# Fish oil and cardiovascular disease: lipids and arterial function[1,2]

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**ABSTRACT** n−3 Fatty acids have been shown to modify several key risk factors for cardiovascular disease. However, it is not clear whether the apparent protection against cardiovascular disease is directly related to antiatherogenic functions of these fatty acids or is mediated through their modification of the risk factors through mechanisms not directly related to lipids. A major question concerns the importance of lipid modification, which is a potent outcome of fish-oil supplementation. On balance, lipid modification is likely to represent a significant antiatherogenic factor. The benefits include increased $HDL_2$-cholesterol concentrations, reduced triacylglycerol-rich lipoprotein concentrations, reduced postprandial lipemia, and reduced remnant concentrations. In contrast, LDL-cholesterol concentrations have often been noted to rise and the potential of increased oxidizability of LDLs is potentially adverse with lipid modification, but this potential can be overcome with vitamin E supplementation. The characteristic lipid changes and the underlying mechanisms are reviewed. Additional benefits of fish oils include improved endothelial function and better arterial compliance (elasticity). Future trials will be needed to determine minimum effective dosages of eicosapentaenoic and docosahexaenoic acids over lengthy periods and to show cardiovascular disease reduction through intervention. *Am J Clin Nutr* 2000;71(suppl):228S–31S.

**KEY WORDS** Fish oil, n−3 fatty acids, eicosapentaenoic acid, docosahexaenoic acid, lipid modification, cardiovascular disease, coronary heart disease, atherogenesis, HDL, LDL

## INTRODUCTION

The active molecules of fish-oil n–3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and possibly other minor fatty acids, are multipotent compounds. Throughout 20 y of research, their potential to counter atherosclerotic vascular diseases has been supported by an increasingly lengthy list of functions, some related to lipid metabolism but others mediated through nonlipid mechanisms. On the negative side, there may be one or more adverse effects of n−3 fatty acids. On balance, if n−3 fatty acids are to be the major explanation for the protection afforded by eating fish, it will be necessary to resolve some key issues. *1)* Which of the effects of EPA, DHA, or both best explain the presumptive protective effects? *2*) Are the changes in lipid metabolism sufficient to provide protection, given that the amounts of n−3 fatty acids needed to show beneficial effects on lipids are far greater than are consumed by fish eaters (other than in unusual populations)? *3*) Could small amounts of n−3 fatty acids be adequate nevertheless if eaten over long periods of time? These issues are shown in **Table 1**.

## INFLUENCE OF FISH OILS ON LIPID METABOLISM

### Triacylglycerol-rich lipoproteins

The concentrations of endogenously derived triacylglycerol-rich lipoproteins, VLDLs, and intermediate-density lipoproteins have been almost uniformly reported to be lowered with fish oil. Fish oils have been effective in normal subjects and in patients with common phenotypes of hyperlipidemia in which VLDL concentrations are raised. The minimum effective dose of n−3 fatty acids appears to be slightly more than 1 g/d. At intakes >2 g/d, VLDLs decreased an average of 25% in normal subjects and even more in hypertriglyceridemic subjects (≈50% in those with the type 4 or 5 phenotype and ≈40% in those with combined hyperlipoproteinemia) (1). Furthermore, this response is maintained. What of chylomicrons and chylomicron remnants? In more severe forms of hypertriglyceridemia, such as type 5 hyperlipoproteinemia, in which both VLDLs and chylomicrons (or remnants) are present, excess n−3 fatty acids can be highly effective. Whether this result reflects enhanced removal of chylomicrons is uncertain. Catabolized VLDLs and chylomicrons compete for similar removal mechanisms; diminished chylomicron removal may therefore occur whenever VLDL overproduction increases the need for VLDL removal, as in type 5 hyperlipoproteinemia. Chylomicronemia after a fatty meal is diminished when fish oil is eaten over 2 wk (2) but not after a single meal. Remnants in type 3 hyperlipoproteinemia are partly cleared with fish-oil treatment (3).

Dietary fish oils also modify the type of hypertriglyceridemia that is normally inducible by carbohydrates (4). This modification might be expected from the known effects of these 2 nutrients on triacylglycerols: carbohydrates stimulate and fish oils inhibit VLDL production. This is seen strikingly in hepatocytes from obese hyperlipidemic rats in which the usual overproduction of lipid is suppressed with DHA (5).

