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Omega-3 polyunsaturated fatty acids in the treatment of atherogenic dyslipidemia

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Abstract

Epidemiological studies have established an association between high triglycerides (TG) plasma levels and increased cardiovascular risk. Increased TG levels, commonly coupled with low HDL-C levels, are common in high cardiovascular risk subjects including those with dyslipidemia, metabolic syndrome and type 2 diabetes. Management of hypertriglyceridemia (HTG) includes lifestyle modification for mild-to-moderate HTG and pharmacological therapies for the treatment of high and very high TG levels. Among drugs, fibrates, nicotinic acid and omega-3 polyunsaturated fatty acids may be considered. Omega-3 fatty acids reduce plasma TG levels by several mechanisms; beside the effects on TG, omega-3 can also influence the levels of other lipids and lipoproteins including HDL-C and LDL-C. Clinical trials have also shown that omega-3 fatty acid supplementation is effective also when added in combination with other lipid-lowering drugs. These findings suggest that omega-3 fatty acids may be usefully considered for the management of high TG levels.

Keywords: Triglycerides; Omega-3 polyunsaturated fatty acids; Hypertriglyceridemia; Dyslipidemia

1. Introduction

In the blood, triglycerides (TG) are mainly transported by TG-rich lipoproteins (TRLs), that include very low density lipoproteins (VLDL), which carry endogenous TG, and chylomicrons, which predominantly carry dietary fats. In the capillaries, lipolysis of TRLs generates remnant lipoproteins (RLPs) and pro-inflammatory mediators (saturated fatty acids, oxidized lipids) [1]. Unlike large nascent TRLs, smaller RLPs may enter the endothelial layer where, without the need of oxidative modification, they are rapidly internalized by macrophages and contribute to the formation of foam cells and vascular inflammation [1]. Hypertriglyceridemia (HTG) may result from either increased production or reduced catabolism of TRLs, resulting also in changes of low density lipoprotein (LDL) and high density lipoprotein (HDL) composition and metabolism and in the accumulation of small, dense LDL and HDL, which exhibit pro-atherogenic features [2].

Several epidemiological studies have established a direct association between high TG plasma levels and increased cardiovascular risk [3–8], showing that each 1 mmol/L (88 mg/dL) decrease in TG levels reduces CHD risk by 14% in men and 37% in women [3]. Higher TG levels, commonly associated with low HDL-C levels, are particularly frequent in high cardiovascular risk subjects including those with dyslipidemia, metabolic syndrome and type 2 diabetes. Nevertheless, the role of TRLs in promoting cardiovascular disease is still not completely clarified and data obtained from large clinical trials were often ambiguous. Several reasons may explain this uncertainty: the high variability of TG levels [9], the rightward-skewed distribution in the population, the presence of additional risk factors in HTG subjects and their strict and inverse relationship with HDL-C levels [10], as adjustment for HDL-C often significantly attenuates the relationship between TG and cardiovascular disease.

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TG levels are classified as normal (<150 mg/dL, <1.7 mmol/l), borderline high (150–199 mg/dL, 1.7–2.25 mmol/l), high (200–499 mg/dL, 2.26–5.6 mmol/l) and very high (≥500 mg/dL, ≥5.65 mmol/l) [2] (Table 1). High TG levels are associated with increased cardiovascular risk, very high TG levels (≥500 mg/dL [≥5.65 mmol/l]) may induce acute pancreatitis [2].

The clinical evidence suggests that management of TG levels can impact atherosclerosis and cardiovascular disease [11]. Treatments of HTG include lifestyle modification for mild-to-moderate HTG and pharmacological therapies for the treatment of high and very high TG levels [12]. Among drugs, fibrates, nicotinic acid and omega-3 polyunsaturated fatty acids alone or in combination with statins may be considered [12,13].

