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Mestrado Integrado em Medicina Dentária

Peri-implantitis and its treatment perspective: Overview of Systematic Reviews

Dissertação apresentada à Universidade Católica Portuguesa
para obtenção do grau de Mestre em Medicina Dentária

Bruno Gomes dos Santos Martins

Viseu, 2021

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Viseu, 2021

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(In Portuguese)

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Resumo

Introdução: O Objetivo do presente trabalho é, avaliar de forma sistemática, a melhor literatura possível sobre o tratamento da peri-implantite, procurando encontrar a melhor opção de tratamento disponível.

Materiais e Métodos: Bases de dados eletrónicas (MEDLINE (PubMed®), Web of Science®, Cochrane Library and Cochrane Evidence) foram pesquisadas para se encontrar revisões sistemáticas sobre o tratamento da peri-implantite. Para se recolher a melhor evidencia científica possivel, a Pesquisa foi limitada a revisões sistemáticas que só incluissem *Randomized Controlled Trials/ Controlled Clinical Trials*. Artigos com data de Janeiro de 2014 a Janeiro de 2021 foram incluidos. Outros critérios para inclusão eram língua inglesa e publicados em *peer reviews journals.* Apenas dados sobre peri-implantite e de artigos *Randomized Control Trials* foram avaliados.

Resultados: Nove revisões sistemáticas foram selecionadas para total revisão. Seis das nove incluiram Randomized Control Trials sobre tecnicas nao cirúrgicas, e oito das nove revisões sistemáticas incluiram Randomized Control Trials sobre abordagens cirúrgicas. No total 98 artigos primários foram incluidos dentro das 9 revisões sistemáticas, 59 dos quais únicos, não repetidos

Conclusão: Intervenções não cirúrgicas parecem oferecer algum grau de melhoria clínica, principalmente a nível de sangramento à sondagem; no entanto, estas parecem nao ser suficientes para tratar totalmente a peri-implantite. Técnicas cirúrgicas parecem ser mais eficazes em melhorar, de forma geral, os parametros clínicos, principalmente a profundidade de sondagem, sangramento à sondagem e, a algum nível, os níveis ósseos marginais. Nenhuma técnica cirúrgica específica nem materiais demosntram clara superioridade sobre outros. A previsibilidade das intervenções cirúrgicas também ainda levantam preocupações.

Palavras-Chave: peri-implantite: tratamento; revisão sistemática, resultados clínicos

Abstract

Objectives: Systematically review the best available literature on the treatment of peri-implantitis, in order to try and find the best available treatment option.

Materials and Methods: Eletronic databases (MEDLINE (PubMed®), Web of Science®, Cochrane Library and Cochrane Evidence) were searched for systematic reviews on peri-implantitis treatment. To gather the best available scientific evidence, search was limited to systematic reviews that included Randomized Controlled Trials/Controlled Clinical Trials. Articles from January 2014 till January 2021 were included, in English and in peer reviewed journals. Only peri-implantitis and Randomized Controlled Trial data was assessed.

Results: Nine systematic reviews were gathered for full review. Six out of the nine had randomized controlled trials investigating non-surgical techniques and eight out of the nine had approached surgical (augmentative/regenerative and corrective/resective techniques). In total 98 primary studies were included among the 9 systematic reviews, 59 of them being not repeated between reviews.

Conclusion: Non-surgical interventions appear to offer some degree of clinical improvement, especially on bleeding on probing levels, but they are not likely enough to fully treat peri-implantitis. Surgical techniques seem to be more effective on improving overall clinical parameters, especially probing depth, bleeding on probing and to some extent, marginal bone level, but no specific surgical technique or material (graft or membrane) seem to have clear advantage over other. Surgical interventions predictability is still also a concern.

Keywords: Peri-Implantitis; Treatment; Systematic Review; Outcomes

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Table Sumary

List of Abbreviations

PI: Peri-implantitis
BOP: Bleeding on probing
MD: Mechanical debridement
AB: Antibiotics
PDT: Photodynamic therapy
PD: Probing depth
S: Surgical
NS: Non-surgical
SR: Systematic Reviews
PICO: Population, Intervention, Comparison, Outcome
RCT: Randomized controlled trials
CCT: Controlled clinical trials
PPD: pocket probing depth
CAL: clinical attachment level
SBI: Sulcus bleeding index
MBL: Marginal bone loss
SOP: suppuration on probing
IL: implant loss
IS: implant survival
PROM: patient reported outcome measurement
PlqI: plaque index
CHX: Chlorhexidine
MR: Marginal Recession
aPDT: Anti-microbial photodynamic therapy
RBL: Radiographic bone level
GBR: guided bone regeneration
CPS: cotton pellets
DD: debridement/decontamination
CPC: CetylPirinidium Chloride
DIB: implant shoulder and first bone contact
EMD: Enamel matrix derivative
BMP: Morphogenic protein (BMP)
PDGF: Platelet derived growth factors
RoB: Risk of bias
GRADE: Grading of Recommendations, Assessment, Development and Evaluations
CONSORT: Consolidated Standards of Reporting Trials
AAP: American Academy of Periodontology
DL: Diode Laser

INTRODUCTION

1. Introduction

Dental implants are one of the greatest revolutionary tools in the rehabilitation of patient's function and esthetics, presenting high long-term success rates for partially and fully edentulous individuals.(1)

Earliest dental implant evidence was found in the Mayan Population, near 600AD. At that time, shells pieces were used as implants, to replace mandibular teeth.(1)

In Europe, from the 1500's to the 1800's teeth were gathered from corpses for allotransplantation. Dr. John Hunter, in the 1700s, did earlier teeth implantation experiments, where he observed tooth fixation to the comb of a rooster. Blood vessels from the rooster grew directly to the tooth's pulp.(1)

J. Maggiolo, around 1809, implanted a gold tube into an extraction socket. Healing was allowed and a crown was put over it. Extensive inflammation was perceived after the procedure, but it was early experimentation on dental implants.(1)

In early 1930, after observing the technique for hip implants, Drs. and brothers Alvin and Moses Strock made some experiments with orthopedic screws made out of chromium-cobalt alloy (Vitalium); the screws were implanted in humans and dogs, in order to support missing tooth replacement. The Strock brothers were given credit for the discovery of a biocompatible metal that could be used in the oral cavity of humans and also for the first endosteal implant with success.(1)

After some years of innovation, in 1978, Dr. P. Branemark presented the world with the closest implant material to the now-a-days used implants, as they were a 2-part piece, made out of Titanium, and had root like tridimensional shape. These were the first implants to have a considerable follow up and clinical success, and also where the first ones to present the idea of osseointegration.(1)

Modern implantology began in the middle of 1980, through Dr. Schroeder and Dr. Straumann, in Switzerland. Dental surface modifications started to be studied, in order to improve healing time and osseointegration.(1)

1.2 Dental implants usage rate and considerations concerning complications

In 1999, in the United States, 0.7% of all adults had at least one implant in the oral cavity, while the prevalence rapidly grew to 5.7% in 2015,(2) and, according to the American Academy of Implant Dentistry, about 3 million people in the US are estimated on having dental implants and it is increasing by 500,000 per year, solely in the US.(3)

Despite the high predictability and survival level at 10 and 20 years (averages of 97 and 91% respectively)(4) there is a risk for complications,(5-8) for example, biological ones. These introduced the terms peri-implant mucositis and peri-implantitis (PI).(9) They are an inflammatory disease affecting directly the osseointegrated implant and the local tissue(10) and were considered analogous to gingivitis and periodontitis, common diseases with a plaque-associated pathological condition, through bacterial challenge, that affect the tissues of natural teeth.(9, 11) Sequentially, peri-implantitis may result in implants loss(12) and has been considered as one of the most common reasons for implant failure.(13)

1.3 Peri-implantitis: Prevalence, diagnosis and signs and symptoms

Prevalence of PI is around 20% up to 14-years after implant placement(14) and there is a general concern related to its incidence, which may increase proportionally with more placed implants, depending on the ability and expertise of the doctor, highlighting another important question: the efficiency of the available protocols for PI treatment.(15)

Even though both diseases, mucositis and peri-implantitis, are accepted and known worldwide, there is still a great debate when it come to the diagnostic criteria, which should be made clinically and confirmed through x-rays, simultaneously.(9) The importance of this aspect is related to what treatment approach should be followed. Typical signs and symptoms of peri-implantitis may include: (i) saucer-shaped, with vertical crestal bone destruction along and with

a radiologic image of osseointegration on the apical part, (ii) formation of peri-implant pocket, (iii) bleeding on probing (BOP) that can be present or not, by gentle probing (force under 0.25N), (iv) mucosal swelling and hyperplasia, and (v) an acute infection pain may be associated, but generally it is asymptomatic. The main difference between peri-implant mucositis and peri-implantitis appears to be the presence of bone loss in the latter.(9)

1.4 Peri-implantitis' treatment basic steps and objectives

The basic steps in peri-implant infection therapy includes infection control, nonsurgical debridement, corrective/resective or regenerative/augmentative surgical procedures when/where necessary, and supportive therapy.(16, 17) Thus, after correct diagnosis, the primary objective in the treatment of PI is to alter the microbiota present at the implants' surface, in order to allow it to be suited/tolerated by the host's immune system.(17)

Regarding the previous aspect, it is suggested as major possibility that the total elimination of pathogenic bacteria is the more effective approach.(17)

1.5 Peri-implantitis treatment challenges and intervention options

Nonetheless, an efficient mechanical debridement (MD) is difficult to achieve, although of great importance in the management of dental implant infections.(17) According to Smeets *et al*.,(18) several adjunctive non-surgical therapies have been proposed to aid the problem resolution of the infection. Drug therapy with antiseptic rinses that contain, for example, chlorhexidine or systemic/local antibiotics (ABs) (e.g., tetracycline, doxycycline, amoxicillin, metronidazole, minoxicycline hydrochloride, ciprofloxacin) have been explored in many *in vitro* and *in vivo* studies.(19-27) Moreover, laser and photodynamic (PDT) methods appear to be promising and can be used, but more studies are still required to evaluate the actual value of these therapies in the treatment of PI.(18)

It emerges, then, the surgical procedures which have been proposed to enhance the treatment of PI, the potential of healing and/or tissue regeneration.(17) Therefore, when compared to the efficacy of non-surgical versus surgical treatments, a systematic review with meta-analysis,(28) developed by Ramanauskaite *et al.* (2016), reported that non-surgical methods did not reduce the probing depth (PD) but were effective at reducing soft-tissue inflammation, for example BOP values. As for surgical procedures, most of the reviewed articles were concerning regenerative treatments and the findings suggested that surgical treatment of peri-implantitis is more effective at reducing both PD and BOP.

