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Non-surgical Treatment of Peri-implantitis: A Systematic Review of the Literature

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Abstract

Purpose: To evaluate the scientific evidence on the efficacy of non-surgical treatments of Peri-implantitis.

Material and methods: The effect of mechanical debridement associated with adjunctive measures was compared with mechanical debridement alone on the following outcomes: implant failure, radiographic margin bone level, complications and Peri-implantitis recurrence, changes in probing pocket depth, clinical attachment level and bleeding on probing. A search in MEDLINE-PubMed, Embase and the Cochrane Central Register of controlled trials (CENTRAL) was conducted up to February 2017. Randomized controlled trials (RCT) reporting data on non-surgical professional treatments of Peri-implantitis including at least 10 patients in good systemic conditions were selected for the analysis.

Results: The screening of titles and abstracts resulted in 15 publications meeting the eligibility criteria. The follow-up ranged between 3 and 12 months and the study population varied between 10 and 63 patients. Therapies utilized in the included studies were antiseptics, local and systemic antibiotics, Er:YAG, ND:YAG and diode laser, courettes and ultrasonic devices. One study presented low risk of bias, while 11 studies were with a high risk of bias. No implant failure was reported. One study reported about complications related to therapies employed. Disease recurrence was found in two of the included papers.

One study provided available data on radiographic bone level changes, but no statistically significant differences were found between test and control group at the end of the follow-up.

Conclusions: Non-surgical therapy of Peri-implantitis seems to have a limited efficacy. Only the use of systemic azithromycin associated to mechanical debridement can give better clinical outcomes, indeed in the study of Gomi et al. was reported a greater reduction of 0.96 ± 0.4 mm in the test group compared with the data of the control group after 1 year of follow up.

Keywords: Peri-implantitis; Therapy; Non-surgical; Systematic review

Introduction

The use of dental implants for replacement of missing teeth represents a widely accepted treatment option in oral rehabilitation. Implants have shown satisfactory results in rehabilitation of patient's function and long-term survival rates of approximately 89% after 10 years [1]. Nevertheless dental implants are not free of complications and long-term prognosis can be altered by technical difficulties or infections [2]. Peri-implant disease can be classified as peri-implant mucositis and peri-implantitis. Whereas peri-implant mucositis is characterized by a reversible inflammation limited to the peri-implant mucosa, peri-implantitis is a non-reversible inflammation of peri-implant tissues leading to a reduction of the peri-implant bone level [3]. If no successful treatment is performed, peri-implantitis can bring to implant loss [4-6].

Peri-implant disease is an important pathological entity due to its prevalence and incidence. Peri-implant mucositis has been reported to affect 80% of the subjects and 50% of the implants, while peri-implantitis was identified in percentages ranging between 28% and 56% of subjects and 12% and 43% of implant sites, respectively [7].

Peri-implant disease is infectious in nature and the main etiological factor is the development of a bacterial biofilm on implant surface [8]. After being inserted in bone, the supragingival aspect of implant surface is covered by an organic layer formed by proteins, glycoproteins and lipids and this represents the stratum on which bacterial colonization occurs [9].

A study on composition of the microbiota in peri-implantitis revealed the presence of periodontopathogen microorganisms as *Prevotella intermedia, Porphyromonas gingivalis, Treponema denticola* and *Aggregatibacter actinomycetemcomitans* [10]. On the other hand, a recent review concluded that even if the microbiota associated with peri-implant disease is similar to that of chronic periodontitis, there are cases specifically associated with other bacterial species, as *Peptostreptococcus spp.* or *Staphylococcus spp.* [11].

Although bacterial contamination is the primary etiological factor, there are multiple risk indicators that must be taken into account in

peri-implant disease manifestation and progression, as a previous history of periodontitis and cigarettes smoking [3]. Further factors, as the influence of keratinized mucosa, genetic traits and implant surface are under investigation [12].

The diagnosis of peri-implantitis is based on clinical and radiographic findings. Changes in probing depth associated with bleeding or suppuration on probing indicate the presence of peri-implant inflammation and radiographs are used to confirm peri-implant bone loss [13,14].

The target for the treatment of peri-implant disease is the removal of bacterial biofilm and the disinfection of implant surface. However the presence of screw threads and surface roughness makes implant decontamination a difficult issue. Non-surgical treatment is the first-line intervention to control peri-implant disease.

Different studies on non-surgical approach have reported promising results for inflammation control in terms of reduction of bleeding on probing but whilst peri-implant mucositis can completely heal, there are unpredictable results for the treatment of peri-implantitis [3].

The aim of the present systematic review was to evaluate all the scientific evidence on non-surgical treatment of peri-implantitis and to systematically assess the efficacy of this therapy on implant failure, radiographic margin bone level, complications and peri-implantitis recurrence.

Materials and Methods

The present systematic review was developed and conducted following the PRISMA statement [15] and, before the start; a protocol was set including these definitions [16].

Focused question

Study population

Types of intervention

Types of comparisons

Outcome

Search strategy

Eligibility criteria for study inclusion

Outcome measures

Screening methods and data extraction

Quality assessment and data synthesis

Assessment of heterogeneity and drawing of conclusions

Focused question

The focused question was: "In patients with diagnosed peri-implantitis what are the most effective non-surgical treatment on implant failure, changes in radiographic margin bone level, complications and peri-implantitis recurrence?"

Population, interventions and outcome

The population of interest for this review was represented by humans in good systemic conditions, older than 18 years with at least one implant with diagnosed peri-implantitis.

The definitions used for peri-implantitis were: "plaque-induced progressive marginal bone loss observed on radiographs with clinical signs of infection of the peri-implant soft tissues" [17] for clinical sign and "detectable bone loss from 1-year examination and bone level loss ≥ 1.8 mm" [18] for radiographic evaluation.

The interventions examined were any non-surgical mechanical therapy for biofilm debridement in association or not with any adjunctive measure.

The primary outcomes analyzed were drawn from a previous systematic review of Cochrane Collaboration Group [17].

- Implant failure defined as implant mobility of a previously clinically osteointegrated implant and removal of non-mobile implants because of progressive marginal bone loss or infection.

- Radiographic margin bone level measured as the change on intra-oral radiographs taken with paralleling technique.

- Complications and side effects.

- Peri-implantitis recurrence.

The secondary outcomes were probing pocket depth (PPD), clinical attachment level (CAL) and bleeding on probing (BOP).

Search strategy

Two reviewers (GLS and GP) conducted a literature search independently in three electronic databases: PubMed, Embase and Central up to and including 10 February 2017. The following key words and MeSH terms were used:

Population: ("peri implantitis" or periimplantitis or perimplantitis or peri-implantitis or peri-implant* or "peri implant*" or perimplant* or periimplant* or "Peri-Implantitis" [Mesh]).

Intervention: (Treatment or therapy or prevention or management or maintenance or "non-surgical" or "Therapeutics" [Mesh] or ("Tertiary Prevention" [Mesh] or "Secondary Prevention" [Mesh] or "Primary Prevention" [Mesh]) or "Disease Management" [Mesh])).

In addition, the following journals were hand-searched: Journal of Clinical Periodontology, Journal of Periodontology, Clinical Implant Dentistry, Clinical Oral Implants Research, European Journal of Oral Implantology, International Journal of Oral and Maxillofacial Implants, Journal of Oral Implantology, International Journal of Periodontics and Restorative Dentistry. The reference list of the selected studies was scanned for cross-references. In addition, a search in the grey literature was performed on Opengrey (http://www.opengrey.eu) using the words "peri-implantitis" and "treatment" for this specific database. If it was necessary, authors were contacted to provide missing information. There was no language restriction.

Inclusion and exclusion criteria

Inclusion criteria used were defined as follows:

- Non-surgical professional treatments of peri-implantitis.

- Randomized controlled trials either split-mouth or parallel group design.

- Patients in good systemic conditions who have ≥ 1 implant with peri-implantitis.

Exclusion criteria were, instead, defined as follows:

• Less than 10 patients/group.

Study selection

In the first stage, two independent reviewers (GLS and GP) screened titles and abstracts and did the primary search.

The management of the articles was achieved using commercially available software (Endnote X7, Thomson, London, UK).

Subsequently, the studies that could meet the inclusion criteria and articles with unclear information in the title and abstract were selected for full-text analysis, which was performed independently by the same two reviewers (GLS and GP). Any disagreement was discussed with a third member (RB) until consensus was reached.

Finally full-text analysis was performed, excluding the studies that did not meet inclusion criteria and the reasons of this choice were recorded at any step.

In case of discrepancy between the reviewers, disagreements were discussed with a third person (RB) until the reaching of the consensus.

