FISH OILS IN HUMAN HEALTH

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SUMMARY

Fish oils, rich in n-3 PUFA, give rise to an altered balance of eicosanoids involved in haemostatic regulation. Accordingly they lead to reduced platelet sensetivity to aggregating agents in vitro. Observational studies in man using cross-sectional studies, clinical studies and secondary prevention trials have shown that moderate intakes of fish oil reduces risk of death from coronary heart disease but not necessarily from major coronary heart disease but not necessarily from major coronary events. Improved vasodilation may be involved. Fish oils may also lower post-prandial response to fat ingestion.

INTRODUCTION

Fish oils are rich in long chain n-3 polyunsaturated fatty acids (PUFA). These differ from the PUFA fraction of vegetable oils in two regards. Firstly 18 carbon chain lengths tend to be the longest found in vegetable oils whereas in fish oils the chain lengths extend to 20 and 22. Secondly, in vegetable oils the first double bond is located at carbon six (counting from the methyl end) while in fish oils, the first double bond is in position 3 (counting from the methyl end). Hence vegetable oil PUFA are termed n-6 while those of fish oil are termed n-3. The two families are not interchangeable. That is, since man can only elongate and desaturate PUFA between the last double bond and the carboxyl group, those double bonds existing in dietary oils at the methyl end of the acyl chain remain intact.

The evidence that dietary fish oils play a role in reducing the risk of several diseases comes from epidemiological, experimental and clinical studies. Most of the work has centred on coronary heart disease (CHD), a fact which will be reflected in this review.

The biology of arterial disease

The two most important clinical manifestations of arterial disease are angina pectoris and myocardial infarction. Angina is characterised by a reduction in blood flow through a part of the coronary tree. The greater the demand for blood flow (exercise) the greater the problem (chest pain). The flow of blood is restricted because of the development in the arterial sub-endothelium of a plaque rich in cholesteryl esters. This deposition of plaque material is known as atherogenesis and is increased in the presence of high levels of blood cholesterol. It is a process which takes years to develop and dietary efforts in substituting vegetable oil unsaturated fatty acids for saturated fatty acids aim to retard this process by reducing blood cholesterol.

The development of a myocardial infarction (a heart attack) takes things further. On top of an already narrowed artery, a clot develops, completely blocking blood flow for some period of time leading to damage to the heart muscle. The degree of damage depends on where in the coronary artery the blockage occurs and the severity of the blockage. This process is known as thrombogenesis and takes minutes. Blood cholesterol

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is irrelevant at this stage. What matters now are plasma platelets, the cells involved in clot or thrombus formation. It is within this process that fish oils come into play.

Eicosanoids and platelet function

Essential fatty acids are so termed because they fulfil an essential biological function and cannot be provided by the body itself. It was 40 years after the discovery of essential fatty acids that the basis of their essentiality was elucidated. They are the precursors of the postaglandins or eicosanoids. These compounds are produced by a wide range of cells and function in small quantities as metabolic regulators of activities as diverse as gastric acid secretion, uterine contraction, renal function, gut mobility, blood clotting and so forth. Prior to being converted into the eicosanoids, in response to the appropriate stimuli when and where required, the main dietary essential fatty acid (C18:2 n-6 linoleic acid) is elongated and desaturated to arachidonic acid (C20:4 n - 6). This fatty acid occupies a significant proportion of the sn-2 positions of all cell membrane phospholipids and is the key to understanding the mechanism of fish oil n-3 PUFA.

Arachidonic acid and n-3 PUFA

One of the main n-3 PUFA of fish oil is C20:5 n-3 eicosapentaenoic acid (EPA). It is structurally very similar to arachidonic acid C20:4 n-6. EPA has an additional double bond at carbon 3. Otherwise it is identical. Because the additional double bond is distant from the carboxyl end of the acyl chain (where elongation and desaturation take place) it remains intact through all metabolic fates of EPA. Whereas arachidonic acid gives rise to the normal dienoic eicosanoids, EPA (with its extra double bond tucked away safely at the methyl end) gives rise to trienoic eicosanoids. In some instances dienoic eicosanoids are as biologically effective as trienoic eicosanoids. In other words this is not so. Therein lies the strength of n-3 PUFA from fish oils.

