Fish Oil Consumption and Reduction of Arterial Disease¹,²

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ABSTRACT

Fish oil consumption may help to normalize the prethrombotic state and reduce arterial disease. This antithrombotic potential of fish oil, rich in (n-3) polyunsaturated fatty acids (PUFA), has been attributed to a reduction in platelet activation, a lowering of plasma triglycerides and (vitamin K–dependent) coagulation factors and/or a decrease in vascular tone. Most intervention studies have shown only moderate effects of (n-3) PUFA on these hemostatic variables. On the other hand, the usually small prolongation in bleeding time with fish oil does not appear to lead to bruising or hemorrhage, at least in healthy subjects. This contrasts with the increased bleeding risk accompanying the more prominent antihemostatic effects of antiplatelet and anticoagulant drugs. Here we propose that the beneficial effect of (n-3) PUFA diet is related to downregulation of the mutually positive interactions of platelet activation and coagulation. In addition, we consider the possibility that the dietary effect on hemostatic and lipid factors involves transcription regulation of multiple genes, perhaps in a subject-dependent manner. J. Nutr. 133: 657–660, 2003.

KEY WORDS: • arterial disease • coagulation • fibrinolysis
• fish oil • platelets

The interest in fish oil as a possible antithrombotic nutritional component arose in the mid-1970s with the observation that Greenland Inuits, consuming high amounts of fatty fish, had a tendency toward prolonged bleeding and a low incidence of cardiovascular disease. It was realized that fish and other marine oils are typically enriched in the (n-3) polyunsaturated fatty acids (PUFA), eicosapentaenoic acid, 20:5(n-3), and docosahexaenoic acid, 22:6(n-3). High consumption of (n-3) PUFA (>5 g daily) was thus considered to be responsible for the low incidence of arterial disease (1), although it later appeared that genetic factors also can be involved. Epidemiologic observations have pointed to a clear association between fish oil consumption and reduced risk of coronary heart disease, even with only two fish dishes per week (2).

Early controlled intervention studies, e.g., with men who had recovered from myocardial infarction, also confirmed that regular intake of fatty fish or fish oil capsules reduced death from ischemic heart disease, although without clear effect on the incidence of reinfarction (3). Substantial research since has revealed a variety of changes in the hemostatic system that can explain the antithrombotic potential of fish oil. Surprisingly, however, when reviewing the literature, many described effects of fish oil intervention on surrogate end point measurements, such as hemostatic factors, are variable in outcome. This raises questions concerning the underlying causes and importance of the effect variation.

Membrane Phospholipids, Platelets and Bleeding Time. Dietary (n-3) PUFA influence the composition of membrane phospholipids, an effect that is already detectable at low fish oil intake. Fish oil–derived (n-3) PUFA replace especially arachidonic acid, 20:4(n-6), in the structural phospholipids of platelets and vascular cells by eicosapentaenoate and docosahexaenoate. Because these PUFA are all cleaved from phospholipids by cytosolic phospholipase A₂, fish oil lowers the arachidonate production by the phospholipase and, thereby, the substrate level for cyclooxygenase and lipoxygenase. In platelets and vascular cells, dietary fish oil thereby reduces formation of the (n-6) PUFA-derived prostaglandins and leukotrienes, although this effect is compensated for in part by formation of (n-3) PUFA-derived homologues of these prostanooids (4). For platelets, early work showed that the reduced formation of prostaglandin H₂/thromboxane A₂ by fish oil via cyclooxygenase-1 (COX1) is physiologically important because the COX1 product of fish oil–derived eicosapentaenoate, thromboxane A₂, stimulated platelets in a less effective manner than thromboxane A₂, whereas the platelet-inhibiting effect of endothelial prostaglandin I₃ [derived from (n-3) PUFA] was similar to that of prostaglandin I₃ (derived from arachidonic acid) (5). Fish oil was therefore considered to influence the so-called thromboxane-prostaglandin balance, controlling platelet activation in a favorable, i.e., less platelet-stimulatory way. However, later ex vivo model studies with rats indicated that the (n-3) PUFA-derived prostanooids from the endothelium contributed little to the suppression of platelet activation. Thus, at least in this animal model, it is unlikely that the antithrombotic potential of fish oil depends entirely on an altered thromboxane-prostaglandin balance (6).

