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The use of omega-3 fatty acids in the treatment of oral diseases

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Abstract

Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) have been reported to exert important roles in the inflammatory response. There are many inflammatory diseases in dentistry which support the administration of ω-3 PUFAs as an adjunct therapy during the treatment of these diseases. The aim of this review was to evaluate the use of ω-3 PUFAs as an adjuvant therapy during the treatment of buccal diseases. The review showed that supplementation with ω-3 PUFAs was used for treatment of gingivitis, periodontal diseases, apical periodontitis, stomatitis and orthodontic tooth movement. The results indicate that ω-3 PUFAs decreased the number of pro-inflammatory mediators in the gingival tissues of individuals with gingivitis and periodontitis. In apical periodontitis, the supplementation suppressed bone resorption and promoted bone formation in the periapical area of rats. During orthodontic movement, the supplementation showed a decrease of bone resorption in rats. It also showed that painful symptoms of recurrent aphthous stomatitis were alleviated in supplemented patients. In conclusion, the ω-3 PUFAs may be used as an adjuvant therapy in the treatment of inflammatory diseases that affect the oral cavity. However, more studies are required to elucidate the role of ω-3 PUFAs in decreasing oral cavity inflammatory processes.

1 INTRODUCTION

Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) have been reported to exert important roles in the inflammatory response (Vardar et al., 2004). The major ω-3 PUFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both being able of competitively inhibiting the production of arachidonic acid metabolites via the cyclo-oxygenase and lypoxigenase pathways, thus reducing the pro-inflammatory arachidonic mediators (Calder, 2006). DHA has demonstrated anti-inflammatory effects by interference with interleukin-1 signaling pathways leading to cyclooxygenase-2 induction in endothelial cells (Massaro et al., 2006). In addition, EPA lowers the level of arachidonic acid available for metabolism and competes against arachidonic acid for metabolism to form metabolites of leukotrienes and prostaglandins, decreasing the inflammatory response (Mukaro et al., 2008).

As a consequence of possessing anti-inflammatory properties, ω-3 PUFAs has been accepted as an adjunct therapy in the treatment of chronic inflammatory diseases, such as: rheumatoid arthritis (Akbar, Yang, Kurian, & Mohan, 2017), cardiovascular disease (Schunck, Konkel, Fischer, & Weylandt, 2018), diabetes (Elwakeel & Hazaa, 2015; Cadario et al., 2018) and chronic kidney disease to reduce potential cardiovascular risk (Pluta et al., 2017; Hu et al., 2017). In addition, ω-3 PUFAs and lipid mediators derived from ω-3 PUFAs have been proven to participate in the regulation of bone metabolism (Hogstrom, Nordstrom, & Nordstrom, 2007; Maggio et al., 2009).

There are many inflammatory diseases in dentistry, e.g. periodontal diseases, apical periodontitis, and stomatitis, with immune inflammatory responses induced by mediators such as arachidonic acid metabolites, cytokines, enzymes, and lipopolysaccharides (LPS), which support the administration of ω-3 PUFAs as an adjunct therapy during the treatment of these diseases. Therefore, this review was intended to evaluate the use of ω-3 PUFAs as an adjuvant therapy during the treatment of oral diseases, which could help clinicians in the control of the inflammatory process and the patients in the post treatment symptoms.

2 OBJECTIVES

The aim of this review was to evaluate the anti-inflammatory ability of the ω-3 PUFAs as a supplementary therapy of dental diseases, considering pro-inflammatory mediators, bone resorption and inflammatory cells.

3 MATERIAL AND METHODS

This literature review followed the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2015) and it was registered in the International Systematic review registry (PROSPERO; CRD134254).

The search was performed in May 2018 by two reviewers (MMA and CBMC) using the PubMed, Web of Science, Scopus and Portal Periodicos CAPES databases. These following combinations were used on the databases search (MeSH terms): "apical periodontitis"; "periapical lesions"; "periradicular lesions"; "endodontic infection"; "periodontal disease"; "orthodontic"; "surgery"; "dentistry" combined with "omega-3 fatty acids"; "fish oil"; "docosahexaenoic acid" or "eicosapentaenoic acid". The articles selected were exclusively published in the English language. In addition, a hand search of the literature list was performed.

