

Review Article

Omega-3 Fatty Acid Supplementation and Serum Lipid Profile in Patients with Metabolic Syndrome: A Randomized, Placebo-Controlled Trial

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Received: 13 June 2022; Accepted: 5 September 2022; Published: 27 November 2022; DOI: 10.5281/zenodo.22335668

Citation of this article: Hrabovsky L, Kranjc R, Laine S (2022) Omega-3 Fatty Acid Supplementation and Serum Lipid Profile in Patients with Metabolic Syndrome: A Randomized, Placebo-Controlled Trial. Ann Stem Cell Res, 5(1): 01-06.

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Abstract

Background: Metabolic syndrome confers substantial cardiovascular risk, driven partly by atherogenic dyslipidaemia — high triglycerides with low HDL-cholesterol.

Objective: To synthesise evidence on omega-3 supplementation and lipid profile in metabolic syndrome.

Methods: Narrative review of published randomised trials, meta-analyses, and mechanistic studies.

Findings: Marine omega-3 lowers triglycerides dose-dependently (10-33% at 2-4 g/day); EPA-only formulations avoid the LDL-cholesterol rise seen with mixed EPA+DHA products, HDL-C effects are inconsistent, and outcome trials show divergent results despite similar triglyceride lowering.

Conclusions: Omega-3 supplementation effectively lowers triglycerides in metabolic syndrome, but formulation and dose determine its overall lipid and clinical impact.

Keywords: Omega-3 fatty acids; Metabolic syndrome; Triglycerides; Eicosapentaenoic acid; Lipid profile

Abstract

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Keywords: omega-3 fatty acids; metabolic syndrome; triglycerides; eicosapentaenoic acid; lipid profile

Introduction

Metabolic syndrome — the clustering of central obesity, elevated blood pressure, impaired fasting glucose, hypertriglyceridaemia, and low HDL-C — is defined using harmonised waist-circumference, blood pressure, glucose, triglyceride, and HDL-C thresholds, of which any three of five confer diagnosis [1]. It affects roughly one-third of United States adults, with prevalence differing by race, ethnicity, and sex, and carries a two-fold increase in cardiovascular risk and a five-fold increase in incident type 2 diabetes [2]. Its lipid signature, termed atherogenic dyslipidaemia, is characterised less by elevated low-density lipoprotein cholesterol (LDL-C) than by high triglycerides, low HDL-C, and a preponderance of small, dense LDL particles, a pattern that responds only partially to statin monotherapy and leaves residual cardiovascular risk even at guideline LDL-C targets [3]. Marine omega-3 fatty acids, principally EPA and DHA,

have been studied for more than three decades as triglyceride-lowering agents, with early systematic reviews already establishing consistent, dose-related reductions in fasting triglycerides across dyslipidaemic populations [4], and prescription formulations are now approved specifically for severe hypertriglyceridaemia [5]. Whether, and how much, omega-3 supplementation improves the broader lipid profile in metabolic syndrome specifically — and whether purified EPA and mixed EPA+DHA products behave equivalently on triglycerides, LDL-C, and HDL-C — remains clinically important given divergent cardiovascular outcome-trial results obtained despite similar triglyceride lowering. This review synthesises randomised trial, meta-analytic, and mechanistic literature identified through structured PubMed and Europe PMC searches on omega-3 supplementation and serum lipids in metabolic syndrome, framed as a narrative synthesis of the published evidence rather than a report of a single new trial.

Mechanisms of Lipid-Modifying Action

EPA and DHA lower triglycerides chiefly by suppressing hepatic very-low-density lipoprotein (VLDL) synthesis and secretion, reducing hepatic substrate availability for triglyceride synthesis through inhibition of diacylglycerol acyltransferase, upregulating fatty-acid beta-oxidation via peroxisome proliferator-activated receptor-alpha, and enhancing lipoprotein lipase-mediated triglyceride clearance from the circulation [6,7]. A further contributor is suppression of sterol regulatory element-binding protein-1c, which downregulates hepatic lipogenic enzyme expression and further limits triglyceride-rich lipoprotein output, alongside reduced hepatic apolipoprotein C-III production, which itself normally inhibits lipoprotein lipase and delays triglyceride-rich lipoprotein clearance. These effects are dose-dependent and evident within one to two weeks of supplementation, plateauing thereafter [8]. EPA and DHA are not