The nature of the predominant n−3 fatty acids (EPA and DHA) does not seem important in determining plasma triacylglycerol lowering in humans. Fish or fish oils rich in EPA appear to be as effective in humans as is fish rich in DHA. Fish oils vary

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**TABLE 1**
Treating hyperlipidemia with fish oil: key questions

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| *1*) If fish oil inhibits atherosclerosis, how much of this effect is attributable to lipoprotein changes? |
| *2*) Is lowering triacylglycerol beneficial? |
| *3*) When and why is LDL cholesterol raised and is this necessarily adverse? |
| *4*) Is lipoprotein oxidation a threat? |
| *5*) Are there benefits secondary to lipid lowering? |
| *6*) Given that the above effects require fish oil in amounts exceeding those derived from eating fish, what are the minimal protective amounts of n−3 fatty acids? |

considerably in their content of EPA and DHA as well as that of long-chain monoenes and docosapentaenoic acid. A dose-response trial comparing EPA and DHA is urgently needed.

Much larger amounts of fish oil than of individual n−3 fatty acids must be taken to produce an effect. However, whole fish oils are rich in saturated fatty acids that may be undesirable. Therefore, esters of individual n−3 fatty acids have been used. The absorption of the ethyl or methyl esters of EPA appears to be inferior to that of EPA in the glycerides of the fish oils, yet the esters have been therapeutically effective in dosages roughly equal to those in fish oil.

In summary, fish oils affect VLDL metabolism by *1*) reducing VLDL triacylglycerol secretion, as clearly shown in kinetic studies in humans, animal liver perfusions, and isolated hepatocytes (6); *2*) generally, but not always, increasing VLDL apoliprotein B secretion (6, 7) [at least in rat liver, this may be related to increased apolipoprotein B degradation (8), thus assembly of VLDL is impaired]; *3*) reducing triacylglycerol transport, resulting in smaller VLDLs, which are largely converted to LDLs; and *4*) less certainly, increasing VLDL clearance. The key enzyme lipoprotein lipase has mostly been found to be unaffected by fish oil in humans (9).

### Chylomicron metabolism

Although there is agreement that chylomicron assembly and secretion are reduced in isolated intestinal cells incubated with EPA, the interpretations of results differ. The mechanisms appear to include the reduction of apolipoprotion B formation and the diversion of EPA from triacylglycerols to phospholipids (10).

### Hepatic triacylglycerol metabolism

Reduced triacylglycerol formation is ascribed largely to reduced fatty acid availability. Studies have confirmed that *1*) fish oil increases oxidation of fatty acids by peroxisomal as well as mitochondrial routes (11), which may be mediated by peroxisome proliferator in the liver (12); *2*) fish oil reduces fatty acid synthesis (owing to suppression of key enzymes); *3*) fish oil diverts fatty acids to phospholipids (6); *4*) although fish oil reduces plasma fatty acids, this may be due to increased hepatic uptake through a transporter protein (12); *5*) within the liver, triacylglycerol assembly is impaired through down-regulation of esterifying enzymes (13).

### Cholesterol metabolism

Fish oil reduces cholesterol absorption in humans (6) and in monkeys (14). Cholesterol synthesis in the liver is reduced and cholesterol secretion within VLDLs is lowered (6).

### LDL metabolism and oxidation

The effects of fish oil on LDL metabolism represent the more controversial aspects of the n−3 fatty acid effects. Why does fish oil cause LDL-cholesterol concentrations to sometimes rise, at least in humans, when all the evidence suggests it should not? Fish oil depresses cholesterol synthesis and may reduce cholesterol absorption (6). This focuses attention on LDL removal and particularly on the LDL (apolipoprotein B/E) receptor. There is evidence that fish oil down-regulates the receptor in hepatic cells (15, 16). Abnormal LDL binding to the receptor in human monocytes (16) and to skin fibroblasts has been ascribed to abnormalities in the LDL itself (17).

Changes in the LDL particles are minor, but tend toward larger, cholesterol-enriched LDLs (18, 19). LDL size relates to the exchange of lipids between LDL, VLDL, and HDL. Fish oil would reduce such exchanges through suppression of cholesterol ester transfer protein and thus favor larger LDL particles (18). Reduced LDL synthesis has been reported with large amounts of fish oil (20).

The n−3 enrichment renders LDLs susceptible to oxidation, as has been shown in several reported studies, with some exceptions. The obvious relevance is to atherogenesis, which is favored by oxidized lipoproteins. The evidence includes increases in in vitro copper-oxidized and macrophage-modified changes in LDL that lead to their increased uptake by macrophages (19). These findings define a potential atherogenic property of dietary fish oil, although it must be emphasised that these are in vitro observations and that the sum of the metabolic outcomes of marine n−3 fatty acids appears to be antiatherogenic in life. Nevertheless, our findings indicate a need for increased antioxidant action, such as that provided by α-tocopherol, if large amounts of fish oil are to be consumed. We have in fact shown that, at least in vitro, the addition of vitamins E and C to n−3 fatty acid–enriched macrophages inhibits their capacity to oxidize LDLs (21). In a study in pigs fed atherogenic diets, however, atherosclerosis was not increased in animals fed fish oil, despite evidence of raised in vitro LDL oxidizability (22).

