Cardioprotective Benefits and Nutritional Criteria of Omega -3 Fatty Acids

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Abstract

CVD is a major public health problem. High blood pressure and circulating LDL levels are major risk factors for promoting atherosclerosis, ischemic heart disease or stroke. PUFA act as substrates for eicosanoid formation. Eicosanoids formed from omega 3 are anti-inflammatory in nature and possess cardioprotective effects through various mechanisms with DHA being most potent followed by EPA and ALA in preventing cardiovascular disease. But conversion of ALA to EPA and DHA is less efficient. So, walnuts and flaxseed being very good source of ALA should be included in the diet with dose depending on the severity of disease. Along with this, consumption of fatty fish at least 2 servings per week or fish oil supplementation is necessary for reducing the risk of cardiovascular disease.

Keywords
Pro-atherogenic, Left ventricle hypertrophy, Eicosanoid, Fibrous cap, Arrhythmia

Introduction

Cardiovascular disease (CVD) is a class of diseases that involve the heart or blood vessel. Cardiovascular diseases involving heart are cardiomyopathy, hypertensive heart disease, heart failure, pulmonary heart disease, cardiac dysrhythmias (abnormalities of heart rhythm) and inflammatory heart disease. Diseases of blood vessels involves coronary artery disease (CAD)/ coronary heart disease (CHD)/ ischemic heart disease (IHD) that includes angina and myocardial infarction (commonly known as a heart attack), peripheral arterial disease, cerebrovascular disease/ stroke and renal artery stenosis (Cardiovascular disease).

CVD is a major public health problem in India. Cardiovascular disease has become the leading cause of mortality in India (Reddy et al., 2005) and throughout the world. The epidemiological transition from infectious diseases to non-communicable diseases (NCDs) is seen in India in last two decades (Institute of Health Metrics and Evaluation. GBD Profile: India). Annual Indian stroke
incidence rate is 154 per 100000 (standardized to the world standard population) (Das and Banerjee, 2008) with higher among women. Hypertensive heart disease is most common problem while rheumatic heart disease and atrial fibrillation are less common and attributes to other type of CVD such as aortic aneurysms, peripheral vascular disease, and endocarditis and ultimately increases the burden of mortality and morbidity among Indians.

**Major risk factors for cardiovascular disease**

**Atherosclerosis**

Atherosclerosis is a disease of the arterial wall (Insull 2009). Atherosclerosis is the usual cause of heart attacks, stroke and peripheral vascular disease. The normal arterial vessel consists of three layers namely intima (innermost layer), media and outer layer adventitia. Intima is composed of a single layer of endothelial cells (endothelium), connective tissue, and several smooth muscle cells. Endothelial cells of the intima layer perform two major functions. Firstly, it produces antithrombotic molecules such as heparin sulfate, thrombomodulin, and plasminogen, prostacyclin and nitric oxide (NO), thus, prevents blood clotting. Secondly, vasodilators such as nitric oxide, prostacyclin and vasoconstrictors such as endothelin are produced by endothelial cells that help in contraction of smooth muscle cells in the media. This endothelial-dependent response is called flow-mediated vasodilation (FMD). Impairment of FMD can be used for clinical diagnosis of endothelial function and for early detection of atherosclerosis (Delewii et al., 2012) and endothelial dysfunction that disrupts the integrity of barrier provided by the endothelial cells. This allows circulating high level of LDL to enter the intima. LDL particles bind to proteoglycans, start to accumulate and get oxidised thus causing tissue damage. Damage to intima induces monocyte recruitment, gets differentiated into phagocytic macrophages that plays crucial role in formation of foam cells (Chistiakov et al., 2017). In addition, vascular smooth muscle cells migrate from the media to the intima, proliferate and get differentiated into macrophages (Lao et al., 2015) and ultimately transformed into foam cells (Yu et al., 2013) by absorbing lipoproteins.

