Dietary Factors That Promote or Retard Inflammation

Arpita Basu, Sridevi Devaraj, Ishwarlal Jialal

Abstract—Inflammation plays a pivotal role in all stages of atherosclerosis. Cardiovascular risk factors and metabolic syndrome are typified by low-grade inflammation. Intervention trials convincingly demonstrate that weight loss reduces biomarkers of inflammation, such as C-reactive protein (CRP) and interleukin (IL)-6. Limited studies have shown that certain dietary factors; oleic acid, α-linolenic acid, and antioxidants RRR-α-alpha tocopherol, reduce biomarkers of inflammation. Most of the studies with fish oil supplementation have shown null effects, and conflicting results have been reported with saturated and trans fatty acids, cholesterol, and soy intake. Much further research is needed to define the role of individual dietary factors on the biomarkers of inflammation and the mechanism of the anti-inflammatory effects of weight loss. (Arterioscler Thromb Vasc Biol. 2006;26:995-1001.)

Key Words: C-reactive protein ■ diet ■ inflammation ■ macronutrients ■ micronutrients ■ weight loss

A growing body of literature suggests that inflammation is pivotal in all phases of atherosclerosis, and biomarkers of inflammation (Table 1), especially high sensitivity C-reactive protein (CRP), have been shown in various studies to predict cardiovascular events.1,2

The role of dietary factors in the prevention of cardiovascular disease (CVD) has been the subject of considerable attention. The Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) focuses on therapeutic lifestyle changes as the cornerstone of therapy for CVD. The components include reduced intakes of saturated fat and cholesterol, increased dietary fiber, inclusion of plant sterols/stanols, increased physical activity, and weight control.3 The goal of this review is to examine the efficacy of the different dietary components on biomarkers of inflammation. Particular attention will be paid to various dietary factors which possibly retard inflammation, as well as those that potentially promote this process. Although observational studies are mentioned, the major focus will be on dietary intervention studies in human volunteers, which will allow for a better appreciation of dietary factors that can be targeted clinically to attenuate inflammation.

We searched for all reports of reviews, observational studies, as well as clinical trials that tested the effects of dietary modifications, nutrient supplementation, and weight loss on biomarkers of inflammation in human subjects. A PubMed search was conducted from 1995 through December 2005, by using the terms: biomarkers of inflammation, C-reactive protein, IL-6, fats, cholesterol, carbohydrates, proteins, vitamins, minerals, fiber, antioxidants, weight loss, alcohol, clinical trials, reviews, and epidemiological observations. Our inclusion criteria for clinical trials were random allocation of participants, and study sample limited to men or nonpregnant women.

Weight Loss/Hypocaloric Diets and Inflammation

Elevated CRP levels have been associated with obesity.4 Several studies have been conducted in obese subjects and in...
obese patients with hyperinsulinemia, diabetes, or rheumatoid arthritis. Weight loss achieved through different diet programs (low-fat, high-protein, or hypocaloric diet), in combination with exercise or nutritional counseling, ranged from 3 to 15 kg resulting in concomitant reduction of CRP levels by 7% to 48%. Figure shows the correlation between weight loss and percentage reduction of CRP levels from pooled data from several dietary intervention trials. Although much research is needed to elucidate the mechanisms by which weight loss results in decreased inflammation, lowering of CRP levels can be attributed to a decrease in fat mass which lowers IL-6 levels, which in turn decreases CRP synthesis by the liver, and from other cellular sources.

**Dietary Fatty Acids and Biomarkers of Inflammation**

Table 2 summarizes the role of dietary fatty acids in modulating biomarkers of inflammation in human subjects.

