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# Anti-inflammatory and Atheroprotective Properties of Omega-3 Polyunsaturated Fatty Acids

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## Abstract

Atherosclerosis prevention and treatment remain of great concern in the field of cardiovascular medicine. Altering inflammatory component of atherogenesis has been hypothesized to be beneficial, and thus searching for new anti-inflammatory compounds for cardiovascular disease is warranted. Recent discovery of new lipid mediators, which are generated from essential omega-3 fatty acids, represent a promising new area of investigation. These bioactive compounds, termed specialized pro-resolving lipid mediators (SPMs), have immunomodulatory and potent resolution effects. Moreover, cyclooxygenases inhibitors, such as acetylsalicylic acid, besides blocking eicosanoids production also trigger the biosynthesis of specific epimers of these SPMs. However, it has not been determined whether aspirin interacts synergistically with omega-3 fatty acids to affect atherosclerosis. The described anti-inflammatory and atheroprotective mechanisms of omega-3 fatty acids and aspirin could help in improving the treatment not just for cardiovascular but some of other inflammatory conditions.

**Keywords:** Atherosclerosis; Inflammation; Omega-3 fatty acids; Aspirin

**Abbreviations:** COX: Cyclooxygenase; DHA: Docosa Hexaenoic Acid; EPA: Eicosa Pentaenoic Acid; HETE: Hydroxyeicosa Tetraenoic Acid; HPETE: Hydroperoxyeicosa Tetraenoic Acid; LOX: Lipoxygenase; LT: Leukotriene; PD: Protectin; PG: Prostaglandin; Rv: Resolvin; TX: Thromboxane.

## Introduction

Chronic inflammation is a critical contributing factor to the development of atherosclerosis [1]. Although there are several ongoing trials to assess whether drugs that directly suppress inflammation [2,3], most of the drugs commonly used to treat dyslipidemia are anti-inflammatory, except perhaps for fish oil [4]. The beneficial effects of fish oil appear to be due to long-chain omega-3 polyunsaturated fatty acids (PUFA), namely eicosapentaenoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3). Omega-3 PUFA reduce inflammation through multiple mechanisms, including partial replacement of pro-inflammatory omega-6 arachidonic acid (C20:4 n-6) in cell membranes, a shift in the balance of the eicosanoid production and subsequent downstream effects, and modulation of the production and gene expression of transcription factors and pro-inflammatory cytokines [5].

Aspirin is the only other agent that does have some anti-inflammatory properties and is commonly used in cardiovascular disease, because of its anti-thrombotic effect [6]. By irreversible inhibition of cyclooxygenase 1 (COX-1), aspirin blocks the production of pro-inflammatory lipid mediators from arachidonic acid, such as prostaglandins (PGs), thromboxanes (TXs) and prostacyclins. It is well known that these mechanisms of action made aspirin the most relevant antiplatelet pharmacological agent for preventing and treating cardiovascular diseases (CVD) [7]. Moreover, previous studies showed that omega-3 PUFAs can also affect aggregation by utilizing various pathways [8-10]. Accumulated evidences from in vivo studies on omega-3 PUFAs antithrombotic effects led to the hypothesis that combinatory treatment with aspirin might increase inhibitory action on platelets and result in better CVD outcomes [11,12]. However, the main concern of applying this treatment strategy clinically was reported to be an extra bleeding possibly associated with high dose of PUFAs [13]. Bleeding risk assessment was accomplished in many clinical trials showing that different concentrations of omega-3 PUFAs are generally safe and can be applied along with aspirin [14-16]. Although, the proposed treatment strategy associated with beneficial anthithrombotic effects, alternative combination of aspirin with omega-3 PUFAs is not present in the last official guidelines on coronary artery disease management [17]. In this short review, we comment on our recent paper [18] and related work by others on the combined effect of fish oil and aspirin in a mouse model of atherosclerosis, which suggests that the combination of these two relatively safe and inexpensive medications may be a useful approach for CVD prevention.

A recent major breakthrough in our understanding of inflammation has been the identification of lipid-mediators that resolve inflammation [19]. These potent specialized pro-resolving lipid mediators (SPMs) are produced locally at the sites of inflammation and are derived from omega-3 PUFAs enriched in fish oils, EPA and DHA [20]. Resolvins (Rv), protectins (PD) and maresins (Mar) are examples of anti-inflammatory molecules produced from omega-3 PUFAs (Figure 1) [21]. The synthesis of most of these pro-resolution lipid mediators are also dependent upon either cyclooxygenases (COX-1, COX-2) and lipoxygenases (5-LOX, 12-LOX, 15-LOX) and the presence of arachidonic acid and omega-3 PUFAs substrates. Moreover, COX-2 partial inhibition by acetylsalicylic acid (aspirin; ASA) is known to switch the enzymatic activity from a prostaglandin

endoperoxide synthase to a lipoxygenase that leads to the production of aspirin-triggered (AT) lipid mediators, which also has anti-inflammatory effects (Figure 1) [22]. We, therefore, tested the hypothesis that a combination of fish oils and aspirin may act synergistically in reducing inflammation in a mouse model of atherosclerosis [18].

