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Role of Fish Oils in the Control of Heart Diseases

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Experiments in animals and humans have established that fish oils control heart diseases and the active components responsible are the n-3 polyunsaturated fatty acids (PUFA). Several investigations have proved that fish oils have hypocholesterolemic and hypotriglyceridemic effects and can influence platelet aggregation and blood clotting. Incorporation of n-3 PUFA in cell membranes changes their properties and plays a major role in controlling ventricular fibrillation and subsequent mortality. n-3 PUFA and the lipoprotein fractions containing them are susceptible to oxidation and antioxidants like vitamin E can counter this effect.

Key words: Fish oils, heart diseases, PUFA

Though the share of marine oils in the supply of edible oil is only about 2%, their nutritional significance has been recognized from very early times. Interest in the nutritional and therapeutic qualities of fish oil started with the epidemiological studies in Greenland Eskimos which revealed very low incidence of ischemic heart diseases in them (Bang *et. al.,* 1971; 1976., Kromann and Green, 1980). This was attributed mainly to the long chain n-3 polyunsaturated fatty acids (PUFA) in the normal diet of this population (Dyerberg, 1986; Kagawa, *et. al.* 1982).

Fish Oil Fatty Acids

Fish oils are unique in their fatty acid composition. Several long chain fatty acids, saturated, monounsaturated and polyunsaturated, make them a complex mixture of glycerides and their derivatives (Table 1). More than 90% of the fatty acids in fish oil are straight chain with even number of carbon atoms. Odd numbered and branched chain acids are quantitatively not important.

Saturated acids

Myristic (14:0), palmitic (16:0) and stearic acids (18:0) are the important saturated acids in fish oils (Ackman, 1982.,1989; Stansby *et. al.,* 1990). Saturated acids form 15-35% of total fatty acids (Ackman, 1989). Generally palmitic acid accounts for about 60% of total saturated acids. In tropical fishes the proportion of saturated acids is high (Nair, 1981).

Monounsaturated acids

Monounsaturated acids in fish oils are of exogenous origin (Ackman, 1982) and their proportions show wide variation. In many species this group accounts for

35-50% of the total acids. 16:1, 18:1, 20:1 and 22:1 are most important in this group (Gruger, 1967; Gruger *et. al.*, 1964; Yamada and Hayashi, 1975; Ueda, 1967). However, the proportion of these acids is much lower in Indian fishes and the major acids are 16:1 and 18:1 (Nair, 1981).

Polyunsaturated acids

Two groups of polyunsaturated acids viz. n-6 and n-3 are present in fish oils (Table 1). 18:2 n-6 and 20:4 n-6 are important in the former group and 18:3 n-3, 20:5 n-3 and 22:6 n-3 in the latter. PUFA is about 30-50% of total fatty acids in fishes from Indian waters (Nair, 1981; Reena *et. al.*, 1996). 20:5 n-3 (eicosapentaenoic acid, EPA) and 22:6 n-3 (docosahexaenoic acid DHA) are the most predominant in the polyunsaturated group. These two together may account for about 70-75% of the total PUFA, which is nutritionally most important.

Table 1. Proportions of major fatty acids in the lipids of fishes from Indian waters (Derived from data for 90 species of fish)

Fatty acids	Mean	Range
C14:0	3.0	0.3-9.5
C16:0	25.0	13.4-40.8
C18:0	9.5	3.5-22.9
C16:1 n7	5.5	1.0-13.7
C18:1 n9	13.0	4.6-27.6
C20:4 n6	4.7	1.2-12.6
C20:5 n3	5.3	0.5-11.8
C22:6 n3	21.8	2.4-40.3
Total saturated	40.5	23.2-57.7
Total mono unsaturated	19.0	7.2-41.4
Total polyunsaturated	36.3	8.7-63.3

Fish Oil and Heart Disease

Inclusion of substantial amounts of fish in the regular diet has been shown to play a very positive role in controlling heart diseases (Stansby, 1990). Peifer *et. al. (1962) attributed this to the oils in fish.* Out of 126 patients on a standard diet, only eight were surviving, whereas 36 out of 80 on a high fish diet were surviving after 16-19 years. Kromhout *et. al.* (1985) reported that consumption of fish can reduce the risk of fatal coronary heart attacks. *It was established that the highly* unsaturated n-3 fatty acids, EPA and DHA, are the active components of fish oil responsible for the hypolipidemic and antithrombotic effects.