Data extraction and data analysis

Data from the studies were extracted by two independent reviewers (GLS and GP) in specific forms based on type of study design, number of implants treated, durations of follow-up, dimensions of the populations, mean ages, smoking habits, periodontal health, type of implants, treatments performed, measurement methods, outcomes evaluated, sites and sources of funding. Any disagreement was discussed with a third reviewer (RB) when necessary.

Authors of the manuscripts were contacted when data were incomplete or missing. When the results of a study were published more than once, the most complete dataset was included only one time.

To compare the selected studies, primary and secondary outcomes (probing pocket depth, clinical attachment level and bleeding on probing) were pooled and analyzed using weighted mean differences (WMD) and 95% confidence intervals.

Data were calculated using commercially available software (STATA® 13, StataCorp LP, and Lakeway Drive, College Station, TX, USA).

Statistical significance was defined as a P-value <0.05.

Quality assessment

The quality assessment was conducted in duplicate by two reviewers (RB and GLS). The Cochrane collaboration's tool for assessing risk of bias [19] was used to determine the quality of the full-text articles included, performed in two steps.

Firstly it was considered if the studies met the criteria for the following domains:

• Sequence generation. Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

• Allocation concealment. Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.

• Blinding of participants, personnel and outcome assessors. Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.

• Incomplete outcome data. Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.

• Selective outcome reporting. State how the possibility of selective outcome reporting was examined by the review authors, and what was found.

• Other sources of bias. State any important concerns about bias not addressed in the other domains in the tool.

Subsequently, a judgement was assigned answering to the previous domains. An answer "+" indicates a low risk of bias and an answer "-" indicates a high risk of bias. The answer "?" indicates an unclear risk of bias. Publications were considered as low risk of bias when all the five criteria were low.

Articles were considered as high risk of bias if at least two of the five criteria were unclear or at least one of the criteria was high or if the randomization was not done in a proper way. When one of the criteria was unclear, the protocol was considered as unclear risk of bias.

Results

Screening

The search strategy returned 4105 results. Of all those, 4103 articles were considered after duplicates removal. During the first stage of study selection 4080 publications were excluded based on titles and abstracts.

Study	Reasons of Exclusion
Bach et al. [20]	Lack of data
Javed et al. [21]	Mixed mucositis and peri-implantitis
Karimi et al. [22]	Mixed mucositis and peri-implantitis
Lerario et al. [23]	Mixed mucositis and peri-implantitis
Tang et al. [24]	Mixed mucositis and peri-implantitis
Renvert et al. [25]	Mixed mucositis and peri-implantitis
Renvert et al. [26]	Mixed mucositis and peri-implantitis
Renvert et al. [27]	Mixed mucositis and peri-implantitis
Romeo et al. [28]	Mixed mucositis and peri-implantitis
Sahm et al. [29]	Mixed mucositis and peri-implantitis

Table 1: A total of 10 papers had to be excluded after reading the full-text because they did not fulfill the inclusion criteria of the present review.

In the second stage, 22 potentially relevant publications were evaluated. A total of 10 papers had to be excluded after reading the full-text because they did not fulfill the inclusion criteria of the present review (Table 1). The flow diagram describes the results of search queries (Figure 1). A total of 12 studies were included for the analyses. The pooled analysis comprised 334 patients for 536 implants affected by peri-implantitis.

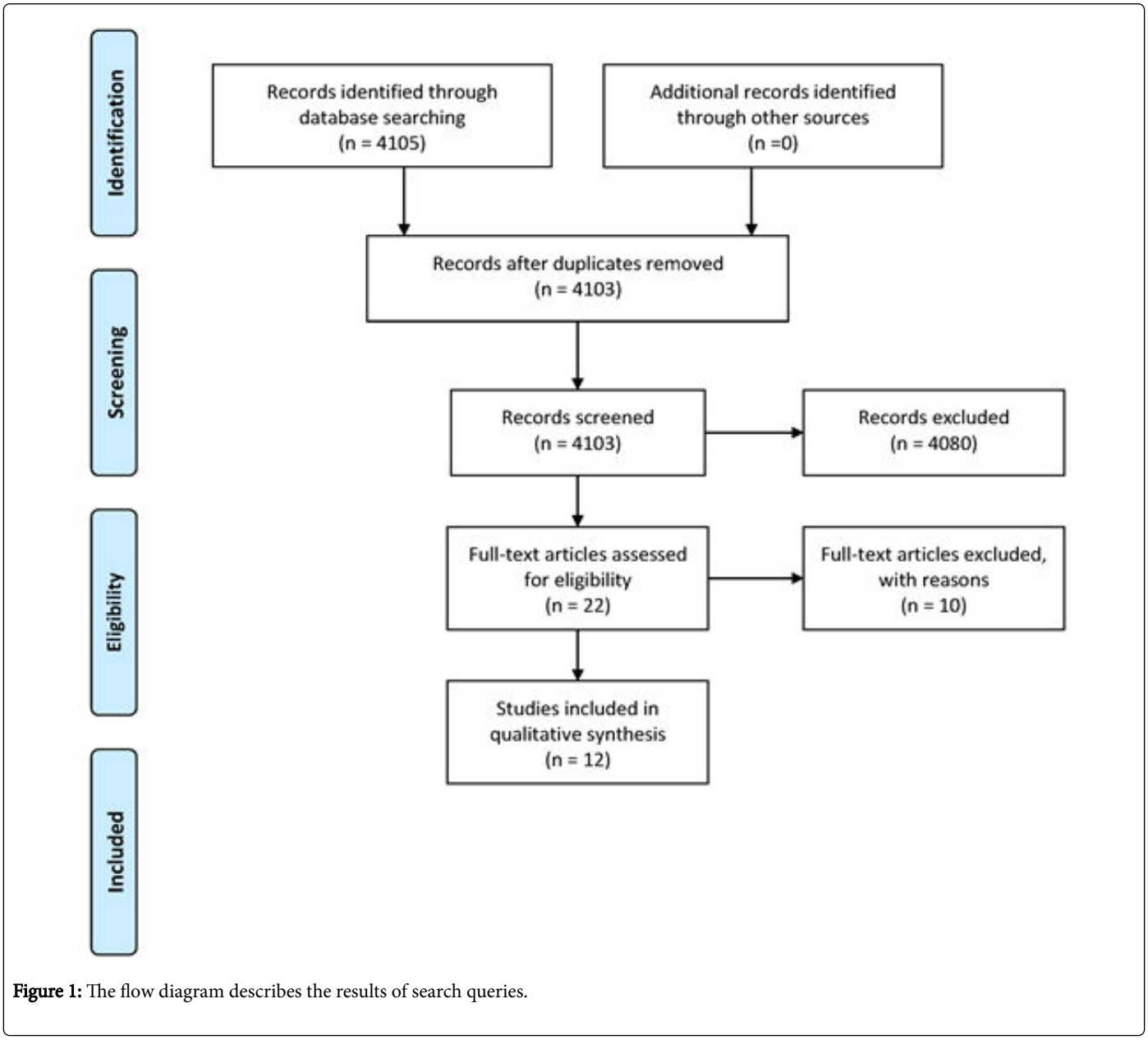

Figure 1: The flow diagram describes the results of search queries.

Study population and study design

Variables of study population and study design are presented in Table 2.

The follow-up of the included studies ranged from 3 to 12 months. Three studies presented a split-mouth design with 3 and 6 months of follow-up. Smoking status was reported in 8 studies and ranged from 0% to 38% [30,31].

The periodontal status of the involved patients was expressed in 8 papers [32-39]. The study population ranged from 10 to 63 subjects and the number of treated implants ranged between 22 and 100.

Six studies specified the implant surface, which were TPS [31,33,40] and SLA [30,31,33,36,40] and 1 study [35] didn't treat TPS or HA surfaces.

In the others six studies, 4 specified only the type of implants used [32,37,38,41] 1 described only the surface as "machined" [34] and the last one didn't report anything [39].

Type of intervention and comparison

The study interventions and comparison were either combined treatments or treatments alone (Table 2).

Therapies employed for mechanical debridement were sonic/ultrasonic scalers [39], plastic/carbon/titanium courettes [30,32,38,39] and the VECTOR® system [32].

Jansaker et al. [37] performed a submucosal mechanical debridement with ultrasonic scaler to all patients and then employed Chloramine perisolve in test group. VECTOR® system was compared with the efficacy of carbon courettes in the study of Karring et al. [32].

To treat the peri-implants infections Schwarz et al. [31,33] performed a professional cleaning with rubber cups and polishing paste, then then they compared the efficacy of Er:YAG laser with plastic courettes with Chlorhexidine 0.2% irrigations and Chlorhexidine 0.2% Gel. Renvert et al. [34] used Er:YAG laser in the test group and PERIO-FLOW in control group. Bassetti et al. [36] first of all treat patients with carbon courettes in combination with Glycine Air Powder, then use or Diode Laser or Minocycline Hydrochloride Microspheres.