1.6 Peri-implantitis current literature evidence and study objective

Albeit scientific evidence on the therapies' efficacy to treat peri-implantitis is limited, clinical evidence suggests that it is predictable when diagnosis and intervention are made as soon as clinically possible.(17)

In this scenario, pursuing clarification for the clinicians in what can be the best option/approach in the treatment of peri-implantitis cases, the purpose of this overview of systematic reviews was to assess the best available literature that studied peri-implantitis. The ultimate goal is to try and find a consensus on the best available treatment option for peri-implantitis when it comes to surgical (s), non-surgical (ns), and adjunctive methods, and help the clinician to better and more efficiently handle peri-implantitis cases.

MATERIALS AND METHODS

2. Materials and Methods

2.1. Protocol Registration

The protocol for the present review was registered in the international prospective register of Systematic Reviews (SR), PROSPERO (CRD42021236759). No deviation from the original specified protocol was present at registration. The basic methodology for the present study followed the guidelines from the *Cochrane Handbook for Systematic Reviews of Interventions* and PRISMA guidelines were also taken into consideration.

2.2. Focus Question

The clinical question was elaborated following the search strategy, and organized according to the PICO (Population, Intervention, Comparison, Outcome) strategy.

The focus question of this review is: “Could patients, who underwent implant treatment and developed peri-implantitis (P), be approached with success only by non-surgical treatment, (I) or it achieves better results with surgical and adjunctive therapies (C), elevating the survival/success rates in short- and long-term of dental implants (O)?”

2.3. Search Strategy

In order to allow an adequate bibliographic base for the study and answer the research question, reaching the proposed objectives, strict research criteria were established with well-defined inclusion and exclusion criteria. For this purpose, a bibliographic search was conducted using MEDLINE (PubMed®), Web of Science®, Cochrane Library and Cochrane Evidence, to collect articles published between January 2014 and January 2021 (7 years) with language restriction (English).

The articles obtained in the search on the aforementioned databases were imported to a citation management software (EndNote X9/Thomson Reuters, Philadelphia, USA) and then screened and analyzed.

Systematic review search following the PICO strategy:

- [P] Peri-implantitis, OR Periimplantitis, OR Peri-implant disease, OR Peri-implant Disease, OR Defect, OR Implant, OR Dental implant; AND
- [I] Implantoplasty, OR Peri-implantitis therapy, OR Treatment, OR Graft, OR Debridement, OR Supportive, OR Chlorhexidine, OR Laser, OR Resective Surgery, OR Membrane, OR Surgical Regenerative Therapy, OR Bone Substitute, OR Regeneration, OR Collagen; AND
- [C] Surgical OR Surgery, AND Non-surgical; AND
- [O] Survival Rate, Success rate, Implant failure rate, Marginal Bone Loss, Bleeding on Probing (BOP), Probing Pocket Depth (PPD), Clinical Attachment Level (CAL).

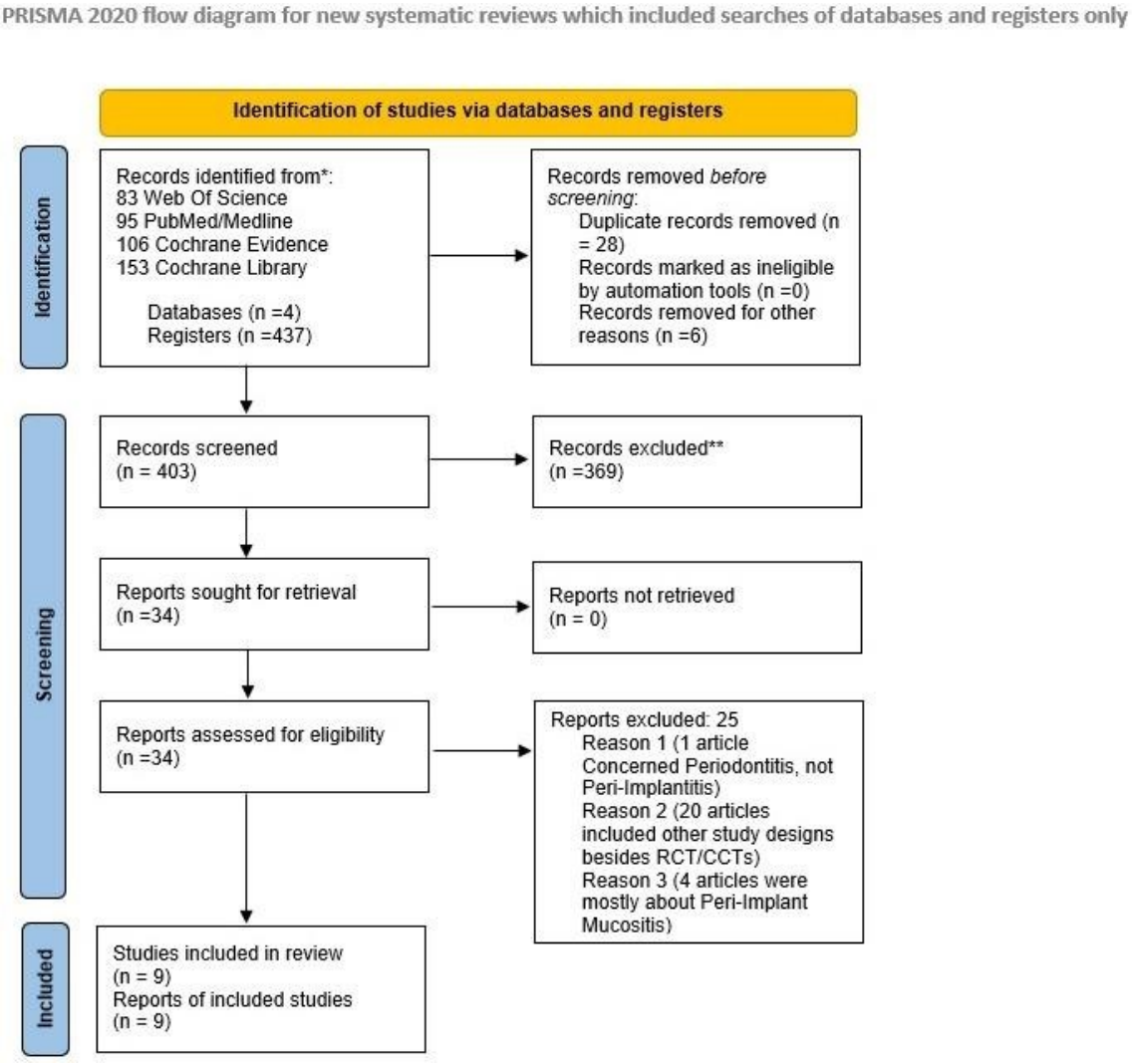

Image 1: *Search Strategy*[29]

2.4. Inclusion Criteria

This systematic review was conducted based on other SRs of human studies, that utilized randomized controlled trials/controlled clinical trials (RCT/CCT). Beyond that, it was used the mandatory simultaneous criteria to find studies published only in English; publication date from January 2014 to January 2021; articles that have the search terms in the title or abstract; journals with peer-review system; only peri-implantitis data from RCTs used in the included studies were assessed.

2.5. Exclusion Criteria

Systematic reviews that included other study types beyond RCT/CCT (only data from RCT were utilized), studies which approached only mucositis, or only abstracts, or e-poster without full-text.

2.6. Screening Process

Search and screening were performed by two independent review authors (B.G.S.M. and G.V.O.F.). Analysis of titles and abstracts was the first step of the process. After that, full papers of the included works were thoughtfully read and analyzed, in agreement with the inclusion and exclusion criteria, for posterior data extraction. Any disagreement between authors was solved by a well-thought-out discussion, involving a third author (R.M.C.).

2.7. Data Extraction

Two independent authors (B.G.S.M. and G.V.O.F.) from the present work extracted, whenever available, the following data included in the SRs: authors; population of patients and implants; age of patients; case definition of PI; PI intervention (non-surgical (ns), surgical (s), with the aid or not of adjunctive measures) of test and control group; follow up period; study parameters concerning primary and secondary outcomes, which included: pocket probing depth or probing depth (PPD or PD), clinical attachment level (CAL), bleeding on probing/Sulcus bleeding index (BOP/SBI), marginal bone loss (MBL), radiographic bone level (RBL) change, plaque index (PIqI), suppuration/suppuration on probing (SOP), bacterial count, gingival recession, implant loss (IL), implant survival (IS), and patient reported outcome measurement (PROM).