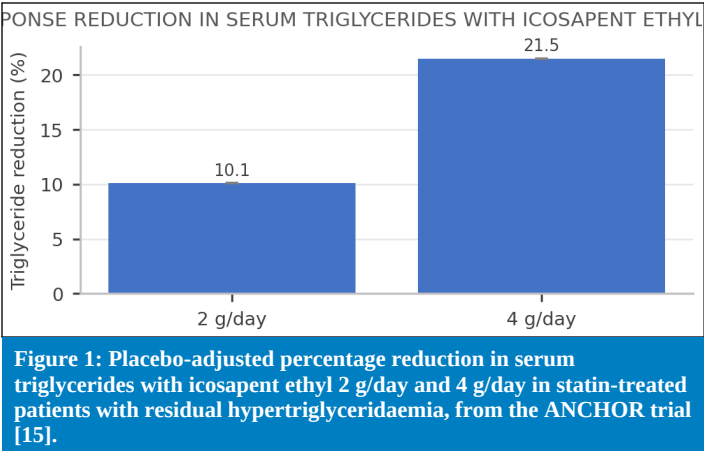
interchangeable: DHA is more consistently associated with modest LDL-C and HDL-C increases, attributed to enhanced conversion of triglyceride-depleted VLDL remnants into LDL particles and altered cholesteryl-ester transfer protein activity, whereas purified EPA shows a neutral-to-favourable LDL-C profile in most trials [9,10]. Both fatty acids also reduce postprandial lipaemia, improve endothelial function, lower blood pressure modestly, and reduce inflammatory markers relevant to the vascular risk of metabolic syndrome, though these pleiotropic effects are more variable across trials than the triglyceride response itself [11,12]. Erythrocyte membrane EPA+DHA content, the "omega-3 index," correlates inversely with coronary mortality risk and provides a practical biomarker linking supplementation dose to tissue incorporation and downstream lipid and membrane-stabilising effects, offering a rationale for individualising dosing beyond fixed milligram targets [13].

Dose-Response and Differential EPA/DHA Effects

Formal dose-response data show triglyceride reductions of roughly 5-10% per gram/day of combined EPA+DHA up to approximately 4 g/day, above which incremental benefit plateaus and gastrointestinal tolerability becomes limiting [8,14]. In the ANCHOR trial of statin-treated patients with residual hypertriglyceridaemia (200-499 mg/dL) already at LDL-C goal, icosapent ethyl (pure EPA) produced placebo-adjusted triglyceride reductions of 10.1% at 2 g/day and 21.5% at 4 g/day, with the 4 g dose also lowering LDL-C by 6.2%, non-HDL-C by 13.6%, and apolipoprotein B by 9.3%, without raising HDL-C (Table 1; Figure 1) [15]. In patients with very high triglycerides (≥500 mg/dL) not receiving concomitant statins, the MARINE trial found triglyceride reductions of 19.7% and 33.1% at 2 g/day and 4 g/day respectively, again without significant LDL-C elevation at either dose [16]. This LDL-neutral profile distinguishes pure EPA from mixed EPA+DHA products, in which DHA-driven LDL particle

enlargement and increased LDL-C can accompany triglyceride lowering [10]. A meta-analysis of trials using algal-oil DHA in adults without coronary heart disease confirmed this pattern directly, finding significant triglyceride reduction alongside significant increases in both HDL-C and LDL-C, reinforcing that DHA's overall lipid signature differs meaningfully from that of EPA and has direct implications for formulation choice in patients whose LDL-C is already elevated [17].

