Dietary modulation of the inflammatory cascade

Dolphus R. Dawson III, Grishondra Branch-Mays,
Octavio A. Gonzalez & Jeffrey L. Ebersole

The control of inflammation has been associated with taking specific oral or parenteral drugs designed to alter or block inflammatory pathways. Moreover, the value of proper nutrition in maintaining good health and balanced immune system is well known and generally we will supplement our diets with certain vitamins and minerals to maintain this balance.

However, we are now realizing the potential benefits of supplementing the diet with other inflammatory mediators, such as essential fatty acids. This review will discuss the immunomodulatory properties of omega-3 fatty acids and other micronutrients, as well as the effect of dietary modulation, on the systemic and oral response to chronic inflammation.

Immune modulation

Omega-3 (n-3) fatty acids

Omega fatty acids are polyunsaturated fatty acids with an acid end (containing the functional carboxylic acid group) and a methyl end (also known as the omega end). In omega-3 fatty acids the first site of desaturation (i.e. the carbon-to-carbon double bond) is located after the third carbon from the omega end. Thus, α-linolenic acid, which harbors three unsaturated carbon-to-carbon double bonds, has a site of unsaturation between the third and fourth carbons from the omega end.

There are three major types of omega-3 fatty acids derived from foods and used by the body: α-linolenic acid; eicosapentaenoic acid; and docosahexaenoic acid. The body converts α-linolenic acid to eicosapentaenoic acid and then to docosahexaenoic acid (Fig. 1). Eicosapentaenoic acid and docosahexaenoic acid are the two types of omega-3 (n-3) fatty acids that serve as important precursors for lipid-derived modulators of cell signaling, gene expression and

inflammatory processes. Most of the α-linolenic acid consumed in the diet comes from plant sources (i.e. flaxseed, walnuts and pecans), with a small percentage in western diets also obtained from chicken and beef. The highest concentrations of eicosapentaenoic acid and docosahexaenoic acid are found in cold-water fish, such as salmon, tuna and herring. The most important polyunsaturated fatty acids biologically are eicosapentaenoic acid and docosahexaenoic acid. Although α-linolenic acid can serve as a precursor for eicosapentaenoic acid and docosahexaenoic acid synthesis in humans, this pathway of synthesis will vary across the general population. Therefore, direct dietary intake of n-3 fats rich in eicosapentaenoic acid and docosahexaenoic acid are of most benefit clinically. However, most western diets are enriched in n-6 polyunsaturated fatty acids derived from vegetable oils such as soybean oil, corn oil and borage oil, and consist of linoleic acid that is converted to arachidonic acid (Fig. 1).

This section will provide evidence that eicosanoids produced from arachidonic acid have critical roles in inflammation and that eicosapentaenoic acid and docosahexaenoic acid give rise to a different group of eicosanoids (termed 'resolvins') that are involved in activities to resolve inflammation, in contrast to those produced from arachidonic acid. Thus, an increased membrane content of eicosapentaenoic acid and docosahexaenoic acid, balanced with a decreased content of arachidonic acid, results in a changed pattern of production of a range of lipid mediators of inflammation. Changing the fatty acid composition of inflammatory cells also affects the production of protein mediators of inflammation (i.e. cytokines, chemokines and adhesion molecules), thus influencing their function (Fig. 2). As a result of their anti-inflammatory capacity, n-3 polyunsaturated fatty acids have been reported to have

therapeutic efficacy in rheumatoid arthritis, inflammatory bowel disease and potentially other inflammatory diseases (discussed later, under 'Effect of dietary modulation in development of systemic disease'), as well as periodontitis (discussed later, under 'Effect of dietary modulation on oral inflammation').

### Incorporation of fatty acids and cell structure

Long-chain fatty acids influence inflammation through a variety of mechanisms, many of which are mediated by, or related to, changes in the fatty-acid

composition of cell membranes. Such changes can modify membrane fluidity, cell signaling (leading to altered gene expression) and the pattern of lipid mediator production. Cells involved in the inflammatory response are typically rich in the n-6 fatty acid arachidonic acid, but the content of arachidonic acid and the ratio of n-3 (eicosapentaenoic acid/docosahexaenoic acid) to n-6 fatty acids can be altered through ingestion of eicosapentaenoic acid and docosahexaenoic acid.

Polyunsaturated fatty acids are important constituents of the phospholipids of all cell membranes. Increased dietary intake of n-3 polyunsaturated fatty acid increases its concentration in complex lipids (triglycerides, phospholipids and cholesteryl esters) within the bloodstream and in the phospholipid pools in membranes of cells and tissues. Thus, following increased intake of eicosapentaenoic acid and docosahexaenoic acid, cells involved in inflammation and their extracellular environment (e.g. blood plasma) are enriched in those fatty acids. Laboratory animals maintained on standard chow have a high content of arachidonic acid (20:4n-6) and low contents of eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3) in the bulk phospholipids of tissue lymphocytes and macrophages (e.g. peritoneal, alveolar and Kupffer cells). However, feeding the animals on a diet containing fish oil, which contains eicosapentaenoic acid and docosahexaenoic acid, results in a higher content of these fatty acids in all these cell types with a concomitant decrease in the content of arachidonic acid (59). Similarly, the bulk phospholipids of blood cells involved in inflammatory
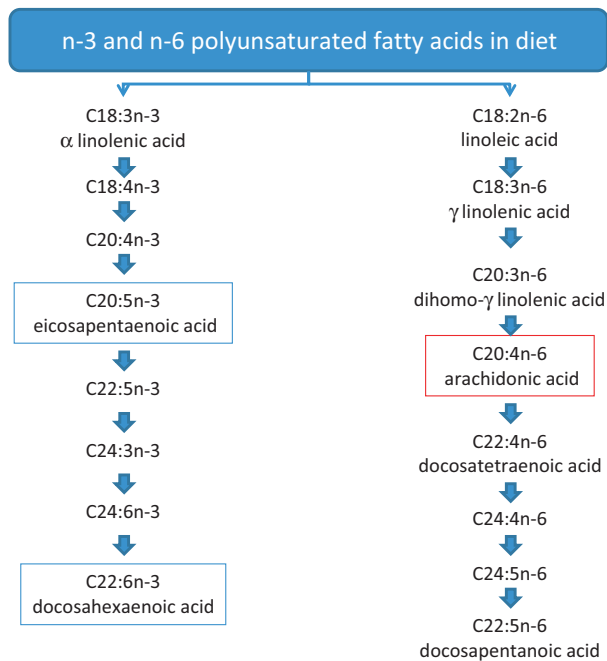

Fig. 1. Elongation and desaturation of polyunsaturated fatty acids from the diet.
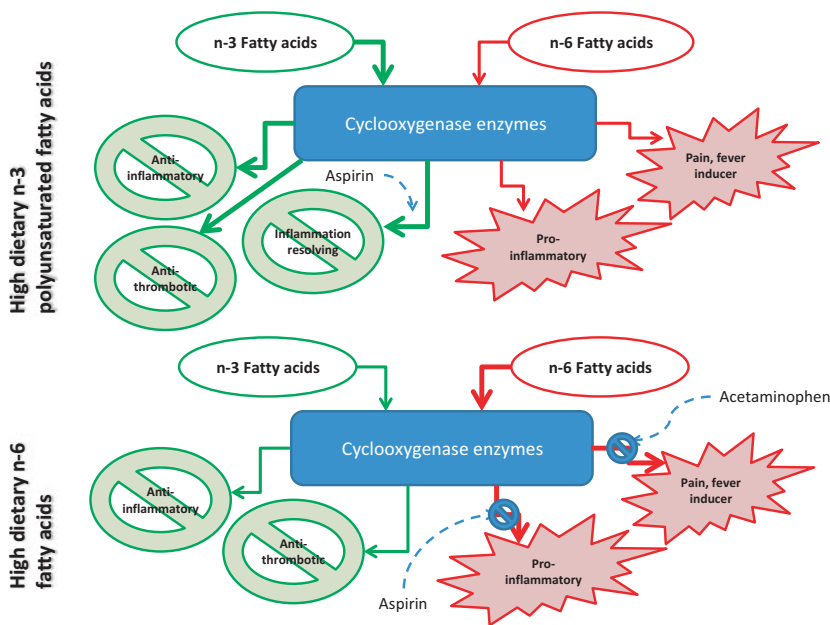
Fig. 2. Effects of dietary n-3 polyunsaturated fatty acids on host responses.

responses in humans consuming a typical western diet contain about 10–20% of fatty acids as arachidonic acid, with about 0.5–1% eicosapentaenoic acid and about 2–4% docosahexaenoic acid (143, 166, 242, 280, 468). This distribution reflects the fact that current intake of n-3 polyunsaturated fatty acids is low in most individuals living in western countries. The fatty-acid composition of these cells can be modified by increasing the intake of n-3 fatty acids (62, 201, 402) and occurs in a dose–response over an interval of days to weeks. Within about 8 weeks a new steady-state composition of the cells is attained, while serum changes are noted as early as 4 weeks (Fig. 3). The increase in the cell-membrane content of n-3 polyunsaturated fatty acids occurs at the expense of n-6 polyunsaturated fatty acids, particularly arachidonic acid. As mentioned earlier, a natural source of eicosapentaenoic acid and docosahexaenoic acid is seafood, especially cold-water oily fish. A recent study demonstrated that oil derived from dietary salmon resulted in a higher rise in eicosapentaenoic acid / docosahexaenoic acid compared with cod oil (116). Additionally, these fatty acids are readily delivered from fish-oil capsules into transport (blood lipids), functional (cell and tissue) and storage (adipose) pools in the body.

However, while dietary supplementation with different classes of polyunsaturated fatty acids results in changes in cell membranes, the effects of these changes on eicosanoid formation and other anti-in-
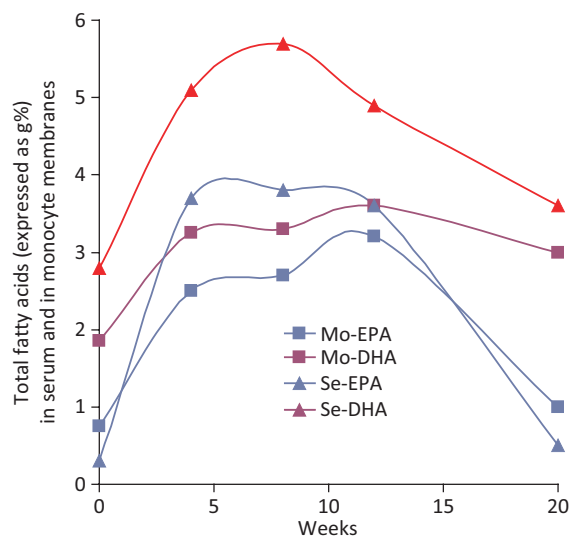
Fig. 3. Incorporation of n-3 polyunsaturated fatty acid into serum and cells. Subjects received a diet containing 23.5% C20:5n-3 eicosapentaenoic acid (EPA) and 13.3% C22:6n-3 docosahexaenoic acid (DHA) as g% of total fatty acids in oils-supplemented diets. Twenty weeks represents washout 8 weeks after stopping the supplement. Adapted from Yaqoob et al. (4).

flammatory functions of cells does not routinely correlate with the alteration in total membrane fatty acids. A recent report suggested that this outcome may be related to compartmentalization of the polyunsaturated fatty acids in organelles and within the cell membranes. The asymmetric distribution of phospholipids in the bilayer membranes of most mammalian cells is well established (219). Aminophospholipids are asymmetrically distributed across the outer and inner portions of the membrane bilayers of most human cells. The physical properties of the membranes are determined in part by the degree of fatty-acid unsaturation. These phospholipids are highly enriched in polyunsaturated fatty acids, and have specific interactions with a number of membrane proteins, altering membrane cation-transport systems (417) and hormone receptor activity (416). These studies indicate that selective incorporation of n-3 fatty acids occurs in the inner membrane phospholipids and that the n-3 phosphatidylserines replace n-6 and n-9 species in erythrocytes. This suggests that dietary alteration in membrane fatty acids could change the degree of asymmetry of phospholipids within cell membranes and that n-3 fatty-acid enrichment may lead to differential effects on the physical properties and functions of the membranes and to variation in cell responses. Similarly, n-3 fatty acids significantly protected erythrocytes from hemolysis and although these fatty acids exhibit a high susceptibility to oxidation, n-3 fatty acids may preserve membrane integrity (257). Finally, a study by Witte et al. (460) found that the fraction of n-3 polyunsaturated fatty acids increased in both red blood cells and white blood cells following consumption of a dietary supplement containing eicosapentaenoic acid / docosahexaenoic acid. Red blood cells demonstrated a linear relationship to the dietary dose of this supplement, but this was not seen in white blood cells, and the magnitude of increase in n-3 polyunsaturated fatty acids was different between the cell types. The findings were interpreted to support that analysis of red blood cell fatty acids reflected the level of dietary supplementation and compliance in the experimental design. However, further analysis of fatty acids in white blood cells would be needed to correlate levels of supplementation and compliance to biologic changes.

