Drug Corner

Omega-3 Fatty Acids : A Promising Therapy for management of Dyslipidemia and improving the Cardiovascular Health

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Asian Indians exhibit a unique pattern of dyslipidemia characterized by elevated triglyceride (TG) levels and a greater incidence of hypertriglyceridemia (HTG). HTG refers to a medical condition characterized by elevated levels of triglycerides in the blood, which is strongly associated with an increased risk of cardiovascular disease (CVD). Thus, the management of hypertriglyceridemia becomes vital. Omega-3 fatty acid (O3FA) supplements containing both eicosapentaenoic acid and docosahexaenoic acid have been shown to reduce plasma TG levels through various mechanisms and play a significant role in the management of hypertriglyceridemia. Various national and international guidelines like Lipid Association of India, ESC/EAS guideline and ACC expert consensus recommend the use of O3FAs in the management of hypertriglyceridemia. O3FAs have also been found to play a significant role in the prevention of CVD, as evidenced by multiple clinical trials. O3FAs offer the other benefits like significant reduction in blood pressure in hypertensive subjects and patients with other CV risk factors such as hyperlipidemia or in patients treated with hemodialysis and TG levels in patients with antipsychotic-induced hypertriglyceridemia. This review article will emphasize the importance of maintaining the levels of TG in Indians and the role of O3FAs in the management of hypertriglyceridemia.

[*J Indian Med Assoc* 2023; **121(5):** 69-74]

Key words **: Omega-3 Fatty Acids, Hyperlipidemia, Cardiovascular diseases.**

Dyslipidemia refers to either lipoprotein overproduction or deficiency, a consequence of abnormal lipoprotein metabolism. This leads to elevated total cholesterol (TC), low-density lipoprotein (LDL-C) cholesterol and triglyceride (TG) concentrations and a decrease in the high-density lipoprotein (HDL-C) cholesterol concentration in the blood. Dyslipidemia has been strongly associated with the pathophysiology of cardiovascular diseases (CVDs). It is a significant independent risk factor for coronary artery disease (CAD) and can lead to the development of atherosclerosis and associated cardiovascular (CV) events[1]. Patients with dyslipidemia have a 2-fold higher risk of developing CVD than those without dyslipidemia. Dyslipidemia is responsible for approximately 4 million CVD-related deaths globally[2].

Distinct pattern of Dyslipidemia in Indians :

The pattern of Dyslipidemia observed in Indians is distinctive and characterized by elevated triglyceride (TG) levels, low levels of high-density lipoprotein cholesterol (HDL-C), moderately high levels of low-density lipoprotein cholesterol (LDL-C), and a higher proportion of small, dense LDL particles. This type of dyslipidemia is commonly referred to as “atherogenic dyslipidemia” and is more prevalent in South Asian populations[3,4].

According to the ICMR-INDIAB study, which included 16,607 subjects, dyslipidemia is highly prevalent among Indian adults, with 79% of the study participants having at least one lipid abnormality. Hypertriglyceridemia was observed in 29.5% of the individuals, decreased HDL-C levels in 72.3% of individuals, and elevated LDL-C levels in 11.8% of individuals[5]. The prevalence and pattern of concomitant cardiovascular (CV) risk factors that modify the impact of dyslipidemia on CV risk (eg, truncal obesity, metabolic syndrome, and diabetes) are also unique in Indians[4]. Although the cause of atherogenic dyslipidemia in Indians is unknown, genetic predisposition and characteristic body composition, such as excess truncal subcutaneous and intra-abdominal fat, may be significant contributors[3]. Thus, Asian Indians have a distinctive pattern of dyslipidemia, which includes a higher incidence of elevated triglyceride levels, commonly referred to as hypertriglyceridemia (HTG).

Hypertriglyceridemia :

The plasma TG level represents the concentration of TG-rich lipoproteins, includingvery-low-density lipoproteins (VLDL), chylomicrons and their remnants[5].

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Received on : 09/05/2023
Accepted on : 13/05/2023

Elevated plasma triglycerides result from excess triglyceride-rich lipoproteins of several different types, most commonly VLDLs but also intermediate-density lipoproteins (or VLDL remnants), chylomicrons, or chylomicron remnants[6].

