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Review Article

Therapy of peri-implantitis: a systematic review

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Abstract

Aim: The objective of this study was to provide a systematic review of randomized controlled and/or comparative clinical trials published in the international peer-reviewed literature in the English language, up to and including July 2007, concerning the efficacy of all treatment modalities implemented for the therapy of peri-implantitis.

Material and Methods: *PubMed* and *The Cochrane Library* databases were searched electronically and numerous journals were examined manually. In the first phase of selection, the titles and abstracts, and in the second phase, complete papers were screened independently and in duplicate by three reviewers (S. K., I. K. K. and M. T.).

Results: The search yielded 1304 possibly relevant titles and abstracts. After the first phase of selection, 13 publications were singled out for a rigorous evaluation. Following the second phase, five studies were selected.

Conclusions: The selected studies are too limited in number and exhibit small sample sizes and short follow-up periods. Therefore, there is a definite need for more well-designed, preferably longitudinal, randomized controlled clinical trials. Within the limitations of the selected studies, mechanical debridement combined with antiseptic/antibiotic therapy, the Er:YAG laser or regenerative techniques may be used for treating peri-implantitis, but the indications for each of these techniques have not been delineated clearly.

Key words: laser; mechanical debridement; peri-implantitis; randomized controlled clinical trial; therapy

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The term ''peri-implantitis'' was introduced in the late 1980s (Mombelli et al. 1987) and was subsequently defined as an inflammatory process affecting the soft and hard tissues around a functioning osseointegrated implant, resulting in loss of supporting bone (Albrektsson & Isidor 1994). By analogy to the aetiology of periodontitis, the pre-requisite and pivotal aetiological factor for the development of peri-implantitis is microbial colonization in the form of microbial plaque biofilms (Mombelli et al. 1988, Becker et al. 1990, Pontoriero et al. 1994; for reviews: Mombelli & Lang 1998, Mombelli 2002).

Conflict of interest and sources of funding statement

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A statistically significantly higher incidence of peri-implantitis for implants placed in patients with a history of chronic periodontitis (28.6%) compared with periodontally healthy subjects (5.8%) has been reported (Karoussis et al. 2003). Additionally, an association between periodontal and peri-implant conditions has been demonstrated for the same population (Brägger et al. 1997, Karoussis et al. 2004). Two recent systematic reviews (Schou et al. 2006, Karoussis et al. 2007) came to the conclusion that implants placed in patients with a history of chronic periodontitis may demonstrate a higher incidence of peri-implantitis than implants placed in patients without such a history; thus, the history of chronic periodontitis may pre-dispose to the development of peri-implantitis.

In light of the aforementioned evidence and given the continuously increasing number of implants placed in everyday clinical practice, it is reasonable to anticipate an increasing prevalence of peri-implantitis, which underlines the necessity for a predictable therapy. Up to and including 2004, no randomized controlled clinical trials had been specially designed to evaluate the effectiveness of therapeutic modalities for peri-implantitis, as revealed by conventional (Roos-Jansåker et al. 2003, Heitz-Mayfield & Lang 2004, Schou et al. 2004) and systematic (Klinge et al. 2002, Romeo et al. 2004) reviews. Instead, as evidenced by the latter systematic reviews (Klinge et al. 2002, Romeo et al. 2004), a plethora of papers considered to represent a lower level of evidence had been published, such as prospective studies without randomization, case reports, case series and experimental studies. This substantial literature, even though scientifically interesting, could not provide strong evidence for the clinical application of

a therapeutic protocol for peri-implantitis owing to the design of these studies. Nonetheless, the therapy of peri-implantitis has been a topic engaging considerable and continually increasing interest. Accordingly, it seems essential to focus assiduously on the latest findings of clinical research.

On the basis of these considerations, the aim of the present study was to perform a systematic review of randomized controlled and/or comparative clinical trials published in the international peer-reviewed literature in the English language, up to and including July 2007, regarding the efficacy of all treatment modalities implemented for the therapy of peri-implantitis.

Material and Methods

Search strategy

In order to systematically review the data available on the subject of interest, the *PubMed* database of the US National Library of Medicine and *The Cochrane Library* (CENTRAL) of the Cochrane Collaboration were used as electronic databases and a literature search was carried out on articles published up to and including July 2007.

The terms and key words used in the search were as follows:

(''Peri-implantitis'' OR ''periimplantitis'')

OR

(''peri-implant*'' OR ''periimplant*'')

During the search in the *PubMed* database, the following limits were applied using the specially designed *Limits* tab:

(1) *Dates:*

Published in the Last:

Published Date: [blank]/[blank]/[blank] to 2007/7/31

(2) *Humans or Animals:* Humans (only)

Additionally, several journals were searched manually up to and including July 2007, as reported below in alphabetical order:

Clinical Oral Implants Research; *Clinical Oral Investigations*; *Implant Dentistry*; *The International Journal of Oral and Maxillofacial Implants*; *International Journal of Oral and Maxillofacial Surgery*; *The International Journal of Periodontics and Restorative Dentistry*; *The International Journal of Prosthodontics*; *The Journal of the American Dental Association*; *Journal of the Canadian Dental Association*; *Journal of Clinical Periodontology*; *Journal of Cranio-Maxillofacial Surgery*; *Journal of Oral and Maxillofacial Surgery*; *Journal of Periodontology*; *The Journal of Prosthetic Dentistry*; *Journal of Prosthodontics*; *Oral Surgery*, *Oral Medicine*, *Oral Pathology*, *Oral Radiology*, *and Endodontics*.

