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Potential mechanisms underpinning the nutritional modulation of periodontal inflammation

Iain L.C. Chapple, PhD, BDS, FDSRCPS, FDSRCS

Inflammatory periodontal diseases affect 10 to 15 percent of the world's population[1] and are a major cause of tooth loss in adults.[2] Epidemiologic studies support associations between periodontal inflammation and systemic diseases, including atherogenic vascular disease,[3] type 2 diabetes[4] and other conditions in which chronic inflammation underlies pathogenic processes or disease outcomes. Periodontitis is initiated by the plaque biofilm,[5] but most tissue destruction results from an abnormal inflammatory immune response in patients predisposed to the condition.[6] The response is characterized by hyperinflammation, which fails to remove the causative pathogens and generates prolonged release of neutrophil proteolytic enzymes, proinflammatory mediators and reactive oxygen species (ROS), which in turn destroy the periodontal attachment.[7] The etiology of an inflated inflammatory immune response is complex (Figure 1), but several common features of hyperinflammation underlie the major chronic diseases of humans[8-10]:

ABSTRACT

Background. Periodontitis results from an inappropriate host response to pathogenic biofilms. Because traditional management approaches have failed to reduce disease prevalence, the research focus has shifted toward managing host-mediated inflammation. In this article, the author reviews the role of nutrition in the development and resolution of inflammation.

Methods. The author reviewed the biomedical literature to elucidate mechanisms by which dietary factors affect inflammatory processes and to establish what evidence exists for macronutritional and micronutritional modulation of inflammation at a cellular and molecular level.

Conclusions. Hyperinflammation characterizes the periodontitis phenotype, and oxidative stress is a key orchestration point for the diverse signaling pathways, which control inflammation. Oxidative stress is modulated by diet, as well as by infection. Recent research has demonstrated that subtle shifts in nutritional status are associated independently with the prevalence of periodontitis. Moreover, the results of contemporary animal and human studies have demonstrated the role of specific micronutrients in the modulation of the host's inflammatory response by reducing inflammatory biomarkers and bone loss.

Clinical Implications. The scientific community is starting to realize the health benefits of diets containing foods naturally rich in antioxidants and omega-3 polyunsaturated fatty acids, as well as the dangers of diets that are high in refined carbohydrates. Nutritional intervention studies in patients with inflammatory periodontitis are needed to evaluate the effect of nutritional approaches to periodontal management.

Key Words. Inflammation; nutrition; periodontitis; carbohydrates; glucose; fats; oxidative stress; antioxidants; polyunsaturated fatty acids; gene expression.
JADA 2009;140(2):178-184.

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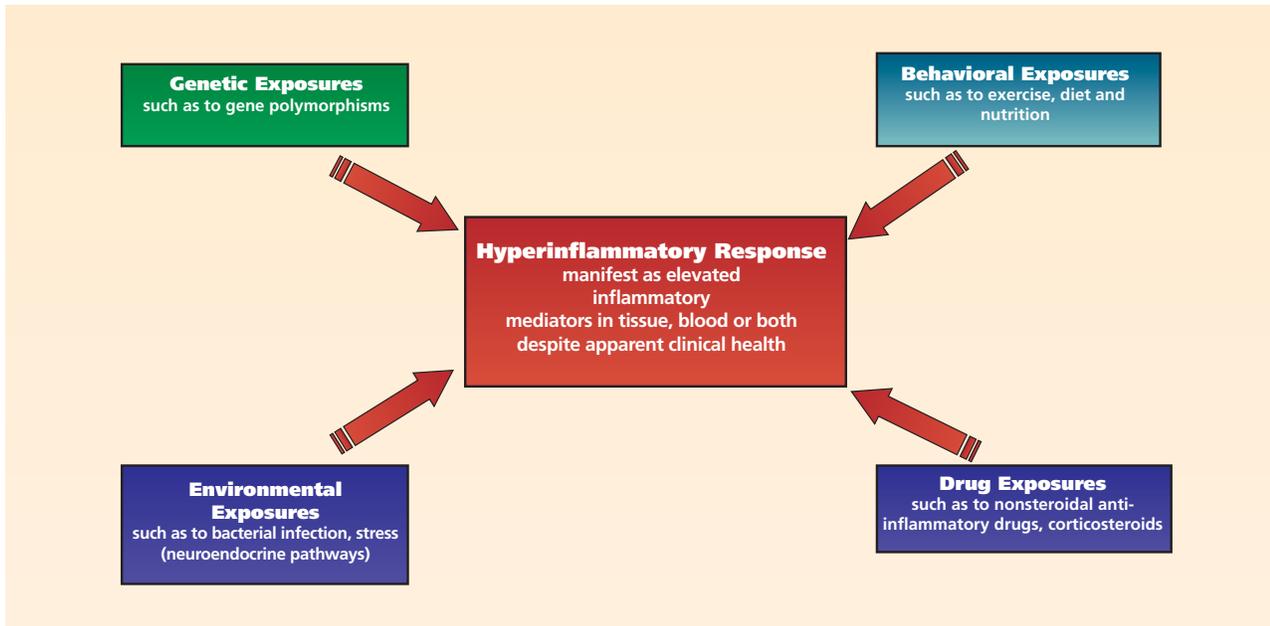
Figure 1. A model describing exposures that may contribute to the modulation of a hyperinflammatory phenotype.

