective surgery. A 3-year clinical trial on rough screw-shaped oral implants. Part I: clinical outcome. *Clinical Oral Implants Research* **16**, 9–18.

Roos-Jansaker, A. M., Renvert, S. & Egelberg, J. (2003) Treatment of peri-implant infections: a literature review. *Journal of Clinical Periodontology* **30**, 467–485.

Rosen, P. S., Marks, M. H. & Reynolds, M. A. (1996) Influence of smoking on long-term clinical results of intrabony defects treated with regenerative therapy. *Journal of Periodontology* **67**, 1159–1163.

Salcetti, J. M., Moriarty, J. D., Cooper, L. F., Smith, F. W., Collins, J. G., Socransky, S. S. & Offenbacher, S. (1997) The clinical, microbial, and host response characteristics of the failing implant. *The International Journal of Oral & Maxillofacial Implants* **12**, 32–42.

Salvi, G. E., Persson, G. R., Heitz-Mayfield, L. J., Frei, M. & Lang, N. P. (2007) Adjunctive local antibiotic therapy in the treatment of peri-implantitis II: clinical and radiographic outcomes. *Clinical Oral Implants Research* **18**, 281–285.

Schwarz, F., Bieling, K., Bonsmann, M., Latz, T. & Becker, J. (2006a) Nonsurgical treatment of moderate and advanced periimplantitis lesions: a controlled clinical study. *Clinical Oral Investigations* **10**, 279–288.

Schwarz, F., Bieling, K., Latz, T., Nuesry, E. & Becker, J. (2006b) Healing of intrabony periimplantitis defects following application of a nanocrystalline hydroxyapatite (Ostim) or a bovine-derived xenograft (Bio-Oss) in combination with a collagen membrane (Bio-Gide). A case series. *Journal of Clinical Periodontology* **33**, 491–499.

Schwarz, F., Sahm, N., Iglhaut, G. & Becker, J. (2011) Impact of the method of surface debridement and decontamination on the clinical outcome following combined surgical therapy of peri-implantitis: a randomized controlled clinical study. *Journal of Clinical Periodontology* **38**, 276–284.

Serino, G. & Turri, A. (2011) Outcome of surgical treatment of peri-implantitis: results from a 2-year prospective clinical study in humans. *Clinical Oral Implants Research*, doi: 10.1111/j.1600.0501.2010.02098.x.

Shibli, J. A., Melo, L., Ferrari, D. S., Figueiredo, L. C., Faveri, M. & Feres, M. (2008) Composition of supra- and subgingival biofilm of subjects with healthy and diseased implants. *Clinical Oral Implants Research* **19**, 975–982.

Slots, J. & Genco, R. J. (1979) Direct hemagglutination technique for differentiating Bacteroides asaccharolyticus oral strains from nonoral strains. *Journal of Clinical Microbiology* **10**, 371–373.

Slots, J. & Reynolds, H. S. (1982) Long-wave UV light fluorescence for identification of black-pigmented Bacteroides spp. *Journal of Clinical Microbiology* **16**, 1148–1151.

Tonetti, M. S. (1998) Cigarette smoking and periodontal diseases: etiology and management of disease. *Annals of Periodontology* **3**, 88–101.

Tonetti, M. S., Pini-Prato, G. & Cortellini, P. (1995) Effect of cigarette smoking on periodontal healing following GTR in infrabony defects. A preliminary retrospective study. *Journal of Clinical Periodontology* **22**, 229–234.

Trombelli, L., Kim, C. K., Zimmerman, G. J. & Wikesjo, U. M. (1997) Retrospective analysis of factors related to clinical outcome of guided tissue regeneration procedures in intrabony defects. *Journal of Clinical Periodontology* **24**, 366–371.

van Winkelhoff, A. J., Tijhof, C. J. & de Graaff, J. (1992) Microbiological and clinical results of metronidazole plus amoxicillin therapy in *Actinobacillus actinomycetemcomitans*-associated periodontitis. *Journal of Periodontology* **63**, 52–57.

Winkel, E. G., Van Winkelhoff, A. J., Timmerman, M. F., Van der Velden, U. & Van der Weijden, G. A. (2001) Amoxicillin plus metronidazole in the treatment of adult periodontitis patients. A double-blind placebo-controlled study. *Journal of Clinical Periodontology* **28**, 296–305.

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Clinical relevance

Scientific rationale for the study: Peri-implantitis is an infectious disease and may lead to implant loss, if left untreated. Treatment strategies used to establish peri-implant health and their efficacy in the clinical reality have not been discussed extensively.

Principal findings: Therapeutic interventions varied significantly among centres. It was hard to eradicate peri-implantitis in our material. Severity of the disease, early disease development, smoking and one type of surgical treatment were statistically significantly associated with treatment failure.

Practical implications: Future randomized controlled clinical trials should focus on the above characteristics associated with treatment failure in an attempt to predict peri-implantitis treatment outcomes.