Marine n-3 Fatty Acids: Basic Features and Background

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ABSTRACT: There is some evidence from epidemiology that intake of n-3 polyunsaturated fatty acids (PUFA) from seafood may protect against coronary artery disease (CAD). This hypothesis is further supported from animal data showing a beneficial effect of n-3 PUFA on thrombosis and atherosclerosis in animals fed fish oils in most, but not all, studies. There are several mechanisms by which an increased intake of marine n-3 PUFA may protect against CAD; the most universal finding is a reduction of plasma triglycerides. It is puzzling, however, that a very low amount of n-3 PUFA, with no known beneficial biochemical effects, seems to be cardioprotective. It has therefore been of paramount interest to perform clinical trials. Such evidence and trials are discussed in later chapters, and the results have been very encouraging.

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This article will first review basic features about the composition of different types of fatty acids. We will primarily deal with n-3 polyunsaturated fatty acids (PUFA) derived from seafood and their content in various types of seafood. We will then address the background for the interest in n-3 PUFA as a way to reduce coronary artery disease (CAD) and comment on their potential beneficial and detrimental biochemical effects in relation to CAD. Other chapters will deal specifically with the effect of n-3 PUFA in atherogenesis, thrombogenesis, and in particular, their effect in clinical trials with hard endpoints—the cornerstone of evidence-based medicine.

n-3 PUFA—An Introduction

Fatty acids are separated into saturated (no double bonds), monounsaturated (one double bond), and PUFA (more than one double bond) with important examples of PUFA shown in Figure 1.

The n-3 PUFA are members of an essential fatty acid family characterized by having their first double bond at carbon atom number 3, as opposed to the other essential fatty acid family, n-6 PUFA, whose members have their first double bond at carbon atom number 6, counted from the methyl end of the carbon chain constituting the backbone of fatty acids (1).

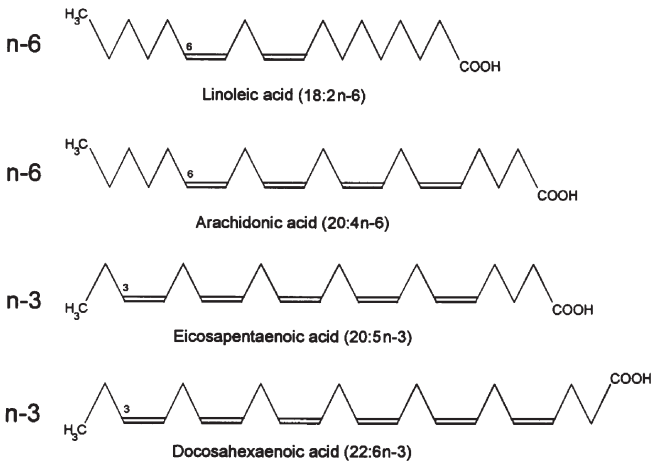

FIG. 1. Major n-3 and n-6 PUFA. The number of carbon atoms is given before and the number of double bonds after the colon. The position of the first double bond counted from the methyl end of the fatty acid separates PUFA into n-3 or n-6 PUFA.

There are two subgroups of n-3 PUFA. One is α-linolenic acid derived from plant oils (canola oil, rapeseed oil, and linseed oil) composed of 18 carbon atoms and 3 double bonds (nomenclature 18:3n-3). The daily intake of this fatty acid in Denmark is ~2 g/d. The other group of n-3 PUFA is derived from seafood; the major marine n-3 PUFA are eicosapentaenoic acid (EPA; 20:5n-3) and docosahexaenoic acid (DHA; 22:6n-3). Because of their larger number of carbon atoms (20 and 22, respectively), these are also sometimes called long-chain n-3 PUFA. α-Linolenic acid can to some (disputed) degree be elongated and desaturated in humans to EPA and DHA; otherwise, EPA and DHA are acquired only from seafood.

The content of n-3 PUFA varies among fish species. It is high in fatty fish such as mackerel, herring, and salmon and low in lean fish such as flounder and cod (Table 1, adapted from Ref. 2). It is worth noting that the content of n-3 PUFA in seafood varies considerably in relation to the location and the time of year of capture (2,3). Furthermore, the way the fish is prepared is also important. It is therefore very difficult to estimate the amount of n-3 PUFA ingested in populations and also in (long-term) clinical trials with fish as the source of n-3 PUFA.

