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Enamel matrix derivative in the Treatment of Peri-implant Diseases - A Systematic Review

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Faculdade de Ciência de Saúde

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Literature Review presented to the Universidade Fernando Pessoa as Part of the Requirements for the obtention of Dental Medicine master's degree

ABSTRACT

Objective: To evaluate the benefit in terms of clinical, histological and radiographic outcomes of the adjunctive use of enamel matrix derivative (Emdogain®; Straumann, Basel, Switzerland) on the non-surgical and surgical treatment of peri-implant diseases.

Methods: A systematic literature search comprised three databases: PubMed, Scopus and Cochrane. Eligible studies were selected based on the inclusion criteria.

Results: Seven studies were selected for data extraction. Two randomized clinical trials using Emdogain® as an adjuvant for non-surgical treatment of peri-implant mucositis; tree cohort studies and and two randomized clinical trials using Emdogain® as an adjuvant for surgical treatment of peri-implantitis. A reduction of the mean bleeding on probing (76.6%), probing depth (3.5mm), *P. gingivalis* counts and mean marginal bone level gain of 2,38±0.92mm was observed.

Conclusions: Emdogain® has a positive effect on clinical and microbiological outcome of non-surgical treatment of peri-implant mucositis. Combined with grafting materials, it seems to improve bone fill after surgical treatment of peri-implantitis. More studies are necessary to determine the effects of Emdogain® alone in the clinical outcome of peri-implantitis treatment.

Keywords: Peri-implant diseases, non-surgical, surgical, treatment, Enamel matrix derivative, Emdogain®

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ABBREVIATION LIST

BOP - Bleeding on Probing

CCT - Controlled clinical trial

EDTA - Ethylenediamine tetra-acetate

EMD - Enamel matrix derivative

HOMIM - Human Oral Microbe Identification Microarray

IL-6 - Interleukin-6

IL-17 - Interleukin-17

MSM - Micro-spherical minocycline

PD - Probing depth

PLS - Partial least square

RCT - Randomized clinical trials

I. INTRODUCTION

Dental implants have become a highly predictable option to rehabilitate, partially or fully, edentulous patients (Balshi et al., 2015; Chappuis et al., 2013).

Nonetheless, they are not free from complications. Being the most common complications, the biological ones, which are defined as peri-implant diseases - peri-implant mucositis and peri-implantitis (Derks et al., 2016). In the 2017 World Workshop on the Classification of Periodontal and Peri‑Implant Diseases and Condition, Caton et al. (2018) described peri-implant diseases as infectious/inflammatory diseases that affect the soft as well as hard tissues around a functioning implant.

The clinical manifestations of peri-implant mucositis are bleeding on probing, increased peri-implant probing depth and suppuration. For peri-implantitis, loss of supporting bone has to be added to the same clinical factors (Zitzmann & Berglundh, 2008).

From a biological point of view, both periodontal and peri-implant inflammatory states are characterized by a dysbiosis with enrichment of anaerobic, Gram negative bacterial species (Roberts & Darveau, 2015) with the same key bacteria association (Kumar et al., 2012; Leonhardt et al, 1999; Mombelli & Decaillet, 2011;; Persson & Renvert, 2014; Zhuang et al., 2016).

Furthermore, it has been shown that peri-implant diseases follow the same pattern than gingivitis and periodontitis, in other words, peri-implant mucositis is a precursor of peri-implantitis, but with a non-linear, accelerated progression pattern (Derks et al., 2016). Therefore, a treatment of this inflammatory state should be attempted without delay once diagnosed.

Heitz-Mayfield & Lang (2010) demonstrated that biofilm maturation and a susceptible host response are the main etiological factors of periodontitis and peri-implantitis. Nevertheless, the rate of progression of the peri-implant diseases may be explained by differences in the host response of these two infections.

Several risk factors have been proposed for the development and progression of peri-implant diseases. Recently, Schwarz et al. (2017) observed that major risk factors for peri-implant diseases include poor bacterial plaque control skills, history of chronic

periodontitis, and no regular maintenance care after implant therapy. Others such as post-restorative presence of submucosal cement, lack of peri-implant keratinized mucosa and positioning of implants that make it difficult to perform oral hygiene and maintenance are potential factors that increase the likelihood of developing peri-implantitis.

The inflammatory state induced by biofilm maturation may result in the loss of implant- supporting bone and could finally lead to the loss of the implant (Lindhe & Meyle, 2008; Pjetursson et al., 2012; Pjetursson et al., 2014). Esposito et al (1998), peri-implant diseases are the etiologic factor for the failure of 10% to 50% of implants at least one year after loading. In their systematic review, Derks and Tomasi (2015) observed that peri-implantitis affected 22% of individuals with dental implants.

Therefore, decontamination of the implant surface and resolution of the inflammatory process are the clinical endpoints of the treatment of peri-implantitis (Serino & Ström, 2009). Since peri-implant diseases and periodontitis share the same etiological factors, the same therapeutic approach has been advocated (Heitz-Mayfield & Lang, 2010; Meffert, 1996; Renvert et al., 2008; Renvert et al., 2012). Management of peri-implant diseases is based on a non-surgical or surgical debridement and decontamination followed by ongoing supportive therapy or regeneration of the peri-implant bone defect to promote the disease resolution (no bleeding and/or suppuration on probing and absence of deep probing pocket depth) and create conditions for patients to maintain these results in the long term.