2.8. Assessment of quality of the Systematic Reviews

The AMSTAR 2 tool was used to evaluate the methodology of each SR included in this study. Two authors (B.G.S.M. and G.V.O.F.) reviewed them independently, through the 16 item criteria. Four options were available to answer each of the criterion: “yes”, “partial yes”, “no” and “not applicable” (0 on table 2).

As AMSTAR2 rating is not meant to generate an overall score and evaluate studies by its’ weakest critical domain, only a final verdict was given to each SR.(30)

RESULTS

3. Results

In total, 9 SRs were included in this study and all RCT studies within those SRs were 98 (Table 1). They accounted for non-surgical, surgical, and adjunctive measures to treat peri-implantitis. As some of the primary studies repeated themselves across SRs, the total number of non-repeated articles was 59.

Non-surgical treatments and adjunctive measures were mainly focused in cleaning the surface of the implant and detoxification of the peri-implant tissues. It involved manual debridement with chlorhexidine/saline/hydrogen peroxide, ultrasound debridement, air abrasive systems with glycine powder, systemic or local ABs, antiseptics, and the usage of laser systems. The non-surgical interventions work best at removing local irritants in peri-implantitis affected tissues and does not help with the bone loss.

Surgical treatments consisted of flap elevation, treatment and detoxification of the implant surface, use (or not) of ABs agent/membranes and grafting materials, depending on if the surgical technique was regenerative or resective. The surgical techniques can, and were combined, with non-surgical/adjunctive techniques in several of the included primary studies.(31-34)

Table 1: *Primary Studies*

SR I / PS	Review 1: Aljohani et al. 2019 (5 PS inc.)	Review 2: Mahato et al. 2016 (18 PS inc.)	Review 3: Chala et al. 2020 (6 PS inc.)	Review 4: Khan et al. 2020 (6 PS inc.)	Review 5: Schwarz et al. 2015 (10 PS inc.)	Review 6: Kotsakis et al. 2014	Review 7: Gao et al. 2020 (2 PS inc.)	Review 8: Sanz-Sanchez et al. 2017 (11 PS inc.)	Review 9: Tomasi et al. 2019 (1 PS inc.)
PS	Aghazadeh et al. 2012	Schär et al. 2013	Renvert et al. 2011	Arisan et al. 2015	Karring et al. 2005	Schär et al. 2013	Galofré et al. 2018	Jung et al. 2009	Isehed et al. 2016
PS	Wohlfahrt et al. 2012	Schwarz et al. 2006	Abduljabbar et al. 2017	John et al. 2015	Schwarz et al. 2005	Schwarz et al. 2012	Tada et al. 2018	Van Assche et al. 2013	Jepsen et al. 2016
PS	Jepsen et al. 2016	Renvert et al. 2006, 2008	Romeo et al. 2016	Machtei et al. 2012	Schwarz et al. 2006	Renvert et al. 2011		Schwarz et al. 2012, 2014, 2016	Wohlfahrt et al. 2012
PS	Schwarz et al. 2010	Persson et al. 2010	Schwarz et al. 2017	Renvert et al. 2011	Renvert et al. 2009	Deppe et al. 2007		Ramel et al. 2012	Andersen et al. 2017
PS:	Schwarz et al. 2013	Hallstrom et al. 2012	Schwarz et al. 2017a	Roos-Jansaker et al. 2017	Renvert et al. 2011	Schwarz et al. 2006		Jung et al. 2015	
PS:		Sahm et al. 2011	Papadopoulos et al. 2015	Sahm et al. 2011	John et al. 2015	Schwarz et al. 2013		Jung et al. 2017	
PS:		Renvert et al. and Persson et al. 2011	Albaker et al. 2018	Hentenaar et al. 2017	Sahm et al. 2011			Amorfini et al. 2014	
PS:		Karring et al. 2005		Isehed et al. 2018	Machtei et al. 2012			Cordaro et al. 2011	
PS:		Machtei et al. 2012		Papadopoulos et al. 2015	Bücher et al. 2004			Meijndert et al. 2008, 2016	
PS:		Aghazadeh et al. 2012		de Waal et al. 2013	Renvert et al. 2006				
PS:		Schwarz et al. 2008,2009		de Waal et al. 2015	Renvert et al. 2008				
PS:		Schwarz et al. 2006a			Schär et al. 2013				
PS:		Wohlfahrt et al. 2012			Bassetti et al. 2013				
PS:		Romeo et al. 2007			Deppe et al. 2007				
PS:		Schwarz et al. 2011,2012			de Waal et al. 2013				
PS:		De Waal et al. 2013			de Waal et al. 2015				
PS:					Papadopoulos et al 2005				
PS:					Romeo et al. 2005, 2007				
PS:					Schwarz et al. 2006, 2009, 2008				
PS:					Roos-Jansaker et al. 2014, 2007, 2011				
PS:					Schwarz et al. 2012				
PS:					Schwarz et al. 2013, 2012, 2011				
PS:					Aghazadeh et al. 2012				
PS:					Wohlfahrt et al. 2012, 2014				

Discription: SR I: SR Included; **PS:** Primary Study

3.1. Non-Surgical (NS) Techniques

Systematic reviews that included this type of treatment were Mahato et al. (2016),(35) Chala et al. (2020),(36) Khan et al. (2020)(33), Schwarz et al. (2015)(31), Kotsakis et al. (2014)(37), and Gao et al. (2020)(38). Didactically, subtopics were done to ease the comprehension and there was no repetition of RCT study if it was included in more than one systematic study, which can be completely observed in **Table 1**.

3.1.1. Non-Surgical Systematic Review 1: Mahato et al.(35)

This SR reported a total of 730 treated patients, with follow ups ranging from 6 months to 4 years. The peri-implantitis diagnosis consisted of the following clinical finds: PD >4mm, bone loss (x-ray confirmation) with at least 1.5mm, exposed implant threads, no mobility, and bacteria presence.

Regarding mechanical non-surgical treatments and detailing each RCT, Karring et al. (2005) and Persson et al. (2010) tested the ultrasound system *versus* carbon fiber curettes. After a 6-month follow-up, no significant changes were observed between the 2 methods. They were both also insufficient to treat the peri-implantitis.

Sham et al. (2011) compared mechanical debridement using an antiseptic agent (MDA) along with powdered amino acid Glycine (AAD), and after 6-month follow-up, limited improvement of the CAL was achieved and BOP was reduced, when compared AAD group and MDA group, but with no significant result.

Schwarz et al. (2006), Renvert et al. (2011), and Persson et al. (2011) compared Er:YAG laser with an air abrasive device, and after a 6-month follow-up, authors found limited improvements in clinical parameters, but the bacterial load was not reduced enough to control peri-implantitis.

About mechanical treatments associated with ABs, two studies were published by Renvert et al. (2006 and 2008). They evaluated the treatment in 32 patients and compared microspheres with minocycline used locally against chlorhexidine gel debridement. One-year after the treatment began, both studies showed significant improvement in plaque index, PD, and BOP. Regarding

bacterial load and microbiota changes, there was no difference between the start of the treatment and the end.

Schär et al. (2013) tried to compare the benefits of photodynamic therapy (PDT) over minocycline microspheres. In both groups mucosal inflammation was significantly reduced after 6 months.

The last RCT included was developed by Hallstrom et al. (2012), who used systemic azithromycin for 4 days and, after 6 months, only oral hygiene improved, and the study could not provide evidence.

3.1.2. Non-Surgical Systematic Review 2: Chala et al. (36)

Three RCT were found comparing laser treatments versus non-surgical options: Renvert et al., Abduljabbar et al., Romeo et al. In the 3-month follow-up period, Renvert et al. did not report any measurements at the three-month mark (no data); Abduljabbar et al. provided plaque index (PIqI), BOP, and Probing Depth (PD), all with $p<0.05$ between the groups. Romeo et al. reported the same outcomes of clinical parameters improvement as Abduljabbar et al., but no p-values were listed.

In the 6 months follow up period, Renvert et al. showed a non-significant result for BOP and PD, respectively, $p=0.22$ and $p=0.55$, for the study group compared to the control one. Abduljabbar et al. also revealed a non-significative p-values (>0.05) for PIqI, BOP, and PD between the 2 groups. With this evidence, regarding non-surgical treatment, it appears that adjunctive laser therapy can improve the results at the 3-month mark, but no important improvement was noted after six months, compared to regular treatment.

3.1.3. Non-Surgical Systematic Review 3: Khan et al.(33)

The authors investigated the non-surgical techniques of the following primary studies Arisan et al., who analyzed the mechanical debridement compared to adjunctive diode laser application; John et al. and Sahm et al. who evaluated the mechanical debridement with topical CHX *versus* air-abrasive device with amino acid glycine powder; Machtei et al. who studied the mechanical debridement with matrix chips *versus* mechanical debridement with CHX chips; Renvert et al. with results of Er:YAG laser *versus* air-abrasive device containing

hydrophobic powder; Roos-Jansaker et al. who studied the mechanical debridement versus adjunctive local application of chloramine gel.