Ultimately, the identified – through electronic and manual search – bibliographies of all investigational and review papers relevant to the subject were scanned. Whenever regarded as necessary, contact with the corresponding author of a study would be carried out, in search of missing, unclear or unpublished data.

Screening and study selection

In the first phase of study selection, the titles and abstracts – whenever available – of all identified papers were screened independently and in duplicate by three of the reviewers (S. K., I. K. K. and M. T.) for potential inclusion in the systematic review, on the basis of predetermined selection criteria. These criteria were determined under the philosophy of making the results of this systematic review as extrapolative as possible.

The selection criteria were agreed upon by all reviewers and included the following:

(1) Publication in the international peer-reviewed literature in the English language.
(2) Randomized controlled or comparative (either of a parallel or of a split-mouth design) clinical trials.
(3) Implementation of therapy for peri-implantitis (by any treatment modality).

It should be noted that all authors used the consensus definition agreed upon in the 1st European Workshop on Periodontology (Ittingen, Switzerland, 1993), as provided in the introductory text (Albrektsson & Isidor 1994).

(4) Presence of at least five patients in each and every group of the study.
(5) Follow-up period of at least 6 months.

In the second phase of selection, the complete text of all studies already singled out in the first phase, as well as the full text of papers without abstract or publications with insufficient data in the title and abstract to allow a clear assessment, were acquired. Following this procedure, these studies were assessed autonomously and in duplicate by three of the reviewers (S. K., I. K. K. and M. T.), based on the same selection criteria. Moreover, in this phase of selection, a number of studies would be excluded from this review, according to specific pre-defined exclusion criteria. The exclusion criteria unanimously agreed upon were as follows:

(1) Previous treatment of peri-implantitis over a period of 12 months before the initiation of the study.
(2) Patients receiving antibiotics over a period of 3 months before the baseline of the study.
(3) History of radiotherapy in the head and neck region of the patients.
(4) Absent or uncompleted periodontal therapy before dental implant placement.
(5) Presence of active inflammation at the implant recipient site at the time of implant placement (defined clearly).

In case of any potential discrepancy among the reviewers, consensus would have to be accomplished by discussion. If a disagreement still remained, it would have to be reported and explained in the text of the present review.

Quality assessment of selected studies

The quality assessment of the eventually selected studies was planned to be conducted autonomously and in duplicate by three of the reviewers (S. K., I. K. K. and I. F.), following the criteria proposed by Esposito et al. (2001) and Roccuzzo et al. (2002), slightly modified, as listed below:

(A) Sample size calculation, estimating the minimum number of participants required to detect a significant difference among the study groups compared.

Grading:

0: Did not exist/not mentioned/not clear

1: Was reported, but not confirmed

2: Reported and confirmed

(B) Randomization and allocation concealment method

Grading:

0: Did not exist/not described/not clear

1: Clearly inadequate: When the method of randomization was other

than a table of random numbers, computer-based random number generator (RNG), tossed coin or shuffled cards; hence, for example, odd/even birth date is a clearly inadequate method of randomization

2: Possibly adequate: In case an adequate randomization method was applied, but the therapist(s) was (were) informed about the randomization sequence before or at the beginning of the procedure and accordingly could potentially be biased during intervention(s)

3: Clearly adequate: In case an adequate randomization method was applied and the therapist(s) was (were) kept unaware of the randomization sequence until immediately before the therapeutic procedure was implemented

(C) Clear definition of inclusion and/or exclusion criteria

Grading:

0: No

1: Yes

(D) Completeness of follow-up (specified reasons for withdrawals and dropouts in each study group)

Grading:

0: No/not mentioned/not clear

1: Yes/no withdrawals or dropouts occurred

(E) Experimental and control groups comparable at study baseline for important prognostic factors

Grading:

0: No

1: Unclear/possibly not comparable for one or more important prognostic factors

2: Yes

(F) Presence of masking

Grading:

0: No

1: Unclear/not complete: Not for all study measurements or evaluations

2: Yes

(G) Appropriate statistical analysis

Grading:

0: No

1: Unclear/possibly not the best method applied

2: Yes

Quality assessment was conducted in two phases. In the first phase, quality assessment was based entirely on the published text of studies and was carried out separately and in duplicate by three of the reviewers (S. K., I. K. K. and I. F.) using the criteria mentioned above. Whenever deemed necessary, contact with the corresponding author of an evaluated study was carried out in search of missing or ambiguous data. Following this procedure, the same reviewers would examine all received answers autonomously and in duplicate. In the second phase of quality assessment, studies would be re-evaluated independently and in duplicate by the same reviewers, utilizing the same quality assessment criteria, but considering the supplementary information provided by the corresponding author.

After forming the scorings in the second phase of quality assessment, an overall estimation of plausible risk of bias (low, moderate, high) would be made for each study selected, based on proposed definitions of the degree of bias (Esposito et al. 2005).

In the event of variance among the reviewers, an effort to reach an agreement would be made by discussion. If this attempt still remained unsuccessful, the differences in quality assessment would have to be reported and accounted for in the present manuscript.

