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Invited Review

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The emerging role of chronic inflammation in the major degenerative diseases of modern society has stimulated research into the influence of nutrition and dietary patterns on inflammatory indices. Most human studies have correlated analyses of habitual dietary intake as determined by a food frequency questionnaire or 24-hour recall with systemic markers of inflammation like high-sensitivity C-reactive protein (HS-CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α). An occasional study also includes nutrition analysis of blood components. There have been several controlled interventions which evaluated the effect of a change in dietary pattern or of single foods on inflammatory markers in defined populations. Most studies reveal a modest effect of dietary composition on some inflammatory markers in free-living adults, although different markers do not vary in unison. Significant dietary influences have been established for glycemic index (GI) and load (GL), fiber, fatty acid composition, magnesium, carotenoids, and flavonoids. A traditional Mediterranean dietary pattern, which typically has a high ratio of monounsaturated (MUFA) to saturated (SFA) fats and ω-3 to ω-6 polyunsaturated fatty acid (PUFAs) and supplies an abundance of fruits, vegetables, legumes, and grains, has shown anti-inflammatory effects when compared with typical North American and Northern European dietary patterns in most observational and interventional studies and may become the diet of choice for diminishing chronic inflammation in clinical practice. (*Nutr Clin Pract*. 2010;25:634-640)

Keywords: diet, Mediterranean; fatty acids; fatty acids, omega-3; omega-6; inflammation; glycemic index; dietary fiber; functional food

Inflammation has recently emerged as an important aspect of the pathophysiology of age-related infirmity and the major chronic diseases of industrialized societies, including cardiovascular disease, type 2 diabetes mellitus, Alzheimer's disease, and many types of cancer. Most observational studies and clinical trials have used high-sensitivity C-reactive protein (HS-CRP) as a biochemical marker of inflammation, because it is relatively stable and easy to measure. Elevation of HS-CRP predicts future development of diabetes mellitus and hypertension more accurately than body mass index (BMI).

Any attempt to create a diet for optimal health must consider the impact of the dietary prescription on systemic inflammation. Part of this impact results from visceral adiposity, because of the inflammatory effects of abdominal obesity. Part of this impact can be attributed to direct or indirect effects of nutrients and dietary pattern on components of the inflammatory response itself. This overview will first consider the relationship between nutrient intake and inflammatory mediators, relying mainly on human observational data, and will then describe observational and interventional trials, primarily those using a Mediterranean-type dietary pattern and its components.

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Nutrient Effects on Chronic Inflammation

Carbohydrates and Glycemic Index

Diets with relatively high glycemic index (GI) and glycemic load (GL) have been associated with elevated risk of coronary heart disease, stroke, and type 2 diabetes mellitus, particularly among overweight individuals.[1] Dietary GI, the mean propensity of carbohydrate in an individual's diet to increase blood glucose level, and dietary GL, the product of dietary GI and quantity of carbohydrate, have shown inconsistent relationships to HS-CRP in observational studies. In the Harvard Women's Health Study,[1] blood levels of HS-CRP showed a small but progressive increase across quintiles of dietary GI, with a highly significant difference between first and fifth quintiles, even with multivariate statistical adjustment. There was no significant association between HS-CRP and GL. Similar findings were reported in a smaller study from the Netherlands.[2] In the Dutch study, each 10-unit increase in dietary GI was associated with a 29% increase in HS-CRP. A study from Tufts University compared the metabolic response to weight loss in healthy, overweight individuals consuming diets of low and high GL. The only significant difference between the 2 groups was a greater decrease in HS-CRP among the low GL dieters.[3] In contrast, a prospective study done at the University of Massachusetts found no relationship between GI or GL and HS-CRP among a population with a relatively high mean GI and GL.[4] It is possible that the relationship between carbohydrate quality and inflammation may only be measurable with relatively low GI diets.

