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FISH AND FISH OIL IN CARDIOVASCULAR DISEASES

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ABSTRACT
Fish and fish oil are the common dietary sources of long chain ω-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The previous studies suggested that regular consumption of these fatty acids reduces the arrhythmias, endothelial dysfunction, circulating triglyceride level, inflammation, sudden death, myocardial infarction and heart failure. This review will focus on the effects of dietary intake of fish and fish oil on coronary artery disease, arrhythmia, myocardial infarction, atrial and ventricular fibrillation, heart rate variability, atherosclerosis, diabetes mellitus, lipid profile, chronic heart failure, stroke and sudden death. The review also explores the effects of use of fish oil in combination with other lipid lowering drugs. This review searches were limited to clinical trials, cohort studies, comparative studies, meta-analysis, randomized control trials (RCT) and systematic reviews. Finally, the review will suggest recommendation for dietary intake of fish and fish oil as ω-3 supplements for cardiovascular disease risk reduction and examine the limitations of the current data.

KEYWORDS: Fish, Fish oil, Omega-3 fatty acids, cardiovascular disease.

INTRODUCTION
Cardiovascular disease (CVD) is the leading cause of death globally. The dietary factors play an important role in determination of CVD risk and in the pathogenesis of CVD. Dietary variables are modified to reduce the risk of CVD.[1] Humans are unable to synthesize long chain polyunsaturated fatty acids. Due to this, the ω-3 fatty acids synthesized in plants and in marine microalgae are essential components of the human diet. Fish and fish oil contain high levels of two ω-3 fatty acids, eicosapentaenoic acid (EPA; C20:5 n-3) and docosahexaenoic acid (DHA; C22:6 n-3) which show cardio protective effects.[2,3] Dietary supplementation of fish and fish oils which are the rich sources of ω-3 fatty acids showed the beneficial effects to the patients with dyslipidemia, atherosclerosis, hypertension, obesity and inflammatory diseases.[4] Due to anti-arrhythmic activities of fish, reduction of thrombotic, inflammatory processes, endothelial dysfunction and serum triacylglycerol (TAG) level take place and high fish consumption was associated with better cardiovascular health. Hence fish diet should be promoted especially in subjects with cardiovascular problems.[5] Finally, the limitations of the current data will be addressed and recommended for the dietary intake of fish and fish oil as ω-3 fatty acid supplements for CVD risk reduction.

CARDIOVASCULAR EFFECTS OF OMEGA-3 FATTY ACIDS ON THE FOLLOWING

Coronary Heart Disease (CHD)
Intake of ω-3 polyunsaturated fatty acids (PUFA) reduces overall mortality, mortality due to myocardial infarction and sudden death in patients with CHD. The meta-analysis of randomized control trial (RCT) included 7951 patients in the intervention and 7855 patients in the control group, observed that risk ratio of non-fatal myocardial infarction (MI) in patients who were on ω-3 PUFA rich diet compared with the control was 0.8 and the risk of fatal myocardial infarction was 0.7, sudden death was associated with a risk ratio of 0.7 and overall mortality was 0.8.[6] The anti-arrhythmic effect of ω-3 fatty acids showed great role in the prevention of sudden cardiac death (SCD) from ventricular fibrillation and in the modulation and prevention of CHD. Dietary intake of fish along with these fatty acids also provides other essential nutrients.[7] ω-3 Supplements whether from dietary source or fish oil, supplements should be increased especially in those with or at risk of CAD.[8] Fish oil supplementation was recommended in the patients with risk factors for SCD such as left ventricular dysfunction, left ventricular hypertrophy, prior cardiac infarction or high grade

ventricular dysrhythimias.[9] In patients undergoing coronary artery bypass surgery (CABG), PUFA administration during hospitalization reduced the hospital stay and the incidence of post-operative atrial fibrillation. After CABG, the PUFA administered patients were hospitalized for significantly fewer days than controls (p= 0.017).[10] Decreased content of EPA+DHA may be associated with increased risk for acute coronary syndrome (ACS). The content of EPA+DHA was measured in 768 ACS patients and age, sex and race matched 768 controls. The association with ACS case status was compared with the blood cell EPA+ DHA. The EPA+DHA content was 20% lower in cases than controls (p<0.001). The multivariable-adjusted odds ratio for case status was 0.77 (p<0.001) for a 1-unit increase in EPA+DHA content. Compared with the lowest EPA+DHA group, the odds ratio for an ACS in the intermediate EPA+DHA group was 0.58 and was 0.31 (p <0.0001) in the highest EPA+DHA group.[11] ω-3 Fatty acids decreased the resting heart rate and improved 1-minute heart rate after exercise. In high-frequency band heart rate variability increased which explained the decreased risk for SCD with ω-3 fatty acid supplements in CHD.[12] Fish consumption compared with little or no fish consumption was associated with relative risk of 0.83 (p<0.005) for total CHD which suggests that fish consumption has significantly lowered the risk of fatal CHD. In middle aged people high consumption of fish was associated with decreased risk of CHD more specifically myocardial infarction and nonfatal CHD compared to moderate intake.[13] In a study by Streppel *et al.*, it was observed that long term fish consumption was associated with decreased CHD and reduced the risk of sudden coronary death.[14] The Nurses' health study on women aged 34-59 years to assess the dietary intake of ω-3 fatty acid and fish consumption showed reduction in CHD risk as the intake of ω-3 fatty acids is increased.[15] Simple dietary interventions of fish or nutritional supplements of fish oils were more accepted than multiple pharmacological treatments.[16] EPA and DHA obtained by consuming different types of fish were more beneficial in CHD and SCD.[17] Higher doses of ω-3 fatty acids lowered the elevated serum triglycerides level.[18]