Results

Study selection

The electronic search in both databases (*PubMed* and *The Cochrane Library*) yielded a total of 1304 potentially relevant titles and abstracts, while the manual search provided no additional papers. Following the first phase of evaluation, 1291 publications were rejected based on the title and the abstract. In the second phase, the complete text of the remaining 13 publications was retrieved for a thorough examination. During this procedure, eight papers (Bach et al. 2000, Tang et al. 2002, Büchter et al. 2004, Romeo et al. 2005, 2007, Persson et al. 2006, Deppe et al. 2007, Salvi et al. 2007), corresponding to six studies, were excluded. The study by Romeo and co-workers corresponded to two publications: part I (Romeo et al. 2005) and part II (Romeo et al. 2007). Similarly, two other papers (Persson et al. 2006, Salvi et al. 2007) constituted the two successive parts of the same study.

Table 1 displays the studies excluded in the second phase of selection and the reason for the exclusion of each study.

It has to be noted that the study by Bach et al. (2000) was excluded because it had not provided the baseline and the final (following 5 years of follow-up) values of plaque, bleeding on probing, probing pocket depth (PPD) and radiographical bone loss around implants. Furthermore, no statistical analysis had been carried out. Therefore, the reported data were considered to be insufficient to support the conclusions of the study. Moreover, it has to be mentioned that the study by Romeo and co-workers contained major inconsistencies between part I (Romeo et al. 2005) and part II (Romeo et al. 2007), primarily regarding the patient population, as well as dates of diagnosis and start of treatment of peri-implantitis. One of the authors of the present systematic review (I. K. K.) suggested the exclusion of part II and the inclusion of only part I. However, after discussion among all authors of this paper, it was deemed safer and more accurate to exclude both part I (Romeo et al. 2005) and part II (Romeo et al. 2007). It should be reported, furthermore, that part I (Romeo et al. 2005) per se contained unclear data as well, such as unclear number of patients in the control group and did not report baseline comparability between the groups of the study.

Eventually, five studies were singled out (Karring et al. 2005, Schwarz et al. 2005, 2006a, b, Renvert et al. 2006), as demonstrated in Table 2.

Table 1. The studies excluded in the second phase of selection and the reason for the exclusion of each study

Excluded study (authors/ publication year)	Reason for exclusion
Bach et al. (2000)	Insufficient data to support the conclusions of the study
Tang et al. (2002)	Not published in the English language (text in Chinese)
Büchter et al. (2004)	Follow-up period <6 months
Romeo et al. (2005, 2007) (cont.)	Inconsistencies between part I (Romeo et al. 2005) and part II (Romeo et al. 2007) of the study
Persson et al. (2006), Salvi et al. (2007)	Not a controlled or comparative study
Deppe et al. 2007 (cont.)	No randomization reported

Cont., study was excluded after attempting to contact its corresponding author.

Table 2. The selected randomized controlled and/or comparative clinical trials after the second phase of selection and their main characteristics

Authors/ publication year	Study design	Implant type	Participants, implants (*N*)/ groups at baseline	Procedures in experimental (or first) group/ sites	Procedures in control (or second) group/ sites	Mean follow-up (months)
Karring et al. (2005)	Randomized controlled split-mouth study	Brånemark®, Straumann®, Astra®	11 patients, 22 implants. Experimental: 11 patients, 11 implants *versus* control: 11 patients, 11 implants	Vector® ultrasonic device	Sub-mucosal mechanical debridement	6
Schwarz et al. (2005)	Randomized comparative parallel group study	Straumann®, Camlog Screw Line®, Spline Twist (MTX)® (cont.) SLA®, TPS®	20 patients, 32 implants. First group: 10 patients, 16 implants *versus* second group: 10 patients, 16 implants	Er:YAG laser	Mechanical debridement and chlorhexidine digluconate	6
Renvert et al. (2006)	Randomized comparative parallel group study	Brånemark®, machined surfaces (cont.)	30 patients, 87 implants (cont.). First group: 16 patients, 50 implants (cont.) *versus* second group: 14 patients, 37 implants (cont.)	Sub-mucosal mechanical debridement and minocycline microspheres	Sub-mucosal mechanical debridement and 1% chlorhexidine gel	12 (cont.)
Schwarz et al. (2006a)	Randomized controlled parallel group study	IMZ, Twin Plus® (SLA®), Camlog Screw Line®, Straumann (SLA®, TPS®), Spline Twist (MTX)®, ZL-Duraplant (Ticer® surface)	20 patients, 40 implants. Experimental: 10 patients, 20 implants *versus* control: 10 patients, 20 implants	Er:YAG laser	Mechanical debridement and chlorhexidine digluconate	12
Schwarz et al. (2006b)	Randomized comparative parallel group study	Brånemark®, Camlog Screw Line®, Straumann (SLA®, TPS®), KSI Bauer Schraube®, Spline Twist (MTX)®, Tapered Screw Vent® (TSV), ZL-Duraplant (Ticer® surface)	22 patients, 22 implants, 22 defects. First group: 11 patients, 11 implants, 11 defects *versus* second group: 11 patients, 11 implants, 11 defects	Access flap surgery and nanocrystalline hydroxyapatite	Access flap surgery and bovine-derived xenograft and collagen membrane (Bio-Gide®)	6

N, number; cont., information provided after contact with the corresponding author of the study; SLA®, sandblasted large-grit acid-etched dental implant surface; TPS®, titanium plasma-sprayed dental implant surface.

