

MINI REVIEW ARTICLE

Role of Eicosapentaeoic Acid as an Anti-Inflammatory Drug in Cardiac Patient

Ahmed Elborae

Department of Cardiovascular Medicine, Cairo University, Cairo, Egypt

ABSTRACT

Inflammation is termed an integral part of our body defense system, which involve recruitment and activation of different cell types and the release of several chemical mediators. However, without proper control of the extent and duration of this response through the “intrinsic anti-inflammatory system”, this might cause injury to the host tissue as well. The development and rupture of atherosclerotic plaque in particular are mutually linked to inflammatory process, where the accumulated subendothelial “bad fat” or LDL. In contrary, not all fat are atherogenic, poly-unsaturated fatty acid (PUFA), and eicosapentoeic acid (EPA) in specific, have proven to have triglyceride lowering and anti-inflammatory effect. The unique chemical structure of EPA enables it to modulate cell membrane function through substituting the omega-6 fatty acid arachidonic acid (AA; 20:4, n-6) in membrane phospholipids of inflammatory cells. The altered fatty acid composition of inflammatory cells inhibit the synthesis of peptide mediators of inflammation such as adhesion molecules or cytokines, and decrease platelet aggregation and thrombus formation.

In this mini review article, we will summarize the evolving data about the potential role of eicosapentaeoic acid as an anti-inflammatory drug.

ARTICLE HISTORY Received 20 Dec 2024; Revised 12 Jan 2025; Accepted 18 March 2025

KEYWORDS Coronary Artery disease, Inflammation, omega 3

Introduction

Inflammation is considered an integral part of our body defense system, and it involves recruitment and activation of different cell types and the release of several chemical mediators. However, without proper control of the extent and duration of this response through the “intrinsic anti-inflammatory system”, this might cause injury to the host tissue as well.¹

Inflammation and atherosclerotic cardiovascular disease

Cumulative data has shown a strong relation between the state of maintained low-grade chronic inflammation and many atherosclerotic cardiovascular disease, the leading cause of morbidity and mortality worldwide. The development and rupture of atherosclerotic plaque in particular are mutually linked to inflammatory process, where the accumulated subendothelial “bad fat” or LDL stimulates both smooth muscle cells and endothelial cells that facilitate the recruitment of lymphocytes and differentiation of monocytes, and upregulation of the toll like receptors (TLRs), in particular TLR4.²

Eicosapentaeoic acid invivo effect

In contrary, not all fat are atherogenic, poly-unsaturated fatty acid (PUFA), and eicosapentoeic acid (EPA) in specific, have proven to have triglycerides lowering and

anti-inflammatory effect. The unique chemical structure of EPA enables it to modulate cell membrane function through substituting the omega-6 fatty acid arachidonic acid (AA; 20:4, n-6) in membrane phospholipids of inflammatory cells. The altered fatty acid composition of inflammatory cells inhibit the synthesis of peptide mediators of inflammation such as adhesion molecules or cytokines, and decrease platelet aggregation and thrombus formation.

EPA is also an important source of eicosanoids which have beneficial effect in contrast with those derived from arachidonic acid. In fact, both EPA and docosahexaenoic acid (DHA) are sources of recently discovered resolvins with anti-inflammatory properties. In human peripheral blood lymphocytes, resolvins decreases cytokine production by activated CD8 + T cells and CD4 + TH1 while limiting CD4 + T-cell differentiation into TH1 and TH17 cells.³

Eicosapentaeoic acid pre-clinical data

In recent animal studies, the administration of EPA in mice led to lower deposition of LDL and reduced macrophages with an increase in smooth muscle cells and collagen content, or in another word “plaque stabilisation” without changing the total cholesterol or HDL content. This was explained by reduction of adhesion molecules and monocyte chemotactic protein 1 (MCP-1) and metalloproteinases synthesis.⁴ Furthermore, EPA has anti-oxidant effect through scavenging reactive oxygen species, and inhibition of lipid peroxidation in membrane

vesicles with even high cholesterol levels. Finally, both EPA and DHA have effects on hemodynamics, adiponectin, and IL-18 levels as well as platelet function in various clinical and experimental studies.⁵

