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Periodontist's New Friend For An Old Foe : Omega - 3 Poly Unsaturated Fatty Acids.

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Abstract

Current treatment modalities for periodontitis aim at suppressing the inflammatory response. Resolution of inflammation was once thought to be a passive process. However, recently it has been recognized that resolution is an active process and involves the generation of various pro-resolving molecules. Host modulatory therapy aims to reduce tissue destruction and stabilize periodontium and up regulate protective response along with down regulating destructive aspects of host response. Omega – 3 Poly Unsaturated Fatty Acid, including Docosahexaenoic Acid and Eicosapentaenoic Acid were shown to have therapeutic value and anti-inflammatory as well as protective actions in periodontitis. Many surveys also support positive effect on the periodontal parameters while treating chronic periodontitis with scaling and root planing and supplementing the patient with oral dose of Omega - 3 PUFA as an adjunctive although innovative, yet sustainable therapy.

Keywords: Host Modulation, Periodontitis, Pro-resolvins, Omega - 3 – Poly Unsaturated Fatty Acids.

Introduction:

In periodontal disease, the tissue destruction is characterized by inflammatory neutrophil mediated tissue injury followed by chronic infiltration of monocytes and the establishment of acquired immune lesion.[1] Although the recent studies have shown that this tissue damage is caused due to host response to infection and not by the infectious agents directly.[2] Most commonly used sources of omega -3-polyunsaturated fatty acids is fish oil, which is the richest sources of omega -3-fatty acid. The other rich sources of omega - 3 - fatty acids are flax seeds, kiwi fruit, walnut, hazelnut, eggs and meat.

Role of omega-3-polyunsaturated fatty acids in health and disease:

Several studies have evaluated the beneficial effects of omega-3 polyunsaturated fatty acids on diverse physiological processes in the body and on a variety of chronic inflammatory diseases like rheumatoid arthritis, cardiovascular diseases and also including periodontal diseases. Omega-3 fatty acids are also beneficial in hypertension, obesity, cancer, diabetes, insulin resistance. It also has anti aging and anti depressant property with a significant role on autonomic functions.

The therapeutic efficacy of dietary supplementation of omega-3 PUFAs in reducing alveolar bone resorption through the reduction of osteoclastic activity and dampening of gingival inflammation through their anti-inflammatory properties.[1]

Omega-3- polyunsaturated fatty acids as anti-oxidant and anti-inflammatory:

Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA), the major omega-3 PUFAs in fish oil, were found to alter cellular functions of polymorphonuclear leukocytes, modulate lymphocyte proliferation and enhance endogenous host antioxidant capacity.[2] Moreover, they were shown to competitively inhibit the production of arachidonic acid metabolites via the cyclooxygenase and lipoxygenase pathways, thus reducing the synthesis of proinflammatory arachidonic acid metabolites accounting for the potent pro-resolving properties of omega-3 PUFAs.[3] In addition, the metabolism of omega-3 PUFAs results in the production of the proresolving lipid mediators, resolvins and protectins with anti-inflammatory and immunoregulatory actions, through regulating the trafficking of inflammatory cells to the sites of inflammation and blocking proinflammatory cytokine production, thus enhancing clearance of inflammation within the lesion to promote tissue regeneration.[3]

Looking at the omega-3 fatty acids in depth we can observe long chain fatty acids influence inflammation through a variety of mechanisms; many of these are mediated by or associated with changes in fatty acid composition of cell membranes. Changes in these compositions can modify membrane fluidity, cell signaling leading to altered gene expression, and the pattern of lipid mediator production. Cell involved in the inflammatory response are typically rich in the omega-6 fatty acid arachidonic acid, but with in the presence of omega- 3 fatty acids they compete for the cyclo-oxeganase pathway and lipo-oxegenase pathway. EPA also gives rise to eicosanoids and these often have differing properties from those of arachidonic acid-derived eicosanoids. EPA and DHA

give rise to newly discovered resolvins which are anti-inflammatory and inflammation resolving. Increased membrane content of EPA and DHA and decreased arachidonic acid content results in a changed pattern of production of eicosanoids and resolvins. Thus, the fatty acid composition of cells involved in the inflammatory response influences their function; the contents of arachidonic acid, EPA and DHA appear to be especially important. The anti-inflammatory effects of omega - 3 PUFAs suggest that they may be useful as therapeutic agents in disorders with an inflammatory component.[4]

Resolvins have unique properties like, it reduces neutrophil infiltration, promotes healing of diseased tissues, regenerates lost soft tissue and bone, prevents connective tissue and bone loss.