<table>
<thead>
<tr>
<th>Biomarkers of Inflammation</th>
<th>Potential Sources</th>
<th>Possible Role in Atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, SAA, fibrinogen (acute phase proteins)</td>
<td>Liver, adipose tissue, macrophages, smooth muscle cells, endothelial cells</td>
<td>CRP associated with production of inflammatory cytokines, chemokines, tissue factor expression, chemotaxis of monocytes; Downregulation of eNOS and prostacyclin; Predisposition to a state of hypercoagulability (increased PAI-1, and decreased tPA)</td>
</tr>
<tr>
<td>Cytokines (IL-1β, IL-6, TNF, IL-7, TNF-α, IL-18 etc)</td>
<td>Endothelial cells, macrophages, adipose tissue</td>
<td>Pro-atherogenic and augment monocyte-endothelial adhesion; IL-7 activates monocytes and enhances production of inflammatory cytokines; IL-18, a strong independent predictor of mortality in patients with coronary artery disease</td>
</tr>
<tr>
<td>Chemokines (MCP-1, IL-8)</td>
<td>Endothelial cells, macrophages</td>
<td>Stimulate chemotaxis</td>
</tr>
<tr>
<td>Adhesion molecules (ICAM, VCAM, E-selectin, P-selectin)</td>
<td>Endothelial cells</td>
<td>Promote monocyte-endothelial adhesion</td>
</tr>
<tr>
<td>PAI-1 (inhibitor of fibrinolysis)</td>
<td>Endothelial cells, adipose tissue, macrophages</td>
<td>Reduced plasma fibrinolysis; Promotes atherothrombosis</td>
</tr>
</tbody>
</table>

ICAM indicates intercellular adhesion molecule; MCP-1, monocyte chemoattractant protein-1; PAI-1, plasminogen activator inhibitor-1; SAA, Serum amyloid A; VCAM, vascular cell adhesion molecule.

**Saturated and Trans Fatty Acids**

Several observational studies have reported a positive correlation between diets with a high content of saturated and trans fatty acids and biomarkers of inflammation. Fung et al found a positive correlation between CRP and the Western diet versus a healthier prudent diet. Although the authors do not correlate CRP with the individual foods or nutrients in the western diet, the overall discussion suggests a positive association between high fat intake, particularly saturated and trans fatty acids from red and processed meats, full-fat dairy products, and french fries, high glycemic index carbohydrates in the Western diet, and inflammation. King et al further examined the National Health and Nutrition Examination survey (NHANES; 1999 to 2000) data, and revealed a modest association between saturated fat consumption and elevated CRP. Analysis of data from the Nurses’ Health Study I cohort revealed a 73% higher level of CRP in women in the highest quintile of trans fat intake compared with the lowest quintile.

Intervention trials with trans fatty acids have been somewhat conflicting. CRP levels increased with trans fatty acid substitution in a high-fat diet (39% fat) in healthy subjects, whereas, 6% substitution of trans fatty acids in a standard fat diet (30% fat), showed no effects on CRP in moderately hypercholesterolemic subjects, although it increased tumor necrosis factor (TNF)α and IL-6 levels in these subjects. Because a high-fat diet (59% fat) has also been shown to promote inflammation in healthy and type 2 diabetic patients, the level of dietary fat may influence the pro-inflammatory actions of saturated or trans fatty acids, which, in turn, may exert differential effects on acute phase proteins and inflammatory cytokines.

**Monounsaturated Fatty Acids (MUFA)**

The Lyon Diet Heart Study demonstrates the cardioprotective effects of a Mediterranean diet on composite measures of coronary recurrence rate after a first myocardial infarction but...
TABLE 2. Summary of Randomized Clinical Trials Examining the Effects of Dietary Interventions (Whole Diet Approach or Enrichment) With Fatty Acids (Saturated, Trans, Monounsaturated, Polyunsaturated, or Conjugated Linoleic Acid) on Biomarkers of Inflammation.

