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EXPERT REVIEWS

Prescription omega-3 fatty acids and their lipid effects: physiologic mechanisms of action and clinical implications

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Hypertriglyceridemia is a risk factor for atherosclerotic coronary heart disease. Very high triglyceride (TG) levels (≥500 mg/dl [5.65 mmol/l]) increase the risk of pancreatitis. One therapeutic option to lower TG levels is omega-3 fatty acids, which are derived from the oil of fish and other seafood. The American Heart Association has acknowledged that fish oils may decrease dysrhythmias, decrease sudden death, decrease the rate of atherosclerosis and slightly lower blood pressure, and has recommended fish consumption or fish oil supplementation as a therapeutic strategy to reduce cardiovascular disease. A prescription omega-3-acid ethyl esters (P-OM3) preparation has been available in many European nations for at least a decade, and was approved by the US FDA in 2004 to reduce very high TG levels (≥500 mg/dl [5.65 mmol/l]). Mechanistically, most evidence suggests that omega-3 fatty acids reduce the synthesis and secretion of very-low-density lipoprotein (VLDL) particles, and increase TG removal from VLDL and chylomicron particles through the upregulation of enzymes, such as lipoprotein lipase. Omega-3 fatty acids differ mechanistically from other lipid-altering drugs, which helps to explain why therapies such as P-OM3 have complementary mechanisms of action and, thus, complementary lipid benefits when administered with statins. Additional human studies are needed to define more clearly the cellular and molecular basis for the TG-lowering effects of omega-3 fatty acids and their favorable cardiovascular effects, particularly in patients with hypertriglyceridemia.

KEYWORDS: docosahexaenoic acid • eicosapentaenoic acid • fish oils • hypertriglyceridemia • Lovaza™ • Omacor® • pancreatitis • prescription omega-3-acid ethyl esters • triglycerides

Hypertriglyceridemia, which is defined as a triglyceride (TG) blood concentration of 150 mg/dl or higher [1], is a common dyslipidemia encountered in clinical practice and occurs with or without elevated cholesterol levels. In the Framingham Offspring Study, 11.7% of women and 22.3% of men had TG levels that were higher than 200 mg/dl (2.26 mmol/l) [2]. The Third National Health and Nutrition Examination Survey (NHANES III) of 8814 adult Americans found that 25% of women and 35% of men had a TG level of 150 mg/dl or higher (≥1.69 mmol/l) [3]. The obesity epidemic [201], along with its metabolic consequences, is an important contributor to the rising prevalence of hypertriglyceridemia [4–7].

For patients with very high TG levels (≥500 mg/dl [5.65 mmol/l]), the initial therapeutic goal is to lower TG levels to prevent pancreatitis [1], which is a potentially life-threatening complication of severe hypertriglyceridemia [1,8,9]. The risk of pancreatitis is especially increased when TG levels are found to be above 1000 mg/dl (11.3 mmol/l) [10]. When TG levels are above 1000 mg/dl (11.3 mmol/l), this is usually the result of a secondary cause of hypertriglyceridemia occurring in individuals with one of the more common genetic hypertriglyceridemic disorders (BOX 1) such as familial hypertriglyceridemia and familial combined hyperlipidemia (FCH) [202], both of which occur in 3% or fewer of the population. Familial hypertriglyceridemia

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(hyperprebetalipoproteinemia) may possibly be due to the presence of a lipoprotein lipase (LPL) inhibitor that results in increased chylomicron and VLDL levels, and is clinically manifested by pancreatitis and eruptive xanthomas, especially when accompanied by secondary causes that exacerbate hypertriglyceridemia, such as hypothyroidism, uncontrolled diabetes mellitus or excessive alcohol intake with fatty liver [11]. FCH is probably due to a variety of apolipoprotein defects, which results in elevations in TG (with the same potential symptoms, as mentioned previously), but also with elevated cholesterol and apolipoprotein B-100 (apoB-100) levels [1,12]. HDL cholesterol (HDL-C) levels may be decreased, and LDL particles may be small and dense and, thus, potentially more atherogenic [13]. FCH is the most common form of nonpolygenic, heritable dyslipidemia, and is found in 10–20% of survivors of myocardial infarction [13] and approximately 20% of patients with coronary heart disease (CHD) under the age of 60 years [14]. Both familial hypertriglyceridemia and FCH may increase CHD risk [12].

Severe hypertriglyceridemia may also represent more rare, underlying genetic dyslipidemias, such as LPL deficiency [15] or homozygous apolipoprotein C-II (apoC-II) deficiency [16], which occur in approximately 1:1,000,000 people (Box 1). In both cases, diagnosis usually occurs during childhood or young adulthood, with the presentation of recurrent pancreatitis, eruptive cutaneous xanthomata, hepatosplenomegaly and lipemia retinalis. Untreated TG levels are usually found to be greater than 2000 mg/dl [1,201]. Both also result in a 'chylomicronemia syndrome', defined as elevated chylomicrons, marked increase in TG levels, and the clinical signs and symptoms described above.

While VLDL particles normally constitute approximately 90% of the TG-containing lipoproteins, and while levels of both VLDL and chylomicron-associated TG increase after meals [17,18], it is the profound increase in TG levels associated with chylomicrons (most often in patients with an underlying, inherent, genetic defect) that is most described to contribute to pancreatitis. Chylomicrons are TG-rich lipoprotein particles that predominantly carry postprandial/postabsorptive TG. Marked increases in chylomicrons are hypothesized to impair circulatory flow in pancreatic capillary beds, leading to ischemia-induced disruption in acinar structure and exposing the TG-rich particles to pancreatic lipase, leading to necrosis, edema and inflammation [19].

Therapeutic interventions to treat hypertriglyceridemia include increased physical exercise [20,21] and a low-calorie diet with reduced consumption of high-glycemic index carbohydrates and alcohol [22]. Other interventions, depending on the patient population, may include lipopheresis, heparinization and insulin [23–25]. Statins and ezetimibe are approved lipid-altering drugs that may modestly reduce TG levels. However, they are mainly used to lower LDL cholesterol (LDL-C) levels. Other lipid-altering agents that are used more specifically to reduce TG levels include niacin, fibrates and omega-3 fatty acids.

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain, polyunsaturated, omega-3 fatty acids that effectively lower TG levels (Table 1) [26–28]. EPA and DHA may be used as monotherapy, or as adjunctive therapy to fibrates and/or nicotinic acid to lower TGs to prevent pancreatitis in patients with very high TG levels [1]. Fish consumption and supplements are dietary sources of omega-3 fatty acids. A prescription combination of omega-3-acid ethyl esters (P-OM3; Lovaza™ Capsules, Reliant Pharmaceuticals, Inc.) is available that contains concentrated forms of EPA (~465 mg), DHA (~375 mg) and other omega-3 fatty acids (~60 mg), for a total of at least 900 mg of omega-3 fatty acids per each 1-g gel capsule. P-OM3 is approved by the US FDA for the treatment of very high TGs (≥500 mg/dl [5.65 mmol/l]) in adult patients. This review examines the pathophysiology of hypertriglyceridemia and possible mechanisms for the TG-lowering effect of omega-3 fatty acids.

Box 1. Examples of factors contributing to hypertriglyceridemia.