Arrhythmia

In high risk individuals of fatal ventricular arrhythmias, regular daily intake of fish oil fatty acids significantly reduced potentially fatal ventricular arrhythmias.[19] Dangerous consequences after MI and ischemic arrhythmia in ischemic cardiac disease (ICD) patients were reduced by the ω-3 fatty acid therapy. Through anti-arrhythmic action and ability to promote plaque stabilization, ω-3 fatty acids derived from fish and fish oil showed great role in secondary prevention of CVD.[20] Dietary fish oil prevents arrhythmia by modulating the pacemaker activity and reduces the cellular Ca^{2+}overload which is responsible for the arrhythmia.[21] The study of Chrysohoou *et al.*, compared the QTc interval of resting electrocardiogram in non-fish consumers and those consuming fish, showed that those consumed fish >300g/week had 13.6% lower QTc interval and long term consumption of fish provides anti-arrhythmic protection at the population level.[22] Prospective cohort study on Danish patients did not show the association between the risk of atrial fibrillation or flutter and ω-3 fish oil from consumed fish.[23] Some of the studies have shown that ω-3 PUFA from fish oil against ventricular arrhythmia, generally cardiac arrhythmia did not show any significant effect in patients with ICD.[24,25] The majority of effect of ω-3 fatty acids are anti-arrhythmic than anti-thrombotic and little effect observed on blood coagulability and fibrinolysis.[26] The systematic review study reported that fish oil supplements were associated with a significant reduction in death from cardiac causes but did not show any effect on arrhythmias.[27]

Diabetes

In diabetic women, higher consumption of fish and long chain ω-3 fatty acids was associated with lower incidence of CHD. Women who consumed fish less than one serving per month compared with fish consumption 1-3 times per month, the relative risk of CHD was 0.70, for once in a week 0.60, for 2-4 times per week 0.64 and for 5 or more times per week 0.36. Higher consumption of fish of ≥5 times per week significantly lowered the incidence of CHD in diabetic women.[28] Plasma lipid modulatory effect was showed by EPA and DHA in CVD risk and diabetes.[29] Fish oil supplementation decreased the triglycerides, raised LDL cholesterol and has no statistically significant effect on glycemic control, total cholesterol, HbA1c, fasting plasma glucose and postprandial plasma glucose in Type 2 diabetes.[30,31] Marine ω-3 fatty acids show beneficial effects on prevention of Type 2 diabetes in Asian population which suggests that association between consumption of fish or fish oil and the development of Type 2 diabetes depends on geographical variation.[32]

Atrial Fibrillation and Ventricular Fibrillation

A study on elderly adults by Mozzaffarian *et al.*, showed that consumption of tuna or other broiled or baked fish are associated with lower incidence of atrial fibrillation (AF) and also fish intake influences the risk of common cardiac arrhythmias.[33] Some of the prospective cohort studies did not observe any reduction in the risk of AF even by taking specific type of fish or by specific method of preparation which concludes ω-3 fatty acids did not have anti-arrhythmic effects.[34,35] The large sample study of Berry *et al.*, on postmenopausal women did not show any association between dietary fish intake and incidence of AF even by considering the amount of fish intake and method of preparation.[36] A randomized controlled trial conducted on patients having implantable defibrillators, fish oil supplementation did not reduce the risk of ventricular tachycardia or ventricular fibrillation.[37]

MI and SCD

The meta-analysis showed that dietary or supplemental intakes of ω-3 fatty acids were more effective in reducing the fatal MI, SCD and overall mortality.[38] ω-3 Fatty acids found in fish are strongly associated with a reduced risk of SCD among men without evidence of prior CVD.[39] Increasing systolic dysfunction was associated with an increased risk of SCD. PUFA reduced the SCD in patients with systolic dysfunction.[40] High fish consumption is associated with the reduction in SCD. Due to the anti-arrhythmic activities of fish, reduction of thrombotic, inflammatory processes and serum triacylglycerol (TAG) level, consumption of fish and its components should be promoted especially in subjects with cardiovascular problems.[41] Decreased SCD rate and other clinical events were observed by treatment of acute MI which were not further reduced by the ω-3 fatty acids.[42]