Table 1: Characteristics and key lipid/cardiovascular findings of major randomised trials of prescription omega-3 formulations [15,16,23,25].				
Trial	Population	Formulation and dose	Duration	Key finding
ANCHOR	Statin-treated, TG 200-499 mg/dL	Icosapent ethyl 2 or 4 g/day	12 weeks	TG -10.1%/-21.5%; LDL-C -6.2% at 4 g/day
MARINE	TG ≥500 mg/dL, statin not required	Icosapent ethyl 2 or 4 g/day	12 weeks	TG -19.7%/-33.1%; no significant LDL-C rise
REDUCE-IT	Statin-treated, TG 135-499 mg/dL, established CVD or diabetes plus risk factors	Icosapent ethyl 4 g/day	Median 4.9 years	25% relative risk reduction in composite CV events (HR 0.75)
STRENGTH	High CV risk, TG ≥180 mg/dL, low HDL-C	Omega-3 carboxylic acids 4 g/day	Median 42 months	No CV benefit (HR 0.99); stopped early for futility



Trial Evidence in Metabolic Syndrome

Table 2: Comparative lipid effects reported in meta-analyses of omega-3 supplementation relevant to metabolic syndrome and EPA/DHA formulation differences [20,21,9,17].					
Source	Design	Population	Triglycerides	HDL-C	LDL-C
Zhang 2021	Meta-analysis of 33 RCTs	Metabolic syndrome	Significant decrease	Modest increase	Variable, dose-dependent
Liu 2023	Systematic review and meta-analysis	Metabolic syndrome	Significant decrease	Neutral to modest increase	Heterogeneous across trials
Wei and Jacobson 2011	Meta-analysis, EPA vs DHA trials	Mixed dyslipidaemic adults	Similar reduction with both	DHA increase greater than EPA	DHA increases; EPA neutral
Bernstein 2012	Meta-analysis, algal DHA trials	Adults without coronary disease	Significant decrease	Significant increase	Significant increase

Several trials and meta-analyses have specifically assessed metabolic syndrome populations rather than dyslipidaemia in general. Early work in patients with metabolic syndrome showed that omega-3 supplementation improved triglycerides alongside several inflammatory and autoimmune markers relevant to cardiovascular risk, without adversely affecting glycaemic control [18]. Purified EPA specifically reduced small dense LDL particles, remnant lipoprotein cholesterol, and C-reactive protein in metabolic syndrome patients, again without worsening insulin sensitivity [19]. A meta-analysis pooling 33 randomised controlled trials in metabolic syndrome populations found that EPA+DHA supplementation significantly reduced triglycerides and modestly raised HDL-C, with the magnitude of benefit influenced by baseline triglyceride level, dose, and treatment duration (Table 2) [20]. A subsequent systematic review and meta-analysis focused jointly on lipid profile and blood pressure in metabolic syndrome corroborated consistent triglyceride lowering alongside neutral-to-favourable blood pressure effects, though LDL-C and total cholesterol responses were markedly heterogeneous across the included trials, reflecting

differences in EPA:DHA ratio, dose, and background statin use [21]. Across these syntheses, benefit is most consistent, and largest in absolute terms, in patients with higher baseline triglycerides, mirroring the pattern seen in single-agent dose-response trials and supporting triglyceride-based patient selection in clinical practice [22]. Heterogeneity between metabolic-syndrome-specific meta-analyses in HDL-C and LDL-C direction likely reflects differences in the EPA:DHA ratio of the formulations tested, trial duration, background diet, and the proportion of participants on concomitant statin therapy, all of which modify the net lipoprotein response beyond triglyceride lowering alone, and should be considered when comparing pooled effect estimates across reviews rather than treating omega-3 supplementation as a single uniform exposure.