Primary

- Familial hypertriglyceridemia (hyperprebetalipoproteinemia)
- Familial combined hyperlipidemia
- Lipoprotein lipase deficiency
- Apolipoprotein CII deficiency
- Familial dysbetalipoproteinemia

Secondary

- Adipocyte hypertrophy and/or visceral adipose tissue accumulation (adiposopathy)
- A positive energy-balance diet with a high fat or high glycemic index content
- Acute alcohol consumption with fatty liver
- Diabetes mellitus
- Hypothyroidism
- Nephrotic syndrome

Medications

- Antiretroviral regimens, especially for HIV disease
- Psychotropic medications, such as some phenothiazines and second-generation antipsychotics
- Bile acid sequestrants
- Non-selective β-blockers, thiazide diuretics
- Cyclophosphamide
- Oral estrogens
- Glucocorticosteroids
- Tamoxifen
- Isotretinoin

Pathophysiology of hypertriglyceridemia

Lipoproteins serve to transport varying types and varying amounts of lipids in the circulation, including TG, cholesterol and phospholipids (Table 2) [29]. The TGs found in lipoproteins are derived from dietary consumption, intestinal secretion and hepatic production [29]. The term 'triglyceride-rich lipoproteins' (TRLs) most often refers to chylomicrons, VLDL and their remnants. Intermediate-density lipoproteins (IDLs) are often considered to represent VLDL remnants (Table 2) [30,31].

Chylomicron particles deliver lipids derived from dietary fat consumption and intestinal absorption to peripheral and hepatic tissues. VLDL particles transport lipids from the liver to peripheral tissues [29,31]. The enzyme LPL, located on the endothelial side of capillaries within fat and muscle tissue, hydrolyzes TG from both chylomicrons and VLDL into free fatty acids, resulting in the formation of chylomicron and VLDL remnants, respectively [29,31]. These remnants may be atherogenic [32,33]. Mutations in the *LPL* gene may impair lipolysis from these TRL and significantly increase TG levels; such mutations have been identified in patients with hypertriglyceridemia-induced pancreatitis [34,35].

Hyperchylomicronemia may occur due to rare genetic defects, resulting in postprandial hypertriglyceridemia, as has already been described. VLDL excess may also be due to genetic defects (Box 1). Beyond rare genetic defects, overproduction of VLDL may have varying etiologies resulting in fasting hypertriglyceridemia. For example, adipose tissue is the major energy storage organ of the body, with calories predominantly stored in the form of TG. During times of positive caloric balance, adipocytes may become excessively enlarged and visceral adiposity may accumulate, resulting in pathologic adipocyte and adipose tissue dysfunction. Physiologically, this adiposopathy results in adverse metabolic and immune consequences resulting in the onset or worsening of clinical metabolic diseases, such as Type 2 diabetes mellitus, hypertension and dyslipidemia (Figure 1) [36,37]. Thus, clinically, excessive and pathogenic adipocyte hypertrophy and an increase in visceral adipose tissue (central obesity) are often associated with hyperglycemia, high blood pressure and hypertriglyceridemia (and low HDL-C levels), which represents a clustering of atherogenic risk factors often described as representing a 'metabolic syndrome' [1].

One of the metabolic manifestations of adiposopathy is a relative increase of intra-adipocyte lipolysis over that of intra-adipocyte lipogenesis, leading to a net release of free fatty acids that may be 'lipotoxic' to body organs [37]. In addition to contributing to the before-mentioned metabolic diseases, increased circulating free fatty acids may also contribute to hepatic steatosis [38,39], which is a common clinical finding among patients with the components of the metabolic syndrome.

With specific regard to TGs, the increase in free fatty acid delivery to the liver increases TG synthesis [40], which can lead to VLDL overproduction [41]. Increased VLDL production is exacerbated if hepatic free fatty acid β-oxidation (metabolism) is impaired (e.g., through genetic limitations or with insulin resistance), thereby leaving more substrate for VLDL synthesis. Nonetheless, it is unknown if the increase in the hepatic cytoplasmic TG pool is truly rate-limiting for VLDL-TG or apoB-100 production [41]. However, once hepatocyte TGs are packaged into VLDL particles, they are then secreted into the circulation [42]. Fasting hypertriglyceridemia ensues, which may also be exacerbated if LPL-mediated lipolysis is impaired and/or the removal of remnant VLDL particles is delayed [43].

In summary, severe hypertriglyceridemia occurs with increased chylomicrons, VLDL particles and/or their remnants, with causality and promotion being due to primary and secondary factors [44,45]. Primary causes include genetic defects (Box 1) [15,16,46–51], while common secondary contributors that may cause or exacerbate hypertriglyceridemia include pathogenic adipose tissue (visceral adiposity and adipocyte hypertrophy), excessive and acute consumption of alcohol, consumption of high-glycemic index carbohydrates [29,52], hyperglycemia, hypothyroidism and nephrotic syndrome.

Table 1. Pharmacotherapy effect of lipid-altering drugs on triglycerides, LDL-C and HDL-C levels.

Lipid-altering agent	Change in triglycerides (%)	Change in LDL-C (%)	Change in HDL-C (%)
Omega-3 fatty acids (EPA/DHA)	↓20–50	↑/no change	↑/no change
Nicotinic acid (niacin)	↓20–50	↓5–25	↑ 15–35
Fibric acids (fibrates)	↓20–50	↑/↓0–20*	↑6–20
Statins	↓ 7–40	↓18–60	↑ 3–15
Bile acid sequestrants (resins)	↑/no change	↓10–30	↑ 3–5
Ezetimibe	↓ 4–11	↓17–22	↑ 2–5

*Fibrates may increase LDL-C levels in some patients with hypertriglyceridemia.
↑: Increase; ↓: Decrease; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; HDL-C: HDL cholesterol; LDL-C: LDL cholesterol.
Adapted from [27,28].