Lipid Profile

A randomized open-label blinded end point analysis (JELIS) performed in Japanese patients with hypercholesterolemia. Patients with a history of coronary artery disease who were given EPA treatment, the major coronary events were reduced by 19% and 10.7% in control group (p=0.048).[43] ω-3 Fatty acids when included in the diet were safe for patients with severe to moderate hypertriglyceridemia and also helped in primary and secondary prevention of CAD.[44] Significantly decreased serum triglycerides by 20-30% and VLDL-cholesterol by 30-40% were observed in patients receiving Omacor at 3, 6 and 12 months compared to placebo. Omacor (ethyl esters of EPA and DHA) was effective in lowering triglyceride level of patients with CHD which is associated with hypertriglyceridemia and also helped in those whose triglyceride remained elevated in spite of Simvastatin treatment.[45] Prescription of ω-3 fatty acids plus Simvastatin decreased the Non-HDL-C and other lipid and lipoprotein parameters to a large extent than Simvastatin alone.[46]

A systematic review showed that fish oil reduces the triglyceride level particularly in people with elevated triglycerides and improves HDL cholesterol, increases LDL cholesterol and no effect on total cholesterol.[47] ω-3 Fatty acid diet increases the proteins present in the HDL and modifies the protein part of HDL particles.[48]

Cardio protective effects

People with a high intake of dietary fish and fish oil supplements have a low rate of CVD. The beneficial effects of ω-3 fatty acids, EPA and DHA found in oily fish such as salmon, lake trout, tuna, herring and in fish oils.[49] Higher consumption of fish and ω-3 fatty acids reduced the risk of thrombotic infarction in women who did not take aspirin regularly.[50] In cardiac transplant recipients, ω-3 fatty acids reduced the heart rate and prolonged the QRS duration which showed that ω-3 fatty acids modify the electrophysiological properties of myocardium.[51] The ω-3 fatty acids modulate the arterial initial uptake and binding of LDL particles by modulating arterial lipoprotein lipase (LpL) and macrophage levels and also inhibit the pro-inflammatory process which reduces the production of inflammatory mediators. These multiple steps of atherosclerosis development affected by ω-3 fatty acids contribute to the anti-atherogenic property.[52] Fish oil decreased the production of TNF-α in heart failure which shows the anti-inflammatory effect and is considered as the novel therapeutic approach in late-stages of heart failure.[53] Beneficial effect of fish is observed only when recommended quantities were consumed.[54] Regular consumption of ω-3 fatty acids reduced the arrhythmias, endothelial dysfunction, circulating triglyceride level and inflammation. The fish diet is also recommended to the people with pre-existing CHD and high triglyceride level.[55]

Recommendation of fish and fish oil

Consumption of DHA and EPA 1g/day for the known CAD and at least 500mg/day for those without disease are beneficial.[8] A dose of about 800-1000mg/day in the combined range of EPA and DHA is recommended for the primary and secondary prevention of CVD.[9]

Long-term intake of fatty fish on an average of 7g/day reduced risk of SCD by 54%.[14]

A dose of 3-5g/day of ω-3 fatty acids reduced triglyceride level by 30-50%, minimizing the risk of both CHD and acute pancreatitis. ω-3 fatty acids incorporated in the diet about 1g/day stabilized the myocardial membrane electrically, resulting in decreased susceptibility to ventricular dysrhythmias and reducing the risk of SCD.[18] A dose of 0.85 to 4.0 g/day of ω-3 fatty acids for about 12-42 months reduced the total mortality and SCD about 20-50%.[20] It was observed that unstable angina and non-fatal coronary events were significantly reduced in the group receiving 1800 mg of EPA daily along with statin compared to the group receiving statin alone.[43] At least 2 servings of fish per week are recommended for the cardio protective effects.[49] Cardiovascular guidelines suggested the healthy individuals to consume oily type fish at least twice a week.[55] At least 250mg/day of long chain ω-3 PUFA or at least 2 servings per week of oily fish are recommended for the general population by the national and international guidelines.[56] A comparative study on the effect of fish and fish oil suggested consumption of equal amount of EPA and DHA from oily fish in a week or fish oil capsules daily is equally effective in improving the lipid profile.[57]

The study conducted to compare the effects of fish oil and soy oil on cardiac autonomic changes, revealed that supplementation of 2g/day of fish oil has significantly increased the heart rate variability compared to soy oil.[58]