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Subjects</th>
<th>Type and duration of dietary intervention/enrichment</th>
<th>Change in biomarkers of Inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saturated and Trans Fatty Acids</td>
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<tr>
<td>Baer et al (10)</td>
<td>50 healthy adult males</td>
<td>Control diet (30% fat) or experimental diets (39% fat) with 8% substitution of oleic acid, trans fatty acid, saturated fatty acids, stearic acid, or trans-18:1; duration 6 weeks</td>
<td>( \uparrow ) CRP and E-selectin levels with trans fat diet compared with control; ( \uparrow ) fibrinogen in stearic acid diet vs control; no difference in any marker between oleic acid diet and control; ( P&lt;0.05 )</td>
</tr>
<tr>
<td>Lichtenstein et al (11)</td>
<td>36 moderately hypercholesterolemic adults</td>
<td>Experimental diets (30% fat) two-thirds fats substituted with soybean oil, semi-liquid margarine, soft margarine, shortening, stick margarine, or butter; duration 35 days</td>
<td>No effect on CRP with any dietary fat type ( (P&gt;0.05) )</td>
</tr>
<tr>
<td>Han et al (12)</td>
<td>19 moderately hypercholesterolemic adults</td>
<td>Experimental diets (30% fat) two-thirds fats substituted with soybean oil, soybeal oil-based stick margarine, or butter; duration 32 days</td>
<td>( \uparrow ) IL-6 and TNF-( \alpha ) with stick margarine diet vs soybean oil diet ( P&lt;0.05 )</td>
</tr>
<tr>
<td>Nappo et al (13)</td>
<td>20 type 2 diabetic patients and 20 matched healthy subjects</td>
<td>High-fat diet (59% fat) or high-carbohydrate diet (73% carbohydrates), with or without antioxidants; duration 4-day study, 1 week apart</td>
<td>( \uparrow ) IL-6, TNF-( \alpha ), ICAM-1, VCAM-1 in healthy and diabetic subjects with high-fat meal; increased levels only in diabetics with high-carbohydrate meal ( P&lt;0.05 )</td>
</tr>
<tr>
<td>Pirro et al. (37)</td>
<td>35 patients with primary hypercholesterolemia and 15 normal control subjects</td>
<td>Low-cholesterol/low-saturated fat diet (30% fat, 5% saturated fat, cholesterol &lt;200 mg); duration 8 weeks</td>
<td>( \downarrow ) CRP levels in hypercholesterolemic patients compared to baseline ( P&lt;0.05 )</td>
</tr>
<tr>
<td>Monounsaturated Fatty Acids</td>
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<tr>
<td>Esposito et al (15)</td>
<td>180 patients with metabolic syndrome</td>
<td>Mediterranean-style diet or prudent diet; duration 2 years</td>
<td>( \downarrow ) hs-CRP, IL-6, IL-7, IL-18, with Mediterranean diet vs prudent diet ( P&lt;0.05 )</td>
</tr>
<tr>
<td>Michalsen et al (16)</td>
<td>101 patients with established and treated CAD</td>
<td>Mediterranean diet group or written advice-only group; duration 1 year</td>
<td>No effects on biomarkers of inflammation ( P&gt;0.05 )</td>
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<tr>
<td>Polyunsaturated Fatty Acids</td>
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<tr>
<td>Rallidis et al (19)</td>
<td>76 male dyslipidemic patients</td>
<td>15 mL linseed oil (8 grams ALA) or 15 mL safflower oil (11 grams LA); duration 12 weeks</td>
<td>( \downarrow ) CRP, SAA, and IL-6 in ALA group; no effects with LA ( P&gt;0.05 )</td>
</tr>
<tr>
<td>Bemelmans et al (20)</td>
<td>103 moderately hypercholesterolemic adults</td>
<td>ALA-enriched (15% ALA, 46% LA) or LA-enriched (58% LA, 0.3% ALA) margarine; duration 2 years</td>
<td>( \downarrow ) CRP in the ALA group vs LA ( P&lt;0.05 )</td>
</tr>
<tr>
<td>Zhao et al. (21)</td>
<td>23 hypercholesterolemic adults</td>
<td>ALA diet (6.5% ALA, 10.5% LA), LA diet (12.6% LA, 3.6% ALA) or AAD (7.7% LA, 0.8% ALA); duration 6 weeks</td>
<td>( \downarrow ) CRP, VCAM-1, and E-selectin in ALA group vs LA; Decreased ICAM-1 in ALA and LA groups vs AAD ( P&lt;0.05 )</td>
</tr>
<tr>
<td>Chan et al (25)</td>
<td>48 obese individuals and 10 lean normolipidemic men</td>
<td>4 grams EPA/DHA, with or without atorvastatin (40 mg) Duration-6 weeks</td>
<td>( \downarrow ) CRP and IL-6 with fish oil + atorvastatin, but not with fish oil alone ( P&gt;0.05 )</td>
</tr>
<tr>
<td>Vega-Lopez et al (26)</td>
<td>80 healthy subjects</td>
<td>1.5 grams EPA/DHA, with or without 800 IU all-rac alpha-tocopherol; duration 12 weeks</td>
<td>No effects on biomarkers of inflammation ( P&gt;0.05 )</td>
</tr>
<tr>
<td>Jellema et al (27)</td>
<td>11 obese men</td>
<td>1.35 grams of EPA + DHA or placebo capsules; duration 6 weeks</td>
<td>No effects on biomarkers of inflammation ( P&gt;0.05 )</td>
</tr>
<tr>
<td>Mori et al (28)</td>
<td>51 treated-hypertensive type 2 diabetic subjects</td>
<td>4 grams, DHA, or placebo; duration 6 weeks</td>
<td>No effects on biomarkers of inflammation ( P&gt;0.05 )</td>
</tr>
<tr>
<td>Geelen et al. (29)</td>
<td>43 men and 41 postmenopausal women</td>
<td>1.5 grams EPA+DHA or placebo; duration-12 weeks</td>
<td>No effects on biomarkers of inflammation ( P&gt;0.05 )</td>
</tr>
<tr>
<td>Ciobotaru et al (30)</td>
<td>30 postmenopausal women using HRT</td>
<td>1.33 grams EPA+DHA, or 2.56 grams EPA+DHA, or placebo; duration 5 weeks</td>
<td>( \downarrow ) CRP and IL-6 with fish oil vs placebo ( P&lt;0.05 )</td>
</tr>
<tr>
<td>Conjugated Linoleic Acid</td>
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<tr>
<td>Risserus et al (33)</td>
<td>60 men with metabolic syndrome</td>
<td>3.4 g CLA, or 3.4g purified f10c12 CLA, or placebo Duration-12 weeks</td>
<td>( \uparrow ) CRP with f10c12 CLA supplementation vs placebo ( P&lt;0.01 )</td>
</tr>
<tr>
<td>Moloney et al (34)</td>
<td>32 adults with diet-controlled type 2 diabetes</td>
<td>3.0 grams CLA isomer mixture or placebo; duration 8 weeks</td>
<td>CLA ( \downarrow ) fibrinogen ( P&lt;0.01 ); no effects on CRP, IL-6 ( P&gt;0.05 )</td>
</tr>
<tr>
<td>Smedman et al (35)</td>
<td>53 healthy volunteers</td>
<td>4.2 grams CLA isomer mixture or placebo; duration 12 weeks</td>
<td>( \uparrow ) CRP with CLA mixture vs placebo ( P&lt;0.01 ) No effects on TNF-( \alpha ) and VCAM-1 ( P&gt;0.05 )</td>
</tr>
</tbody>
</table>