Through these mechanisms, eicosapentaenoic acid and docosahexaenoic acid influence cell and tissue physiology and the way in which cells and tissues respond to external signals. In most cases the effects are compatible with improvements in disease and health-related outcomes. As a result, very-long-chain

n-3 polyunsaturated fatty acids can play a role in achieving optimal health and in protection against disease (Table 1).

Modulation of immune-cell functions

Biologically, the n-3 polyunsaturated fatty acids in fish oil have been shown to attenuate inflammatory processes in humans and in various animal models. These effects have been attributed to protective shifts in plasma lipoprotein patterns, cellular eicosanoid formation decreasing platelet aggregation, reduced leukocyte–endothelium interactions, altered production of proinflammatory and anti-inflammatory mediators and an improved range of immune-cell functions (61, 62, 65, 149, 212, 400). As noted earlier, the fundamental mechanism by which omega-3 polyunsaturated fatty acids alter destructive inflammatory responses relates to the enrichment of membrane phospholipids with eicosapentaenoic acid and docosahexaenoic acid. Polyunsaturated fatty acid intake can influence the concentrations of complex lipids, lipoproteins, metabolites and hormones that in turn influence inflammation. Oxidized polyunsaturated fatty acids (enzymatically or nonenzymatically) can act directly on inflammatory cells via surface or intracellular receptors. Mononuclear inflammatory cells may also access fatty acids from lipoproteins by hydrolyzing them extracellularly (66, 261). Thus, cells involved in inflammatory processes are exposed to fatty acids, including polyunsaturated fatty acids, in many different forms, and they may access fatty acids from their environment by a variety of mechanisms.

Table 1. Effects of n-3 polyunsaturated fatty acids on mediators of inflammation

Mediator	Function	n-3 polyunsaturated acid effect
Lipid mediators		
Arachadonic acid	Eicosanoid precursor; platelet aggregation; white blood cell stimulant	↓
Leukotriene	Neutrophil chemoattractant	↓
Prostacyclin	Prevents platelet aggregation; vasodilation	↑
Thromboxane	Vasoconstriction; platelet aggregation	↓
Clotting/tissue factors		
Fibrinogen	Acute-phase protein; blood clotting factor	↓
Tissue plasminogen activator	Increases endogenous fibrinolysis	↑
Platelet-derived growth factor	Chemoattractant/growth factor for macrophages	↓
Platelet activation factor	Activates platelets and white blood cells	↓
Reactive oxygen		
Reactive oxygen species	Cell damage; enhances low-density lipoprotein uptake; stimulates arachadonic acid metabolism	↓
Lipid hydroperoxides	Stimulates the formation of eicosanoids	↓
Peptide mediators		
Interleukin-1beta	Free radical formation; procoagulants; elevated intercellular adhesion molecule 1	↓
Tumor necrosis factor-alpha	Lymphocyte proliferation; altered PAI-1	↓
Interleukin-6	Alter acute-phase proteins	↓
C-reactive protein	Acute-phase reactant	↓
Blood lipids		
Very-low-density lipoprotein	Related to high-density lipoprotein and high-density lipoprotein levels	↓
High-density lipoprotein	Lower risk of cardiovascular disease	↑
Lipoprotein (a)	Atherogenic lipoprotein	↓
Triglycerides	Lipemia	↓
Insulin	Sensitivity	↑

Peptide mediators described in text.

Once resident in cell membranes, observations have been made regarding the primary effects of polyunsaturated fatty acids on the cells: (i) they affect membrane properties, changing the microenvironment of transmembrane receptors and altering interactions with their ligands (239); (ii) they affect the ability of membrane-associated proteins to associate with the membrane and to form multiprotein complexes involved with cell-signaling systems (179, 209); (iii) various inflammatory mediators interact with the membrane receptors and initiate G-protein-linked responses (e.g. activation of phospholipase A_2) that are involved in liberating phospholipids for conversion to a wide variety of eicosanoids (407); (iv) membrane phospholipids are substrates for the generation of second messengers, such as diacylglycerol, with the fatty-acid composition of these messengers determined by the precursor phospholipid influencing their activity (127); and (v) membrane phospholipids are substrates for the release of polyunsaturated fatty acids intracellularly as signaling ligands for transcription factors and a variety of nuclear receptors (94, 253). As an example, dietary fish oil, rich in n-3 polyunsaturated fatty acids, can alter immune-cell function and aid in the resolution of chronic inflammation, including arthritis, Crohn's disease, dermatitis, psoriasis and ulcerative colitis (5, 63, 149, 400, 401). It has been demonstrated that dietary fish oil, as well as purified docosahexaenoic acid, alter the fatty acid composition of the $CD4^+$ T-cell plasma membrane (18) and appear to modulate T-cell function via alteration of lipid raft structure and the translocation of signaling molecules (209).

The multitude and complexity of potential mechanisms has made it difficult to understand fully the actions of polyunsaturated fatty acids within individual aspects of the inflammatory processes. The difficulty is also related to the variety of *in vitro* and *in vivo* experimental approaches for the presentation of polyunsaturated fatty acids of interest to inflammatory cells in order to document their effects. Thus, the effects of polyunsaturated fatty acids on the responses of lymphocytes (67), monocytes / macrophages (64, 137, 308), neutrophils (16, 166, 170, 428) and endothelial cells (94, 205, 372) have been demonstrated. Consequently, the magnitude of data clearly indicates that n-3 polyunsaturated fatty acids can diminish the activity of inflammatory cells and reduce the levels of inflammatory mediators potentially contributing to improving health (163).

Inflammation is a normal defense mechanism that protects the host from infection and other noxious challenges. It is a crucial activity to initiate pathogen-killing and tissue-repair processes to restore tissue homeostasis. Inflammatory responses are normally well regulated to minimize collateral tissue damage. Thus, this regulation requires the activation of feedback pathways, such as the inhibition of proinflammatory signaling cascades, the production of anti-inflammatory mediators, alterations in inflammatory mediator receptor density or release and recruitment / activation of regulatory cells (10, 61, 62, 149, 401). Pathological inflammation involves the dysregulation of these control processes, related to genetic variation in the host and / or characteristics of the extrinsic / intrinsic stimuli of the inflammation. The response involves an increased blood supply to the site of inflammation; increased capillary permeability, which enables larger biomolecules to traverse the endothelium; leukocyte migration into the surrounding tissues in response to the release of chemoattractants and up-regulation of adhesion molecules in the vessels; and the release of mediators from leukocytes at the site of inflammation.

These mediators normally would play a role in host defense, but when produced inappropriately or in an unregulated manner can cause damage to host tissues, leading to disease. Several of these mediators may act as chemoattractants to amplify the inflammatory processes. Moreover, some of these inflammatory mediators may escape the inflammatory site, enter the circulation and exert systemic effects, such as interleukin-6 inducing the hepatic synthesis of acute-phase proteins (e.g. C-reactive protein) and tumor necrosis factor-α eliciting metabolic effects within skeletal muscle, adipose tissue and bone. These processes can lead to irreparable damage to host tissues and disease symptoms, irrespective of the cause of the inflammation. n-3 Polyunsaturated fatty acid appears to have the capacity to modulate the range of cellular functions that can lead to the 'loss of function' associated with chronic inflammatory responses.

Cyclooxygenase / lipoxygenase. Eicosanoids are key mediators and regulators of inflammation and immunity and are generated from 20-carbon polyunsaturated fatty acids. Eicosanoids, which include prostaglandins, thromboxanes, leukotrienes and other oxidized derivatives, are generated from arachidonic acid by specific metabolic processes (Fig. 4). These eicosanoids are involved in modulating the intensity and the duration of inflammatory responses (63, 141, 212, 254, 318), that can be cell and stimulus specific. As many of these biomolecules have opposing activities, the overall physiological or pathophysiological outcomes will depend upon the
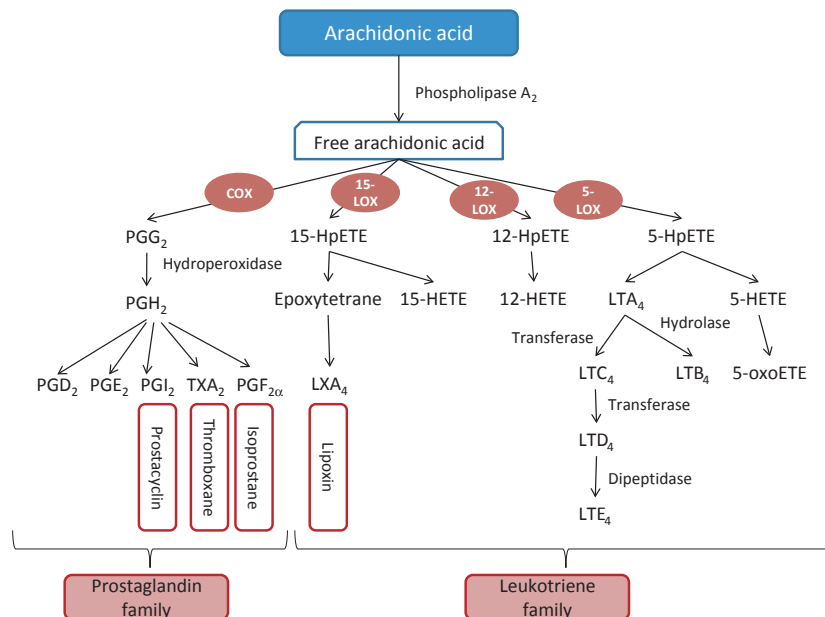
Fig. 4. Eicosanoid production from arachidonic acid. 5-HETE, 5-hydrooxyeicosatetraenoic acid; 5-HpETE, 5-hydroperoxy-eicosatetraenoic acid; 5-oxoETE, 5-oxo-6,8,11, 14-eicosatetraenoic acid; 5-LOX, 5-lipoxygenase pathway; 12-HETE, 12-hydroxyeicosatetraenoic acid; 12-HpETE, 12-hydroperoxy-eicosatetraenoic acid; 12-LOX, 12-lipoxygenase pathway; 15-HETE, 15-hydroxyeicosatetraenoic acid; 15-HpETE, 15-hydroperoxy-eicosatetraenoic acid; 15-LOX, 15-lipoxygenase pathway; COX, cyclooxygenase pathway; LTA_4, Leukotriene A_4; LTB_4, Leukotriene B_4; LTC_4, Leukotriene C_4; LTD_4, Leukotriene D_4; LTE_4, Leukotriene E_4; LXA_4, Lipoxin A_4; PGD_2, Prostaglandin D_2; PGE_2, Prostaglandin E_2; $PGF_{2\alpha}$, Prostaglandin F_2; PGH_2, Prostaglandin H_2; PGG_2, Prostaglanding G_2; PGI_2, Prostaglandin I_2; TXA_2, thromboxane A_2.

cells present, the nature of the stimulus, the timing of eicosanoid generation, the concentrations of different eicosanoids generated and the sensitivity of target cells and tissues to the eicosanoids generated. A recent study demonstrated that oil derived from dietary salmon resulted in a greater increase in eicosapentaenoic acid / docosahexaenoic acid compared with cod oil. Moreover, the levels of eicosapentaenoic acid and docosahexaenoic acid were negatively correlated with lipopolysaccharide-induced tumor necrosis factor-α, interleukin-8, leukotriene B_4, thromboxane B_2 and tissue factor in whole blood (116).