The structure of the clinical question was according to the PICO method (population, interventions, comparison, and outcome): Is the ω-3 PUFAs able to reduce the inflammation when used as an adjunct on dental therapy? The Population of the study was patients and animals that had to be submitted to dental procedures because of inflammatory diseases. The intervention was the supplementation of ω-3 PUFAs topically or systemically associated with oral intervention; Comparison was made with patients that did not receive the ω-3 PUFAs as an adjunct treatment. Thus, the only studies that were selected were those with humans or animals that had the ω-3 PUFAs used as a supplementary therapy on dental procedures, being these papers published in the English language. The patients that received just the dental treatment were utilized as a comparison and the outcome searched was the improvement of the inflammatory conditions of the subjects that had the ω-3 PUFAs administered compared with those that received just the dental assistance.

The inclusion criteria were as follows: Articles that analyzed the use of ω-3 PUFAs as a potential anti-inflammatory supplement in rats or in humans and studies published in English that compared patients that received ω-3 PUFAs as a treatment after their oral intervention topically or systemic with patients that received a placebo treatment. Retrospective studies, in vitro studies, computational studies, and case series were excluded from the review. As exclusion criteria we had papers not published in English and studies that did not have a comparison between a ω-3 PUFAs supplemented group to groups that received just dental procedure.

The established criteria enabled the selection of articles by titles that had the abstracts read. If they did not fit the systematic review, they were excluded. The remaining studies were full read and reviewed by two reviewers (MMA and CBMC) that independently evaluated titles and abstracts from the electronic search and assessed them regarding the exclusion criteria applied. Communications were excluded: when they were not related to the application of omega-3 polyunsaturated fatty acids in dentistry; when there was not a full manuscript involved, or when the concentrations of EPA and DHA dietary per day were not specified or standardized. Any title included by either reviewer was submitted to a second screening step, the full-text evaluation. Disagreement arising between reviewers was solved by discussion mediated by an experienced referee (LTAC).

3.1 Data Analysis and Additional analysis

The level of inter-examiner agreement about the titles and abstracts retrieved from the databases were determined by the application of the Kappa test. Additional analysis was performed using Kappa scores to calculate inter-reader agreement during the inclusion process for publications retrieved from the databases. In this study the kappa test was of 90,91%, (p=0,909091), with three disagreements between the investigators.

3.2 Risk of bias in individual studies

The Cochrane risk of bias tool was used to determine the risk of bias of the chosen papers (Higgins, 2009). In this tool, the aspects of bias risk are evaluated individually without assigning scores and are divided into six domains: random

sequence generation, allocation concealment, blinding of outcome assessors, blinding of participants and personnel, incomplete outcome data, and selective outcome reporting. Comprising the assessment of selection, performance, attrition, reporting, and detection bias. Each domain is classified as having a low risk, unclear risk, or high risk of bias (Landis & Koch, 1977).

4 RESULTS

4.1 Search Strategy

Fig. 1 Details the flow of the search strategy. A total of 49 articles were identified, of which 17 were replicated studies and were removed, leaving 32 articles. The abstracts of all remaining articles were screened, and 11 articles were excluded because they did not meet the search criteria and were not related to the aim of the review. The remaining 21 articles were read in full, and 6 of them were excluded because the concentrations of EPA and DHA dietary per day were not specified or standardized.

Of the final 15 articles, 8 involved the supplementation with ω-3 PUFAs in the presence of periodontitis, 2 involved the supplementation with ω-3 PUFAs in the presence of gingivitis, 3 articles involved the supplementation with ω-3 PUFAs in the presence of periapical periodontitis, 2 articles involved the supplementation with ω-3 PUFAs in the presence of recurrent aphthous stomatitis, and 1 article involved the supplementation with ω-3 PUFAs in the presence of orthodontic movement.

The study design of all articles were appropriate and showed appropriate samples regarding the source, size, methods, and inclusion and exclusion criteria. All studies have an acceptable control group, which allows comparing the effect of Omega 3 treatment between the groups. The studies included according to PICOS scheme can be found in Table 1. Moreover, the risk of bias is reported in Table 2 and demonstrated that all studies have no serious confounding factors neither distorting influences or erroneous bias, which could decrease the reliably of this study.