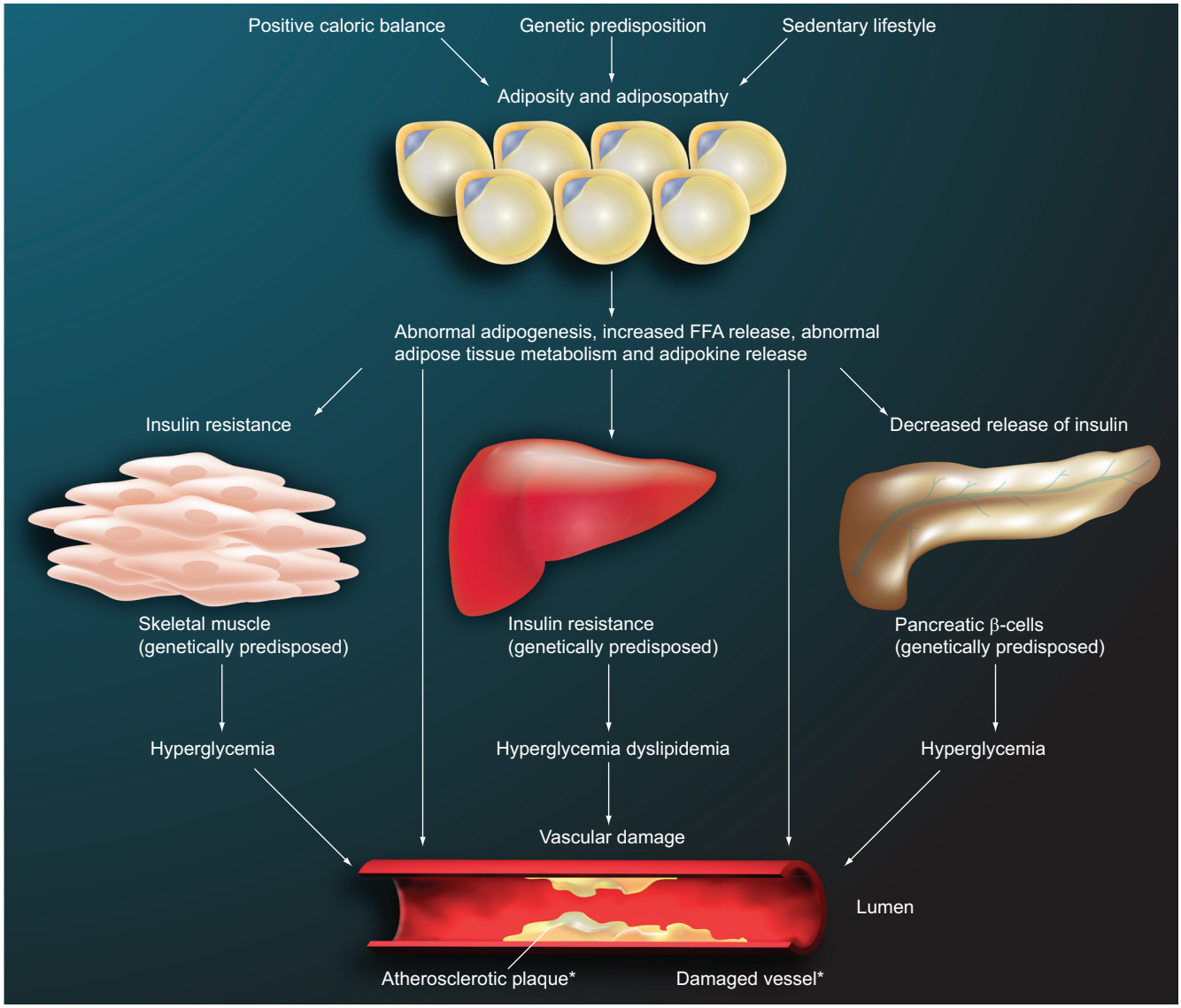

Figure 1. Relationship between adiposopathy (pathogenic adipose tissue) and metabolic disease. Increased circulating FFAs may be lipotoxic to muscle, liver and pancreas. When adipocytes become excessively enlarged, especially in the setting of visceral adiposity, adipocyte and adipose tissue dysfunction (i.e., 'adiposopathy') may result in adverse metabolic consequences. One of the manifestations of adiposopathy is a relative increase of intra-adipocyte lipolysis over that of intra-adipocyte lipogenesis, leading to a net release of FFAs, insulin resistance and diminished pancreatic insulin secretion, all leading to hyperglycemia and possible diabetes mellitus, as well as other metabolic diseases. Steatosis, or 'fatty liver', is another consequence of increased FFA delivery to the liver.
FFA: Free faty acid.
Adapted with permission from Future Medicine Ltd [7].

Lipid atherosclerotic risk factors & mechanisms of the potential atherogenicity of hypertriglyceridemia

Hypertriglyceridemia is a risk factor for CHD, particularly in women [53], although it is unclear if hypertriglyceridemia is always an independent risk factor [54,55]. What does seem clear is that when hypertriglyceridemia is combined with elevated total and LDL-C levels, then CHD risk is amplified [56,57]. The increased CHD risk with combined hyperlipidemia may be due to several mechanisms, many of which may or may not be independent of one another.

Increased non-HDL-C levels

VLDL and its remnants carry cholesterol and, thus, constitute a component of non-HDL-C. Non-HDL-C is the sum of cholesterol carried by atherogenic lipoproteins (e.g., LDL, VLDL, IDL, lipoprotein (a) and lipoprotein remnants), and is thought to be a better predictor of CHD risk than LDL-C levels alone [58–60]. Mechanistically, an increase in atherogenic lipoprotein levels enhances cholesterol delivery to endothelial plaques, promotes atherosclerotic progression, and increases the risk of plaque rupture resulting in an increased risk of a CHD event.

Table 2. Physical–chemical characteristics of lipoproteins.

Lipoprotein	Density (g/ml)	Lipid (%)*		
		Triglyceride	*Cholesterol*	*Phospholipid*
Chylomicrons	0.95	80–95	2–7	3–9
VLDL	0.95–1.006	55–80	5–15	10–20
IDL	1.006–1.019	20–50	20–40	15–25
LDL	1.019–1.063	5–15	40–50	20–25
HDL	1.063–1.21	5–10	15–25	20–30

*Percentage composition of lipids; apolipoproteins make up the rest.
IDL: Intermediate-density lipoprotein; VLDL: Very-low-density lipoprotein.
Adapted with permission from [188].

Increased apolipoprotein B-100 (apoB-100) levels

Another marker that is thought to be a better predictor of CHD risk than LDL-C levels alone is a measurement of apoB-100 [58]. Each LDL, VLDL and IDL particle contains one apoB-100 molecule. Thus, apoB-100 reflects the number of circulating atherogenic lipoproteins, and this may account for why this measurement is a strong predictor of CHD risk [61]. Increased TRL through increased VLDL particles and their remnants increases apoB-100 levels and, thus, may increase CHD risk.

Increased small, dense LDL particles

Elevated TG levels are often associated with, and may contribute to, small, dense LDL particles. The generation of small, dense LDL particles often results from an interplay of various enzymes, including LPL, hepatic lipase and cholesteryl ester transfer protein [62]. Although all LDL particles are considered atherogenic, small, dense LDL particles may be more atherogenic than larger LDL particles. As with hypertriglyceridemia, not all analyses support that LDL particle size is an independent predictor of CHD [63]. However, if small, dense LDL particles are more atherogenic, then this is likely because they may be more able to penetrate arterial walls and have less resistance to oxidative stress. Small, dense LDL particles may also be associated with increased thrombosis, which may increase CHD events.

Decreased HDL-C levels

High TG levels are often associated with, and may contribute to, low HDL-C levels [1]. High HDL-C levels are generally associated with decreased CHD risk. Conversely, lower HDL-C levels may be associated with increased CHD risk [1]. Mechanistically, if lower HDL-C levels are directly associated with increased CHD risk, it is likely due to decreased flux of cholesterol from atherosclerotic plaques, or possibly due to other effects, such as a reduced anti-inflammatory response otherwise attributable to HDL particles.

Post- & preprandial hyperlipidemia & TRL remnant formation

Postprandial hypertriglyceridemia may be an independent risk factor for CHD, which suggests that chylomicrons (even though they contain apoB-48, not apoB-100) and their remnants may

Table 3. Clinical studies of 4 g/day prescription omega-3-acid ethyl esters for the treatment of patients with severe hypertriglyceridemia.

Study	Patients (n)	Duration (weeks)	Baseline TG; mg/dl (mmol/l)	Change from baseline (%)			Ref.
				TG	*LDL-C*	*HDL-C*	
Harris *et al.*	42	16	926 (10.4)	-45	+31	+13	[79]
McKeone *et al.*	40	6	500–2000 (5.6–22.6)	-26	No data	+14	[189]
Abe *et al.*	27	>28	876 (9.8)	-47	No data	NS	[190]
Pownall *et al.*	40	6	801 (9.0)	-39	+17	NS	[191]
Westphal *et al.*	12	6	1210 (13.6)	-40	+46	NS	[192]
Stalenhoef *et al.*	28	12	872 (9.8)	-37	+30	+11	[193]

HDL-C: HDL cholesterol; LDL-C: LDL cholesterol; NS: Not significant; TG: Triglyceride.
Adapted from [85].