In a literature review, Renvert et al. (2008) observed that mechanical non-surgical therapy could be effective in the treatment of peri-implant mucositis lesions, especially with the use of adjunctive treatments, including the use of antibiotics, antiseptics, and laser. However, in peri-implantitis lesions non-surgical therapy was not found to be effective. These results started to be refuted recently though by Mettraux et al. (2016) and Nart et al. (2020) which observed promising results.

Nonetheless, surgical exposure of the implants and the mechanical debridement/decontamination of the implant surfaces are still advocated to treat most of these lesions. Renvert et al. (2012) shown to be a predictable method for treating peri-implant disease in the short term. However, complete disease resolution seems to

be dependent on the initial bone loss at implants (Serino & Turri 2011). Furthermore, in the long-term, supportive periodontal therapy seems to play a crucial role in the maintenance of the results (Serino et al., 2015).

In order to improve the results of the surgical treatment, several protocols have been proposed, including the use of bone grafts/bone substitutes with and without membranes, and have reported clinical and radiographic improvements (Roos-Jansåker et al., 2011; Schwarz et al., 2009; Schwarz et al., 2013; Schwarz et al., 2017). In both non-surgical and surgical approaches, there is not a clear gold standard, and Faggion et al. (2014), Heitz-Mayfield & Mombelli, (2014), on their systematic review, concluded that the evidence available is insufficient to allow specific recommendations for peri-implant diseases treatment. However, Schwarz et al. (2015), in their systematic review, found that adjunctive products may improve the efficacy of treatments at peri-implantitis sites.

Recently, enamel matrix derivative (EMD) (Emdogain®; Straumann, Basel, Switzerland) has been tested as an adjunctive tool in both non-surgical and surgical peri-implant diseases treatment. EMD is prepared from porcine enamel matrix and consists mainly of amelogenin and ameloblastin (Riksen et al., 2014). It is used for various purposes, including periodontal regeneration and root coverage (Cordaro et al., 2012; Miron et al., 2016). Indeed, the rationale behind its use in surgical treatment of periodontitis is to accelerate wound healing and periodontal regeneration (Bosshardt, 2008; Esposito et al. 2008; Hammarstrom et al., 1997; Miron et al., 2015). It has also been demonstrated to have antibacterial properties that inhibit the growth of gram-negative bacteria such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans* and *Prevotella intermedia* (Spahr et al., 2002; Walter et al., 2006).

In addition, the results of studies on dogs showed that EMD has a positive effect on bone regeneration around the dental implants, especially associated with guided bone regeneration (Casati et al., 2002; Ikawa et al., 2019). All of the above-mentioned characteristics suggest that enamel matrix derivatives might have a potential added value in the treatment of peri-implant diseases.

Finally, the aim of this systematic review is to answer the following PICO question: In patients with peri-implant diseases (P), the adjunctive use of EMD (I), when compared with any treatment protocol without EMD (C) on the non-surgical or surgical treatment of peri-implant diseases, adds any benefit in terms of clinical, histological and radiographic outcomes (O).

I.1 Material and methods

Protocol development and eligibility criteria

A protocol was developed and followed the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement (http://www.prisma-statement.org).

The focused question was formulated based on the PICOS guidelines:

1. Population (P) = Humans with peri-implant disease.
2. Intervention (I) = Non-surgical and surgical treatment for peri-implant diseases with EMD (Emdogain®).
3. Comparison (C) = Comparison results of the interventions included in the selected literature.
4. Outcome (O) = Clinical results: implant survival, probing depth (PD) reduction, bleeding on probing (BOP), bone level, soft tissue gain, local plaque index, whole mouth plaque index. Microbiological results: *P. gingivalis*, Interleukin-6 and Interleukin-1 counts, HOMIM (Human Oral Microbe Identification Microarray), Microbiota characterization.
5. Study design (S) = Randomized clinical trials (RCT), controlled clinical trials (CCT), cohort studies or clinical trials.

Search Strategy

An electronic search of three databases, PubMed, Scopus and Cochrane, was performed until 30 of April of 2020. The articles were included if, after full text reading, were referring peri-implant mucositis, peri-implantitis, non-surgical or surgical treatment with Emdogain®

Search terms

The electronic search strategy included terms related to the intervention and used the following combination of keywords: ((Emdogain OR EMD OR (Enamel matrix derivative)) AND (Peri-implantitis OR (Peri-implant diseases) OR (peri-implant mucositis) OR (dental implant) AND (Non-surgical OR Surgical OR Therapy OR Treatment))

Inclusion criteria

1. Randomized controlled clinical trials, controlled clinical trials, cohort studies or clinical trials.
2. Studies focused on the non-surgical or surgical treatment of peri-implant diseases with the use of EMD (Emdogain®).

Exclusion criteria

In vitro and animal studies, case series, case reports, and studies not meeting all inclusion criteria.

Screening and selection of studies

Publication records and titles identified by the electronic search were screened based on the inclusion criteria. A second selection was made by screening the abstracts. Therefore, full texts of the selected articles were obtained. Then, articles that met the inclusion criteria were processed for data extraction. All screening and selection were made by two independent researchers (X.B. and T.R.A).

Assessment of risk of bias

The methodological quality of RCT and CCT studies were assessed guided by the Cochrane Handbook. Each study was classified into the following groups: low risk of bias if all quality criteria were judged as “present,” moderate risk of bias if one or more key domains were “unclear,” and high risk of bias if one or more key domains were not “present.”