AAD indicates average American diet; HRT, hormone replacement therapy. 
\( \uparrow \) indicates increased and \( \downarrow \) indicates decreased.
did not measure biomarkers of inflammation in these subjects. Whereas the authors ascribe part of the benefit to α-linolenic acid (ALA), the role of individual dietary factors (oleic acid, α-linolenic acid, or antioxidants) in the Mediterranean diet, in modulating inflammation is not yet defined.14 Esposito et al reported the anti-inflammatory effects of a Mediterranean-style diet in patients with metabolic syndrome, without CVD, who randomly received instructions to follow either a control diet or the Mediterranean-style diet. Although the macronutrient composition of the 2 diets were similar (carbohydrates 50% to 60%, proteins 15% to 20%, total fat <30%), the patients consuming the Mediterranean-style diet had higher intakes of fruits, vegetables, nuts, whole grains, and olive oil in comparison to the control group. These patients showed a concomitant decrease in serum concentrations of hsCRP and cytokines (IL-6, IL-7, and IL-18, P<0.05), and decreased insulin resistance compared with the control group.15 However, Michalsen et al reported null effects with a Mediterranean diet in patients with medically treated coronary artery disease (CAD), on biomarkers of inflammation.16 Thus, a Mediterranean-style diet, high in oleic acid or monounsaturated fatty acid content, fiber, and antioxidants may reduce inflammation, and corresponding coronary events in middle-aged adults; however, their effects in patients with heart disease need further investigation. Baer et al also demonstrated that 8% substitution of oleic acid led to a significant decrease in IL-6 concentrations, compared with consumption of a saturated or trans fatty acid-substituted diet. Furthermore, there was no difference in biomarkers of inflammation between oleic acid diet (39% fat) and the standard fat control diet (30% fat). Thus, oleic acid does not promote inflammation, and may actually offset the pro-inflammatory effects of a high-fat diet, or those seen with substitution of saturated or trans fatty acids.10

