Will the dietary intake of fish prevent atherosclerosis in diabetic women?²

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The pioneering observations in Greenland Eskimos suggest that high intakes of n-3 fatty acids from fish and sea mammals prevent cardiovascular disease. This is in contrast with the high frequency of cardiovascular disease in Western populations, who have low fish intakes and high intakes of cholesterol and saturated fat. This presumed benefit of n-3 fatty acid intake from fish stimulated a large volume of scientific research (1). The evidence has suggested that dietary n-3 fatty acids might ameliorate the atherosclerotic process itself, which is the cause of coronary artery disease. Populations that consume more n-3 fatty acids from fish have a lower incidence of coronary artery disease. Patients with coronary artery disease who eat fish appear to have a lower subsequent rate of coronary artery disease and lower total mortality, especially from sudden death. The decrease in deaths from coronary artery disease as a result of fish-oil n-3 fatty acid intakes results from their antiarrhythmic effects (less sudden death from ventricular fibrillation and ventricular tachycardia), but myocardial infarction still occurred from thrombotic atherosclerosis. These studies included clinical trials in male survivors of myocardial infarction as well as epidemiologic associations in both men and women. Fish-oil feeding experiments in humans have shown many potential antiatherogenic effects (2, 3): a lowering of plasma lipid and lipoprotein concentrations and decreased platelet aggregation, an antithrombotic action (4, 5). Other factors believed to be involved in the pathogenesis of atherosclerosis are also affected by n-3 fatty acids (3), including the inhibition of intimal hyperplasia in canine autologous vein grafts, a decreased endothelial cell production of a platelet-derived growth factor–like protein, an increased activity of endothelium-derived nitric oxide (vasodilating), and a reduction in the cytokines involved in the inflammatory response associated with atherosclerosis.

Furthermore, fish oil has prevented the development of experimental atherosclerosis in pigs and rhesus monkeys. In the pig study, the intima of the coronary arteries was damaged by a balloon catheter at the same time that the animals were fed cholesterol and fat, and severe coronary atherosclerosis resulted (6). When the pigs were fed cod liver oil, which is rich in n-3 fatty acids, cholesterol, and saturated fat, a lower incidence of atherosclerosis developed despite little effect on the lowering of plasma cholesterol. This result suggests that fish oil had an effect on atherosclerosis that was unrelated to plasma lipid concentrations. In another study, the ingestion of fish oil led to less carotid atherosclerosis in monkeys fed a diet high in cholesterol and fat; the monkeys experienced some reduction in total cholesterol and LDL cholesterol (7). The data to date in humans have been inconclusive in showing that fish oil prevents restenosis after coronary artery balloon angioplasty.

In this issue of the Journal, the association between high fish and n-3 fatty acid intakes and a reduction in the incidence of atherosclerosis was given further credence (8). Fish intake was associated with a reduced progression of coronary atherosclerosis in postmenopausal women with coronary artery disease. In particular, the consumption of ≥2 servings of fish or ≥1 serving of tuna or dark fish each week was associated with smaller increases in the percentage of stenosis of the coronary arteries as documented by angiography. This association was particularly evident in diabetic women after adjustments for age, cardiovascular disease risk factors, and the dietary intakes of fatty acids, cholesterol, fiber, and alcohol. This association was not significant in nondiabetic women. Fish consumption was also associated with a smaller decrease in minimum coronary artery diameter and with fewer new lesions. These data are buttressed by the observation that the fish-oil fatty acids eicosapentaenoic and docosahexaenoic acids are actually incorporated into the phospholipids and cholesterol esters of severe atherosclerotic lesions in humans (3). Thus, it makes sense that a high consumption of fish oil will prevent the progression of atherosclerosis.

A particularly important finding of this study was that the benefit of a high fish-oil intake was especially apparent in diabetic women. Diabetes has now been ranked as a major risk factor for subsequent heart disease, in the same category as a previous episode of coronary artery disease. The incidence of diabetes has greatly increased as a result of the epidemic of obesity. The results of this study agree well with the epidemiologic observation that the risk of coronary heart disease is much lower in diabetic women who consume fish (9).

Despite the favorable effect of fish intake on coronary atherosclerosis in postmenopausal women with overt coronary artery disease, one must be cautious in interpreting these data. Fish intake did not prevent atherosclerosis but rather reduced its progression. In other words, atherosclerotic progression occurred more slowly with fish consumption. Clearly, this multifactorial

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disease—atherosclerosis—is not going to be cured or even prevented by fish intake alone. The predominant risk factors for coronary artery disease—smoking, hypertension, hyperlipidemia (particularly elevated LDL-cholesterol concentrations), obesity, diabetes, and low physical activity—must still be dealt with to obtain the best possible outcome. As far as diet is concerned, intakes of the predominant progenitors of atherosclerotic plaque—dietary cholesterol and saturated fat—must be reduced. What needs to be added to the usual low-fat diet prescription of fruit, vegetables, grains, beans, and small amount of animal products is fish.

Dietary factors that contribute to the development and progression of atherosclerosis, namely dietary cholesterol and fat (particularly saturated fat), have been known for almost 100 y. Monkeys fed egg yolk developed high cholesterol concentrations and severe coronary atherosclerosis (10). The removal of cholesterol from the monkeys’ diets led to normal cholesterol concentrations and a considerable reduction in the amount of atherosclerotic plaque, from 60% blockage to 20% occlusion.

The influence of dietary factors on chronic disease is always of great interest, especially because these factors apply to atherosclerotic coronary artery disease. Dietary changes made to prevent disease have special value in that the cost of these changes is minimal compared with that associated with clinical interventions, and these changes can be applied to the whole population as a public health measure. The encouragement of fish consumption as a measure to prevent the ravages of coronary artery disease is an important public health message.

REFERENCES