Sub-division and main results of the studies selected

According to the therapeutic modality implemented for the therapy of peri-implantitis, the studies selected were subsequently sub-divided as follows (Tables 2 and 3):

- One study (Karring et al. 2005) provided information on the efficacy of sub-mucosal debridement alone for the therapy of peri-implantitis utilizing an ultrasonic device (Vector® system, Dürr Dental, Bietigheim-Bissingen, Germany) or carbon fibre curettes. Treated sites were characterized by bleeding on probing, PPD $\geqslant$ 5 mm, radiographical loss of supporting bone $\geqslant$ 1.5 mm and some implant threads exposed to peri-implant pocket environment. No statistically significant differences were reported for the implants treated either by the ultrasonic device or manually between baseline and 3 as well as 6 months, regarding bleeding on probing, PPD and radiographical bone loss.
- Two studies (Schwarz et al. 2005, 2006a) compared the efficacy of the Er:YAG laser with that of the combination of mechanical debridement (using plastic curettes) and antiseptic (0.2% chlorhexidine digluconate) administration for the treatment of peri-implantitis.

In the first study (Schwarz et al. 2005), the Er:YAG laser device was used for the treatment of moderate-to-advanced peri-implantitis lesions. These lesions demonstrated PPD $\geqslant$ 4 mm, bleeding on probing, suppuration and radiographical bone loss. The results obtained at 6 months after therapy suggested that both treatment modalities (Er:YAG laser/combination of mechanical debridement and chlorhexidine) were equally efficacious in significantly improving peri-implant PPD and clinical attachment level (CAL), but it appeared that the Er:YAG laser provided a significantly enhanced clinical outcome with respect to reduction of bleeding on probing compared with the adjunctive application of chlorhexidine.

The second study (Schwarz et al. 2006a) exhibited certain similarities in its design, and the results obtained at 6 months corroborated the findings reported in the previous study (Schwarz et al. 2005). However, at 12 months and in both groups, the mean values of peri-implant PPD and CAL were not statistically significantly different from the corresponding values at baseline. These findings led the authors to conclude that the efficacy of the Er:YAG laser seems to be limited to a 6-month period, particularly for advanced peri-implantitis lesions (defined as lesions of initial PPD $>$ 7 mm on at least one aspect of the implant and radiographical marginal bone loss $>$ 30% of implant length).

- One study (Renvert et al. 2006) compared the combination of oral hygiene instructions, mechanical debridement and topical application of minocycline microspheres in peri-implant lesions (with bone loss corresponding to no more than three implant threads) with the combination of oral hygiene instructions,

Table 3. The selected randomized controlled and/or comparative clinical trials after the second phase of selection and their main results

Authors/ publication year	Implant survival rate	Probing pocket depth (mm)	Clinical attachment level (mm)	Bone loss (mm)	Comments/notes
Karring et al. (2005)	Not clearly reported (probably 100% in both study groups)	At baseline. Experimental: 5.8 ± 1.1, control: 6.2 ± 1.6. At 6 months. Experimental: 5.8 ± 1.2, control: 6.3 ± 2.2	Not reported	At baseline. Experimental: 6.8 ± 1.7, control: 7.4 ± 2.1. At 6 months. Experimental: 7.1 ± 1.9, control: 7.7 ± 2.6	Five patients were smokers
Schwarz et al. (2005)	First group: 100%, second group: 100% (cont.)	At baseline. First group: 5.4 ± 1.2, second group: 5.5 ± 1.5. At 6 months. First group: 4.6 ± 1.1, second group: 4.8 ± 1.4	At baseline. First group: 5.8 ± 0.9, second group: 6.2 ± 1.5. At 6 months. First group: 5.1 ± 0.9, second group: 5.6 ± 1.4	Not measured precisely (cont.)	All patients had no systemic diseases that could influence the therapy outcome and all were not smokers
Renvert et al. (2006)	First group: 100%, second group: 100% (cont.)	For all four sites per implant. At screening. First group: 3.9 ± 0.7, second group: 3.9 ± 0.3. At 12 months. First group: 3.6 ± 0.6, second group: 3.9 ± 0.4	Not obtained (cont.)	For both the sites per implant. At screening (cont.). First group: 1.15 ± 0.83, second group: 1.05 ± 0.92. At 12 months (cont.). First group: 1.08 ± 0.83, second group: 1.04 ± 1.01	Five patients in the first group and three patients in the second group were current smokers, while six patients in the first group and seven patients in the second group were former smokers
Schwarz et al. (2006a)	Experimental: 100%, control: 100% (cont.)	At baseline (cont.). Experimental: moderate lesions 4.290 ± 0.5567, advanced lesions 6.010 ± 0.5405; control: moderate lesions 3.820 ± 0.7391, advanced lesions 5.910 ± 0.9871. At 12 months (cont.). Experimental: moderate lesions 4.170 ± 0.2869, advanced lesions 5.630 ± 0.3093; control: moderate lesions 3.930 ± 0.5165, advanced lesions 4.880 ± 0.2098	At baseline (cont.). Experimental: moderate lesions 5.000 ± 0.4243, advanced lesions 6.570 ± 0.7056; control: moderate lesions 4.460 ± 0.6995, advanced lesions 6.500 ± 0.9333. At 12 months (cont.). Experimental: moderate lesions 5.060 ± 0.1955, advanced lesions 6.500 ± 0.6074; control: moderate lesions 4.810 ± 0.5801, advanced lesions 5.790 ± 0.4909	Not measured precisely (cont.)	All patients had no systemic diseases that could influence the therapy outcome and all were not smokers
Schwarz et al. (2006b)	Experimental: 100%, control: 100% (cont.)	At baseline. First group: 7.0 ± 0.6, second group: 7.1 ± 0.8. At 6 months. First group: 4.9 ± 0.6, second group: 4.5 ± 0.7	At baseline. First group: 7.5 ± 0.8, second group: 7.5 ± 1.0. At 6 months. First group: 5.7 ± 1.0, second group: 5.2 ± 0.8	Not obtained (cont.)	All patients had no systemic diseases that could influence the therapy outcome and all were not smokers