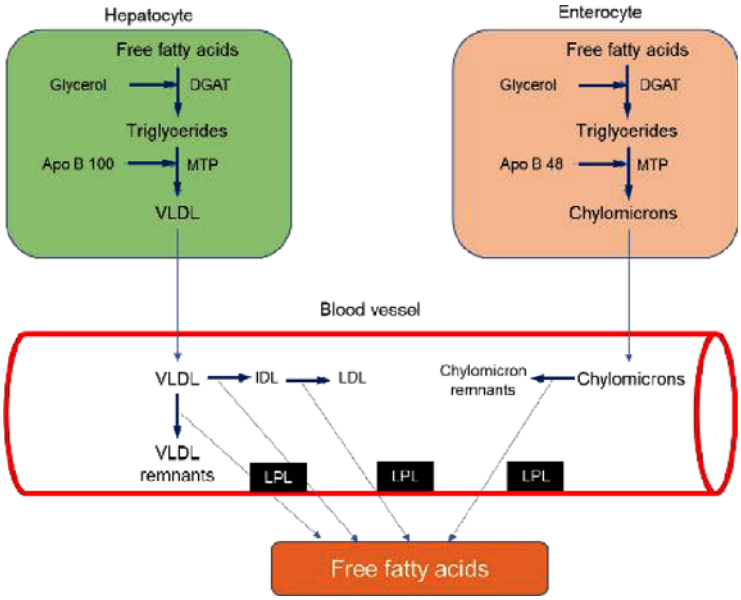
Pathophysiology of Hypertriglyceridemia :

Under normal conditions, the liver packages endogenous lipids into very-low-density lipoprotein (VLDL) particles, which mainly contain triglycerides (TG), while dietary lipids absorbed in the intestine are incorporated into chylomicrons (Fig 1). Chylomicrons are quickly cleared as their TG content is hydrolyzed by lipoprotein lipase (LPL) at adipose and muscle tissue capillary beds, releasing free fatty acids (FFA) for cellular metabolic activities leaving behind chylomicron remnants. Similarly, VLDL is hydrolyzed by LPL, leaving behind remnants of VLDL particles in the bloodstream and intermediate-density lipoprotein (IDL) particles that are smaller in size and enriched in cholesteryl esters. The levels of TG-rich lipoproteins in circulation are determined by LPL activity. The liver primarily clears remnants through various receptors present on the surface of hepatocytes, including the LDL receptor, VLDL receptor, LDL receptor-related protein 1 (LRP1), and heparan sulfate proteoglycans (HSPGs), which facilitate the hepatic clearance of these lipoproteins. Another pathway for lipoprotein clearance involves syndecan 1, a core component of HSPG, which is essential for both the binding and degradation of VLDL remnant particles. Any disruption that causes increased production of chylomicrons and/or VLDL particles or a reduction in their metabolic breakdown will result in elevated levels of TG[7].

Need for management of Hypertriglyceridemia :

Elevated levels of triglycerides in the blood have been linked to the presence of small, dense LDL particles and lower levels of HDL cholesterol, both of which are associated with an increased risk of CVD[8]. A study conducted on 3216 American Indians withoutany CVD at baseline reported a 32% higher risk for developing coronary heart disease (CHD) in patients with high TG and low HDL-C levels than those with normal TG and HDL-C levels over a follow-up period of 17.7 years. In patients with established CHD, it was found that patients with TG levels ≥500 mg/dl were at 68% increased risk of mortality as compared to those with TGs <100 mg/dl[5]. According to a study conducted by Miller and colleagues in patients who had experienced a myocardial infarction, a decrease of 10 mg/dL in TG levels was associated with a 1.8% reduction in the risk of experiencing a CV event. The management of HTG becomes crucial because of the higher prevalence ofelevated TG levels as a component of atherogenic dyslipidemia and by controlling TGs, the risk of developing CVD can be reduced[7].

Role of Omega-3-fatty acids (eicosapentaenoic acid and docosahexaenoic acid) in management of hypertriglyceridemia :



Apo: Apolipoprotein, DGAT: diacylglycerol acyltransferase, IDL: Intermediate density lipoprotein, LDL: Low-density lipoprotein, LPL: Lipoprotein lipase, MTP: Microsomal triglyceride transfer protein, VLDL: Very low-density lipoprotein.

