

Inflammation: Exploring Links to Risks for Chronic Diseases

Inflammation is an increasingly important topic among health professionals. It is a biological process initiated by the immune system in response to injury, irritation or infection. The purpose of the acute inflammatory response is to promote the removal of the stimulus and initiate the healing process. Currently, prolonged or chronic inflammation is getting attention because it has been implicated in the etiology of several diseases including cardiovascular disease (CVD), diabetes, rheumatoid arthritis, cancer and neurodegenerative diseases such as Alzheimer's disease. Recent research suggests that diet can play a key role in ameliorating inflammation and reducing the burden of chronic disease.

This update describes the inflammatory process and discusses the potential for use of inflammatory markers in clinical practice. In addition, epidemiologic and clinical studies evaluating the role of various foods and food components in reducing inflammation are reviewed, as are strategies for implementing anti-inflammatory dietary patterns. While there are a number of inflammatory health conditions that nutrition may influence, this article focuses on CVD, which often co-exists with other chronic diseases.

The Inflammatory Process

Acute versus Chronic Inflammation

Acute inflammation is a short term (minutes to days), non-specific reaction to a harmful stimulus (e.g., microbial infections, surgical trauma and hypoxia or reperfusion injuries). It is initiated by several chemical mediators that promote vascular and cellular changes to facilitate the flow of plasma and leukocytes (predominantly neutrophils and macrophages) to the site of injury. Thus, acute inflammation is associated with a profound but transient increase in the level of several inflammatory mediators. Under normal conditions, this response is down-regulated following removal of the stimulus. Importantly, chronic inflammation results when the cause of the inflammation persists and there is continued recruitment of monocytes, and later lymphocytes, to the site of injury. This perpetuates a cycle of tissue damage and a state of constant low-grade inflammation (1).

Markers of Inflammation

Inflammation has been implicated in every phase of atherosclerosis, from initiation and progression to plaque rupture (2). Numerous markers of inflammation that can be measured in clinical practice have been identified. These include pro-inflammatory cytokines [tumor necrosis factor (TNF)- α , interleukin (IL)-1 and 6], acute phase proteins [C-reactive protein (CRP), fibrinogen, serum amyloid A (SAA)], hemostatic factors [fibrinogen, plasminogen activator inhibitor-1 (PAI)-1] and adhesion molecules [selectins, soluble inter- and vascular cell adhesion molecules: (sICAM-1) and (sVCAM-1)]. Of these, the American Heart Association (AHA) and Centers for Disease Control and Prevention (CDC) have identified CRP as an appropriate marker for risk stratification in primary prevention, particularly in persons with multiple established CVD risk factors (3).

C-reactive protein

CRP is an acute phase protein produced primarily by the liver, but also by smooth muscle cells and adipocytes, in response to increased circulating levels of IL-6. There are multiple mechanisms by which CRP mediates inflammation, including increased expression of adhesion molecules, PAI-1 and monocyte attractant proteins, reduced nitric oxide availability and increased low-density lipoprotein cholesterol (LDL-C) uptake by macrophages. During acute inflammation, CRP levels can increase to 10-20 mg/L, but it is the CRP concentration during "normal," apparently healthy states that predicts increased CVD risk. High-sensitivity (hs)CRP assays are used to categorize patients with low (<1 mg/L), average (1.0-3.0 mg/L) or high (>3.0 mg/L) risk for future cardiovascular (CV) events. These assays are widely available, reproducible and standardized according to World Health Organization criteria. CRP levels are stable for prolonged periods of time and are not influenced by diurnal changes.