Fiber content of the diet may influence the relationship between carbohydrate quality and systemic inflammation. A recent review of 7 studies on the relationship between weight loss and HS-CRP reported that for 6 studies in which fiber consumption was quantified, significantly greater reductions in HS-CRP concentrations (25–54%) were seen with increased fiber consumption (≥3.3 g/MJ).[5] The Women's Health Initiative failed to detect an effect of fiber consumption on HS-CRP, but found a significant inverse relationship between habitual dietary fiber intake and interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), important mediators of inflammation.[6] The effect occurred at relatively high fiber consumption (24 g/day) and held for both soluble and insoluble fiber. The impact of fiber may be related to its effect on glycemia. An Italian study found that the inverse association between fiber intake and HS-CRP was independent of weight but associated with reduction in fasting glucose with higher consumption of dietary fiber.[7]

Fat: Quality and Quantity

An analysis of data from the National Health and Nutrition Examination Survey (NHANES 99-00), found that levels of saturated fatty acids (SFA) in serum phospholipids were positively correlated with HS-CRP and fibrinogen, another inflammatory marker. By contrast, phospholipid-polyunsaturated fatty acid (PUFA) levels were inversely associated with HS-CRP.[8] A study of Indian adolescents and young adults found that dietary SFAs were the single most important nutrient contributing to increases in serum HS-CRP levels, after adjusting for relevant variables. For every 1% decrease in energy intake from SFA, HS-CRP was calculated to decrease by 0.14 mg/L.[9] In contrast, a Swedish study of healthy elderly men and women failed to identify a relationship between levels of SFA in cholesteryl esters and HS-CRP.[10] Varied mechanisms have been proposed to account for the pro-inflammatory effect of dietary SFA. Analysis of these possible mechanisms lies outside the scope of this study.[11]

Trans-fatty acid (TFA) consumption has also been positively associated with markers of systemic inflammation. In the Harvard Nurses Health Study, TFA intake was positively associated with soluble TNF-receptor 1 and 2. TFA intake was not associated with IL-6 or HS-CRP concentrations overall but was positively associated with IL-6 and HS-CRP in women with higher BMI, and HS-CRP levels were 73% higher among those in the highest quintile of TFA compared with the lowest quintile.[12]

TNF-α levels were positively associated with TFA and SFA consumption in patients with congestive heart failure, and event-free survival was decreased in patients with higher TNF-α. Consumption of PUFAs in general and ω-3 fatty acids in particular showed the opposite association.[13]

A recent review of observational and interventional data concluded that the TFA pro-inflammatory effects (increased TNF-α, IL-6, and HS-CRP) were associated with markers of vascular endothelial dysfunction and were most striking when compared with the effects of *cis* unsaturated fatty acids.[14]

Numerous experimental and observational studies in humans have found an inverse association between dietary consumption of ω-3 fatty acids (ω-3 PUFA) and systemic markers of inflammation.[15] In the MESA (Multi-Ethnic Study of Atherosclerosis) study, long-chain ω-3 PUFA intake was inversely associated with plasma concentrations of IL-6 and the inflammatory marker, matrix metalloproteinase 3 (MMP-3), independent of other measured variables. Non-fried fish consumption was inversely related to IL-6 levels, whereas fried fish was not.[16]

In an observational study from Australia, plasma HS-CRP concentration was negatively correlated with blood levels of total ω-3 fatty acids and eicosapentaenoic acid (EPA, 20:5n3).[17] Among patients with stable coronary artery disease (CAD), levels of EPA and docosahexaenoic acid (DHA, 20:6n3) in erythrocyte membrane lipids were inversely associated with HS-CRP and IL-6. The inverse association of ω-3 fatty acids with HS-CRP and IL-6 was not modified by multiple variables, including statin use.[18]

Among young Japanese women, a protective effect of ω-3 PUFAs against HS-CRP elevation was found only when ω-3 PUFAs supplied greater than 1.1% of dietary calories.[19]

AN interventional study in Norway evaluated the effect of ingesting salmon containing different amounts of omega ω-3 fatty acids on inflammatory biomakers. Salmon were fed 3 different regimens to modulate the ω-3 fatty acid content in the fish. Patients with stable CAD ate 700 g of salmon (with varying n-3 PUFA content) weekly for 6 weeks. Only patients fed the filets with a high ω-3 fatty acid content experienced any dietary effect, with a significant reduction of IL-6.