After a follow up at the 3-month mark, Roos-Jansaker et al. found no significant difference between regular manual debridement (ultrasonic and hand scalers) and the adjunctive usage of a chloramine gel, for all clinical parameters studied. Although no statistically difference was found between groups, both of them presented significantly improvements in the evaluated clinical outcomes (PIqI, PD, CAL, and BOP).

Arisan et al. reached similar results, founding no statistically significant difference between conventional debridement and the adjunctive use of diode laser among the investigated parameters (PD, PIqI, and BOP). At the six-month follow-up, nonetheless, both treatment modalities showed improvement across the same parameters, when compared to baseline data. The only parameter where a significant difference was found, between groups, concerned the MBL. In the laser group, participants showed a greater MBL after six months compared to the control group, despite there was no differences on the baseline values for both groups.

Machtei et al.(2012) attempted to evaluate the effectiveness of a proposed treatment protocol for peri-implantitis. Participants were subjected to intensive, constant, applications of chips containing chlorhexidine, to the affected sites, as adjunctive aid to conventional debridement. They received either hydrolyzed gelatin matrix chips (MatrixC) or a biodegradable matrix containing CHX chips (PerioC) and clinical measurements took place at weeks 2, 4, 6, 8, 12, and 18 post intervention, with the participants coming back for a final evaluation after 6 months. Reports showed that the PerioC group participants had a greater improvement in PPD ($p=0.07$) and CAL gain *versus* the MatrixC group. No differences were detected between groups when comparing BOP, but both groups experienced significant boosts across all clinical parameters, over the 6-month follow-up. The authors concluded the frequent placing of PerioC and MatrixC, along with mechanical debridement, resulted in substantial improvement in sites of peri-implantitis.

John et al. investigated air abrasive treatment *versus* manual mechanical debridement, with the aid of local application of chlorhexidine. The authors found

that the devices using air abrasion managed to significantly decrease the mean BOP scores, when comparing to the conventional debridement technique. This result, however, was found to be an anomaly, as no differences were reported across PIqI, PD, Marginal Recession (MR), or CAL gain between groups. At the end of this study (after 12 months), the authors concluded that both treatment options were feasible, as both of them resulted in comparable and significant CAL gain. Air-abrasive devices also resulted in a greater reduction of BOP.

Sahm et al. did the same investigation as John et al., reaching akin conclusions with their study. Clinical measurements were taken at the 3- and 6-month mark, at follow up appointments. The group treated with the air-abrasive device had significantly lower BOP values when compared to the conventional debridement group. Other parameters, such as PI, MR, PD, and CAL gain did not reveal any difference between groups.

Renvert et al. compared the effectiveness of an air-abrasive machine *versus* an Er:YAG laser. Data found revealed that both treatment options allowed for statistically significant improvement in clinical parameters, including BOP, suppuration on probing (SOP), PIqI, PD, and MBL, but with no difference between the groups' values.

3.1.4. Non-Surgical Systematic Review 4: Schwarz et al.(31)

Regarding alternative measures for biofilm detoxification, it was included six RCTs. Renvert et al. (2009) used the same type of treatment in the test group as Karring et al. (2005), employing an ultrasound device along with a hydroxyapatite polish. Schwarz et al. and Renvert et al. (2011) described the laser erbium-doped yttrium aluminum garnet (Er:YAG), used as a monotherapy. The studies from Renvert et al. (2011) and Sahm et al. (2011) and John et al. (2015) focused on air abrasive therapy, using glycine powder.

One RCT by Machtei et al. (2012) was included concerning adjunctive antiseptic therapy *versus* ultrasonic debridement. After CHX matrix applications at 2, 4, 6, 8, 12, and 18 weeks, the 6-month post intervention follow-up revealed greater PD reduction with CHX chips than with placebo chips, but the significance was not reported.

As for adjunctive ABs therapy with mechanical debridement, three RCTs were accounted for Renvert et al. (2006) and Renvert et al. (2008) which used, respectively, minocycline microspheres applied one time, or at 30 and 90 days, and compared the results with the usage of CHX gel at 1.0%. 12-month post intervention, both RCTs reported significantly higher reductions in BOP in repeated applications and PD in single application, when compared to the control therapy. Bücher et al.(2004) found the same results as the two previous RCTs using doxycycline hyclate as adjunctive measure to mechanical debridement.

Schär et al.(2013) and Basetti et al.(2013) compared the use of local ABs treatment as adjunctive measure, using minocycline microspheres *versus* anti-microbial photodynamic therapy (aPDT). At the 12-month follow-up, test and control groups revealed significant improvements of the evaluated parameters, but no clinical nor immunological improvements were detected.

This SR detected that, in the nonsurgical treatment of peri-implantitis, there was a slight tendency favoring either local antibiotic therapy or alternative methods for plaque removal, such as Er:YAG laser or glycine powder polishing. Nonsurgical treatment of peri-implantitis also commonly failed to make any significant change when it comes to microbiological improvements, due to the high frequency of residual BOP scores at implant sites.

3.1.5. Non-Surgical Systematic Review 5: Kotsakis et al.(37)

This SR included four primary studies. Renvert et al. (2011) used an air-abrasive device as control as treatment of peri-implantitis in 100 sites. At the 6-month mark, PD did not show any significant improvements intragroup or intergroup. On the other hand, BOP was significantly reduced in both groups.

Two other studies from Schwarz et al. (2005 and 2006) used an identical treatment therapy, with Er:YAG laser to treat peri-implantitis. The control groups used mechanical debridement with plastic curettes and 0.2% chlorhexidine. The obtained results suggested that a significant reduction of PD and attachment loss can be anticipated at 6 months after intervention, but at the 12-month mark, the improvements are expected to not be maintained. Mean reduction of PD and attachment loss was lower than 1mm in both studies, and no significant difference

was found between test and control groups. Whereas reduction of BOP was significant compared to baseline values, and significantly higher in the groups where Er:YAG laser was used.

3.1.6. Non-Surgical Systematic Review 6: Gao et al.(38)

This SR evaluated the additional effect of *Lactobacillus* probiotics in the treatment of peri-implant diseases. Only two studies of this SR concerned the possible effects of probiotic *Lactobacillus* in the treatment of peri-implantitis. The remaining articles were about the effect of this probiotic in peri-implant mucositis, and, therefore, were not included in the present review.

Both studies took place in 2018, one in Spain (Galofré et al.) and the other in Japan (Tada et al.). Galofré et al. found that BOP and PD, at implant level, showed significant improvements after treatment in the probiotic group (with the nonsurgical intervention being a subgingival debridement with ultrasonic device, using carbon tips and carbon curettes).

The study from Tada et al. revealed that an important decrease of PPD was achieved after the probiotic was initiated, but the difference was not significant between groups; the same was observed when it came to BOP values. The nonsurgical intervention was comprised by oral hygiene instructions, supragengival scaling and Azithromycin (500mg/once a day) for three days. The test group received the probiotic, and the control group received a placebo.

3.2. Surgical Techniques

Systematic reviews including this type of treatment: Aljohani et al. (2019),(32) Mahato et al. (2016),(35) Chala et al. (2020),(36) Khan et al. (2020),(33) Schwarz et al. (2015),(31) Kotsakis et al. (2014),(37) Sanz-Sanchez et al. (2017),(34) and Tomasi et al. (2019).(39) Didactically, subtopics were done to ease the comprehension and there was no repetition of RCT study if it was included in more than one systematic study, which can be completely observed in **Table 1**.

3.2.1. Surgical Systematic Review 1: Aljohani et al.(32)

All of the primary studies included involved the effectiveness of surgical regenerative interventions in the treatment of peri-implantitis. Five studies were selected by Aljohani et al. They accounted for 200 patients (127 women and 73 men) and 226 implants. Mean age of 56 years of age, in a 26- to 76-year-old interval. Three out of the 5 studies noted the smoking status and history of periodontitis. Those 3 reported values ranging from 40.9 to 69.6% of patients who smoked, while 50 to 95.2% had history of periodontal treatment or tooth loss due to periodontal disease.

A study (Aghazadeh et al. 2012) differentiated the use of autogenous bone grafts *versus* bovine xenograft with the use of resorbable bovine collagen membrane in both groups. Two studies (Jepsen et al. 2016, Aghazadeh et al. 2012) used porous titanium granules without a membrane. Two other studies used natural bone mineral with collagen membrane (Schwarz et al. 2010, 2013).

The Detoxification methods used were 3% hydrogen peroxide and saline (Aghazadeh et al. 2012, Jepsen et al. 2016), 24% EDTA gel and saline (Wohlfahrt et al. 2012), implantoplasty and Er: YAG laser (Schwarz et al. 2013), saline solution only (Schwarz et al. 2010).

The study of the Wohlfahrt et al. (2012) used the submerged implant treatment, while the other 4 used a non-submerged technique. In all studies, the patients received both ABs (azithromycin, amoxicillin, or metronidazole) and chlorhexidine mouthwash post operation. Only Schwarz et al. (2010) prescribed chlorhexidine and no AB.

Only the study by Wohlfahrt et al. 2012 measured and noted the peri-implant keratinized mucosa. This was the only study to establish a weak positive correlation ($r=0.371$) between existent keratinized mucosa and increases in peri-implant bone level.

It was reported that all interventions reduced PPD significantly in all groups when compared to baseline data, however, the reduction was insignificant ($p>0.05$) in all studies between groups. The highest mean reduction was 3.1mm reported by Aghazadeh et al. (2012), who used a bovine xenograft with a collagen membrane. The lowest mean reduction was 1.2mm reported by Schwarz et al.