Polyunsaturated Fatty Acids (PUFA)
The relationship between dietary n-3 fatty acids [α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)], and inflammation has been relatively well-studied among the major dietary macronutrients. Epidemiological studies indicate that there is an inverse association between dietary ALA and risk of myocardial infarction.17,18 Randomized trials have reported anti-inflammatory effects of ALA. Rallidis et al reported a significant reduction of CRP and IL-6 levels (P<0.01), after ALA supplementation (8g ALA), whereas LA supplementation (11 grams LA) decreased cholesterol levels with no significant effects on inflammation in male dyslipidemic patients. The ratio of n-6:n-3 was 1.3:1 in ALA supplemented group, and 13.2:1 in LA supplemented group.19 Bemelmans et al also reported a lowering of CRP levels in moderately hypercholesterolemic men and women after consumption of an ALA-enriched margarine than in those consuming a LA-enriched margarine.20 However, in a substitution study in hypercholesterolemic men and women, reported by Zhao et al, both ALA and LA significantly reduced CRP and intercellular cell adhesion molecule-1 (intercellular adhesion molecule-1 [ICAM-1]), respectively. It should be noted that in this study, both substitution diets had high levels of LA (10.5% and 12.6%), and had half of the total fats derived from walnuts, walnut oil, and flaxseed oil, and saturated fatty acids provided only 8% of the total energy. The n-6:n-3 ratio was 4:1 and 2:1, respectively, in LA-substituted and ALA-substituted diets. Although the authors do not discuss the protein content of walnuts in modulating inflammation, there might be a role of specific amino acids in walnuts (eg, arginine), which may also contribute to a decrease in inflammation in the two dietary groups. In this study, both ALA and LA substituted diets (17% of total energy) were found to lower serum lipids (total and low-density lipoprotein [LDL] cholesterol, and triglycerides) as well as biomarkers of inflammation.21 Thus, a low ratio of n-6:n-3 PUFA is desirable. The average American diet comprises of an excess of n-6 fatty acids compared with n-3 fatty acids, amounting to a ratio of 10 to 20:1, and it has been suggested that this imbalance could potentially promote a prothrombotic state.22

Although some epidemiological studies have shown an inverse correlation between dietary fish or fish oil (EPA and DHA) consumption and biomarkers of inflammation,23,24 intervention trials have not yet confirmed these effects. Chan et al reported a significant decrease of hsCRP in obese dyslipidemic individuals after a 6-week treatment with 40 mg/d of atorvastatin alone, and in combination with 4 g/d of fish oil (Omecor capsules; 45% EPA and 39% DHA), but no effects in the group treated with fish oil alone.25 Similarly null effects with EPA and DHA supplementation were seen in healthy subjects,26 in slightly obese individuals,27 in treated hypertensive type 2 diabetic subjects,28 and also in postmenopausal women.29 In contrast to the null effects reported by several studies following fish oil consumption on biomarkers of inflammation, Cubotaru et al reported a significant decrease in CRP and IL-6 levels in postmenopausal women on hormone replacement therapy (HRT) after a 5-week consumption of 1.3g/d of n-3 fatty acids from fish oil compared with placebo (safflower oil). However, it needs to be pointed out that these women on HRT, had high levels of CRP to start with and in the same study, the group that received 2.56 g/d of n-3 fatty acids from fish oil did not have a decrease in CRP or IL-6 that was significant from placebo.30 Thus, among the n3 fatty acids, ALA appears to be anti-inflammatory. ALA is the precursor of EPA, and there is limited conversion of ALA to DHA.31 EPA has been inversely associated with IL-6 in observational studies, and further intervention trials with n3 fatty acids, alone or in combination, will confirm these observations.32