4.2 Omega-3 polyunsaturated fatty acids and periodontitis

The majority of the publications in the literature reporting the use of ω-3 PUFAs in dentistry investigate individuals with periodontitis - a chronic immunoinflammatory disease with progressive loss of attachment of gingival tissues leading to the destruction of the periodontal ligament and adjacent supporting alveolar bone (Kesavalu et al., 2006).

The inflammatory response of rats with periodontal disease induced by LPS derived from *Escherichia coli* was evaluated comparing rats that had supplementation with ω-3 PUFAs and rats that did not have supplementation with ω-3 PUFAs. Although there is no statistically significant differences between the groups regarding the alveolar bone loss (Vardar et al., 2005; Vardar-Sengül et al., 2006), the supplementation with ω-3 PUFAs reduced the levels of prostaglandin E2, prostaglandin F2α and leukotriene B4 in gingiva (Vardar et al., 2003; Vardar et al., 2005), suggesting that ω-3 PUFAs could have an influence in bone metabolism, even though the mechanism through which ω-3 PUFAs influence the bone remodeling is unclear. On the other hand, a study performed in rats using *Porphyromonas gingivalis* to induce periodontal disease showed that animals that were treated with ω-3 PUFAs had significantly less alveolar bone resorption when compared with rats without dietaryω-3 PUFAs (Kesavalu et al., 2006), demonstrating the action of ω-3 PUFAs in the bone metabolism. One hypothesis is that ω-3 PUFAs could have enhanced the calcium absorption (Haag & Kruger, 2001; Kesavalu et al., 2007; Shanfeld, Jones, Laster, & Davidovich, 1986), which is favorable for the bone formation. A study using the same animal model found that the die with ω-3 PUFAs has pro-inflammatory effects in regulating tissue responses to *Escherichia coli* infections, increasing pro-inflammatory gene expression mediators such as IL-1β and TNF-α. The increased of serum IL-1β levels antagonize the induction of osteocalcin synthesis. When the IL-1β is increased, the bone reabsorption level is potentialized, because IL-1β can counteract any osteoblastic induction by osteocalcin through promotion of osteoclast activity (Vardar- Sengül et al., 2006). Moreover, the authors concluded that the diet with ω-3 PUFAs could be a suitable nutritional prevention and/or intervention strategy in treating chronic immunoinflammatory lesions, such as periodontitis (Kesavalu et al., 2007). Also, another study using rats with periodontal disease induced by LPS, evaluated the prophylactic diet (14 days before periodontal

disease induction) and therapeutic diet (14 days after periodontal disease induction) of ω-3 PUFAs in the matrix metalloproteinases (MMPs) (Vardar-Sengül et al., 2008). The results showed that the prophylactic diet with ω-3 PUFAs may inhibit MMP-8 in gingival tissues, but not MMP-13 and MMP-14. All these MMPs are important molecules that act in the extracellular matrix degradation during periodontal diseases. The therapeutic diet with ω-3 PUFAs may increase gingival tissue inhibitor of MMPs-1 (TIMP1) expression (Vardar-Sengül et al., 2008). It is important to know that an imbalance between MMPs and TIMPs results in periodontal tissues destruction (Pozo et al., 2005). Another study using mice evaluated the influence of the diet with fish oil (tuna oil), which contains ω-3 PUFAs in the alveolar bone loss of rats with periodontal disease induced by periodontopathic bacteria. The results showed that all mice with periodontitis that had diets with ω-3 PUFAs showed a lower alveolar bone loss when compared to mice that did not receive the same diets (Bendyk, Marino, Zilm, Howe, & Bartold, 2009).