- ROS and oxidative stress;
- cytokines and acute-phase proteins (such as C-reactive protein [CRP]);
- matrix metalloproteases (MMPs) (such as MMP-8);
- lipid mediators (such as prostaglandins E2 and F2α);
- adipokines from white adipose tissue (such as leptin and tumor necrosis factor alpha [TNFα]).

Researchers have found irrefutable evidence that macronutrients and micronutrients modulate proinflammatory and anti-inflammatory cascades,[11] which influence a person's baseline inflammatory status. The functionality of nutrients in human biology extends beyond that of being fuels for energy production and cofactors in metabolism, to acting as molecular cues that are capable of modulating gene and protein expression at a molecular level. This review highlights mechanisms whereby key macronutrients and micronutrients modulate inflammation (Figure 2; Box). While the medical literature is replete with evidence directly describing the mechanistic actions of such nutrients on inflammatory status,[11,12] there remains a paucity of scientific data regarding this topic in the periodontal literature.

NUTRITIONAL ACTIVATION OF PROINFLAMMATORY CASCADES

Refined complex carbohydrate/glucose. Diets high in complex carbohydrates are generally healthy (Box), whereas those rich in refined carbohydrates can be major causes of chronic inflammation.[11,12] Exaggerated postprandial surges in glucose (and triglycerides) result from high-calorie diets—in particular, from diets containing refined and processed foods rich in glucose and lipids that the body absorbs into the bloodstream rapidly.[13] Elevated glucose and lipid levels generate ROS at a rate that exceeds endogenous antioxidant defenses, and oxidative stress results.[11,14] Investigators have noted that this "postprandial dysmetabolism" plays a role in the genesis of inflammation.[11,13] Multiple elevations in glucose eventually lead to chronic inflammatory pathologies such as coronary artery disease.[11] The excess tissue glucose and triglyceride levels exceed the capacity of the Krebs cycle and elec-

ABBREVIATION KEY. AGEs: Advanced glycation end products. **AP-1:** Activating protein-1. **CHO:** Carbohydrates. **CRP:** C-reactive protein. **GSH:** Reduced glutathione. **GSSG:** Glutathione disulfide (oxidized glutathione). **IL:** Interleukin. **LOO:** Lipid peroxyl radical. **LOOH:** Lipid hydroperoxide. **MMP:** Matrix metalloprotease. **NF-κB:** Nuclear factor–kappa B. **OH:** Hydroxyl radical. **oxLDL:** Oxidized low-densitylipoproteins. **ω-3PUFAs:** Omega-3 polyunsaturated fatty acids. **PPARs:** Peroxisome proliferator–activated receptors. **PUFA:** Polyunsaturated fatty acid. **ROS:** Reactive oxygen species. **TLR:** Toll-like receptor. **TNF:** Tumor necrosis factor. **TNFα:** Tumor necrosis factor alpha.