Foam cell increases in size and intensify plaque formation. In the media, smooth muscle cell is responsible for the production of vascular extracellular matrix consisting of elastin, proteoglycans and fibrillar collagen (Munro and Cotran 1988). Migration of smooth muscle cells from media to intima and the secretion of large amounts of collagen firstly give rise to fibrous lesions consisting of lipid-loaded macrophages and smooth muscle cells covered by a fibrous cap (Tabas 2002) and secondly, shifts the balance towards extracellular matrix metabolism. This activates apoptosis pathway resulting in death of smooth muscle and foam cells.

Diminished collagen synthesis weaken the fibrous cap strength ultimately results into rapture of atherosclerotic plaque (Cullen et al., 2003; Arroyo and Lee 1999). Atheroma may go through episodes of haemorrhage with or without calcification. Rapture of plaque initiate both platelet adhesion and aggregation on the exposed vascular surface and the activation of the coagulation cascade, leading to thrombosis, progressive vessel narrowing and may may result in myocardial infarction or sudden death (Legein et al., 2013).
Hypertension

Left ventricle hypertrophy (LVH) becomes an independent risk factor for congestive heart failure, ischemic heart disease, arrhythmia, sudden death (Katholi and Couri 2011) and stroke. An increase in left ventricular wall stress caused by high blood pressure stimulates collagen formation and hypertrophy of the myocardium with a disproportionate increase in fibrous tissue that impairs left ventricular diastolic function (Kahan and Bergfeldt 2005). These changes lead to a progressive decline in contractility of heart (Vasan et al., 1999) and ultimately cardiac ischemia, myocardial infarction or heart failure (Torpy et al., 2004).

PUFA (Polyunsaturated Fatty acid)

PUFAs act as substrates for eicosanoid formation. Some are proinflammatory in nature whereas some are beneficial. PUFAs also serve as substrates for lipid oxidation and the production of reactive oxygen species. The more common PUFAs in our diet are the omega (n)-6 and n-3 fatty acids. PUFA should provide 6 – 10% of total energy. Sources of Linoleic acid (LA) or omega 6 polyunsaturated fatty acid are vegetable oils such as safflower and corn oils whereas major source of alpha linolenic acid are plant sources that includes flaxseed and walnuts and long chain omega-3 polyunsaturated fatty acids (n – 3 LC PUFAs) that includes Eicosapentanoic acid (EPA) and Docosahexaenoic Acid (DHA) are abundantly found in fish and fish oil.

PUFA metabolism

Linoleic acid and ALA on consumption undergoes a series of desaturation and elongation steps to produce highly unsaturated longer-chain arachidonic acid (AA) in n – 6 pathway and eicosapentenoic acid (EPA) and docosahexaenoic acid (DHA) in n – 3 pathway (Engler and Engler 2006). AA and EPA compete with each other for release by phospholipases and for conversion into potent regulatory eicosanoids in the tissue membrane (Harris 2006). Free AA serves as a substrate for the enzymes cyclooxygenases (COX - 2) to produce two-series prostaglandins (PGE2) (vasodilator), prostacyclins (PGI2) (platelet aggregator) and thromboxanes (TXA2) (vasoconstrictor) (Lagarde et al., 2018) eicosanoids that are pro – inflammatory in nature. n-3 PUFA plays beneficial role in shifting the production of AA-derived pro – inflammatory eicosanoids to anti – inflammatory eicosanoids by competing with AA for incorporation into cell membrane or by inhibiting the enzymes COX-2 (Chitranjali et al., 2015) thereby decreasing two- and four-series PG and TX production and increasing the three- and five-series PG, PGI and TX production (Adkins and Kelley 2010).

Mechanism of action of Omega – 3 fatty acid

The cardioprotective effect of Omega – 3 fatty acid is well established and in this section, we will briefly review to extend our knowledge.