In animal models, the rats infected with *Escherichia coli* were treated orally by the gavage method with the ω-3 PUFAs (40 mg/kg; 60% EPA and 40% DHA) for 14 days (Vardar et al., 2005). Those animals that received the combined treatment with ω-3 PUFAs prophylactic supplementation did not present any reduction of the bone resorption, as well as, the animals that did not receive any kind of supplementary treatment (Vardar-Sengül et al., 2006). However, the studies using *Porphyromonas gingivalis* to infect the rats and that had the fish oil added to their food (Kesavalu et al., 2006, Bendyk et al., 2009) (24.6% of ω-3 PUFAs and 35%) for 8 weeks had lower alveolar bone loss. The authors (Kesavalu et al., 2007) used the same model of study (Kesavalu et al., 2006) during 22 weeks and obtained expressive results in the reduction of alveolar bone resorption. Contrary to the different results reported regarding the action of ω-3 PUFAs in the decrease of alveolar bone resorption, all studies evaluated showed an effective anti-inflammatory action in the periodontal disease of rats treated with ω-3 PUFAs at different doses and periods. Studies have shown that anti-inflammatory action of the ω-3 PUFAs requires a minimum application period of 14 days and that prophylactic supplementation for the same period increases EPA and DHA levels in the cell membrane, making it stronger and more difficult to undergo lysis (Yüceyar et al., 1999; Browning et al., 2012). An important finding is that the studies pointed out that the effect on bone metabolism were best observed in prolonged ω-3

PUFAs administration (Martin-Bautista et al., 2010; Kruger, Coetzer, de Winter, Gericke, & Van Papendorp, 1998), corroborating to the findings of this review (Kesavalu et al., 2006; Kesavalu et al., 2007; Bendyk et al., 2009). The action of the ω-3 PUFAs can inhibit the differentiation, activation and function of the osteoclasts, reducing the levels of RANKL induced by pro-inflammatory cytokines (Rahman, Bhattacharya, & Fernandes, 2008), leading to a suppression of inflammatory cytokines, activation of NF-κB, which results in less bone resorption (Sun et al., 2003). Besides, it inhibits LPS induced NF-κB activation in a macrophage cell line (Camandola et al., 1996).

Three studies evaluated the diet with ω-3 PUFAs in human periodontal health. A randomized clinical study evaluated the effect of ω-3 PUFAs on clinical outcome during the periodontal treatment. Both, the test and the placebo groups were treated with non-surgical periodontal treatments. The results showed that the supplementation with 1 g of ω-3 PUFAs (180 mg EPA; 120 mg DHA - 3 capsules per day for 4 months) did not influence the clinical outcomes. But, it showed lower levels of glucose and high-density lipoproteins after periodontal therapy (Martinez et al., 2014). Another clinical trial evaluated the impact of ω-3 PUFAs (300 mg; 180 mg EPA; 120 mg DHA - 1 capsules per day for 12 weeks) in conjunction with scaling and root planning on salivary markers in patients with chronic periodontitis. For this, the control group was treated with scaling and root planning and received a placebo, while the treatment group was treated with scaling and root planning and received ω-3 PUFAs. The results from this study demonstrated that dietary supplementation with low-dose of ω-3 PUFAs improved the salivary TNF- α without any significant impact on clinical parameters in patients with chronic periodontitis. According to the authors, those results suggest that the systemic benefits of dietary with ω-3 PUFAs may not be identified as periodontal health (Deore et al., 2014). On the other hand, a randomized, double-blinded, placebo-controlled, clinical trial evaluated the effect of low-dose ω-3 PUFAs supplementation (6,25 mg EPA; 19,19 mg DHA - 1 time per day during 6 months) in patients with chronic periodontitis. For this, the control group was treated with scaling and root planning and given a placebo, while the treatment group was treated with scaling and root planning and given ω-3 PUFAs. The results showed that the supplementation with ω-3 PUFAs reduced gingival inflammation, pocket depth, and attachment level gain, showing beneficial effects as an alternative adjunct therapy, complementing the local treatment

of periodontal diseases (Keskiner, Saygun, Bal, Serdar, & Kantarci, 2017). Only one of the studies that evaluated the effects of ω-3 PUFAs in humans showed better clinical outcomes. The results showed that the supplementation with ω-3 PUFAs for 6 months may reduce gingival inflammation, pocket depth, and attachment level gain. A dosage of 3.1–8.4 g per day of the EPA and DHA may reduce levels of reactive oxygen species in stimulated human neutrophils (Luostarinem & Saldeen, 1996) and monocytes (Fisher et al., 1990). Other clinical trials that had ω-3 PUFAs supplemented for less than 6 months did not find any difference in the results (Geelen et al., 2004). Additional, studies have shown that small doses of ω-3 PUFAs do not have an impact on monocyte chemotaxis, and also, they do not have an impact on the generation of leukotriene B4, prostaglandin E2 and TNF-α (Murphy et al., 2006; Schmidt et al., 1996) from activated monocytes. The differences between researchers could be a result of ω-3 PUFAs being synthetized in different laboratories, also, the period of dietary supplementation and the number of patients were different. Moreover, the control of the dietary supplementation might have been different. According to the results, it is important to perform other studies to evaluate the ω-3 PUFAs supplementation benefits during the periodontal treatment in humans standardizing the models, procedures and specially the ω-3 PUFAs supplementation.