II. RESULTS

Search

Figure 1 depicts the flow chart summarizing the results of the search. The electronic search rendered 111 potential references in PubMed, 61 in Scopus and 27 in Cochrane. After duplicates discarded, titles and abstracts revision, 22 articles were selected for full-text screening. At the end of the process, 7 articles were selected for data extraction regarding the selection's criteria of this literature review.

Risk of Bias in Individual Studies

No single RCT assessed with Cochrane Handbook demonstrated low risk of bias for all the criteria and the majority of studies showed a moderate risk of bias (Table 1). Most of them provided a detailed report about randomization but not regarding other key domains such as allocation concealment and blinding of the participants, thereby increasing the potential risk of bias. Faramazi et al. (2015), Isehed et al. (2016) and Isehed et al. (2018), have an unclear risk of bias. Kashefimehr et al. (2017) has a high risk of bias.

II.1 Non-Surgical Treatment Results

Description of selected studies

Table 2 depicts the methodological characteristics of the selected studies. Two randomized clinical trials, Faramarzi et al., 2015; Kashefimehr et al,. 2017, have compared the outcomes of a non-surgical treatment of peri-implant diseases with and without EMD. Faramarzi et al., 2015 has also made the comparison with the use of micro-spherical minocycline (MSM) in a third group.

All studies included healthy subjects with Peri-implant mucositis and\or mild peri-implantitis. Smokers were excluded. The mean age was 47,71±2.17. The number of included patients were 64 (Faramarzi et al., 2015) and 41 (Kashefimehr et al., 2017). The two studies had a follow-up of 3 months. Both of them used a non-surgical mechanical debridement with ultrasonic device and glycine-based powder air-polishing to remove subgingival biofilm of the affected site before the EMD application. However, Kashefimehr et al., 2017, waited two weeks after the mechanical

debridement before using ethylenediamine tetra-acetate (EDTA) to decontaminate the implant and placing after the EMD in the affected sites. All the implants in the study of Faramarzi et al. (2015) were of the same brand (Dentis) with absorbable blasted media surface treatment.

Clinical results

None of the two RCT studies reported implant loss during the 3-month follow-up. Both of them examined the clinical benefits of EMD in terms of BOP reduction and PD reduction, both with statistically significant positive adjunctive effects (Table 2). BOP was reduced by 50% and PD was reduced by 1.5mm compared with the control group. Regarding local plaque index score and the whole mouth plaque index score, both were reduced in the EMD and the Control group but without statistically significant difference between the two groups (p=0.33 and p=0.734 respectively) (Kashefimehr et al., 2017).

Microbiological and inflammatory results

The two included studies did not evaluate the same microbiological outcomes; therefore, the comparison is not possible. Nonetheless, the reduction of *P. gingivalis* counts was found significantly greater in the EMD group than the control group after 3 months (p=0.026) (Faramarzi et al., 2015). In addition, the reduction of Interleukin-6 (IL-6) and Interleukin-17 (IL-17) has also been observed significantly higher in the EMD group than in the control group (p=0.08 and p=0.002 respectively) (Kashefimehr et al., 2017)

II.2 Surgical Treatment results

Description of selected studies

Table 3 depicts the methodological characteristics of the selected studies. A total of five studies, two RCT and three prospective cohort studies, were selected for data extraction regarding the selection's criteria of this literature review. One RCT study, Isehed et al., 2018 is actually the follow up of the other study from the same group, Isehed et al., 2016, and one cohort study, Froum et al., 2015, is the continuity of the

previous cohort study, Froum et al., 2012 with the addition of 62 new patients. All studies included healthy subjects with peri-implantitis with PD ≥ 4mm. Smokers were included except in one cohort study (Mercado et al., 2018). In total, from the 159 patients included in those studies, 145 were treated with EMD and only 14 without EMD. The implants treated consisted of various types and specifications, knowing that most of them were titanium micro-rough surface implants from different manufacturers such as Biomet 3i, Nobel Biocare, Straumann, and AstraTech. Isehed et al., 2016; 2018, however did not give any information regarding the dental implants included.

The two RCT studies, Isehed et al., 2016; 2018 have compared the outcomes of peri-implant diseases treatment with and without EMD after the surgical debridement and surface decontamination of the affected sites at 1, 3 and 5 years.

The tree cohort studies, Froum et al., 2012; Froum et al., 2015 and Mercado et al., 2018, used EMD in peri-implant diseased sites. The follow-up of these studies varies between 2 and 10 years.

All studies have used a surgical debridement and surface decontamination of the affected implants, but it is important to note that the protocols used were very different. For example, the use of tetracycline and air-powder abrasive with sodium bicarbonate powder has been reported in two studies (Froum et al., 2012; Froum et al., 2015) and EDTA in on other one (Mercado et al., 2018). Besides, some studies used EMD with the addition of other regenerative material: xenograft and connective tissue graft (Froum et al., 2012; Froum et al., 2015 and Mercado et al., 2018) and platelets derived growth factor (Froum et al., 2012; Froum et al., 2015). Regarding maintenance care programs after treatment, all the studies focused on oral hygiene reinforcement and mechanical debridement with specific tools, including curettes, scalers and ultrasonic devices. However, in three studies, (Froum et al., 2012; Froum et al., 2015 and Mercado et al., 2018), additional surgical procedures, and systemic antibiotics, if required, were administered.