Arisan et al. [40] used plastic courettes associated, in test group, with Diode Laser. In the study by Abduljabbar et al. [41] an Nd:YAG laser was employed as an adjunctive measure to plastic courettes in the test group. Antibiotics and antiseptics were used as chemical agents for treatment of peri-implantitis.

In the study by Gomi et al. [39] systemic azithromycin was prescribed starting 3 days before non-surgical therapy with a doses of 500 mg/day for 3 days, in the test group, as an adjunctive measure to ultrasonic Scaler with plastic tips and plastic courettes. Büchter et al. [30] subgingival irrigations with 8.5% doxycycline were performed in adjunction of plastic courettes and Chlorhexidine 0.2% irrigations in test group.

Antiseptic therapy was performed using 0%, 1% and 0%, 2% subgingival irrigations in association with mechanical treatments in 4 studies [30,31,33,38] while in one paper 0%, 2% or 1% chlorhexidine gel was applied [31]. In one study [36], 0%, 5% chlorhexidine chips were employed in association with ultrasonic debridement and compared with placebo.

John et al. [38] performed a study in which given supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste to all patients and treated the test group with carbon curettes and Chlorhexidine 0.1% submucosal irrigation with Chlorhexidine 1% gel submucosal application, while the control group received submucosal application of Amino acid Glycine powder.

In 5 studies patients have received treatments before their allocation in test and control groups [30,31,36,38,39] while in the remaining protocols no previous interventions were performed [32-35,37,40,41].

Method of measurement

Three of the selected studies [32,34,41] used intraoral radiographs to evaluate changes in peri-implant marginal bone levels. In one study [40] orthopantomography was used to assess peri-implant marginal bone levels.

In the study by Karring et al. [32] and by Abduljabbar et al. [41] marginal bone changes were calculated as the distance in mm between the bone crest and the most apical bone to implant contact point.

In a similar manner, Renvert et al. [34] calculated the distance between a reference points to the deepest point of the bone lesion in mm.

In the study by Arisan et al. [40] the distance in mm between implant shoulder and the bottom of the defect was assessed by calibrated software.

Study	Study Design	Case definition	Participants	Type of Implants	Treatments	Method of measurement	Results	Site and Fundings
Buchter et al. [30]	RCT parallel, 2 Groups Single-Blind, 4 months follow-up	Chronic peri-implantitis: >50% bone loss around implants	28 individuals (-0), 48 implants Aged: 55 Smoking status: 32% Smokers, Periodontal Status: NA	Type of Implant: ITI, Straumann® Surface: SLA	Test: Plastic Courettes +Chlorhexidine 0.2% Irrigations+Doxycycline 8.5% Irrigations Control: Plastic Courettes +Chlorhexidine 0.2% irrigations Supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste.	PCP 11, 4 sites/implant	PPD, PAL BOP	NA
Schwarz et al. [31]	RCT parallel, 2 groups, 6 months follow up	Probing Depth 4 mm in association with RX bone loss, BOP or SUP on probing	20 individuals (-0) 32 implants Aged: 50 Smoking Status: No Smokers Periodontal Status: NA	Type of Implant: No Cylindrical Implants Surface: 17 SLA, 15 TPS	Test: Er:YAG laser Control: Plastic Courettes +Chlorhexidine 0.2% irrigations +Chlorhexidine 0.2% Gel	PCP 12, 6 sites/implant	PI, BOP, PPD, MR, CAL	NA
Karring et al. [32]	RCT split-mouth, 2 Groups	BOP, PPD 5 mm, 1.5 mm Rxbone loss and exposed implant	11 individuals (-0), 2 implants/individual Aged: 50-78 Smoking Status: NA	Type of Implant: Screw-Shaped, 4 Br5nemark, 8 ITI, 10 Astra Same implants/individual	Test: Vector® Control: Carbon Courettes Supramucosal/gingival professional implant/tooth cleaning with	LL 20, 4 sites/implant, Intraoral RX	PL, BOP, PPD, PI, RX bone level	NA, Durr Dental

	Single-Blind, 6 months follow up	thread (Mombelli and Lang 1998)	Periodontal Status: Exclusion of Chronic Severe Periodontitis		rubber cups and polishing paste.			
Schwarz et al. [33]	RCT parallel, 2 Groups, 12 months follow up	Rx bone loss <30% or >30%. PPD >4 mm, PPd>7 mm at least in 1 site, BOP/SUP	20 individuals (-0) 40 impiants Aged: 54 Smoking Status: No Smokers, occasional Smokers Periodontal Status: Health/ Treated	Type of implant: IMZ "twin plus", ITI, MTX, ZL Duraplant, Camlog Surface: SLA, TPS	Test: Er:YAG laser Control: Plastic Courettes +Chlorhexidine 0.2% irrigations +Chlorhexidine 0.2% Gel	PCP 12, 6 sites/implant	PI, BOP, PPD, REC, CAL	Germany, Arbeitsgemeinschaft fur Kieferchirurgie innerhalb der Deutschen Gesellschaft flir Zahn-, Mund- and Kieferheilkunde
Renvert et al. [34]	RCT parallel, 2 groups, 6 months follow up	Rx bone loss>3 mm, PPD>5 mm +BOP/SUP	42 individuals (-0) 100 implants Aged: 68 Smoking Status: NA Periodontal status: Health/Treated	Surface: 70 Machined, 30 Medium Rough	Test: Er:YAG laser Control: PERIO-FLOW Supragingival Scaling with ultrasonic device	Hawe Click-Probe Calibrated force 0.2 N 4 sites/implant	PPD, BOP, FMPS, PI, intra-oral standardized radiograph	Sweden, EMS & KAVO & Philips
Machtei et al. [35]	RCT parallel, 2 groups, 6 months follow up	PPD 6-10 mm, positive BOP, Rx bone loss	60 individuals (-4) 77 implants Aged: 59 Smoking Status: 38% Smokers Periodontal Status: Health/ Treated	Surface: no TPS or HA coated	Test: Ultrasonic Debridement +matrix 0.5 mg CHX Control: Ultrasonic Debridement +matrix gelatine Carbon Courettes+Glycine Air Powder	UNC 15	PPD, BOP, CAL REC	Israel, Dexcel Pharma
Bassetti et al. [36]	RCT parallel, 2 groups, 12 months follow-up	PPD 4-6 mm +BOP, 0.5-2 mm RX bone loss between suprastructure installation and pre-screening appointment.	40 individuals (-1) 1 implant/ individual, Aged: 58 Smoking status: NA, Periodontal Status: 26 subjects with history of periodontitis	Type of Implant: Titanium screw-shaped Implants, Straumann® Surface: SLA	Test: Photodynamic therapy Control: Minocycline Hydrochloride Microspheres Submucosal mechanical debridement with ultrasonic scaler	UNC 15 Calibrated force 0.15-0.25 N, 6 sites/implant, ELISA and PCR	PPD, CAL BOP, REC, mPII, Microbiological Sample	Switzerland, Bredent Medical GmbH & Co. KG
Roos Jansaker et al. [37]	RCT split-mouth, 2 groups, 3 months follow up	RX bone loss 2 mm, BOP/SUP +,PPD>4 mm	18 individuals (-2) 36 implants Aged: 72 Smoking status: 37,5% Periodontal status: Healthy/Treated	Type of implants: 7 ASTRA, 9 NOBEL	Test: Chloramine perisolve+Ultrasonic mechanical debridement Control: Ultrasonic mechanical debridement Supramucosal/gingival professional implant/ tooth cleaning with rubber cups and polishing paste.	Hawe Click-Probe Calibrated force 0.2 N 4 sites/implant	FMPS, PI, PPD, CAL BI, BOP	Sweden, RLS Global AB
John et al. [38]	RCT parallel, 2 groups, Single-Blind, 12 months follow-up	Initial-Moderate Peri-Implantitis: PPD ≥ 4 mm +BOP/SUP, RX bone loss <30% compared to the situation after implant placement.	32 individuals (-7) 36 implants Aged: 62 Smoking status: non-smokers Periodontal status: Healthy/Treated	Type of Implant: Screw-type titanium implants. 5 Branemark, 10 Camlog Screw Lines® 9 ITI, 2 Frialit®, 7 Tapered Screw Vent®, 3 NA	Test: Carbon Courettes +Chlorhexidine 0.1% submucosal irrigation +Chlorhexidine 1% gel submucosal application Control: Aminoacid Glycine Powder submucosal application Supragingival Scaling	PCP 12, 6 sites/implant	PI, BOP, PPD, GR, CAL	Germany, EMS
Gomi et al. [39]	RCT parallel, 2 Groups, 12	Patients corresponding to CIST class C or D (Lang).	20 individuals (-0), 1 implant/ individual Aged: 68 Smoking Status: NA	NA	Test: Ultrasonic Scaler with plastic tips+Plastic Courettes+Systemic Azitromicin starting 3 days before 500	NA, 6 sites/ implant, PCR	PPD, BOP, GI, Microbiological Sample, Host-Derived Biomarkers	Japan, NA