(2013), where implants were treated with implantoplasty technique and saline solution.

The effect of intervention on BOP was reported by 4 out of 5 studies, which verified a significant reduction when compared to before treatment (Schwarz et al. 2010; Aghazadeh et al. 2012, Schwarz et al. 2013, Jepsen et al. 2016). Wohlfahrt et al. (2012), reported no difference between the 2 groups (intergroup) nor compared to the baseline (intragroup). None of the studies noted a statistical reduction between tested groups, except Schwarz et al. (2010). The highest percentage reduction occurred in patients treated only with implantoplasty and saline (85.2% of reduction) (Schwarz et al. 2013), whereas the lowest reduction was 25.9% in Class Ic defect group by Schwarz et el. (2010).

The effect of intervention on radiographic bone level (RBL) was not reported in 2 out of 5 studies (Schwarz et al. 2010, 2013). In the other 3, evidence of increased bone level was obtained, when compared to baseline in all intervention groups. However, the increase was not significant in all groups. Two studies reported that the use of porous titanium granules led to significant increase in radiographic defect filling compared to control groups (Wohlfahrt et al. 2012, Jepsen et al. 2016).

Aghazadeh et al. 2012, indicated that the use of bovine xenograft led to an increase in defect fill *versus* the autogenous bone group. However, this increase was limited and relatively insignificant. The highest mean defect filling was reported in the porous titanium granules group (3.6mm) by Jepsen et al. (2016). The lowest was found by Wohlfahrt et al. (2012), with a value of 0.1mm in the control group.

In the conclusions of this SR, Aljohani et al. said that regenerative surgical treatment revealed clinical improvements in the included studies when compared to pretreatment status. However, none of the selected studies proved a statistical significance in their approach.

3.2.2. Surgical Systematic Review 2: Mahato et al.(35)

This SR included surgical technique, involving 9 RCTs but as 2 were already cited in the SR above, 7 RCTs will be described from this study. Then,

Schwarz et al. published two articles (2008 and 2009), where the first one had a 2-year follow-up, and the second, a 4-year follow-up. The 2008 study showed that both nanocrystalline hydroxyapatite and the combination of natural bone mineral plus a collagen membrane, produced similar results when it came to significant clinical reduction of PD and CAL gain. In the 2009 study, on the other hand, the combination of natural bone mineral plus collagen membrane revealed to be more efficacious in clinical parameters improvement. Nonetheless, another study of Schwarz et al. (2006) concluded that nanocrystalline hydroxyapatite along with guided bone regeneration (GBR) also improved clinical parameter.

Schwarz et al. (2011 and 2012) did two advanced peri-implantitis studies evaluating and comparing the efficacy of Er:YAG laser versus plastic curettes and cotton pellets (CPS) soaked in sterile saline solution in surface debridement/decontamination (DD). In both procedures, the implantoplasty took place at the exposed implant surface. It was also used an augmentation technique with natural bone mineral and collagen membrane. 24 months after treatment, the CPS group showed significant decrease in BOP and the radiographic bone fill inside the bony defect was the same between groups. CAL values were different, but not significantly.

In the study of de Waal et al. (2013), the authors showed adjunctive benefits when the addition of 0.12% CHX + 0.05% CetylPirinidium Chloride (CPC) was made, comparing it to a placebo-solution. This solution was added after a resective surgical treatment, with apical positioning of the flap, bone re-contouring, and surface debridement. Although the suppression of anaerobic bacterial growth was greater with the CHX and CPC solution, it did not lead to a superior and significant final clinical result.

Romeo et al. (2007) tried to differentiate the efficacy of resective surgery and implantoplasty. The 3-year follow-up suggested that the MBL was significantly less after implantoplasty treatment.

The conclusion reached by systematic review of Mahato et al.(35) was that in more advanced cases of peri-implantitis, a combined surgical treatment of resective and regenerative procedures, followed by implant surface decontamination, has shown promising outcomes in osseointegration. Most of surgical protocols include pre- and post-operative systemic AB, along with CHX

rinses post-op. Even though the different treatment types cannot be compared, the expected outcome of surgical procedures to treat peri-implantitis is favorable.

3.2.3. Surgical Systematic Review 3: Chala et al.[36]

This SR included four RCTs observing the adjunctive use of laser in surgical treatments of periimplantitis: Deppe et al. (2007), Papadopoulos et al. (2015), Schwarz et al. (2017), and Albaker et al. (2018).

Involving the open flap resective therapy, Papadopoulos et al. found that both groups had the same clinical outcomes, with the laser offering no additional benefits six months after the procedure. Albaker et al. found the same data in their study, at both six and twelvemonth follow-up. Deppe et al. assessed CAL and radiographic distance from implant shoulder and first bone contact (DIB). The data showed values from four months and five-year follow-ups. The only superior value found was the CAL in residual bone ($p<0.05$) at both follow up checks. When it comes to the DIB, a significant difference was found at the five-year mark for residual bone.

As defended by Papadopoulos et al. and Albaker et al., there is strong evidence that laser effect has no beneficial effect after six months. This is in partial consensus with Deppe et al., who also failed to find statistically significant changes between groups after four months (except for the CAL). However, at five-year follow-up, did manage to find significantly better results for the test group.

For open flap regenerative therapy, Deppe et al. revealed that, in augmentation bone procedures, there was a statistically significant difference only found after 4 months. For DIB, a difference was also found for the augmented bone at the four-month mark. They, then, concluded that the decontamination method played a secondary role after five years of the treatment, which is in direct agreement with the one result found by Schwarz et al. (2017), who also reported that, after seven years, the outcome was not related to the method of decontamination of the implant surface.

Summarizing, there is strong scientific evidence that corroborates that both treatments (mechanical debridement alone and mechanical debridement

plus laser surface decontamination, followed by GBR) resulted in similar outcomes at long-term. (36)

For the comparison between laser types, Papadopoulos et al. used a diode laser and found no statistically significant difference between groups at the three-month mark. Schwarz et al. used a Er:YAG laser and failed to find any clear significant benefit in the usage after six months or seven years. Therefore, it can be said that there is strong scientific evidence that this type of laser (Er:YAG) had no significant benefits in clinical outcomes.

For antimicrobial photodynamic therapy (aPDT), Albaker et al. disclosed no additional benefits after the six- and twelve-month follow-up ($p>0.05$, in all clinical parameters). In this case, none of the results were reviewable since Albaker et al. provided no clinical measurements in three months.

3.2.4. Surgical Systematic Review 4: Khan et al.[33]

This SR included 5 RCTs that reported on surgical intervention for PI treatment, but 2 of them were already reported previously. Then, 3 will be reported are the following: Hentenaar et al. (2017), de Waal et al. (2015), and Isehed et al. (2018).

These three studies evaluated the following methods: (i) combination of resective surgery, (ii) apically positioned flap, (iii) bone recontouring and the usage of either saline, and (iv) placebo or 0.12% CHX + 0.05% CPC solution. These studies tried to compare these treatment options to the addition of a 35% phosphoric acid, 0.12%CHX + 0.05% CPC, and 2%CHX solution, respectively.

Hentenaar et al. concluded that the adjunctive application of 35% phosphoric acid resulted in an immediate greater reduction of anaerobic bacterial load on the surface of the implant, as well as significantly lowering the count of dental implants that were culture positive. Although this method showed successful decontamination of the implant surface, the phosphoric acid application did not show meaningful clinical measurements improvement after the 3-month follow-up when compared to the control group.

In 2015, de Waal et al. investigated the use of 0.12% CHX + 0.05% CPC as group 2 and increasing the CHX to 2% in the group 1 (test). This investigation

failed to find significant differences in either microbiological or clinical measurements between the two groups in a 12-month follow-up. Concluding, the authors stated that a 0.12% CHX + 0.05% CPC reduced the anaerobic load on the surface of the implant better than debridement only. Nonetheless, this did not translate to improvements in clinical outcomes.

Isehed et al. tried to investigate the application of regenerative surgical treatment to treat peri-implantitis with or without an adjunctive enamel matrix derivative (EMD), in a 5-year follow up. Therefore, no significant difference was found at baseline between groups in any of the parameters (BOP, SOP, and MBL). At the end of the 5 years, four out of 13 (31%) of the implants were lost or had to be treated again, due to infection in the group with EMD, compared to 7 out of 12 (58%) in the group without EMD. Authors concluded that EMD treatment was associated with a greater implant survival up to 5 years but, at the end of the study, there was still no differences between the test group and the control group.

Khan et al. conclude within their work claiming that the field of PI treatment is lacking the quality of study design/methodological methods needed to make any assertive conclusion about the efficacy of any PI treatment.

3.2.5. Surgical Systematic Review 5: Schwarz et al.[31]

This SR included mostly RCTs already presented, aforementioned, in this work. In order to avoid bias and duplicate data, they will not be reported again. The authors, however, claimed that the studies available showed that resective surgery (apical repositioning of the flap + bone contouring) along implantoplasty was more effective in reaching and maintaining disease resolution, *versus* resective surgery solo.

Augmentative surgical techniques of the intrabony defect component, with the use of porous titanium granules was linked with higher radiographic defect fill, even though it failed to improve BOP and PD. Clinical outcomes achieved with adjunctive augmentative procedures were superior to surgical measures alone. However, surgical procedures with and without soft tissue resection were grouped together, and, due to that, interpretation of overall results was difficult.