Refined Carbohydrates

**Some Antioxidants
Polyunsaturated Fatty Acids**

Proinflammation

Anti-inflammation

Refined Carbohydrates (Box)

Saturated Fats
Dairy products: creams, cheeses, butter
Animal fats: suet, lard, fatty meats
Oils: coconut oil, palm kernel
Saturated fatty acids: lauric, myristic, palmitic, stearic

Antioxidants
Carotenoids (from green vegetables and tomatoes and other fruits): alpha-, beta- and gamma-carotene, lycopene, lutein, retinol, cryptoxanthine, zeoxanthine
Polyphenols (from vegetables, red wine, tea, pomegranates): gallic acid, flavone, cinnamic acid, pyrocatechol (catechin, quercetin, ferulic acid, hydroxytyrosol esters), pyrogallol (gallocatechins), resorcinol (resveratol), phloroglucinol (most flavenoids)
Vitamins (from fruits and vegetables): vitamin C (kiwi, citrus fruits), vitamin E (plant oils, soy, corn oil, nuts, green vegetables), vitamin A (fish oil), vitamin D (soy milk, margarine, fish oils, sunlight)
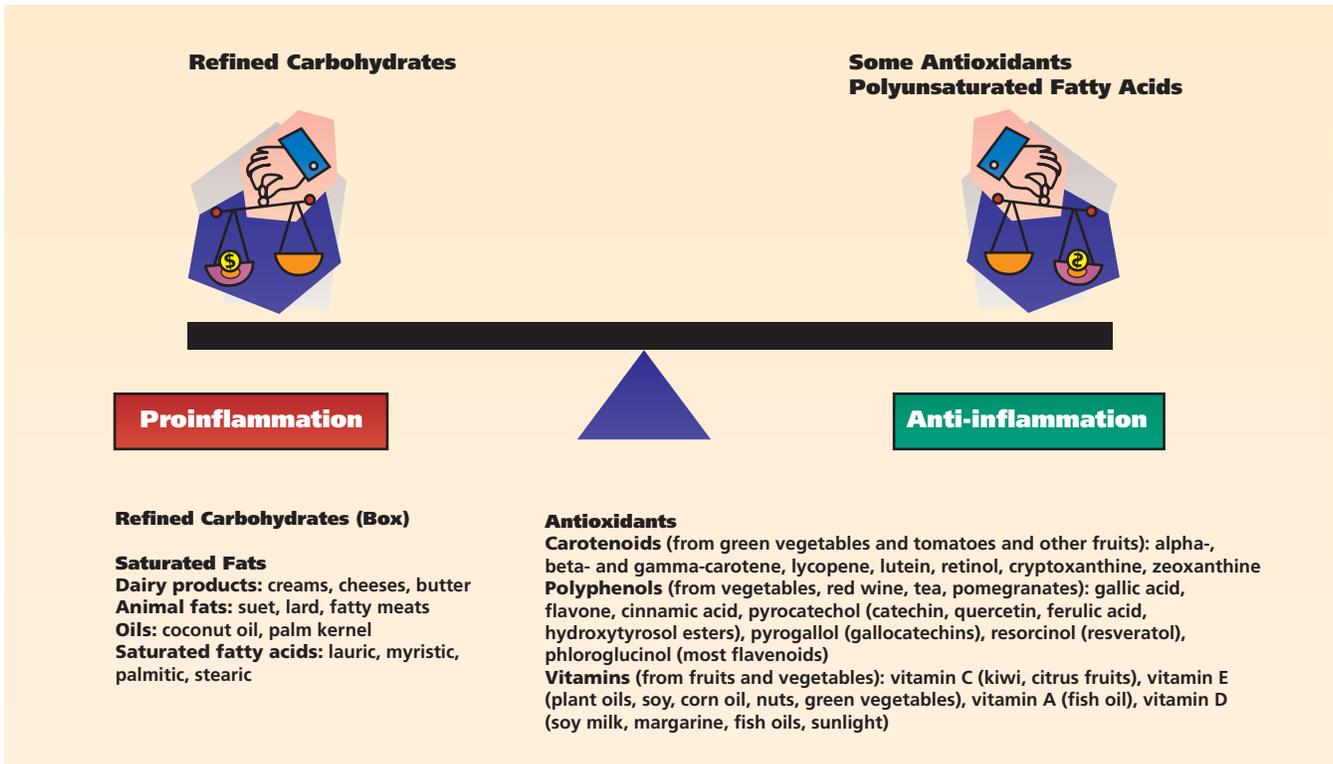
Figure 2. Macronutrients and micronutrients mechanistically associated with the regulation of inflammatory processes.