Due to the high heterogeneity within the studies, a meta-analysis was not feasible.

Clinical results

Out of a total of 215 implants treated with EMD in 145 patients, 2 were lost at 6 months post-surgery (Froum et al., 2015), 2 at 12 months (Isehed et al., 2016) and 2 at

5 years (Isehed et al., 2018), yielding a 97.67% survival rate. However, it should be noted that in the RCT study, Isehed et al. (2018), no statistically significant differences in survival rate were found between the EMD group (69%) and the control group (42%) (p=0.48).

The marginal bone level gain, radiographically calculated, was higher in the cohort studies using EMD in combination of xenogenic bone mineral craft (Froum et al., 2012; Froum et al., 2015; Mercado et al., 2018) with a mean of 2,38±0.92mm. In the RCT study using only EMD, Isehed et al., 2016 and Isehed et al., 2018, the mean bone level gain was 1.4mm at the end of the 5 years follow-up. Furthermore, the latter studies have shown no significant difference between surgical treatment with EMD (1.4mm) and without EMD (1.3mm) regarding this outcome (p=0.90).

Bleeding on probing was significantly reduced in the cohort studies (Froum et al., 2012; Froum et al., 2015 and Mercado et al., 2018) with a mean of 87.1% reduction. Isehed et al., 2018, find a BOP reduction of 44,4% in the EMD group and 60% in the non-EMD group at 5 years.

Similar results regarding PD reduction can be observed. A mean of 5,17±3.7mm reduction in the cohort study (Froum et al., 2012; Froum et al., 2015 and Mercado et al., 2018) and 2.8mm in the EMD-group in the RCT study (Isehed et al., 2016). In this last study, no statistically significant difference between the surgery with or without EMD has been found (p=0.270)

A soft tissue gain in Froum et al., 2012 and Froum et al., 2015 of 1,1±0.14mm and 0,52±1.44mm respectively has been measured, knowing that both studies have used connective tissue graft in addition of EMD. Without a connective tissue graft, Mercado et al., 2018 has seen no significant soft tissue gain at 5 years of follow-up (0.6mm; p>0.05).

Regarding the full mouth plaque score and the full mouth bleeding score, the RCT studies, Isehed et al., 2016, did not observe any significant difference between EMD and non-EMD group (p=0.297 and p=0.347 respectively)

Microbiological results

Only the RCT study Isehed et al., 2016 examined the biological impact of a surgical treatment of peri-implant diseases with EMD. The microbiota of the subgingival

biofilm was characterized by the HOMIN microarray (http://mim.forsyth.org/homim.html) which analyses the presence of more than 300 oral bacteria. This resulted in a decrease from 106 species/phylotypes to 94 species/phylotypes among the 2-week follow-up both in EMD and non-EMD group. However, at the 12-month follow-up, the numbers increased and reached pre-treatment levels. There was no significant difference between the two treatments at any follow-up occasion. However, the statistical tool partial least square (PLS) modelling identified a higher prevalence of Gram-positive/aerobic bacteria over the entire follow-up period in the EMD-treated patients in comparison with no EMD-treated patients.

III. DISCUSSION

III.1 Principal findings

The results of this systematic review, based on the data extraction of the 7 publications that corresponded to the selection's criteria, indicate a high variability in terms of treatment protocols, supportive care, follow-up and on how the outcomes were reported, therefore a meta‑analysis was not feasible. Moreover, no RCT studies included in the review are exempted of bias, so the results should be interpreted with caution. The scientific evidence regarding the clinical and microbiological performance of EMD in conjunction with non-surgical and surgical treatment of peri-implant diseases are promising but still limited.

Clinical outcomes

Regarding the non-surgical treatment of peri-implant mucositis or mild peri-implantitis with EMD, Kashefimehr et al. (2017), found that EMD combined with mechanical debridement significantly reduced PD (1.5mm) and BOP (-50%) after 3 months, while no significant improvement was obtained in areas treated with non-surgical treatment alone ($p<0.001$). Faramarzi et al. (2015), confirmed these results, however the improvement in clinical parameters was similar with the adjunctive use of EMD or MSM. Those findings are higher than the one observed by Sahm et al. (2011), who obtained a smaller PD reduction (0.6±0.6 and 0.5±0.6), 3 months after the mechanical treatment of mild to moderate PI by using only an air-abrasive device with amino acid

glycine powder or using carbon curettes and antiseptic therapy with chlorhexidine; and Renvert et al. (2009) in mild cases of PI with non-surgical debridement (titanium hand instruments or ultrasonic device) after 6 months (mean PD reduction of 0.2mm). It suggests that EMD, as an adjunctive to non-surgical treatment of peri-implant mucositis, has a positive effect on clinical outcome. Comparative studies with other adjuvant, other than MSM, would be interesting.

Regarding surgical treatment of peri-implantitis, in the RCT study included in this review, Isehed et al. (2018), 31% of implants treated with EMD and 58% treated without EMD were lost due to reinfection. No statistical difference was observed ($p=0.48$). These implants lost percentage seems very high compared with the one found in the cohort studies included in the present review (Froum et al. 2012; Froum et al. 2015; Mercado et al. 2018). Indeed, on the 200 implants treated with EMD, only 2 implants were lost at 6 months post-surgery (Froum et al., 2015) yielding a percentage of 0.01. However, using the statistical tool PLS modelling, Isehed et al. (2018), found that adjunctive EMD was associated with implant survival, BOP and PD reduction.