2. Effects of omega-3 fatty acids on lipids and lipoproteins

Omega-3 fatty acids used for the treatment of HTG include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), that can be used as monotherapy or in combination with other TG-lowering drugs in the presence of very high TG levels. EPA+DHA 2–4 g/day reduce TG by 25–30%, but larger decrease may be observed (up to 45%) in subjects with higher baseline TG levels [14]. EPA and DHA reduce TG by several mechanisms: they increase fatty acid degradation, reduce hepatic VLDL-TG synthesis and secretion and enhance clearance of plasma TG [15]. However, LDL-C levels may rise on treatment, due to the increased conversion of VLDL to LDL, being this effect present particularly in subjects with severe HTG; in subjects with mild-to-moderate HTG the increase in LDL-C upon treatment with omega-3 is not significant when compared to TG and VLDL reduction. Further, the extent of LDL-C increase is related to the extent of TG reduction as suggested by several studies [16,17]. However, available data indicate that the increase of LDL-C is not due to an increase of LDL particle number but to a shift from the smaller dense LDL (more atherogenic) to the larger and less atherogenic LDL particles, thus possibly attenuating the atherogenic potential of LDL profile [18–20].

Several meta-analyses have evaluated the effects of omega-3 fatty acid supplementation on HDL, with variable results. A meta-analysis including 47 studies and more than 16,000 subjects showed that fish oil supplementation significantly reduces TG levels, without significant effects on total cholesterol and minor effects on LDL-C and HDL-C, which showed non-significant increase [21]. On the contrary, potentially beneficial changes on HDL particles have been reported with omega-3 fatty acid treatment, including an increased HDL-C/apoA-I ratio, which suggests a cholesterol enrichment of larger HDL particles, and an increased HDL2/HDL3 ratio, an effect that is related to the TG content of HDL particles [22]. These HDL subclass changes were observed also with low doses of omega-3 fatty acids [22]. Two studies have also suggested an impact of omega-3 fatty acids in the metabolism of HDL: in fact they showed a reduction of the fractional catabolic rate and production of HDL apoproteins without relevant changes in their amount [23,24]. In addition, a proteomic analysis revealed that some HDL-associated proteins are positively modulated by omega-3 fatty acid supplementation, including PON1, clusterin, apoA-I, apoE and apoCIII, suggesting that omega-3 may modulate HDL protein composition and thus HDL functionality without altering HDL-C levels [25].

Overall the effects of omega-3 fatty acids, which reduce TG, reduce small dense while increase large buoyant LDL and increase HDL-C, may result in an improved lipid profile.

Table 1
Classification of serum TG levels

TG classes	TG levels
Normal	<150 mg/dL (<1.7 mmol/l)
Borderline high	150–199 mg/dL (1.7–2.25 mmol/l)
High	200–499 mg/dL (2.26–5.6 mmol/l)
Very high	≥ 500 mg/dL (≥5.65 mmol/l)

3. Efficacy of omega-3 fatty acids in dyslipidemia: results from clinical trials

3.1. Omega-3 fatty acid supplementation in HTG

The main pharmaceutical form of omega-3 fatty acids is a mixture of EPA (47%) and DHA (38%) in the ethyl ester form (P-OM3). In subjects with very high TG (≥500 mg/dL [≥5.65 mmol/l]), 4 g/day P-OM3 for 4 months reduced TG levels by 45% ($p < 0.00001$) and VLDL-C by 32% ($p < 0.0001$), while it increased HDL-C by 13% ($p = 0.014$) and LDL-C by 31% ($p = 0.0014$) [14] (Table 2). Similar results were obtained in subjects with TG ≥500 mg/dL after 6-week treatment (TG: −38.9%, $p = 0.001$; HDL-C: +5.9%, $p = 0.057$; LDL-C +16.7%, $p = 0.007$); total cholesterol was also significantly reduced (−9.9%, $p < 0.004$) due a large reduction of VLDL-C (−29.2%, $p = 0.001$) [26] (Table 2).