ω-6 PUFA consumption shows variable effects on inflammation. Both anti-inflammatory and pro-inflammatory effects have been described[21] and 2 reviews have suggested that higher dietary ω-6 PUFAs may increase the quantity of ω-3 PUFAs needed to reduce inflammatory markers.[22]

For Japanese men, but not women, there is an inverse relationship between dietary intake of both ω-3 and ω-6 PUFA and HS-CRP. Among specific PUFAs, only alpha-linolenic acid (18:3n3) and linoleic acid (18:2n6) showed clear inverse relationships with HS-CRP.[23]

The ATTICA study in Greece found that total plasma ω-3 fatty acids were inversely associated with HS-CRP, IL-6, and TNF-α; and plasma ω-6 fatty acids were inversely associated with HS-CRP, IL-6, and fibrinogen. The calculation with the strongest inverse association with all inflammatory markers, however, was the plasma ω-3/ω-6 ratio. In contrast to the significant influence of plasma fatty acids, there was no association between dietary fatty acid intake and the investigated markers.[24]

A dietary intervention was designed to reduce the ω-6/ω-3 ratio by increasing alpha-linolenic acid and decreasing alpha-linoleic acid. This involved replacing other vegetable oils with olive and rapeseed, and replacing meat with fish for 3 days a week. The intervention was associated with a significant reduction in TNF-α, but not HS-CRP.[25]

A recent review of experimental data reported that the quantity and quality of fat influences the acute inflammatory response to a single meal. The authors concluded that SFA content and the ratio among PUFAs of ω-3 to ω-6 have emerged as major determinants of the magnitude of postprandial inflammatory response, with high meal SFA increasing inflammatory indices and high ω-3/ω-6 PUFA ratio decreasing them.[26]

A few studies suggest that dietary consumption of monounsaturated fatty acids (MUFA), oleic acid in particular, may have anti-inflammatory effects.[27,28] In the ATTICA study, plasma levels of MUFA were inversely associated with HS-CRP and IL-6. Among Japanese women and men, higher intakes of oleic acid are associated with decreased HS-CRP.[23,29]

In an experimental study of healthy men, a single 1,000 Kcal meal containing 45% MUFA produced a 2-hour postprandial decrease in HS-CRP of 6%.[30] In an 8-week dietary intervention in the Netherlands, overweight subjects received a high-SFA or MUFA diet and then had biopsies of abdominal fat pads. Consumption of the SFA diet resulted in increased expression of adipose tissue genes promoting inflammation whereas the MUFA diet led to an anti-inflammatory gene expression profile, associated with an increase in plasma and adipose tissue oleic acid content.[31]

Carotenoids

In the Women's Health and Aging Study, participants with the highest serum levels of α-carotene and total carotenoids were significantly less likely to be in the highest tertile of serum IL-6 at baseline and those with the lowest levels of α- and β-carotene, lutein/zeaxanthin, or total carotenoids were significantly more likely to have increasing IL-6 levels over a period of 2 years.[32]

An interesting study from England correlated the incident risk of inflammatory polyarthritis with diet. The mean daily intakes of the carotenoids zeaxanthin and beta-cryptoxanthin were 20% and 40% lower, respectively, in cases than in controls, but there were no significant differences in the intakes of other carotenoids. The authors concluded that a modest increase in β-cryptoxanthin intake, equivalent to 200 mL of freshly squeezed orange juice per day, is associated with a reduced risk of developing inflammatory arthritis.[33] As a corollary, a clinical trial in Denmark demonstrated that 500 mL of orange and black currant juice daily for 4 weeks decreased HS-CRP and fibrinogen, but not IL-6, in patients with peripheral arterial disease, whereas a sucrose drink had the opposite effect.[34]

Flavonoids

In a U.S. population survey, consumption of flavonoids was inversely related to HS-CRP levels. Among the flavonoid compounds investigated, quercetin, kaempferol, malvidin, peonidin, daidzein, and genistein each had inverse associations with serum HS-CRP concentration, even after adjustment for total fruit and vegetable consumption.[35]

Based upon studies in vitro, numerous mechanisms for anti-inflammatory effects of flavonoids have been described, many of them derived from enzyme inhibition.[36] Correlating in vitro effects with clinical effects is problematic because of poor absorption of naturally occurring flavonoid glycosides and extensive conjugation of the flavonoid aglycones after absorption.