Conjugated Linoleic Acid (CLA)
and Inflammation
A supplementation study of t10c12 CLA, CLA mixture (t10c12 + c9t11), or placebo in men with metabolic syndrome, revealed that t10c12 CLA significantly increased CRP levels (110%) compared with placebo. There was no difference in CRP levels between CLA mixture and placebo groups, suggesting an unfavorable effect of t10c12 CLA in inflammation and cardiovascular disease. Recently, Smedman et al reported a significant increase in CRP levels, compared with placebo, after a 3-month supplementation of CLA mixture (4.2 g/d) in healthy volunteers. Human supplementation with CLA is thus not recommended until further information from studies on the mechanisms of
CLA and specific CLA isomers at the molecular level are conducted.33,34,35

**Cholesterol**

Whole-egg supplementation significantly increased CRP levels in healthy, lean, insulin-sensitive subjects, but had no effects in obese or insulin resistant groups whose inflammatory marker levels were already elevated at baseline. It has been shown earlier that obesity or insulin resistance is associated with an impaired cholesterol absorption. This may explain the lack of effects of cholesterol feeding in these groups.36 Pirro et al have demonstrated the attenuation of inflammation after an 8-week dietary intervention with a low-cholesterol/low-saturated-fat diet in patients with primary hypercholesterolemia.37

Thus, from the studies discussed so far it appears that the overall quantity of fat intake, the sources and type of dietary fat, with special emphasis on ALA and oleic acid, and the ratio of n-6:n-3 fatty acids in the diet, collectively play a crucial role in modulating inflammation. Although the combination of fatty acids (oleic acid and α-linolenic acid) in the Mediterranean diet seems to exert anti-inflammatory effects, their individual role in attenuating inflammation remains inconclusive and should be the focus of future research.

**Carbohydrates, Dietary Fiber, and Inflammation**

Esposito et al emphasized meal modulation of cytokines (IL-8, IL-18, and adiponectin) as a therapeutic approach toward attenuating atherogenic inflammatory activities in diabetic patients. Thirty patients with newly diagnosed type 2 diabetes mellitus and 30 matched healthy subjects were randomly assigned to consume 3 isoenenergetic meals (780 kcal), separated by 1-week interval; a high-fat meal (28% carbohydrates, 12% protein, and 60% fat, 2.8 grams fiber), a high-carbohydrate low-fiber meal (70% carbohydrate, 11% protein, 19% fat, 4.5 grams fiber), and a high-carbohydrate high-fiber meal (67% carbohydrate, 11% protein, 22% fat, 16.8 grams fiber). Whereas the high-fat meal increased IL-18 concentrations and decreased adiponectin concentrations from baseline in both nondiabetic and diabetic subjects, the high-carbohydrate high-fiber meal, decreased IL-18, from baseline, in both types of subjects. The high-carbohydrate low-fiber meal significantly decreased adiponectin concentrations in diabetic subjects, whereas IL-8 concentrations were not affected by any of the 3 meals. However, there were no significant differences in any biomarkers of inflammation between the 3 dietary groups.38 Jenkins et al further postulated the anti-inflammatory effects of a dietary portfolio treatment in hyperlipidemic adults, wherein a combination of soy proteins, viscous fiber, plant sterols, and almonds lowered CRP levels, similar to the statin-treated group.39 Thus, although a diet high in fiber and complex carbohydrates is a better choice than refined carbohydrates, but their role in reducing inflammation needs further investigation.

