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LIPIDMEDIATORS PRO-INFLAMMATIONRESOLUTION IN PERIODONTAL DISEASE: REVIEW OF LITERATURE

[1]João AbadioOliveira Neto, [1]Carolina Filippin, [1]Jeniffer Fernandes Cristina, [1,2]Andreia Borges-Scriboni, [2]Idiberto José Zotarelli Filho and [1,2]Patrícia Garani Fernandes

[1]University Center North Paulista (Unorp) - São José do Rio Preto – SP, Brazil
[2]Post graduateandcontinuingeducation (Unipos), Street Ipiranga, 3460, São José do Rio Preto SP, Brazil 15020-040

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ABSTRACT

Periodontitis is classified as an inflammatory disease of the tissues of dental support caused by the deregulated production of inflammatory mediators against bacterial plaque, capable of destroying the periodontal ligament and alveolar bone, and can be of three types: chronic, aggressive and with manifestation of systemic diseases. The inflammatory process is the body's first defense response to disease facilities. However, exacerbation of the condition with excessive demand for inflammatory mediators may lead to the destruction of host tissue and produce irreversible pathologies. Within the non-prolonged inflammation there are biological and biochemical processes capable of removing the harmful stimulus, inducing the tissue repair through chemical mediators and lipid mediators, which are responsible for the end of the inflammation. After initiation of the inflammatory cascade, the following processes involving exacerbation or resolution of inflammation are controlled by inflammatory chemical mediators derived from cell production such as cytokines, and by lipid mediators from arachidonic acid, such as lipoxins, resolvins, maresinas.

Corresponding author

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INTRODUCTION

Bacterial-induced inflammation is the leading cause of bone loss in many diseases such as septic arthritis, osteomyelitis, and periodontitis. One of the reasons why bone loss is perpetuated is the prolonged or even exacerbated duration of inflammation (Vidal, 2009). Since the inflammatory process is the first defense reaction of the organism to a tissue injury, it becomes an essential mechanism in the body maintenance against facilities of diseases harmful to health. The inflammation encompasses biological and biochemical processes, whose presence of vascular and cellular components, complement system, coagulation and soluble substances aim to remove the harmful stimulus and cover the inflammatory picture until there is repair of the local tissue.

That said, inflammation acts by isolating the lesion as the first stage at the beginning of the immune response by which the infection is eliminated and the lesion repaired. However, prolongation of the inflammatory response generates an exacerbated release of pro-inflammatory mediators, which are capable of destroying host tissue and produce irreversible pathological changes (AlpdoganKantarci, 2003). After initiating the inflammatory cascade, the subsequent mechanisms are controlled by the actions of chemical mediators, which are produced by various cells such as mast cells, platelets, and leukocytes. Low molecular weight lipid mediators, such as lipoxins, are derived from arachidonic acid generated in the acute inflammatory response and play an important role in the process of inflammatory auto-synchronicity. Cytokines and chemokines, proteins and other molecules such as gasses, nitric oxide, carbon monoxide, reactive oxygen species and nucleotides, are also recognized as

inflammatory (AlpdoganKantarci, 2003). Overproduction of inflammatory mediators, such as prostaglandins and leukotrienes, is associated with the progression of acute inflammation to chronic inflammation due to the physiological changes caused by them. The desired inflammatory processes are self-limiting, suggesting the presence of anti-inflammatory pathways and pro-endogenous resolution of inflammation (Marcelo, 2000). According to Van Dyke et al. (2013) (Van Dyke, 2015), the resolution of inflammation and the recovery of homeostasis at the tissue level occur through a perspicacious biochemical process called programmed resolution. In this context, pro-inflammatory resolution lipid mediators are specialized endogenous immunological substances that comprise the resolvins, lipoxins, proteins and maresins, effectively responsible for the end of inflammation (Marcelo, 2000). This literature review aimed to show / elucidate the role of some lipid mediators pro-inflammation resolution in periodontal disease through its mechanism of action.