Eicosanoids and arterial function

The endothelium is capable of producing an eicosanoid called prostacyclin ($Pg\ I_2$), a dienoic eicosanoid normally produced from membrane phospholipid arachidonic acid (C20:4 n-6). If the diet is enriched in n-3 PUFA containing EPA (C20:5 n-3) it begins to produce less $Pg\ I_2$ and more $Pg\ I_3$, a trienoic eicosanoid. Both are equi-effective in their metabolic role of inhibiting platelet aggregation (clot formation) and of vasodilation. Blood platelets are capable of producing a different eicosanoid, thromboxane A_2 ($T_x\ A_2$) from the normal essential fatty acid derivative, arachidonic acid (C20:4 n - 6). If the diet is enriched in n-3 PUFA containing EPA (C20:5 n-5), it begins to produce less T_xA_2 and more $T_x\ A_3$, a trienoic eicosanoid. They are not equi-effective. T_xA_3 is considerably less potent than T_xA_2 in promoting platelet aggregation. It therefore follows that diets rich in n-3 PUFA tip the balance in favour of the endothelium against the platelet, which explains why fish-oil eating Eskimos bleed longer than we do !

Fish oils and coronary heart disease

Diets rich in fish oil alter the fatty acid composition of almost all membrane phospholipds. There is a steady increase in EPA (C20:5 n-3) and in its sister long chain n-3 FUFA docosahexaenoic acid (DHA; C22:6 n- 3) with a decline in the level of arachidonic acid (C20:4 n-6). There is an attendant decline in the sensitivity of platelets to

aggregating stimuli, particularly to collagen which is found in the sub-endothelial space and is exposed with endothelial damage. The reduced responsiveness of platelets to collagen has been repeatedly shown (Thorngren and Gustafson 1981; Atkinson et al. 1987). There are therefore attractive theoretical reasons why n-3 PUFA should lower heart disease. However, the recent report of the British Nutrition Foundation's Task Force on Unsaturated Fatty Acids (British Nutrition Foundation 1992) have indicated several inconsistencies between this apparently beneficial effect seen in vitro with observational studies in man. For example, Elwood et al. (1991) found no association between platelet responsiveness to collagen and the frequency of myocardial infarction in 1,800 middle aged men. If the details of the clotting mechanism are considered other anomalies appear. In the final step of clot formation fibrinogen is converted to fibrin. High levels of fibrinogen are known to elevate the risk of heart disease (Meade et al. 1986). Fibrinogen is unaltered by dietary fish oil. Clot fibrin is dissolved in the fibrinolytic pathway. A key component of this is tissue plasminogen activator tPA. Fish oils do not influence tPA and seem not to have a definitive effect on the fibrinolytic pathway. Thus while fish oils, at a simple level influence clot formation in vitro, they seem to play a little role in the wider coagulation and fibrinolytic pathways. However, the observational studies in man all point to a protective effect.

Human studies of fish oil in coronary heart disease

A number of cohort studies have examined the relationship between fish consumption and coronary heart disease in man. Kromhout et al. (1985) and Shekelle et al. (1985) both found a reduced risk of coronary heart disease with fish consumption up to 44 g/d. In contrast, Curb and Reed (1985) and Vollset et al. (1985) found no such effect. The difference in findings has been attributed by The British Nutrition Foundation's Task Force on Unsaturated Fatty Acids (British Nutrition Foundation 1992) to dose. The first two studies were at the lower end of fish intake with few subjects eating fish twice a week or more. The latter two studies had this level of intake as their lowest level of consumption. It may be that above very moderate amounts of fish consumption, little further benefit is to be obtained.