As reviewed by others (4,7–9), many but not all human intervention studies indicate that fatty fish or fish oil intake reduces platelet activation. This effect is determined mainly as a reduced aggregation tendency of platelets (in vitro) or as a reduced production of the platelet secretion product.
β-thromboglobulin (in vivo). It is primarily but not exclusively obtained under conditions in which production of thromboxane A$_2$ is a rate-limiting step in the platelet-activation process. Typically, even at higher doses of (n-3) PUFA (≥6 g/d), only about half of the reviewed studies described significant effects on platelet function. Accordingly, in spite of the firm evidence that dietary (n-3) PUFA modify the phospholipid fatty acid composition and alter the platelet eicosanoid metabolism, these modifications are not accompanied by proportionally reduced platelet activation (10). Together, these data indicate that the antithrombotic potential of fish oil is unlikely to result only from diminished thromboxane A$_2$ production by the platelets.

Some of the published studies reported a significant prolongation in the bleeding time after supplementation of (n-3) PUFA, whether in association with a reduced thromboxane formation or platelet function (4,11). A prolonged bleeding time is compatible with the antithrombotic potential of (n-3) PUFA. Combined administration of fish oil and aspirin resulted in a further prolongation of the bleeding time, whereas fish oil did not improve the aspirin-induced inhibition of platelet aggregation (12). This can be taken as another indication that fish oil and aspirin affect hemostasis via different mechanisms.

**Blood Lipids and Fibrinolysis.** One of the first demonstrated effects of fish oil (1), one now confirmed in most reports, is a reduction in plasma triglycerides (13). This (n-3) PUFA effect is particularly prominent in hypertriglyceridemic patients (14), and is explained by a reduced secretion of VLDL from the liver. As reviewed elsewhere (8,13,15), there is no consistent effect of (n-3) PUFA on total cholesterol level or cholesterol in LDL. In some studies, e.g., with hyperlipoproteinemic patients, even an adverse increase in cholesterol (total or LDL) was observed. It thus appears that fish oil only partially improves the lipid profile in blood, thus reducing only some of the risk factors of atherothrombosis.

Few studies have been conducted to investigate whether fish oil has a positive, increasing effect on fibrinolysis. Particular attention has been paid to plasminogen activator inhibitor type 1 (PAI-1) activity. PAI-1 is a fibrinolysis inhibitor, which complexes with circulating tissue-type plasminogen activator and abolishes plasminogen activation and fibrin degradation. High PAI-1 levels are associated with increased risk of arterial disease either causally or as a marker. As reviewed elsewhere (16), few authors have reported that fish oil reduces PAI-1 activity, but the majority of the investigators showed significant increases in this factor. This increase, depending on the levels of other fibrinolysis variables, would point to a higher rather than an improved procoagulant state.

**Coagulation and Relation to Platelet Activation.** Until recently, when global coagulation assays often lacked sensitivity, anticoagulant effects of fish oil were considered to be absent or small (4,16). In some of the published human studies, however, fish oil appeared to reduce the levels of one or more coagulation factors, including moderate reductions in factors VII and X, each of which is implicated in thrombin formation (17–19). Both coagulation factors require vitamin K–dependent carboxylation for coagulant activity, which supports the notion that fish oil can interfere with vitamin K action. With the development of modern, sensitive assays, this topic is receiving new attention. In recent diet studies with rats, (n-3) PUFA reduced the levels of the vitamin K–dependent factors II and X to such a degree that sensitive clotting assays were affected (20). In particular, the process of tissue factor–induced thrombin generation, which is driven by the vitamin K–dependent coagulation factors, was reduced after intervention with low doses of (n-3) PUFA (21). In rats, this anticoagulant effect was not augmented by vitamin K depletion and was accompanied by a lowering of factor V, which is vitamin K independent (22). Some human studies also reported reduced factor V activity after fish oil ingestion (17). Another factor that can be decreased in response to fish oil is fibrinogen (factor I), particularly in subjects with high baseline levels (18,23). Fibrinogen, an independent cardiovascular risk factor, is a vitamin K–dependent protein, that is required for both coagulant activity and platelet function. Thus, part of the literature points to an anticoagulant action of fish oil, although less potent than that of anticoagulant therapy, which is partly independent of vitamin K.