Magnesium

In the Women's Health Initiative Observational Study, magnesium (Mg) intake was inversely associated with HS-CRP, IL-6, and TNF-α-R2 in a dose-dependent manner after adjustment for multiple variables including dietary fiber, fat, fruit, and vegetables intake. No significant ethnic differences were observed.[37] A similar effect of dietary Mg was seen in the Harvard Nurses Study. Whole grain was the main contributor to dietary Mg, followed by green leafy vegetables, nuts, and legumes. Among individual food groups, however, the inverse associations were statistically significant only for green leafy vegetables and nuts with HS-CRP and for green leafy vegetables with IL-6.

The inverse relationship between dietary Mg and inflammation is so strong that Mg intake was the most highly rated factor in a 42-item dietary anti-inflammatory index developed at the University of South Carolina.[38]

Food, Dietary Pattern, and Inflammation

Fruits and vegetables

Numerous studies have shown an inverse correlation between fruit and vegetable consumption and serum levels of inflammatory markers.[39] This effect has been seen not only with adults, but also with adolescents[40] and is not confined to Western populations.[41]

The MESA study examined relations between dietary patterns and markers of inflammation, correlating answers to a food-frequency questionnaire with concentrations of HS-CRP and IL-6. Four dietary patterns were derived: (1) fats, oils, processed meats, fried potatoes, salty snacks, and desserts; (2) beans, tomatoes, refined grains, and high-fat dairy products; (3) whole grains, fruit, nuts, and green leafy vegetables; and (4) fish, and dark-yellow, cruciferous, and other vegetables. Pattern 1 was positively associated with HS-CRP and IL-6; patterns 3 and 4 were inversely associated with HS-CRP and IL-6. Results were independent of demographics and lifestyle factors, and waist circumference and were not modified by race-ethnicity.[42]

German researchers placed healthy nonsmoking men on diets containing only 2 servings a day of fruits and vegetables for 4 weeks and then placed them on diets of increasing fruit and vegetable consumption for another 4 weeks. Those randomized to 8 fruit/vegetable servings a day had a significant decline in HS-CRP.[43]

Mediterranean Diet

Much of the research concerning dietary patterns and inflammation has looked to the Mediterranean dietary pattern or its components. The term "Mediterranean diet" is usually applied to a spectrum of diverse dietary patterns traditionally found in the olive-growing regions of southern Europe, with olive oil as a major source of fat, ample consumption of vegetables, fruits, legumes, cereals, and fish, with a moderate intake of red wine during meals.[44] Compared with standard Western diets, the Mediterranean dietary pattern is considered to be relatively high in α-linolenic acid (approximately 2 grams per day or 1% of total calories) and low in linoleic acid, with an ω-3:ω-6 ratio of 1:7.[45]

In southern Europe, adherence to a traditional Mediterranean diet is associated with a 9% reduction in total and cardiovascular mortality, a 6% reduction in cancer, and a 13% reduction in Parkinson's and Alzheimer's disease incidence.[44] Following the pioneering work of the Lyon Heart Diet Study in the 1990s, research on regional Mediterranean diets has been conducted in Italy, Spain, and Greece.

Among a large population of healthy Italians, HS-CRP was inversely associated with a high intake of olive oil, vegetables, legumes, soups, fruits, and fish.[46] Italian men and women who met criteria for metabolic syndrome were randomized to a Mediterranean diet which increased their consumption of fruits, vegetables, nuts, whole grain, and olive oil, or an American Heart Association (AHA) prudent diet with a higher content of carbohydrate and a lower content of MUFA and ω-3 PUFA. After 2 years, patients ingesting the Mediterranean diet had significantly reduced serum concentrations of HS-CRP, IL-6, IL-7, and IL-18 than patients on the AHA diet.[47]

A smaller study of Spanish men and women with high risk of cardiovascular disease found no association between adherence to a Spanish Mediterranean diet and reduced inflammatory markers, but did find an inverse association between IL-6 and consumption of fruits and cereals; levels of HS-CRP and IL-6 were lowest in those with the highest consumption of olive oil and nuts.[48]