MATERIALS AND METHODS

Experimental and clinical studies were included (case reports, retrospective, prospective and randomized trials) with qualitative and / or quantitative analysis. Initially, the key words were determined by searching the DeCS tool (Descriptors in Health Sciences, BIREME base) and later verified and validated by MeSh system (Medical Subject Headings, the US National Library of Medicine) in order to achieve consistent search.

Mesh Terms

The words were included *periodontitis, inflammatory diseases, omega 3, nutrology*. For further specification, the *periodontitis* description for refinement was added during searches. The literature search was conducted through online databases: Pubmed, Periodicos.com and Google Scholar. It was stipulated deadline, and the related search covering all available literature on virtual libraries.

Series of Articles And Eligibility

A total of 45 articles were found involving temporomandibular dysfunction. Initially, it was held the exclusion existing title and duplications in accordance with the interest described this work. After this process, the summaries were evaluated and a new exclusion was held. A total of 33 articles were evaluated in full, and 25 were included and discussed in this study.

Literature Review

Periodontitis is an inflammatory disease of the tissues of dental support resulting from specific microorganisms, which promote a progressive destruction of the periodontal ligament and the alveolar bone, and may be accompanied by periodontal pockets and / or gingival retractions. In 1999, the consensus of Periodontia International classified three clinical manifestations of periodontitis: chronic, aggressive and as a manifestation of systemic diseases (Armitage em, 1999). Excessive and unregulated production of destructive enzymes and inflammatory mediators, taken as a response of the host, to the presence of subgingival plaque causes severe damage to the supporting tissue. These sequels are caused by cytokines, prostaglandins and metalloproteinases (MMPs), considered as the inflammatory mediators, whereas lipoxins, resolvins and protectins are mediators of the resolution of inflammation, whose function is to contain the inflammatory process (Newman, 2016). Cytokines are able to transmit signals from one cell to another potentiating the immune response and modulating immunoinflammatory responses against infections, so they are considered essential inflammatory mediators in periodontics. Cells such as neutrophils, macrophages, lymphocytes, fibroblasts, and periodontal resident epithelial cells are responsible for producing cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). IL-1β and TNF-α are responsible for maintaining damage to the periodontium because they are considered potent inhibitors of bone formation and also because they act in the stimulation of bone resorption. This process initiates and perpetuates the innate immune response in periodontal tissues through vascular changes and migration of effector cells, such as neutrophils in the periodontium, so that the immune response is normal to the presence of subgingival bacteria (Newman, 2016 Thomas, 2011 and Van Dyke, 2015). In arachidonic acid, a polyunsaturated fatty acid found in the plasma membrane of cells, the products of the lipoxygenase pathway are leukotrienes whereas those of the cyclooxygenase pathway are prostaglandins and thromboxane. Due to its high capacity of vasodilation and consequent increase in cellular cytokine production, prostaglandins (Pgs) are considered important inflammatory mediators, mainly prostaglandin E2 (PGE2), which is produced in the periodontium by macrophages and fibroblasts, by inducing MMPs, to participate in osteoclastic bone resorption and to contribute to the tissue damage capable of leading to periodontal disease (Newman, 2016). Matrix metalloproteinases (MMPs) are a group of proteolytic enzymes produced by a cellular variety represented by neutrophils, macrophages, fibroblasts, epithelial cells, osteoblasts and osteoclasts, with degradation ability of components of extracellular matrices such as collagen and elastin.

OfthemanyMMPs, MMP-13 isresponsible for theproteolyticdegradationofextracellularmatrixcomponentsincl udingcollagenfibrils in the bonematrix, proving their participation in thecascadeof periodontal degradation (Irina Massova, 1998; Woessner, 1991 and Anqi Gao, 2003). In periodontal disease, MMPs are mainly blocked by TIMP-1 (metallopeptidase inhibitor 1), and can also be inhibited by the antibiotic class of tetracyclines, which led to the sub-antimicrobial formulation of doxycycline as a systemic adjuvant treatment in the management of properties anti-MMP (Newman, 2016). Lipoxins, generated from arachidonic acid and induced by cytokines released in the acute inflammatory process such as IL-β, have a low concentration biological activity and signal the resolution of inflammation based on its inhibitory action of neutrophilic recruitment, chemotaxis, chemotaxis and adhesions. In addition, they alert macrophages to the process of phagocytosis of apoptotic cells participating in the site of inflammation without an inflammatory response (Newman, 2016). E-series resolvins, which are derived from the eicosapentaenoic omega-3 fatty acid (EPA), inhibit about 50.0% of neutrophil infiltration and transmigration, inhibiting the production of pro-inflammatory and immunological mediators. The inadequate intercession of the inflammatory process can be considered a decisive factor in the manifestation of periodontal pathogenesis, given that the release of inflammatory mediators, such as cytokines and prostanoids, severely aggravates tissue damage.