4.3 Omega-3 polyunsaturated fatty acids and gingivitis

Gingivitis is a common periodontal disease caused by an interaction between host immune responses and biofilm of pathogenic microorganisms in dental plaque (Kantarci, Hasturk, & Van Dyke, 2006). The first report relating the supplementation with ω-3 PUFAs and gingivitis compared the levels of leukotrienes and prostaglandins in the gingival tissue of humans with gingivitis supplemented with ω-3 PUFAs, and humans with gingivitis without supplementation. The studies had the clinical aspects evaluated by the authors. Although there were no statistically significant differences among the groups, the authors concluded that ω-3 PUFAs revealed a predisposition towards the reduction of inflammation (Campan, Planchand, & Duran, 1997), lowering gingivitis index (Rosenstein, Kushner, Kramer, & Kazandjian, 2003) and concluded suggesting other studies. The high daily dose of ω-3 PUFAs (1.8 g - 3 capsules per day) associated with short period of administration (8 days) may explain the decrease of

inflammatory activity in the gingiva in the groups receiving the treatment. According to some authors, in situ integration of ω-3 PUFAs is probably not yet complete after only 8 days of treatment (Campan et al., 1997). Afterwards, another study was performed to evaluate the ω-3 PUFAs on immune system regulation, measuring the levels of TNF-α and IL-1β in rats (Araghizadeh et al., 2014). Besides the immune system, the efficacy of prophylactic and/or therapeutic doses of ω-3 PUFAs (60 mg/ kg for 15 days) was also evaluated. The results showed that rats that had prophylactic and therapeutic supplementation with ω-3 PUFAs had lower levels of IL-1β and TNF-α compared to rats that did not have diets with ω-3 PUFAs. Moreover, the rats that had only therapeutic supplementation with ω-3 PUFAs had lower levels of TNF-α compared with the rats with gingivitis that did not receive supplementation. The histological analysis showed that the supplementation with ω-3 PUFAs decreased the tissue inflammation, especially when the prophylactic dose was used (Araghizadeh et al., 2014). Both studies are in agreement that ω-3 PUFAs might reduce proinflammatory mediators in gingiva, such as prostaglandins, leukotrienes and cytokines, such as TNFα and IL-1β (Campan et al., 1997; Araghizadeh et al., 2014) which could be explained by the fact that cyclooxygenase and lipoxygenase pathways of leukotrienes and prostaglandins (inflammatory mediators derived from the arachidonic acid cascade) would have been inhibited by ω-3 PUFAs, consequently reducing the cytokines levels (Mukaro et al., 2008).

4.4 Omega-3 polyunsaturated fatty acids and apical periodontitis

Apical periodontitis is an inflammatory disease characterized by inflammatory bone resorption in response to intracanal bacterial infection (Kawashima, Okiji, Kosaka, & Suda, 1996) and by the presence of fibrous and granulated tissue as well as by infiltrates of various inflammatory cells, for example, T lymphocytes, B lymphocytes, and macrophages (Liapatas, Nokou, & Rontogianni, 2003). The effects of ω-3 PUFAs orally gavage supplementation (40 mg/kg; 60% EPA and 40% DHA) for 45 days were evaluated using a model of apical periodontitis induced by pulp exposure in rats. The results showed that supplementation with ω -3 PUFAs not only inhibited the action of osteoclasts, leading to less bone loss, but also promoted an increase of osteoblasts, leading to bone remodeling. This fact suggests that ω -3 PUFAs can act on 2 different