Evidence supports a direct relationship between the arachidonic acid content of inflammatory cell phospholipids and the ability of those cells to produce decreases in prostaglandin E_2 in the presence of eicosapentaenoic acid or docosahexaenoic acid (255, 270, 363). Moreover, it is well documented that the amounts of prostaglandin E_2 and proinflammatory leukotrienes produced by human inflammatory cells can be significantly decreased by dietary fish oil supplementation for a period of weeks to months (242, 272, 407, 439). Eicosapentaenoic acid is also a substrate for the cyclooxygenase and lipoxygenase enzymes that produce eicosanoids, but the mediators produced have a different structure from the arachidonic acid-derived mediators and are often much

less biologically active. Furthermore, eicosapentaenoic acid-derived eicosanoids may antagonize the action of those produced from arachidonic acid (428) (Fig. 4). Additionally, the lipoxin family of molecules derived from arachidonic acid is clearly anti-inflammatory (discussed later).

The biologic effect of eicosanoids depends largely upon the relative masses, in tissues, of eicosanoids derived from the n-6 fatty acids, dihomogammalinolenic acid and arachidonic acid, and the n-3 fatty acid, eicosapentaenoic acid. Generation of this tissue balance is related to the relative cellular masses of these precursor fatty acids, the competition between them for entry into and release from cellular phospholipids and their competition for the enzymes that catalyze their conversion to eicosanoids. These observations provide the context for the effective use of these fatty acids in dietary therapies directed at modulation of eicosanoid production. As noted, these eicosanoids critically influence a wide range of physiologic and pathologic processes, including inflammation and immunity (61–63, 212, 400).

Antioxidants. The effects of n-3 polyunsaturated fatty acids on oxygen radicals and antioxidants have been reported as major effectors of these dietary supplements (21, 63, 148, 149, 426, 427). Fatty acids

in membrane lipids are vulnerable to free radical-initiated oxidation that can be generated either by xenobiotics or by normal aerobic cellular metabolism, resulting in the formation of lipid peroxides (133, 403). Lipid peroxides in biological membranes are highly destructive and toxic biomolecules. Lipid peroxide by-products have been implicated in the etiology of a number of diseases, including cardiovascular diseases and atherosclerosis (78, 129, 437). Recent studies have investigated the effect of n-9 (olive oil), n-6 and n-3 polyunsaturated fatty acid ethyl esters on basal (uninduced) and Fe^{2+}/ascorbate (induced) lipid peroxidation in salivary glands of mice. The results showed that tissue susceptibility to lipid peroxides increased in the following order: olive oil < corn oil < safflower oil < n-3 ethyl esters. n-3 Polyunsaturated fatty acids increased the superoxide dismutase and catalase activities in salivary gland tissue. The authors concluded that feeding olive oil increases the resistance of salivary glands to induced and uninduced lipid peroxides (22). The salivary glands secrete various proteins (immunoglobulin A) and antioxidant enzymes that serve a vital role in maintaining optimal health of the oral cavity (including gingival and periodontal tissues) and the upper respiratory tract. Dietary lipids have a profound effect on lipid peroxides in salivary glands, which clearly indicates that these lipids probably have a similar effect on other mucosal tissues.

Chemotaxis and adhesion molecules. Various chemoattractants, including leukotriene B_4, bacterial peptides and human serum, are crucial molecules for host-cell (neutrophils and monocytes) chemotaxis to local sites of challenge (39, 207, 263, 396, 445). n-3 Polyunsaturated fatty acids have been shown to decrease both the distance of cell migration and the number of cells migrating to inflammatory stimuli (374). Additional studies have suggested that the chemotactic effect may be a more specific function of eicosapentaenoic acid within the n-3 polyunsaturated fatty acids family; however, the mechanism remains unclear and may be related to reduced expression or antagonism of receptors for these chemoattractants (166, 334). *In vitro* and *in vivo* studies (5, 39, 202, 281, 282, 372, 428) have also reported a decreased expression of adhesion molecules (e.g. intercellular adhesion molecule-1 and vascular cell adhesion molecule-1) on the surface of mononuclear immune cells and endothelial cells, related to the administration of n-3 polyunsaturated fatty acids. These findings also supported a decreased interaction between leukocytes and endothelial cells that would be predicted to alter local inflammatory responses.

Cytokines/chemokines. In addition to effects on inflammation mediated by changes in the pattern of eicosanoids and other lipid mediators, n-3 polyunsaturated fatty acids have been shown to alter the production of inflammatory proteins including chemokines, cytokines, growth factors and matrix metalloproteinases. This effect may be mediated by altered activation of key transcription factors involved in regulating the expression of genes encoding inflammatory proteins, including nuclear factor kappa-light-chain-enhancer of activated B cells and peroxisome proliferator-activated receptor-gamma. Nuclear factor kappa-light-chain-enhancer of activated B cells is the principal transcription factor involved in the up-regulation of inflammatory cytokine, adhesion molecule and cyclooxygenase-2 genes (6, 230), while peroxisome proliferator-activated receptor-gamma may have an anti-inflammatory action by interfering with the activation of nuclear factor kappa-light-chain-enhancer of activated B cells. Eicosapentaenoic acid and docosahexaenoic acid inhibit lipopolysaccharide induction of nuclear factor kappa-light-chain-enhancer of activated B cells, alter mitogen-activated protein kinase activation and the production of interleukin-6, interleukin-8 and tumor necrosis factor-α by endothelial cells (192, 446) and monocytes (253, 286, 308). Dietary fish oil supplementation alters the activation of nuclear factor kappa-light-chain-enhancer of activated B cells in lymphocytes (67, 123, 203, 443), as well as the production of various cytokines (e.g. tumor necrosis factor-α, interleukin-1β and interleukin-6) by challenged macrophages (46, 60, 354, 442). Similar dietary effects have been reported in human studies (2, 34, 77, 118, 273, 426). The relative contributions of eicosapentaenoic acid and docosahexaenoic acid in dietary fish oil appear to be important in determining the effect of supplementation on the individual.

Phagocytosis. The role of different families of fatty acids in modulating phagocytosis and the oxidative burst has also been investigated. An *in vitro* study showed that macrophages cultured in elevated levels of linolenic acid demonstrated enhanced phagocytosis and decreased oxidative burst (137). Kew et al. (201) examined the effects of altering the type of n-3 polyunsaturated fatty acids in mouse diets on monocyte and neutrophil phagocytosis. There was no significant effect of dietary docosahexaenoic acid on

monocyte or neutrophil phagocytic activity; however, dietary eicosapentaenoic acid decreased the number of phagocytic monocytes and neutrophils in a dose-dependent manner. This same group also examined the relationship between the fatty acid composition of human immune cells and the function of those cells over a range of fatty acid intake. Wide variations in fatty acid composition of peripheral blood mononuclear cell phospholipids and immune cell functions were identified among the population examined. The proportions of total polyunsaturated fatty acids, of total n-6 and n-3 polyunsaturated fatty acids, and of several individual polyunsaturated fatty acids in peripheral blood mononuclear cell phospholipids were positively correlated with phagocytosis by neutrophils and monocytes, neutrophil oxidative burst, lymphocyte proliferation and interferon-gamma production. Therefore, variations in the fatty acid composition of peripheral blood mononuclear cell phospholipids account for some of the variability in immune cell functions among healthy adults (200).

Finally, the expression of CD36, a multifunctional adhesion receptor and a scavenger receptor for oxidized low-density lipoproteins, on monocytes was evaluated. Incorporation of eicosapentaenoic acid and docosahexaenoic acid into cellular phospholipids resulted in a significant reduction of CD36 expression at both mRNA and protein levels, whereas the incorporation of arachidonic acid and linoleic acid increased CD36 expression. This specific down-regulation of CD36 by n-3 polyunsaturated fatty acids would be predicted to represent another mechanism that may contribute to the beneficial effects of n-3 polyunsaturated fatty acids in regulating chronic inflammation (331).

Resolution of inflammation

Eicosapentaenoic acid and docosahexaenoic acid also give rise to resolvins and protectins through pathways involving cyclooxygenase and lipoxygenase (Fig. 5) (246, 384, 385, 388). These lipid mediators have anti-inflammatory and inflammation-resolving capabilities. Resolvin E1, resolvin D1 and protectin D1 all inhibit migration of neutrophils from capillaries and limit neutrophil infiltration at sites of inflammation (17, 384). Both resolvin and protectin appear to inhibit the production of interleukin-1β and tumor necrosis factor-α (27, 378). The role of resolvins and related compounds is increasing in importance because the resolution of inflammation is crucial in shutting down the active inflammatory process and in limiting tissue damage (70, 171, 409, 429, 464).

Resistance to infections

The effect of dietary lipid intake on resistance to infection suggests that those fatty acids are involved in the modulation of immune responses through different and complex pathways. Dietary supplementation with fish oil significantly increased the survival of mice following *Klebsiella pneumoniae* infections (48, 49). Mice fed diets enriched with fish oil had higher survival, significantly reduced bacterial translocation to the liver, improved barrier function and improved microbial killing in a gut-derived sepsis model with *Escherichia coli* (140). A range of polyunsaturated fatty acids, including n-3 linolenic acid, significantly inhibited growth of *Helicobacter pylori* (421). Such reports demonstrate the effectiveness of dietary n-3 fatty acids in improving resistance to extracellular pathogens. Dietary fish oil reduced survival and impaired bacterial clearance in mice challenged with the intracellular pathogen, *Listeria monocytogenes* (135, 136). Mice fed fish oil showed decreased Kupffer cell phagocytosis, oxidative burst and expression of adhesion molecule (CD18) and of surface Ia, and an increased death rate, when challenged with *Salmonella typhimurium* (81, 112).
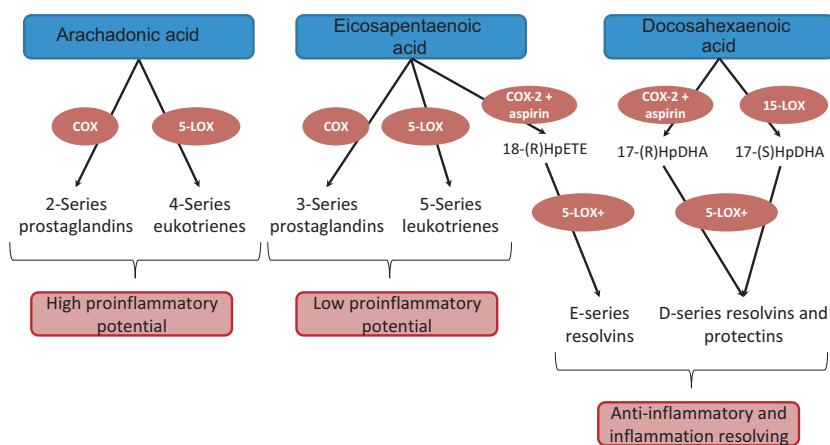
Fig. 5. Lipid mediators from arachadonic, eicosapentaenoic and docosahexaenoic acids. 5-LOX, 5-lipoxygenase pathway; 15-LOX, 15-lipoxygenase pathway; COX, cyclooxygenase pathway; COX-2, cyclooxygenase 2; HETE, hydrooxyeicosatetraenoic acid; HpDHA, hydroperoxydocosahexanoic acid; HpETE, hydroperoxy-eicosatetraenoic acid.