	months follow up		Periodontal Status: Chronic Periodontitis		mg/day Control: Ultrasonic Scaler with plastic tips+Plastic Courettes			
Arisan et al. [40]	RCT split-mouth, 2 groups, 6 months follow up	BOP/SUP, plaque, pain, 4-6mm PPD, <3 m of marginal bone loss (MBL)	10 individuals (-0) 48 implants Aged: 55 Smoking Status: non-smokers Periodontal Status: Healthy	Type of implant: 15 MIS, 12 Camlog Biotechnologies, 8 Nobel Biocare, 7 Biohorizons	Test: Plastic Courettes +Diode Laser Control: Plastic Courettes	PQ-OW, 4 sites/implant, PCR, OPT	PPD, PI, BOP, Microbiological Sample, MBL	Turkey, Istanbul University Research Fund
Abduljabbar et al. [41]	RCT parallel, 2 groups, Single-Blind, 6 months follow up	BOP on at least 30% of the periimplant sites, PPD 4 mm and/or loss of supporting bone (3 mm) around a functional implant	63 individuals (-0) 74 implants Aged: 41 Smoking Status: non-smokers Periodontal Status: NA	Type of implant: Straumann Bone Level implants	Test: Plastic Courettes +Nd:YAG laser Control: Plastic Courettes	NA, 6 sites/ implant, standardized radiograph	PPD, BOP/ SUP, PI, CBL Microbiological Sample, MBL	Saudi Arabia Deanship of Scientific Research at King Saud University

Table 2: Variables of study population, study design and comparison were either combined treatments or treatments alone.

Changes in the secondary outcomes were assessed by probing with calibrated periodontal probes. In two studies the type of periodontal probe used was not specified [39,40]. Measurements were performed either at four [30,32,34,37,40] or six sites/implant [31,33,36,38,39,41].

In 3 papers probing was performed with calibrated force ranging from 0.15 N to 0.25 N [34,36,37].

Probing pocket depth was assessed in all studies as the distance in millimetres between the gingival margin and the bottom of the sulcus/pocket. Clinical attachment level was assessed in seven of the selected studies [30,31,33,35-38].

While Bassetti et al. [36] and Machtei et al. [35] calculated the CAL the sum of PPD and REC, other authors measured the CAL as the distance in millimetres from the implant neck to the bottom of the sulcus/pocket.

All of the selected studies evaluated bleeding on probing. Büchter et al. [30], Schwarz et al. [31], Karring et al. [32], Schwarz et al. [33], John et al. [38], Gomi et al. [39] and Arisan et al. [40] evaluated if BOP was evident in the first 30 sec after probing, while Bassetti et al. [36] evaluated the presence of bleeding in the first 10-15 sec after probing.

Four studies [34,35,37,41] evaluated the presence/absence of bleeding on probing after probing pocket depth assessment. Three [30,31,39] studies don't specify if they were sponsored. Three [33,40,41] studies received funding from university. The remaining six groups [32,34-38] were sponsored by companies of the product tests in their trials.

Study #	**1# Buchter et al. [30]**	**2# Schwarz et al. [31]**	**3# Karring et al. [32]**	**4# Schwarz et al. [33]**	**5# Renvert et al. [34]**	**6# Machtei et al. [35]**	**7# Bassetti et al. [36]**	**8# Roos-Jansaker et al. [37]**	**9# John et al. [38]**	**10# Gomi et al. [39]**	**11# Minn et al. [40]**	**12# Abduljabbar etal. [41]**
Random sequence generation	"Randomization being from a computer-generated table"	"Randomization was performed by coin toss"	"One implant was chosen at random (by choosing a sealed envelope out of a bunch of 22 identical envelopes) was treated by Vector system,	The patients were randomly assigned to the following test and the control groups according to a computer-generated protocol (Rand	"The allocation was carried out using a computer software program (SPSS Inc.) for the randomization"	Randomization was performed using a computer-generated sequence	No information in the paper	The randomization was performed with a random number generator, generated by atmospheric noise (http://yeww.random.org).	No information in the paper	No information in the paper	Coin toss	"Randomization was done, by tossing a coin"

			while the other with sub mucosal debridement with a carbon fibre curettes"	List, DatInf GmbH, Tub-ingen, Germany)"								
Allocation concealment	No information in the paper	Before treatment the patients were randomly assigned to the treatment groups"	No information in the paper	No information in the paper	A clinician not involved with the study sequenced the study subjects to the therapy allocated.	Eligible patients at baseline visit were assigned a randomization number starting from 601. Each randomization number was randomly assigned to one of the two letters A or B; each letter assigned randomly to one of the two treatments MatrixC or PerioC.	No information in the paper	No information in the paper	No information in the paper	"After these instructional visits, the patients were randomly allocated to a testgroup (n=10) or a control group (n=10)"	"At the beginning of the treatment"	No information in the paper
Blinding of outcome assessment	Nessuna informazione presente nell'articolo. In una revision e di Esposito 2012: The measurements at 18 weeks were taken by another surgeon than the one who did the baseline measurements and the treatment"	"All measurements were made at six aspects per implants by one blinded and previously calibrated investigator"	The same investigator (ESK) carried out the treatment of all the implants and made all the recordings at baseline examination, while another investigator who was unaware of the treatment delivered made all the follow-up treatment."	No information in the paper	When performing their study tasks, the study examiner (M. N.) and the therapist (C. L.) were not jointly present with the study subjects. Study subjects were instructed not to discuss therapy with the study examiner. The study examiner was unaware of study treatment allocations,	To ensure examinees blindness, two separate investigators attended to each patient	"One blinded and calibrated examiner assessed the clinical parameters at six sites per implant"	No information in the paper	"All measurements were made at six aspects per implants by one blinded and previously calibrated investigator"	No information in the paper	No information in the paper	"All clinical and radiographic assessments were performed by an experienced and calibrated examiner (TA) who was blinded to the study groups"

					and performed all clinical measurements."							
Incomplete outcome data	No Drop-Out	1 patient in the mechanical debridement group had a severe pus formation and was moved in the laser group but their results were not reported	No Drop-Out	2 patients of the mechanical debridement group were excluded due to severe pus formation and treated with laser. No data were given.	No Drop-Out	Four patients, all from the MatrixC were exited from the study. One required extended antibiotic use (non-related).	1 patient missed the 9 month follow-up but completed the study, 1 patient missed the 12 month follow-up	No information in the paper	7 patients did not complete the study, but only 5 were reported as Drop-Out in the text	No Drop-Out	No Drop-Out	No Drop-Out
Selective reporting	Data for all patients seem to be reported	Lack of data of the patient excluded	Lack of standard deviation data of the BOP parameter	Missing data for the patients excluded by the authors and radiographs	Data at patient level not presented	Data for all patients seems to be reported	Data for all patients seems to be reported	Data for all patients seems to be reported	Lack of data of 2 patients excluded	Data for all patients seems to be reported	Data for all patients seems to be reported	Data for all patients seems to be reported
Other bias	None apparent	None apparent	None apparent, sponsored by Durr Dental	None apparent	None apparent, sponsored by EMS, KAVO	None apparent, sponsored by Dexcel Pharma	None apparent, sponsored by GmbH & Co.	None apparent, sponsored by RLS Global AB	None apparent, sponsored by EMS	None apparent	None apparent	None apparent

Table 3: Data from the quality assessment.

Interestingly the group of Renvert et al. [34] was sponsored by both companies whose products were compared.

Quality assessment

Data from the quality assessment are reported in and in Tables 3 and 4. All studies were considered to have a high risk of bias except one, which presents a low risk [35].

Study #	**1#**	**2#**	**3#**	**4#**	**5#**	**6#**	**7#**	**8#**	**9#**	**10#**	**11#**	**12#**
Quality criteria	**Buchter et al. [30]**	**Schwarz et al. [31]**	**Karring et al. [32]**	**Schwarz et al. [33]**	**Renvert et al. [34]**	**Machtei et al. [35]**	**Bassetti et al. [36]**	**Roos-Jansaker et al. [37]**	**John et al. [38]**	**Gomi et al. [39]**	**Ansan et al. [40]**	**Abduljabbar et al. [41]**
Random sequence generation	+	-	?	+	+	+	?	+	?	?	-	-
Allocation concealment	?	+	?	?	?	+	?	-	?	+	+	?
Blinding of outcome assessment	?	+	+	-	+	+	+	-	+	?	-	+

Incomplete outcome data	+	-	+	-	+	+	+	-	?	+	+	+
Selective reporting	+	-	-	-	?	+	+	+	-	+	+	+
Other bias	+	+	+	+	+	+	+	+	+	+	+	+
Total Bias	-	-	-	-	-	+	-	-	-	-	-	-

Table 4: Descriptive analysis of primary variables.