Epidemiologic studies consistently report that hsCRP levels are a strong, independent predictor of future CV events among apparently healthy individuals. In the Women's Health Study (WHS), 27, 939 women were stratified by quintile of baseline hsCRP and followed for occurrence of first CV events

(mean follow-up 8 years) (4). Relative risk for CV events increased progressively from lowest (RR=1.0; \leq 0.49 mg/L) to highest (RR=4.5; $>$ 4.19 mg/L) quintile of hsCRP. Even after adjustment for other established CVD risk factors (diabetes, smoking, hypertension and hormone replacement therapy), relative risk for women in the highest quintile for hsCRP remained high (RR=2.3). When combined with LDL-C, hsCRP provided increased prediction of CV events more than LDL-C or hsCRP alone, and even predicted CV events at thresholds below that for LDL-C therapy (i.e. $<$ 130 mg/dL). Furthermore, hsCRP improved the prediction of CV events based on the Framingham Risk Score. The results from the WHS are consistent with other prospective studies conducted in the US and Europe (5-7).

Lipoprotein-associated phospholipase A₂

Recently, lipoprotein-associated phospholipase A₂ (Lp-PLA₂), a pro-inflammatory enzyme produced by macrophages and foam cells surrounding atherosclerotic plaques, has been proposed as a potential clinical biomarker (8). Because Lp-PLA₂ is produced directly at the site of injury, it is a measure of vascular, rather than systemic, inflammation and may predict the presence or formation of rupture-prone plaques. There are other clinical advantages; Lp-PLA₂ has low biological variability and appears to be impervious to general infections or arthritis. In 2006, a consensus panel evaluated the clinical usefulness of Lp-PLA₂ mass concentration for risk stratification, establishing a clinical cut point $>$ 235ng/mL for identifying individuals at high risk for future CV events (9). However, a recent update supports a lower value; $>$ 200 ng/mL (8). Several commercial laboratories classify Lp-PLA₂ levels $<$ 200 ng/mL as low, 200-235 ng/mL as borderline high and $>$ 235 ng/mL as high risk. At present, Lp-PLA₂ testing is recommended for individuals classified as moderate-high risk based on Framingham risk criteria, as well as for patients with Metabolic Syndrome and/or hyperglycemia ($>$ 100 mg/dL) (8).

Epidemiologic studies demonstrate a relationship between increased levels of Lp-PLA₂ and risk for CV events and stroke [reviewed by Corson et al (10)], independent of body mass index, lipids, insulin resistance and inflammatory markers, such as CRP. Generally, relative risk doubles for individuals in the highest versus lowest quintile for Lp-PLA₂. Furthermore, in combination with CRP, Lp-PLA₂ may assist in identifying individuals with low LDL-C ($<$ 130 mg/dL) who are at increased risk for CV events (5). Lipid-modifying medications that

also stabilize plaques, such as statins, fibrates and ezetimibe, effectively reduce Lp-PLA₂ (11), and this also occurs with drug therapy in combination with niacin (vitamin B-3) or omega-3 (n-3) fatty acids. The effectiveness of other dietary components for lowering Lp-PLA₂ requires further investigation.

Diet and Inflammation

Epidemiologic Evidence

Beneficial Associations

When stratified by intake, higher consumption of dietary fiber and whole grains (12-16), nuts and seeds (17), fruits and vegetables (18) and fish (19) have been associated with lower levels of CRP, IL-6, TNF- α (and receptors), E-selectin or SAA. Moderate alcohol intake (5-7 drinks/week) is linked with lower levels of CRP compared to infrequent or no consumption of alcohol (20). Favorable associations also have been reported for increased dietary intake (highest versus lowest) of magnesium (21), flavanoids (22), arginine (23), total and long chain [icosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] n-3 fatty acids (24, 25). When incorporated as part of a healthy dietary pattern, these foods are associated with lower levels of CRP, IL-6, E-selectin or homocysteine (26-28).

