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REVIEW

Fish oil and ischaemic heart disease

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Fish oil products are available with or without prescription and are widely used by patients with ischaemic heart disease (IHD). The interest in fish oils, rich in the long chain n-3 polyunsaturated fatty acids (PUFA), eicosapentaenoic acid (n-3 20:5) and docosahexaenoic acid (n-3 22:6), originates primarily from the pioneering work of Dyerberg and Bang.[1] Prompted by the low incidence of acute myocardial infarction in Eskimos in Greenland they suggested that a very high dietary intake of n-3 PUFA's from marine food offered protection against IHD. They showed that the Eskimos had a beneficial lipid pattern and that their balance between pro-aggregatory thromboxanes and anti-aggregatory prostacyclins was shifted towards an anti-thrombotic state compared with Danes.[1] There is also evidence from Japan and Holland that dietary intake of fish protects against IHD.[2] In the American MRFIT study the daily intake of n-3 PUFA was inversely related to IHD mortality in middle-aged men.[3] However, no such relation was found in the American Physicians' Health Study.[4]

Experimental studies of atherogenesis and arterial thrombogenesis in various animal species lend some support to the hypothesis that dietary intake of n-3 PUFA's may play a part in primary or secondary prevention of IHD or both.[5]

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n-3 PUFA: Pathophysiology and influence on cardiovascular risk factors

Dietary intake of fish or fish oil concentrates results in the incorporation of n-3 PUFAs into the membranes of human cells and gives rise to multiple actions on various biochemical factors or cellular events that may play a part in the development and progression of coronary atherosclerosis and its major complication, thrombosis.[2] Fish oil supplementation in patients with IHD reduced plasma triglyceride, whereas the effect on total cholesterol, LDL cholesterol, and HDL cholesterol was unpredictable and usually slight.[6] In some studies total cholesterol[7] and LDL cholesterol[8] were even reported to increase. Theoretically, highly unsaturated fatty acids could enhance the risk of oxidative modification of LDL, but the results of studies of this important issue have been conflicting.

After the intake of n-3 PUFA platelet aggregability was inhibited and the bleeding time slightly prolonged, at least in part by a reduced production of bioactive thromboxane but probably also because of increased synthesis of prostacyclins.[8 9] Studies in pigs indicated that n-3 PUFAs can stimulate the synthesis of endothelium-derived relaxing factor.[10] This may contribute to the favourable change in the interaction between platelets and the vessel wall and may also be partly responsible for the reduction in blood pressure shown after dietary supplementation with n-3 PUFA in patients with mild hypertension.[11 12] The risk of clinically significant episodes of bleeding is very low[2 13]—probably lower than after a low dose of aspirin.

The synthetic activity of leucocytes is reduced after intake of fish oil mainly because the production of bioactive leukotrienes is decreased.[14] Both synthesis of interleukin-1 and tumour necrosis factor by mononuclear cells[15] and of platelet-derived growth-factor-like protein by endothelial cells[16] are inhibited after intake of n-3 PUFA. There is evidence that n-3 PUFAs reduce blood viscosity.[17] Fish oil may impair fibrinolysis by increasing the plasma concentration of plasminogen activator inhibitor. This has also been shown for patients with IHD[7] and is a potentially negative effect of fish oil supplements. The modulation of inflammatory responses could theoretically increase the risk of infection and cancer, but there are no clinical data to support this.

Clinical studies in patients with ischaemic heart disease

CHRONIC STABLE ANGINA PECTORIS

In an open study Saynor *et al* reported that patients with chronic stable angina pectoris given supplements of fish oil had a dramatic decrease in the number of angina attacks.[18] This finding was not confirmed in a placebo controlled study in 36 patients.[19] Other studies on small groups of patients were also negative: so at present there is no evidence that fish oil provides any symptomatic benefit in these patients.

ACUTE MYOCARDIAL INFARCTION

Burr *et al*[20] investigated the effect of dietary advice to increase the intake of fatty fish (at least two fish meals per week or alternatively fish oil (0·9 g of n-3 PUFA daily) for two years) in a randomised trial with a factorial design in 2033 men who recently had recovered from an acute myocardial infarction. There was a significant 29% reduction in the total number of deaths and in the number of deaths due to IHD in the group randomised

Table 1 Randomised controlled trials on the effect of fish oil on the rate of restenosis after percutaneous coronary angioplasty (PTCA)

Study	*No of restenoses Fish oil (%)*	*No of cases Control (%)*	*Main result*	*n-3 PUFA/day*	*Treatment started before PTCA? (days)*
Slack *et al*	8/50 (16)	21/63 (33)	+	2·7	No
Dehmer *et al*	8/43 (19)	18/39 (46)	+	5·4	Yes (7)
Grigg *et al*	15/54 (28)	19/60 (32)	0	3·0	No
Milner *et al*	21/95 (22)	35/99 (35)	+	4·5	No
Reis *et al*	44/124 (35)	15/62 (24)	0	6·0	Yes (1–7)
Nye *et al*	5/36 (14)	18/71 (25)	+	3·6	No
Bairati *et al*	18/59 (31)	29/60 (48)	+	4·5	Yes (21)
Kaul *et al*	19/58 (33)	13/49 (27)	0	3·0	Yes (1–7)
Total	138/519 (27%)	168/503 (33%)			