Eicosapentaenoic acid clinical outcome data

Human studies also have proven the neo-vasculogenic effect of EPA in human endothelial cells through modulation of the expression of the c-lit protein on the PI3-K/Akt/eNOS pathway, and preventing ischemic injury⁶. In the ANCHOR study, administration of EPA at a dose of 4 g/day for 12 weeks reduced the oxidation of LDL by 13.3%, and remnant lipoprotein-cholesterol (RLP-C) by 25.0% compared to the placebo group in patients treated with statins and high triglycerides (between 200-500 mg/dL). Similarly, in hyperlipidemic patients, the administration of EPA at a dose of 1.8 g/day for 3 months restored endothelium-dependent vasodilation compared to that found in the group of normolipidemic patients.⁷

In contrast to previous Triglycerides (TGs)-lowering trials, IPE reduced the composite cardiovascular (CV) events as reported in the REDUCE-IT trial. The trial had investigated the effects of IPE 4 g/d vs. mineral oil placebo on residual CV disease risk in about 8000 statin treated patients with TGs (≥ 135 and < 499 mg/dL) and established CV disease or diabetes with at least one additional risk factor. The primary endpoint was composite MACE (CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, and coronary revascularization).

REDUCE-IT showed a 25% relative risk reduction (HR: 0.75, 95% CI: 0.68–0.83, $P < .001$) and 4.8% (95% CI: 3.1–6.5) absolute risk reduction of the primary endpoint. This reduction in events achieved significance after only 21 months following randomization, indicating an early benefit with IPE treatment. Additionally, although all patients were enrolled based on adherence to statin therapy, the risk reduction with IPE did not differ based on the type of statin (lipophilic or lipophobic) the patients received. Finally, despite the baseline TG threshold required for enrollment in REDUCE-IT, IPE conferred a consistent risk reduction regardless of baseline or achieved TG levels, indicating that TG lowering itself does not explain the mechanism of event reduction in IPE-treated patients.⁸

The benefits with IPE beyond TG lowering may indicate direct effects of EPA on progression of atherosclerosis not reproduced with low dose or mixed n3-FA preparations that include DHA in the formulation. Imaging studies indicate that EPA has direct effects on plaque progression in patients with coronary artery disease. Integrated backscatter intravascular ultrasound (IB-IVUS) was used to measure changes in coronary thin-cap fibroatheroma in IPE treated patients versus statin alone in the Combination Therapy of Eicosapentaenoic Acid and Pitavastatin for Coronary Plaque Regression Evaluated by Integrated Backscatter Intravascular Ultrasonography (CHERRY) trial.⁹ The IPE plus statin intervention was associated with a significant reduction in plaque volume concomitant with a decrease in the Arachidonic acid (AA)-EPA ratio compared with statin alone. A similar randomized trial of IPE plus statin versus statin alone found a significant increase in fibrous cap thickness with IPE plus statin therapy versus statin therapy alone using optical

computed tomography (OCT).¹⁰ The randomized Effect of Vascepa on Improving Coronary Atherosclerosis in People with High Triglycerides Taking Statin Therapy (EVAPORATE) trial used multidetector computed tomography to measure the effects of IPE in statin-treated patients compared to statin alone. IPE (4 g/day) treatment for 18 months correlated with reduced low attenuation plaque (LAP) volume by 17% compared with baseline. This may be particularly important in explaining the reductions of MI with IPE, as patients with a LAP burden of more than 4% are more likely to experience an MI.¹¹