Cont., information provided after contact with the corresponding author of the study.

mechanical debridement and 1% chlorhexidine gel application. Peri-implant lesions exhibited radiographical loss of bone $\leqslant 3$ implant threads and one or more peri-implant sites with probing depth $\geqslant 4$ mm, coupled with bleeding and/or suppuration on probing and occurrence of putative pathogenic bacteria. The results obtained after a follow-up period of 12 months showed that only a limited reduction in bleeding on probing was achieved and that the mean peri-implant PPD remained unchanged (3.9 mm) in the chlorhexidine group. On the other hand, in the minocycline group, the reduction of bleeding on probing was statistically significantly greater than that in the chlorhexidine group, coupled with an improvement in mean peri-implant PPD (from 3.9 mm to 3.6 mm). These results suggested that the topical application of chlorhexidine provides limited or no adjunctive clinical improvements when treating shallow peri-implant lesions compared with using mechanical debridement alone.

- Another selected study (Schwarz et al. 2006b) evaluated and compared the efficacy of two bone regenerative procedures for the treatment of moderate intra-bony peri-implantitis lesions (PPD > 6 mm and radiographical intra-bony component

> 3 mm). In particular, the defects were randomly treated either with a combination of access flap surgery and the application of nanocrystalline hydroxyapatite or with a combination of access flap surgery, the application of a bovine-derived xenograft (Bio-Oss®, Geistlich, Wolhusen, Switzerland) and the placement of a bioresorbable porcine-derived collagen membrane (Bio-Gide®, Geistlich, Wolhusen, Switzerland). Nanocrystalline hydroxyapatite is a nanosized ceramic bone graft substitute that has been demonstrated by animal studies (Thorwarth et al. 2005, Chris Arts et al. 2006) to lead to undisturbed osseous integration, without requiring the adjunctive use of a membrane. However, in the aforementioned study (Schwarz et al. 2006b), following 6 months of non-submerged healing, nanocrystalline hydroxyapatite compromised the initial (especially during the first 10 days) adhesion of the mucoperiosteal flaps in all patients having received it, whereas this phenomenon was not manifested in the group treated by guided bone regeneration. At 6 months, clinically significant improvements in clinical parameters were reported for both nanocrystalline hydroxyapatite and guided bone regeneration (Table 3).

Because of the limited number of available randomized controlled and/or comparative clinical trials, it was decided as preferable to retain all the existing material without making any distinction based on the clinical characteristics/parameters (or their range) of peri-implantitis lesions.

Quality assessment of the studies selected

The results provided by the independent as well as the duplicate quality assessment of these studies by three of the reviewers (S. K., I. K. K. and I. F.) were unanimous (κ score: 1.00), both before and after contact with the corresponding author of each study, as presented in Table 4.

Table 4 reveals that sample size calculation (quality criterion A) was not performed in any study. Furthermore, it was observed that all five studies had relatively small sample sizes. Thus, based on proposed definitions of degrees of risk of bias (low, moderate, high) (Esposito et al. 2005), the risk of bias was estimated to be high for all selected studies. On the other hand, however, it has to be stressed that all the remaining criteria (B, C, D, E, F and G) were fulfilled by these studies, with the sole exception of criterion E for the study by Karring et al. (2005).

Meta-analysis

On account of substantial discrepancies (high heterogeneity) among the selected studies (principally varying therapeutic regimens for the treatment of peri-implantitis and presence of baseline peri-implant lesions of different morphology, severity and extent), it was considered not to be feasible to carry out any meta-analysis.

Discussion

The present study performed an assiduous analysis and evaluation, by means of a systematic methodology, of any accessible information up to and including July 2007, originating from randomized controlled and/or comparative clinical trials, on the efficacy of all treatment modalities utilized for the therapy of peri-implantitis.

Until now, no methodology has been established as a gold standard approach for the treatment of peri-implantitis. Thus, a synopsis of information on the efficacy of various implemented treatment modalities will be outlined following a division analogous to the phases of periodontal therapy. Hence, therapy of peri-implantitis comprises (a) the non-surgical phase, which includes debridement by mechanical means, ultrasonic or laser devices, either alone or combined with antiseptic and/or antibiotic agents and (b) the surgical phase, utilizing either resective or regenerative techniques, as described in the following paragraphs:

Use of mechanical debridement alone for non-surgical therapy of peri-implantitis (Tables 2 and 3)

The study by Karring et al. (2005) demonstrated that sub-mucosal debridement alone, accomplished by utilizing either an ultrasonic device or carbon fibre curettes, is not sufficient for the decontamination of the surfaces of implants with peri-implant pockets $\geqslant$ 5 mm and exposed implant threads. Within the limitations of this study (pilot study with a duration of only 6 months, a small sample size of only 11 patients, absence of calibration of the examiners and different examiners for the initial and final measurements), it seems reasonable to suggest that mechanical or ultrasonic debridement alone may not be an adequate modality for the resolution of peri-implantitis. Further, randomized controlled clinical trials with longer periods of follow-up and a higher number of participants are

Table 4. Scorings provided by quality assessment of the finally selected studies before and after contact with their corresponding author (scorings formed after contact have been placed in parentheses)

Authors/publication year	A (0–2)	B (0–3)	C (0–1)	D (0–1)	E (0–2)	F (0–2)	G (0–2)	Estimated risk of bias
Karring et al. (2005)	0	3*	1*	1*	1	2*	2*	High
Schwarz et al. (2005)	0 (0)†	3*	1*	1*	2*	2*	2*	High
Renvert et al. (2006)	0 (0)†	3*	1*	1*	2*	2*	2*	High
Schwarz et al. (2006a)	0 (0)†	3*	1*	1*	2*	1 (2)*,†	2*	High
Schwarz et al. (2006b)	0 (0)†	2 (3)*,†	1*	1*	2*	2*	1 (2)*,†	High

*The maximum possible score has been achieved.