PUFA, polyunsaturated fatty acids. + = statistically significant reduction in restenosis rate in the fish oil group compared with the control group. 0 = no statistical significant difference between the groups.

to a higher dietary intake of fatty fish. This difference was apparent after a few months. However, the number of non-fatal acute myocardial infarctions was higher in the group advised to eat fish. Therefore it seems unlikely, that the underlying protecting mechanism in this study was anti-thrombotic. Burr *et al* suggested that dietary fish oil may have an anti-arrhythmic effect.[20] Indeed such an effect has been reported in animals[21] and should be investigated in humans.

RESTENOSIS AFTER PTCA

About 25–40% of patients who undergo elective percutaneous transluminal coronary angioplasty (PTCA) develop restenosis within the first six months despite an initially successful procedure. The effect of fish oil supplementation on the incidence of restenosis has been evaluated in eight controlled trials (table 1).[22–29] In five of the trials the incidence of restenosis was reduced after fish oil supplementation[22 23 25 27 28] whereas no such effect was found in three.[24 26 29]

Table 1 shows that the design of the studies varied in terms of the dose of n-3 PUFA. It seems logical to start treatment with n-3 PUFA at least one week before PTCA to ensure cellular incorporation of n-3 PUFAs by the time of the procedure. This was done in only two of the studies.[23 28] Some of the studies were hampered by the lack of angiographic end points.[22 25 26 29] In our opinion systematic angiography is mandatory, preferably six months after PTCA (or before when symptoms occur). Computer-assisted analysis of the degree of stenosis is preferable. Though the recent study by Bairati *et al*[28] may be criticised because of a high exclusion rate of patients, it fulfils these criteria. In this study fish oil supplementation significantly reduced the incidence of restenosis.[28] Furthermore, a dietary intake of >0·15 g/day n-3 PUFA was also associated with a lower frequency of restenosis.[28] In the study by Nye *et al* supplementation with n-3 PUFA reduced the frequency of restenosis compared with placebo, but was not better than combination therapy with aspirin/dipyridamole.[27] In some of the other studies all the patients were on permanent aspirin treatment.[23 26 29]

In a recent meta-analysis of seven randomised trials[22–28] O'Connor *et al*[13] reported a significant reduction in the rate of restenosis in the patients treated with fish oil (odds ratio = 0·71; 95% confidence interval 0·54 to 0·94; p = 0·016 (two tailed)). O'Connor *et al* concluded that this was compatible with a small to moderate benefit of fish oil but that the result requires confirmation in a single randomised clinical trial with a large number of patients.

CORONARY BYPASS SURGERY

In a preliminary report on fish oil a daily dose of 4·5 g n-3 PUFA was compared with low dose aspirin. There was no difference in the frequency of late vein graft occlusion between the two groups.[30]

DOSE AND SOURCE OF n-3 PUFA

In the studies in which fish oil supplements have been given to patients with IHD the daily dose of n-3 PUFA usually has been 2-7 g. Studies on the effect of fish oil on the rate of restenosis after PTCA do not suggest that the possible inhibition of restenosis was related to the dose of n-3 PUFA given. The exact dose of n-3 PUFA given in the DART study[20] is not known, but on average the mean daily dose did not exceed 1 g. Some of the potential beneficial biochemical and cellular effects of fish oil supplementation are dose dependent,[2 9 17] and at present the optimal daily dose of n-3 PUFA is unknown.

Fish oil supplementation and consumption of fish are different approaches. When a fish meal is eaten the amount of n-3 PUFA's varies with the type of fish eaten (table 2). The tendency to reduce the total saturated fat intake may also be important: fish often is eaten instead of food with a high content of saturated fat. If a fish oil concentrate is used it should not contain much vitamin A or D (to prevent hypervitaminosis); it should contain a high content of n-3 PUFA's and should be enriched with antioxidants.

Table 2 Content of n-3 PUFAs in selected seafoods*

Type	*g n-3 PUFAs/100 g*
Mackerel	1·5–2·5
Herring	1·2–1·7
Salmon	1·0–1·4
Tuna	0·5–1·6
Trout	0·5–1·6
Oyster	0·4–0·6
Shrimp	0·2–0·5
Crab	0·2–0·4
Cod	0·2–0·3
Flounder	−0·2
Haddock	−0·2

*Approximate values (considerable variations by location of capture, season, etc). PUFAs, polyunsaturated fatty acids.

Conclusion

Epidemiological studies suggest that dietary intake of fish protects against IHD. Intake of n-3 PUFAs has several beneficial effects on the biochemical factors and cellular functions involved in atherogenesis and thrombogenesis. The pathophysiology and clinical effects of fish oil should be studied further in patients with IHD. Large-scale trials are needed especially in patients with acute myocardial infarction and unstable angina pectoris but also in patients undergoing PTCA and coronary bypass surgery.

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