Increased dietary n-3 polyunsaturated fatty acids suppressed leukotriene B_4 and prostaglandin E_2 synthesis, accompanied by an increased number of *Mycobacterium tuberculosis*, in guinea pigs (270, 324). Thus, diets rich in n-3 fish oil also alter host resistance to intracellular bacterial pathogens. In addition, mice fed with fish oil showed delayed clearance of influenza virus and impaired production of interferon, virus-specific immunoglobulin A and virus-specific T-lymphocyte cytotoxicity (57, 58).

The role of n-3 polyunsaturated fatty acids in shaping and regulating inflammatory processes suggests that the level of exposure to these fatty acids determines the development and severity of inflammatory diseases. The recognition that n-3 polyunsaturated fatty acids have anti-inflammatory capabilities supports dietary supplementation of patients with inflammatory diseases as a clinical strategy. For many inflammatory diseases and conditions there are too few studies to draw a clear conclusion of the possible efficacy of n-3 polyunsaturated fatty acids as a treatment. Moreover, the dose of n-3 polyunsaturated fatty acid required to prevent or to treat different inflammatory conditions remains ill-defined, although it is evident that the anti-inflammatory effects of these fatty acids are dose-dependent (353). One facet of these differences is that the precise nature of the inflammation, including critical cells, mediators and signaling systems, will differ across chronic inflammatory conditions (63) and these activities may show different sensitivities to n-3 polyunsaturated fatty acids. Additional details, linking these biologic effects of n-3 polyunsaturated fatty acids to specific systemic and local inflammatory lesions, are given in the sections 'Effect of dietary modulation in development of systemic disease' and 'Effect of dietary modulation on oral inflammation'.

Micronutrients in immune modulation

It has been clearly established that in addition to the protein-energy intake that is critical for basic nutritional purposes, the presence of vital dietary minerals, such as iron, zinc, iodine, selenium, copper, phosphorous, potassium and magnesium, as well as vitamins A, the B complex, C, D and E, are also crucial players for an overall healthy state throughout life (38, 86, 154). This group of minerals (or trace elements) and vitamins are named micronutrients, as, in contrast to other nutrients, they are needed in tiny quantities (a few thousandths of a gram or less each day) (15). Micronutrients are important as cofactors in several enzymatic reactions and for the

production of hormones and other substances that are required for regulating biological processes associated with growth, development, hematopoiesis and immune functions (45, 51, 97). Evidence specifically associated with the effects of micronutrients on the immune-inflammatory response and the outcome when they are used as dietary supplements will be discussed later in this article.

Vitamins and antioxidant supplements in immune modulation

Vitamins are organic substances that are not synthesized by the body and are necessary for normal metabolism. In general, vitamins can be classified into water-soluble vitamins (i.e. folate, vitamin B_6, vitamin B_{12} and vitamin C) and fat-soluble vitamins (i.e. vitamin A, vitamin D and vitamin E). Most water-soluble vitamins are absorbed easily from the proximal gastrointestinal tract, whereas fat-soluble vitamins are absorbed in the mid- and distal ileum because digestion of fat by bile and pancreatic lipase is required (410). In addition to nutritional impacts on infections, various studies have identified the capacity of dietary modulation with vitamins to affect a myriad of host responses. The role of vitamins on the immunoinflammatory response and host resistance to infection has been previously reviewed (128, 260). Briefly, vitamin B_6, vitamin B_{12} and folate have been shown to interfere with immune functions through their involvement in the biosynthesis of nucleic acid and protein (79, 348). The T-lymphocyte plays a critical role in determining the type and extent of immune response via the production of cytokines in response to stimulation (290). T-helper 1 subset lymphocytes produce interleukin-2 and interferon-gamma, which enhance cell-mediated immunity, while the T-helper 2 subset produces interleukins 4, 5, 6 and 10, and boosts humoral immunity. The T-helper 0 subset of lymphocytes produces both T-helper 1 and T-helper 2 type cytokines. Particularly, vitamin B_6 and folate appear to maintain a T-helper 1 response and natural-killer cell function, respectively (79, 256, 350). Although oxidative stress is a critical mechanism for killing pathogens, it could also damage cell integrity and tissues. Vitamin C has shown effective antioxidant properties that are important for maintaining the redox integrity of cells and protection against reactive oxygen species generated during the respiratory burst and inflammatory responses (438), and the ability to enhance neutrophil, monocyte and natural-killer cell functions (169, 398). With regards to the fat-soluble proteins, vitamin A, which acts through all-*trans*

retinoic acid and nuclear retinoic acid receptors, appears to be essential for epithelial cell differentiation, humoral antibody responses, cell-mediated immunity and supporting a T-helper 2 anti-inflammatory response (413). Vitamin D is normally metabolized to $1,25(OH)_2D_3$, which exerts its function in virtually all immune cells because most express vitamin D receptors, except for B cells (71, 434). It has been shown that vitamin D promotes the differentiation of monocytes to macrophages and that its metabolite, $1,25(OH)_2D_3$, inhibits the maturation of dendritic cells that produce IL-12 and also enhances the production of IL-10 (i.e. a T-helper 2 response) (226, 267, 431). Finally, vitamin E is considered as the most important fat-soluble antioxidant, which protects the membrane lipids from oxidative damage, reduces the production of prostaglandin E_2 in macrophages, improves T-helper 1 responses in old mice demonstrating a defect in this function and suppresses T-helper 2 responses (160, 271). Of note, several clinical studies have shown positive effects of supplementation of vitamin E on the immune response, particularly in aged populations (159, 274, 275). The outcomes included significantly increased T-cell proliferation, thus improving the $CD4^+/CD8^+$ T-cell ratio, and decreased oxidative stress in healthy adults (237).

In animal studies, inflammatory stimuli are influenced by dietary intake of copper, zinc, selenium, *N*-acetylcysteine and vitamin E, and a cocktail of antioxidant nutrients have reduced the inflammatory symptoms in inflammatory joint disease, acute and chronic pancreatitis, and adult respiratory distress syndrome (148). Thiobarbituric acid reactive substances are routinely used as a measure of oxidative stress that contributes to destructive lipid peroxidation by-products (248, 361). Following vitamin E supplementation, the levels of thiobarbituric acid reactive substances were found to be significantly lower than baseline levels in subjects with type 2 diabetes (465). Various reports describe an array of effects of altered nutrition on resistance to infections. Impaired antioxidant defenses may contribute to disease progression with HIV, and treatment with antioxidants may slow the progression of AIDS (148). Protein-energy malnutrition is associated with greater malaria morbidity and mortality, and controlled trials of either vitamin A or zinc supplementation suggested the potential of these substances to substantially reduce clinical complications of malaria attacks (392). Treatment of established infections with vitamin A is effective in measles-associated complications (422).

In response to periodontal pathogens, polymorphonucleotides release destructive oxidants, proteinases and other factors that can damage host tissues (119, 120). Oxidants (H_2O_2, free radicals and hypochlorous acid) enhance the production of interleukin-1, interleukin-8 and tumor necrosis factor in response to inflammatory stimuli, and antioxidant defenses protect the host against the damaging influences of this type of cytokine/oxidant response. An increased plasma content of peroxidative by-products (thiobarbituric acid reactive substances), a decreased antioxidant plasma capacity, together with a reduced lag time for *in vitro* oxidation of low-density lipoprotein, and diminished plasma nitric oxide bioavailability were observed in aged subjects. Thus, advancing age increases the susceptibility of low-density lipoprotein to oxidative modifications and favors platelet activation through an oxidized low-density lipoprotein-induced decrease of nitric oxide bioactivity (99). In experimental models of liver injury induced by ethanol, the cytotoxic activity of tumor necrosis factor-α is principally mediated through tumor necrosis factor receptor p55. The plasma levels of tumor necrosis factor soluble receptor p75 are positively correlated with thiobarbituric acid reactive substances. Tumor necrosis factor receptor p55 probably mediates the cytotoxicity of tumor necrosis factor-α, and that cytotoxic effect could be amplified by glutathione peroxidase depletion in enhancing lipid peroxidation (298). A physiological increase of oxidative stress has been observed in pregnancy. The effect of a daily combined supplement of iron and vitamin C in the third trimester of pregnancy on lipid peroxidation (plasma thiobarbituric acid reactive substances) was evaluated. In the supplemented group, the plasma iron level was higher than in the control group and the plasma levels of thiobarbituric acid reactive substances were significantly enhanced. These data show that pharmacological doses of iron, associated with high vitamin C intake, can result in uncontrolled lipid peroxidation (232). An increase in plasma tumor necrosis factor-α and nitric oxide was blunted by glycine feeding of rats. Hemorrhagic shock resulted in oxidative stress (significant elevations in thiobarbituric acid reactive substances with an elevated oxidized/reduced glutathione ratio) and this was accompanied by a reduced activity of the antioxidant enzymes manganese- and copper, zinc-superoxide dismutase, glutathione peroxidase and catalase, overexpression of inducible nitric oxide synthase and activation of nuclear factor kappa-light-chain-enhancer of activated B cells. Glycine ameliorated oxidative stress and the impairment in

antioxidant enzyme activities, inhibited the activation of nuclear factor kappa-light-chain-enhancer of activated B cells and prevented the expression of inducible nitric oxide synthase. Dietary glycine blocks the activation of different mediators involved in the pathophysiology of liver injury after shock (269). An additional study investigated a complex of oxidative stress markers in patients with chronic renal failure and evaluated the relationship between different oxidative stress markers and the degree of renal failure. The findings suggested that renal patients are in a state of oxidative stress compared with healthy controls. Free-radical-mediated oxidative stress has been implicated in adverse tissue changes in a number of diseases. In view of the role of oxidative processes in noninsulin-dependent diabetes mellitus (type 2 diabetes mellitus), in this study we investigated the oxidant and antioxidant status of plasma in patients with noninsulin-dependent diabetes mellitus and the effect of vitamin E supplementation on oxidative stress, and the antioxidant defense system. Following vitamin E supplementation, the levels of thiobarbituric acid reactive substances were found to be significantly lower than the baseline value of type 2 diabetes mellitus. On the other hand, the activities of glutathione peroxidase-px and superoxide dismutase were significantly higher than baseline values (145). Lipid peroxide by-products have been implicated in the etiology of a number of diseases, including cardiovascular diseases and atherosclerosis (361, 465).

Studies in mouse models showed that feeding n-3 polyunsaturated fatty acids significantly increased superoxide dismutase, catalase, glutathione peroxidase and glutathione-*S*-transferase (glutathione peroxidase-*S*-transferase) activities (21, 126, 435), maintained superoxide dismutase, catalase and glutathione peroxidase activity as well as (190) increased mRNA expression in the kidney (80). A number of reports have described the potential contribution of antioxidants to oral inflammation and disease (20, 245, 289, 303, 462). These studies have generally been oriented towards providing exogenous antioxidants as dietary supplements, with a few of the studies actually demonstrating a moderating effect.

Trace elements in immune modulation

The contribution of trace elements to the immune function and resistance to infection, as well as their role in controlling inflammation, has also been a focus of research during the last decade (45, 91, 260, 457). The evidence particularly related to the immunomodulatory effects of zinc, iron, selenium and copper in the adaptive and the innate immune responses, as well as their impact on infectious diseases, will be discussed for each element.