A cardiovascular health study, a comparative study between ischemic stroke and hemorrhagic stroke concluded that ischemic stroke mortality is reduced in those individuals who consumed fish more than once in a month compared to hemorrhagic stroke and also suggests that consumption of fish at least twice per week help for the prevention of thrombotic infarction as well as CHD.[59] For those with CHD, intake of 1g/day of EPA plus DHA from oily fish or supplements are advised.[60]

Mechanism of Action of ω-3 fatty acids

ω-3 Fatty acids reduce the arachidonic acid (AA) present in the membrane phospholipids of inflammatory cells, platelets and endothelial cells. Due to this, the production of AA-derived pro-inflammatory mediators such as prostaglandin (PG)-E_2, thromboxane (TX)-B_2, leukotriene (LT)-B_4, hydroxyl-eicosatetraenoic acid (5-HETE) and LT-E_4 are reduced.[61] Long term intake of EPA inhibits the Rho kinase activity of up-regulating pro-inflammatory molecules and down-regulating endothelial nitric oxide synthase (eNOS).[62,63] The down regulation of the activity of Nuclear Transcription Factor Kappa B(NF)-kB is the key role to regulate the gene expression in inflammatory responses. The ω-3 fatty acids inhibit the NF-kB by the activation of peroxisome proliferator–activated receptor (PPAR)[64,65] and also reduce the transcription of inflammatory cytokines. These effects explain the anti-inflammatory effect[66] of ω-3 fatty acids which also helps in stabilization of unstable plaque.[67] EPA and DHA show the cardio-protective effects by changing the mitochondrial membrane phospholipid concentration which helps to improve the mitochondrial function and the efficiency of ATP generation.[68] EPA competes with arachidonic acid for cyclo-oxygenase and lipo-oxygenase enzymes, leading to decreased synthesis of thromboxane A_2 which is the strong platelet agonist and increases the synthesis of thromboxane A_3 which is relatively inactive. EPA also increases the different family of eicosanoids-the three series PGs and TXs. So high dose of ω-3 fatty acids shows platelet inhibition effect.[69-71]

ω-3 Fatty acids lower the triglyceride level by decreasing the VLDL assembly and secretion. The reduced activity of sterol receptor element-binding protein-1c by ω-3 fatty acids leads to inhibition of lipogenesis. By activating the peroxisome PPAR-α, ω-3 fatty acids favor the β-oxidation in mitochondria and peroxisomes and also reduces the fatty acid substrate for triglyceride synthesis.

EPA reduces the pro-atherogenic factor, remnant lipoprotein (RLP) which is produced from triacylglycerol-rich chylomicrons and VLDL in hyper-lipidemic patients.[72-74]

Fish oils improve the endothelium dependent relaxation of atherosclerotic coronary arteries.[75] Nitric oxide and endothelium-derived hyperpolarizing factor causes the endothelium-dependent relaxation which is favored by EPA.[76] Nitric oxide also inhibits platelet aggregation and adhesion, leukocytes adhesion and smooth muscle cell proliferation in endothelial cells. DHA reacts with interleukin (IL)-1, IL-4, tumor necrosis factor-α, or lipopolysaccharide, decreases the expression of vascular cell adhesion molecule-1, intercellular adhesion molecule-1 and E-selectin, and secretion of IL-6 and IL-8.[77]

EPA and DHA show a role in decreasing the infiltration of macrophage and thickened fibrous cap in human carotid arteries.[78] EPA helps to reduces the development of atherosclerotic lesions by suppressing the production of matrix metalloproteinase (MMP) by macrophages.[79] Omega-3 fatty acids increased the voltage that required for membrane depolarization by inhibiting voltage-gated sodium channels and directly influence heart rate.[80] ω-3 Fatty acids also exhibit a modulation of action on L-type calcium (Ca) channels, preventing cytosolic Ca overload during ischemia.[81] By increasing the vegal tone, omega-3 fatty acids have autonomic control which explains the anti-arrhythmic effects of ω-3 fatty acids.[82] Decreased resting systolic and diastolic blood pressure by incorporating EPA and DHA into membrane phospholipids, ω-3 fatty acids increase the systemic arterial compliance.[83]

By improving the autonomic sympathetic balance, increasing the fibrinolytic activity, decreasing the whole blood viscosity and increasing red blood cell deformability, ω-3 fatty acids show the cardio protective role.[84]

CONCLUSION

There is a sufficient evidence supporting risk reduction of CVD due to fish consumption, particularly the intake of oily fish which is high in ω-3 fatty acids. Dietary intake of fish was found to be mostly consistent with respect to protection from heart disease and stroke. Higher fish intake was associated with lower incident rates of heart failure in addition to lower SCD, stroke and myocardial infarction. The addition of ω-3 fatty acids to a healthy diet appears to be safe when used for the primary and secondary prevention of CAD. The benefits of fish consumption are not only limited to reduced CVD risks, but it also provides other nutrients.

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