We can observe the same disparity between RCT studies and cohort studies regarding other clinical outcomes. Froum et al. (2012; 2015) and Mercado et al. (2018) reported a higher mean marginal bone level gain (1.77±1.99mm and 4.6±0.73mm, respectively), PD reduction (4.6±0.73mm; 5.1±2.2mm) and BOP reduction (73.3% and 91.10%) while Isehed et al. (2016; 2018) observed a smaller mean marginal bone level gain (0.9mm and 1.4mm), PD reduction (2.8mm) and BOP reduction (30% and 44.4%).

An explanation for these different results may have been the surface decontamination protocol used to treat peri-implantitis. Indeed, Froum et al. (2012; 2015) used, in addition do manual curettes, air-powder abrasive and topic Minocycline and Tetracycline. Marcado et al. (2018) preferred ultrasonic instrumentation and EDTA whereas Isehed et al. (2016; 2018), in their RCT studies, used only ultrasonic instrumentation. Based on previous reviews, (Heitz-Mayfield et al., 2014; Suarez et al., 2013; Valderama et al. 2013), no decontamination protocol seems to be more effective than others and so cannot explain the heterogeneity of clinical outcome observed in this systematic review.

To promote wound healing and regenerative tissue, Froum et al. (2012, 2015), in their cohort studies, combined EMD with bone graft and platelet-derived growth factor-BB

(PDGF-BB) whereas Mercado et al. (2018) used combined osteoconductive deproteinized bovine bone mineral with 10% collagen (DBBMC) and Doxycycline. The purpose of using a bone graft is to fill the intrabony defect around the implant with peri-implantitis. A recent meta-analysis about the efficacy of reconstructive surgical therapy of peri-implantitis, written by Tomasi et al. (2019), shows a mean PD reduction of 2.8mm at 12 months, based on 13 studies. Nonetheless, in the cohort studies included in this review, PD reduction was between 5.1±2.2mm and 5.4±0.5mm. This difference could be explained by the ability of PDGF-BB to improve bone fill in periodontitis treatment (Khoshkam et al., 2015; Nevins et al., 2005) as well as EMD capacity to stimulate proliferation and differentiation of osteoblasts (Li et al., 2017; Schwartz et al., 2000) and wound healing (Miron et al., 2015). The differences in clinical outcomes between the cohort studies (Froum et al., 2012; Froum et al., 2015; Mercado et al., 2018) and the RCT studies by Isehed et al. (2016; 2018), who used only EMD without any grafting material, may suggest that EMD alone has less capacity to improve surgical treatment of peri-implantitis than when combined with other bone filling adjunctive material. Moreover, Isehed et al. (2016, 2018) was not able to present any statistically significant difference of marginal bone level gain and PD reduction between the group treated with EMD alone and the control group at the end of follow-up time.

The type and frequency of supportive care after treatment may be as well, a factor of the results heterogeneity. In fact, Froum et al. (2012; 2015) and Mercado et al. (2018), in their cohort studies, enrolled patients in supportive periodontal treatment every week to every 6 months with the possibility of additional surgical procedure if required. Mercado et al. (2018) observed a BOP recurrence in 50% of treated implants at 12-month follow-up without peri-implant maintenance for 6 months. This percentage dropped at 20% after resuming a supportive treatment protocol. We might suspect that the different supportive therapy used in the studies included in this review had an impact on their long-term clinical outcomes.

Microbiological and inflammatory outcomes

As in periodontal diseases, biofilm is the main etiologic factor of peri-implant diseases (Mombelli et al., 1987). In 2014, Persson and Renvert compared the biofilm of healthy

implant sites and peri‑implantitis sites and found it was associated with higher counts of 19 bacterial species, including *Porphyromonas gingivalis* (Persson & Renvert, 2014). *P. gingivalis* is an anaerobic Gram-/negative anaerobic bacteria species with different virulence factors which can invade host cells, induces an inflammatory response and destruction of extracellular matrix and bone and induce peri-implantitis (Holt et al., 1999). The main outcome of one study included in this systematic review, Faramarzi et al. (2015), was changes in the counts of *P. gingivalis*. It showed a decrease of these bacteria after treatment, with a higher reduction on the EMD group than the control group at two-week and three-month intervals. The inhibitory effect of EMD on the growth of Gram-/negative periodontal pathogens such as *P. gingivalis* (Spahr et al., 2002) could explain this result. But it should be added that Faramarzi et al. (2015), have observed the same decrease with the use of MSM, which is consistent with a previous study (Renvert et al., 2006). In the RCT study, Isehed et al. (2016) observed a microbiological difference between the EMD group and the control group, 2 weeks and 3 months after treatment, however, at 12-month follow-up this difference was not relevant. Nevertheless, with the use of statistical tool PLS modelling, microbiota from EMD-treated implants were statistically associated with more Gram+/positive bacteria over the follow-up period, whereas no EMD-treated microbiota was characterized by more Gram-/negative bacteria commonly found in peri-implantitis. More Gram+/positive were statically associated with higher diminution of BOP and PD, even though it was not observed clinically. The author suspects that all these findings emphasize the important role of using an antibacterial adjuvant for both surgical and non-surgical treatment of peri-implant diseases.