bone cells and improve the pathogenic results of the bone loss of this disease (Azuma et al., 2017). Later, the same group investigated the effects of ω-3 PUFAs on pro and anti-inflammatory mediators. In addition, the effects of ω-3 PUFAs on triglycerides levels of rats with apical periodontitis were also evaluated. The results showed that ω-3 PUFAs reduced the triglyceride levels of rats, which were previously increased due to the presence of apical periodontitis (Azuma et al., 2018). The results showed that supplementation was able to decrease the expression of proinflammatory mediators and increase the expression of anti-inflammatory mediators in periapical tissues (Azuma et al., 2018a). The lipid mediators such as Lipoxins derived from omega-3s (Van Dyke, 2011) and Resolvins derived from DHA and EPA (Keinan, Leigh, Nelson, De Oleo, & Baker, 2013) have a variety of anti-inflammatory actions. Lipoxins were effective in inhibiting leukocyte recruitment and were found in the crevicular gingival fluid of patients with active periodontitis (Pouliot, Clish, Petasis, Van Dyke, & Serhan, 2000). The resolvins appear to reduce inflammation and alveolar bone loss (Hasturk et al., 2007). They are involved in the generation of reactive oxygen species (Damgaard et al., 2017) and in the preservation of bone (Gyurko & Van Dyke, 2014). The decreased expression of the proinflammatory cytokines TNF-α, IL-1β and IL-6 may have been reduced by the action of the two major components of ω-3 PUFAs (DHA and EPA) since they are capable of inhibiting the lipoxygenase and cyclooxygenase pathways of the arachidonic acid cycle. With the inhibition of these two pathways, there is a decrease in the production of pro-inflammatory molecules and, consequently, a decrease in inflammation (Alam, Bergens, & Alam, 1991). On anti-inflammatory mediators, this result contradicts previous studies that found no differences in IL-10 expression among individuals with periodontal disease, independent of ω-3 PUFAs supplementation (Kesavalu et al., 2007). According to the authors, discrepancy can be attributed to differences in dietary composition or experimental time. Studies have also shown that the anti-inflammatory effects associated with ω-3 PUFAs are dose- and time-dependent (Kremer et al., 1990). Thus, the authors concluded that those studies lay the groundwork for further investigations of ω-3 PUFAs as a therapeutic regimen for apical periodontitis (Azuma et al., 2017, 2018, 2018a).

4.5 Omega-3 polyunsaturated fatty acids and recurrent aphthous stomatitis

Recurrent aphthous stomatitis is a common oral mucosal disease causing idiopathic recurrent oral ulceration without extra-oral manifestations (Seoudi, Bergmeier, Drobniewski, Paster, & Fortune, 2015). Several studies have demonstrated the role of immunologic factors, stress, trauma, cessation of smoking, and luteal phase of the menstrual cycle in the etiopathogenesis of recurrent aphthous stomatitis (Porter & Scully, 2007). The goals of current therapeutic approaches include the management of pain and functional impairment, as well as reducing the duration and frequency of recurrences (El-Khouli & El-Gendy, 2014).

There is one study in the literature that evaluated the effects of ω-3 PUFAs as an alternative treatment against recurrent aphthous stomatitis. The double-blind placebo-controlled study showed that daily ω-3 PUFAs treatment promoted a significant reduction in number of ulcers, duration of ulcers, and level of pain by 3 months that persisted for 6 months. These positive results might be due to the capacity of ω-3 PUFAs in altering cellular functions to modulate lymphocyte proliferation, and to significantly increase the activities and mRNA expression of endogenous host antioxidant enzymes including glutathione peroxidase, superoxide dismutase and catalase, thus enhancing clearance of inflammation within the lesion and promoting tissue regeneration (Shanfeld et al., 1986; Kremer et al., 1990; Kesavalu et al., 2007). In addition, ω-3 PUFAs acts in the production of arachidonic acid metabolites, down regulating the production of pro-inflammatory mediators, limiting tissues damage (Schwab, Chiang, Arita, & Serhan, 2007).

The results found in the control of pain and inflammation of recurrent aphthous stomatitis in both studies may be related to the dose and time of treatment of ω-3 PUFAs that was equal in both studies. They used previous studies that administered daily 3g of ω-3 PUFAs for 6 months. The criteria of selection of the dosage was because these studies showed decreased inflammation and less alveolar bone loss of oral diseases. In this context, they considered mature to apply the same concentration during the same period of time (Luostarinen & Saldeen, 1996; Keskiner et al., 2017).

