n-3 Fatty acids and antioxidants in coronary heart disease

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Evidence that n-3 polyunsaturated fatty acids (PUFA) protect against coronary heart disease has accumulated over the past 25 years starting from pioneering epidemiological work on populations (Eskimos and Japanese) eating large amounts of fish-based n-3 fatty acids.

Interest in n-3 fatty acids was first focused on the issue of heart disease prevention and the following early observations were made: platelet function is effectively and favorably modified by a high intake of fish oils, resulting in reduced thrombotic tendency. In fact replacement of platelet arachidonate (AA) by eicosapentaenoic acid (EPA), an alternative substrate for cyclooxygenase, results in reduced formation of thromboxane A_2 and in the production of the less active thromboxane A_3 helping to explain the prolonged bleeding time. In addition, PGI_3, the antiaggregatory prostaglandin derived from EPA, has effects comparable to those of the AA-derived PGI_2. Other 3-series eicosanoids derived from EPA (e.g., PGE_3, leukotriene B_5) also have reduced physiological activity relative to their 2-series counterparts. These differences in metabolism between the EPA and AA-derived metabolites are likely to be the basis for both the diminished thrombogenic vigor observed in subjects taking fish oils, but also for their anti-inflammatory properties. EPA-derived leukotrienes (LT-5 series) in fact have less potent leukocyte activating effects than their AA-derived (LT-4 series) counterpart. Thus, part of the anti-atherogenic mechanism of ω3 fatty acids is likely due to their impact on eicosanoid metabolism.

Lipoprotein metabolism is also affected by n-3 fatty acids, but apparently not via alterations in the eicosanoid system. The triglyceride-reducing (both fasting and postprandial) effects of these fatty acids have been well established, and the mechanism involves an inhibition of hepatic triglyceride synthesis and secretion with a possible effect on triglyceride clearance still being investigated. Total cholesterol levels usually do not change, whereas small increases in HDL cholesterol have frequently been reported. Like the triglyceride-lowering fibrate drugs, LDL cholesterol levels can rise with n-3 fatty acid treatment, particularly in subjects with significant hypertriglyceridemia; in other patients changes are uncommon. Non-lipid effects on coronary heart disease risk factors such as fibrinogen, blood viscosity or platelet aggregation may also explain some of the beneficial effects of fish oils on thrombosis and atherosclerosis. Finally, n-3 fatty acids may also play a role in the reduction of blood pressure and thereby may reduce the risk for coronary heart disease. Mechanistic studies have shown that n-3 fatty acids exert additional effects on the arterial walls, such as inhibition of the expression of adhesion molecules, and on myocardial cells, such as modulation of ion channel function and contractile activity. Various population studies and controlled trials have shown that greater intakes of n-3 fatty acids through the diet or as supplements favorably affect the progression and the outcome of cardiovascular diseases.

The most recent test of the effects of n-3 fatty acids on coronary heart disease morbidity and mortality was the GISSI-Prevention trial. This study conducted in Italy on 11 324 patients with known coronary heart disease, divided into four groups in a factorial design, showed that in patients (about 50% of the total) assigned to take 1 g/day n-3 fatty acids with or without vitamin E (300 mg), after 3.5 years of follow-up, total mor-

tality was 21% lower than in patients treated differently, and the incidence of sudden cardiac death was reduced by 45%. The findings of the GISSI-Prevention study provide strong support for the use of n-3 fatty acids in secondary prevention of acute coronary syndromes. The mechanisms by which n-3 fatty acids protect against cardiac death are not definitely known, but may relate to their ability to prevent cellular damage during periods of ischemic stress.

Recently, evidence has also been provided that an enhanced intake of the 18 carbon n-3 fatty acid, α-linolenic, mainly present in vegetable fats and oils, is protective vs coronary heart disease in secondary prevention trials.

It must be pointed out, however, that enhanced intakes of n-3 fatty acids should be associated with a reduction of n-6 fatty acids (mainly linoleic acid) since these interfere with the favorable effects of n-3 fatty acids. Our current intake of linoleic acid is such that the ratio of n-6/n-3 fatty acids in the diet is in the range of 10:1, while the optimal value is considered 4-5:1.

n-3 Fatty acids are highly unsaturated and therefore potentially highly oxidizable substrates, a condition that has raised concern due to the enhanced atherogenicity of oxidatively modified LDL. However, although LDL from subjects on a high n-3 fatty acid intake, enriched in n-3 fatty acids, are more susceptible to oxidation in *ex vivo* assessments, the antiatherogenic properties of n-3 fatty acids, shown in animals and humans, rule out any possible involvement of enhanced lipid peroxidation *in vivo*.

Fish is a frequent component of diets which are also rich in antioxidant and other protective agents, as is the case of the Mediterranean diets, largely based on a high intake of fruit, vegetables and legumes. The hypothesis of a role of oxidatively modified lipid and apoprotein components of the lipoproteins at the onset and during the progression of atherosclerotic lesions has greatly stimulated research in this area, with special attention to the eventual protective effects of antioxidants. The following major issues have been explored and partly elucidated: evidence for a role of peroxidation processes, in relation to the mechanisms of the disease; assessment of reliable markers of enhanced oxidation *in vivo*; identification of new antioxidant and biologically active compounds in diets, in addition to the classical antioxidant vitamins; studies (observational, metabolic and controlled trials) aimed at assessing both the correlations between biomarkers of oxidation and disease progression, and the possible beneficial effects of antioxidants on the disease. While research is actively progressing, certain conclusions can be drawn: diets rich in antioxidants, including compounds such as phenols and flavonoids, are protective, and their consumption by the population at large should be encouraged; antioxidant supplements are protective in secondary prevention trials; individuals with definite evidence (biomarkers) of enhanced *in vivo* oxidation may benefit from antioxidant supplementation. An additional category of potent antioxidants in our diet, which have been only partly investigated, are phenolics and flavonoids present in wine and olives/olive oil. These compounds in addition to antioxidant activities are able to exert a variety of favorable activities on various types of cells (platelets, leukocytes, macrophages) and are also quite effectively absorbed.

In conclusion, our diet should aim at providing an integrated array of minor protective compounds: the n-3 fatty acids, associated with a reduced intake of n-6 fatty acids, the antioxidant vitamins (E, C, beta-carotene) and other non-vitamin antioxidants, fibers, etc. These factors should be included in diets which also have a proper energy intake, a correct balance between the major fatty acid classes (low saturates, high monounsaturated fatty acids, and an adequate intake of polyunsaturated fatty acids with an optimal n-6/n-3 ratio of about 5:1).