Fig 1 — Triglyceride metabolism

Introduction to Omega-3-fatty acids :

Omega 3 (ω 3 or n 3) is a structural descriptor for a family of polyunsaturated fatty acids (PUFAs). The size of the fatty acid chain affects its function, with short-chain fatty acids having less than six carbons, medium-chain fatty acids having six to 12 carbons, and very long-chain O3FAs having 12 carbons or more. The very long chain O3FAs include α-linolenic acid (ALA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). ALA is an essential fatty acid because it cannot be synthesized in humans and, thus, must be consumed in the diet. ALA is a plant-derived O3FA that can be converted to EPA and DHA in mammals. However, the conversion of ALA to EPA is modest, and the subsequent conversion of EPA to DHA is also very low. Thus, preformed EPA and DHA are best obtained through dietary sources such as fish or oily marine seafood[9,10].

Prescribed O3FAs supplements have been shown to reduce fasting and non-fasting TG

levels by 20%-50% (Table 1) and increase the LDL particle size[5,10]. Nonprescription fish oil products are not interchangeable with prescription omega-3 products due to differences in O3FA content and bioavailability. As well as, prescription O3FA supplements have undergone more rigorous safety and efficacy evaluation than dietary supplements[10,11].

Several national and international guidelines such as Lipid Association of India (LAI) 2020 guideline,ESC/EAS 2019 guideline, and ACC Expert Consensus 2021also recommend the use of O3FAs in the management of HTG[5,11,12].

Mechanism of Omega-3-fatty acids in hypertriglyceridemia :

Different mechanisms have been proposed and investigated to demonstrate the effect of O3FAs on lipoprotein metabolism (Fig 2). O3FAs reduce plasma triglycerides and offer CV protection by increasing the oxidation of fatty acids, resulting in decreased hepatic lipogenesis and subsequent VLDL production. They also enhance the lipolysis of increased triglyceride-rich lipoproteins (chylomicron), have anti-inflammatory effects, and exert CV protection viapro resolving lipid mediators. Additionally, O3FAs also reduce the risk of thrombosis.[13]

In a study conducted by Grevengoed, *et al*, a new mechanism was proposed for the reduction of plasma and liver TGs by O3FAs. The researchers discovered that O3FAs generate N-acyl taurines, which conjugate with bile acids and aid in the absorption of fats. The omega-3 fatty acid–derived N-acyl taurines (NATs) accumulated significantly in bile and plasma following O3FA supplementation. One of these NATs (DHA NAT) was found to inhibit intestinal triglyceride hydrolysis and lipid absorption, resulting in lower plasma triglycerides and protection against hepatic triacylglycerol accumulation in mice fed with a high-fat diet[13].

Table 1 — *Effect of different medications effect on triglyceride levels*[5]

Medication	Reduction of TG levels
Omega-3-fatty acids	20-50%
Niacin	20-50%
Statins*	10-30%
Ezetimibe	5-10%

*High potency statins and higher doses of statins result in greater triglyceride reduction. Patients with higher baseline triglyceride levels achieve greater reduction with the same statin dose.

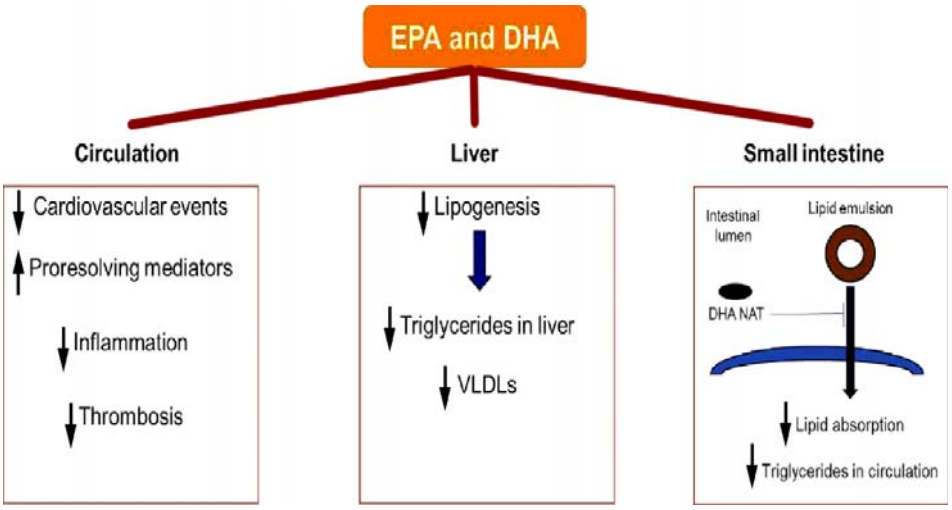


Fig 2 — Mechanisms for omega-3 fatty acid triglyceride-lowering effect

Clinical evidence of Omega-3 fatty acids in the treatment of hypertriglyceridemia :

Table 2 presents the different clinical trials demonstrating the effect of EPA and DHA on TG and other blood lipid parameters in patients with HTG.