Adverse Associations

Higher intakes of saturated and *trans* fatty acids (versus lowest intake) are linked with increased inflammation [CRP, IL-6, TNF- α (and receptors), E-selectin, sICAM-1 or sVCAM-1] (15, 26). Coffee consumption ($>$ 200 ml/d versus 0 ml/d) also is associated with higher levels of CRP, IL-6, TNF- α , and SAA (29). Several studies have shown negative associations between a Western dietary pattern, that is high in saturated and *trans* fatty acids (e.g., from sweets, desserts, fries, and red and processed meats) and CRP, IL-6, E-selectin, homocysteine, sICAM-1 or sVCAM-1 (26-28). In the WHS, Levitan et al. (30) reported that high dietary glycemic index (GI), but not glycemic load (product of GI and carbohydrate), was associated with increased CRP.

Evidence from Randomized Controlled Trials (RCTs)

Bioactive Components

Findings from in vitro and animal models have identified multiple mechanisms by which bioactive components from foods such as tomatoes (lycopene), green tea [epigallocatechin gallate (EGCG)], turmeric—a spice often used in curry powder—(curcumin) and soybeans (isoflavones) provide CV benefits. Lycopene and EGCG have potent antioxidant effects, curcumin inhibits enzymes responsible for the synthesis of pro-inflammatory eicosanoids and isoflavones exert estrogenic activity. The potential for these bioactives to exert anti-inflammatory effects in humans is an active and emerging area of investigation. While some RCTs have reported favorable reductions in inflammation or improved antioxidant status following supplementation with lycopene (31-33), EGCG (34, 35) or curcumin (36, 37), others have shown no effect. There is promising evidence for isoflavones (from soy protein or soy nuts) incorporated as part of a Therapeutic Lifestyle Change (TLC) (38) or Dietary Approaches to Stop Hypertension (DASH) diet (39) compared to these diets without isoflavones. Several short term studies (4 to 6 weeks), however, have reported no effect on CRP or adhesion molecule concentrations with isoflavone supplementation of 10 to 73 mg/d (40-42).

Foods

Promising anti-inflammatory effects have been reported for some foods or dietary patterns, although results from RCTs investigating bioactive components on inflammation are generally inconsistent.

Fish and fish oil supplements

Long chain polyunsaturated fatty acids (PUFA: EPA+DHA) are mainly found in fish and fish oil supplements and are well known for their role in regulating inflammation. In healthy volunteers, 9 g/d of fish oil (2.7 g EPA+DHA) for 4 wks decreased IL-1 β (78%-81%) and TNF- α (70%-76%) (43), and in patients with Alzheimer's disease, fish oil supplementation (2.3 g/d EPA+DHA) for 6 months decreased IL-6 35% (compared with placebo, -15%) (44). A slightly lower intake of fish oil (2.1 g EPA+DHA) for 8 weeks reduced ICAM-1 (-10%), but not CRP, VCAM-1, E- or P-selectin (45).

Whole grains and fiber

Whole grain foods contain several bioactive components (including dietary fiber, vitamins, minerals, antioxidants and other phytoprotectants), which may act synergistically to

reduce inflammation and CVD. In subjects with Metabolic Syndrome, CRP decreased 38% following 12 week consumption of a hypocaloric diet with whole grain foods (~5 servings/d) (46); however, short term (6 weeks) isocaloric substitution of whole grain (7 servings/d) for refined grain foods failed to lower CRP or IL-6 in healthy overweight subjects (47). A high fiber (30 g/d) DASH diet or psyllium-fiber supplemented diet (30 g/d) for 3 weeks reduced CRP 14%-18% in lean normotensive, but not obese hypertensive individuals (48); and similarly in overweight/obese individuals, psyllium-fiber supplementation (7 or 14 g/d for 3 months) did not reduce CRP or IL-6 (49).

Nuts

Numerous potential anti-inflammatory components have been identified in nuts, including phytosterols, carotenoids, fatty acids and polyphenols. In hypercholesterolemic patients, a Mediterranean-style diet enriched with walnuts (40-65 g/day for 4 weeks) decreased sVCAM-1 levels 20%, compared with the same diet without walnuts (50). Zhao et al (51) reported that a 6-week high PUFA diet enriched with walnuts, walnut oil and flaxseed oil decreased CRP 75% in hypercholesterolemic subjects. In the Prevención con Dieta Mediterránea (PREDIMED) Study, a Mediterranean diet including 1 oz/d raw nuts (walnuts, almonds and hazelnuts) reduced oxidized LDL 10% compared to a control diet (35% fat) (52); and in hyperlipidemic subjects, daily intake of almonds (73 g/d for 4 weeks) decreased oxidized LDL (14%) compared to a low-saturated fat diet (<5% energy) (53).