A second strand of evidence is derived from angioplasty studies. This cardiac procedure physically reduces arterial occlusion. Relapse, known as restenosis, is common, with up to 30% - 40% of cases showing significant restenosis. The results of the various studies are confounded by the concomitant use of aspirin which is used as an anti-platelet drug. High doses of fish oil over long periods (3.1g n-3 PUFA over 6 months) has been found to lower restenosis by 30% (Cheng et al. 1990)).

A third strand of evidence, and by far the most potent, is that of Burr et al. (1989). Some 2033 men under the age of 70 years who had suffered an acute myocardial infarction took place in a study lasting just over two years. They were randomly divided into 8 groups of about 250 per group. One group received no specific advice. One group received advice on lowering fat intake to 30% of energy with a P:S ratio of 1.0 (fat advice). One received advice to increase intake of cereal fibre to 18g/d (fibre advice). One was advised to eat two portions per week of fatty fish (fish advice). Every possible combination of these three advice approaches were then applied to the remaining 4 groups. With the exception of "fish advice" no other intervention reduced coronary death rates. Fish advice significantly reduced coronary deaths, the effect being evident within the first 200 days of the trial. Fish intake did not influence the frequency of second heart attacks. However, it did improve survival. This raises a key question about the effects of fish oil and how it may be protective against heart disease fatality.

Dietary fish oil and vasodilation

Both prostacyclin and thromboxane influence vasodilation, prostacylin being vasodilatory and thromboxane being vasocontrictory. With fish oil feeding, the vasoconstrictive effect of thromboxane is reduced because the trienoic thromboxane is weak in this regard. Fish oils should therefore favour vasodilation and aid in tissue perfusion. Ageing is associated with the development of small secondary coronary (collateral) arteries. For that reason older people cope better with equal cardiac insults than younger people. Undoubtedly these secondary coronary arteries are smaller than the main coronary vessels and under normal circumstances are of little importance. They may assume considerable significance following a heart attack. It remains possible that part of the process which fish oils play in protecting against heart disease is in the perfusion of these smaller vessels through enhanced vasodilation. Two studies from our laboratory lend indirect support to this concept. Rats gavaged with ethanol develop haemorraghic lesions of the stomach. Rats chronically fed corn oil show reduced degree of stomach lesions consistent with data to show that gastric PgE2 is cytoprotective in this regard (Gibney and Hunter 1992). If corn oil reduces the degree of lesioning by furnishing an above average supply of cytoprotective eicosanoids, it follows that fish oils should make things worse by inhibiting production of this process. They don't. Fish oils in these studies were as protective as corn oil. Histological examination of the lesions suggested that vasodilation by fish oils overcame the pathological vasoconstriction of ethanol gavage.

To study the vasodilatory effect of fish oil further, we turned to the use of Doppler Ultrasound to measure blood flow in the superior mesenteric artery (SMA) following a meal. Six healthy female volunteers had SMA blood flow parameters measured in the post prandial phase and at 2 and 4 hours of the post-prandial phase, at baseline and after 4 weeks supplementation with a low dose of fish oil (5g/d). The results are summarized in Table 1. As expected, SMA blood flow rose after feeding and did not differ with fish oil supplementation. What did change was end diastolic pressure. This is a parameter used clinically to investigate vasodilation and these results show a marked vasodilation with fish oil. This model allows the effect of fish oil on vasodilation during a sudden increase in blood-flow to be measured. It may provide a useful model for the study of the probable paller in coronary collateral circulation during the sudden surge in flow following an occlusive clot.