Effectiveness of fish oil in heart disease is through its multipronged action on lipid metabolism. n-3 PUFA influence lipid metabolism at various levels. The major pathways through which fish oils and n-3 PUFA control heart diseases are by hypocholesterolemic, hypotriglyceridemic, antithrombotic and antiarrhythmic action.

Hypocholesterolemic action

Early studies in experimental animals and human have shown that fish oils are effective hypocholesterolemic agents. Jones (1974) observed that a diet low in fat and cholesterol and high in PUFA reduced serum cholesterol and this helped to achieve a modest success in improving the morbidity due to atherosclerotic diseases. Feigenbaum *et. al.* (1961) found an inverse relationship between levels of dietary PUFA and cholesterol in plasma and aorta.

Harris (1989) reported that inclusion of fish oil reduced the level of saturated fats in the diet and concluded that the lowering of cholesterol is primarily due to the lower levels of saturated fats in the diet. But a recent study in rats showed that supplementation of diet with 1% PUFA lowered total serum cholesterol by 66% (Nair, *et. al., under publication*). In this experiment there was only a marginal lowering of saturated acids in the experimental diet but the hypocholesterolemic effect was significant. Thus the conclusion of Harris (1989) that lower levels of saturated acids are primarily responsible for lowering cholesterol levels needs further examination.

Highly unsaturated fats are capable of reducing the concentration of plasma lipids of hypercholesterolemic rats (Peifer *et. al.*, 1960). Parks and Crouse (1992) reported a 20-30% reduction of total and low density lipoprotein (LDL) cholesterol by a fish oil diet in African green monkey. Studies on humans showed that there was either a decrease or no effect on LDL cholesterol in most normolipidemic subjects (Illingworth *et. al.*, 1984; Nestel, 1986). Hamsters ingesting a diet containing 10% sardine oil had significantly lower plasma total cholesterol, very low density lipoprotein (VLDL) cholesterol and LDL cholesterol than those ingesting 10% soybean oil or 10% coconut oil (Lin, *et. al.*, 1995). Kobatke *et. al.* (1989) found that serum total cholesterol concentrations were significantly decreased by DHA in rats fed on hypercholesterolemic diet. Hirari *et. al.* (1989) investigated the effects of DHA ethyl esters (3.6g/day) on serum lipids of hyperlipidemic patients. Total cholesterol concentrations were reduced after 8 weeks of DHA administration. Childs *et. al. (1990)* found that levels of LDL cholesterol and apolipoportein B were lowered significantly using EPA rich pollack oil or DHA rich tuna salmon-blend oil. Sanders and Hinds (1992) have reported similar results in healthy male volunteers.

Increase in the levels of total cholesterol and LDL cholesterol as a result of feeding fish oil or n-3 PUFA also has been reported (Atkinson *et. al.*, 1987; Barcelli *et. al.*, 1985; Haines *et. al.*, 1986; and Bruckner *et. al.*, 1987). There are a number of factors other than the diet involved in lipid and lipoprotein metabolism and these have to be taken into account while considering the reported variations.

Hypotriglyceridemic effect

Hypertriglyceridemia is a possible risk factor in coronary heart disease (Galli, 1996). Criqui et. al. (1993) reported positive association between plasma triglyceride and coronary mortality in subjects with low HDL and LDL cholesterol levels. Though its reliability as an independent indicator is doubtful (Criqui *et. al., 1993*) there are reports confirming it as independent predictor of subsequent myocardial infarction (Castelli, 1986; Reardon *et. al.*, 1985; Carlson, *et. al.*, 1979).

Fish oil has potential effect in the treatment of hypertriglyceridemia. Dietary intake of long chain n-3 PUFA, especially EPA and DHA, lower plasma concentration of triglycerides (Sanders *et. al.*,1981). Simons *et. al.* (1985) found that 4.6g n-3 PUFA per day would lower triglyceride levels by 50% in patients with high triglyceride levels.

Decreased triglyceride synthesis is a major cause for the reduced secretion of VLDL-triglycerides (Rustan *et. al.*,1988). Availability of unesterified fatty acids in the liver plays an important role in regulation of VLDL synthesis and secretion. Very long chain n-3 PUFA decrease the level of unesterified fatty acids in plasma (Rustan *et. al.*, 1992). This may lead to reduced triglyceride formation in liver due to lack of fatty acids as substrate for lipoprotein production. Wong *et. al.* (1984) demonstrated that reduction in triglyceride synthesis was accompanied by an increase in ketone production in perfused livers from fish oil fed rats. The action of fish oil in this regard is similar to that of clofibrate, a drug used for lowering triglyceride levels. Fish oil does not reduce the activities of hepatic detoxifying enzymes and hence may be safer than the drug.