BOX

Sources of complex and refined carbohydrates.

COMPLEX CARBOHYDRATES			REFINED CARBOHYDRATES
Vegetables*	**Fruits***	**Grains/Nuts***	
Asparagus	Apples	Barley	Bread: white
Broccoli	Blueberries	Bread: whole grain	Cake containing white flour
Beans: green	Cherries	Bread: oat bran	Candy
Cabbage	Cucumbers	Buckwheat	Carbonated beverages
Cauliflower	Grapefruits	Corn	with added sugars
Celery	Kiwi	Millet	Corn syrup (maple syrup)
Carrots	Oranges	Muesli	Fruit juices and drinks
Onions	Pears	Oatmeal	Honey
Potatoes	Plums	Pasta: whole wheat	Jellies
Spinach	Raspberries	Rice: brown	Pasta: white
Sprouts	Red grapes	Peanuts	Ices, sherbet
Watercress	Tomatoes	Pistachios	Sugar: table
			Sugar: icing

* Fruits and vegetables contain some naturally occurring simple carbohydrates, rather than complex carbohydrates, but they do not contain refined or added sugars.

tron transporters on the inner mitochondrial membranes to generate adenosine triphosphate. Electron leakage leads to the single electron reduction of molecular oxygen, thus forming superoxide ($O_2^- \bullet$) and, further downstream, ROS (Figure 3). Researchers have applied the term "meal-induced inflammation" to postprandial oxidative stress and have demonstrated its association with recorded increases in CRP and proinflammatory cytokines.[15]

Excess glucose resulting from overnutrition also is mechanistically linked, through insulin metabolism, with the formation of free fatty acids (via increased liver synthesis of lipoproteins, which form free fatty acids in the circulatory system) and the formation of triglycerides within adipocytes (after increased uptake of adipocyte glucose). Insulin production in response to excess carbohydrate levels also decreases breakdown of fat (lipolysis) within adipose tissue, increasing adiposity. Researchers regard adipose tissue as an endocrine organ capable of secreting adipocytokines such as tumor necrosis factor (TNF), interleukin (IL)-6, IL-1, adiponectin and leptin.[16] These adipocytokines also trigger ROS production in inflammatory cells
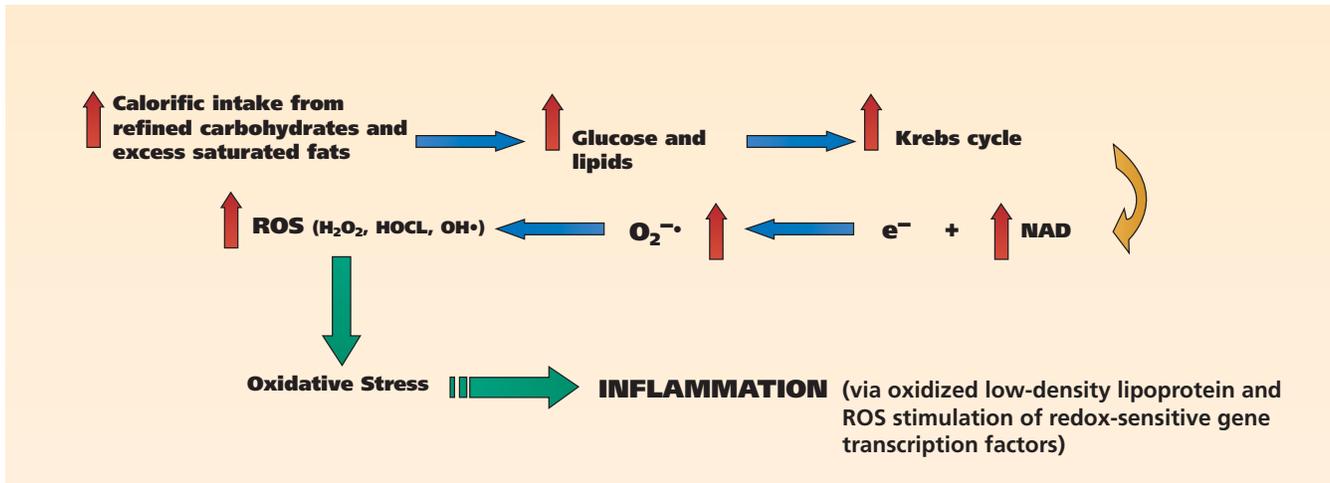
Figure 3. Postprandial dysmetabolism: diets rich in refined carbohydrates and saturated fats stimulate inflammation via the generation of excess ROS and oxidative stress. H_2O_2: Hydrogen peroxide. HOCl: Hypochlorous acid. e^-: Electron. NAD: Nicotinamide adenine dinucleotide. $O_2^-\bullet$: Superoxide. OH•: Hydroxyl radical. ROS: Reactive oxygen species.

