Guest Editorial

Periodontal Disease: Resolving Inflammation

For most of the population in today's world, life is becoming increasingly complex. Oral health and dentistry are no exceptions to this trend. Fortunately, multiple branches of science are converging, bringing to light novel findings to arm dental professionals with new ways of helping their patients in the quest for better oral health.

We now know that oral health mirrors systemic health.[1] As with a building, the foundation is what makes everything strong. The literature evidence overwhelmingly supports that a low-sugar diet rich in fiber, vitamins, minerals, moderate in complex carbohydrates, adequate in protein, and providing "good fats," i.e., a preponderance of omega-3 *vs* omega-6 polyunsaturated fatty acids (FA) leads to better overall health and lower premature morbidity and mortality.

Indeed, zeroing in on periodontal health, Baumgartner et al[2] did a controlled "stone-age" study where the participants ate a stone-age diet and performed no dental hygiene; this resulted in marked reductions in gingival and periodontal inflammation. Woelber et al,[3] in an effort to obtain dietary recommendations compatible with the realities of daily life, furthered the "stone-age" study findings by undertaking a small randomized controlled pilot study comparing the results of a diet low in carbohydrates, high in antioxidants and fiber, and rich in vitamins C, D, and in omega-3 FA *vs* controls who ate a typical Western diet. The results? After 4 weeks, despite no significant change in plaque values, the group with the improved diet showed significantly reduced gingival and periodontal inflammation.

Specifically, increased dietary omega-6 over omega-3 FA intake has been shown to promote low-grade chronic inflammation (LGCI).[4] This LGCI is a systemic, chronic metabolic dysregulation caused by poor dietary omega-3 FA intake. A stone-age hunter/gatherer diet would have contained an omega-6: Omega-3 FA ratio of approximately 1:1. For people that eat typical Western developed world diets, that ratio is now closer to 15:1, leading to higher blood levels of inflammatory cytokines.[4]

Why is that? When cells (including human gingival and periodontal ligament fibroblasts) are exposed to inflammatory stimuli, the enzyme phospholipase A2 (PLA2) cuts off some of the FAs in the second (sn-2) position from cell membrane phospholipids. That sn-2 position is usually occupied by arachidonic acid (AA), which is the omega-6 FA precursor to the eicosanoids (prostaglandins and leukotrienes) that generally have pro-inflammatory or pro-thrombotic effects.[4,5] Prostaglandin E2 and leukotriene B4 are the key AA metabolites in the inflammatory response. Significantly, they are associated with soft tissue and bone loss, including periodontal disease.[6-8]

In the sea and in fresh water, algae synthesize eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two typical omega-3 FAs, which then enter the food chain when algae-eating organisms and fish are eaten by larger fish. Crucially, omega-3 FA like EPA and DHA compete with AA for the sn-2 position in membrane phospholipids. Therefore, if omega-3 dietary intake is high, when PLA2 is stimulated, it will find more EPA or DHA instead of AA at that position. The eicosanoids and lipid mediators derived from EPA and DHA will instead have desirable anti-inflammatory or antithrombotic effects.[4,5] However, as noted by Fialkow,[5] fish oils are delicate and oxidize easily. So reliable, high-quality sources are needed for effective health benefits.

In medical and dental education, inflammation is taught as being a passive process; i.e., simply a diminution, dilution, and dissipation of the inflammatory mediators that are present during injury/inflammation. However, in both health care communities, general awareness of key lipid mediators critical to the resolution of inflammation is only just beginning, despite the existence of over 2,000 peer-reviewed articles in PubMed.

Therefore, I would now like to introduce the "specialized pro-resolving lipid mediator" (SPM) superfamily to those of our esteemed readers who have not yet encountered it: The resolvins (Rvs), protectins (PDs), and maresins (MaRs), all omega-3 derived; and the lipoxins [(LXs), derived from AA]. These SPMs actively mediate the resolution of inflammation.[9,10]

Significantly, anti-inflammatory action is different from pro-resolving action: In periodontal disease, SPMs start their programmed tasks during inflammation by beginning to limit the recruitment of neutrophils to the inflamed periodontal tissues, while at the same time stimulating the recruitment of macrophages to remove apoptotic neutrophils and increasing microbial killing by innate immune cells. They also counter-regulate inflammatory cytokine

formation and increase production of anti-inflammatory interleukins like IL-10. Therefore, the actions of the SPMs are to reduce collateral tissue damage by neutrophils/phagocytes, enhance antimicrobial action, enhance macrophage clearance of dying neutrophils, and to counter the actions of inflammatory mediators while enhancing the production of anti-inflammatory mediators; all these actions promote tissue regeneration.[10]

Periodontal disease (PD) is a classic chronic inflammatory condition, and nonsteroidal anti-inflammatory drug (NSAID) anti-inflammatory therapy has been suggested to ameliorate it.[11-13] Of special note, aspirin [but not other NSAIDs nor acetaminophen (paracetamol)] impacts the LX circuit by triggering the biosynthesis of endogenous epimers of LX, termed the "aspirin-triggered lipoxins" that share the potent anti-inflammatory actions of LX. The curious reader is referred to Serhan and Savill[14] and Chiang et al[15] for more information.

Because the resolvins, protectins, and maresins are derived from omega-3 FA, to maintain health and/or tip the balance toward resolution of inflammation, one needs much greater intake of omega-3 *vs* omega-6 FA. Indeed, preliminary randomized controlled trials[16,17] show that omega-3 supplementation increases tissue SPMs. Therefore, while we await unequivocal confirmation from additional large, randomized controlled clinical trials, we already have enough basis to counsel patients with periodontal disease to increase their dietary intake of omega-3 oils and eat a diet low in simple carbohydrates, high in antioxidants and fiber, and rich in vitamins C and D, working with their physicians as needed. Not only will this help with periodontal disease management, but it will greatly benefit their systemic health.

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