The intake of long-chain marine n-3 PUFA varies considerably among populations; intake is very high in traditionally living Greenland Eskimos (10-14 g/d), low in Western populations (<0.5 g/d), and intermediate in countries such as Japan

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Abbreviations: CAD, coronary artery disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFA, polyunsaturated fatty acids.

TABLE 1
The Approximate Content of n-3 Polyunsaturated Fatty Acids (PUFA) in Seafood[a]

Seafood	g n-3 PUFA/100 g
Mackerel	1.8–5.3
Herring	1.2–3.1
Salmon	1.0–2.0
Trout	0.5–1.6
Tuna	0.5–1.6
Halibut	0.5–1.0
Shrimp	0.2–0.4
Cod, plaice, flounder	~0.2

[a]Depends on variables such as season and place of capture.

and Norway (1-3 g/d). The content of n-3 PUFA in cod liver oil is ~20%, and can be up to 90% (30–60% in many preparations) in fish oil capsules.

Epidemiology

There is some evidence from epidemiologic data that populations with a high intake of marine n-3 PUFA have a low risk of CAD. This has been shown most clearly in Greenland Eskimos (4), but a low occurrence of CAD has also been reported in Alaskan Eskimos (5). In studies from Japan, the incidence of CAD was also lower in fishing villages compared with farming villages with a lower intake of fish (6). The possible association between consumption of seafood and CAD has also been studied in Western populations with an average intake of n-3 PUFA <0.5 g/d. In Zutphen, a Dutch area included in the Seven Countries Study, an inverse correlation between fish consumption and CAD was reported in middle-aged men during 20 yr of follow-up (7). A similar inverse correlation between heart disease and fish consumption in Caucasian populations was reported by some, but not by all investigators (for review see Refs. 1 and 8). Importantly, only in the study from Finland (9) was there a positive correlation between fish consumption and CAD, which the authors attributed to a high content of mercury in the fish consumed. In the Health Professionals Study, there was no correlation between fish consumption and CAD, but an inverse correlation between dietary α-linolenic acid intake and CAD was noted (10). In a recent review of the literature, Marckmann and Grønbœk (8) concluded that fish consumption at 40–60 g daily markedly reduced CAD mortality in populations at high, but not low risk for CAD.

Finally, it is of interest that fish consumption in the Physicians Health Study had no protective effect against cardiovascular mortality, but total mortality and the risk of sudden cardiac death were indeed reduced in those who ate fish (11).

It is puzzling why an intake of fish (and n-3 PUFA) of this order of magnitude seems to offer protection against CAD, because the beneficial biochemical effects of n-3 PUFA (see below) have not been shown at this low dosage (1). The possibility that components in fish other than n-3 PUFA might contribute to this effect therefore must be kept in mind, and it may be that fish consumption is associated with a healthier lifestyle including more prudent dietary habits.

Marine n-3 PUFA and Risk Factors for CAD

The risk of CAD is determined in part by inherited genetic traits, age, and gender, all risk factors that cannot be modified. Known modifiable risk factors for CAD include smoking, hypertension, adiposity, high plasma levels of low density lipoprotein (LDL) cholesterol, and low levels of high density lipoprotein (HDL) cholesterol; the effect of hypertriglyceridemia on cardiac risk remains controversial (12,13). High levels of plasma homocysteine, fibrinogen, and coagulation factor VII as well as impaired fibrinolysis are also associated with an increased risk of CAD (12,13). Several other risk factors for CAD have been proposed and the list of risk factors grows steadily with new research (14).

The effect of n-3 PUFA on risk factors for CAD has been investigated in many studies (1). Although dietary n-3 PUFA in practical doses (in contrast to common public belief) have no effect on LDL cholesterol levels, they slightly increase the antiatherogenic HDL_2 cholesterol, and substantially decrease plasma triglycerides (15,16). n-3 PUFA may also decrease blood pressure by 2–5 mm Hg, in particular in patients with high blood pressure (1,17). Most studies have shown no effect of n-3 PUFA on plasma fibrinogen and coagulant factor VII levels (1), but n-3 PUFA do slightly reduce platelet reactivity and may impair fibrinolysis (1). Other potential effects of n-3 PUFA with respect to preventing atherosclerosis and thrombosis by modifying risk factors for CAD include a reduction in leukocyte reactivity, an improvement of vessel wall function, and a beneficial effect on blood rheology (1,18). The biochemical effects of n-3 PUFA are commonly seen after daily doses between 2 and 5 g and are dose dependent; the most favorable effects are achieved with the higher doses of n-3 PUFA (1).