Study outcome, descriptive analysis of primary variables: Among the included studies, no implant failures are reported at the end of follow-up. Peri-implantitis recurrence was reported in three studies. The study by Schwarz et al. [33], reported disease recurrence in all the treated implants at the 6 months follow-up control, so all patients had to be treated with surgical therapy.

The study by Bassetti et al. [36] reported 5 recurrences, 3 in the control group treated with minocycline and 2 in the test group, treated with photodynamic therapy. The study of Renvert et al. [34] reported that the 11% of the patients in the test and in the control group still presented pus on probing.

Only one of the selected studies Gomi et al. [39] reported 11 complications, 10 made up analgesic administration to treat pain given by non-surgical procedures and 1 case of diarrhoea following the consumption of azithromycin. Four trials [32,34,40,41] reported the changes in radiographic bone level.

The group of Renvert [34], instead, found a mean difference of 0.3 ± 0.9 mm in the laser group and of 0.1 ± 0.8 mm in the air-flow group, failing to found a clinical relevance in this outcome.

In the study by Arisan et al. [40] statistically significant mean bone changes were found in both groups between baseline and the 6 months follow-up (F=38.34, p<0.0001). A statistically significant difference was found also comparing the test and control groups at the end of the follow-up period (0.5227 mm, adjusted p=0.0013) in favour of the laser group.

The group of Karring et al. [32] showed no statistical significant differences between baseline and the 6- month control regarding bone changes, neither within each treatment group nor between treatments, with a difference, after 6 months, of -0.3 ± 1 mm in test group and -0.3 ± 0.8 mm in control group.

In the study of Abduljabbar et al. [41] at baseline and at 6-month follow-up, the mean crestal bone loss was comparable among individuals in groups 1 and 2, with a base-line 1.8 mm of mean loss and 1.7 mm at the follow-up in group 1 and 2.1 mm of mean crestal bone loss at the base-line, that change in 2.2 mm at follow-up in group 2.

Study outcome, descriptive analysis of the changes in probing pocket depth: Data about secondary outcomes are presented in Tables 5 (PPD), 6 (CAL) and 7 (BOP).

Study	Intervention/Control	Measurement Method	Test Difference	Control Difference	Difference	P value
Büchter et al. [30]	Test: Plastic Courettes+Chlorhexidine 0.2% Irrigations +Doxycycline 8.5% Irrigations Control: Plastic Courettes +Chlorhexidine 0.2% irrigations Supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste.	PCP 11, 4 Sites/implant	1.15 ± 0.23 mm	0.56 ± 0.30 mm	0.59 ± 0.53 mm	0.046
Schwarz et al. [31]	Test: Er:YAG laser Control: Plastic Courettes+Chlorhexidine 0.2%	PCP 12, 6 Sites/implant	0.8 ± 0.1 mm	0.6 ± 0.1 mm	0.2 ± 0.2 mm	<0.001
Karring et al. [32]	Test: Vector® Control: Carbon Courettes Supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste.	LL 20, 4 Sites/implant	0 ± 0.1 mm	0.1 ± 0.6 mm	0.1 ± 0.7 mm	>0.1
Schwarz et al. [33]	Test: Er:YAG laser Control: Plastic Courettes+Chlorhexidine 0.2% Irrigations+Chlorhexidine 0.2% Gel	PCP 12, 6 Sites/implant	0.33 ± 2.3 mm	0 ± 2.64 mm	0 ± 3.22 mm	<0.05
Renvert et al. [34]	Test: Er:YAG laser Control: PERIO-FLOW Supragingival Scaling with ultrasonic device	Hawe Click-Probe Calibrated force 0.2 N 4 Sites/implant	0.8 ± 0.5 mm	0.9 ± 0.8 mm	0.1 ± 1.3 mm	P=0.55
Machtei et al. [35]	Test: Ultrasonic Debridement+matrix 0.5 mg CHX Control: Ultrasonic Debridement+matrix gelatin Carbon Courettes+Glycine Air Powder	UNC 15	2.13 ± 0.22 mm	1.73 ± 0.19 mm	0.40 ± 0.31 mm	0.178

Bassetti et al. [36]	Test: Photodynamic therapy Control: Minocycline Hydrochloride Microspheres Supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste.	UNC 15 Calibrated force 0.15 N-0.25 N 6 Sites/implant	0.36 ± 0.03 mm	0.49 ± 0.01 mm	0.07 ± 0.04 mm	>0.05
John et al. [38]	Test: Carbon Courettes+Chlorhexidine 0.1% Submucosal irrigation+Chlorhexidine 1% gel submucosal application Control: Aminoacid Glycine Powder Submucosal application Supragingival Scaling.	PCP 12, 6 Sites/implant	0.5 ± 0.9 mm	0.4 ± 0.9 mm	0.1 ± 1.8 mm	>0.05
Gomi et al. [39]	Test: Ultrasonic Scaler with plastic tips+Plastic Courettes+Systemic Azithromycin starting 3 days before 500 mg/day Control: Ultrasonic Scaler with plastic tips+Plastic Courettes	NA, 6 Sites/implant	1.19 ± 0.39 mm	0.23 ± 0.01 mm	0.96 ± 0.4 mm	0.01
Arisan et al. [40]	Test: Plastic Courettes+Diode Laser Control: Plastic Courettes	PQ-OW, 4 Sites/implant	0.17 ± 1.41 mm	0.21 ± 0.83 mm	0.04 ± 2.24 mm	<0.001

Table 5: Differences in PPD between baseline and the end of the investigation for test and control groups.

In the study conducted by Büchter et al. [30] treatment in the test group was performed using plastic courettes in association with Chlorhexidine 0.2% and Doxycycline 8.5% irrigations whilst in the control group plastic courettes with Chlorhexidine 0.2% irrigations were employed.

Between the start and the end the test group showed a mean PPD reduction of 1.15 ± 0.23 mm, while in the control group was 0.56 ± 0.30 mm, with a statistically significant difference between groups of 0.59 ± 0.53 mm (p=0.046).

In the study by Schwarz et al. [31] all the patients were initially treated with supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste. The test group was treated with Er:YAG laser, and the control group with plastic courettes in association with 0.2% chlorhexidine irrigations and gel.

The difference of PPD between baseline and 12 months follow-up in the test group was 0.8 ± 0.1 mm, and 0.6 ± 0.1 mm in the control group. A statistically significant difference between groups of 0.2 ± 0.2 mm was found (p<0.001).

Karring et al. [32] performed a split-mouth study comparing the Vector® system in the test group with carbon courettes in the control group, finding a difference of 0 ± 0.1 mm and 0.1 ± 0.6 mm respectively. No significant differences between group could be found (0.1 ± 0.7 mm, p>0.1).

In another study, Bassetti et al. [36] used carbon courettes and Glycine air powder on all patients. In this protocol, photodynamic therapy (test) and Minocycline Hydrochloride microspheres (control) were compared. The Authors found a difference of 0.36 ± 0.03 mm and 0.49 ± 0.01 mm, respectively. There was a difference of 0.07 ± 0.04 mm between groups with a p value>0.05.

Schwarz et al. [33] evaluated the efficacy of Er:YAG laser, compared to plastic courettes, 0.2% chlorhexidine irrigations and the use of 0.2% chlorhexidine gel. They found a difference between baseline and 12 months follow-up amounting to 0.33± 2.3 mm in the test group and 0 ± 2.64 mm in the control group. Mean inter-group differences were 0 ± 3.22 mm.

Renvert et al. [34] analyzed the effect of Er:YAG laser in comparison to Perioflow. They found a PPD reduction of 2.13 ± 0.22 mm in the test group and 1.73 ± 0.19 mm in the control group. The inter-group difference amounted to 0.40 ± 0.31 mm. No statistical differences are reported between baseline and 6 months follow-up.

Machtei et al. [35] studied the efficacy of the association of ultrasonic debridement and a matrix containing 0.5 mg of chlorhexidine compared to the association of ultrasonic debridement and a gelatin matrix. The test group showed a reduction of 2.13 ± 0.22 mm, while the control groups a reduction of 1.73 ± 0.19 mm. The inter-group difference amounted to 0.40 ± 0.31 mm. No statistical differences could be found.