In the RCT study, Kashefimehr et al. (2017), emphasize the significantly decreased amount of IL-6 and IL-17 in the EMD group as compared to the control group. IL-6 is an interleukin which plays a role in the immune response and stimulates Th17 cells to produce IL-17 leading to activation of osteoclasts and bone loss along with IL-1β and TNF-α (Koh et al., 2007). Based on a meta‑analysis, the release of IL‑1β was reported to be significantly increased at mucositis and peri‑implantitis sites, when compared with healthy implant sites (Faot et al., 2015). The decreased amount of IL-6 and IL-17 suggest that EMD may play a role in controlling the inflammatory state of peri-implant

disease areas, helping reduce BOP and PD, by diminishing pro-inflammatory cytokines and regulating the immune system.

III.2 Confounding factors

Local factors may influence the outcome of peri‑implant diseases treatment: implant placement/positioning; prosthesis design; presence of keratinized mucosa; implant surface and design; osteo defect configurations.

It has been previously demonstrated that inadequate access for oral hygiene due to prosthesis design/contours was related to the presence of peri-implantitis (de Tapia et al., 2019). It is also important to consider access for adequate local plaque control after the peri‑implantitis has been treated, which highlights the importance of supportive care. The studies included in this review present a heterogeneity regarding the prosthesis supported by the implant, like crowns, bridges and overdentures and placement/positioning which could have an impact of clinical outcome after treatment as well as clinical registration of PD. In addition, the sensitivity and standardization of assessing bone gain from radiographs might not be optimal. Inherent measurement variability in the radiographs should be considered. Furthermore, in three studies included in this review, Froum et al., 2012; Froum et al., 2015 and Mercado et al., 2018, was performed as a connective tissue graft, if needed, to maximize the amount of keratinised tissue. The absence of an adequate band of keratinized peri‑implant mucosa has been suggested to have a negative influence on treatment outcomes due to discomfort when performing oral hygiene resulting in increased plaque accumulation (Roccuzzo et al., 2016). The studies present in this review included a variety of implant designs and surfaces and it has been previously reported that it can influence the outcomes of surgical therapy of peri-implantitis (Carcuac et al., 2017; Roccuzzo et al., 2017).

Another factor that influences treatment outcomes is the severity of bone loss and defect configuration. In this review, Faramazi et al. (2015) and Kashefimehr et al. (2016) reported a bone loss of less or equal to 2mm at baseline before treatment; a mean of 5.1mm±1.1mm and 3.8mm±2.28mm in Froum et al (2011; 2015); 5.6mm in Isehed et al. (2016; 2018) and 6.92mm±1.26mm for Mercado et al. (2018) demonstrating a high heterogeneity of defect configuration. Initial bone loss and

different defect configurations that may increase the difficulty of an adequate debridement, which in turn, has been suggested to influence the healing (Roccuzo et al., 2016; Schwarz et al., 2010)

III.3 Limitations of the review

The low number of RCT currently available, small subject number; high or unclear risk of bias in most of the included studies; heterogeneity in methodologies and treatment modalities among studies and wide variation in terms of follow-up periods. Finally, no study compared the impact of EMD alone combined with non-surgical debridement to treat moderate or severe peri-implantitis.

IV. CONCLUSION

Based on studies with a rather limited statistical power, the present systematic review suggests that:

- EMD has a positive effect on clinical outcome of non-surgical treatment of peri-implant mucositis.
- EMD combined with grafting materials seems to improve bone fill after surgical treatment of peri-implantitis.
- There is still a lack of evidence regarding the effects of EMD alone in the clinical outcome of peri-implantitis treatment.
- EMD has a positive effect on the diminution in the counts of *P. gingivalis* and the inflammation state of peri-implant mucositis sites.

Furthermore, better designed randomized clinical trials are needed to clearly demonstrate and understand the potential role of EMD on the outcomes of non-surgical and surgical treatment of peri-implant diseases.

V. BIBLIOGRAPHY

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Figure 1. Flowchart of the bibliography research methodology