The absorption rate of the ethyl esters of EPA and DHA requires an additional enzymatic digestion and is dependent on fat meal content. Recently, a novel omega-3 free fatty acid formulation has been developed, containing 55% EPA and 20% DHA; the free fatty acid form significantly increased EPA and DHA plasma concentrations compared to the ethyl ester form in overweight subjects during low-fat diet [27], suggesting a potential therapeutic advantage of the free fatty acid formulation for the treatment of severe HTG. The EVOLVE trial evaluated the efficacy and safety of this omega-3 formulation 2, 3 and 4 g/day for 12 weeks in subjects with fasting TG levels ≥500 mg/dL and <2000 mg/dL; all doses significantly reduced TG levels (2 g: −26%, $p < 0.01$; 4 g:

Table 2
Effects of omega-3 fatty acids on lipids and lipoproteins in HTG

	TG	VLDL-C	HDL-C	LDL-C	TC	Non-HDL-C
HTG [14]	−45%, $p < 0.00001$	−32%, $p < 0.0001$	+13%, $p = 0.014$	+31%, $p = 0.0014$		
HTG [26]	−38.9%, $p = 0.001$	−29.2%, $p = 0.001$	+5.9%, $p = 0.057$	+16.7%, $p = 0.007$	−9.9%, $p = 0.004$	
HTG [a]	−26% (2 g), $p < 0.01$ −31% (4 g), $p < 0.001$					−8% (2 g), $p < 0.05$ −10% (4 g), $p < 0.01$
Statin-treated with persistent HTG [a]	−15% (2 g), $p < 0.001$ −21% (4 g), $p < 0.001$	−14% (2 g) −22% (4 g)		+5% (2 g), $p < 0.05$ +1% (4 g), *ns*		−4% (2 g), $p < 0.05$ −7% (4 g), $p < 0.001$
HTG (AMR101) [28]	−19.7% (2 g), $p = 0.0051$ −33.1% (4 g), $p < 0.0001$	−15.3% (2 g), $p < 0.05$ −28.6% (4 g), $p < 0.001$	+1.5% (2 g), *ns* −3.6% (4 g), *ns*	+5.2% (2 g), *ns* −2.3% (4 g), *ns*	−6.8% (2 g), $p < 0.05$ −16.3% (4 g), $p < 0.0001$	−8.1% (2 g), $p < 0.05$ −17.7% (4 g), $p < 0.0001$
Statin-treated with persistent HTG (AMR101) [30]	−10.1% (2 g), $p = 0.0005$ −21.5% (4 g), $p < 0.0001$	−10.5% (2 g), $p < 0.01$ −24.4% (4 g), $p < 0.0001$	−2.2% (2 g), *ns* −4.5% (4 g), $p < 0.01$	−3.6% (2 g), *ns* −6.2% (4 g), $p = 0.0067$	−4.8% (2 g), $p < 0.01$ −12% (4 g), $p < 0.0001$	−5.5% (2 g), $p = 0.0054$ −13.6% (4 g), $p < 0.0001$

[a] www.omthera.com/pdf/11512_OmtheraP3ResultsFINAL.pdf.

Table 3
Effects of omega-3 fatty acids on lipids and lipoproteins in atherogenic dyslipidemia

	TG	VLDL-C	HDL-C	LDL-C	TC	Non-HDL-C
Primary hypercholesterolemia [31] (omega-3 vs placebo)	−16.7% vs +2.0% $p < 0.0001$	−16.7% vs +2.0% $p < 0.0001$	+1.5% vs −1.7% $p = 0.033$	+3.4% vs −0.7% $p = 0.010$	+0.5% vs −0.7% *ns*	+0.3% vs −0.4% *ns*
Statin-treated hypercholesterolemic [32] (omega-3 vs statin) [32]	−9% vs −4% $p < 0.0001$ $p < 0.0001$		*ns*	−25% vs −25%	−19% vs −19%	
Mixed dyslipidemia [34] (omega-3 vs statin)	−54.7% vs −32% $p < 0.05$	−47.9% vs −23% $p < 0.05$	+20.7% vs +17.9% $p < 0.05$	−35.5% vs −38% *ns*	−31.9% vs −27.1% $p < 0.05$	−40.8% vs −34.9% $p < 0.05$
Statin-treated with persistent HTG [35] (omega-3 vs statin)	−29.5% vs −6.3% $p < 0.001$	−27.5% vs −7.2% $p < 0.001$	+3.4% vs −1.2% $p < 0.001$	+0.7% vs −2.8% $p = 0.052$	−4.8% vs −1.7% $p = 0.001$	−9.0% vs −2.2% $p < 0.001$
Atherogenic dyslipidemia [36] (omega-3 vs placebo)	−28% $p < 0.001$	−27% $p < 0.001$	+4.2% $p < 0.01$	+8.8% $p < 0.01$	+1% *ns*	
Subjects with high TG and non-HDL-C [37] (omega-3 vs statin)	−45.4% vs −26.9% $p < 0.001$	−54.3% vs −37% $p < 0.001$	+12.4% vs +10% $p = 0.007$	−29.3% vs −31.5% *ns*	−31.5% vs −27.4% $p = 0.002$	−40.2% vs −33.7% $p < 0.001$
Type 2 diabetes [41] (omega-3 vs placebo)	−25% $p < 0.00001$	−36% $p = 0.04$	*ns*	+5.7% $p = 0.05$	*ns*	