Lipid lowering effect

Hypertriglyceridermia can promote atherogenesis and is an important independent risk factor for coronary heart disease. Omega-3 fatty acids are best known for their triglyceride-lowering effect (Benes et al., 2018) by reducing hepatic VLDL synthesis and by clearance of triglyceride from serum. n – 3 PUFA reduces VLDL triglyceride synthesis by three mechanisms. Firstly n – 3 PUFA reduces the substrate i.e. fatty acid needed for triglyceride synthesis either by increase in β-oxidation (Rombaldova et al., 2017) or by decreasing hepatic delivery of non-esterified free fatty acids or by reducing lipogenesis. Another way for reducing
triglyceride synthesis is by shift of lipid synthesis toward phospholipids rather than triglycerides or by reducing the activity of hepatic enzyme such as diacylglycerol acyltransferase (DGAT) or phosphatidic acid phosphohydrolase (PAP) (Harris and Bulchandani 2006; Scorletti and Byrne 2018). Omega-3 fatty acid also increases lipoprotein lipase activity, thus increase serum clearance of triglyceride (Harris et al., 2008). However, this may cause an increase in low-density lipoprotein cholesterol that can be considered part of the normal physiologic process in correcting high triglyceride (Samuel et al., 2011) but may not be harmful in present context. Change in triglyceride level is inversely correlated with the LDL particle size. Lowering triglyceride level causes an increase in LDL particles of larger size (Mori et al., 2000) that may be anti-atherogenic in nature rather than atherogenic effect (Jacotot 1996). Supplementation with docosahexanoic acid is possibly being more effective than eicosapentanoic acid and ALA (Kelley et al., 2007; Maki et al., 2005; Scorletti and Byrne 2018) in treating hypertriglycerideremia and secondary prevention of CV disease such as myocardial infarction and cardiac death (Arca et al., 2017).

The key enzyme of cholesterol biosynthesis is 3-hydroxy-3-methyl-glutaryl CoA (HMG-CoA) reductase. n – 3 PUFA suppresses the expression of HMG –CoA reductase enzyme thus, prevent cholesterol synthesis and convert excess cholesterol into bile (Balogun and Cheema, 2015). Supplementation with n-3 PUFA also exerts its cardioprotective effect by increasing the concentration of HDL cholesterol in the blood (Dunstan et al., 1997).

**Anti-arrhythmic effects**

Anti – arrhythmic effect of n-3 fatty acid is mediated through electrical stabilization of myocytes (Harrison and Abhyankar 2005). Ca2+, Na+, and K+ are important regulators of membrane excitability and contractility and decrease in uniformity in this has shown to result in decreased cardiac contractility and increased incidence of arrhythmias (Doshi and Marx 2009). EPA and DHA modulate the activity of calcium channels (Endo and Arita 2016) whereas EPA blocks the sodium-calcium channel thus helps to prevent fatal arrhythmia (Xiao et al., 2001). DHA being the most potent n–3 PUFA followed by EPA and ALA (Moreno et al., 2012).