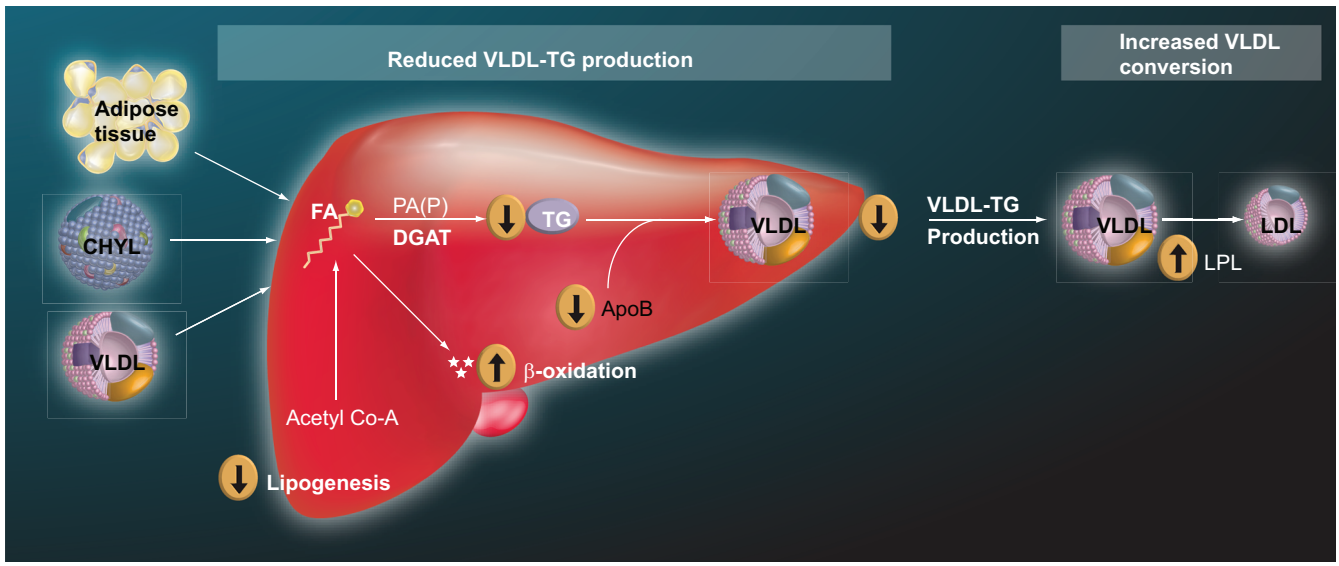

Figure 2. Potential TG-lowering mechanisms of eicosapentaenoic acid and docosahexaenoic acid. Pathogenic adipose tissue, increased postprandial CHYL and increased VLDL particles may increase free FA delivery to the liver, and increase hepatic lipid content, which are substrates for TG synthesis and, thus, VLDL production. Most evidence supports that omega-3 fatty acids inhibit hepatic TG synthesis, decrease VLDL production/secretion and increase VLDL metabolism by: decreasing lipogenesis by decreasing the enzymatic conversion of acetyl CoA to FAs; increasing β-oxidation of FA; inhibiting both PAP (an enzyme that catalyzes that reaction of converting PA to DAG) and DGAT (an enzyme that catalyzes the final step in TG synthesis); potentially increasing the degradation of apolipoprotein B; and increasing LPL activity, which is an enzyme that increases the conversion of VLDL particles to LDL particles.
CHYL: Chylomicrons; DAG: diacylglycerol; DGAT: Diacylglycerol acyltransferase; FA: Fatty acid; LPL: Lipoprotein lipase; PA: Phosphatidic acid; PAP: phosphatidic acid phosphatase/phosphohydrolase; TG: Triglyceride; VLDL: Very low-density lipoprotein.
Adapted from [98].

be atherogenic [64–68]. If true, then an increase in atherogenicity through this mechanism may have practical consequences for clinicians and their patients. For example, patients may sometimes believe that as long as their fasting lipid levels are well-controlled with lipid-altering drug therapy (e.g., statins), then food choices and diet composition no longer affect their CHD risk. But if postprandial lipemia does contribute to atherosclerosis, then it is possible that even with lipid-altering drug administration, poor dietary habits may still increase CHD risk.

Similarly, preprandial increases in TRL remnants may also increase CHD risk, with some studies suggesting that VLDL remnants, or IDL, are strong and independent risk factors for atherosclerotic progression [69]. Animal studies have suggested that the generation of very large TRLs may not necessarily be atherogenic because they are unable to penetrate arterial endothelia [70]. However, when apoB-48-containing chylomicrons and apoB-100-containing VLDL particles undergo circulatory metabolism by lipoprotein lipase, then TRL remnants may be generated, resulting in smaller, more dense particles that are relatively depleted of TG, phospholipid and apoC, and enriched in cholesteryl esters and apoE [32]. TRL remnants may promote atherogenesis through impairment of endothelium-dependent vasorelaxation, enhancement of platelet aggregation and subendothelial macrophage uptake resulting in foam cell formation.

Increased potential for thrombosis

Elevated (postprandial) TG levels may unfavorably affect the coagulation system, increasing plasminogen activator inhibitor-1, an inhibitor of fibrolysis. Factor VII may also be increased, which may also increase the risk of thrombosis [71]. An increase in the risk of thrombosis increases the risk of CHD events.

Increased apolipoprotein C-III (apoC-III) levels

ApoC-III, an apolipoprotein found on chylomicron, VLDL, IDL and HDL particles, inhibits LPL activity. An elevated apoC-III level may be associated with increased CHD risk [72]. This is most likely because it reflects the concentration of TRL. ApoC-III may also directly activate vascular endothelial cells, which promotes inflammatory cell adhesion and recruitment [73] and, thus, may directly contribute to the inflammatory process of atherosclerosis.

Biochemistry & nutritional aspects of omega-3 fatty acids

Omega-3 fatty acids are polyunsaturated fats in which the first double bond counting from the terminal (omega) methyl group is at carbon 3 [74]. Major omega-3 fatty acids include α-linolenic acid (ALA [18:3N-3]), EPA (20:5N-3) and DHA (22:6N-3) [75,76]. In general, fatty acids are of varying sizes, which affects function. Short chain fatty acids usually have less

than six carbons. An example would be butyric acid, which is a four-carbon fatty acid found in butterfat. Medium chain fatty acids usually have six to 12 carbons. An example would be lauric acid, a 12-carbon fatty acid that is the main component of coconut oil. ALA, EPA and DHA are all considered long-chain fatty acids because each have 12 carbons or more.

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 omega-3 fatty acid that can be converted to EPA and DHA in mammals [76]. However, the conversion of ALA to EPA is modest (<1%) and the subsequent conversion of EPA to DHA is also very low [76]. Thus, while not necessarily essential fatty acids, preformed EPA and DHA are best obtained through dietary sources.

The best dietary sources of EPA and DHA include fatty or oily marine seafood, such as salmon, herring, mackerel, halibut and tuna [77]. Some fresh-water fish may contain significant amounts of omega-3 fatty acids, and include lake herring, lake trout, fresh-water salmon and whitefish [203]. The omega-3 fatty acid content of these fish may be increased with farming [77]. Some concerns have been raised about the environmental impact and residual pesticide and antibiotic content of selected types of fish [204]. However, the risks from contaminants potentially contained in oily fish consumption may be outweighed by the potential benefits [78]. The American Heart Association (AHA) has acknowledged that EPA and DHA may decrease dysrhythmias, decrease sudden death, decrease the rate of atherosclerosis and slightly lower blood pressure, and has recommended fish consumption or fish oil supplementation as a therapeutic strategy to reduce cardiovascular disease [77]. While reducing TG levels may have cardiovascular benefits, it is unclear as to how much (if any) of these before-mentioned benefits are related to omega-3 fatty acid's TG-lowering effects and how much is due to TG-independent effects.