Zinc. Zinc is an essential mineral for several biological ∕ biochemical functions, including growth and development, apoptosis, the activity of more than 100 enzymes related to the basic metabolism of macromolecules (i.e. proteins and nucleic acids), heme synthesis, CO_2 transport and hematopoiesis, among others (131, 211, 419). In addition, zinc has been shown to be critical for the normal development, differentiation and function of cells from both arms of the immune system, and for innate and adaptive immunity. Deficiencies in zinc appear to be a prevalent human health problem particularly related to children, the elderly and patients with immunosuppressive disorders (e.g. sickle cell anemia and AIDS), enteritis, celiac disease and diarrhea (33, 45, 338). Importantly, short periods of zinc supplementation substantially improve immune defense within this group of individuals (422). Evidence related to the immunomodulatory effects of zinc has been elegantly reviewed in recent publications (128, 183, 333, 337). In general, zinc appears to play a critical role in chemotaxis and in the levels of oxygen radicals (i.e. oxidative burst) produced by neutrophils, as well as in efficient pathogen phagocytosis and killing by macrophages; however, zinc can also act as an antioxidant because it is a key cofactor for the activity of the antioxidant enzyme superoxide dismutase (183, 333, 458). Interestingly, zinc deficiency has been associated with a specific reduction in T-helper 1 cytokines (i.e. interferon-gamma, interleukin-2 and tumor necrosis factor-α), but did not affect the production of T-helper 2 cytokines (i.e. interleukin-4, interleukin-6 and interleukin-10). Additionally, lower levels of zinc appear to reduce natural-killer cell function, complement activity (37) and activation of nuclear factor kappa-light-chain-enhancer of activated B cells (228). With regard to the adaptive immune response, zinc appears to be involved in the early processes of B- and T-cell maturation, as well as in the efficient production of CD4$^+$ memory T-cells after antigen encounter (37, 132). Patients with zinc deficiency exhibit thymic atrophy and impaired function of the thymic hormone, thymulin, which is important for the expression of T-cell markers, T-cell function and interleukin-2 production (335, 336). Moreover, at the molecular level zinc stimulates the autophosphorylation of the protein tyrosine kinase Lck by noncovalent interactions in CD4 and CD8 cells, leading to T-cell activation (328). Interestingly,

inflammation appears to be linked to zinc homeostasis. Thus, the proinflammatory cytokine interleukin-6 enhances zinc uptake and intracellular storage by hepatocytes through the up-regulation of membrane zinc transporters and the zinc-binding protein methallothionein (251, 376). Therefore, a significant decrease in the plasma levels of zinc (hypozincemia) is normally associated with inflammation (330). Zinc also has shown a direct effect on cytokine production by monocytic cells, altering intracellular pathways activated by toll-like receptor (i.e. toll-like receptor-4) activation and reducing proinflammatory cytokine production in a dose–response manner (156, 157). In general, the production of proinflammatory cytokines is modulated by zinc in a biphasic manner, where low concentrations of zinc increase the release of cytokines, whereas higher concentrations lead to a complete abrogation of cytokine release (157).

Iron. Iron is an essential micronutrient involved in oxygen delivery, metabolism and redox regulation. In contrast to other elements that are regulated by eliminating excess, iron requires more complex cellular mechanisms of conservation, and uptake should be limited until iron is required (453). Normally in the host, iron is only available bound to specific proteins, such as transferrin, lactoferrin and ferritin, or complexed to heme within hemoproteins (167). The role of iron in infection and inflammation has been extensively studied (313, 373, 451), and the general consensus indicates that both elevated and reduced iron availability affect the host immune responses, as well as susceptibility to infections, which highlights the importance of a normal level of iron for health (373). As iron is essential not only for the host immune response but also for the proliferation and survival of pathogens, the mechanisms to control iron levels need to be tightly regulated in order to guarantee a protective response with a simultaneous restricted access to iron for pathogens (313). The main effect of iron on the immune system appears to be associated with T-cells and cell-mediated immunity, whereby reduced proliferation and maturation of T-cells, as well as impaired function of macrophages and neutrophils, are related to low iron levels (36, 55). Specifically, reduced transcription and function of critical enzymes for bacterial killing during phagocytosis are associated with iron deficiency (i.e. inducible nitric oxide synthase, myeloperoxidase and NADPH oxidoreductase) (55, 142). In addition, antigen-specific, polyclonal T-cell proliferation and CD28 expression (a key costimulatory T-cell receptor) are reduced in iron-depleted mice (231). Importantly,

iron status and the production of inducible nitric oxide synthase by macrophages are regulated by interferon-gamma; thus, increased iron levels result in decreased activity of inducible nitric oxide synthase and vice versa (452). The association of iron with tumor necrosis factor-α seems to be more complex and, while in some cases higher levels of this proinflammatory cytokine have been related to hypoferremia, macrophages may also increase intracellular iron in the presence of tumor necrosis factor-α, which results in the activation of nuclear factor kappa-light-chain-enhancer of activated B cells and the expression of genes relevant for macrophage function (393). On the other hand, a significant body of evidence supports the fact that elevation in the levels of iron stores generally increase disease susceptibility and impair the inflammatory response to infections such as tuberculosis, malaria, *Yersinia enterocolitica* and some viruses (340, 349). Of note, iron levels in the gingival crevicular fluid increased threefold following ligature-induced periodontitis in beagle dogs compared with the healthy controls, which might play an important role in the growth and virulence of periodontopathogens (295). Similarly, chronic inflammatory diseases (i.e. diabetes, obesity, metabolic syndrome and atherosclerosis) are highly influenced by iron status, with aggravated disease expression associated with increased iron stores and loading (189, 346, 433). The hormone hepcidin is an important link between iron and inflammation or infections, with the production of hepicidin being directly correlated with iron levels and enhanced by the proinflammatory cytokines interleukin-6 and interleukin-1β, via stimulation with toll-like receptor 2 and toll-like receptor 4 (222, 241, 329). Thus, infection and inflammation are generally associated with increased production of hepcidin. Overall, iron metabolism and storage reflect a complex molecular process that appears to change depending on the cell type and certain environmental and genetic conditions; this perhaps explains the controversial results obtained on the anti-inflammatory and anti-infectious properties of iron in several *in vitro* and *in vivo* studies.

Selenium. Selenium is a trace element normally found in the amino acid selenocysteine, which is a member of the selenoproteins (e.g. gluthatione peroxidase and type I iodothyronine deiodinase) that are essential for human and animal life (223, 380). Besides the property of selenium as a regulator of thyroid hormones, growing evidence indicates that selenium also modulates immunoinflammatory responses. Infact, selenium deficiencies decrease the

affinity and expression of interleukin-2R on T-cells, and alter T-cell proliferation and differentiation, as well as lymphocyte cytotoxicity reactions (213, 215, 362). Specifically, decreased proliferation of CD8$^+$ T cells, increased proliferation of CD4$^+$ T cells and decreased immunoglobulin M and immunoglobulin G responses have been shown to occur in animal models as a result of selenium deficiencies (32, 214, 220). Growing evidence supports a fundamental role of selenium in the control of the inflammatory response, and several *in vitro* studies indicate that selenium appears to have an important role in the control of inflammation induced by pathogens, including bacteria and viruses (102). In addition, a reduction in the levels of selenium has been observed with the severe inflammatory response syndrome, sepsis and higher levels of C-reactive protein (259, 370). Interestingly, variation in selenium levels could affect the course of viral infections in which lower levels of selenium increase HIV-1 replication and enhance mutations of the influenza A virus (182, 299). Although the anti-inflammatory mechanisms of selenium are not totally understood, it has been suggested that it could have effects on macrophage activity, as well as in balancing the redox state. In this function the selenoenzymes thioredoxin and gluta-thione peroxidase play a key role in removing excess damaging lipid-hydroperoxides, hydrogen peroxide and peroxinitrites produced during oxidative stress. Additionally, selenium regulates the activity of transcription factors (i.e. nuclear factor kappa-light-chain-enhancer of activated B cells and activator protein-1) and associated gene expression (125, 457). In fact, selenium reduced the levels of tumor necrosis factor-α and cyclooxygenase 2 produced by macrophages in response to lipopolysaccharide, and down-regulated the expression of adhesion molecules (i.e. intercellular adhesion molecule 1 and vascular cell adhesion molecule 1) (440, 470). Additional anti-inflammatory mechanisms associated with selenium involve the metabolism of arachidonic acid and ei-cosanoids (74, 75), and perhaps reduced monocyte adhesion and migration through endothelial cells in a biological mechanism that could involve selenium-induced shedding of L-selectin, with soluble L-se-lectin as a negative regulator of inflammation (7).

Copper. Similarly to the trace elements discussed earlier, copper also has a role in the cytosolic defense mechanisms against reactive oxygen and nitrogen species (218), events that are linked to its role as a cofactor for specific enzymes (e.g. cytochrome *c* oxidase and superoxide dismutase, copper, zinc superoxide dismutase) and electron transport proteins involved in energy and antioxidant metabolism (250). Among the effects of copper deficiency in humans, anemia, neutropenia, bone abnormalities, arthritis, and arterial and myocardial disease have been reported (115, 221, 326, 469). The effects of copper as a modulator of the immunoinflammatory response have been extensively addressed and reviewed (50, 327, 344). Specifically, the main effect of copper appears to be on neutrophil and macrophage functions, whereby impaired phagocytosis and microbial killing via the respiratory burst are reduced with lower levels of copper (19, 173). Likewise, copper deficiency seems to attenuate the production of interleukin-2 mRNA and protein in Jurkat human T-cell lines (174), which is consistent with the reduction of CD4$^+$ and CD8$^+$ T-cell populations in rats with lower levels of dietary copper (25, 26). In addition, copper appears to be important for natural-killer cell function (224). The role of copper in inflammation, and the effects of controlling copper levels in chronic inflammatory disorders that develop in the elderly (such as arthritis) have been described for several years, although the concept remains controversial (277–279). In addition, higher levels of copper and iron have also been related to several aging-associated inflammatory disorders, such as atherosclerosis, Alz-heimer's disease and diabetes, among others. This has generated great interest in terms of the development of therapeutic strategies to lower the availability of free copper (53). The main role of copper, as for other trace elements in inflammation, appears to be as a cofactor for metalloenzymes, whose main function is regulating the oxidant / antioxidant status of the tissues. As an example, the enzyme methallothionein modulates the binding and the exchange / transport of radicals of heavy metals such as zinc, cadmium or copper under physiological conditions, protecting the cells from heavy-metal toxicity and from the release of gaseous mediators such as hydroxyl radicals or nitric oxide. Thus, methallothionein would be a negative regulator of inflammation induced by an excess of these metals, including copper (185). Superoxide dismutase is an important enzyme in cellular oxygen metabolism whose function is also regulated by copper and zinc, and superoxide dismutase has been linked to the expression of proinflammatory cyto-kines, such as tumor necrosis factor-α, matrix metal-loproteinase 2 and matrix metalloproteinase 9 (265). Consistently, copper levels appear to show a positive correlation with the plasma levels of tumor necrosis factor-α and interleukin-1β in patients with rheuma-toid arthritis (472).

Trace element supplementation: effects on inflammation and infection. In general, evidence shows that micronutrient deficiencies are commonly found in ill patients and could also occur as a result of inadequate intake during nutrition therapy (42, 410). The recommended dietary allowance of micronutrients, based on the US Food and Nutrition Board guidelines, has been recently reviewed by Sriram & Lonchyna (410). Changes in plasma micronutrient concentrations observed during inflammation, and their immuno-modulatory and anti-inflammatory properties, as discussed above, have generated interest in their use as dietary modulators for the control of inflammation and infection. However, their complex metabolism and the interactions that occur among them, as well as the effect of micronutrients (e.g. iron) on some intra-cellular pathogens make implementation more challenging (100). It has been suggested that the dramatic changes in the micronutrient milieu may be the host's attempt to optimize the immune response and deprive invading microorganisms of essential micronutrients for replication (100). Even though micronutrients have a critical role in the immune response, there remains inconclusive evidence concerning the effectiveness of vitamins and mineral supplementation in the reduction of morbidity and mortality, particularly in the elderly population (412). Specifically, preclinical and clinical evidence suggests that although iron is essential for immune function, supplementation with iron does not decrease morbidity and mortality, and may even increase it under certain circumstances (100, 339). This could be caused by the complexity of the mechanisms of iron homeostasis, which would explain the differences observed in epidemiological studies related to this micronutrient (377). Several studies in animal models have shown that iron supplementation may lead to an increased inflammatory activity through the generation of reactive oxygen species in inflammatory bowel disease (312), and oral iron supplementation may increase intestinal inflammation and colon carcinogenesis in animal models of colitis (229).