The obtained results did not grant the statement of any potential superior protocol in augmentation therapies.

The authors of this SR,[31] then, concluded that surgical therapies, such as augmentative and resective techniques, along adjunctive procedures, may have a beneficial clinical effect.

3.2.6. Surgical Systematic Review 6: Kotsakis et al.(37)

In the SR from Kotsakis et al. (2014), the authors investigated the effect of different wavelengths (laser therapy) in the treatment of PI. Only two RCT using surgical therapies were included. Both primary studies were already reported, but the effect of wavelength was not a variable in the previous study. Nonetheless, based on the information that was currently available, Kotsakis et al. claimed that no superiority of laser treatment was found when compared to conventional treatment of peri-implantitis. The authors, due to the high heterogeneity and low number of studies included, cautiously claim that non-surgical laser therapy might be appropriate, and worth investigating, as phase I therapy for peri-implantitis.

3.2.7. Surgical Systematic Review 7: Sanz-Sanchez et al.(34)

This SR (2017) investigated the effect of lateral bone augmentation procedures in the outcomes of implant and peri-implant health. When it comes to lateral bone augmentation procedures, the authors found that BOP had alterations for all of the treatment options but the results were not statistically significant (test x control groups), and the RCT studies included had low heterogeneity. Therefore, no difference could also be detected when comparing a group that used xenograft with native collagen membrane compared to other types of membranes.

The addition of different biological factors, such as bone morphogenic protein (BMP) and platelet derived growth factors (PDGF) also did not change the outcome significantly. The use of autogenous bone blocks along a bioabsorbable collagen membrane showed similar results when compared to using the bone block solo. The change in BOP values within each treatment option was evaluated in this study's meta-analysis. There was no significant

change as time gone by, for overall interventions. Using a cross-linked membrane plus a particulate xenograft revealed a statistically significant reduction in BOP values.

Data on PPD showed no significant differences between test and control groups. Radiographic alterations in crestal bone levels were also found to be not statistically different when comparing test and control groups.

Overall, assessing each treatment option independently, the meta-analysis from Sanz-Sanchez et al.(34) revealed that the interventions resulted in an overall low value of BOP, although without any significant statistical difference among them. Gauging other peri-implant aspects like MBL, PPD, and plaque level, similar results were found among different surgical options, both for short- and long-term follow-ups.

3.2.8. Surgical Systematic Review 8: Tomasi et al.(39)

Tomasi et al. (2019) included 16 studies, but only 3 out of them included control groups and were designed as RCT. The remaining 13 studies were determined to be observational studies and therefore, not accounted for in the present work. The 3 RCT included were already reviewed behind (Wohlfahrt et al. 2012, Isehed et al. 2016, and Jepsen et al. 2016). With that being said, Tomasi et al. suggested that reconstructive surgical therapy for peri-implantitis is an achievable concept, but it is also clear that the evidence is limited, and more studies are required.

The available evidence found in this review allowed them to claim that the low number of RCT studies limited the evidence level that reconstructive therapy can have in dealing with peri-implantitis defects. Also, the lack of RCT studies for the most commonly used procedures, the heterogeneity between studies, and the selected outcome measures being so discrepant are factors that limited the investigation(39).

3.3. Quality Assessment

Utilizing the AMSTAR2 rating tool,(30) four of the included SRs were considered to be of High Quality (Schwarz et al. 2015, Kotsakis et al. 2014, Gao et al. 2020 and Tomasi et al. 2019), three of moderate quality (Aljohani et al. 2019 Khan et al. 2020 and Sanz-Sanchez et al. 2017), one of low quality (Chala et al. 2020) and one of critically low quality (Mahato et al. 2016).

AMSTAR 2 16 questions are as follows:(30)

1. Did the research questions and inclusion criteria for the review include the components of PICO?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

A table with the above questions answered and the final verdict is exposed below.

Table 2: *AMSTAR 2 rating of the included Systematic Reviews*

	AMSTAR 2 Criteria Questions																
Studies	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**Verdict**
Aljohani et al. 2019	Y	Y	Y	PY	Y	Y	N	PY	Y	N	0	0	Y	Y	0	Y	**Moderate Quality**
Mahato et al. 2016	Y	PY	Y	PY	Y	Y	PY	PY	N	N	0	0	N	N	0	Y	**Critically Low Quality**
Chala et al. 2020	Y	PY	Y	PY	N	N	PY	PY	PY	N	0	0	N	Y	0	Y	**Low Quality**
Khan et al. 2020	Y	PY	Y	Y	Y	Y	PY	Y	Y	Y	0	0	Y	Y	0	Y	**Moderate Quality**
Schwarz et al. 2015	Y	Y	PY	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	**High Quality**
Kotsakis et al. 2014	Y	Y	Y	PY	Y	Y	Y	Y	PY	N	Y	Y	Y	Y	Y	Y	**High Quality**
Gao et al. 2020	Y	Y	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	**High Quality**
Sanz-Sanchez et al. 2017	Y	Y	Y	PY	Y	N	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	**Moderate Quality**
Tomasi et al. 2019	Y	Y	Y	PY	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	**High Quality**

Discription: Y: Yes; **PY:** Partial Yes; **N:** No; **0:** Not Aplicable

The authors themselves utilized different rating tools to assess the quality of their SRs, which is also important to be taken into consideration.

In the SR from **Mahato et al.,**[35] no bias/quality table of studies was available. The authors only mentioned that the inclusion of articles only in the English language could be a cause for bias.

In the study from **Chala et al.,**[36] authors claimed that, for quality assessment, a grade scale was applied based on some criteria, which were:

- Randomization and Blindness
- Comparison of baseline status between groups (severity of pathological condition)
- Description of protocol (treatment and irradiation)
- Measurement of clinical parameters (baseline and follow up)
- X-ray evaluation (baseline and follow up)

Final study classification was made regarding the number of positive answers to each individual criterion.

- Four to five positive questions: High Quality
- Two to three positive questions: medium quality
- One positive question: Low quality

Scientific Evidence level was evaluated by study evaluation concerning the following criteria:

- Strong evidence level: Conclusion confirmed by at least two investigations.
- Contradictory scientific evidence: conclusion confirmed by studies in which findings are conflicting.

After the quality assessment was made, all the included studies were considered "high quality" with only one study scoring four (all the others scored five), due to missing X-ray information.

No bias information was available.

In the SR from **Khan et al.,**[33] the authors used the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) tool to verify the quality of evidence for each treatment option.

Concerning the Risk of Bias (RoB), the 2019 Cochrane Collaboration bias assessment tool was the chosen option to evaluate the included studies. The tool utilizes five main domains to assess each study as having low, concerning or high RoB.

Regarding the quality of evidence, assessed by the GRADE tool, four of the publications were considered to be of low quality of evidence, and the other nine were considered to be of very low quality. Due to this fact, the real effect of interventions is most likely to be considerably removed from the approximate effect for most interventions.

Schwarz et al.,[31] in their SR, presented a table where they assessed the RoB from the selected randomized studies utilizing the Cochrane collaborations Tool.

A qualitative assessment was made independently by both authors of the study in phase I, mainly through the published full-text article. In phase II, disagreements were solved by discussion between authors.

In the SR from **Kotsakis et al.,(37)** authors utilized the revised CONSORT (Consolidated Standards of Reporting Trials) tool for evaluation of the RCTs. A supplementary table was reported to exist online with this data but could not be found online for confirmation.

Regarding the RoB, three studies were considered to be of high risk of bias (Deppe et al. 2007, Schwarz et al. 2006, Schwarz et al. 2005), one moderate risk of bias (Schär et al. 2013) and two low risk of bias (Schwarz et al. 2012, Renvert et al. 2011).

Gao et al.,[38] utilized the GRADE assessment tool to evaluate the quality of evidence provided by the included articles. The Cochrane Collaboration's RoB tool was used to assess the RoB. The studies included from this SR were only two, from Galofré et al. 2018 and Tada et al. 2018, as the others concerned peri-implant mucositis and not PI. Both of them were classified as having a low risk of

bias. GRADE assessment revealed moderate quality of evidence from both studies.

The SR **from Sanz-Sanchez et al.**[34] reported that the quality of the included RCTs was reviewed by one of the authors, utilizing the Cochrane Collaboration Recommendations. Each of the following criterion was assessed as low, high or unclear RoB:

1. Selection bias (sequence generation and allocation concealment)
2. Performance bias (blinding of participants/researchers)
3. Detection bias (blinding of outcome assessment)
4. Attrition bias (Incomplete data report)
5. Selective report bias (Report of selective outcomes)
6. Other potential RoB

Jung et al. 2017, Schwarz et al. 2014 and 2016 reported a low RoB in all criteria. The study from Jung et al. 2015 also had a low RoB score in all parameters except for one. The remaining studies' scores are listed in the table below.

Tomasi et al.[39] mentioned that regarding the RoB of individual studies, within the included RCTs, only the one from Isehed et al. 2016 was rated as having a low RoB. The authors of the SR claimed that apparently, the difficulty was to blind the examiner during X ray assessment, evaluating grafts for bone replacement (detection bias).

As it concerns publication bias, none significant was found for the three RCTs in the matter of MBL and PD lowering.

With all of this being said, the conclusions each author reached with its' SR cannot be interpretated at ease.

DISCUSSION

4. Discussion

4.1. NS Discussion

Six SRs included NS approaches to PI treatment.