In our study, apoE-null mice were put on the following purified customized diets: Omega-3 PUFA deficient (OD), Omega-3 PUFA Rich (OR) (1.8 g Omega-3 PUFAs/kg·diet per day), Omega-3 PUFA Rich plus ASA (ORA) (0.1 g ASA/kg. diet per day), or an Omega-3 PUFA deficient plus ASA (ODA), with supplement levels equivalent to human doses. As we anticipated, mice on the ORA diet had lower tissue levels of arachidonic acid derived prostanoids compared to omega-3 PUFAs enriched diet alone [18]. Specifically, for prostaglandin D2 (PGD2), prostaglandin E2 (PGE2), prostaglandin F2α (PGF2α) and 15R-hydroxyeicosatetraenoic acid (15-HETE), the ORA group had lower values than either the ODA or OR groups. Moreover, only mice on the ORA diet had significantly reduced atherosclerosis compared to the OD and OR diet groups, as determined by en face analysis of the aorta. We also observed significantly lower serum proinflammatory cytokines concentration of mammalian keratinocyte chemoattractant (mKC) and monocyte chemoattractant protein-1 (MCP-1) in the OR and ORA diet groups. The other measured cytokines (IFN-γ, TNF-α, IL-1b, IL-6, IL-10 and IL-12p70) were not significantly differing between the groups.

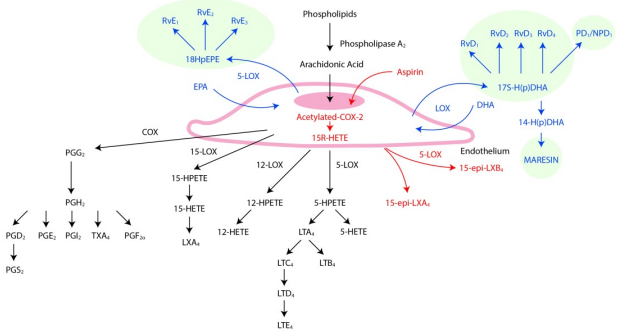


**Figure 1:** Biosynthesis of eicosanoids and specialized pro-resolving mediators.

In support of our findings it has been shown by others that plasma level of aspirin-triggered lipoxin are significantly lower in patients with peripheral atherosclerosis than in healthy volunteers [23]. Another aspirin-triggered mediator, aspirin-triggered resolvin D3 (AT-RvD3), has also been described to have a protective action for injured mucosa and helps restore epithelial barrier and function [24]. Although, we did not measure AT-RvD3 in our experiment, the highest concentration of AT-RvD1 was detected in mice in the ORA diet. However, complete suppression of COX-2 and the corresponding reduction in prostaglandin production has been shown to enhance arterial stiffness in humans [25]. Patients with metabolic syndrome showed an increase in plasma E-series resolvins without any alteration in plasma SPMs after addition of aspirin [26]. Overall, these observations suggest that anti-inflammatory action of aspirin are determined not only by the inhibition of COXs but may also involve alternative SPMs pathway activation and perhaps the availability of omega-3 PUFAs [27]. Interestingly, patients with coronary artery disease are deficient in aspirin-triggered forms, such as AT-RvD3, AT-lipoxin B4 (AT-LXB4) and treatment of these patients with omega-3 PUFAs (Lovaza) restores these lipid mediators to normal levels [28]. Moreover, topical RvE1 application in rabbit model attenuates enhanced atherogenesis and inhibits vascular inflammation by stimulating resolution of inflammation [29]. A combination treatment with RvE1 and atorvastatin in mice also resulted in a more prominent reduction of atherosclerotic lesion area [30].

An unexpected finding from our study was the effect of the diets on proprotein convertase subtilisin/kexin type 9 (PCSK9). Both on the OR and ORA diets, we observed a significant reduction of PCSK9 hepatic mRNA levels and PCK9 protein in the plasma compared to the OD and ODA diets. Because we did not observe these changes on just the ODA diet, these changes are most likely due to the addition of fish oils to the diet. PCSK9 is known to bind to the LDL-receptor, leading to its degradation [31]. Recently, two monoclonal antibody therapies against PCSK9 have been approved for lowering LDL-C [32]. They have also been reported to significantly reduce plasma triglycerides (TG) levels [33] although, no significant lipid differences were observed among the diet groups in our study. These ambiguous results might be explained by different cholesterol composition in the applied diets. The diet used in the previous studies [34,35] contained significant levels of cholesterol (~ 2000 ppm), whereas we utilized a customized purified EPA+DHA-deficient diet with a relatively low cholesterol level (<40 ppm).

It will be important to extend our work in other animal models and to ultimately test the combination of fish oils and aspirin in a clinical trial. Furthermore, a greater understanding eicosanoid metabolism and the role of SPMs in catabasis of inflammation-associated diseases may lead to new insights for the treatment of other inflammatory diseases, such as asthma, rheumatoid arthritis, psoriasis, lupus, and periodontitis, which are known to also have a predisposition to atherosclerosis.

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