via the nicotinamide adenine dinucleotide phosphate oxidase (that is, the enzyme complex that generates functional superoxide radicals from oxygen and glucose) and redox-sensitive gene transcription factors, such as nuclear factor–kappa beta (NF-κB) and activating protein-1 (AP-1),[7] further enhancing inflammatory cascades and oxidative stress. NF-κB and AP-1 trigger production of predominantly proinflammatory cytokines and are controlled by the ROS (activation)/antioxidant (deactivation) balance within the cell.

Oxidative stress is associated with reduced pancreatic beta-cell function and induction of insulin resistance[17] as well as reduced intracellular antioxidant capacity.[18] Thus, chronic elevations in glucose levels induce oxidative stress and, in the longer term, insulin resistance, further elevating plasma glucose levels. Chronic hyperglycemia leads to the creation of advanced glycation end products (AGEs) by nonenzymatic glycation of proteins, which, on binding to their surface receptor for AGEs, trigger further ROS and proinflammatory sequelae by various cells.[19,20]

Saturated fats. Many of the pathways to inflammation stimulated by saturated fats are linked integrally to the aforementioned mechanisms that are associated with high caloric intake from refined carbohydrates and oxidative stress. Additionally, diet-induced hyperlipidemia induces oxidative stress and downstream inflammation,[21] and lipoproteins formed by liver hepatocytes can be converted to free fatty acids within the circula-

tion and taken up by adipocytes, thus acting as a source of proinflammatory adipokines. Furthermore, under conditions of oxidative stress, lipid peroxidation (a chain reaction induced by ROS attack on the polyunsaturated fatty acid [PUFA] side-chains of lipid membranes) arises,[7] low-density lipoproteins are oxidized (oxLDL) and the oxLDLs bind to a group of pattern recognition receptors called "toll-like receptors" (TLR-2/4) on inflammatory cell membranes, triggering NF-κB activation via the protein-kinase-C enzyme and other related pathways. NF-κB transcribes several proinflammatory cytokines.

NUTRITIONAL DOWNREGULATION OF PROINFLAMMATORY CASCADES

Antioxidants. Antioxidants antagonize oxidative stress and proinflammatory events by
■ preventing lipid peroxidation and its sequelae (such as oxLDL formation);
■ removing ROS, thereby preventing NF-κB and AP-1 activation;
■ stimulating anti-inflammatory gene transcription factors (such as nuclear erythroid 2 p45-related factor 2).
■ improving insulin sensitivity, thus abrogating any effects of high levels of glucose in the blood and tissues[22];
■ preventing direct damage to proteins (for example, oxidation of α1-antitrypsin) and DNA.[7]