The concept of assessing the individual risk of CAD as the sum of risk factors, instead of focusing on single risk factors, e.g., high plasma cholesterol, is very important as stressed in the recently published guidelines on prevention of CAD (12,13). n-3 PUFA induce several beneficial changes in risk factors (Table 2), which in our view make them very attractive in the prophylaxis and treatment of the multifactorial disease, CAD (19).

TABLE 2
Suggested Beneficial Effects of n-3 Polyunsaturated Fatty Acids (PUFA) in Coronary Artery Disease (CAD)[a]

Triglycerides ↓
HDL_2-cholesterol ↑
Platelet reactivity ↓
Monocyte reactivity ↓
Neutrophil reactivity ↓
Blood pressure ↓
Improvement of vasoreactivity
Antiarrhythmic properties

[a]↑ represents an increase; ↓ represents a decrease.

n-3 PUFA: Types and Safety

Lean fish provide low amounts of n-3 PUFA but contain little saturated fat and cholesterol and can be recommended for reducing the risk of CAD. Fatty fish have a lower content of saturated fat than most meat servings and may for this reason, independent of likely beneficial effects of n-3 PUFA, be a better food source.

The concept of substituting fish for other food sources and not supplementing fish oils to the habitual diet must be emphasized. However, if fish oils are considered, products of high quality with declared amounts of EPA and DHA, and with antioxidants added, should be chosen.

Concern has been expressed about increased consumption of fish due to intake of heavy metals and pesticides from contaminated fish (9). The risk is low but must not be neglected, and pollution of the sea and its fish should be monitored by international organizations. During industrial processing, it is possible to remove toxic substances from fish oil concentrates.

PUFA (including n-3 PUFA) are susceptible to oxidation due to their high number of double bonds. This may be of importance because of the suggested pivotal role of oxidation of LDL in atherogenesis (20). However, epidemiologic data do not suggest increased atherosclerosis in fish consumers. Whether increased intake of n-3 PUFA leads to clinically relevant enhanced *in vivo* oxidation of LDL continues to be debated (21). Nevertheless, oxidation of n-3 PUFA in fish oil concentrates should be minimized before their intake, which can be achieved by the addition of antioxidants (vitamin E), proper storage, and encapsulation.

There has been concern about an increased risk of bleeding, especially after consumption of larger doses of fish oil concentrates, but there is very little clinical evidence in support of this (22). Furthermore, there is no indication that n-3 PUFA are contraindicated in patients treated with aspirin or anticoagulation, but this has been studied only to a very limited extent (1).

It has been claimed, on the basis of limited data, that n-3 PUFA are detrimental to glycemic control in patients with overt diabetes or impaired glucose intolerance, but recent data have discarded this hypothesis (17,23,24). Although immune responses may be reduced by n-3 PUFA, there is no evidence that intake of n-3 PUFA is associated with an increased risk of cancer or serious infections (1,22). Overall, we conclude that dietary fish and n-3 PUFA are unlikely to promote health problems (25).

In summary, there is some evidence from epidemiology that intake of n-3 PUFA from seafood may protect against CAD. There are several mechanisms by which an increased intake of marine n-3 PUFA may protect against CAD. It is puzzling, however, that a very low amount of n-3 PUFA, with no known beneficial biochemical effects, seems to be cardioprotective. On the other hand, it is reassuring that there is little indication that increased consumption of fish is harmful.

On the bases of epidemiology and the biochemical effects reported, it has therefore been of paramount interest to perform clinical trials, because properly conducted clinical trials remain the cornerstone for a decision to increase the intake of marine n-3 PUFA in the prevention and treatment of CAD. Such evidence and trials are discussed in later chapters, and it should be noted here that the results have indeed been encouraging.

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