P-OM3 triglyceride-lowering effects & potential adverse experiences

Omega-3 fatty acids reduce TG levels in humans [79–81]. The amount of EPA and DHA typically administered for the treatment of hypertriglyceridemia is 2–4 g/day [77]. EPA and DHA have similar TG-lowering effects [82], and lower both fasting [83,84] and postprandial [82,83] TG levels. P-OM3 (4 g/day for ≥6 weeks) significantly reduces TG levels in subjects with severe hypertriglyceridemia (Table 3) [85]. While ALA is an omega-3 fatty acid, it does not significantly reduce TG levels at typically administered doses [86,87].

P-OM3 may reduce TG levels more effectively than fish oil formulations containing less omega-3 fatty acids, and may have greater bioavailability [88]. Owing to the requirements in achieving a prescription status, P-OM3 has undergone more rigorous safety and efficacy evaluation and verification than dietary supplement omega-3 fatty acids [89–91]. Selected dietary supplement omega-3 fatty acids do not appear to contain contaminants in sufficient concentrations to pose a potential health risk [89]. However, individual supplements vary considerably in the amount of their omega-3 fatty acid content. P-OM3 has undergone the processes necessary to achieve FDA approval, verifying its consistent omega-3 fatty acid content [90].

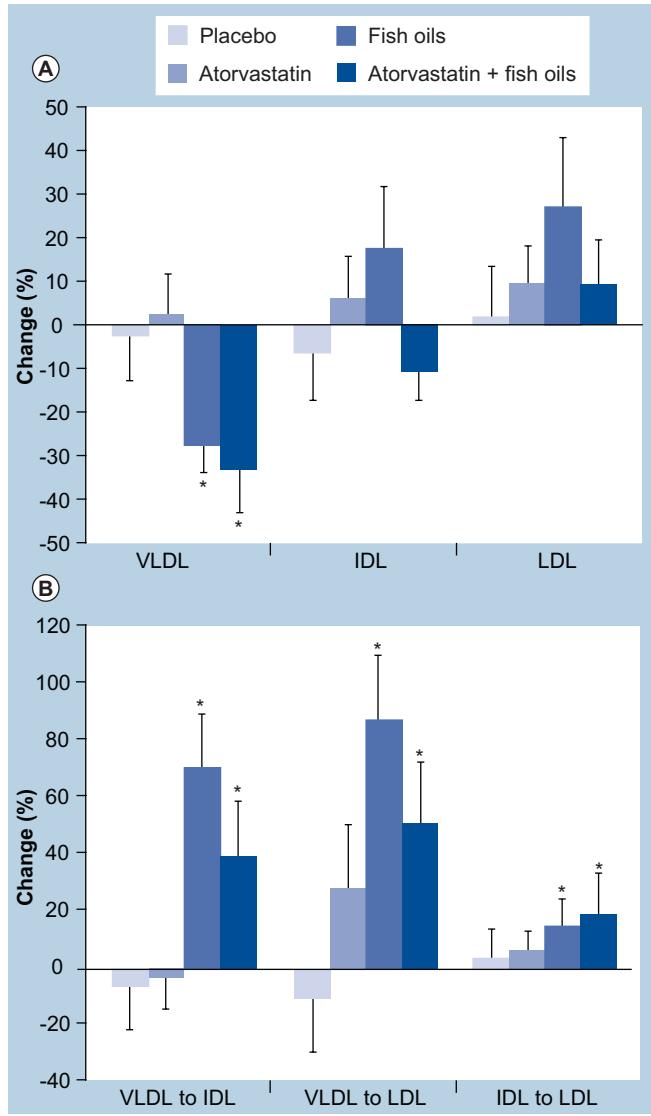

Figure 3. Effects of statins, fish oils and their combination on lipoprotein secretion rate (not lipid levels) and conversion.
P-OM3 and atorvastatin lower triglyceride levels by different mechanisms. **(A)** Percentage change in the secretion rate of apoB-containing lipoproteins into the plasma. **(B)** Percentage change in the interconversion of apoB-containing lipoproteins. P-OM3, alone or in combination with atorvastatin, increased conversion of TG-rich lipoproteins to LDL.
*$p < 0.01$ compared with placebo group.
IDL: Intermediate-density lipoprotein; P-OM3: Prescription omega-3-acid ethyl esters; VLDL: Very-low-density lipoprotein.
Reproduced from [118].

The most common drug-related adverse experiences attributable to P-OM3 include a mild, numerical increase in eructations (belching) and dyspepsia [92], which are substantially

Table 4. Effects of prescription omega-3-acid ethyl esters plus simvastatin on lipid and lipoprotein parameters compared with simvastatin alone.

Parameter	BL	EOT	Median change (%)	BL	EOT	Median change (%)	p-value
	P-OM3 + simvastatin (n = 122)			*Placebo + simvastatin (n = 132)*			
Non-HDL-C	137	123	-9.0	141	134	-2.2	<0.0001
TG	268	182	-29.5	271	260	-6.3	<0.0001
VLDL-C	52	37	-27.5	52	49	-7.2	<0.05
ApoB	86	80	-4.2	87	85	-1.9	<0.05
HDL-C	46	48	+3.4	43	44	-1.2	<0.05
LDL-C	91	88	+0.7	88	85	-2.8	0.05

ApoB: Apolipoprotein B-100; BL: Baseline (mg/dl); EOT: End of treatment (mg/dl); HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; Median change (%): Median percent change from baseline; P-OM3: Prescription omega-3-acid ethyl esters; TG: Triglycerides; VLDL: Very-low-density lipoprotein cholesterol.
Adapted from [92].

mitigated by the purification process used for P-OM3 [89]. P-OM3 does not have any known, clinically significant drug interactions. Some reports have suggested that omega-3 fatty acids may impair platelet aggregation and increase bleeding times [93,94]. Clinical trial data suggest that P-OM3 does not increase clinical bleeding, even in patients receiving warfarin anticoagulants, aspirin and other older antiplatelet agents [89,95,96]. P-OM3 has also been described to sometimes increase levels of liver transaminases, such as alanine aminotransferase. Thus, alanine aminotransferase levels should be monitored periodically during P-OM3 therapy [92]. Finally, studies of omega-3 fatty acids, including P-OM3, have often reported a transient increase in glucose levels, but not increases in measures of long-term glucose control, such as fructosamine or hemoglobin A1C [27].

Omega-3 fatty acids: TG-lowering mechanisms

As discussed above, omega-3 fatty acids are well-known to reduce TG blood levels. However, the mechanisms by which EPA and DHA reduce serum TGs are not well-known or completely understood. Simply put, preclinical and clinical studies provide compelling evidence that EPA and DHA can reduce hepatic VLDL-TG synthesis/secretion and enhances TG clearance from circulating VLDL particles (Figure 2) [97]. Regarding hyperchylomicronemia, both EPA and DHA may equally accelerate chylomicron TG clearance by promoting increased lipoprotein lipase activity [82].