On the other hand, growing evidence supports a more promising use of selenium and zinc as dietary modulators. Thus, elevated intake of selenium may be associated with reduced cancer risk and may alleviate other pathological conditions including oxidative stress and inflammation (including the systemic inflammatory response syndrome), thus counteracting the virulence of HIV in AIDS progression (43, 125). Most recently, the use of antioxidant vitamins C and E, as well as trace elements (i.e. selenium and zinc) to control oxidative stress and inflammation commonly found in bronchial asthma has been suggested; however, several randomized controlled clinical trials have not generated conclusive results of the benefits of this type of dietary intervention (284, 357). A number of randomized controlled intervention trials with an intake of up to 1 g of vitamin C and up to 30 mg of zinc have been conducted, and these trials support a beneficial role of supplementation with these micronutrients to ameliorate the symptoms and shorten the duration of respiratory tract infections (e.g. the common cold) and to reduce the incidence of pneumonia, malaria and diarrheal infections, especially in children and the elderly in developing countries (456). In addition, it has been shown that zinc supplementation can correct plasma oxidative-stress markers and proinflammatory cytokine levels in the elderly (28, 337), and could improve immune competence and minimize the therapeutic side effects related to gastrointestinal inflammatory disorders (e.g. ulcerative colitis and Crohn's disease) (381). Supplementation with selenium and vitamin E in a double-blind study showed significant alleviation of articular pain and morning stiffness in rheumatoid arthritis patients (1). The anti-copper drug, tetrathiomolybdate, has been tested in preclinical studies of neurodegenerative disorders (e.g. Wilson's disease, a disease of copper toxicity) and has been shown to demonstrate excellent efficacy to control fibrotic, inflammatory, autoimmune and neoplastic changes, as well as Alzheimer's disease (54). Alternatively, variations in the levels of trace elements (i.e. selenium, zinc, copper and iron) either in the plasma or in local tissue levels (synovial fluid) has been associated with rheumatoid arthritis and osteoarthritis (469).

Micronutrient supplementation as a preventive strategy to control inflammatory disorders, such as type 2 diabetes mellitus, has shown promising results, particularly with vitamins D, C and E; however, more robust clinical trials are necessary (139). Similarly, selenium and vitamin E supplementation induced significant alleviation of articular pain in rheumatoid arthritis patients (1).

It has been previously shown that micronutrient deficiencies (e.g. of vitamin C) may contribute to the severity of periodontal breakdown (11, 345); however, there is limited evidence on the effect of supplementation with micronutrients in periodontal disease. Recent cross-sectional studies showed that the plasma levels of vitamin C and zinc were decreased, and the copper levels increased, in diabetic patients with periodontitis compared with nondiabetic individuals with periodontitis (420), and the clinical parameters were significantly improved in patients

with periodontitis receiving dietary supplementation of vitamin D and calcium (283). Although supplementation with vitamin C reduced inflammatory responses in ligature-induced periodontitis in rats (423), a prospective interventional study showed that the total antioxidant capacity, which is measurable in plasma and has been previously shown to be reduced in patients with chronic periodontitis, was improved with nonsurgical treatment, but supplementation with vitamin C did not offer an additional effect (4). Analyzing more representative sample sizes in cross-sectional studies found that reduced dietary vitamin C increased the risk for periodontal disease and its supplementation enhanced a weak, but significant, clinical improvement of the periodontal tissues (12, 303). Staudte et al. (411) demonstrated *in vitro* that vitamin C reduced the cytotoxic and apoptotic effects of *Porphyromonas gingivalis* on human gingival fibroblasts.

In general, micronutrient supplementation, particularly of vitamins A, C and D, zinc and selenium, appears to have beneficial effects in individuals with certain degrees of nutrient deficiencies (i.e. malnourished children, women of reproductive age and the elderly) or inflammatory diseases (e.g. rheumatoid arthritis). However, because of the great variability in habitat conditions, health status and dietary requirements of the population, it seems to be critical to adjust micronutrient supplementation based on those variables. As the long-term effect of micronutrients supplementation on chronic inflammatory disorders has not yet been fully documented, future controlled clinical studies will be necessary.

Effect of dietary modulation in development of systemic disease

There has been a great deal of interest in nutrition and the development of systemic disease. According to the Centers for Disease Control, the prevalence of obesity, cardiovascular disease, and diabetes (i.e. CDC reports increase from 5.6 million in 1980 to 20.9 million in 2010; http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm) has increased significantly over the past years, along with an increase in dietary intake (196, 206). Several inflammatory diseases, including periodontal disease, have common risk factors that will be explored in association with metabolic syndrome. According to the American Heart Association, 'metabolic syndrome is a descriptor used for a group of risk factors associated with cardiovascular disease and diabetes that include abdominal obesity, insulin resistance and / or glucose tolerance, elevated blood pressure, a pro-inflammatory state, a prothrombotic state and atherogenic dyslipidaemia.' The National Cholesterol Education Program's Adult Treatment Panel III report suggested that the primary outcome of metabolic syndrome is cardiovascular disease because there are multiple risk factors associated with this disease (152, 153). They noted that most individuals with metabolic syndrome also have insulin resistance and many have visceral obesity. In order to make a diagnosis of metabolic syndrome, the The National Cholesterol Education Program's Adult Treatment Panel III report states that an individual must have three or more of the risk factors. The potential association of the aforementioned conditions is related to a cascade of cellular and molecular events that have been found to be common in several chronic inflammatory conditions, including periodontal disease. It has been postulated that two of the primary contributors to the pathogenesis of metabolic syndrome may be obesity and insulin resistance, both of which have been linked to other systemic conditions.

Obesity

Two measures of obesity have been utilized. Obesity is defined by a body mass index of ≥ 30 kg / m^2 [World Health Organization (314)] and abdominal / visceral obesity, when the waist circumference is more than 102 cm in male subjects or more than 88 cm in female subjects (302). Obesity has been identified as a contributor in hypertension, high serum cholesterol, low high-density lipoprotein cholesterol and hyperglycemia, all of which have been identified as risk factors for cardiovascular disease and diabetes (152). Also, several studies have demonstrated a relationship between an increase in periodontal disease severity and obesity (9, 368).

Many studies have evaluated the links among obesity, periodontal disease, diabetes and cardiovascular diseases, which share many of the same risk factors. We also observe, as previously mentioned, that the levels of many of the same proinflammatory mediators are elevated in these conditions. The concept that obesity leads to the stimulation of adipose tissue, resulting in an inflammatory response that enhances the development of insulin resistance and leads to type 2 diabetes mellitus, has been demonstrated by the presence of an increased number of obese patients who develop type 2 diabetes mellitus and release adipocyte-derived hormones and cytokines that stimulate the immune response

and the link to metabolic syndrome (175, 210, 397). Several studies have also linked increased levels of tumor necrosis factor-α with insulin resistance through elevated levels of C-reactive protein, which inhibits the insulin receptor and adiponectin (175, 399, 430). Furthermore, another study (306) suggested that tumor necrosis factor-α may play a similar role in type 2 diabetes mellitus and periodontal disease as in the adipose tissue of obese individuals and thus could act as a risk factor for periodontal inflammation. In addition, C-reactive protein is also associated with increasing the innate inflammatory responses by stimulating prothrombotic factors such as plasminogen activator inhibitor 1, which is important in cardiovascular disease (98, 322, 358).

The deposition of abnormal or excessive adipose tissue leads to an alteration in the regulation of hormones, such as leptin and adiponectin, and of inflammatory cytokines, such as tumor necrosis factor-α, interleukin-6, interleukin-1β and transforming growth factor β (110, 164), and similarly to the responses by macrophages, the adipocytes may contribute to the characteristic pathophysiologic changes seen in metabolic syndrome. Local inflammation within adipose tissue contributes to systemic insulin resistance and systemic inflammation (459). Studies have also shown a correlation between adipocyte size and total body weight and the number of mature macrophages found within white adipose tissue (450, 463). In the presence of excess dietary intake, monocytes are attracted and there is an increase in their numbers in fat storage, which intensifies the inflammatory process that is moderated by cytokines and adipocyte hormones. The release of hormones and cytokines plays a specific role in the development of the inflammatory response in obesity.

Adipocyte hormones and cytokines

In addition to the commonly known proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-6, interleukin-1 and transforming growth factor β, which influence several chronic inflammatory diseases such as obesity, cardiovascular disease, periodontal disease and diabetes, several adipocyte hormones have also been identified that influence systemic disease. The release of these cytokines and hormones are often elevated in obesity and they play various roles in how the body responds. The nutritional and hormonal conditions are controlled by enzymes that are part of the biosynthesis of triacylglycerol and lipolysis (208). This change occurs during food ingestion, with an increase in insulin secretion.

Adipokines

Leptin is a hormone, secreted by adipocytes, which activates the hypothalamus, signaling neural pathways that coordinate a number of biological processes such as the regulation of weight and energy metabolism (87, 134, 288, 415). Leptin is elevated in obesity and during inflammatory processes (315). In obesity, it has been demonstrated that there is a reduced capacity for leptin transportation across the blood–brain barrier (130).

Adiponectin is a hormone produced by adipocytes that is involved in glucose and lipid metabolism. The concentration of adiponectin is decreased in obese subjects (158), and several studies have demonstrated that both expression of adiponectin mRNA in adipose tissue and plasma adiponectin levels are also decreased in rodent models of obesity (177, 467). A relationship has been shown between reduced levels of adiponectin in type 2 diabetes mellitus and insulin resistance, which are important in the development of other inflammatory diseases (40, 41, 467). In one study, adiponectin-deficient mice were evaluated to determine if adiponectin is protective against diabetes and cardiovascular disease. The authors found that the glucose-lowering effect of insulin was impaired significantly, suggesting that adiponectin does have an impact on normal regulation of insulin sensitivity and that it plays a role in glucose homeostasis (227).

Resistin is a hormone secreted mainly by adipocytes in rodents and by macrophages in humans (347, 379). It appears to play a physiological role in the regulation of metabolism, in adipogenesis and as a factor in inflammation (414), and evidence suggests that resistin can induce the production of inflammatory cytokines (56, 243). It has also been demonstrated that the administration of resistin can induce hepatic insulin resistance, which supports a role in glucose metabolism (347). It has been demonstrated that resistin can decrease glucose transport by adipocytes and it can inhibit the differentiation of the cells (208).

Insulin resistance

Insulin resistance is thought to be a state in which hyperinsulinemia occurs in order for the body to utilize glucose normally by insulin target tissues. It is thought that while a state of hyperinsulinemia can be tolerated, eventually failure of the pancreatic beta-cells and full-blown diabetes occurs (351). Insulin resistance is often associated with type 2 diabetes

mellitus in which there may be an increase in glucose production by the liver, impaired insulin secretion by pancreatic beta-cells and resistance in peripheral tissues, such as muscle cells (351). In addition, insulin appears to play a role in cardiovascular disease through its effect on vascular tissues. For example, insulin plays a role in differentiation and regeneration in skeletal muscle and it has been documented that it increases skeletal muscle blood flow and glucose uptake, while modulating vascular tone. Insulin promotes nitric oxide production by endothelial cells, and its production can be altered in insulin resistance, which may contribute to vascular pathology (30, 471). Other studies have noted that individuals with insulin resistance associated with obesity, hypertension and type 2 diabetes mellitus had blunted insulin-mediated endothelium-dependent vasodilation and decreased endothelium-derived nitric oxide production (85). The connection to diminished insulin-stimulated blood flow associated with endothelial dysfunction is a prominent component of hypertension, coronary heart disease and atherosclerosis (29, 296).