John et al. [38] performed a study in which given supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste to all patients and treated the test group with carbon curettes and Chlorhexidine 0.1% submucosal irrigation with Chlorhexidine 1% gel submucosal application, while the control group received submucosal application of Amino acid Glycine powder. Differences were of 0.5 ± 0.9 mm in the test group, 0.4 ± 0.9 mm in the control group, 0.1 ± 1.8 mm between groups and P value was >0.05.

In the study included by Gomi et al. [39], all patients received Supragingival Scaling using ultrasonic scaler with plastic tips and plastic courettes. In the test group systemic subministration of 500 mg/day of Azithromycin was performed, starting 3 days before. The control group was treated with mechanical debridement alone. There was a difference of PPD of 1.19 ± 0.39 mm in the test group, 0.23 ± 0.01 mm in the control group and 0.96 ± 0.4 mm between groups, with a p value of 0.01.

Arisan et al. [40] performed a study in which the test group was treated with plastic courettes plus one application of diode laser, while in the control group only plastic courettes were employed.

A mean PPD reduction of 0.17 ± 0.41 mm was found in the test group, and of 0.21 ± 0.83 mm in the control group. Between test and control group there was a difference of 0.04 ± 2.41 mm with a p value <0.001.

Study outcome, descriptive analysis of the changes in clinical attachment level: Only six of the selected studies reported clinical attachment level values and in one of them [36] the method of measurement was not clear.

The largest reduction in CAL was found by Machtei et al. [35] with a mean value of 2.21 ± 0.23 mm in the test group and 1.56 ± 0.25 mm in the control group. The difference between groups was statistically significant and amounted to 0.65 ± 0.34 mm (P=0.05).

Instead, Bassetti et al. [36] found the lowest mean CAL reduction with an average value of 0.16 ± 0.04 in the test group, 0.19 ± 0.07 mm in the control group and a difference between groups of 0.03 ± 0.11 mm.

In this protocol no statistically significant differences between groups could be found at the end of the follow-up period (P>0.05). The study by Büchter et al. [30] reported a gain of 1.15 ± 0.03 mm in the test group using plastic courettes, submucosal irrigations of 0%, 2% chlorhexidine and 8,5 doxycycline, and a gain of 0.33 ± 0.06 mm in the control group using plastic courettes and submucosal irrigations with 0%, 2% chlorhexidine. The inter group difference was statistically significant (P=0.024) and amounted to 0.82 ± 0.09 mm.

Schwarz et al. [31] reported a mean gain of 0.6 ± 0.1 mm in the test group and 0.7 ± 0 mm in the control group, with a difference of 0.1 ± 0.1 mm between groups (P>0.05). In a another study Schwarz et al. [33] found a gain in CAL of 0.25 ± 2 mm in the test group and 0.15 ± 2.2 mm in the control group with a mean intergroup difference of 0.1 ± 2.1 mm employing the same treatment modalities.

John et al. [38] reported a gain of 0.5 ± 1.1 mm and 0.6 ± 1.3 mm in the test and control groups respectively, with a non-significant difference between groups amounting to 0.1 ± 0.3 mm (P>0.05).

Study outcome, descriptive analysis of the changes in bleeding on probing: All the included studies reported the BOP outcome. Four of the selected papers [31,32,40,41] didn't report standard deviations for this parameter so were not included in the resuming Table 7.

Büchter et al. [30] reported a mean reduction of 0.27 ± 0.01 in the test group and of 0.13 ± 0.01 in the control group, with a difference of 0.14 ± 0.02 between groups and a significant P value of 0.01.

Schwarz et al. [33] found a reduction of 45.83 ± 38.7 in the test group and 25.33 ± 22.6 in the control group, with an inter-group difference of 16 ± 30.7 (P<0.01).

In the study by Bassetti et al. [36] a reduction of 2.52 ± 0.25 was found in the test group while the control group showed a reduction of 2.31 ± 0.08, with a difference between groups amounting to 0.21 ± 0.33 and a statistically considerable P value (<0.05).

Machtei et al. [35] found a reduction of 57.5 ± 7.92 with ultrasonic debridement and a matrix containing 0.5 mg of chlorhexidine and a reduction of 45.5 ± 8.8 using ultrasonic debridement and a matrix gelatin. The inter-group difference was 12.1 ± 6.7 in favor of the test group but no statistically significant differences could be found between groups (P=0.3125).

John et al. [38] reported a mean reduction value of 41.2 ± 29.5 in the control group, 16.6 ± 33.4 in the test group, with an relevant difference of 24.6 ± 63.9 and a P value <0.05.

In the study by Gomi et al. [39] a reduction of 24.5 ± 3.9 was found in the test group and of 6.1 ± 1.5 in the control group, setting a difference between groups of 18.4 ± 5.4 with a very low P value (<0.001).

In a more recent study, Jansaker et al. [37] reported a mean reduction of 0.67 ± 0.58 in the test group, which was treated with the association of ultrasonic mechanical debridement and chloramine perisolve and a decrease of 0.64 ± 0.54 in the control group using mechanical debridement alone. An inter-group difference of 0.03 ± 1.12 was found (P=0.001).

Discussion

The limitations of the present review consist in the paucity of available data and reliable data from studies included. In fact we found a great heterogeneity in the protocols utilized, indeed they have evaluated different endpoints with different follow-up and most of the studies have a high risk of bias.

Non-surgical therapy of peri-implantitis has the primary aim to decontaminate implant surface by the bacterial biofilm, which can reduce implant failure, disease recurrence and parameters such as clinical attachment level, probing pocket depth and bleeding on probing, possibly without causing side effects to the patient. This systematic review was conducted to evaluate the present literature and to provide scientific evidence on the existing RCTs evaluating different therapeutic protocols for non-surgical treatment of peri-implantitis.

The primary endpoints selected were implant failure, changes in radiographic marginal bone level, presence of complications and recurrence of peri-implantitis while the secondary variables were the change in probing pocket depth, gains in clinical attachment level and reduction of bleeding on probing.

In none of the included studies implant failure was adopted as a primary variable, but Authors reported data about this parameter. Among the papers included in the present review, no implant failure was reported at the end of the follow-up period.

Disease recurrence was reported in three trials. In particular, Bassetti et al. [36] reported disease recurrence in 5 of the 39 included implants, treated either with photodynamic therapy or with the application of minocycline microspheres. In a previous trial [33], the test group was treated with Er:YAG laser and the control group with subgingival manual debridement. After six months, the Authors found deterioration in clinical parameters of all patients and had to re-treat the patients and performed bone augmentation procedures.

In another trial in which Er:YAG laser and air-abrasives were employed [34] after six months of follow-up, 11% of the patients in the test and in the control group still presented pus on probing.

These data underline the fact that in short-term evaluation, poor conclusions can be drawn on the efficacy of non-surgical therapy of peri-implantitis to arrest disease progression and stabilize clinical parameters. Studies with longer follow-up are needed.

Moreover, in some of the studies included in this systematic review, treatments were performed only one time, while in other papers the therapies were applied multiple times so the effect of repeated-application versus single application of therapies needs to be further investigated.

One paper reported about complications related to treatments. In this study, systemic Azithromycin in association to subgingival debridement was administered to test group patients, while in the control group only subgingival debridement was performed. The majority of complications consisted in pain related to mechanical therapy (10 subjects from both groups) that was controlled with the administration of analgesics, and only one patient in the test group presented diarrhoea.

Among the included studies, four trials [32,34,40,41] reported about radiographic bone changes before and after therapy. The authors were unable to find clinically significant differences both in the test and in the control group between baseline and the end of the study.

There is a general tendency toward better results when treatment combinations are performed for non-surgical mechanical therapies in terms of PPD reduction (Table 5) and CAL gain (Table 6). These results are in agreement with a recent systematic review by Faggion et al. [42], also assessing the influence of additional treatments in association with mechanical debridement alone for non-surgical therapy of peri-implantitis.