**Alcohol and Inflammation**

Moderate alcohol intake has been associated with beneficial effects on markers of inflammation in type 2 diabetic patients.40 A 4-week consumption of 30 g/d of alcohol from red wine led to a significant decrease in serum concentrations of hsCRP (21%), as well as endothelial adhesion molecules (vascular cell adhesion molecule-1 [VCAM-1], ICAM-1) in healthy adult men.41 Whereas this amount of red wine exceeds the dose for moderate drinking, however, as an essential component of the Mediterranean diet,41 red wine consumption (1 to 2 glasses/d) has been associated with reduced inflammation.

**Proteins and Inflammation**

Consumption of arginine-rich foods, like nuts and fish, have been shown to lower CVD risk by reduction of inflammatory markers.42 However, clinical trials have shown null effects with soy isoflavones or soy proteins on biomarkers of inflammation.43,44 A soy-based meal replacement (MR) plan (SlimFast Soy), replacing 2 meals per day with the continuing use of fruits and vegetables as snacks and a third regular meal, has been shown to promote weight loss, improve metabolic profile, and lower CRP levels in diabetic subjects at 6 months in comparison to those on an individualized diet plan (IDP).45 Although it suggests that substitution of soy protein to a calorie-restricted diet may promote weight loss, which in turn has been shown to reduce CRP, as discussed earlier in this review, it does not support the conclusion that soy proteins lower inflammation.

**Micronutrients and Inflammatory Markers**

Among the various micronutrients, the existing body of data reveal RRR-α-tocopherol, and to some extent γ-enriched mixed tocophers, to be anti-inflammatory, whereas in case of other micronutrients, data remain insufficient and inconclusive.46–49 Limited observational studies have shown a strong inverse association between dietary total antioxidant capacity, individual serum carotenoids and vitamins, and magnesium, and markers of inflammation.50–53 Recently, Miller et al performed a meta-analysis of 19 randomized controlled trials, using either vitamin E alone, or in combination with other micronutrients, and reported an increase in all-cause mortality with high dosages of vitamin E (≥400 IU/d).54 Their conclusions were strongly contested by various experts who argued that the authors did not take into consideration the different forms of vitamin E on inflammation, and the wide heterogeneity in the studies selected cannot support the application of the results to general or healthy population.55 Furthermore, the recently reported data from the Women’s Health Study showed a highly significant 24% reduction in the secondary end point of cardiovascular deaths, and a significant 26% reduction in major cardiovascular events among the subgroup of women aged at least 65 years. The study administered 600 IU of RRR-α-tocopherol on alternate days in 39 876 healthy US women for 10 years.56 Thus, whereas RRR-α-tocopherol is anti-inflammatory (≥600 to 800 IU/d),44 the effects of high doses of natural forms of vitamin E on cardiovascular end points have essentially been negative. Further research needs to focus on other forms of vitamin E, such as γ-tocopherol or combination of natural tocopherols, with weight loss to determine whether their effects are additive.

In addition to individual dietary nutrients, research has also focused on the anti-inflammatory factors in foods such as the flavonoids and catechins. A 4-week consumption of green tea (600 mL/d) significantly decreased plasma soluble P-selectin levels in adult male smokers but had no effects on CRP
levels. Phillips et al reported a significant decrease in CRP levels after dietary supplementation of a combination of mixed tocopherols, flavanoids, and docosahexaenoate in untrained healthy nonsmoking males undergoing eccentric exercise. Thus, it is difficult to attribute benefit to a single dietary factor, and the possibility of synergy between dietary factors needs to be borne in mind.

It appears from the available literature that a combination of dietary factors, such as, in the Mediterranean diet, portfolio diet, or the prudent diet may retard inflammation, possibly by nutrient–nutrient synergy, but does not clarify the role of individual factors in the process. Weight loss/hypocaloric diets are definitely associated with reduced inflammation and overall risk reduction of CVD. Also, most of the studies have reported effects on CRP, whereas a few have focused on pro-inflammatory cytokines such as IL-1β, IL-6, or TNF-α. Future research needs to focus on the role of specific dietary factors on biomarkers of inflammation, because they may modulate inflammation through different mechanisms. Therapeutic lifestyle changes remain the cornerstone in modulating inflammation and cardiovascular disease and much further research is needed to define the anti-inflammatory or pro-inflammatory effects of specific dietary factors.

Acknowledgments

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