Basically, Resolvin E1 (RvE1) and Resolvin E2 (RvE2), two major products in the family of EPA-derived resolvins, were originally isolated *in vivo* from murine dorsal air pouches treated with aspirin and EPA and were also generated *in vitro* from co-incubation of human endothelial cells with PMNs. RvE1 is spontaneously produced in healthy subjects and levels are increased in individuals taking aspirin and/or EPA. Transcellular formation of RvE1 can occur with the conversion of C20:5 to 18R-HEPE (18R-hydroxyeicosapentaenoic acid) by endothelial cells expressing COX-2 and treated with aspirin.

Similar to 15(R)-HETE in 15-epi-LX formation, 18R-HEPE can be released from endothelial cells to neighboring leukocytes for subsequent conversion by 5-LOX to RvE1 via a 5(6) epoxide-containing intermediate. This interaction is blocked by selective COX-2 inhibitors but not by indomethacin or acetaminophen. Using gas chromatography-MS and liquid chromatography-tandem-MS-MS-based lipidomic analysis, the basic structure of this compound was elucidated as 5S,12R,18R-trihydroxy-6Z,8E,10E,14Z,16E-EPA and complete stereochemistry was confirmed using total organic synthesis. This compound was found to be highly stereoselective both in vivo and in vitro.[5]

RvE1 decreases PMN tissue accumulation by blocking human PMN transendothelial migration and facilitating apical PMN clearance from mucosal epithelial cells. Other bioactions of RvE1 include attenuation of LTB4-BLT1 pro inflammatory signaling (NF-kB activation), inhibition of PMN superoxide anion generation in response to TNF-α or the bacterial surrogate peptide N-formyl-methionyl-leucylphenylalanine, stimulation of macrophage phagocytosis of apoptotic PMNs, inhibition of dendritic cell migration and cytokine release, and upregulation of CCR5 expression on leukocytes.

In addition to potent anti-inflammatory properties in acute inflammation, administration of RvE1 in a rabbit model of periodontitis also resulted in complete regeneration of damaged tissues, including bone, and normalization of systemic markers of inflammation, including C-reactive protein and IL-1b. Moreover, pre-treatment with RvE1, in contrast to molecules of the LX series, also conferred dramatic protection from inflammation-induced tissue and bone loss in periodontitis. In the murine dorsal air pouch model, RvE1 proved to be logorders more potent than its dexamethasone or aspirin counterparts. Only nanogram amounts of RvE1 reduced leukocyte infiltration by 50–70% as compared with microgram amounts of dexamethasone or milligram amounts of aspirin. Recent studies have revealed that RvE1 is a potent modulator of proinflammatory leukocyte expression molecules, such as L-selectin, and selectively

disrupts thromboxane-mediated platelet aggregation.[6,7]

Archidonic acid derivatives and omega – 6 produce prostaglandin e2 (pge2), thromboxane a2, leukotriene b4 which are pro inflammatory and strong chemo attractants. Whereas, omega – 3 produces prostacyclin, thromboxane a3, leukotriene b5 which are weak inflammatory and weak chemo attractants. Researchers have also found omega 3 fatty acid supplementation reduced the ability of monocytes to produce Interluekin – 1 upon stimulation with endotoxin.[8]

RvE2 is a second member of the EPA-derived family of E-series Rvs, and shares homology to RvE1. The full stereochemical structure for RvE2 is 5S,18(R/S)-dihydroxy-eicosapentaenoic acid. RvE2 is synthesized by human PMNs in amounts greater than RvE1, equipotent to RvE1 when given intravenously and additive to RvE1 at low doses when given intraperitoneally. The RvE2 receptor is yet to be molecularly characterized. RvE2 stops zymosan-induced PMN infiltration and displays potent anti-inflammatory properties in murine periodontitis.[9]

Gingival tissue levels of prostaglandin E2, prostaglandin F2a, leukotriene B4, and platelet activating factor, which are major inflammatory mediators and contribute to bone destruction in periodontal disease, and suggested that decreased alveolar bone loss may have been seen with longer periods of omega-3 administration.