Researchers have demonstrated antioxidant depletion in periodontitis locally in the periodontium[23] and within plasma, where investigators found an inverse relationship between reduced
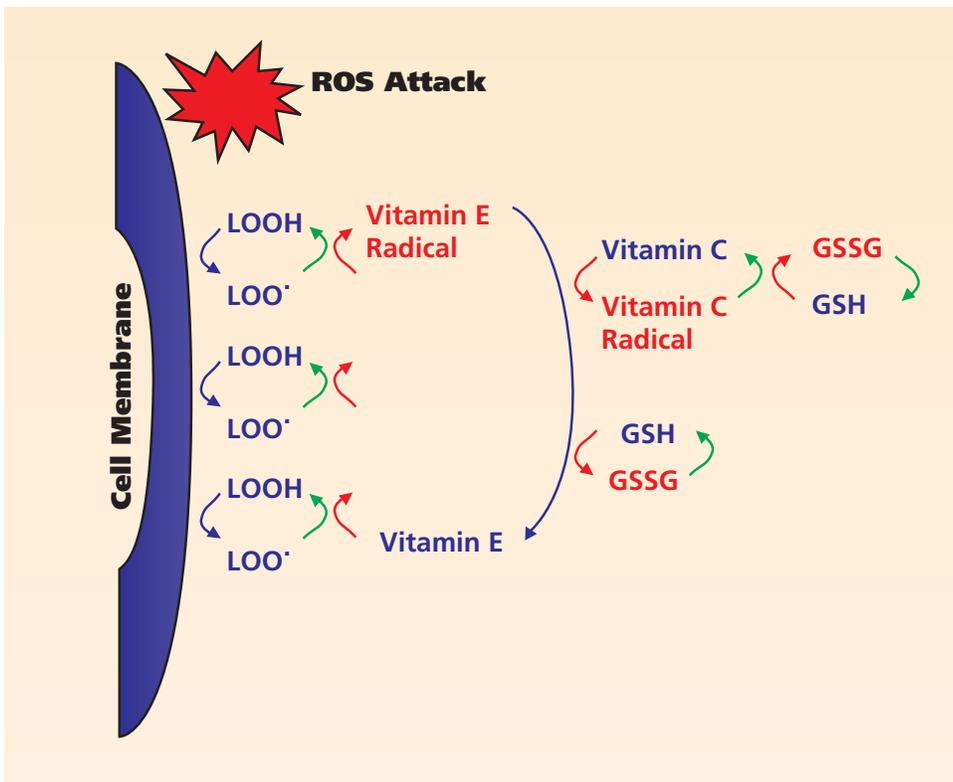
Figure 4. Efficacy of antioxidant cascades in removing lipid peroxyl radicals (LOO•) formed by the attack of reactive oxygen species (ROS) on cell membrane polyunsaturated fatty acid side-chains. Reduced glutathione (GSH) acts as a key chain-breaking antioxidant, forming oxidized glutathiones (GSSGs) rather than secondary radicals. LOOH: Lipid hydroperoxide.

key intracellular antioxidant redox-regulator of NF-κB, as a novel approach to downregulation of hyperinflammatory events.[26] GSH levels appear depleted in periodontitis[27] and methods of enhancing intracellular GSH may prove beneficial.

Omega-3 PUFAs. PUFAs of the omega-3 form (ω-3PUFAs) found in fish oils lower postprandial triglyceride levels[28] and confer anti-inflammatory and cardiovascular protective effects.[29] ω-3PUFAs also inhibit lipid mediators of inflammation (such as prostaglandin E$_2$, arachidonic acid, 5-lipoxygenase and cyclo-oxygenase), modulate lymphokine production and increase antioxidant capacity,[30-32] and are reported to decrease osteoclast activity.[33] Kesavalu and colleagues[34] demonstrated that rats infected with *Porphyromonas gingivalis* and fed a diet rich in ω-3 PUFAs for 22 weeks experienced less bone loss than did control rats fed a diet rich in n-6 PUFAs. Gene expression levels of IL-1β and TNFα decreased, and those of interferon-γ and intracellular antioxidant enzymes increased.[35] One mode of action of PUFAs includes the downregulation of proinflammatory gene expression via the nuclear peroxisome proliferator–activated receptors (PPARs) (Figure 5); others include inflammation-resolving mediators derived from ω-3 PUFAs (resolvins).[36]