A recent meta-analysis conducted on 13 RCT that enrolled 127 477 patients, including three recent large-scale RCTs of omega-3 PUFAs (REDUCE-IT, ASCEND, and VITAL) demonstrated that the administration of omega-3 PUFAs led to a reduction in the risk of cardiac death in secondary prevention. Nevertheless, the difference between the positive effect of icosapent ethyl reported in the REDUCE-IT study and the lack of benefit of the mixed carboxylic acids EPA and DHA in the STRENGTH study is still questionable, with some explanations. First, the omega-3 PUFAs were administered as an ethyl ester formula in the REDUCE-IT study and as non-esterified fatty acids in the STRENGTH study. Second, the DHA component of omega-3 PUFAs may be ineffective or even harmful, although there are no studies addressing the atherosclerotic cardiovascular disease (ASCVD) outcomes of DHA monotherapy till now. Importantly, it is now clear that the therapeutic effects are strictly dose-dependent, where studies conducted on volunteers have highlighted that an intake of >2 g EPA + DHA/day is required to modulate inflammatory processes.¹²

Conclusion

EPA has a proven anti-inflammatory effect through modulation of cell membrane fat composition and signaling, and improves endothelium function through its anti-oxidant effect, which result in reduction of atherosclerotic plaque formation, progression, and vulnerability, which eventually translates into improved clinical outcome.

References

1. Liu CH, Abrams N, Carrick DM, et al. Biomarkers of chronic inflammation in disease development and prevention: Challenges and opportunities. *Nat. Immunol.* 2017, 18, 1175–1180.
2. Bäck M, Yurdagul A Jr, Tabas I, et al. Inflammation and its resolution in atherosclerosis: Mediators and therapeutic opportunities. *Nat. Rev. Cardiol.* 2019, 16, 389–406.
3. Saini RK, Keum YS. Omega-3 and omega-6 polyunsaturated fatty acids: Dietary sources, metabolism, and significance—A review. *Life Sci.* 2018, 203, 255–267.
4. Matsumoto M, Sata M, Fukuda D, et al. Orally administered eicosapentaenoic acid reduces and stabilizes atherosclerotic lesions in ApoE-deficient mice. *Atherosclerosis* 2008, 197, 524–533.
5. Mason RP, Jacob RF. Eicosapentaenoic acid inhibits glucose-induced membrane cholesterol crystalline domain formation through a potent antioxidant mechanism. *Biochim. Biophys. Acta* 2015, 1848, 502–509.
6. Chiu S-C, Chiang E-PI, Tsai S-Y, et al. Eicosapentaenoic acid induces neovasclogenesis in human endothelial progenitor cells by modulating c-kit protein and PI3-K/Akt/eNOS signaling pathways. *J. Nutr. Biochem.* 2014, 25, 934–945.

7. Bays HE, Ballantyne CM, Braeckman RA, et al. Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: Effects on circulating markers of inflammation from the MARINE and ANCHOR studies. *Am J Cardiovasc Drugs* 2013 , 13, 37–46.
8. Bhatt DL, Steg PG, Miller M, et al. Cardiovascular risk reduction with Icosapent Ethyl for hypertriglyceridemia. *New England Journal of Medicine*. 2019;380:11–22.
9. Watanabe T, Ando K, Daidoji H, et al. A randomized controlled trial of eicosapentaenoic acid in patients with coronary heart disease on statins. *J Cardiol*. 2017;70:537–44.
10. Nishio R, Shinke T, Otake H, et al. Stabilizing effect of combined eicosapentaenoic acid and statin therapy on coronary thin-cap fibroatheroma. *Atherosclerosis*. 2014;234:114–9.
11. Budoff MJ, Bhatt DL, Kinninger A, et al. Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial. *Eur Heart J*. 2020;41:3925–32.
12. Hu Y, Hu FB, Manson JE. Marine omega-3 supplementation and cardiovascular disease: An updated meta-analysis of 13 randomized controlled trials involving 127 477 participants. *J. Am. Heart Assoc*. 2019, 8, e013543.