−31%, $p < 0.001$) (Table 2). The free fatty acid formulation also reduced non-HDL-C (8% with 2 g, $p < 0.05$; 10% with 4 g, $p < 0.01$) (http://www.omthera.com/pdf/11512_OmtheraP3ResultsFINAL.pdf) (Table 2). In statin-treated patients with persistent HTG, omega-3 free fatty acids reduced TG by 15% with 2 g ($p < 0.001$) and by 21% with 4 g ($p < 0.001$), VLDL-C by 14% and 22%, and non-HDL-C by 4% ($p < 0.05$) and 7% ($p < 0.001$), respectively; LDL-C showed a slight increase (5% with 2 g, $p < 0.05$, and 1% with 4 g, n.s.) (Table 2).

AMR101 is a high purity prescription form containing ≥96% EPA ethyl ester. In the MARINE trial AMR101 has been evaluated in patients with severe HTG (≥500 mg/dL and ≤2000 mg/dL [≥5.65 mmol/l and ≤22.6 mmol/l]) [28]: 4 or 2 g/day for 12 weeks reduced TG levels by 33.1% ($p < 0.0001$) and 19.7% ($p = 0.0051$), respectively [28]. In subjects with higher baseline TG levels (>750 mg/dL), TG were reduced by 45.4% ($p = 0.0001$) and 32.9% ($p = 0.0016$), respectively. AMR101 also significantly reduced VLDL-C (−28.6% and −15.3%), non-HDL-C (−17.7% and −8.1%) and total cholesterol (−16.3% and −6.8%), but no changes were reported on LDL-C [28] (Table 2), probably due to the absence of DHA. AMR101 also significantly reduced small LDL particle concentration [29]. In statin-treated patients with persistent HTG (200–500 mg/dL (2.26–5.65 mmol/l), AMR101 significantly reduced TG levels by 21.5% (4 g/day, $p < 0.0001$) and 10.1% (2 g/day, $p = 0.0005$), VLDL-C by 24.4% ($p < 0.0001$) and 10.5% ($p < 0.01$), non-HDL-C by 13.6% ($p < 0.0001$) and 5.5% ($p = 0.0054$) [30]; also LDL-C was reduced although to a lesser extent (−6.2%, $p < 0.01$; −3.6%, NS) (Table 2). An AMR101 ongoing trial is evaluating the effect of AMR101 on cardiovascular events in high risk patients with HTG and on statin (http://clinicaltrials.gov/show/NCT01492361).

3.2. Effects of omega-3 in dyslipidemia

In subjects with isolated primary hypercholesterolemia and absence of elevated TG levels (Type IIa dyslipidemia), P-OM3 4 g/day significantly reduced VLDL-C and TG levels by 16.7% ($p < 0.0001$), while it increased LDL-C (+3.4%, $p = 0.01$); no significant changes were observed in HDL-C [31]. Nuclear magnetic resonance analysis of the lipoprotein profile showed that LDL particle size and large LDL increased with P-OM3 treatment; similarly, large HDL particle levels and HDL particle size increased during treatment with P-OM3 [31] (Table 3).

The Japan EPA Lipid Intervention Study (JELIS), which evaluated the effects of long-term use of EPA (1.8 g/day) in statin-treated hypercholesterolemic (TC ≥250 mg/dL) subjects, showed a reduced frequency of major coronary events and a reduction of TG levels compared to statin alone (9% vs 4%, $p < 0.001$), with similar decrease in total cholesterol and LDL-C levels [32] (Table 3). A sub-analysis of this trial has suggested that specific subgroups of subjects, such as those with abnormal levels of TG (≥150 mg/dL) and HDL-C (<40 mg/dL), may particularly benefit from EPA supplementation [33].