Study	Intervention/Control	Measurement Method	Test	Control	Difference	P value
Büchter et al. [30]	Test: Plastic Courettes+Chlorhexidine 0.2% Irrigations+Doxycycline 8.5% Irrigations Control: Plastic Courettes+Chlorhexidine 0.2% irrigations Supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste.	Distance from the implant shoulder to the bottom of the peri-implant pocket 4 Sites/implant	1.15 ± 0.03 mm	0.33 ± 0.06 mm	0.82 ± 0.09 mm	0.024
Schwarz et al. [31]	Test: Er:YAG laser Control: Plastic Courettes + Chlorhexidine 0.2% Supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste.	From the implant neck to the bottom of the probable sulcus 6 Sites/implant	0.6 ± 0.1 mm	0.7 ± 0 mm	0.1 ± 0.1 mm	>0.05
Schwarz et al. [33]	Test: Er:YAG laser Control: Plastic Courettes+Chlorhexidine 0.2% Irrigations+Chlorhexidine 0.2% Gel Supragingival Scaling with Ultrasonic device	From the implant neck to the bottom of the probeable sulcus 6 Sites/implant	0.25 ± 2 mm	0.15 ± 2.2 mm	0.1 ± 2.1 mm	p>0.05
Machtei et al. [35]	Test: Ultrasonic Debridement+matrix 0.5 mg CHX Control: Ultrasonic Debridement+matrix gelatin Carbon Courettes+Glycine Air Powder	PD+GR	2.21 ± 0.23 mm	1.56 ± 0.25 mm	0.65 ± 0.34 mm	P=0.05
Bassetti et al. [36]	Test: Photodynamic therapy Control: Minocycline Hydrochloride Microspheres Supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste.	NA 6 Sites/implant	0.16 ± 0.04 mm	0.19 ± 0.07 mm	0.03 ± 0.11 mm	>0.05
John et al. [38]	Test: Carbon Courettes+Chlorhexidine 0.1% Submucosal irrigation+Chlorhexidine 1% gel submucosal application Control: Aminoacid Glycine Powder Submucosal application	From the implant neck to the bottom of the probeable Pocket 6 Sites/implant	0.5 ± 1.1 mm	0.6 ± 1.3 mm	0.1 ± 0.3 mm	>0.05

Table 6: There is a general tendency toward better results when treatment combinations are performed for non-surgical mechanical therapies in terms of PPD reduction and CAL gain.

However, these data must be carefully evaluated, because all except one of the included studies [35] presented a high risk of bias.

Among the different treatment combinations, it seems that the association of mechanical debridement and local antiseptics can bring to better clinical results.

Data by Machtei et al. [35] show reduction of 0.40 ± 0.31 mm greater in PPD when a 0.5 mg chlorhexidine matrix is associated to mechanical debridement with an ultrasonic device compared with the control group in which a gelatin matrix was employed with mechanical debridement.

The study of Gomi et al. [39] is the only study in which systemic antibiotics were employed. The greater results in PPD reduction (1.19 ± 0.39 mm of reduction in the test group and 0.23 ± 0.01 mm in the control group) if compared with topic antibiotics agents, can be explained by the difference in drugs administration. In fact, while with topic agent's higher concentrations of the drug can be reached in a pocket; the crevicular fluid is able to wash it out rapidly, as demonstrated in the study by Goodson et al. [43].

Instead, using systemic antibiotics agents is possible to obtain lower concentrations in a periodontal/peri-implant pocket, but a continuous drug delivery.

These data have to be evaluated taking into account that studies presented different methods of implant surface decontamination and different combinations of treatments. When further interpreting the results of the qualitative analysis, it could be also noted that combination of treatments result in greater reductions of BOP. Decrease in this parameter could be seen both in test and control groups, but the test groups showed statistically greater improvement than the controls. Only six of the selected studies reported data on Clinical Attachment Level changes from baseline to the end of the follow-up period.

In terms of CAL gain, it seems that the use of antiseptic agents in association to mechanical therapy is able to provide better results. In particular, Machtei et al. [35] found a statistically significant greater CAL gain of 0.65 ± 0.34 mm better in the test group, when 0.5 mg chlorhexidine matrix is associated to mechanical debridement.

Study	Intervention/Control	Measurement Method	Test	Control	Difference	P value
Büchter et al. [30]	Test: Plastic Courettes+Chlorhexidine 0.2% Irrigations +Doxycycline 8.5% Irrigations Control: Plastic Courettes +Chlorhexidine 0.2% irrigations Supramucosal/gingival professional implant/tooth cleaning with rubber cups and polishing paste.	Presence of bleeding within 30 s after the pocket had been probed with a periodontal probe, 4 Sites/ implant	0.27 ± 0.01	0.13 ± 0.01	0.14 ± 0.02	0.01
Schwarz et al. [33]	Test: Er:YAG laser Control: Plastic Courettes+Chlorhexidine 0.2% Irrigations +Chlorhexidine 0.2% Gel Supragingival Scaling with Ultrasonic device	Presence if bleeding was evident within 30 s after probing, or absent, if no bleeding was noticed within 30 s after probing, 6 Sites/implant	45.83 ± 38.7	25.33 ± 22.6	16 ± 30.7	p<0.01
Machtei et al. [35]	Test: Ultrasonic Debridement+matrix 0.5 mg CHX Control: Ultrasonic Debridement+matrix gelatine Carbon Courettes+Glycine Air Powder	NA	57.5 ± 7.92	45.5 ± 8.8	12.1 ± 6.7	P=0.3125
Bassetti et al. [36]	Test: Photodynamic therapy Control: Minocycline Hydrochloride Microspheres Supramucosal mechanical debridement with Ultrasonic Scaler	Presence of bleeding within 10-15 s after the pocket had been probed with a periodontal probe, 6 Sites/implant	2.52 ± 0.25	2.31 ± 0.08	0.21 ± 0.33	<0.05
Jansaker et al. [37]	Test: Chloramine perisolve+Ultrasonic mechanical debridement Control: Ultrasonic mechanical debridement Supramucosal/ gingival professional implant/tooth cleaning with rubber cups and polishing paste.	Presence of bleeding 4 Sites/implant	0.67 ± 0.58	0.64 ± 0.54	0.03 ± 1.12	P=0.001
John et al. [38]	Test: Carbon Courettes+ hlorhexidine 0.1% Submucosal irrigation+Chlorhexidine 1% gel submucosal application Control: Aminoacid Glycine Powder Submucosal application Supra gingival Scaling	Present if bleeding was evident within 30 s after probing, or absent, if no bleeding was noticed within 30 s after probing, 6 Sites/implant	16.6 ± 33.4	41.2 ± 29.5	24.6 ± 63.9	<0.05
Gomi et al. [39]	Test: Ultrasonic Scaler with plastic tips+Plastic Courettes +Systemic Azithromycin starting 3 days before 500 mg/day Control: Ultrasonic Scaler with plastic tips+Plastic Courettes	Scored positive if bleeding was visible within 30 s after probing, 6 Sites/implant	24.5 ± 3.9	6.1 ± 1.5	18.4 ± 5.4	<0.001

Table 7: Descriptive analysis of the changes in bleeding on probing.

The other studies reporting on CAL changes were unable to find statistically significant differences between test and control groups.

In general, there is a lack of consistency of data and this could be due to the following factors:

1. Although all the included studies are RCTs on non-surgical treatment of peri-implantitis, a high heterogeneity in study nature and concept can be seen. In some protocols, the application of treatment was performed one time, while other RCTs are based on repeated applications. Combination of treatments is based on the association of different mechanical and chemical agents. Since most of the trials are based on the association of different treatments, it is difficult to discriminate which can be the most effective.

2. RCTs included are different in their design, either split-mouth or parallel groups design.

3. There is a lack of standardization in the control groups. This means that nowadays no gold-standard therapy is established for non-surgical treatment of peri-implantitis. Often, the same therapies are used both as a test or a control group. Furthermore comparisons between completely different types of interventions are made.

These problems were treated in a recent systematic review in which the authors pointed out that the quality of evidence on peri-implantitis is low, even if the most recent publications show a higher level of report [44].

Even if statistically significant improvements in clinical parameters can be found with the different treatments alone or in combination, one may argue if these results are clinically significant. Within the limitations of the present systematic review, it seems that combinations of treatments result in a greater reduction in PPD when compared with treatments alone.

In order to better define which therapy can provide better clinical outcomes, researches should follow some important features. First of all therapies should be defined and clearly distinguished for test group, while control group should not receive any adjunctive treatment. This is because no gold-standard therapy is now eligible for peri-implantitis. The sample of population should be well described reporting data about sex, age and ethnicity and about risk factors such as smoke and diabetes. Number and type of implants per patient and their sites should be reported for each group involved. The same trained assessor should measure the outcome variables and the methods of recording and then register measurements over time, detailing every intervention or drop out. Follow-up measurements should continue every two months for at least 12 months, conforming to set methods.

Conclusion

Non-surgical therapy of peri-implantitis seems to have a limited efficacy. The association of mechanical debridement and adjunctive measures seems to provide slightly greater benefits. In particular the use of systemic azithromycin associated to mechanical debridement

can give better clinical outcomes; indeed in the study of Gomi et al. [39] was reported a greater reduction of 0.96 ± 0.4 mm in the test group compared with the data of the control group after 1 year of follow up.

Clinical trials on this topic are characterized by a great heterogeneity and nowadays there is no gold-standard therapy that can be used as control. Better and standard designed clinical trials and with longer follow-up are needed.