4.6 Omega-3 polyunsaturated fatty acids and orthodontic tooth movement

During orthodontic tooth movement, alveolar bone remodeling is induced and regulated by constant exertion of mechanical forces (Yan et al., 2015), which is accompanied by the appearance of osteoclasts and subsequent alveolar bone resorption, probably mediated by the local production of pro-inflammatory mediators (Yamasaki, Shibata, & Fukuhara, 1982; Shanfeld et al., 1986).

There is only one study in the literature regarding the influence of ω-3 PUFAs at the periodontal ligament during an experimental orthodontic tooth movement in rats. The results showed that the diet with ω-3 PUFAs (10% fish oil mixed in diet during 6 weeks) reduced the number of osteoclasts on the pressure side during tooth movement. In addition, the diet with ω-3 PUFAs reduced the bone loss during tooth movement (Iwami-Morimoto, Yamaguchi, & Tanne, 1999). These results may be explained because prostaglandins are related to the inflammatory process in the periodontal tissues around teeth that are orthodontically moved, highlighting the role of ω-3 PUFAs to inhibit the cyclooxygenase pathway, and the consequent production of prostaglandins (Yamasaki, Shibata, & Fukuhara, 1982; Shanfeld et al., 1986). Animal models that mixed ω-3 PUFAs with the diet (Kesavalu et al., 2006; Benkyk et al., 2009) had lower alveolar bone resorption when compared to those who used the oral gavage method of administration (Vardar et al., 2005; Vardar-Sengül et al., 2006).

4.7 Limitations of the present review

The limitations of the present review include the possibility that relevant studies were not included. This may have happened because only articles written in English were selected. Our team has chosen to use only articles published in the English language by considering the easier accessibility and that most manuscripts published in high impact journals are written in English. Moreover, possible variations in our final results may be due to the possible existence of other synonymous and abbreviated terms that were not used in our search strategy.

Moreover, the heterogeneity of the studies selected may impact the generalizability of the results. We decided to include studies conducted in animals and humans aiming to not only explore the clinical outcomes but also the inflammatory modulation attributed to omega 3 in different inflammatory process in the oral cavity. Although the findings presented in the manuscript are not conclusive, they can lay the

groundwork for further investigations of omega 3 as an adjuvant therapeutic regimen for the treatment of oral diseases.

5 CONCLUSIONS

According to the literature findings, supplementation with ω-3 PUFAs may be used as an adjuvant therapy during treatments of oral diseases that involve inflammatory processes and bone resorption. However, as there is relatively little information in the literature about the use of ω-3 PUFAs, further investigations in humans are paramount to elucidate the mechanisms of action of ω-3 PUFAs in reducing inflammation in the oral cavity.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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Table 1. Summary of included studies and PICO

Campan et al. 1997	Patients with gingivitis.	Systemic supplementation with ω-3 PUFAs.	Comparison was made with patients that received placebo as an adjunct treatment.	ω-3 PUFAs induced a tendency towards reduced inflammation but it was not possible to conclude significant efficacy.
Iwami-Marimoto et al. 1999	Rats subjected to experimental orthodontic tooth movement.	Systemic supplementation with ω-3 PUFAs .	Comparison was made with rats that received placebo during tooth movement.	ω-3 PUFAs reduced osteoclastic activity and alveolar bone resorption.
Vardar et al. 2005	Rats subjected to experimental periodontitits.	Systemic supplementation with ω-3 PUFAs.	Comparison was made with rats that received placebo after periodontitis induction.	ω-3 PUFAs reduced PGE2, PGF 2α, and LTB 4 levels in gingival tissues.
Vardar-Sengul et al. 2006	Rats subjected to experimental periodontitits.	Systemic supplementation with ω-3 PUFAs.	Comparison was made with rats that received placebo after periodontitis induction.	ω-3 PUFAs was not effective in preventing LPS-induced alveolar bone loss.
Kesavalu et al. 2006	Rats subjected to oral infection with *P. gingivalis.*	Systemic supplementation with ω-3 PUFAs.	Comparison was made with infected rats that received placebo	ω-3 PUFAs modulated alveolar bone resorption.
Kesavalu et al. 2007	Rats subjected to oral infection with *P. gingivalis.*	Systemic supplementation with ω-3 PUFAs.	Comparison was made with infected rats that received	ω-3 PUFAs modulated the local gingival inflammatory response