**Anti – thrombotic effect**

Supplementation with long-chain omega-3 polyunsaturated fatty acid (LCn-3 PUFA) plays a significant role in reducing the risk of cardiovascular disease due to its anti-inflammatory and anti-thrombotic effects (Adili et al., 2017). Platelet aggregation plays a pivotal role in the development of CVD by initiation of process of thrombosis (Jackson 2007). Consumption of n-3 PUFAs reduces formation of the platelet activator Thromboxane A2 (TXA2) by increasing the concentration of Prostacyclin or PGI2 that act as vasodilator and platelet inhibitor (Lagarde et al., 2018). Thus, production of platelet-activating factor (PAF) is suppressed resulting in inhibition of platelet aggregation (DeCaterina et al., 1990; Dyerberg et al., 1978). Thus, n-3 PUFA-supplementation reduces ADA (adenosine diphosphate), collagen and arachidonic acid induced platelet aggregation (Gao et al., 2013) and consequently increases bleeding time but within safe limit with no adverse effects on human health (Jeansen et al., 2017). Among n – 3 LC PUFA, EPA was more effective than DHA in males (Phang et al., 2009) whereas in females, DHA was more effective in reducing platelet aggregation. This may be due to inverse relationship between testosterone levels and EPA supplemented platelet aggregation (Phang et al., 2012).
Table 1 Summary of beneficial effects of flaxseed supplementation on various cardiovascular outcomes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Dose and Duration/Treatment</th>
<th>Placebo</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>(Akrami et al., 2018)</td>
<td>30 to 60 years old diagnosed with Metabolic Syndrome</td>
<td>25 mL/d Flaxseed oil for 7 weeks</td>
<td>Sunflower oil</td>
<td>Reduction in SBP, DBP, LDL and TG</td>
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<td>(Bloedon et al., 2008)</td>
<td>Men and Post-menopausal women between the ages of 44 and 75 with hypercholesterolemia</td>
<td>40 g/day flaxseed for 10 weeks</td>
<td>Wheat bran</td>
<td>Increased serum levels of ALA Significant reduction in total cholesterol, LDL-C, Apo-B and HOMA-IR index</td>
</tr>
<tr>
<td>(Dodin et al., 2008)</td>
<td>Menopausal women</td>
<td>40 g/d of flaxseed for 12 months</td>
<td>Wheat germ</td>
<td>Significant increase in apo A-1, EPA, ALA, HDL Significant decrease in LDL and total plasma cholesterol</td>
</tr>
<tr>
<td>(Machado et al., 2015)</td>
<td>Overweight adolescents</td>
<td>28 g/d of flaxseed for 11 weeks</td>
<td>Wheat bran</td>
<td>Significant reduction in the DBP, TG Increase in HDL level</td>
</tr>
<tr>
<td>(Paschos et al., 2007)</td>
<td>Male aged 35 to 70 years, first diagnosed for dyslipidaemia, without evidence of CHD</td>
<td>15 ml of flaxseed oil per day for 12-week</td>
<td>Safflower oil</td>
<td>Significant decrease in SBP and DBP by approx. 5 mm Hg or 3–6%.</td>
</tr>
<tr>
<td>(Pilar et al., 2014)</td>
<td>Metabolic syndrome persons of 45 and 55 years of age</td>
<td>40 g/day of golden flaxseed for 28 days</td>
<td>---</td>
<td>Reduction in TG, LDL, total cholesterol Significant reduction in TBARS level Increase in plasma HDL level</td>
</tr>
<tr>
<td>(Ricklefs-Johnson et al., 2017)</td>
<td>Adults between 18-75 years of age diagnosed with T2D at least 6 months prior to enrollment</td>
<td>28 g/d of ground flaxseed for 8 weeks</td>
<td>Ground psyllium</td>
<td>Reduction in Cholesterol, LDL-C, TBARS and increase in Nitric Oxide</td>
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</tbody>
</table>
### Table 2 Summary of beneficial effects of fish oil supplementation on various cardiovascular outcomes