Reduced VLDL-TG synthesis by omega-3 fatty acids

Several mechanisms have been proposed as to how omega-3 fatty acids may reduce TG synthesis, reduce the incorporation of TG into VLDL particles, and ultimately reduce TG secretion. Omega-3 fatty acids may decrease hepatic lipogenesis, increase β-oxidation of fatty acids, and increase degradation of apoB-100 [97,98].

Decreased hepatic lipogenesis through a decreased enzymatic conversion of acetyl CoA to fatty acids

Peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element-binding proteins (SREBPs) are transcription factors that play a major role in regulating lipid metabolism. The nuclear receptors liver X receptor (LXR)α and retinoid X receptor (RXR)α typically form a heterodimer that regulates expression of the *SREBP-1c* gene by binding to the *SREBP-1c* promoter [99]. SREBPs regulate the expression of cholesterol-, fatty-acid-, and TG-synthesizing enzymes. Activation of the transcription factor SREBP-1c stimulates the synthesis of lipogenic enzymes such as acetyl-CoA carboxylase-1 (ACC1) and fatty-acid synthase (FAS) [100].

Fish-oil feeding in mice is associated with significant decreases in hepatic *SREBP-1c* mRNA expression and decreases in TG levels [101]. Fish oils may inhibit LXR/RXR heterodimer binding to the *SREBP-1c* gene promoter, thereby suppressing *SREBP-1c* mRNA expression [102] and, thus, decreasing lipogenic enzyme activity. DNA microarray analysis from rat livers indicates that *SREBP-1* gene expression is decreased with a DHA-enriched diet compared with low fat, high fat, or low fat plus fenofibrate diets [103]. Data from HepG2 human hepatoma cells support the notion that EPA decreases TG synthesis by suppressing the expression of *SREBP-1c* mRNA and SREBP-1c protein [104]. However, not all evidence entirely supports this proposed mechanism of TG-lowering by omega-3 fatty acids, in that rat studies suggest that EPA-induced suppression of SREBP-1c may be independent of LXRα [105].

Increased β-oxidation of fatty acids

Fatty acids, which are substrates for TG synthesis, are degraded by the β-oxidation pathway. An increased rate of hepatic fatty acid oxidation can decrease the amount of fatty acids available for TG synthesis and decrease the amount of TG available for incorporation into VLDL particles. Rat studies show that EPA and/or DHA increase free fatty acid β-oxidation in peroxisomes

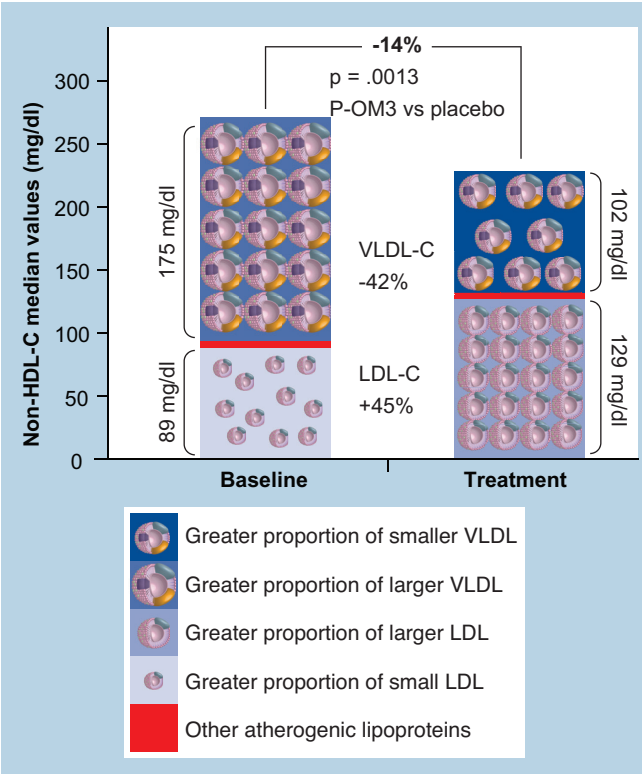

Figure 4. Effect of P-OM3 on non-HDL-C in patients with triglycerides of 500 mg/dl. Non-HDL-C is reduced in many P-OM3 trials, concomitantly with an apparent paradoxical increase in LDL-C levels. This can be explained by P-OM3's increased conversion of VLDL to LDL particles. Thus, in this case, P-OM3 resulted in a decrease in VLDL-C levels and decrease in VLDL particle size, and an increase in LDL-C levels and increase in LDL particle size, with a net decrease in the total cholesterol carried by atherogenic lipoproteins, as represented by non-HDL-C.
HDL-C: HDL cholesterol; LDL-C: LDL cholesterol; P-OM3: Prescription omega-3-acid ethyl esters; VLDL: Very-low-density lipoprotein.
Reproduced from [92].

and mitochondria [98], leaving less substrate available for TG and VLDL synthesis. Evaluation of healthy human subjects taking 9 g of omega-3 fatty acids containing 5.4 g EPA and 3.6 g DHA per day [106] also supports a faster rate of hepatic fatty acid oxidation. EPA binds to all PPAR subtypes (PPAR-α, -β and -γ) [75], and PPAR-α may be involved in omega-3 fatty acid modulation of fatty acid β-oxidation. But, as before, not all evidence is supportive of this mechanism, in that other studies in rats [98,103] and monkeys [107] have shown that EPA and/or DHA had no significant effect on β-oxidation.

Inhibition of phosphatidic acid phosphatase/phosphohydrolase & diacylglycerol acyltransferase

Phosphatidic acid phosphatase/phosphohydrolase (PAP) is an enzyme that catalyzes the conversion of phosphatidic acid to diacylglycerol. Diacylglycerol acyltransferase (DGAT) is an enzyme that catalyzes the final step in TG synthesis. Both are key enzymes involved in TG synthesis in the liver. Results from preclinical studies are divided with regard to the effect of EPA and DHA on PAP and DGAT activity. Some studies show that EPA and DHA inhibit the activity of PAP and DGAT in rat liver microsomes; other studies show no such effect [98]. Thus, the extent to which the TG-lowering effects of EPA and DHA depend on the inhibition of PAP and/or DGAT activity is unclear.

Enhanced TG clearance by omega-3 fatty acids

Omega-3 fatty acids may increase TG removal from circulating VLDL and chylomicron particles, through increased hydrolysis by LPL. Specifically, EPA and DHA may increase LPL activity, and, thus, increase LPL-mediated clearance of TRL [82,108]. EPA increases PPAR-γ mRNA in cultured adipocytes [109], and PPAR-γ mRNA levels in adipose tissue of obese subjects may be positively correlated with plasma EPA concentrations [109]. Agonism of the transcription factor PPAR-γ may increase LPL activity in adipose tissue [110]. Therefore, it is plausible that an increased LPL activity associated with EPA and DHA treatment may be due, in part, to increased activity of PPAR-γ.

Additionally, DHA may be a ligand for the farnesoid X receptor (FXR) [111], which is a nuclear receptor found in the liver and intestine, and for which bile acids are a natural ligand. FXR may also play a role in lipid homeostasis. ApoC-III resides on the surface of VLDL and LDL particles and inhibits the activity of LPL, thereby slowing the clearance of TG-rich lipoproteins [112]. Conversely, apoC-II activates LPL [113]. FXR suppresses apoC-III gene expression [114] and induces apoC-II [115] and VLDL-receptor gene expression [116], all of which may contribute to the TG-lowering action of FXR agonists. Although speculative, FXR-induced changes in the expression of apoC-II, apoC-III, and/or VLDL-receptor gene may also play a role in LPL activity and the TG-lowering effect of DHA. Irrespective of the mechanism, omega-3 fatty acids increase TRL clearance, and decrease their circulating half-life [82].