Table 1. Table showing the main literary findings on the treatment of periodontitis

Author	Year	Review
Pouliot&Serhan [16]	1999	They found that both lipoxin-A4 and ATL (aspirin triggered lipoxin) are regulators of neutrophil-directed TNF2 and incite interleukin-4 in exudates and, therefore, regulate mediators that play a significant role in the pathogenesis of the disease periodontal.
Perrettiet al [17]	2002	They have shown that blockade of PMN infiltration by ASA and DEX is a domain shared by aspirin-triggered lipoxins (ATL) and glucocorticoid-induced annexin 1 (ANXA1) peptides which are both generated in vivo and work on lipoxin A4 Receiver (ALXR / FPRL1) to cease the PMN diapedesis. These structurally binding diverse interact in a specific and direct manner with recombinant human ALXR evidenced by specific radio ligand binding and function, as well as the immunoprecipitation of PMN receptors. In addition, the combination of peptides derived from ATL and ANXA1 limited the infiltration of PMN and reduced the formation of inflammatory mediators (i.e., prostaglandins and chemokines) in vivo. Together, these results indicate functional replicates in endogenous lipid and peptidic endogenous anti-inflammatory circuits that are spatially and temporally separated, where both ATL and specific peptides derived from ANXA1 act together in ALXR to reduce the recruitment of PMN to inflammatory loci.
Alpdogan [2]Kantarci& Thomas E. Van Dyke [9]	2003	They found that periodontal disease is a model of great importance in which several aspects of lipid mediators can be studied. As well as a local phenomenon is represented in which the tissue injury mediated by neutrophils is an important contributing factor for the development of the disease. Thus, studies aimed at clarifying the pathogenetic mechanisms in periodontal disease will certainly increase our understanding of many sequelae of disease as well. In this scenario, lipoxins and lipid mediators present not only an exciting area of research, but also have potential for the development of new treatment strategies.
Tsaiet al.[18]	2005	They found that the growth of lipid peroxidation levels may play a role in the inflammation and destruction of the periodontal region in periodontal disease.
Serhanet al.[19]	2008	This study showed recently discovered cellular and molecular mechanisms for the solution of inflammation, exposing essential roles for eicosanoids, such as lipoxins and new families of endogenous chemical mediators, identified as resolvins and protectins. These mediators contain anti-inflammatory and pro-resolution properties with leukocytes, form the protection of the organs and incite mucosal antimicrobial defense. Together, they command local inflammatory responses at many levels to stimulate resolution.
E.A. Lilly et al. [20]	2010	Annexin-A1 immunoprecipitation was reported from proteins removed from cells treated with phosphate buffered saline PBS. Epithelial cells resulted in nullification of inhibitory activity. Taken together, the results indicated that annexin-A1 is a strong candidate for the effector protein of anti-Candida epithelial cells.
Van Dykeet al.[6]	2011	It has been demonstrated in this study that pharmacological anti-inflammatory agents [non-steroidal anti-inflammatory drugs (NSAIDs)] show to prevent and delay the progression of periodontitis in animals and humans. However, the type of side effects of NSAIDS or other receptor inhibitors or antagonists precludes its use in periodontal treatment. The isolation and characterization of lipid mediatorsproresolvins that are receptor agonists have opened a new area of research for possible therapeutic agents for the manipulation of inflammatory periodontal disease.
Sandra M. Barbalho et al.[21]	2011	They have demonstrated that resolvins, protectins and maresinas, soon described, come from AGP ω3 and have shown important results in the reduction of inflammatory processes. Therefore, it can be said that the study of these substances and the delineation of their effects can bring new horizons in the treatment of inflammatory diseases, with lower costs and side effects.
Jia et al.[22]	2013	They found that Aggregatibacteractinomycetemcomitans (Aa) enabled innate immune signaling and the oxidation of low density lipoproteins (LDL), which may facilitate the progression of the atheroma.
Hager R. ZeinElabdee et al.[23]	2013	They observed that the proportions of predecessors of pro-resolution / pro-inflammatory lipid mediators appear to be more significant to describe the condition of AgP disease than the accumulation of specific lipid mediators.
Manuela R. C. Sete and Carlos M. S. Figueredo. [10]	2013	Recent studies have shown that the use of omega 3 added to conventional periodontal treatment, done by scaling and root planing, leads to better clinical and microbiological results. The authors found that omega 3 appears to help in the solution of inflammation, which could motivate its use as an adjunct to periodontal treatment.
Gao et al. [9]	2013	First described the LPS stimulation of osteoblasts leads to the transcriptional activation of matrix-13 metalloproteinase (MMP-13), a regulator of central bone resorption. Importantly, overexpression of SOCS3 has been shown to lead to a considerable decrease of LPS-induced MMP-13 expression in primary murine calvaria osteoblasts. Those obtained showed that SOCS3 can work as a significant regulatory mediator in inflammatory bone diseases in view of MMP-13.
Herrera et al.[24]	2015	They observed that the H2S-releasing fraction in compound ATB-346 not only does not affect the effects of naproxen in periodontal disease, it also improves bone quality and avoids gastric mucosa insults due to inhibition of prostaglandin, thus characterizing potentially new auxiliary therapy for diseases of the periodontium.
M H Petri et al.[25]	2017	They found that ATL prevented the development of atherosclerosis through reduced localized and systemic inflammation mediated by Fpr2 (Formyl 2 peptide receptor). The results say that this anti-inflammatory and pro-resolving agent has therapeutic competence to treat atherosclerosis.