Mahato et al. claimed that, overall, even though NS treatment could significantly improve clinical parameters, bacteria responsible for pathogenesis are not decreased.(35) This claim is confirmed by most of the recent works.(11, 40, 41)

Chala et al. reported that, in all of the included RCTs, regarding NS treatment and adjunctive laser use, none of them could show complete resolution of the local inflammation.(36) This, as supported by many of the available literature) is an open door to the progression of PI.(42-44)

The used lasers and respective wavelengths in the included RCTs were as follows: DL 670nm (in antimicrobial PDT), Nd:YAG 1064nm and Er:YAG 2940m.(36)

The DL intervention groups presented equally efficient improvement across clinical parameters, reducing mucosal inflammation(37) compared to control, but ended up also showing a higher marginal bone loss.(33) The benefits from the PDT with DL were significant up to 6months post intervention, but at the 12-month mark, benefits had wear on.(37)

With the Er:YAG laser, no group showed a positive response at 6 months. A positive response would have been PD <5mm, no BOP and no SOP. No one, in each group of the study, reached this outcome.(36)

With the Nd:YAG laser, no statistical difference was found in bone loss around crestal bone at 3 and 6 months follow up. Plaque Index, BOP and PD were statistically significantly lower in patients that received MD + adjunctive Nd:YAG laser applications in the 3 month follow up. At the 6 months follow up, the improvement was significantly reduced, meaning that the laser application made tissue healing happen faster than with MD alone.(36)

Authors, referencing another SR, state that the use of laser during a NS approach should be investigated as a previous intervention for posterior surgical treatment.(36)

The SR from Chala et al. state that, based on the included RCT, NS intervention can be efficient in controlling the inflammation of peri-implant tissue for six months.

Also, Kotsakis et al. in their SR had four NS RCTs about the effects of various laser wavelengths on PI treatment. Authors claimed that NS treatments with laser adjunctive tools, showed reduced attachment loss and PD. Both were decreases under 1mm.(37)

The most recent American Academy of Periodontology (AAP) best evidence consensus of Laser therapy for PI treatment, in 2018, revealed similar data from the two previously cited SRs.

Authors stated that, among their evaluated studies, the SR and meta-analyses they performed did not identify significant PD lowering nor CAL gain, when combining lasers with NS techniques.(40) These finding are similar to another AAP consensus from Chambrone et al., regarding the use of PDT, that also utilizes low wavelength lasers, as for example, DL.(45) DL showed promising results in two recent reviews, when it comes to PD reduction and CAL gain, but further, better designed investigations, should be planned.(40, 45)

Concerning BOP, the laser consensus from AAP report conflicting results, as some studies stated that significant reduction was achieved when lasers were used instead of regular MD, but other studies failed to find significant data.(40) Even the ones that found positive effect on reducing BOP levels showed limited time-frame effect (6 months).(40)

The MA from Lin et al. exhibited data that corroborated no added benefits in PIql reduction when lasers were applied as adjunctive measure to regular MD.(40)

Concluding, with the current evidence found in the two previous SR with RCTs and the most recent AAP consensus, laser as an adjunctive tool for the NS treatment of PI has limited benefits. Only Er:YAG, CO2 and DL could be analyzed

with the current evidence,(40) as studies for other laser types did not use a control group to support the evaluations made.(40, 41, 45)

With that being said, further RCTs should be elaborated to clarify the role adjunctive laser application can have in the NS PI treatment.

Khan et al. investigating the management of PI lesions without the use of systemic AB, in association with NS options, found that there is a lack of high-quality clinical trials in the investigated area. All interventions assessed by the authors were considered to be of either low or very low quality of evidence, putting in jeopardy the actual effect of the interventions *versus* the estimated effect.(33)

Concerning NS options, the adjunct use of chloramine gel as detoxification measure had the same effect as NS MD alone. Both of them, however, showed statistically significant clinical parameters improvement, for a 3 months follow up. With a short follow up period and only 18 people included into the study, the quality of intervention was not the desired.(33)

Reporting the investigation of MatrixC and PerioC chips application, post NS treatment, the PerioC group revealed a greater PPD reduction (2.19mm) *versus* MatrixC (1.59mm), as well as a greater CAL gain (2.21 mm vs 1.56mm).(33) However, no differences in BOP at the 6 month follow up was noted between groups. The SR authors considered this RCT to be well conducted and with positive results, suggesting further investigation.(33)

Air-abrasion device *versus* manual MD and local chlorhexidine application showed similar results. Both revealed PD reduction and CAL gains, but the air abrasion with Glycine powder had a greater BOP reduction power.(33) Suggestions were made about the efficacy of NS therapy along the adjunctive aid of air-abrasion device, concerning a threshold effect level. As both studies that investigated this combination of therapies had methodological concerns and a high RoB, results have to be interpreted with caution.

The conclusion reached in the SR from Schwarz et al. is that the found WMD in BOP scores favored adjunctive AB therapy, applied locally, or alternate debridement methods, such as laser application or air abrasive polishing with glycine over the control measure applied in most RCTs. PD scores did not show the same improvements, using either conventional debridement methods or

adjunctive/alternative approaches, such as air abrasive polishing, PDT, antiseptic CHX chips, AB and lasers.(31)

Authors also claim that the deeper the probing site, the more limited is the efficacy. Several studies found increased BOP between 3 and 12 months of follow up after NS intervention in those severe cases. Treatment efficiency was higher in moderately deep sites.(31)

Nonetheless, investigators alert that PD scores can be influenced by several other factors, including implant positioning, implant-abutment connection, occlusal load and soft tissue thickness.(31)

Regarding the adjunctive effect of Lactobacillus probiotic with NS measures (supra gingival scaling with ultrasound - carbon fiber tips- and titanium curettes) one study showed significantly improved BOP and PD at implant level, post intervention, on the probiotic group.(38) The other study encountered significant PD decrease after Probiotic application, but BOP was not significantly different between test and control groups.(38) Although this this probiotic field is not new in oral healthcare(46) it is as an adjunctive measure in the NS treatment of PI. More studies are still required to prove any kind of significant difference with the application of probiotic single strains or mixes.(38, 46)

As for the NS therapeutic options for treating PI reported above, most findings were confirmed in the latest consensus report of Working group 3, made by Renvert et al.(41) The authors of this consensus report conclude that air-abrasive polishing apparatus, Er:YAG laser, manual or ultrasound drive curettes can in fact be used to treat PI.(41) Most of aforementioned treatments show some degree of clinical improvement, i.e., reduced BOP and, in a few cases, PD reduction of measurements of 1mm or less. In more serious cases, NS treatment for complete disease resolution is. most likely, not enough.(11, 41)

4.2. Surgical discussion

The 8 SRs had data from RCTs regarding the surgical treatment of PI are: Aljohani et al., Mahato et al., Chala et al., Khan et al., Schwarz et al., Kotsakis et al., Sanz-Sanchez et al. and Tomasi et al.

4.2.1. Regenerative approaches

Aljohani et al. gathered data from RCTs that evaluated the efficacy of surgical regenerative treatments for PI.(32)

Authors claimed that all of the studies revealed improvements of clinical parameters when compared do baseline.(32) Nonetheless, all studies failed to prove any statistical significance based on their different surgical approaches when it came to PD, BOP, RBL or vestibular margin recession.(32)

Highest PD reduction was reported in studies that utilized bone substitutes (Bovine derived xenograft and porous titanium granules). Authors suggested that bone substitute materials may be better in improving PD, versus other non-regenerative S treatments.(32)

Regarding BOP, no RCT showed superiority between them and the different used techniques, even though significant improvement was found in all of them.(32)

RBL was another investigated parameter, and studies that utilized bone substitutes had increased RBL compared to base levels. No study could prove that the chosen technique was more reliable or better than the others. Highest bony defect fill was accomplished with porous titanium granule usage, followed by bovine xenograft and lastly autogenous bone.(32)

One of the included studies by Aljohani et al. had a 48 and 84 month follow up, regarding two different methods for surface debridement and also different detoxification method, in the surgical treatment of PI. After access flap surgery, removal of inflammatory tissue and implantoplasty in both groups, the first one was treated with Er:YAG laser, and the second one received MD with plastic curettes, cotton pellets and saline (sterile). Both groups, after detox and cleaning, received natural bone mineral and a collagen membrane. At both of the aforementioned checkup periods, no statistical difference was found between the two groups. It was ultimately concluded that the outcome of the treatment was not influenced by the different method of decontamination.(32, 47)

Aljohani concluded their work by stating that, within the limitations of the included RCTs, Porous Titanium granules had the best effect on bone defect filling (confirmation via X ray) and the better PD results were with the Xenograft,

bovine derived. Defect shape has also an effect on this predicted filling.(32) No clear advantage was shown to support the use of Er:YAG laser, submerged implant technique or membranes. Other well designed RCT studies, with long term follow up and a large sample size, are required to take better conclusions.(32)

Chala et al. in their SR, had similar findings to Aljohani et al. in what concerned regenerative approaches; there is not enough evidence to clearly recommend a specific surgical regenerative technique nor material to be used. It was also suggested that the means of detoxification have a minor role in the treatment outcome.(36)

Data from a RCT from the SR of Khan et al corroborated that the use of Enamel matrix derivative (EMD) was associated with implant success (survival).(33) The follow up period was 5 years, and authors anticipated that EMD could have prompt healing capacity and anti-microbial effect. (33) Despite the long follow up, the cited RCT had a high RoB and sample was of small size, so the quality of this evidence is very low.(33)

Data from the most recent consensus report on the surgical treatment of PI(48) from 2019 confirm the findings from Aljohani et al. and Chala et al. Although surgical augmentative/regenerative technique procedures result in better clinical and radiographic outcomes for treating PI, there is no concrete evidence to support a specific use of a single material, membrane or product.(48)

Regarding the decontamination process, Khoury et al. and Koo et al. also failed to detect any significant effect of a certain decontamination method(48, 49) supporting the previous find from Schwarz et al. in 2017.