The processes of platelet activation and coagulation are intimately linked and are mutually stimulatory (24). Activated platelets provide glycoproteins and a phosphatidylserine-containing outer membrane, the site at which coagulation factors assemble and become activated (Fig. 1). In the presence of phosphatidylserine-exposing membranes, thrombin formation in plasma is at least three times greater. Conversely, the thrombin that is generated is one of the most potent platelet agonists known. This positive interaction of platelet activation and coagulation can be quantified under physiologic conditions by measuring the generation and inactivation of thrombin in platelet-rich plasma (25). As indicated in Figure 2, partial anticoagulant therapy with coumarin and partial platelet inhibition with aspirin have additive, suppressive effects on thrombin generation when measured with platelets and plasma. A similar, reduced and delayed generation of thrombin was also measured in plasma from healthy volunteers after a regular intake of (n-3) PUFA (Vanschoonbeek, K., unpublished data, 2002). Together, these data illustrate that, with fish oil, the combination of a moderate antiplatelet and anticoagulant effect is more thromboprotective than either effect alone (see Fig. 1).

![Figure 1](https://academic.oup.com/jn/article-abstract/133/3/657/4688034/fig-article-abstract/133/3/657/4688034)
Adverse physiological effects. Successful antiplatelet and anticoagulant therapies are often accompanied by an increased risk of bleeding. Fish and fish oil supplements, although generally well tolerated, have as their main adverse side effect a mild gastrointestinal discomfort, appearing as a fishy aftertaste, belching, nausea, flatulence or loose stools. Published fish oil intervention studies with healthy subjects do not provide indications for increased bleeding, even after a daily intake of ≥6 g (n-3) PUFA. Various papers explicitly mention the absence of easy bruising or clinical signs of (postoperative) bleeding after fish oil intake by patients with cardiovascular disease (26–28). Positive interactions between (n-3) PUFA intake and oral anticoagulants have been noted, but these appear to occur in the absence of clinically relevant bleeding (29). There is only an incidental report of a patient with minor nasal bleeding after a fish oil diet with concomitant anticoagulant therapy (30). In another study, fatal coagulopathy occurred in a patient after abdominal aortic aneurysm resection, but here a causal relationship of fish oil supplementation and the bleeding diathesis was reported to be uncertain (31). Only the Zutphen epidemiologic study, investigating the association between fish consumption and stroke incidence in the Netherlands, concluded that large amounts of seafood may increase hemorrhagic subtypes of stroke, whereas the consumption of only small amounts of fish reduce the incidence of ischemic stroke (32). Vasodilation is another reported effect (usually advantageous) of (n-3) PUFA on the vascular system. However, a meta-analysis of clinical trials showed that the vasodilating effect was most pronounced in hypertensive patients and had little effect on healthy normotensive people (33). Thus, from the current literature, there seems to be little reason to be concerned about disadvantageous effects, at least when fish oil is not combined with anticoagulant treatment.

Variable transcriptional regulation. As indicated, the usually mild and diverse thrombosis-reducing effects of (n-3) PUFA intervention for platelets, plasma lipids and coagulation factors show high interstudy variation. Some fish oil effects, such as changes in triglycerides, fibrinogen and other factors, seem to be most prominent in patients with increased basal values. Even within studies, there is considerable variation in effects observed among individual subjects. Recent findings give an attractive explanation for the diverse and variable effects of (n-3) PUFA on hemostatic and lipid factors, i.e., influence on gene expression. Feeding fish oil to mice was found to down-regulate the hepatic mRNA level of sterol regulatory element-binding protein-1, which controls several lipogenic genes (34). Also in mice, (n-3) PUFA suppress the endogenous peroxisome proliferator-activated receptor α (PPARα), a ligand-activated transcription factor system (35), whereas oxidized (n-3) PUFA activate PPARα (36). Genetic polymorphisms of (hemostatic) factors may be associated with a variable, subject-dependent response to PUFA of genes coding for apolipoproteins (37). New research should indicate how important transcription factors and other regulatory elements are in mediating fish oil effects on the hemostatic system, e.g., regulation of hepatic secretion of triglycerides and (vitamin K–dependent) coagulation factors, and controlling the expression of platelet proteins. This can also reveal whether genetic components are involved in the subject-to-subject response variation to (n-3) PUFA, such as polymorphisms in one or more hemostatic genes.

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Due to space restrictions, relatively few citations could be included. We thank all authors in the field, apologizing for not having cited their work.

Literature Cited