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Dose / Treatment</th>
<th>Duration</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>(Alfaddagh et al., 2017)</td>
<td>Patients mean age 63.0 years with stable coronary artery disease</td>
<td>1.86 g of EPA and 1.5 g of DHA/day</td>
<td>30 months</td>
<td>Subjects aged &lt;64.2 years had significantly less progression of non calcified plaque ((P=0.013) (primary endpoint) and fibrous, calcified, and total plaque volume compared with older subjects.</td>
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<td>(Bays 2006)</td>
<td>patients with myocardial infarction (MI)</td>
<td>4 capsules/day (2 capsules given twice daily) alone or in combination with (HMG-CoA) reductase inhibitors {1 capsule containing 465 mg of EPA and 375 mg of DHA along with 4 mg (6 IU) of vitamin E}</td>
<td>6 months</td>
<td>Increases high-density lipoprotein cholesterol levels Helps in controlling hypertriglyceridemia Mildly increases plasma levels of low-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>(Casanova et al., 2017)</td>
<td>Adults with triglycerides 150–499 mg/dL</td>
<td>1800 mg/day (60%EPA and 40%DHA)</td>
<td>12 weeks</td>
<td>Significant reduction in peripheral and aortic systolic blood pressure, pulse wave velocity and improvement in flow-mediated dilation</td>
</tr>
<tr>
<td>(Caniato et al., 2006)</td>
<td>Subjects suffering from schizophrenia or schizoaffective disorder</td>
<td>10 g of fish oil capsule (Each 1 gm capsule contained approximately 180 mg of EPA and 120 mg of DHA)</td>
<td>28 days (4 weeks)</td>
<td>Statistically significant reduction in mean serum triglyceride levels of 22%. Increase in total cholesterol and low-density lipoprotein cholesterol by 6.6% and 22%</td>
</tr>
<tr>
<td>(Dokholyan et al., 2004)</td>
<td>Adults 30 to 54 years of age</td>
<td>8 capsules/day (60 mg of EPA)</td>
<td>12 weeks</td>
<td>Reductions in DBP and SBP but not statistically significant</td>
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<tr>
<td>Study (Year)</td>
<td>Participants</td>
<td>Intervention</td>
<td>Duration</td>
<td>Results</td>
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<tr>
<td>Elajami et al., 2017</td>
<td>Patients aged 36 to 80 years with stable coronary artery disease</td>
<td>Placebo - Olive oil (4:1 ratio) plus 15 mg of GLA and 10 IU of vitamin E per capsule</td>
<td>12 months</td>
<td>A significant reduction in triglyceride level (P&lt;0.001) with increase in high-density lipoprotein cholesterol level (P=0.01) in non-diabetic subjects. Significant reduction in triglyceride level (P=0.005) without a change in high-density lipoprotein cholesterol in diabetic subjects.</td>
</tr>
<tr>
<td>Grenon et al., 2015</td>
<td>Patients aged 50 and older with lower-extremity PAD (peripheral artery disease)</td>
<td>Placebo - Safflower oil</td>
<td>1 month</td>
<td>Improved serum triglyceride level. Increased the production of n-3 PUFA–derived products in patients.</td>
</tr>
<tr>
<td>Kenny et al., 1992</td>
<td>Normotensive men having blood pressure less than 140/90 mm Hg</td>
<td>Placebo - Safflower oil</td>
<td>7 days</td>
<td>Significantly reduced vascular resistance, plasma triglycerides. Increase in plasma EPA levels.</td>
</tr>
<tr>
<td>Kumar et al., 2011</td>
<td>Patients 18 to 75 years old with paroxysmal atrial fibrillation</td>
<td>Placebo - Safflower oil containing a total dose of 1.5 g DHA and 0.3 g EPA</td>
<td>30 days</td>
<td>Decreases susceptibility to initiation atrial fibrillation within pulmonary vein and thus has antifibrillatory effect.</td>
</tr>
<tr>
<td>Study (Ref)</td>
<td>Participants</td>
<td>Intervention</td>
<td>Duration</td>
<td>Outcomes</td>
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<tr>
<td>Metcalf et al., 2008</td>
<td>Patients with ischemic heart disease</td>
<td>3 g/day encapsulated fish oil providing 540 mg/day EPA and 360 mg/day DHA</td>
<td>6 weeks</td>
<td>Antiarrhythmic effect&lt;br&gt;Decreases the inducibility of ventricular tachycardia in patients at risk of sudden cardiac death (SCD)</td>
</tr>
<tr>
<td>Oikonomou et al., 2018</td>
<td>Patients aged 18 to 80 years old, with chronic ischemic heart failure, Left Ventricle systolic dysfunction (Left ventricle ejection fraction &lt;40%)</td>
<td>2 g/day (46% eicosapentaenoic acid and 38% docosahexaenoic acid) Placebo - Olive oil</td>
<td>8 weeks</td>
<td>Improvement in inflammatory and fibrotic status, endothelial function, systolic and diastolic performance of left ventricle, left ventricle performance indices, systemic inflammation and fibrosis biomarkers</td>
</tr>
<tr>
<td>O'Keefe et al., 2006</td>
<td>Patient with myocardial infarction</td>
<td>3 capsule/day (75 mg of EPA and 195 mg of DHA per 500-mg capsule) Placebo - 50:50 mix of corn and olive oils</td>
<td>2 sequential 4-month periods (total 8 months)</td>
<td>Decreases HR at rest from 73 ± 13 to 68 ± 13 beats/min (p &lt;0.0001)&lt;br&gt;Improved 1-minute HR recovery after exercise (−27 ± 10 to −32 ± 12 beats/min, p &lt;0.01)&lt;br&gt;Increases HR variability (p &lt;0.02)&lt;br&gt;Decrease the risk for sudden cardiac death</td>
</tr>
<tr>
<td>Samuel et al., 2011</td>
<td>Patients of age 45 to 75 years having triglyceride levels ranging from 500 to 2,000 mg/dl</td>
<td>4 g EPA plus 3.6 g DHA /day</td>
<td>30 days</td>
<td>Triglycerides and total cholesterol decreases by 41% and 12%.&lt;br&gt;HDL and LDL increases by about 4% and 24%</td>
</tr>
<tr>
<td>Siasos et al., 2013</td>
<td>Smokers, aged 27.63±2.65 years old</td>
<td>2g/day (46% EPA and 38% DHA)</td>
<td>12 weeks</td>
<td>Significant improvement in FMD (p &lt; 0.05) and PWV (p &lt; 0.01)&lt;br&gt;Significantly decreased levels of TNFα (tumor necrosis factor-α) (p &lt; 0.05) and IL-6 (interleukin-6)(p = 0.01) and ...</td>
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increased levels of PAI-1 (plasminogen activator inhibitor-1) (p = 0.05)