†After contact with the corresponding author of the study.

A, sample size calculation; B, randomization and allocation concealment method; C, clear definition of inclusion/exclusion criteria; D, completeness of follow-up (specified reasons for withdrawals and dropouts in each study group); E, experimental and control groups comparable at study baseline for important prognostic factors; F, presence of masking; G, appropriate statistical analysis.

certainly required in order to provide stronger evidence for this conclusion.

Use of the Er:YAG laser alone for non-surgical therapy of peri-implantitis (Tables 2 and 3)

According to Schwarz et al. (2005), the Er:YAG laser and the combination of mechanical debridement/chlorhexidine are equally efficacious at 6 months after therapy in significantly improving peri-implant PPD and CAL, but the use of the Er:YAG laser provides a significantly higher reduction of bleeding on probing compared with the adjunctive application of chlorhexidine. However, in a subsequent study (Schwarz et al. 2006a), the efficacy of the Er:YAG laser appeared to be limited to a 6-month period, particularly for advanced peri-implantitis lesions. It was further suggested that a single course of treatment with the Er:YAG laser may not be adequate for achieving a stable therapy of peri-implantitis and that additional therapeutic measures, such as supplementary use of the Er:YAG laser and/or subsequent osseous regenerative procedures, might be required. Because the plaque index of patients deteriorated during the study, another interpretation of the results, nonetheless, could be that oral hygiene measures were possibly less than adequate and the inability to control peri-implant inflammation was the result of this insufficient plaque control, rather than the lack of longevity of the activity of the Er:YAG laser per se.

In conclusion, the use of the Er:YAG laser appears to be an efficacious modality for the treatment of peri-implantitis on a short-term basis of 6 months, as evidenced by improvements in clinical parameters, but it seems that a greater number of well-designed randomized controlled clinical trials are required in order to clarify whether these positive short-term clinical outcomes can be maintained over the course of time or whether the laser has to be repetitively used and/or combined with other therapeutic modalities.

Use of mechanical debridement combined with antiseptic agents for non-surgical therapy of peri-implantitis (Tables 2 and 3)

Because mechanical debridement alone appeared to be insufficient for the decontamination of implant surfaces, it was considered rational to examine the efficacy of the adjunctive use of chemical antiseptic agents for non-surgical therapy of peri-implantitis.

The study by Schwarz et al. (2005) demonstrated that the treatment of peri-implant infection by mechanical debridement with plastic curettes combined with antiseptic (0.2% chlorhexidine) therapy may lead to statistically significant improvements in bleeding on probing, peri-implant PPD and CAL at 6 months compared with baseline (Table 3). It has to be noted, nevertheless, that because the residual – at 6 months – PPD of the peri-implant lesions had a mean value of 4.8 ± 1.4 mm and the residual CAL exhibited a mean value of 5.6 ± 1.4 mm, the therapy of peri-implantitis may be regarded as incomplete. Therefore, in peri-implant lesions with an initial (before any therapy) PPD > 5 mm, as that reported in this study (Schwarz et al. 2005), the combination of mechanical debridement and antiseptic therapy may provide an improvement in clinical parameters, but residual defects continue to exist following therapy, suggesting that supplementary treatment may be required.

In another study with a similar design (Schwarz et al. 2006a), analogous trends were generally observed in the control group and, in general, bleeding on probing, peri-implant PPD and CAL improved statistically significantly at 12 months compared with baseline (Table 3). However, certain results of this study followed a different pattern and their interpretation appears to be difficult. Quite paradoxically, for moderate lesions (initial PPD 4–6 mm on at least one aspect of the implant and radiographical marginal bone loss $< 30\%$ of implant length), both mean peri-implant PPD and CAL increased from baseline to 12 months, whereas for advanced lesions (initial PPD > 7 mm on at least one aspect of the implant and radiographical marginal bone loss $> 30\%$ of implant length) they both decreased (Table 3). Another intriguing finding was that the mean plaque index increased from baseline to 12 months, both for moderate and advanced lesions, implying that oral hygiene measures were ineffective. In any case, because an adequate level of oral hygiene was not achieved, the results of this study should be interpreted with caution.

The difference in the results obtained by Schwarz et al. (2005) and Renvert et al. (2006) can presumably be explained by the difference in the severity of the treated peri-implant lesions. Thus, it appears that the addition of antiseptic therapy to mechanical debridement does not provide adjunctive benefits in shallow peri-implant lesions (mean PPD < 4 mm) (Renvert et al. 2006), but seems to provide additional clinical improvements in deep peri-implant lesions (mean PPD > 5 mm) (Schwarz et al. 2005).