Endogenous lipid mediators that have the domain function on inflammation offer a potential for effective adjuvant therapeutics in controlling periodontitis, changing the focus of treatment to resolution of inflammation and no longer for inhibition of the inflammatory response (Newman, 2016). Therapeutic resources involving drugs responsible for blocking the inflammatory process aiming at modulating the host's response are intended for the resolution of inflammation without causing damage or damage to the host's health with the potential to soften the immunosuppressive process. Thus, the scientific community has been searching for alternative forms for the treatment of chronic inflammatory disease, such as the case of periodontal disease. A diet rich in fatty acids, such as omega3, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), is considered a palliative therapeutic alternative in search of a specific inflammatory response of the host to the infectious process (Manuela, 2013).

DISCUSSION

The use of omega 3, including DHA and EPA, reveals a high anti-inflammatory therapeutic value capable of protecting the body from inflammatory diseases, such as periodontitis, due to its action in reducing the production of inflammatory mediators, derived from arachidonic acid, being the prostaglandins, thromboxanes and leukotrienes. However, recent studies show that omega 3 serves as a substrate for formation of lipid mediators, a class composed of lipoxins, protectins and resolvins that is able to modulate the beneficial actions of this powerful fatty acid. This new group of lipid mediators may be the basis for a series of anti-inflammatory actions related to omega 3, although they are not fully understood (Manuela, 2013). Contrary to what is presumed, some eicosanoids of arachidonic acid can be considered concomitant, that is, they have a pro-inflammatory action and an anti-inflammatory response simultaneously. This fact can be found in PGE2, which, in addition to having a proinflammatory role, is considered a potent inhibitor of the production of two important inflammatory cytokines (tumor necrosis factor (TNF) -α and interleukin (IL) -1).