Greek researchers studied adherence to a Mediterranean diet among healthy adults in the Attica region. Those in the highest tertile of adherence averaged 20% lower HS-CRP, 17% lower IL-6 levels, 14% lower white blood cell counts, 6% lower fibrinogen levels, and a borderline reduction in TNF-α, when compared with those in the lowest tertile.[49] Similar results were found among patients who had survived myocardial infarction, with a progressive decrease in HS-CRP and IL-6 as "units" of dietary adherence increased.[50]

When Greeks with abdominal obesity were placed on a Mediterranean diet for 2 months, however, there was no effect on HS-CRP, although indices of endothelial function (flow-mediated vasodilatation and diastolic blood pressure) improved.[51]

Clinical trials of a Mediterranean dietary intervention applied to northern European populations have shown mixed results. Germans with CAD showed no effect on HS-CRP or fibrinogen over 1 year; however, 80% were being treated with statins, which have a profound effect on HS-CRP that is independent of diet.[52] In a Norwegian study, 3 years of adherence to a Mediterranean dietary pattern diet reduced the inflammatory cytokine IL-18 but not other inflammatory markers.[53] Scandinavian patients with rheumatoid arthritis experienced a significant reduction in HS-CRP and pain while following a Cretan-style Mediterranean diet. Although the effect was independent of weight loss, it was not significantly different from the response to a vegetarian diet.[54]

A few interventional studies have examined the influence of individual foods on inflammatory markers in humans. The results of studies on those foods showing significant effects in controlled studies *in vivo* are summarized in Table 1. With the exception of tea, all of these foods are components of the Mediterranean dietary pattern.

Table 1. Foods associated with a decrease in inflammatory markers in human interventional studies

Food	Study duration	Effect	Ref
Extra virgin olive oil	1 meal	Decreased TXB2 and LTB4 in comparison with corn oil, non-virgin olive oil	55
Tomato juice	10 days	Reduced neutrophil airway influx in asthmatics	56
Tomato drink	26 days	Reduced TNF-α production by whole blood	57
Whole tomatoes	28 days	No change in CRP	58
Walnuts	1 meal	Decreased monocyte mRNA for TNF-α and IL-6 with no change in serum levels	69
Red wine	4 weeks	Reduced CRP and fibrinogen	60
Garlic powder	3 months	No effect on CRP, TNF-α	61
Flaxseed flour	2 weeks	Reduced CRP, fibronectin and serum amyloid A in obese subjects	62
Tea, black	12 weeks	40-50% reduction of CRP in subjects with CRP>3 mg/L	63
Tea, black	6 weeks	Decreased CRP and platelet aggregation in healthy men	64
Tea, green	4 weeks	No effect on CRP in men	65
Tea, green	4 weeks	No significant effect on CRP in male smokers	66
Cherries, sweet	4 weeks	Reduced CRP and CCL5, no effect on IL-6 in healthy adults	67

CCL5, chemokine (c-c motif) ligand 5; CRP, c-reactive protein; IL, interleukin; mRNA, messenger ribonucleic acid; TXB, thromboxane; TNF, tumor-necrosis factor.

Conclusion

Habitual dietary pattern appears to have a moderate influence on chronic, low-grade systemic inflammation, an important risk factor for diseases of aging and industrialization. Available evidence indicates that consumption of Mg, fiber, ω-3 PUFAs, MUFAs, flavonoids, and carotenoids from food is associated with decreased levels of inflammatory markers in serum, whereas SFA, TFA, high-GI carbohydrates, and a high ω-6/ω-3 PUFA ratio are associated with increased levels of inflammation. The Mediterranean dietary pattern may best fulfill requirements for an anti-inflammatory diet, at least in the Western world. Because the culinary attributes of this dietary pattern make it culturally familiar to most North Americans, widespread adoption of a Mediterranean-type anti-inflammatory diet may have significant public health benefits. Inclusion of some foods that are not considered central to the Mediterranean diet might enhance its anti-inflammatory benefits, especially flaxseed meal and black tea.

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