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STATE-OF-THE-ART PAPER

The Effects of Diet on Inflammation

Emphasis on the Metabolic Syndrome

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Reducing the incidence of coronary heart disease with diet is possible. The main dietary strategies include adequate omega-3 fatty acids intake, reduction of saturated and trans-fats, and consumption of a diet high in fruits, vegetables, nuts, and whole grains and low in refined grains. Each of these strategies may be associated with lower generation of inflammation. This review examines the epidemiologic and clinical evidence concerning diet and inflammation. Dietary patterns high in refined starches, sugar, and saturated and trans-fatty acids, poor in natural antioxidants and fiber from fruits, vegetables, and whole grains, and poor in omega-3 fatty acids may cause an activation of the innate immune system, most likely by an excessive production of proinflammatory cytokines associated with a reduced production of anti-inflammatory cytokines. The whole diet approach seems particularly promising to reduce the inflammation associated with the metabolic syndrome. The choice of healthy sources of carbohydrate, fat, and protein, associated with regular physical activity and avoidance of smoking, is critical to fighting the war against chronic disease. Western dietary patterns warm up inflammation, while prudent dietary patterns cool it down. (J Am Coll Cardiol 2006;48: 677–85) © 2006 by the American College of Cardiology Foundation

A low-fat diet (≤30% of total calories) is still considered by many physicians to be a healthy choice for both primary and secondary prevention of cardiovascular disease (CVD) (1). An unintended consequence of emphasizing low-fat diets may have been to promote unrestricted carbohydrate intake, which reduces high-density lipoprotein cholesterol (HDL-C) and raises triglyceride levels, exacerbating the metabolic manifestations of the insulin resistance syndrome, also known as the metabolic syndrome (2,3).

Three dietary strategies may help prevent coronary heart disease (CHD) (4): 1) increase consumption of omega-3 fatty acids from fish or plant sources; 2) substitute nonhydrogenated unsaturated fats for saturated and trans-fats; and 3) consume a diet high in fruits, vegetables, nuts, and whole grains and low in refined grains (Fig. 1). The effects of diet on CHD can be mediated through multiple biologic pathways other than serum lipids, including oxidative stress, subclinical inflammation, endothelial dysfunction, insulin sensitivity, blood pressure, and thrombotic tendency (5).

Current evidence supports a central role for inflammation in all phases of the atherosclerotic process (6). Circulating markers of inflammation, such as C-reactive protein (CRP), tumor necrosis factor (TNF)-alpha, and some interleukins (IL-6, IL-18), correlate with propensity to develop ischemic events (7–9); moreover, circulating phase reactants elicited by inflammation may not only mark increased risk for vascular events but in some cases may also contribute to their pathogenesis (10). Increasing attention has also been paid to the direct vascular effects of plasma proteins that originate from adipose tissue, especially adiponectin, which exhibits potent anti-inflammatory and antiatherosclerotic effects (11). Low plasma adiponectin levels are an independent risk factor for future development of type 2 diabetes (12), whereas high plasma adiponectin concentrations are associated with a lower risk of myocardial infarction in men (13). Moreover, it has become increasingly clear that inflammation strictly correlates with endothelial dysfunction and insulin resistance, with the best evidence coming from patients with the metabolic syndrome (14).

We put forward the hypothesis that each dietary strategy associated with a lower CHD risk may in fact be associated with lower generation of a proinflammatory milieu, which may be one important mechanism linking healthy diets to reduced CHD risk. Criteria used for study selection to be included in the current review were English language, relevance to clinicians, study design, and venue of publication. Because controlled trials with clinical end points and assessment of inflammatory markers were lacking, we gave weight to observational studies and dietary interventional trials reporting intermediate end points.

INCREASE CONSUMPTION OF OMEGA-3 FATTY ACIDS

The benefits of omega-3 fatty acids in decreasing the risk of sudden cardiac death have been demonstrated in animal, epidemiologic, metabolic, and small clinical trials (15). These compounds have long been recognized to have anti-inflammatory activity, and their use in consolidated inflammatory diseases, such as rheumatoid arthritis and Crohn's disease, is expanding (16). Omega-3 fatty acids decrease the arachidonic acid content of cell membranes,

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Abbreviations and Acronyms

ALA = alpha-linolenic acid
CHD = coronary heart disease
CRP = C-reactive protein
CVD = cardiovascular disease
IL = interleukin
sICAM = soluble intercellular adhesion molecule
sVCAM = soluble vascular cell adhesion molecule
TNF = tumor necrosis factor

resulting in the synthesis of eicosanoids that have fewer inflammatory properties than those derived from omega-6 fatty acids. Although omega-3 fatty acids may inhibit the synthesis of proinflammatory cytokines, such as TNF-alpha, IL-1, and IL-2 (17) and decrease expression of adhesion molecules on the endothelium (18), the results of ex vivo human studies investigating the effect of omega-3 fat intake on inflammatory markers are not conclusive but may have been influenced by the specificity of cells investigated and assay procedures (19).