Such an anti-inflammatory action can be justified from studies that indicate a decrease in the production of leukotrienes of series 418 caused by PGE2, in addition to inhibition of lipooxygenase-5 and induction of lipooxygenase-15, which promotes the formation of lipoxins increasing the effectiveness of resolution of inflammation (Manuela, 2013). In 2001, Lappin et al. (Lappin, 2002) two groups of patients were separated: one group composed of aggressive periodontitis patients and the other group with chronic periodontitis, both groups were dosed cytokine concentration through biopsies in the granulation tissues of the diseased sites. The collected material was pretreated with specific antibodies detecting the anti-inflammatory cytokine IL-2, IL-4, IL-6, IL-10, IL-15, TNF-a and IFN-g. In the results, the concentration of IL-4 and IL-6 in patients with aggressive periodontitis was shown to be higher in relation to IL-2 and IFN-g, thus comprising a higher amount of Th2-derived cells on Th1 compared to patients with chronic periodontitis. It has also been pointed out in patients with aggressive profile greater IL-5 uptake by acting in place of IL-2. Also in this work, there was a greater distribution of leukocytes expressing the anti-inflammatory cytokine IL-10 in relation to IL-6 and TNF-a, which act as a pro-inflammatory cytokine. Such a result indicates a supposed variation of cells in the inflammatory infiltrate designated for resolution of inflammation as well as aid in the inume response of periodontal disease (Lappin, 2001). Homeostasis, within its limits, is considered as a process of maintenance of the internal environment that offers the basal biological balance through anti-inflammatory mediators in order to favor healing even in the medium of microorganism, as is the case of resolvin E1 (RvE1) (Hasturk, 2006 and Van Dyke, 2015). According to Hasturk et al. (Hasturk, 2006).

RvE1 has no antibacterial action, however, other scientific findings have demonstrated through models of periodontal disease that such a mediator is able to control the inflammatory condition and eliminate gram-negative pathogens arising from organism and present in the buccal flora (Hasturk, 2006). Van Dyke et al. (2015) stated that although leukocytes are critical in defense against oral pathogens present in the host, chronic inflammation of the periodontium can cause advanced periodontal bone loss due to the individual's inability to treat the inflammatory lesion. In an experiment in rabbits with periodontitis, Hasturk et al. (Hasturk, 2006), mediators that aid in curing inflammation, such as lipoxins (LXA4) and resolvins (RvE1), inhibit periodontal bone loss by allowing periodontal restructuring. Previous data reveal that in addition to anti-inflammatory actions, lipoxins have direct anabolic practices in bone increasing the induction of bone regeneration. In experiments with transgenic rabbits the administration of stable lipoxin analogs resulted in a drastic decrease in leukocyte infiltrate, as well as reduction of bone loss and inflammation (Saxlin, 2008). Although the authors' disagreement regarding the intrinsic association of lipoxin and the reduction of periodontal inflammation is scarce, Saxlin et al. (Saxlin, 2008), pointed out that there was no consistent association between serum lipids and deep periodontal pockets (6.0 mm or more), a result that differs from other numerous studies which indicate a striking relationship between periodontal infection and the unfavorable lipid composition. The differentiation of the results shows that this study requires better evaluation (Saxlin, 2008).

Conclusion

Bacteria are the main cause of inflammation, and the result of this inflammatory process are diseases and consequently bone loss. The inflammatory process is of paramount importance for the reaction of the body to this harmful stimulus, taking the front, until the balance and the tissue repair of the affected place is established. When this inflammatory response is prolonged, a large release of aggressive pro-inflammatory mediators is generated, which can destroy the tissue of the host instead of repairing it and causing changes in the pathology irreversibly. The overproduction of inflammatory mediators such as prostaglandin and leukotrienes is directly linked to the progression of acute inflammation to chronic inflammation due to the physiological changes caused by these mediators. In fact, the ideal would be for these mediators to be self-limiting. There is still much to be studied about mediators, many of their functions and how they are activated, what is already known is the relationship with a diet rich in omega 3. It is necessary to look for elements that give this dynamic about an effective treatment for production self limiting of these mediators, thus achieving an effective treatment, avoiding further tissue destruction.

Conflict of interests: There is no conflict of interest between authors.

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