| Subjects (mean age 44 ± 12 years) with MetS | 2g/day (46% EPA and 38% DHA) | 12 weeks | Significant improvement in FMD (flow-mediated dilation) and PWV (Carotid-femoral pulse wave velocity) (p < 0.001)
Significant decreased in IL-6 levels and increased PAI-1 levels (p<0.05)
Significant decrease in fasting triglyceride levels and in serum total cholesterol levels (p< 0.05). |

**Anti – inflammatory effects**

Evidence from both human and animal studies suggests that n – 3 PUFA has anti – inflammatory effects. n-3 PUFA plays beneficial role in shifting the production of AA-derived pro – inflammatory eicosanoids to anti – inflammatory eicosanoids by competing with AA for incorporation into cell membrane or by inhibiting the enzymes COX-2 (Chitranjali et al., 2015), thereby, decreasing two- and four-series PG and TX production and increasing the three- and five-series PG, PGI and TX production (Adkins and Kelley 2010).

The production of several inflammatory cytokines such as TNF-α (tumor necrosis factor-α), IL-1β, IL-6 (interleukin-6), IL-8 etc. that may contribute towards development of atherosclerosis (Tortosa-Caparrós et al., 2017) are also reduced by supplementation with omega 3 especially fish oil capsules (Siasos et al., 2013; Simopoulos 2002; Tousoulis et al., 2014). Eicosapentaenoic acid (EPA) on oxidation act as potent inhibitor of leukocyte interactions with the endothelium and thus improves inflammation (Sethi 2002).