Conflict of Interest Notification

The authors declare no conflict of interest concerning the contents of the study. The study was self-founded by the authors.

References

1. Pjetursson BE, Bragger U, Lang NP, Zwahlen M (2007) Comparison of survival and complication rates of tooth-supported fixed dental prostheses (FDPs) and implant-supported FDPs and single crowns (SCs). Clin Oral Impl Res 18: 97-113.
2. 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. J Clin Periodontol 29: 197-212.
3. Lindhe J, Meyle J (2008) Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology. J Clin Periodontol 35: 282-285.
4. Esposito M, Hirsch J, Lekholm U, Thomsen P (1999) Differential diagnosis and treatment strategies for biologic complications and failing oral implants: a review of the literature. Int J Oral Maxillofac Implants 14: 473-490.
5. Quirynen M, De Soete M, van Steenberghe D (2002) Infectious risks for oral implants: a review of the literature. Clin Oral Impl Res 13: 1-19.
6. Leonhardt A, Dahlen G, Renvert S (2003) Five-year clinical, microbiological, and radiological outcome following treatment of peri-implantitis in man. J Periodontol 74: 1415-1422.
7. Zitzmann NU, Berglundh T (2008) Definition and prevalence of peri-implant diseases. J Clin Periodontol 352: 286-291.
8. Lang NP, Berglundh T (2011) Periimplant diseases: where are we now?--Consensus of the Seventh European Workshop on Periodontology. J Clin Periodontol 38: 178-181.
9. Furst MM, Salvi GE, Lang NP, Persson GR (2007) Bacterial colonization immediately after installation on oral titanium implants. Clin Oral Impl Res 18: 501-508.
10. Shibli JA, Vitussi TR, Garcia RV, Zenobio EG, Ota-Tsuzuki C, et al. (2007) Implant surface analysis and microbiologic evaluation of failed implants retrieved from smokers. J Oral Implantol 33: 232-238.
11. Mombelli A, Decaillet F (2011) The characteristics of biofilms in peri-implant disease. J Clin Periodontol 38: 203-213.
12. Tomasi C, Derks J (2012) Clinical research of peri-implant diseases--quality of reporting, case definitions and methods to study incidence, prevalence and risk factors of peri-implant diseases. J Clin Periodontol 39: 207-223.
13. Heitz-Mayfield LJ (2008) Peri-implant diseases: diagnosis and risk indicators. J Clin Periodontol 35: 292-304.
14. Serino G, Turri A, Lang NP (2013) Probing at implants with peri-implantitis and its relation to clinical peri-implant bone loss. Clin Oral Impl Res 24: 91-95.
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151: 264-269.
16. Needleman IG (2002) A guide to systematic reviews. J Clin Periodontol 29: 6-9.
17. Esposito M, Grusovin MG, Worthington HV (2012) Interventions for replacing missing teeth: treatment of peri-implantitis. Coch Database of Syst Rev 1: CD004970.
18. Fransson C, Lekholm U, Jemt T, Berglundh T (2005) Prevalence of subjects with progressive bone loss at implants. Clin Oral Impl Res 16: 440-446.
19. Higgins JPT, Green S (2010) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration.
20. Bach G, Neckel C, Mall C, Krekeler G (2000) Conventional versus laser-assisted therapy of periimplantitis: a five-year comparative study. Implant Dent 9: 247-251.
21. Javed F, Abduljabbar T, Carranza G, Gholamiazizi E, Mazgaj DK, et al. (2016) Efficacy of periimplant mechanical debridement with and withoutadjunct antimicrobial photodynamic therapy in the treatment ofperiimplant diseases among cigarette smokers and non-smokers. Photodiagnosis Photodyn Ther 16: 85-89.
22. Karimi MR, Hasani A, Khosroshahian S (2016) Efficacy of antimicrobial photodynamic therapy as an adjunctive to mechanical debridement in the treatment of peri-implant diseases: a randomized controlled clinical trial. J Lasers Med Sci 7: 139-145.
23. Lerario F, Roncati M, Gariffo A, Attorresi E, Lucchese A, et al. (2016) Non-surgical periodontal treatment of peri-implant diseases with the adjunctive use of diode laser: preliminary clinical study. Lasers Med Sci 31: 1-6.
24. 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.
25. 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. J Clin Periodontol 33: 362-369.
26. Renvert S, Lessem J, Dahlén G, Renvert H, Lindahl C (2008) Mechanical and Repeated Antimicrobial Therapy Using a Local Drug Delivery System in the Treatment of Peri-Implantitis: A Randomized Clinical Trial. J Periodontol 79: 836-844.
27. Renvert S, Samuelsson E, Lindahl C, Persson GR (2009) Mechanical non-surgical treatment of peri-implantitis: a double-blind randomized longitudinal clinical study. I: clinical results. J Clin Periodontol 36: 604-609.
28. Romeo U, Nardi GM, Libotte F, Sabatini S, Palaia G, et al. (2016) The Antimicrobial Photodynamic Therapy in the Treatment of Peri-Implantitis. Int J Dent.
29. Sahm N, Becker J, Santel T, Schwarz F (2011) Non-surgical treatment of peri-implantitis using an air-abrasive device or mechanical debridement and local application of chlorhexidine: a prospective, randomized, controlled clinical study. J Clin Periodontol 38: 872-878.
30. 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. Brit J Oral Maxillofac Surg 42: 439-444.
31. Schwarz F, Sculean A, Rothamel D, Schwenzer K, Georg T, et al. (2005) Clinical evaluation of an Er:YAG laser for nonsurgical treatment of periimplantitis: A pilot study. Clin Oral Impl Res 16: 44-52.
32. Karring ES, Stavropoulos A, Ellegaard B, Karring T (2005) Treatment of peri-implantitis by the Vector system. Clin Oral Impl Res 16: 288-293.
33. Schwarz F, Bieling K, Bonsmann M, Latz T, Becker J (2006) Nonsurgical treatment of moderate and advanced periimplantitis lesions: a controlled clinical study. Clin Oral Investig 10: 279-288.
34. Renvert S, Lindahl C, Roos Jansåker AM, Persson GR (2011) Treatment of peri-implantitis using an Er:YAG laser or an air-abrasive device: a randomized clinical trial. J Clin Periodontol 38: 65-73.
35. Machtei EE, Frankenthal S, Levi G, Elimelech R, Shoshani E, et al. (2012) Treatment of peri-implantitis using multiple applications of chlorhexidine chips: A double-blind, randomized multi-centre clinical trial. J Clin Periodontol 39: 1198-1205.

36. Bassetti M, Schär D, Wicki B, Eick S, Ramseier CA, et al. (2014) Anti-infective therapy of peri-implantitis with adjunctive local drug delivery or photodynamic therapy: 12-month outcomes of a randomized controlled clinical trial. Clin Oral Impl Res 25: 279-287.
37. Roos-Jansaker AM, Almhojd US, Jansson H (2017) Treatment of peri-implantitis: clinical outcome of chloramine as an adjunctive to non-surgical therapy, a randomized clinical trial. Clin Oral Implants Res 28: 43-48.
38. John G, Sahm N, Becker J, Schwarz F (2015) Nonsurgical treatment of peri-implantitis using an air-abrasive device or mechanical debridement and local application of chlorhexidine. Twelve-month follow-up of a prospective, randomized, controlled clinical study. Clin Oral Investig 19: 1807-1814.
39. Gomi K, Matsushima Y, Ujiie Y, Shirakawa S, Nagano T, et al. (2015) Full-mouth scaling and root planing combined with azithromycin to treat peri-implantitis. Aus Dent J 60: 503-510.
40. Arısan V, Karabuda ZC, Arıcı SV, Topçuoğlu N, Külekçi G (2015) A randomized clinical trial of an adjunct diode laser application for the nonsurgical treatment of peri-implantitis. Photomed Laser Surg 33: 547-554.
41. Abduljabbar T, Javed F, Kellesarian SV, Vohra F, Romanos GE (2017) Effect of Nd:YAG laser-assisted non-surgical mechanical debridement on clinical and radiographic peri-implant inflammatory parameters in patients with peri-implant disease. J Photochem Photobiol B 168: 16-19.
42. Faggion CM, Listl S, Frühauf N, Chang HJ, Tu YK (2014) A systematic review and Bayesian network meta-analysis of randomized clinical trials on non-surgical treatments for peri-implantitis. J Clin Periodontol 41: 1015-1025.
43. Goodson JM (1989) Pharmacokinetic principles controlling efficacy of oral therapy. J Dent Res 68: 1625-1632.
44. Graziani F, Figuero E, Herrera D (2012) Systematic review of quality of reporting, outcome measurements and methods to study efficacy of preventive and therapeutic approaches to peri-implant diseases. J Clin Periodontol 39: 224-244.