Nutrigenomic studies have highlighted the importance of variations in gene structure (for instance, at the transcription factor binding site) on differential responses of patients to specific nutrients.[37] Grimble and colleagues[38] demonstrated that ω-3PUFA supplementation decreased TNFα production by blood monocytes in patients who expressed high baseline production and vice versa. Kornman and colleagues[39] also demonstrated that the benefits of 12 weeks' nutrition using a botanical agent (containing rose hips, blueberries and blackberries) on stimulated mono-
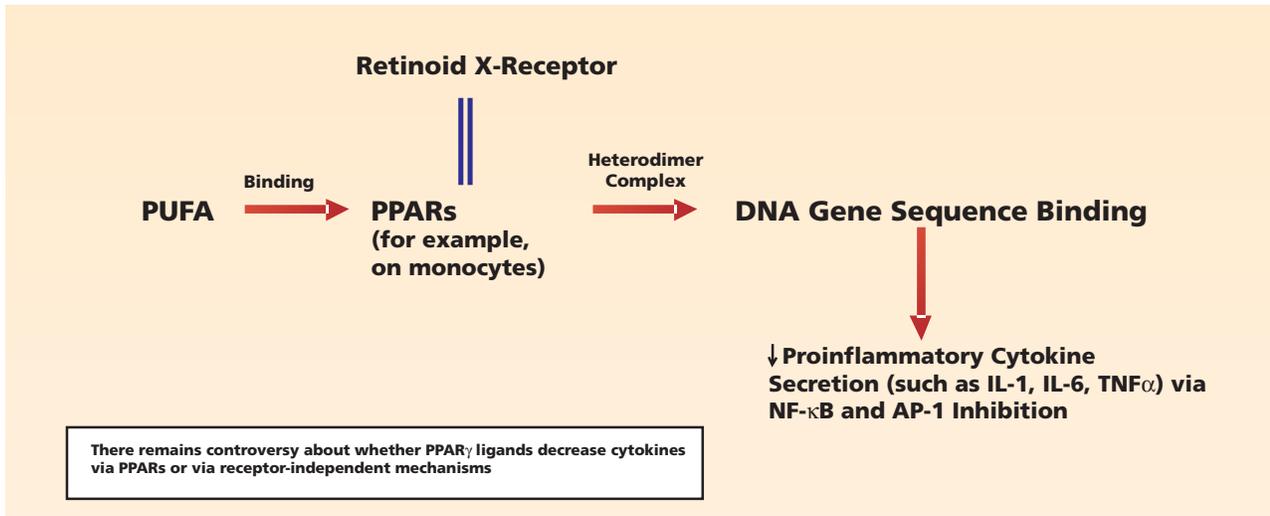
concentrations of plasma total antioxidants and vitamin C and increased prevalence of periodontitis.[24] Intervention studies involving patients with periodontitis and demonstrable vitamin deficiencies, however, are lacking. Therefore, the rationale for individual vitamin supplements as therapeutics in the absence of frank deficiency is flawed because of the potential for in vivo vitamin-radical formation; the need for cooperative antioxidant cascades to be augmented (Figure 4); and the need for only subtle increases in antioxidant status necessary to downregulate proinflammatory gene transcription.[7] Intervention studies performed in the 1980s (reviewed by Chapple and Matthews[7]) using individual vitamin supplements investigated only patients who did not have vitamin deficiency, who were in good periodontal health or both. A recent study of patients with metabolic syndrome provided early indications of the potential of antioxidants found naturally in foods to reduce periodontal inflammation (at clinical and biomarker levels) in patients with disease.[25] Additionally, researchers have proposed reduced glutathione (GSH), the

Figure 5. Downregulation of proinflammatory cascades by omega-3 polyunsaturated fatty acids (PUFAs) working via nuclear peroxisome proliferator–activated receptors (PPARs). AP-1: Activating protein-1. IL: Interleukin. NF-κB: Nuclear factor–kappa B. TNFα: Tumor necrosis factor alpha.

cyte IL-β production were significantly greater in patients with an IL-β polymorphism that overproduced the cytokine (IL-1[Pos]), relative to those with the low-producing polymorphism (IL-1[Neg]). Moreover, the investigators recorded significantly more patients with IL-1[Pos] than patients with IL-1[Neg] who experienced reduced serum CRP with the botanical versus placebo supplementation.[39]

CONCLUSIONS

The evidence for the effect of nutrition on inflammation is robust. It highlights the health benefits of a diet containing foods naturally rich in antioxidants and PUFAs, as well as the dangers caused by diets with high levels of refined carbohydrates (glucose). Nutritional intervention studies in patients with inflammatory periodontal diseases are under way, and such interventions offer great potential as novel therapeutic strategies. However, until more data are available from the results of micronutritional intervention studies of patients with periodontitis, practitioners should provide advice regarding healthy macronutrition by encouraging intake of fruits, vegetables and fish oils. ■

Disclosure. Dr. Chapple reported no disclosures.

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