However, the benefits derived from adding antiseptic therapy to mechanical debridement in peri-implant lesions with PPD between 4 mm and 5 mm still remain unknown. Finally, there is a definite need for more randomized controlled clinical trials on this subject, preferably with a follow-up period of more than 12 months.

Use of mechanical debridement combined with local application of antibiotics for non-surgical therapy of peri-implantitis (Tables 2 and 3)

The study by Renvert et al. (2006) demonstrated that the adjunctive benefits derived from the addition of an antibiotic (minocycline, Arestin®, OraPharma Inc., Warminster, PA, USA) to mechanical debridement tend to be greater, although to a limited extent, than those achieved by the combined use of an antiseptic (chlorhexidine) and mechanical debridement. The improvements in peri-implant probing depths obtained by the adjunctive use of minocycline can be maintained during a short-term period of 12 months. Nevertheless, whether these benefits are ephemeral or not is an issue presently open to doubt.

A point of interest is that the peri-implant lesions treated in the study by Renvert et al. (2006) exhibited bone loss corresponding to no more than three implant threads. It is still open to question whether deeper peri-implant lesions can be adequately treated non-surgically by a combination of a local antibiotic and mechanical debridement.

The efficacy of the combination of local antibiotics other than minocycline with mechanical debridement in the therapy of peri-implantitis has to be investigated by future randomized controlled clinical trials, preferably longitudinal. Finally, there are no such clinical trials available nowadays on the systemic administration of antibiotics for the therapy of peri-implantitis.

Surgical treatment of peri-implantitis (Tables 2 and 3)

To date, no randomized controlled clinical trials are available on the use of access flap surgery (open flap debridement) alone for the therapy of peri-implantitis.

A randomized comparative clinical trial (Romeo et al. 2005, 2007) concluded that resective surgical procedures coupled with implantoplasty could have a positive influence on the survival rates of rough-surfaced implants affected by peri-implantitis as well as on peri-implant clinical parameters, such as PPD, suppuration and sulcus bleeding. These data are certainly interesting and important for everyday clinical practice, but unfortunately this study had to be excluded from the present systematic review based on a reasoning mentioned already (Table 1).

The study by Schwarz et al. (2006b) demonstrated that both nanocrystalline hydroxyapatite and guided bone regeneration provided clinically significant improvements in clinical parameters following 6 months of non-submerged healing. The 2-year results (Schwarz et al. 2008) of the same clinical study once more demonstrated that both treatment modalities were efficacious in providing clinically significant reductions of PPD and gains in CAL, but the application of the combination of natural bone mineral and collagen membrane seemed to correlate with greater improvements in those clinical parameters and, hence, was associated with a more predictable and enhanced healing outcome. Unfortunately, the relatively small sample size of the study (22 patients) did not allow a reliable statistical comparison of the efficacy of the two therapeutic procedures. In general, more data on various regenerative techniques for treating peri-implantitis have to be accumulated.

Conclusions

General conclusions

- The available randomized controlled and/or comparative clinical trials are limited in number and have short follow-up periods and small sample sizes, thereby exhibiting a high risk of bias.
- It is still dubious which therapeutic strategies are the most efficacious for the treatment of peri-implantitis lesions according to their morphology, extent and severity.
- However, this conclusion in no way suggests that currently implemented treatment modalities may not provide beneficial outcomes in clinical practice.

Specific conclusions

Despite the less than adequate level of existing evidence, certain data tend to indicate the following:

- Sub-mucosal debridement alone may not be adequate for the removal of bacterial load from the surfaces of implants with peri-implant pockets $\geqslant 5$ mm.
- The use of the Er:YAG laser can improve peri-implant clinical parameters within 6 months, but it remains unclear whether these effects can be maintained over time.
- The combination of minocycline and mechanical debridement appears to provide an improved treatment outcome, although to a limited extent, compared with the combination of chlorhexidine and mechanical debridement, at least during a short-term period of 12 months.
- Guided bone regeneration or the application of a bone substitute (nanocrystalline hydroxyapatite) can be efficacious for the treatment of peri-implantitis lesions.

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References

Albrektsson, T. & Isidor, F. (1994) Consensus report of Session IV. In: Lang, N. P. & Karring, T. (eds) *Proceedings of the 1st European Workshop on Periodontology*, pp. 365–369. London: Quintessence Publishing Co. Ltd.

Bach, G., Neckel, C., Mall, C. & Krekeler, G. (2000) Conventional versus laser-assisted therapy of periimplantitis: a five-year comparative study. *Implant Dentistry* **9**, 247–251.

Becker, W., Becker, B. E., Newman, M. G. & Nyman, S. (1990) Clinical and microbiologic findings that may contribute to dental implant failure. *International Journal of Oral and Maxillofacial Implants* **5**, 31–38.

Brägger, U., Bürgin, W. B., Hämmerle, C. H. & Lang, N. P. (1997) Associations between clinical parameters assessed around implants and teeth. *Clinical Oral Implants Research* **8**, 412–421.

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

Chris Arts, J. J., Verdonschot, N., Schreurs, B. W. & Buma, P. (2006) The use of a bioresorbable nano-crystalline hydroxyapatite paste in acetabular bone impaction grafting. *Biomaterials* **27**, 1110–1118.

Deppe, H., Horch, H.-H. & Neff, A. (2007) Conventional versus CO_2 laser-assisted treatment of peri-implant defects with the concomitant use of pure-phase β-tricalcium phosphate: a 5-year clinical report. *International Journal of Oral and Maxillofacial Implants* **22**, 79–86.