Benefits of Omega-3-fatty acids in prevention of CVD : Clinical evidence

Large-scale epidemiological studies, clinical outcome trials, and meta-analyses have established the role of O3FAs in preventing atherosclerosis[8]. Table 3 presents the clinical trials demonstrating the effect of O3FAs in the prevention of CVD.

Other beneficial effects of Omega-3-fatty acids :

A high intake of O3FA has been associated with cardiovascular protective effects, improving endothelial function and reducing atherosclerosis through their beneficial effects on BP, lipid profile, platelet aggregation, and anti-inflammatory properties. Various epidemiological and clinical studies suggest that consumption of O3FA can reduce BP in hypertensive subjects and patients with other CV risk factors, such as hyperlipidemia or in patients treated with hemodialysis (Table 4)[20]. It has been demonstrated that Atypical antipsychotics (AAPs) frequently lead to marked elevation of serum triglyceride levels with modest alterations in other lipid profiles.

Table 2 — Clinical trials demonstrating the effect of EPA and DHA on TG levels and other lipid parameters

Study	Patient characteristics	Study design	No. of patients	Treatment Duration (week)	Treatment groups	Results
Harris W S, et al.1997[14]	Severe HTG patients (500 and 2000 mg/dL)	Parallel	42	16	O3AEE (4g/d) vs. placebo	O3FA significantly reduced mean TG concentrations by **45%,** cholesterol by **15%**, VLDLC by **32%** and cholesterol: HDL-C ratio by **20%,** and increased HDL-C by **13%** and LDL-C by **31%.**The placebo did not affect these parameters. O3FA was well tolerated, and no patient discontinued medication because of side effects.
COMBOS STUDY (COMBination of prescription Omega-3 with Simvastatin)[15]	HTG patients (TG levels ≥200 and < 500 mg/dL)	multicenter, randomized, double-blind, placebo-controlled, parallel-group study	256	8	O3FA 4 g/d* + simvastatin 40 mg/d vs. Placebo + simvastatin	The combination of O3FA + simvastatin, as compared to monotherapy with statin, showed significantly greater reduction in non-HDL-C (-9.0% vs -2.2%), TG (29.5% vs 6.3%) and VLDL-C (27.5% vs 7.2%), total cholesterol: HDL-C ratio (9.6% vs 0.7%), a significant increase in HDL-C levels (3.4% vs -1.2%). There was no significant difference in the frequency of AEs between groups. Drug-related serious AEs were not found.
Roth EM, et al. 2009[16]	HTG patients (≥500 mg/dL)	Randomized, 8-week, double-blind, placebo-controlled followed by open-label, 8-week extension study	163	16	OMFAs (4 g QD) + fenofibrate 130 mg QD vs. fenofibrate 130 mg QD + placebo	TG levels were reduced to a greater extent than monotherapy with fenofibrate alone (**7% decrease**). With combination therapy, LDL-C levels were increased to a greater extent (**9% increase**). When subjects who had received 8 weeks of fenofibrate monotherapy were treated with O3FAs during the 8-week, open-label extension study, TG levels were reduced by an additional **17.5%.**These results indicate that the addition of omega-3 fatty acids to fenofibrate will further decrease TG levels.
Shearer GC, et al. 2012[17]	Metabolic syndrome patients	Randomized controlled trial	60	16	O3AEE (4g/d) + extended-release niacin (2g/d) vs. individual drugs and placebo	In the niacin group TGs were decreased by 30%, in the O3FAs group by 22%, and in the **combination group by 42%**compared to the placebo group.

*Each 1-g capsule of omega-3 fatty acids contains eicosapentaenoic acid (EPA) 465 mg and docosahexaenoic acid (DHA) 375 mg.