Statins & P-OM3 reduce TG levels by different mechanisms

Coadministration of P-OM3 with statins improves the lipid profile in patients with hypertriglyceridemia to a greater extent than statin treatment alone [117–120]. Statins inhibit hydroxymethylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol biosynthesis. Inhibition of cholesterol synthesis leads to reduced hepatic cholesterol content, which in turn increases LDL receptor expression and activity and, thus, clears more LDL-C from the circulation. LDL-C levels are reduced. Upregulated LDL receptors may also increase clearance of other TG-containing lipoproteins, at least partially accounting for the modest TG-lowering effects of statins. The degree of TG lowering with P-OM3 is generally similar in statin-treated patients compared with nonstatin-treated patients because the mechanisms of actions of P-OM3 differ from that of statins [118]. Specifically, P-OM3 decreases the rate of VLDL secretion and

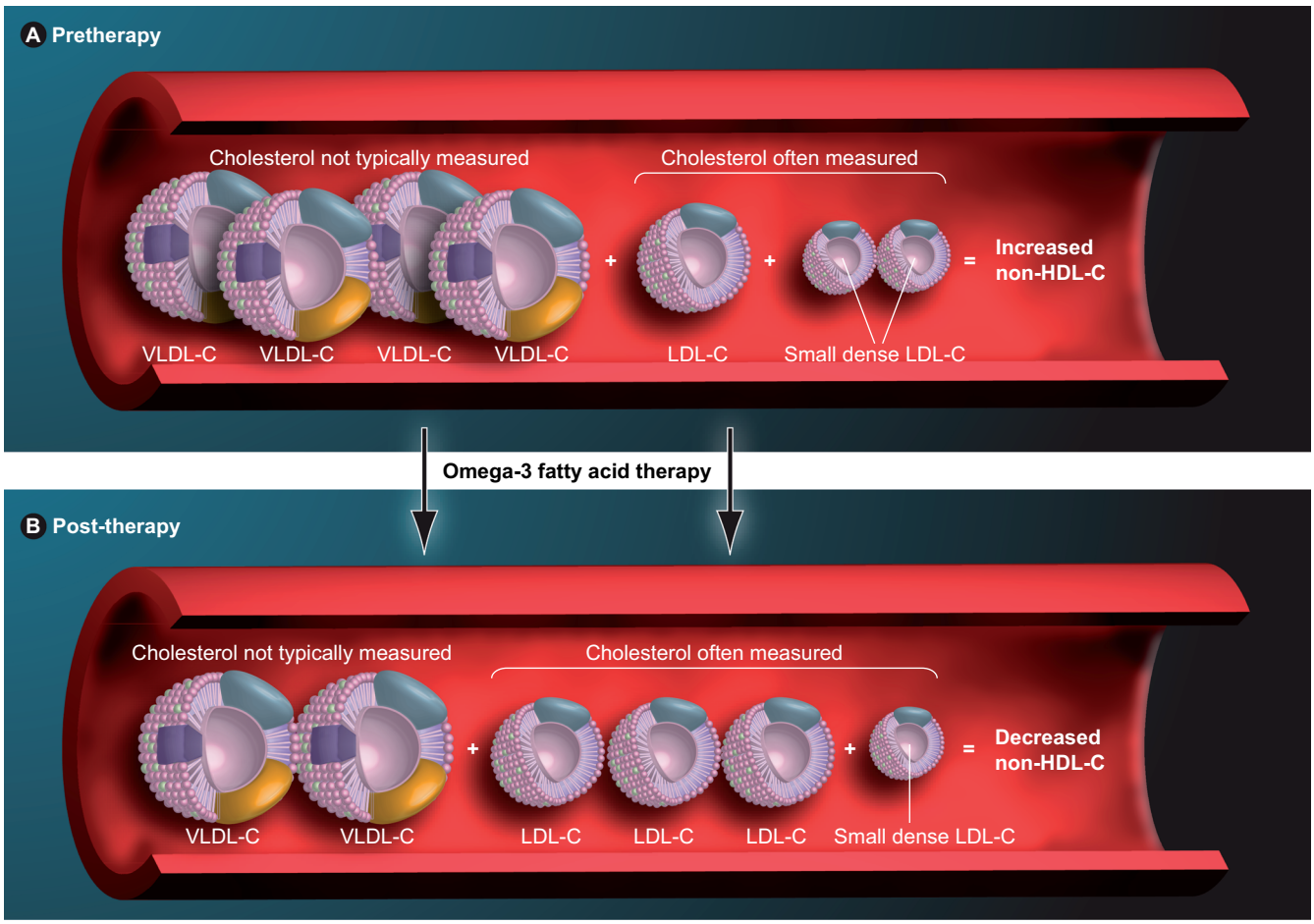

Figure 5. Revealing the underlying atherogenic potential of hypertriglyceridemia. Many patients with hypertriglyceridemia have increased cholesterol carried by atherogenic particles, which is best assessed by measuring non-HDL-C levels. VLDL particles are considered to be atherogenic. Omega-3 fatty acid therapy decreases the cholesterol carried by VLDL particles, and is a cholesterol effect not typically measured in clinical practice. Omega-3 fatty acids may also decrease VLDL particle size. Conversely, omega-3 fatty acids may increase LDL-C levels, which is a lipid parameter that is often measured in clinical practice. This is thought to be due to the increased conversion of VLDL particles to LDL particles. Finally, omega-3 fatty acids may increase LDL particle size, which may render them less atherogenic. Overall, despite a potential increase in LDL-C levels, many studies have reported that P-OM3 reduces non-HDL-C, which may be a better predictor of atherosclerotic coronary heart disease risk than LDL-C alone.
HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; P-OM3: Prescription omega-3-acid ethyl esters; VLDL: Very-low-density lipoprotein.

increases the conversion of VLDL to IDL and LDL (Figure 3), while statins decrease apoB-containing lipoproteins, such as VLDL, IDL and LDL [118].

In patients with persistent hypertriglyceridemia after achieving LDL-C treatment goals, as might occur after statin administration in combined hyperlipidemic patients, it is then recommended that non-HDL-C (total cholesterol minus HDL-C) levels be reduced to values less than 30 mg/dl added to the LDL-C treatment goal. Thus, it is relevant that in a study of statin-treated patients with persistent hypertriglyceridemia, P-OM3 added to ongoing simvastatin therapy produced significant additional improvements in reducing non-HDL-C levels and other lipid and lipoprotein parameters to a greater extent than simvastatin alone (Figure 3 & Table 4) [120]. Thus mechanistically, in patients treated with statins and P-OM3, LDL-C levels may be reduced as a result of the statin-induced increase in hepatic LDL receptor activity. IDL and VLDL remnants may be reduced by P-OM3 impairment of VLDL synthesis and secretion. VLDL may also have enhanced clearance through enhanced LPL activity (by P-OM3) and upregulation of LDL receptor (by statins). This is an illustrative example of complementary mechanisms of actions by these two lipid-altering drugs, which may be of benefit in patients with combined hyperlipidemia.

With regard to other lipid parameters, EPA and DHA administration is sometimes associated with a modest increase in HDL-C levels. LDL-C levels may be variably increased. As with fibrates, the degree of LDL-C elevations observed with

Table 5. Ongoing prescription omega-3-acid ethyl esters trials registered at The US NIH.