It has also been shown that an excess of circulating fatty acid levels and fat deposits in organs can lead to insulin resistance, impaired function of pancreatic beta-cells and apoptosis (176). The presence of excess glucose can lead to the formation of free fatty acids, which form triglycerides within adipocytes. Ultimately this excess leads to the inadequate breakdown of fat and to the production of proinflammatory mediators from adipose tissue (83). Furthermore, an accumulation of macrophages within adipose tissue is positively associated with body weight and insulin resistance (450). The authors noted, by evaluating macrophage and nonmacrophage cell populations that were isolated from adipose tissue, that it was the adipose-tissue macrophages that were responsible for almost all expression of adipose-tissue tumor necrosis factor-α, along with inducible nitric oxide synthase and interleukin-6 expression. For example, tumor necrosis factor-α affects insulin resistance by triggering reactive oxygen species. Also, a large percentage of patients with type 2 diabetes mellitus are overweight. It has been shown that both lean and obese patients with type 2 diabetes mellitus have day-long elevations in the plasma free fatty acid concentration, which they are unable to metabolize normally after ingestion of a mixed meal or oral glucose load (287, 352). Hence, it appears that similar pathways are activated in the pathogenesis of both insulin resistance and obesity, both of which are risk factors in metabolic syndrome.

Connection to periodontal disease

If we look at some of the individual risk factors for metabolic syndrome there are studies that suggest a relationship with periodontal disease. Several studies have noted an association with increased risk for periodontal disease in obese patients, especially those with an increased body mass index (9, 366, 367, 461), and that increased levels of resistin and adipokine secretion are associated with periodontal disease in Japanese women (369). In patients with cardiovascular disease with a history of ischemia and fatal strokes and / or perivascular disease, some studies show an association with periodontal disease and tooth loss (181, 191, 294). Others have looked at elevated serum levels of C-reactive protein, which are present in periodontal infections and are also linked to an increased risk for cardiovascular disease (305). The evidence on the relationship with diabetes and the prevalence and severity of periodontal disease has been well documented. A meta-analysis by Khader et al. (204) demonstrated that diabetic patients have a significantly higher severity of periodontal disease when compared with nondiabetic patients (187, 341). Other studies have shown a small reduction in glycosylated hemoglobin levels in diabetic patients after having periodontal treatment, which again suggests a relationship between the two diseases. However, future studies are needed to determine the extent to which they impact a reduction in diabetic control. It has also been demonstrated that patients with multiple risk factors for metabolic syndrome were also at a higher risk for periodontal disease (292). The authors in the study evaluated 2,478 adults and found that risk factors for metabolic syndrome, such as body mass index, blood pressure, fasting blood glucose levels, triglycerides and hemoglobin A1C, were elevated in patients with periodontal pockets of ≥4 mm. In another study, using National Health and Nutrition Examination Survey III data, it was found that individuals who met the criteria for metabolic syndrome were more likely to have periodontal disease; however, the authors noted that the association between metabolic syndrome and periodontal disease was most correlated in women. Furthermore, the authors showed that individuals with two or more risk factors for metabolic syndrome were more likely to have periodontal disease, especially if they were female subjects, than were individuals without any metabolic components (14). Nesbitt et al. (300) evaluated the association of bone loss in a subpopulation of patients who were defined as having metabolic syndrome according to the The National Cholesterol Education

Program's Adult Treatment Panel III report and were enrolled in the Baltimore Longitudinal Study of Aging. Using panoramic radiographs, they determined the severity of alveolar bone loss and noted that waist circumference and systolic blood pressure were greater in patients, particularly in men with periodontal disease, even after adjusting for the white blood cell count. In another study that evaluated patients with severe periodontitis and healthy controls, the authors did note an increase in the white blood cell count, in the levels of low-density-lipoprotein cholesterol and in the nonfasting glucose levels, and the presence of dyslipidemia, in the periodontitis patients, which was somewhat different from a previous study (301). Despite the evidence that links periodontal disease with other systemic diseases, there is a need to conduct future studies to understand these relationships and mechanisms better because of the presence of variation in the design and assessment of the outcomes of current studies, which creates potential variation in how the results are interpreted.

Impact of diet

Dietary modulation of systemic diseases may be evaluated in part by elucidating the impact of nutrition in chronic conditions. Many of the pathways to inflammation are related to high caloric intake from refined carbohydrates and oxidative stress, which is stimulated by changes in the metabolism of adipose tissue (83). As previously mentioned, elevated levels of glucose and lipids can lead to the production of reactive oxygen species, which, when maintained over time, can lead to pathology in coronary disease and diabetes. Investigators have evaluated potential interventions that could modulate the host response as the evidence continues to show the negative impact of obesity on chronic inflammatory diseases. The impact of dietary modulation in human biology is related to several factors including energy production, metabolism and modulation of gene and protein expression. The impact of these interventions may affect anti-inflammatory pathways (310). It has also been documented that obesity and its impact on the modulation of inflammation can be altered by diet and exercise (8, 238). The concept of host modulation relates to creating an environment that allows the body's natural defense mechanisms to respond to an inflammatory insult in a favorable way. Some suggest that extrinsic neutralization of inflammatory cytokines would be an appropriate therapeutic approach for chronic inflammatory conditions, using either monoclonal antibodies or modified receptor proteins to reduce the action of tumor necrosis factor-α (111, 124).

Antioxidants are thought to be important in the down-regulation of proinflammatory responses. One such response is an improvement in the insulin sensitivity, which reduces high glucose levels in blood and tissues (319). While additional information is needed, one study demonstrated that antioxidants found in foods could reduce periodontal inflammation (82). It has also been suggested that the level of glutathione peroxidase may be a component in reducing the proinflammatory response because the levels of glutathione peroxidase are depleted in periodontitis (188) (discussed later, under 'n-3 Polyunsaturated fatty acids and periodontitis in humans').

In one study, the authors evaluated the effects of eicosapentaenoic acid on the prevention and reversal of insulin resistance when a high-fat diet was used. The authors found that while the mice on the high-fat diet developed obesity and glucose intolerance, the mice that were fed a high-fat diet plus eicosapentaenoic acid gained weight but had normal glucose tolerance and a reduction in adipose inflammation (193). These studies show a protective and anti-inflammatory effect of intervention with n-3 polyunsaturated fatty acid. More studies are needed to determine the long-term effects of dietary modulation. In addition, some studies suggest that diets rich in n-6 fatty acids could also provide a cardiovascular benefit (178, 454). In the Cretan Mediterranean diet study, the effect of an alpha-linolenic acid diet and antioxidants was evaluated in a patient population in regards to reducing cardiac mortality. A reduction in cardiac events and mortality were observed, which was maintained over time (95, 96).

Curcumin (diferuloylmethane), which is isolated from a herb called *Curcuma longa*, is derived from turmeric and is also thought to have anti-inflammatory effects (395). Curcumin has a direct effect on several metabolic actions associated with cyclooxygenase 2, DNA polymerase, lipoxygenase, glycogen synthase kinase 3β and tumor necrosis factor-α, all of which are important in the inflammatory process (395). In rodent models, it was noted that obese animals fed various doses of curcumin had a lower level of plasma free-fatty acids (332), which may suggest an additional antioxidant effect and a reduction of oxidative stress. In another study the authors evaluated two rat models – surgically induced myocardial infarctions and hypertensive heart disease – in salt-sensitive rats to evaluate the potential therapeutic role of curcumin (291). They found that curcumin inhibited the deterioration

of systolic function and heart failure increases in myocardial thickness and diameter, measuring the myocardial cell hypertrophy using atrial natriuretic factor and beta-type natriuretic peptide.

Another study evaluated the potential anti-inflammatory effect of curcumin in a rat model of periodontitis. The findings from this study noted that curcumin had no effect on the extent of alveolar bone loss, a dose-dependent inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells and reduced p38 mitogen-activated protein kinase in the periodontally diseased tissues, resulting in a reduction in the inflammation and the breakdown of connective tissues (155). The anti-inflammatory effects of curcumin have also been evaluated in human trials on patients with various systemic inflammatory conditions. For example, a study evaluated patients with ulcerative colitis and noted that patients treated with curcumin had a decrease in morbidity and that remission was maintained (161). Another study evaluated the effect of curcumin on patients with Crohn's disease and showed improvement in clinical outcomes (172). Other groups of plant-based polyphenols have also been evaluated and studies have suggested a decreased or lowered risk for systemic diseases such as diabetes and cardiovascular disease, thought to reflect its anti-inflammatory and antioxidant properties, such as stimulating glucose uptake in insulin-sensitive and noninsulin-resistant tissues (72, 73, 240, 321). Other potential strategies to modulate chronic inflammatory diseases include the use of vitamin supplements like vitamin D, C and E to help decrease the severity of type 2 diabetes mellitus. Accordingly (138, 139), several studies have suggested that vitamin D is associated with a decrease in diabetes risk, vitamin C has been associated with the prevention of protein glycation and may be a scavenger for reactive species, while vitamin E has been associated with lymphocyte proliferation and the inhibition of lipoxygenase.

While several potential therapeutic dietary options have been shown to have anti-inflammatory and/or antioxidant effects, many are animal studies or limited human trials. The mechanism by which each therapeutic option creates a beneficial outcome continues to be related to decreasing the oxidative stress and subsequently providing an anti-inflammatory effect. However, the mechanism of action is often unclear and complicated as to how host modulation actually occurs. The effectiveness and safety of therapeutic dietary options in humans needs to be fully explored. As the evidence continues to point to nutritional interventions that are effective against chronic inflammatory diseases, more clinical trials will be needed to determine dosages and the most appropriate transport vehicles for delivery.

Effect of dietary modulation on oral inflammation

Dietary modulation of the immune system: caloric restriction

Modulation of the immune response by diet has been observed by either supplementing the diet with specific nutrients or restricting the overall caloric intake. The effects of caloric restriction on aging have been studied extensively. Positive health benefits or increased lifespans have been reported in some species, such as the fruit fly, while other species have less subtle responses (408). Long-term studies on caloric restriction and aging in nonhuman primates have been conducted by the National Institutes on Aging and collaborators (233–236, 268, 404). These studies in nonhuman primates reported many of the benefits seen in rat models when a caloric restriction regimen of at least 30% was followed. The benefits included improved serum lipid and glucose profiles, lower blood pressure and increased insulin sensitivity. Further work supports that distinct metabolic pathways are influenced by caloric restriction (356) and are independent from lipid and weight profiles seen in aging animals without caloric restriction. Studying the effects of caloric restriction in humans is daunting as a result of the challenge of maintaining the restriction for long enough to see therapeutic effects. Research is underway to investigate molecules or compounds that alter the expression of specific genes or target specific physiologic processes and cause the same changes seen in full caloric restriction (184, 236, 448). This has been described as caloric restriction mimetics. Caloric restriction has been, in addition to aging, used to study the effects of bacterial challenge on the immune response using an oral model.

Oral models of infection and immunity

Oral models of infection and immunity have been developed in mice, rats, dogs and nonhuman primates, with the latter model presenting several advantages and applications (76, 151, 266, 316, 371). These models, particularly when using a ligature-induced model of periodontitis, allow the local immune response to a polymicrobial infection to be studied while minimizing study-site morbidity. These oral

models of infection have been used to correlate the systemic and the local responses to bacterial challenge (13, 90, 104, 106, 293, 360). These animal-model systems for periodontitis have been exploited in a variety of ways (258): (i) rodent models of periodontal disease have been useful in developing an understanding of the characteristics of adaptive immune-response mechanisms in periodontitis (23, 24, 195, 216, 252, 444, 466); (ii) the canine model has been used to focus on gingival inflammation and on the effects of topical antimicrobials, as well as on the effects of nonsteroidal anti-inflammatory medications on alveolar bone loss (320, 447); and (iii) studies in sheep are related to rapidly progressing periodontitis (101, 186). Substantial literature also supports that various aspects of human periodontal disease may be assessed in animal models that possess similar oral structures to the human periodontium (e.g. rat epithelium and baboon periodontal tissues) (258). The ligature-induced model of periodontitis in the nonhuman primate model has provided a critical understanding of host–microbiota relationships during disease progression (104, 107). Experimental ligature-induced periodontitis in animals has, in addition to providing insight to host immune responses, allowed the study of antimicrobial and regenerative therapies for chronic periodontitis and peri-implantitis (31, 44, 121, 306, 317). Rat models of induced periodontitis have allowed the study of alveolar bone loss and regenerative therapies; however, these models often involved pathogens that were exogenous to the rat. The nonhuman primate models of periodontitis are similar to disease progression in humans (89, 147, 375). The immune responses in the ligature-induced nonhuman primate model also parallel those seen in human periodontitis (90, 105, 106, 391).