EPA is oxygenated to produce the E-series resolvins while DHA produced resolvins or protectins of the D-series (Calder 2007). Resolvins and protectins exhibit their anti-inflammatory properties by inhibiting the action of leukocyte and direct impact on macrophage-directed clearance mechanisms (Serhan 2010). It possesses its beneficial effects in the picomolar and nanomolar range (Serhan et al., 2002) and therefore contributes towards reducing inflammations associated with atherosclerosis.

**Endothelial dysfunction**

Omega-3 stimulates the activity of nitric oxide synthase enzyme responsible for nitric oxide production. In this way, omega-3 improves arterial stiffness and endothelial function in patients with high risk of cardiovascular disease (Casanova et al., 2017).

**Nutritional considerations for omega 3**

The therapeutic strategy for preventing cardiovascular disease (CVD) is mainly through increasing the use of omega -3 fatty acids. Supplementation with omega-3
polyunsaturated fatty acids possess cardioprotective effects through improving lipid profile, control cardiac arrhythmia, reduces platelet aggregation, improves vascular endothelial function and prevents inflammations associated with atherosclerosis (Nishizaki et al., 2017). Among all omega 3, DHA is most potent followed by EPA and ALA in preventing cardiovascular disease (CVD). Conversion of ALA to EPA are approximately 0.2% to 6% and the synthesis of DHA is 0.05% or less. Conversion of ALA to EPA and DHA is higher in women than men of same age (Burdge and Wootton 2002) is due to the action of oestrogen that may regulate the desaturation/elongation pathway. Thus, higher level of DHA is found in women using oral contraceptive pill, postmenopausal women receiving oestrogen-based hormone replacement therapy and in pregnant women (due to increase in secretion of oestrogen by the placenta) (Burde 2006). So, walnuts and flaxseed being very good source of ALA should be included in the diet for promoting healthy heart but at the same time, fish oil supplementation is necessary for reducing the risk of cardiovascular disease.

**Flaxseed**

Results from various epidemiological studies (Table 1) suggests that consumption of 12 – 25 ml/day of flaxseed oil or 28 – 40 gm/day of ground flaxseed powder for 2 – 3 months duration plays beneficial role in significant reduction of SBP, DBP, total cholesterol, TG, LDL levels and causes an increase in serum level of ALA, EPA, HDL, Nitric oxide that helps in primary and secondary prevention of cardiovascular disease.

**Walnut**

The cardioprotective benefits of walnut are attributed to its fatty acid profile. It is rich in omega 3 fatty acid and has 4.2: 1 omega 6 to omega 3 ratio that is beneficial in prevention of CVD. 30 g of walnut consumed for five times per week for five weeks shows decrease in total cholesterol and LDL cholesterol (Olmedilla-Alonso et al., 2008). Replacing 30 g of saturated fat with 43 g of walnut significantly reduced LDL-cholesterol and apolipoprotein-B but no effect was seen on biomarkers of inflammation and endothelial dysfunction (Wu et al., 2014). Consumption of 42.5 g of walnuts per 2400 kcal for 6 days in a week cause an increase in plasma EPA, DHA, ALA and decrease in AA (Chiang et al., 2012). Daily ingestion of 56 g of walnuts for 16 weeks causes improvement in FMD and reduction in systolic blood pressure (Katz et al., 2012). Thus, consumption of 30 to 60 g of walnut daily helps in reducing risk of cardiovascular disease and coronary heart disease (Hayes et al., 2016).

**Effect of fish oil supplements on cardiovascular disease risk factors**

There are several pathways that explain long chain omega-3 polyunsaturated fatty acids (n – 3 LC PUFAs) intake could potentially alter risk for fatal and nonfatal cardiac events. The mechanisms through which n – 3 LC PUFAs intake might alter CVD risk have been reviewed in previous sections in detail but the dose for most of these effects have not been fully and clearly described elsewhere. Table 2 shows the effects of fish oil consumption on risk factors for cardiovascular disease.