Trial	Dose of P-OM3	Duration of treatment	ClinicalTrials.gov ID
A Randomized Controlled Trial of Mycophenolate Mofetil in Patients With IgA Nephropathy	Not listed	2 years	NCT00318474
An Evaluation of Simvastatin 20 mg Plus Omacor® 4 g Compared to Simvastatin 20 mg Plus Placebo in Subjects With Mixed Dyslipidemia	4 g/day	6 weeks – crossover (12 weeks total)	NCT00487591
The Effect of Fish Oil Supplementation on Endothelial Function, Heart Rate Variability and Intimal Media Thickness of Patients With Coronary Artery Disease	2 g/day	12 months	NCT00454493
Omega-3 Fatty Acids for High Triglycerides in HIV-Infected Patients	Not listed	Not listed	NCT00346697
Omacor for Perimenopausal Depression & Somatic Symptoms for Perimenopause	Not listed	8 weeks	NCT00517972
Niacin, N-3 Fatty Acids and Insulin Resistance	Not listed	Not listed	NCT00286234
Lovaza's Effect on the Activation of Platelets (LEAP)	1, 2, 4, 8 g/day	24 weeks	NCT00515541
Vascular and Lipid Effects of Omega-3 Fatty Acids in People With Moderately Elevated Triglycerides (OMEGA)	Not listed	8 weeks	NCT00504309
Fish Oil for Atrial Fibrillation – Effects and Mechanisms	Not listed	6 months	NCT00552084
Omega-3 Fatty Acids for the Prevention of Atrial Fibrillation After Cardiac Surgery	Not listed	Not listed	NCT00446966
The Outcome Reduction With Initial Glargine Intervention Trial (ORIGIN)	Not listed	Not listed	NCT00069784
A Study of Cardiovascular Events in Diabetes (ASCEND)	1g/day	Not listed	NCT00135226
Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF (GISSI-HF)	1 g/day	Not listed	NCT00336336
Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction	1 g/day	12 months	NCT00251134
Evaluation of Efficacy and Safety of Omacor (Omega-3-Acid Ethyl Esters) as Add-on Therapy in Hypertriglyceridemic Subjects Treated With Antara (Fenofibrate)	Not listed	Not listed	NCT00246636
Evaluation of Efficacy and Safety of Omacor, Co-Administered With Atorvastatin, in Subjects with Hypertriglyceridemia	4 g/day	16 weeks	NCT00435045
Evaluation of Efficacy and Safety of Lovaza (Omega-3-Acid-Ethyl Esters) in Recurrent, Symptomatic Atrial Fibrillation	4 g/day	6 months	NCT00402363
Omacor for the Treatment of Vascular Dysfunction in Patients with Type 2 Diabetes Mellitus	4 g/day	6 weeks	NCT00328536
Omacor and Cardiovascular Risk Factors in HIV Patients on HAART Treatment	4 g/day	12 weeks	NCT00296153
Lovaza Therapy of Peripheral Arterial Disease	4 g/day	12 months	NCT00569686
Effect of Omacor on Triglycerides in HIV Infected Subjects	Not listed	12 weeks	NCT00598910
Study to Evaluate the Efficacy and Safety of Omega-3 Fatty Acids for the Treatment of IgA Nephropathy	4 g/day	24 months	NCT00549692
Use of Omega-3 Fatty Acids (Fish Oil) in Patients with Chronic Hepatitis C Infection	4 g/day	To be determined by hepatitis C genotype	NCT00547716

P-OM3: Prescription omega-3-acid ethyl esters.
Data from [205].

Table 5. Ongoing prescription omega-3-acid ethyl esters trials registered at The US NIH (cont.).

Trial	Dose of P-OM3	Duration of treatment	ClinicalTrials.gov ID
Effects of Fatty Acid Delivery on Heart Metabolism and Function in Type 2 Diabetes	4 g/day	4 months	NCT00577590
Efficacy of Omega-3 Fatty Acids on Borderline Personality Disorder	1680, 3360 mg/day	12 weeks	NCT00437099
Effects of Fish Oils on Inflammation and Insulin Resistance	4 g/day	12 weeks	NCT00579436
Omega 3 Fatty Acids and Atrial Fibrillation	1g/day	6 months	NCT00508248

P-OM3: Prescription omega-3-acid ethyl esters.
Data from [205].

P-OM3 treatment is generally related to the pretreatment TG levels. P-OM3 increases LDL-C levels the most in patients with the highest pretreatment TG levels (Table 3). The reason for the increased LDL-C levels with omega-3 fatty acids is related to the increased conversion of VLDL particles to LDL particles (Figures 4 & 5). For example, weight loss in overweight subjects with hypertriglyceridemia has been shown to raise LDL-C, and this effect has been attributed to a reduction in the fractional catabolic rate of LDL [121]. As reviewed earlier, owing to their complementary mechanisms of action, concurrent treatment with statins may mitigate the rise in LDL-C in patients with hypertriglyceridemia treated with P-OM3 [120].

Expert commentary

Omega-3 fatty acids lower TG levels through decreased hepatic secretion of TG-containing lipoproteins and enhanced clearance of TG from circulating TG-containing lipoproteins. In combination with statins, omega-3 fatty acids are effective in improving many lipid parameters beyond that of statin alone, due to their complementary mechanisms of action.

Five-year view

Due to its unique benefits, interest continues to increase regarding new formulations of omega-3 fatty acids, such as potential combination agents with other lipid-altering drugs, such as niacin, fibrates and statins.

In addition to its therapeutic use for hypertriglyceridemia, omega-3 fatty acids, in general, have also been studied for potential efficacy in the treatment of numerous noncardiac conditions, such as inflammatory and arthritic disorders [122–135], neurologic/neuropsychiatric disorders [122,136–148], ophthalmic disorders [149,150], women's health issues [135,151,152], cancer [153–155] and other disorders [156–158]. However, the benefits in treating many, if not most of these noncardiac disorders have yet to be definitively proven. Results of future clinical trials should better define the efficacy and safety of omega-3 fatty acid therapy in these conditions.

In contrast to noncardiovascular effects, the evidence supporting the cardiovascular benefits of omega-3 fatty acid therapy is more compelling [27,77,159], and includes possible antidysrhythmic [160–170], antiatherogenic [82,171–179], antithrombotic [172,180–184] and anti-inflammatory endothelial effects [183,185–187]. However, yet again, more definitive evidence is needed in order to substantiate these potential benefits. As such, ongoing clinical trials are seeking to better define these potential beneficial effects of omega-3 fatty acids. Specific ongoing cardiac and noncardiac P-OM3 trials are registered at ClinicalTrials.gov [205] and summarized in Table 6.

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Key issues

- Severe hypertriglyceridemia (≥500 mg/dl [5.65 mmol/l]) should be treated to reduce the risk of pancreatitis.
- The omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) effectively lower triglyceride (TG) levels.
- In patients with persistent elevation of TG levels (>200 mg/dl [2.26 mmol/l]) while on statin therapy, the treatment goal is to reduce non-HDL-C levels in patients with persistent hypertriglyceridemia.
- In statin-treated patients, omega-3 fatty acids may effectively reduce non-HDL-C levels.
- The mechanisms of action of EPA and DHA are not completely known, but appear to include a combination of decreased hepatic secretion of TG-containing lipoproteins (very low-density lipoprotein) and enhanced clearance of TG from circulating TG-containing lipoproteins (VLDL and chylomicrons) from the bloodstream.

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