Table 1 Blood velocity and flow in the superior mesenteric artery of adult healthy volunteers using Doppler ultrasound

	SMA Blood velocity (cm/sec)				Blood flow (l / min)	
	Peak systolic		End disastolic*			
Time (hr)	Pre	Post	Pre	Post	Pre	Post
0	142	133	25	30	1.54	1.38
1	376	208	39	67	2.77	3.03
4	157	123	33	21	1.90	1.01

* $P < 0.001$ for period x time interaction by repeated measures. Anova.
Gibney et al. (1993) unpublished

Fish oils and blood lipids

The most dramatic effect of n-3 PUFA rich fish oils on plasma lipids is on plasma triacylglycerol (TAG). This subject has been covered in an extensive review by Grundy and Denke (1990). Unlike plasma cholesterol, which for 40 years has been positively associated with increased risk of CHD, plasma TAG has generally been dismissed as a contender for risk. Recent data from the Caerphilly and Speedwell and Collaborative Heart Disease Studies (Bainton et al. 1992) has provided direct evidence that plasma TAG is directly associated with increased risk of CHD. No evidence of an association between plasma total cholesterol and risk of CHD was observed, while a marked protective effect of plasma high-density lipoprotein cholesterol was seen. These results will need to be confirmed before plasma TAG can be considered as an independent risk factor for CHD. Previous studies of plasma TAG and CHD have not always used fasting blood samples and so cannot be considered in this context. This study, however, highlights once again, the fragile nature of the data associating blood lipids with CHD.

Fish oils and post-prandial lipid metabolism

Almost all the epidemiological evidence linking plasma lipids and CHD has relied on fasting blood samples. In recent years it has become recognised that given that we spend most of the day in the post-prandial phase, this should become a consideration in the area of blood lipids and CHD. There are several reasons for this renewed interest Elevated pos t-prandial levels of plasma TAG depress plasma HDL_2-cholesterol levels, believed to be the major protective component of HDL (Patsch et al. 1987). Core remnants of the main TAG-rich lipoprotein (very low density lipoprotein, VLDL) may be atherogenic (Floren et al. 1989). Finally, Karpe et al. (1993) have shown that the extent of the post-prandial TAG response is a significant positive predictor of the proportion of plasma low-density lipoprotein (LDL) as dense LDL ($d = 1.040 - 1.063$ kg/l). This LDL subfraction is known to be a significant predictor of risk of CHD to an extent far greater than total LDL (Swinkels et al. 1989).

Fish oils markedly attenuate the magnitude of the post-prandial lipid response in man. In direct acute comparisons of fats rich in n-3 or n-6 PUFA or in saturated fatty acids (SFA), the order of magnitude of the post-prandial response is SFA > n-6 PUFA > n-3 PUFA. Chronic fish oil ingestion lowers the post-prandial response to acute ingestion of these three fat types, the same order being retained.

Fish oils and non-cardiac diseases

A central feature of the role of n-3 PUFA rich fish oils in CHD is their capacity to alter eicosanoid function. The prostaglandin family of the eicosanoids are produced via the enzyme cyclooxygenase. An alternate pathway, involving the enzyme lipoxygenase, gives rise to another family of eicosanoids, the leukotrienes. These play a central role in the inflammatory process. Accordingly there has been considerable interest in the use of fish oils in such diseases. The mechanism is the same as in CHD. The main leukotriene produced by polymorphonuclear cells is leukotriene B_4 (LTB_4). As the level of fish oil in the diet increases, more LTB_5 is produced and less LTB_4 is produced. The biological potency in terms of chemotaxis and other functions is reduced with LTB_5. Hence its possible role in ameliorating inflammation. This area has been reviewed extensively (eg. Simopoulos 1991). The n-3 rich fish oils have been shown to play a beneficial effect in such inflammatory diseases as arthritis, psoriasis, ulcerative colitis etc.

CONCLUSION

Fish oils play an important role in providing fatty acids which the body can use to create a more favourable balance in areas such as haemostasis and inflammation. An important area of research which must be addressed is that of dose response. Many studies use high doses over short periods. Longer studies with lesser doses are needed if fish oils are to be incorporated at low levels in common foodstuffs.

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