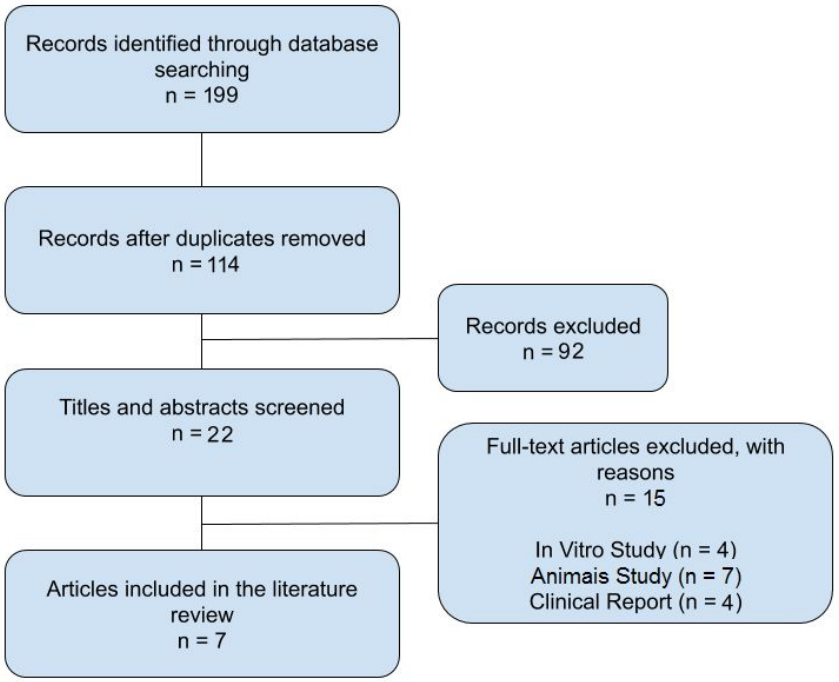

Table 1. Risk of bias assessment of the included studies

	Faramarzi. et al. (2015)	Kashefimehr et al. (2017)	Isehed et al. (2016)	Isehed et al. (2018) Continuity of: Isehed et al. (2016)
Random sequence generation	Low risk	Unclear risk	Low risk	Low risk
Allocation concealment	Unclear risk	High risk	Unclear risk	Unclear risk
Blinding of participants and personnel	Low risk	High risk	Unclear risk	Unclear risk
Blinding of outcome assessment	Low risk	Unclear risk	Low risk	Unclear risk
Incomplete outcome data	Unclear risk	Unclear risk	Low risk	Unlear risck
Selective reporting	Low risk	Low risk	Unclear risk	Unclear risk

TABLE 2 Table with the comparison of Non-Surgical treatment studies selected

Study Details								Clinical Results				Biological Results		
Study	**Study Design**	**Population**	**Inclusion criteria**	**Exclusion Criteria**	**Treatment**	**Supportive care**	**Follow-up**		**BOP reduction (%) (p Value)**	**PD reduction (mm) (p Value)**	**Local plaque index reduction (%)**	**Whole mouth plaque index reduction (%)**	**P. gingivalis reduction counts (%) (p Value)**	**Interleukin-6 reduction (%) (p Value)**	**Interleukin-17 reduction (%) (p Value)**
Faramarzi et al. (2015)	Randomized clinical trial	Pacients: n = 64 F 31, M 33 Mean age: 47.9±1.77 yr Control group: n = 21 F 10, M 11 Implants: n = NR EMD group: n = 20 F 10, M 10 Implants: n = NR MSM group: n = 23 F 11, M 12 Implants: n = NR	Adults ≥ 18 years Implant functional for at least one year Peri-implant mucositis and\or mild peri-implantitis: BOP No soft tissue recession With or without minimal radiographic bone loss (≤2 mm) PD≥4 mm in at least one site	Smoking Pregnancy and lactation Drug and alcohol addiction Poorly uncontrolled diabetes or debilitating systemic disease Use of systemic or local antibiotics in the past 3 months Regular intake of anti-inflammatory drugs in the past three months Allergies to tetracycline-class drugs Any intervention for treatment of peri-implant inflammation in the past three months Poor oral hygiene Severe periodontal disease	Pretreatment phase: Home hygiene oral instruction Non chirurgical mechanical debridement: US + GAP + antiseptic therapy EMD group: EMD (1mg) in affected sites MSM group: MSM (1mg) in affected sites	NR	2 weeks 3 months	Control group EMD group MSM group	20 (= 0.109) 50 (<0.001) 60 (<0.001)	0 (= 0.098) 1.5 (<0.001) 2 (<0.001)	NA NA NA	NA NA NA	5.3 (<0.001) 100 (= 0.041) 81.7 (<0.001)	NA NA NA	NA NA NA
Kashefimehr et al. (2017)	Randomized clinical trial	Pacients: n = 41 F 20, M 21 Mean age: 47.7±2.19 yr Control group: n = 21 F 10, M 11 Implants: n = 21 EMD group: n = 20 F 10, M 10 Implants: n = 20	Adults ≥ 18 years Implant functional for at least one year Peri-implant mucositis and\or mild peri-implantitis: BOP No soft tissue recession With or without minimal radiographic bone loss (≤2 mm) PD≥4 mm in at least one site"	Smoking Pregnancy and lactation Drug and alcohol addiction Uncontrolled systemic disease or infectious diseases Undergoing radiotherapy in the head or neck area Any intervention for treatment of peri-implant inflammation in the past 3 months Untreate/active periodontal lesions Antibiotics during the past 3 months Medication affecting periodontal tissu condition PD ≥ 6 mm at the baseline examination	Pretreatment phase: Full-mouth debridment + Home hygiene oral instruction Non chirurgical mechanical debridement: US + GAP EMD group: EDTA + EMD 2 weeks after mechanical debridment	Description: NR Frequency: 3 months Adjunctive treatment: Surgical interventions if needed	3 months	Control group EMD group	0 (=0.109) 50 (< 0.0001)	0 (=0.098) 1.5 (< 0.0001)	25 (< 0.0001) 25 (< 0.0001)	5 (= 0.848) 13.5 (< 0.0001)	NA NA	24 (= 0.028) 52 (< 0.0001)	18.6 (= 0.264) 61.3 (< 0.0001)

PD: probing depth; BOP: bleeding on probing; NR: not reported; NA: not assassed
EDTA: ethylenediamine tetra - acetate; GAP: glycine-based powder air-polishing; MSM: micro-spherical minocycline