Esposito, M., Coulthard, P., Worthington, H. V. & Jokstad, A. (2001) Quality assessment of randomized controlled trials of oral implants. *International Journal of Oral and Maxillofacial Implants* **16**, 783–792.

Esposito, M., Grusovin, M. G., Coulthard, P., Thomsen, P. & Worthington, H. V. (2005) A 5-year follow-up comparative analysis of the efficacy of various osseointegrated dental implant systems: a systematic review of randomized controlled clinical trials. *International Journal of Oral and Maxillofacial Implants* **20**, 557–568.

Heitz-Mayfield, L. J. & Lang, N. P. (2004) Antimicrobial treatment of peri-implant diseases. *International Journal of Oral and Maxillofacial Implants* **19** (Suppl.), 128–139.

Karoussis, I. K., Kotsovilis, S. & Fourmousis, I. (2007) A comprehensive and critical review of dental implant prognosis in periodontally compromised partially edentulous patients. *Clinical Oral Implants Research* **18**, 669–679.

Karoussis, I. K., Müller, S., Salvi, G. E., Heitz-Mayfield, L. J. A., Brägger, U. & Lang, N. P. (2004) Association between periodontal and peri-implant conditions: a 10-year prospective study. *Clinical Oral Implants Research* **15**, 1–7.

Karoussis, I. K., Salvi, G. E., Heitz-Mayfield, L. J. A., Brägger, U., Hämmerle, C. H. F. & Lang, N. P. (2003) Long-term implant prognosis in patients with and without a history of chronic periodontitis: a 10-year prospective cohort study of the ITI® Dental Implant

System. *Clinical Oral Implants Research* **14**, 329–339.

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

Klinge, B., Gustafsson, A. & Berglundh, T. (2002) A systematic review of the effect of anti-infective therapy in the treatment of peri-implantitis. *Journal of Clinical Periodontology* **29** (Suppl. 3), 213–225.

Mombelli, A. (2002) Microbiology and antimicrobial therapy of peri-implantitis. *Periodontology 2000* **28**, 177–189.

Mombelli, A., Buser, D. & Lang, N. P. (1988) Colonization of osseointegrated titanium implants in edentulous patients. Early results. *Oral Microbiology and Immunology* **3**, 113–120.

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. & Lang, N. P. (1987) The microbiota associated with successful or failing osseointegrated titanium implants. *Oral Microbiology and Immunology* **2**, 145–151.

Persson, G. R., Salvi, G. E., Heitz-Mayfield, L. J. & Lang, N. P. (2006) Antimicrobial therapy using a local drug delivery system (Arestin) in the treatment of peri-implantitis. I: microbiological outcomes. *Clinical Oral Implants Research* **17**, 386–393.

Pontoriero, R., Tonelli, M. P., Carnevale, G., Mombelli, A., Nyman, S. R. & Lang, N. P. (1994) Experimentally induced peri-implant mucositis. A clinical study in humans. *Clinical Oral Implants Research* **5**, 254–259.

Renvert, S., Lessem, J., Dahlén, 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.

Roccuzzo, M., Bunino, M., Needleman, I. & Sanz, M. (2002) Periodontal plastic surgery for treatment of localized gingival recessions: a systematic review. *Journal of Clinical Periodontology* **29** (Suppl. 3), 178–194.

Romeo, E., Ghisolfi, M. & Carmagnola, D. (2004) Peri-implant diseases. A systematic review of the literature. *Minerva Stomatologica* **53**, 215–230.

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.

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

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

Salvi, G. E., Persson, G. R., Heitz-Meyfield, 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.

Schou, S., Berglundh, T. & Lang, N. P. (2004) Surgical treatment of peri-implantitis. *International Journal of Oral and Maxillofacial Implants* **19** (Suppl.), 140–149.

Schou, S., Holmstrup, P., Worthington, H. V. & Esposito, M. (2006) Outcome of implant therapy in patients with previous tooth loss due to periodontitis. *Clinical Oral Implants Research* **17** (Suppl. 2), 104–123.

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 peri-implantitis 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., Sculean, A., Bieling, K., Ferrari, D., Rothamel, D. & Becker, J. (2008) Two-year clinical results following treatment of peri-implantitis lesions using a nanocristalline hydroxyapatite or a natural bone mineral in combination with a collagen membrane. *Journal of Clinical Periodontology* **35**, 80–87.

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

Tang, Z., Cao, C., Sha, Y., Lin, Y. & Wang, X. (2002) Effects of non-surgical treatment modalities on peri-implantitis. *Zhonghua Kou Qiang Yi Xue Za Zhi* **37**, 173–175.

Thorwarth, M., Schultze-Mosgau, S., Kessler, P., Wiltfang, J. & Schlegel, K. A. (2005) Bone regeneration in osseous defects using a resorbable nanoparticular hydroxyapatite. *Journal of Oral and Maxillofacial Surgery* **63**, 1626–1633.

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Clinical Relevance

Scientific rationale for the study: The present systematic review aimed at evaluating randomized controlled and/or comparative clinical trials on the efficacy of all modalities used for the therapy of peri-implantitis.
Principal findings: To date, mechanical debridement combined with antiseptic/antibiotic therapy, Er:YAG laser or regenerative techniques may be successfully implemented for treating various cases of peri-implantitis, but the indications of each technique have not been accurately demarcated.
Practical implications: The techniques mentioned above should be considered as possible therapeutic modalities for peri-implantitis, but currently available evidence does not support the superiority of any technique over the other.