			placebo.	
Vardar-Sengul et al. 2008	Rats subjected to experimental periodontitits.	Systemic supplementation with ω-3 PUFAs.	Comparison was made with rats that received placebo after periodontitis induction.	Administration of therapeutic ω-3 PUFAs may increase gingival TIMP-1 expression
Araghizadeh et al. 2013	Rats subjected to experimental gingivitis.	Systemic prophylactic supplementation with ω-3 PUFAs.	Comparison was made with rats that received placebo before gingivitis induction.	Prior consumption of ω-3 PUFAs is effective in reducing inflammation in induced rat gingivitis.
Deore et al. 2014	Patients with gingivitis treated with scaling and root planing.	Systemic supplementation with ω-3 PUFAs.	Comparison was made with patients that received placebo as an adjunct treatment.	ω-3 PUFAs reduced gingival inflammation, pocket depth, and attachment level gain.
El-Khouli & El-Gendy 2014	Patients that had recurrent minor aphthous ulcer.	Systemic supplementation with ω-3 PUFAs.	Comparison was made with patients that received placebo.	ω-3 PUFAs treatment achieved a significant reduction in number of ulcers, duration of ulcers, and level of pain.
Martinez et al. 2014	Patients with generalized chronic periodontitis treated with scaling and root planing	Systemic supplementation with ω-3 PUFAs.	Comparison was made with patients that received placebo.	The ω-3 PUFAs dietary supplementation had no effect on clinical outcome of treatment
Azuma et al. 2017	Rats subjected to experimental apical periodontitis	Systemic prophylactic and therapeutic supplementation	Comparison was made with rats that received placebo before and	ω-3 PUFAs suppressed inflammation and bone resorption and increased bone formation

		with ω-3 PUFAs.	after apical periodontitis induction	in the periapical area.
Keskiner et al 2017	Patients with chronic periodontitis treated with scaling and root planing	Systemic supplementation with ω-3 PUFAs.	Comparison was made with patients that received placebo.	ω-3 PUFAs improves salivary TNF-a without any significant impact on clinical parameters in patients with chronic periodontitis.
Azuma et al. 2018	Rats subjected to experimental apical periodontitis	Systemic prophylactic and therapeutic supplementation with ω-3 PUFAs.	Comparison was made with rats that received placebo before and after apical periodontitis induction	ω-3 PUFAs reduced triglycerides levels in rats with apical periodontitis
Azuma et al. 2018a	Rats subjected to experimental apical periodontitis	Systemic prophylactic and therapeutic supplementation with ω-3 PUFAs.	Comparison was made with rats that received placebo before and after apical periodontitis induction	ω-3 PUFAs reduced inflammation in rat apical periodontitis

Table 2. Summary of risk of bias assessment

Camapan et al. 1997	High	Unclear	High	High	High	Unclear	High

Iwami-Marimoto et al. 1999	Unclear	High	Unclear	Unclear	High	Unclear	High
Vardar et al. 2005	Unclear	High	Unclear	Unclear	High	Unclear	High
Vardar-Sengul et al. 2006	Unclear	High	Unclear	Unclear	High	Unclear	High
Kesavalu et al. 2006	High	High	Unclear	Unclear	High	Unclear	High
Kesavalu et al. 2007	High	High	Unclear	Unclear	High	Unclear	High
Vardar-Sengul et al. 2008	Unclear	High	Unclear	Unclear	High	Unclear	High
Araghizadeh et al. 2013	Unclear	High	Unclear	Unclear	High	Unclear	High
Deore et al. 2014	High	High	High	High	High	Unclear	High
El-Khouli & El-Gendy 2014	High	High	High	High	High	Unclear	High
Martinez et al. 2014	High	High	High	High	High	Unclear	High
Azuma et al. 2017	Unclear	High	Unclear	High	High	Unclear	High
Keskiner et al 2017	High	High	High	High	High	Unclear	High
Azuma et al. 2018	Unclear	High	Unclear	High	High	Unclear	High
Azuma et al. 2018a	Unclear	High	Unclear	High	High	Unclear	High

Figure Legend

Figure 1. Inclusion and exclusion strategy