Antithrombotic action

Platelet aggregation and blood clotting are controlled by prostacyclin (PGI2) synthesized in vessel walls and thrombaxane (TXA2) produced by platelets. TXA2 is the aggregating factor and PGI2 has the opposite effect. Under normal conditions body maintains a proper balance of the two. Any imbalance will result in diseases. Both are synthesized from arachidonic acid (20:4 n-6). Similar products (TXA_3 and PGI3) are formed from EPA. TXA3 does not promote platelet aggregation whereas PGI3, like PGI2 is an antiaggregating agent. Dietary supplementation of EPA and DHA results in increased levels of these acids in tissues (Swanson and Kinsella, 1986; Gudbjarnason and Oskarsdottir, 1977; Bruckner *et. al.*, 1984). EPA and DHA are competitive inhibitors for cycloxygenase (Bruckner *et. al.*, 1984) and lead to alterations in the synthesis of prostaglandins. Thus, n-3 PUFA in diets will have favorable antithrombotic effects. These are more pronounced when the availability of n-6 PUFA is low. In this condition more n-3 PUFA get incorporated into phospholipids limiting the availability of n-6 PUFA for prostaglandin synthesis. Comparatively long bleeding time, significantly low platelet counts and high threshold for adenosine diphosphate for secondary phase platelet aggregation found in Greenland Eskimos (Dyerberg and Bang, 1979) have been attributed to the influences of marine oils on the prostanoid metabolism.

Antiarrhythmic action

Ventricular fibrillation (VF) arising out of the electrical imbalance of cardiac muscle is a major cause of mortality. It has been proved that n-3 PUFA help in reducing the incidence of VF (Nair *et. al.*, 1997). Various mechanisms have been suggested to explain the antiarrhythmic effects of n-3 PUFA like modification of the eicosanoid system or the fatty acid composition of phospholipids and effect on the myocardium, Ca^{++} channels, enzymes, receptors of inositol lipid cycle, cell signaling etc.

Oxidised Fatty Acids and Lipid Metabolism

PUFA are highly susceptible to oxidative changes. PUFA on oxidation yields highly reactive lipid peroxidation products that promote atherosclerosis. These include harmful and toxic oxidized phospholipids and sterols. Staprans *et. al. (1996) observed* that oxidized lipoproteins may be playing a major role in the etiology of atherosclerosis. Oxidized lipids in the diet increase oxidized lipoproteins in circulation. It has been shown that the products of LDL oxidation are transferred from minimally oxidized LDL to HDL. Hence it has been proposed that HDL may protect against some of the atherogenic effects of oxidized LDL by accepting and transporting such oxidation products (Bielicki *et. al.,* 1996). Elevated levels of LDL are associated with an increased risk of atherosclerosis. However, the reason for atherogenicity of LDL in patients supplemented with fish oil is not clear. It has been proposed that oxidation of LDL increases its atherogenicity and susceptibility to oxidative modification and is one of the most important factors (Steinberg *et. al., 1989).* Suzukawa *et. al.,* (1995) studied the effect of n-3 PUFA on LDL oxidisability and concluded that enhanced *in vitro* susceptibility need not necessarily be reflected in the *in vivo* situation.

However, evidence of an indirect nature on the adverse effects of fatty acid oxidation on lipid metabolism emanates from the results of experiments using antioxidants along with PUFA. An inverse relationship between plasma vitamin E levels and mortality from ischemic heart disease was observed in epidemiological studies (Gey *et. al.,* 1991). In animal experiments also antioxidants and vitamin E have been reported to prevent atherosclerosis (Anthony and Bush, 1992). Oxidisability of PUFA has some effect on the overall lipid metabolism and, in the absence of antioxidants, these may prove harmful.

Dietary supplementation of n-3 PUFA or fish oil is beneficial to the heart. The mechanisms involved are complex and not fully understood. They exert a variety of influences on plasma lipids and lipid metabolism like lowering plasma triglycerides and cholesterol, altering the proportions of lipoprotein fractions, altering relative proportions of important metabolites like eicosanoids, changing the membrane structure and thereby affecting the biochemical, mechanical and electrical properties of tissue. The beneficial effects of dietary fish oil is the net result of all these inter-related activities.

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