Table 3 — *Clinical trials demonstrating the effect of O3FAs in the prevention of CVD*

Study	Patient characteristics	Study design	No. of patients	Treatment groups	Follow-up (Years)	Results
REDUCE-IT study[18]	Patients at high risk for CV events due to elevated TG levels (135-499 mg/dL) and with established CVD or DM +aged ≥50 years + ≥1 risk factor for CVD, well-controlled LDL-C (40-100 mg/dL) and on statin therapy	Multicenter, randomized, double-blind, placebo-controlled trial	8179	2 g of icosapent ethyl BID vs. placebo.	4.9	Icosapent Ethyl as compared to placebo demonstrated an: • **25% reduction** in risk of development of composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or unstable angina • **26% reduction** in risk of development of composite of CV death, non-fatal MI, or non-fatal stroke.
GISSI-P[19]	Patients who have suffered from MI within 3 months	Multicenter, open-label	11,324	O3FA (1 g daily) vs. vitamin E (300 mg daily) vs. both or none	3.5	O3FA but not vitamin E demonstrated an • **10% reduction**in risk of developing composite of death, non-fatal myocardial infarction, and stroke. • **14% reduction**in risk of death • **17% reduction**in risk of CV death.

Antipsychotic-induced dyslipidemia further increases the risk of developing metabolic complications and CVD. Despite its burden, antipsychotic-induced dyslipidemia is often left untreated. O3FAs supplementation reduces TG levels with minimal side effects, making it an excellent candidate for use in psychiatric patients. O3FA have been uniformly reported to lower TG levels in antipsychotic medications-induced hypertri-glyceridemia patients (Table 4)[21-23].

Safety information :

O3FA have shown safe and relatively mild side-effect profiles. Omega-3 fatty acids (O3FA) have been found to have a safe and relatively mild side effect profile. Some of the most commonly reported adverse reactions (with an incidence of over 3% and higher than placebo) include constipation, gastrointestinal disorders, vomiting, increased ALT and AST levels, pruritus, and rash. It is important to note that long-term use of O3FA supplements, particularly at higher dosages, may increase the risk of atrial fibrillation. Additionally, O3FA supplementation may also prolong bleeding time. Therefore, patients who take O3FA along with anticoagulants or other drugs that affect coagulation, such as antiplatelet agents, should receive periodic monitoring. O3FA supplementation of up to 1 g/day is generally well-tolerated and does not increase bleeding time, except for occasional dysgeusia[27-29].

Table 4 — *Clinical evidence demonstrating the other beneficial effect of EPA and DHA*

Study	Patient characteristics	Study design	No. of patients	Treatment groups	Duration	Results
Guo XF, et al. 2018[24]	Four studies were performed in healthy subjects, while the rest of the studies were conducted in subjects with dyslipidemia or diabetes mellitus	Meta-analysis of RCTs	20 RCTs were included	EPA and DHA monotherapy	-	**First meta-analysis evaluating the effects of EPA/DHA as monotherapy on blood pressure and inflammatory markers.** EPA intervention significantly reduced systolic BP (-2.6 mmHg), especially in subjects with dyslipidemia (-3.8 mmHg). Supplemental DHA significantly reduced diastolic BP in subjects with dyslipidemia (-3.1 mmHg). Both EPA (-0.56 mg/L) and DHA (-0.5 mg/L) significantly reduced the concentrations of C-reactive protein (CRP), respectively, especially in subjects with dyslipidemia and higher baseline CRP concentrations. **EPA and DHA have independent (BP) and shared (CRP concentration) effects on risk factors of chronic diseases.**
Naini AE, et al. 2015[25]	Continuous ambulatory peritoneal dialysis (CAPD) patients	Randomized double-blind clinical trial		O3FA 3g/d vs. placebo	8 weeks	O3FA showed a **reduction in mean systolic BP** (–22.2 ± 14.2 mmHg) while the systolic BP was increased in the placebo group increased (+0.5 ± 30.2 mmHg) ($P < 0.0001$). O3FA showed **greater reduction in mean diastolic BP** (–11.95 ± 11.9 mmHg) as compared to placebo group (–1.1 ± 17.3 mmHg) ($P = 0.001$) **O3FA significantly reduced BP in CAPD patients.**
XU F, et al. 2018[26]	Schizophrenia patients with metabolic syndrome (MetS) who received long-term olanzapine monotherapy	Randomized placebo-controlled trial	80	O3FA group received fish oil containing 720 mg of EPA and 480 mg of DHA vs. placebo group received 100 mg per day of vitamin E.	12-week	There was a significant correlation between O3FA and reduced TG levels. O3FA decreased TNF-alpha levels after 12 weeks of treatment. **O3FAs benefit TG metabolism in patients with olanzapine-induced MetS, paralleled by decreased inflammation levels.**

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