TABLE 3 Table with the comparison of Surgical treatment studies selected

Study Details								Clinical Results							Biological Results	
Study	**Study Design**	**Population**	**Inclusion criteria**	**Exclusion Criteria**	**Treatment**	**Supportive care**	**Follow-up**		**Implants lost**	**Marginal bone level gain (mm) (*p* Value)**	**PD reduction (mm)**	**BOP reduction (%)**	**Soft tissue gain (mm)**	**Full mouth plaque score (%)**	**Full mouth bleeding score (%)**	**HOMIM**	**Microbiote characterization**
Froum et al. (2012)	Cohort Study	Pacients: n = 38 F 20, M 18 Mean age: 58 yr Smokers: n = NR Implants: n = 51	BOP PD ≥ 6 mm BL ≥ 4 mm	Uncontrolled diabetes mellitus Osteoporosis Bisphosphonate therapy Chemotherapy radiation therapy Implants with ≥ 80% bone loss, pain, or mobility	Pretreatment phase: Full-mouth debridment and instructions in oral hygiene Surgical debridement Surface decontamination: Curettes + APB + STS + TET + CHX Regenerative: EMD + XBM + PDGF + CTG (if KT <2 mm) + CM Systemic antibiotics for 10 days: Amoxicillin or Clindamycin	Description: Surface debridment and oral hygiene homecare procedures Frequency: every week during 6 weeks every 6 - 8 weeks Adjunctive treatment: Additional surgical procedure if required Implants: n = 2	3 - 7.5 years mean: 3.70 yr	EMD	0	3.28 ± 0.37	5.2 ± 0.14	82,3%	1.1 ± 0.15	NA	NA	NA	NA
Froum et al. (2015) Continuity of: Froum et al. (2012)	Cohort Study	Pacients: n = 100 F 53, M 47 Mean age: 58.08 yr Smokers: n = 19 Implants: n = 170	BOP PD ≥5 mm BL ≥ 3 mm	Uncontrolled diabetes mellitus Osteoporosis Bisphosphonate therapy Chemotherapy radiation therapy	Pretreatment phase: Full-mouth debridment and instructions in oral hygiene Surgical debridement Surface decontamination: Curettes + APB + STS + MIN + CHX Regenerative: EMD or PDGF + XBM + CTG (if KT <2 mm) + CM	Description: NR Frequency: every 2 – 3 month Adjunctive treatment: Additional surgical procedure if required Implants: n = 28	2 - 10 years mean: 3.60 yr	EMD	2	1.77 ± 1.99	5.10 ± 2.20	91.1%	0.52 ± 1.44	NA	NA	NA	NA
Isehed et al. (2016)	Randomized clinical trial	Pacients: n = 29 Drop-out: n = 1 Smokers: n = 10 No EMD group: n = 14 F 9, M 5 Drop-out: n = 0 Implants: n = 14 EMD group: n = 15 F 9, M 6 Drop-out: n = 1 Implants: n = 15	BOP, PD ≥ 5 mm, BL ≥ 3 mm	Uncontrolled diabetes mellitus Intake of antibiotics or antiinflammatory medication during the past 3 months Using drugs with gingival hyperplasia as a known side effect.	Pretreatment phase: Full-mouth debridment and instructions in oral hygiene Surgical debridement Surface decontamination: US + STS EMD group: 0.3 ml EMD applied on the implant from the bottom of the bone defect	Description: NR Frequency: every 3 mouths	12 months	No EMD group	1	-0.1	3	30%	NA	0	11	The total numbers of species/phylotypes did not differ significantly by treatment at any follow-up occasion	Gram-/anaerobic
								EMD group	2	0.9 (0.295)	2.8 (0.270)	30%	NA	3 (0.297)	10 (0.347)		Gram+/aerobic
Isehed et al. (2018) Continuity of: Isehed et al. (2016)	Randomized clinical trial follow-up	Pacients: n = 25 Drop-out: n = 3 Smokers: n = 7 No EMD group: n = 13 Drop-out: n = 2 Implants: n = 13 EMD group: n = 12 Drop-out: n = 1 Implants: n = 12				Description: NR Frequency: every 3 - 6 mouths	1 - 3 - 5 years	No EMD group	6	1.3 (0.043)	NA	60%	NA	0	NA	NA	NA
								EMD group	2	1.4 (0.051)	NA	44,4%	NA	28.6	NA	NA	NA
Mercado et al. (2018)	Cohort Study	Patients: n = 30 F 19, M 11 Mean age: 44.9±11 yr Smokers: n = 0 Implants: n = 30 mean age: 9±3.8	BOP BL > 20%, PD > 4 mm, Implants >2 yrs in function FMBS < 20 %	Uncontrolled diabetes mellitus Pregnant/lactating Bisphosphonate therapy >2 implants with PI Untreated periodontal disease Smoking	Pretreatment phase: Full - mouth ultrasonic debridement and manual curettage Surgical debridment Surface decontamination: US + EDTA + STS Regenerative: XBM + 0.35 ml EMD + DOX mix + CTG if needed	Description: Full-mouth debridment Implant debridement if needed Frequency: 1 - 3 weeks, 3 - 6 months every 4 moutsh	5 years	EMD	0	4.3 ± 0.73 (<0.01)	5.4 ± 0.5 (<0.01)	80%	0.6 (>0.05)	< 20	< 20	NA	NA

BL: bone loss; PD: probing depth; BOP: bleeding on probing; NR: not reported; NA: not assassed
APB: air - powder abrasive with sodium bicarbonate powder; CHX: chlorhexidine; CM: collagen membrane; CTG: connective tissue graft; DOX: doxycycline; EDTA: ethylenediamine tetra - acetate; KT: keratinized tissue; MIN: minocycline; PTGF: platelets derived growth factor; STS: Steril saline; TET: tetracycline; US: Ultrasonic instrumentation; XBM: xenogenic bone mineral