Red wine

Resveratrol, flavanoids and polyphenols are key bioactive compounds found in red wine. The mechanism by which alcohol may improve inflammation is via inhibition of LDL oxidation. A daily intake of red wine (150 ml: 15 g/d alcohol) for 3 weeks did not reduce CRP (54); however, a slightly higher intake (2x160 ml red wine/d: 30 g/d alcohol) for 4 weeks reduced CRP (20%), fibrinogen (10%) and IL-1 α (21%) in healthy men (55).

Dietary Patterns

To date, two prominent dietary patterns, the Portfolio diet and the Mediterranean diet, have shown anti-inflammatory effects. In a series of studies (56, 57), Jenkins et al reported that a diet very low in saturated fat that includes whole grains and reduced-

fat dairy products, plus plant sterols, soy protein, viscous fibers and almonds (Portfolio diet), lowered CRP 28%. Remarkably, this reduction in CRP was similar to that induced by a low-fat diet, plus 20 mg lovastatin (57). When subjects with CRP levels >3.5 mg/L were excluded from the analysis, CRP was reduced 16% and 23% in the statin and Portfolio groups, respectively (56). Substantial reductions in CRP (40%), as well as IL-6, IL-7 and IL-18 also were reported following 2 years consumption of a Mediterranean-style diet that included whole grains, fruits, vegetables, nuts and olive oil, compared with consumption of a prudent diet (50%-60% carbohydrate, 15%-20% protein, <30% total fat), in patients with Metabolic Syndrome (58).

Lifestyle Behaviors

Regular exercise training and weight loss also may play a role in inflammation. In weight stable, healthy participants, CRP decreased 55% in individuals with high CRP (>3.0 mg/L) following a 6-month supervised exercise training program (59), and in obese women, following a one year weight loss (16% weight loss) program (~1200 kcal/d), CRP decreased 32% (60). In a 1 year calorie or exercise induced weight loss trial (energy deficit 16%-20%), CRP decreased only in the calorie restricted group (30%) (61) despite similar weight loss in both groups (8% and 11%) (62). Most notably, a review of 33 weight loss intervention studies found that for each 1 kg of weight loss, the mean change in CRP level was -0.13 mg/L, and trials with and without an exercise component reported CRP reductions of 0.14 mg/L and 0.02 mg/L, respectively (63).

Conclusion

Inflammation is central to the development of CVD. Research has identified inflammatory biomarkers for CVD risk stratification. They are currently being used to evaluate the effectiveness of intervention strategies to reduce inflammation. There is evidence from epidemiologic studies supporting an anti-inflammatory effect of several foods and/or their bioactive components; however, their independent effects following RCTs are inconsistent. Nevertheless, several anti-inflammatory benefits have been reported for tomatoes (lycopene), fish (n-3 fatty acids) and whole foods, such as nuts (1.5-3 oz/d) and wine (~250 ml/d), in addition to soy isoflavones and whole grains, when combined with a reduced-fat diet or weight loss, respectively.

It is also evident that dietary patterns, such as the Portfolio or Mediterranean diets, rich in whole grains, fruits, vegetables, nuts and seeds, fish, vegetable oils and proteins from soy and other legumes, are beneficial. Maintaining or achieving a healthy body weight and exercise also are important. Incorporating lifestyle components such as those recommended in the *Dietary Guidelines for Americans* (64) (i.e., consuming a varied and healthy diet, maintaining a healthy body weight and participating in regular physical activity) help promote a low inflammatory risk status.

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