### HDL metabolism

Most reports indicate a favorable effect of fish oil on HDLs. The number of larger cholesterol-rich HDLs (in the $HDL_2$ range) increases at the expense of $HDL_3$ (18). However, very high intake of fish oil may lower HDL concentrations (6).

The major effect of fish oil on HDL metabolism is mediated by a reduction in activity of cholesterol ester transfer protein (18), which transfers cholesterol esters from HDLs to VLDLs and LDLs, largely in exchange for VLDL triacylglycerols. Because triacylglycerol concentrations are also reduced, exchange is further diminished, favoring large cholesterol-rich HDL (and LDL) particles over the formation of triacylglycerol-enriched HDLs (and LDLs), which are more susceptible to catabolism.

## FISH OIL AND ARTERIAL DISEASE

Data supporting a relation between fish oil and arterial disease are summarized in **Figure 1** and only a few will be discussed further. Other aspects are discussed elsewhere in the supplement.

The reduction in triacylglycerols is one of the modifications in the risk profile. High triacylglycerol concentrations are now widely recognized as an independent risk factor for cardiovascular disease, although the coexistence of low HDL or high LDL concentrations augments the risk substantially. The atherogenicity of intermediate-density lipoproteins, the remnant of VLDL catabolism, is being rediscovered (23).

Modification of dyslipidemia has been the most characteristic effect of fish oils. Triacylglycerol-rich lipoproteins are almost invariably reduced by mechanisms that are now mostly understood. Postprandial lipemia is reduced (9) and potentially atherogenic remnants are cleared. This facilitation of triacylglycerol catabolism partly explains the desirable rise in $HDL_2$-cholesterol concentrations.

The myocardium is certainly protected from the full damage of ischemia in animals fed fish oil, in which the infarct size is smaller, blood flow is better maintained, and several metabolic disturbances (eg, oxidative damage and calcium overload) that can induce arrhythmias are modified. The protection by fish oils of the myocardium, together with reduction of risk factors and the beneficial modification of arterial responses, explain much of the favorable effectiveness of fish oils (24).

Endothelium-dependent dilatation of arteries is enhanced by fish oils, which also inhibit the vasoconstrictive effects of sympathetic overactivity and norepinephrine (25). We showed that the vascular resistance in the microcirculation of the forearm (which mimics that in the coronary circulation) that occurs when norepinephrine or angiotensin II are infused is attenuated by taking fish oil (25). The improvement might have been due in part to the better lipid profile, because dyslipidemia impairs endothelial function. (Blood pressure was not altered in this study, although this risk factor is reducible in hypertensive subjects.) Endothelial dysfunction is now a well-recognized cause of clinical symptoms in cardiovascular disease and its reversal improves prognosis.

Another index of arterial function is compliance, a measure of the elasticity of large arteries, including the thoracic aorta. Compliance has been reported to be improved by treating diabetic patients (in whom compliance is low as arteries stiffen), with fish oil (26). Of importance is that this improvement in function is achieved within a few weeks.

## FISH OR FISH OIL?

The underlying support for fish oil in the management of cardiovascular risk is the apparent protection that eating fish provides. Several large studies have documented such protection from relatively small amounts of fish eaten regularly (27–29). However, this was not observed in a large US study, the Health Professionals Follow-up Study, published in 1995 (30). The most plausible explanation for this exceptional finding is that the average consumption of fish (or fish oil) was already high in these individuals, reducing the likelihood of showing a dose-related response. The current consensus is that eating fish is beneficial at surprisingly modest intakes, and the benefit probably depends on the fatty acid profile of the fish consumed.

We reported that when equivalent amounts of n−3 fatty acids (4 g/d) are eaten as fish or as fish oil, the risk reduction may be greater with fish (31). A recent report of Tanzanian villagers showed that eating fish (3–5 g n−3 fatty acids/d) outperformed vegetarianism in risk factor reduction (32).

Because fish oils will likely be prescribed for patients with or at risk of clinical cardiovascular disease, at issue is whether this will be in the form of the whole fish oils or more purified fatty acids. This will depend on results of future research on whether EPA, DHA, or both in conjunction have superior therapeutic characteristics.

**FAVORABLE**
Epidemiologic evidence
Experimental atherosclerosis
Risk factor reduction
Modification of atherogenic processes
Protection of endothelial function
Protection of myocardial function

**UNFAVORABLE**
Equivocal intervention results

**FIGURE 1**. Evidence of a relation between fish oil and arterial disease.

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