**Effect of fish oil on plasmalipid profile**

Literature indicates that elevated triglyceride levels are an important independent risk factor for coronary heart disease. As shown in Table 2, a significant reduction in plasma triglycerides is a common effect of fish oil supplementation. Dose ranging from 2600 – 4000 mg of EPA and 1200 – 3600 mg for DHA given for 1 month period (Caniato et
al., 2006, Grenon et al., 2015 and Samuel et al., 2011) or EPA (1860 mg) and DHA (1500 mg) given for 6 – 12 months period (Bays 2006, Elajami et al., 2017) was found to be beneficial in controlling hypertriglyceridemia and increasing HDL level. But at the same time, there is slight increase in plasma total cholesterol and LDL level. The rise in total cholesterol and LDL cholesterol is therefore of concern. The elevation resulting from omega-3 fatty acids supplementation, however, may not be a harmful one due to elevations in larger, cardioprotective apolipoprotein subfractions rather than atherogenic subfractions (Jacotot, 1996).

**Preventive effect of fish oil on hypertension, endothelial function and atherosclerosis**

Endothelial dysfunction can be seen as an inherent feature in subjects with heart disease. Endothelial function assessed by flow mediated dilation (FMD) is related to the principal cardiovascular risk factors (Witte et al., 2005). The primary cause of FMD is release of nitric oxide by endothelial cells (Raitakari and Celermajer, 2000). Pulse Wave Velocity (PWV) is a measure of arterial stiffness. Results from Table 2 shows that fish oil capsule containing 920 – 1080 mg of EPA and 720 – 760 mg of DHA when given for 2 – 3 months exerts beneficial effect on endothelial function by significant improvement in FMD and reduction in PWV (Casanova et al., 2017, Oikonomou et al., 2018, Siasos et al., 2013, Tousoulis et al., 2014). Fish oil capsules providing 1800 mg of EPA and 1500 mg of DHA given for 1 month significantly reduces non – calcified and fibrous, calcified plaque formation in patients with coronary artery disease (Alfaddagh et al., 2017). Omega-3 PUFA's causes reduction in plaque formation and improvement in endothelial dysfunction by restoring nitric oxide bioavailability (Zanetti et al., 2017) thus, reducing cardiovascular disease risk such as hypertension and atherosclerosis.

**Other cardioprotective benefits of fish oil supplementation**

Fish oil 6 g/day containing a total dose of docosahexaenoic acid (DHA) 1.5 g and eicosapentaenoic acid (EPA) 0.3 g given for 30 days shows antifibrillatory effect in patients with paroxysmal atrial fibrillation (Kumar et al., 2011). Fish oil capsule containing 540 mg of EPA and 360 mg of DHA given for 45 days decreases tachycardia and arrhythmias in patients with ischemic heart disease (Metcalf et al., 2008) (Table 2).

In conclusion, consumption of fatty fish at least 2 servings per week is recommended for patients without coronary artery disease as fatty fish is high in EPA and DHA (Lichtenstein et al., 2006). Fish oil supplements are suggested as an alternative to fatty fish consumption for secondary prevention of CAD (Weitz et al., 2010).

**References**


Akrami, A., Nikaein, F., Babajafar, S., Faghii, S. and Yarmohammadi, H., 2017. Comparison of the effects of flaxseed oil and sunflower seed oil consumption on serum glucose, lipid


Chiang, Y.L., Haddad, E., Rajaram, S., Shavlik, D. and Sabaté, J., 2012. The effect of dietary walnuts compared to fatty fish on eicosanoids, cytokines, soluble endothelial adhesion molecules and lymphocyte subsets: a randomized,
controlled crossover trial. Prostaglandins, Leukotrienes and Essential Fatty Acids, 87(4-5), pp.111-117.


of Cardiology, 108(5), pp.691-697.
fasting non-HDL-cholesterol and apolipoprotein B in healthy Caucasian subjects: a randomized controlled cross-over clinical trial. Metabolism-Clinical and Experimental, 63(3), pp.382-391.