Systemic responses to induced oral infections have also been studied in nonhuman primates to elucidate the relationships between periodontitis and adverse pregnancy outcomes (76, 108). While animal models provide insights into some potential interactions between periodontitis and broad systemic events, such as adverse pregnancy outcomes, it is often difficult to find the same causal evidence in humans. To date, for example, there is a lack of conclusive evidence from multicenter randomized controlled trials to support that nonsurgical periodontal therapy reduces preterm birth or low birth weight in humans (276, 311, 455). However, the ligature-induced periodontitis model has also provided further evidence for the role of diet in modulating local and systemic inflammation.

Caloric restriction effects on oral inflammation

Models of oral inflammation in nonhuman primates have been utilized to understand the dietary effects of caloric restriction on the host response during bacterial challenge. The severity and extent of clinical markers of periodontitis, as well as systemic and local immune responses, were evaluated in a cross-sectional study of 81 rhesus monkeys (*Macaca mulatta*) subjected to 30% caloric restriction or control diets (355). The results highlighted gender differences in the host response: the cohort of male monkeys exhibited greater periodontal inflammation than did the female monkeys; and caloric restriction reduced inflammation risk to a greater degree in male monkeys than in female monkeys. This gender difference in host response was similarly reflected in the antibody response, with the female monkeys exhibiting an elevated, specific adaptive immune response that may have been protective when compared with the male monkeys (109).

In a follow-up longitudinal study, 55 young, healthy rhesus monkeys placed on either caloric restriction or *ad libitum* diets were subjected to ligature-induced periodontitis (52). Clinical measures, including the plaque index, probing depth and clinical attachment levels, were evaluated at baseline, and at 1, 2 and 3 months following ligature placement. The results showed that caloric restriction resulted in a significant reduction in the progression of periodontal destruction, as measured by clinical attachment loss. These studies highlight the long-term effects of dietary modification of inflammatory responses by caloric restriction. Dietary modification in humans by caloric restriction remains a major sociological challenge as the rates of obesity and related comorbid conditions, such as metabolic syndrome, continue to rise. Modifying the diet by supplementation may be a more practical way to address these challenges.

Dietary supplementation: n-3 polyunsaturated fatty acids and periodontitis

n-3 Polyunsaturated fatty acids in rodent models

As discussed earlier, under 'Immune modulation', dietary n-3 polyunsaturated fatty acids, once incorporated in sufficient levels, provide an array of positive cellular and immunologic benefits. Therefore, it is important to understand if these levels reach

clinical significance in animal models when a chronic inflammatory process is present.

Rat models of periodontitis have been useful for exploring host–bacteria interactions in the oral environment (23, 24), as well as systemic sequelae, such as liver disease, from the induced oral infection (424). Challenging rats with periodontopathogens such as *Aggregatibacter actinomycetemcomitans*, *P. gingivalis* or *Treponema denticola* has been shown to result in significant horizontal alveolar bone loss in numerous studies (122, 198, 217, 418, 436). Dietary supplementation with n-3 polyunsaturated fatty acids has been investigated in the rat model to assess the effects on alveolar bone loss during a bacterial challenge. These studies showed that dietary consumption of n-3 polyunsaturated fatty acids results in significantly less alveolar bone loss than in control-fed rats when challenged with periodontopathogens and in decreased production of proinflammatory cytokines (197, 199). Modulation of the host response to the provoked inflammation included a decrease in the levels of proinflammatory cytokines, such as interleukin-1β and tumor necrosis factor-α (197).

n-3 Polyunsaturated fatty acids in nonhuman primates

The effects of n-3 polyunsaturated fatty acids have also been studied in nonhuman primates. Table 1 illustrates these effects on various organs and tissues in a variety of nonhuman primates (3, 84, 88, 144, 162, 180, 247, 249, 262, 264, 323, 325, 342, 359, 394, 449).

Understanding key host response–bacterial relationships in animal models is critical in assessing mechanisms of dietary modulation of the immune response. Of course, the ultimate goal is to assess these effects in humans during naturally occurring chronic periodontitis.

n-3 Polyunsaturated fatty acids and periodontitis in humans

Periodontal disease is a common disorder that can lead to irreversible alveolar bone loss and subsequent tooth loss. It is clear from studies of humans and animal models of periodontitis that the destructive process occurs as a result of an immunoinflammatory response. Current theory holds that gingival tissue destruction around affected teeth results from the local release of inflammatory mediators secondary to colonization by complex bacterial biofilms containing characteristic pathogenic opportunistic microorganisms (146). The human subgingival crevice is a habitat for a complex microbiota, consisting of more than 700 species of bacteria (225, 406). This juxtaposition of the septic environment of the subgingival crevice with host tissues is expressed as a chronic inflammation with recurrent acute phases of tissue destruction. Several potential periodontopathogens have been studied and have been shown to activate host inflammation, induce bone-destructive inflammatory mediators (i.e. interleukin-1, interleukin-6 and tumor necrosis factor-α) and to contribute to tissue damage (47, 343). Thus, these mediators, and others, such as prostaglandin E_2, platelet activating factor, C-reactive protein and leukotriene B_4, have substantial support as target molecules during destruction of the periodontium. The effect of n-3 polyunsaturated fatty acids on local and systemic inflammatory responses, as well as the effect on the subgingival microflora, are not well defined but are an area of interest for modifying the host response to the disease (83). Various epidemiological studies and animal studies have related nutrition to periodontitis (92, 93, 117, 365, 368, 425). These observations may well be unlinked to specific nutritional components, but reflect a general relationship between dietary intake and susceptibility to periodontitis. The importance of inflammation in the destruction of the periodontal tissues has been known for over 50 years, but the concept of immunomodulation to prevent periodontal destruction or to enhance the benefits of traditional therapy has received little attention until recently.

Dietary supplementation increases the serum levels of the desired nutrients. This is followed by cellular incorporation to allow epigenetic modifications that alter inflammatory pathways (35). Recent studies have focused on n-3 polyunsaturated fatty acids because of their effects on proinflammatory and anti-inflammatory cytokines (441). Investigations into the effects of n-3 polyunsaturated fatty acids on gingivitis are limited and have mixed results (68, 69, 103). Cellular incorporation of eicosapentaenoic acid and docosahexaenoic acid were demonstrated, and reductions of inflammatory cytokines were seen but did not reach statistical significance. An epidemiological study examined associations between dietary n-3 polyunsaturated fatty acid intake and periodontitis prevalence in a subset of the National Health and Nutrition Examination Survey between 1999 and 2004 (297). In this study the periodontitis inclusion criteria qualified if only one tooth had a probing depth of >4 mm and clinical attachment loss of >3 mm. Despite the low threshold for disease criteria, higher levels of docosahexaenoic acid were associated with a lower prevalence of periodontitis. There is a paucity of studies assessing clinical

outcomes of treating periodontitis with n-3 polyunsaturated fatty acids as an adjunct. We are currently investigating the effects of dietary supplementation with n-3 polyunsaturated fatty acids as an adjunct to nonsurgical periodontal therapy in subjects with chronic periodontitis by evaluating local and systemic measures of periodontitis as well as effects on subgingival microbiota. A study investigating this approach in periodontitis patients combined with low-dose aspirin yielded reductions in the salivary levels of RANKL and matrix metalloproteinase 8 and a favorable shift in the frequency of pockets with a depth of ≤4 mm (113). Several studies have evaluated the potential beneficial effects of n-3 polyunsaturated fatty acids and n-6 fatty acids in fish oils for modulating the host response in chronic inflammatory diseases, such as cardiovascular disease and periodontal disease. One study evaluated how the administration of n-3 polyunsaturated fatty acids and low-dose aspirin would influence the outcomes of healing after periodontal-regenerative therapy (114). The authors noted that the experimental group showed a greater reduction in mean probing pocket depth and gain in clinical attachment, and a decrease in interleukin-1β vs. the control group that received regenerative therapy and placebo. Another study (150) demonstrated that using an n-3 polyunsaturated fatty acids supplement decreased the production of tumor necrosis factor-α by blood monocytes in patients who initially had high levels of tumor necrosis factor-α. This would support potential anti-inflammatory effects. Host modulation has been employed as a strategy for nonsurgical treatment of periodontitis, and studies evaluating subantimicrobial doses of doxycycline, and local antimicrobial therapy in conjunction with scaling and root planing, have yielded gains in clinical attachment in subjects with chronic severe periodontitis (114, 307, 364). As previously discussed, studies in a rat model demonstrated that the experimental group infected with *P. gingivalis* who were given a diet rich in n-3 polyunsaturated fatty acids had less bone loss and a decrease in gene expression of inflammatory mediators such as tumor necrosis factor-α and interleukin-1β vs. the control group (244). The animal and human studies support that n-3 polyunsaturated fatty acids have an anti-inflammatory effect that could be used as a dietary intervention in chronic inflammatory lesions such as periodontal disease.

Lipid-derived mediators for resolving inflammation

Recently, mediators derived from fatty acids, such as n-3 polyunsaturated fatty acids, have been investigated for their effects on resolving inflammation. These lipid-derived mediators include resolvins, lipoxins, protectins and maresins and modify the inflammatory response by changing polymorphonucleotide chemotaxis, enhancing macrophage uptake and stimulating an antimicrobial response (309, 383–387, 390). These mediators provide a proactive approach to resolving inflammation and the potential to provide additional tools to improve the host response to periodontitis (168, 194, 285, 382, 389, 432). A locally applied topical resolvin (RvE1) in a rabbit model provided immediate resolution of the acute inflammation (165). When aspirin is consumed, dietary n-3 polyunsaturated fatty acids can be metabolized into E and D series resolvins via the lipoxygenase pathway and, as one outcome, can induce macrophages to have improved phagocytosis of bacteria and apoptotic neutrophils (405). Therefore, the consumption of n-3 polyunsaturated fatty acids and aspirin can modify the host response to chronic inflammation. These studies have provided a better understanding of the mechanisms to actively resolve inflammation, and perhaps the combination of topical resolvins, as well as endogenous eicosanoid-derived and synthetic mediators of inflammation, will enhance the capacity of the host response to chronic periodontitis.

Summary

This review has focused on the capacity of various dietary manipulations, regarding both the quality of ingested biomolecules and the quantity of calories, to affect the inflammatory, innate and immune responses. In particular we focused on trying to provide an overview of how these different strategies could be engaged as preventive and therapeutic approaches for the management of an array of chronic inflammatory diseases. The review attempted to identify more concrete linkages of how individual dietary components alter host-cell functions at the molecular level that could translate into improvement in clinical presentation of the host. We noted many commonalities in the underlying mechanisms of chronic inflammatory diseases and similarities in how these dietary host-modulating approaches could alter the disease progression. In particular, the review provides a snapshot of the somewhat limited literature available suggesting the potential to modify chronic adult periodontitis using dietary manipulation, and, as importantly, cross-related literature that provides insights into the future management of

periodontitis using biological therapeutics that have been shown to be effective in other mucosal and systemic inflammatory diseases.

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