In subjects with mixed dyslipidemia (TC 253 mg/dL, LDL-C 254 mg/dL, HDL-C 36 mg/dL, TG 326 mg/dL) the addition of P-OM3 4 g/day to simvastatin resulted in reduced TG and VLDL-C levels (−54.7% and −47.9%, respectively) compared to simvastatin alone (−32.0% and −23.0%, respectively) [34]; also HDL-C was increased more after omega-3 supplementation (20.7% vs 17.9%, $p < 0.05$), suggesting an improvement of lipid and lipoprotein profile in dyslipidemic subjects (Table 3). The Combination of Prescription Omega-3 with Simvastatin (COMBOS) trial evaluated the effects of P-OM3 ethyl ester addition to statin-treated patients with persistent HTG (≥200 and <500 mg/dL) [35]: TG and VLDL-C levels were significantly reduced by the combination therapy (−29.5% and −27.5%) as compared to simvastatin (−6.3% and −7.2%, respectively); no relevant changes were reported in LDL-C levels in both groups, but an increase in HDL-C was observed with the combination therapy compared to simvastatin (+3.4% vs −1.2%, $p < 0.001$) [35] (Table 3). These findings were confirmed by other studies [36,37] (Table 3).

When combined with fenofibrate, P-OM34 4 g/day induced a greater TG reduction compared to fenofibrate alone (60.8% vs 53.8%) in subjects with very high TG levels (≥500 mg/dL [5.65 mmol/l]) [38]. In subjects treated for 8 weeks with fenofibrate and given P-OM3 during the open-label extension study TG levels were further reduced by 17.5% [38]. Similarly, when given in combination with niacin, P-OM3 4 g/day induced a greater reduction of TG and VLDL-C compared to niacin alone (33% and 27% compared to 21% and 19%) in patients with metabolic syndrome [39]. Furthermore, the combination therapy induced also changes of lipoprotein subfractions resulting in increased LDL and HDL particle size [39].

4. Omega-3 fatty acid therapy in diabetes

High plasma TG and low HDL-C levels are features of metabolic syndrome and type 2 diabetes. In addition, higher levels of small dense LDL and TG-rich lipoproteins and their remnants have been observed in these metabolic disorders. The hypersecretion of large TG-rich VLDL particles leads to cholesterol depletion and TG enrichment of LDL and HDL, resulting in atherogenic alterations of LDL and HDL composition [40]. Furthermore, subjects with metabolic syndrome and type 2 diabetes are at high cardiovascular risk despite low or normal levels of LDL-C achieved with statin therapy, and dyslipidemia represents an important risk factor for these patients.

The role of omega-3 fatty acid supplementation in diabetes is still unclear. A meta-analysis of randomized controlled trials showed that in subjects with type 2 diabetes omega-3 fatty acids reduced TG levels (−25%, $p < 0.00001$), VLDL-C (−36%, $p = 0.04$) and VLDL-TG (−39.7% $p = 0.03$), with a slight increase in LDL-C

(5.7%, $p = 0.05$) and no effects on total cholesterol or lipid subfractions [41] (Table 3). These observations have been confirmed also in a successive meta-analysis including more recent trials [42]. Overall, type 2 diabetics seem to benefit from omega-3 supplementation, as shown in several studies [43–46]; although also non-significant effects have been reported [47].

5. Concluding remarks

The management of hypertriglyceridemia, which is often associated to other lipid and lipoprotein abnormalities and to additional cardiovascular risk factors, represents a crucial step to reduce cardiovascular risk. Omega-3 fatty acid supplementation significantly modulates TG levels and may influence also lipoprotein levels, thus impacting the lipoprotein profile. In addition, omega-3 fatty acids seem to have further cardioprotective effects, independent from TG-lowering mechanisms. Overall, subjects with HTG seem to benefit from omega-3 fatty acid supplementation.

Conflict of interest

AP has no conflict of interest to report. ALC declares the following conflict of interest: acting as speaker for Sigma-Tau industries.

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