Observational studies. In 405 healthy men and 454 healthy women, intake of omega-3 fatty acids eicosapentaenoic acid (EPA) and docosaexaenoic acid (DHA) was inversely associated with plasma levels of markers of TNF-alpha activity, such as soluble TNF receptors 1 and 2; moreover, high intake of both omega-3 and omega-6 fatty acids was associated with the lowest level of inflammation (20). Therefore, the combination of omega-3 and omega-6 fatty acids may work well on CHD risk, as demonstrated by other cross-sectional data indicating that the combined intake of both fatty acids is associated with a lower risk of CHD than either type of fatty acid alone (21). Another cross-sectional study (22) of 727 women from the Nurses' Health Study I cohort demonstrated lower concentrations of many markers of inflammation and endothelial activation, including CRP, IL-6, and E-selectin, among those in the highest quintile of omega-3 fatty acids compared with those in the lowest quintile. In a randomly sampled cohort of 470 healthy middle-aged women and men from the Los Angeles Atherosclerosis Study (23), increased dietary intake of omega-3 fatty acids was associated with a blunted effect of the variant 5-lipoxygenase genotype (lacking the common allele) to increase carotid artery intima-media thickness and circulating CRP levels. In the ATTICA study, those who consumed at least 300 g of fish per week had 33% lower CRP compared with non-fish consumers (24). Lastly, in subjects with existing CHD, granulocyte DHA content was inversely associated with CRP levels (25).

Interventional studies. Changing the proportion of omega-3 fatty acids of the diet may influence circulating markers of inflammation and endothelial activation in hypercholesterolemic subjects fed 2 diets low in saturated fat and high in polyunsaturated fats (PUFA), as compared with an average American diet (26). The alpha-linolenic acid (ALA) diet (6.5% of energy from ALA) decreased CRP, vascular cell adhesion molecule-1, and E-selectin more than the linoleic acid (LA) diet (12.6% energy from LA). In another study, dietary supplementation with ALA (15 ml linseed oil per day) for 3 months in 50 dyslipidemic subjects significantly decreased CRP (38% compared with baseline values), serum amyloid A (23%), and IL-6 (10%) levels independent of lipid changes (27). Consumption of an ALA-enriched margarine was also associated with lowering of CRP levels in hypercholesterolemic subjects (28). However, most of the studies using fish oil or pure omega-3 fatty acids supplementation have failed to show any effect on CRP levels (29–33), unless the fish oil supplement was given at a high dose (14 g/day) (34).

Although some epidemiologic studies have shown an inverse correlation between dietary intake of fish or fish oil and circulating markers of inflammation, clinical trials have not yet confirmed these effects. On the other hand, ALA appears to have anti-inflammatory potential, and future studies should focus on this.

SUBSTITUTE NONHYDROGENATED UNSATURATED FATS FOR SATURATED AND TRANS-FATS

Reducing trans-fat. Higher intake of trans-fats or, to a lesser extent, saturated fats has been shown to be associated with increased CHD risk among 80,082 women in the Nurses' Health Study cohort, whereas higher intakes of polyunsaturated (nonhydrogenated) and monounsaturated fats were associated with decreased risk (35). It is not entirely clear, however, whether the effects of this substitution are primarily due to introducing beneficial effects of unsaturated fats, moving away from the detrimental effects of saturated and trans-fats, or both. Moreover, the relation with CHD risk is explained only partially by the adverse

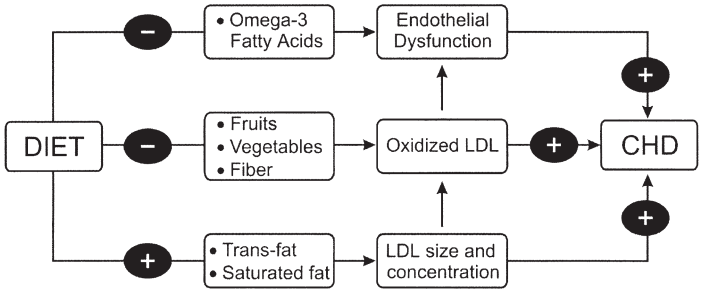

Figure 1. Some mechanisms through which unhealthy dietary patterns may lead to coronary heart disease (CHD). LDL = low-density lipoprotein.