Safety of Omega-3 Fatty Acids

Omega-3 fatty acids have been a part of the human diet for millennia. It has been estimated that the ratio of omega-6 to omega-3 fatty acids in the diet of early humans was 1:1. The ratio in the United States today has risen to 10:1 because of the combination of reduced omega-3 fatty acid intake and the widespread use of vegetable oils rich in linoleic acid. Because of the well-known competition between the omega-6 linoleate and the omega-3 -linolenate for metabolic conversion to longer-chain, physiologically activemetabolites, reducing the former while increasing the latter (or simply increasing the latter) is a strategy for increasing tissue levels of omega-3 fatty acids.109 Another obvious strategy is to simply consume more EPA and DHA, an approach that minimizes the significance of the ratio.

Since the first omega-3 fatty acid advisory, the FDA has ruled that intakes of up to 3 g/d of marine omega-3 fatty acids are GRAS (Generally Recognized As Safe) for inclusion in the diet. This ruling included specific consideration of the reported effects of omega-3 fatty acids on glycemic control in patients with diabetes, on bleeding tendencies, and on LDL cholesterol. Moreover, the FDA recently has approved a qualified health claim for EPA and DHA omega-3 fatty acids in dietary supplements.

Although the safety of low intakes does not seem to be an issue, and supplements are essentially mercury free, some side effects of omega-3 fatty acid supplementation do occur.

Perhaps the most common is a fishy aftertaste. In the GISSI Prevention study, which provided 0.85 g of omega-3 fatty acids per day for 3.5 years, 3.8% of patients discontinued taking their supplements (compared with 2.1% for the vitamin E group). Gastrointestinal disturbances and nausea were the most commonly reported side effects, with 4.9% and 1.4% reported, respectively, compared with 2.9% and 0.4% in the vitamin E group. When 12 capsules containing 6 g of omega-3 fatty acids were fed to 41 patients for 2.4 years, three patients dropped from the study claiming intolerance to the capsules.46 In a 6-

month trial providing 275 patients with 6.9 g of EPA+DHA in 10 capsules daily, there was no difference between the fish oil and corn oil control groups for any adverse event. Gastrointestinal upset was reported by 8% of the latter and 7% of the former. Finally, although refined and concentrated omega-3 fatty acid products contain virtually no methyl-mercury and are very low in organochloride contaminants, less well-controlled preparations can contain appreciable amounts.[10]

Current status of omega-3- fatty acids in periodontitis

Various studies have also shown that omega – 3 fatty acids inhibits periodontal pathogens like *P.gingivalis*, *P.intermedia*, which are some of the most pathogenic micro organisms for periodontium. It also inhibits collagenase activity, supresses interleukin-1, 6 and TNF-α production along with suppression of lipopolysacchride activity. Omega – 3 also shows inhibitory effect on osteoclastic bone resorption, thus it helps in prevention of periodontal disease.

El-Sharkawy et al.[1] have recently evaluated the therapeutic benefits of omega-3 PUFAs plus low-dose aspirin as a new strategy targeting the host modulatory response. This regimen was utilized to augment the clinical outcomes of standard periodontal therapy (scaling and root planing) in a 6 months clinical study on patients with chronic periodontitis. They concluded that this adjunctive treatment provided a sustainable, low-cost intervention for treatment of inflammatory periodontal diseases.

Most of the studies done have shown the dosage of 900mg to 1500mg per day for 3 to 6 months have shows significant improvement in the periodontal parameters along with the conventional scaling and root planing in the patients suffering from periodontitis.

Conclusion:

In light of available evidences, it can be concluded that omega – 3 fatty acids has unlimited potential as anti inflammatory, anti carcinogenic, anti thrombogenic and pro-resolving agent. Still more interventional, randomized controlled studies and systematic reviews are required to determine its efficacy as an adjunct to scaling and root planing in treatment of periodontitis.

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