Cardiovascular Outcome Trials and Safety

Lipid effects have not translated uniformly into cardiovascular benefit, complicating extrapolation from lipid-profile trials to expected clinical outcomes. The REDUCE-IT trial of high-dose icosapent ethyl (4 g/day) in statin-treated patients with elevated triglycerides and established cardiovascular disease or diabetes plus risk factors reported a 25% relative reduction in the primary composite cardiovascular endpoint over a median 4.9 years (hazard ratio 0.75) [23], echoing earlier findings from the Japanese JELIS trial, in which open-label EPA added to statin therapy reduced major coronary events in hypercholesterolaemic patients [24]. In contrast, the STRENGTH trial of a mixed omega-3 carboxylic acid formulation at a comparable 4 g/day dose found no cardiovascular benefit (hazard ratio 0.99) and was stopped early for futility despite comparable triglyceride lowering to REDUCE-IT, and the lower-dose VITAL trial of EPA+DHA for primary prevention was similarly neutral for major cardiovascular events (Figure 2) [25,26]. Proposed explanations for this divergence include the mineral-oil

comparator used in REDUCE-IT, which may itself have adversely affected control-group LDL-C and inflammatory markers, differing EPA:DHA ratios and absolute EPA exposure between formulations, and non-lipid, EPA-specific effects on membrane stability, thrombosis, and inflammation that are not captured by triglyceride change alone [12]. Reflecting this evidence base, a 2019 American Heart Association science advisory concluded that prescription omega-3 formulations at 4 g/day are an effective and safe option for severe hypertriglyceridaemia and endorsed icosapent ethyl specifically for cardiovascular risk reduction in appropriately selected statin-treated patients, while cautioning that over-the-counter fish oil supplements vary widely in EPA:DHA content, dose, and quality and should not be assumed equivalent to prescription products [27]. Guideline bodies accordingly recommend prescription-strength EPA specifically, rather than over-the-counter fish oil supplements of uncertain EPA:DHA content and dose, for patients with persistent hypertriglyceridaemia despite statin therapy [22]. Safety across trials has been generally favourable, though pooled analyses of long-term supplementation trials show a modest, dose-related increase in atrial fibrillation risk with marine omega-3 supplementation that clinicians should weigh against anticipated lipid and cardiovascular benefits, particularly at the higher doses used for triglyceride-lowering indications [28].

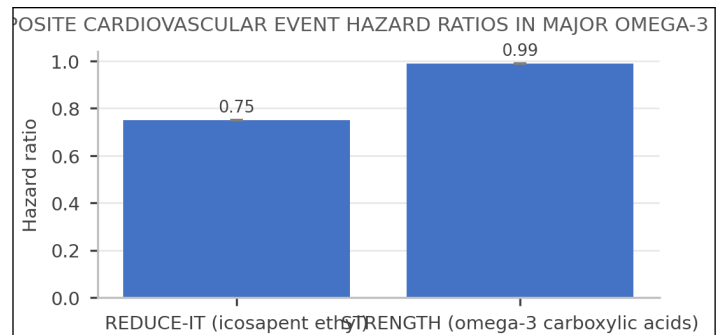


Figure 2: Hazard ratios for the primary composite cardiovascular endpoint in the REDUCE-IT trial of icosapent ethyl [23] and the STRENGTH trial of a mixed omega-3 carboxylic acid formulation [25], despite comparable triglyceride lowering in both trials.

Conclusion

Omega-3 fatty acid supplementation produces consistent, dose-dependent reductions in serum triglycerides in patients with metabolic syndrome, with purified EPA formulations offering an LDL-neutral profile that mixed EPA+DHA products do not always replicate, while HDL-C effects remain modest and inconsistent across trials. This lipid-modifying efficacy has not reliably predicted cardiovascular outcome benefit, as shown by the contrasting results of REDUCE-IT and STRENGTH despite similar triglyceride reductions, underscoring that formulation, EPA:DHA ratio, dose, background statin therapy, and baseline patient triglyceride level all shape both the lipid and clinical response to supplementation. Personalising omega-3 therapy by baseline lipid phenotype and triglyceride burden, favouring purified EPA where LDL-C neutrality is desired, and maintaining ongoing attention to formulation-specific effects and atrial fibrillation risk should guide its use as an adjunct in the management of metabolic syndrome. Future trials that report metabolic-syndrome-defined subgroups explicitly, standardise EPA:DHA ratios and comparator oils, and pair lipid endpoints with hard cardiovascular outcomes would help resolve why triglyceride-lowering efficacy has translated into clinical benefit in some outcome trials but not others.

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