The SR from Mahato et al. had the lowest quality assessment among the included SRs. This was because no quality assessment, of the included RCTs, was made available in the study. Also, no RoB was evaluated. As such, the conclusions reached by the authors might not be the most accurate of scientifically proven data.

Mahato et al. claimed that their study noted that disease resolution is satisfactory with surgical treatment.(35) Authors also claim that, if the bony defect is small, Implantoplasty can be improve the defect.(35) Authors also claimed that

guided bone regeneration or application of a bone substitute can be an effective treatment for PI. (35) This is an overly simplified affirmation that cannot be made with certainty, as the effectiveness of the surgical procedure can be variable and literature to support its predictability and long term success are scarce.(48, 50)

The SR from Schwarz et al. found similar study findings to the ones that have been reported so far, further reassuring that surgical augmentative/regenerative techniques are useful and can lead to better clinical outcomes than ns techniques. Still, no clear "gold standard" for technique nor materials are reported. Submerged implant healing seems to have better overall results, compared to non-submerged ones.(31)

The SR from Kotsakis only included two studies that concerned surgical treatments of PI. The final outcome was that, compared to the non-surgical approaches, surgical interventions reduced, at least twice as much, the clinical parameters, obtaining therefore, improved treatment outcomes.(37) Authors state that this conclusion is in line with other reviews about PI treatment and outcomes; a consensus start to be stablished that NS interventions have a limited range of effect, and so, surgical interventions are starting to be the "go-to" procedure.(37)

Results from the SR of Sanz-Sanchez et al. revealed that lateral bone augmentation interventions and various bony replacements and different used membranes can maintain steady results overtime, when it comes to reducing inflammation of the mucosa and also keeping bone levels unaltered.(34) Evaluating each treatment technique by itself, no significant BOP, margin bone level, PD and PI change was found. These results are both for short, 3 months to 3 years, and long period, 5 years or more, follow ups.(34)

Overall, data and information from the included SRs and most recent consensus reached the same conclusion regarding regenerative/augmentative techniques: clinical parameters improvements are likely to happen, outcomes are expected to improve post intervention, but by how much, is not an easy parameter to estimate. Also, no technique nor materials have shown clear superiority over another.

4.2.2. Resective approaches

In the SR from Chala et al, about resective approaches, authors first analyzed that most of the included studies where a resective technique was used, a full mouth MD was first realized, in order to maximize the reduction of bacterial count.(36) The SR also states that findings among studies utilizing resective techniques are expected to present contrasting results, as many of the factors that have direct impact on the outcome is yet to be fully understood (i.e etiology, pathogenesis, surgical technique and expertise).(36)

All surgical resective techniques aim to cease exacerbated inflammatory response in the tissue, responsible for PI development. Soft tissue margin also must be kept around the implants' neck.(36) The use of DL for implant decontamination along with soft tissue resection showed significant improvement in CAL and PD in two of the included studies.(36) Nonetheless, taking into consideration the study design and evaluation by the SR authors, this is not strong enough of an evidence to fully prove the benefit of laser versus conventional debridement, in combination with resective surgery.(36)

Khan et al. in their SR, found data from RCTs that evaluated resective procedures along some different adjunctive measures. The use of 35% phosphoric Acid combined with a resective intervention and detoxification with saline.(33) A greater repression of anaerobic bacteria was identified at implant surface in the test group; nevertheless, no improved clinical outcomes were detected along with that reduced load of anaerobic bacteria at the 3-month follow up.(33) A hypothesis suggested by the authors theorize that, although low pH acids have reported bactericidal effects and no sequels on titanium implant surface, acidic solutions might hinder new osseointegration.(33)

Also concerning detoxification methods simultaneously used with resective surgical interventions, included RCTs investigated a 0.12%CHX+0.05% CPC solution, that revealed a significant bacterial load reduction on implant surface, but, as the previously cited study, failed to find important outcome results in a 12-month follow up.(33) The same study was later replicated, now comparing 0.12% CHX + 0.05% CPC and 2% CHX. No significant differences were found between the applied solutions, although both showed effectiveness in improving clinical and microbiological outcomes (3, 6 and 12 month follow up).(33)

The adjunctive use of DL in the surgical resective treatment showed to improve CAL significantly, but no other positive outcome was registered over surgical resective treatment solo.(33) As no other clinical parameters were improved, the benefits from DL adjunctive use were considered limited;(33) this included RCT had a high RoB and reduced sample sizes, being considered by the authors of the SR, of very low quality.(33)

The SR from Schwarz et al. reported a study that utilized implantoplasty as adjunct measure to open flap debridement, bone recontouring and apical flap repositioning. At the 24-month follow up, the study had to be halted at the control group, as perpetual signs of active PI inflammation were present.(31) This group had done the same procedures as the test group, except for the implantoplasty. Both groups also received local and systemic ABs (metronidazole plus tetracycline hydrochloride for 3 minutes, and 8 days of Amoxicillin, respectively).(31) In the group where implantoplasty was executed, RBL was stable at the 3 year follow up, but mucosal recessions were more prevalent (with no pseudo pockets).(31)

The recent study from Roccuzzo et al on a clinical update and surgical procedures outcomes approached the most recent works about resective techniques.

About open flap approaches with resective measures, authors claim that a five year study, evaluating the aforementioned surgical technique, alongside the use of systemic antibiotics, 54% of the implants were classified as having no present disease, having received successful treatment.(50) The same study also made a significant statistical link with a PD ≥ 6mm and lower MBL. This meant that active PI was present or progressing, at the one year follow up.(50) This comes in agreement with the findings from the aforementioned SRs.

The Consensus from Khoury et al. also corroborates these findings, concluding that clinical parameters are, most of times, improved when surgical resective techniques are conducted, but clear benefits are yet to be reported when it comes to systemic AB use.(48) The group 4 FDI consensus report also state that significant improvements were found especially in studies that utilized adjunctive implantoplasty, with diamond or arkansas burs and silicone

polisher.(48) Concerns still revolve around implantoplasty, as titanium particles might linger inside the oral cavity and may be health hazardous.(48)

Implantoplasty might have another downside, as there are concerns for the consequence of altering the implants' surface, mainly on how it effects its' structural integrity; it might compromise load distribution and implant fracture might have more tendency to occur.(50) More studies are needed to fully understand the effects of Implantoplasty, but as for now, the controversy stands.

CONCLUSIONS

5. Conclusions

Within the limitations of the study, after having systematically analyzed the included SRs and discussed the obtained results with some of the more recent consensus, in order to try and answer the focus question from the present work, the following conclusions can be taken:

1) NS interventions for treating PI have limited effects and are, most likely, not enough to stop PI development nor to resolve it. NS options can improve clinical parameters like BOP and PD in a lesser degree, but are recommended in initial stages of the disease, or for a more effective action, to treat peri implant mucositis and stop the evolution to fully set PI. The greater the PD, more limited seems to be the effect of the NS approach.

2) NS interventions with alternative/adjunctive methods, like lasers and local AB/anti-septic therapy may have a tendency for better clinical results/outcomes, although some results remain controversial.

3) Er:YAG laser, Air-abrasive polishing with Glycine Powder, MD with curettes or ultrasound and local AB/anti-septic measures have shown to have slightly better clinical results when used in conjunction in NS approaches. None of the above techniques were enough to significantly reduce the bacterial load on the implant surface. The ones that did, only reduced the present pathogenic bacteria amount for 6 months, at most.

4) As NS therapies seem to be insufficient to successfully treat PI, the more appropriate option appears to be a surgical approach, that can either be regenerative/augmentative or resective.

5) Findings for regenerative/augmentative techniques seem to be generally positive, as they display better clinical and radiographic outcomes in the investigated studies. To predict the degree of improvement with the surgical intervention is something that is hard to do.

6) As for the materials used in this type of approach, no clear superiority was demonstrated by any of them. Autologous bone remains the “gold standard” but sometimes resorption of the material can happen too fast, and the regenerative process can end up in failure. The generally better

results in PD improvement and radiographic bony fill were obtained with Bovine-derived Xenograft and porous titanium granules. Submerged implant healing seems related to better clinical improvements.

7) When it comes to the detoxification method for implant surface in surgical therapies, no method revealed to be superior to another.

8) In resective surgical techniques, clinical parameters are also improved most of the times, but a clear benefit from the use of AB is still to be fully reported.

9) Implantoplasty seems to demonstrate significant improvements of clinical parameters in surgical interventions for the treatment of PI. This procedure can be done with diamond or arkansas burs, along with silicone polishers.

10) Some concerns still arise from Implantoplasty execution such as lingering titanium particles in the oral cavity or structural integrity implications, as the procedure involves mechanical modification of the implants' exposed threads.

To a definitive answer to the proposed question, more well thought out, properly designed and with larger samples RCTs need to be planned. Establishing a definite standard for PI diagnosis to utilized across all PI investigation studies would also help to even the field and facilitate interventions comparison.

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