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Review

Potential benefits of eicosapentaenoic acid on atherosclerotic plaques

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ABSTRACT

Residual cardiovascular (CV) risk remains in some patients despite optimized statin therapy and may necessitate add-on therapy to reduce this risk. Eicosapentaenoic acid (EPA), an omega-3 polyunsaturated fatty acid, lowers plasma triglyceride levels without raising low-density lipoprotein cholesterol levels and has potential beneficial effects on atherosclerotic plaques. Animal studies have shown that EPA reduces levels of pro-inflammatory cytokines and chemokines. In clinical trials utilizing a wide spectrum of plaque imaging modalities, EPA has shown beneficial effects on plaque characteristics. Studies of patients with coronary artery disease receiving statin therapy suggest that EPA may decrease plaque vulnerability and prevent plaque progression. EPA also decreased pentraxin-3 and macrophage accumulation. A large, randomized, Japanese study reported that EPA plus a statin resulted in a 19% relative reduction in major coronary events at 5 years versus a statin alone in patients with hypercholesterolemia ($P = 0.011$). Icosapent ethyl, a high-purity prescription form of EPA ethyl ester, has been shown to reduce triglyceride levels and markers of atherosclerotic inflammation. Results of an ongoing CV outcomes study will further define the potential clinical benefits of icosapent ethyl in reducing CV risk in high-risk patients receiving statin therapy.

Contents

1. Introduction

In patients with atherosclerosis, residual cardiovascular (CV) risk may remain despite optimized treatment with a statin [1]. Add-on therapy may be needed in some patients to reduce this risk. Atherosclerosis is a complex, multifaceted disease process in which lipoprotein retention, endothelial dysfunction, oxidative stress, foam cell formation, and inflammation lead to plaque formation and progression, plaque rupture, platelet aggregation, and thrombus formation (Fig. 1) [2,3]. Historically, the importance of lipid levels has been emphasized in reducing CV risk; however, the need to target multiple and additional

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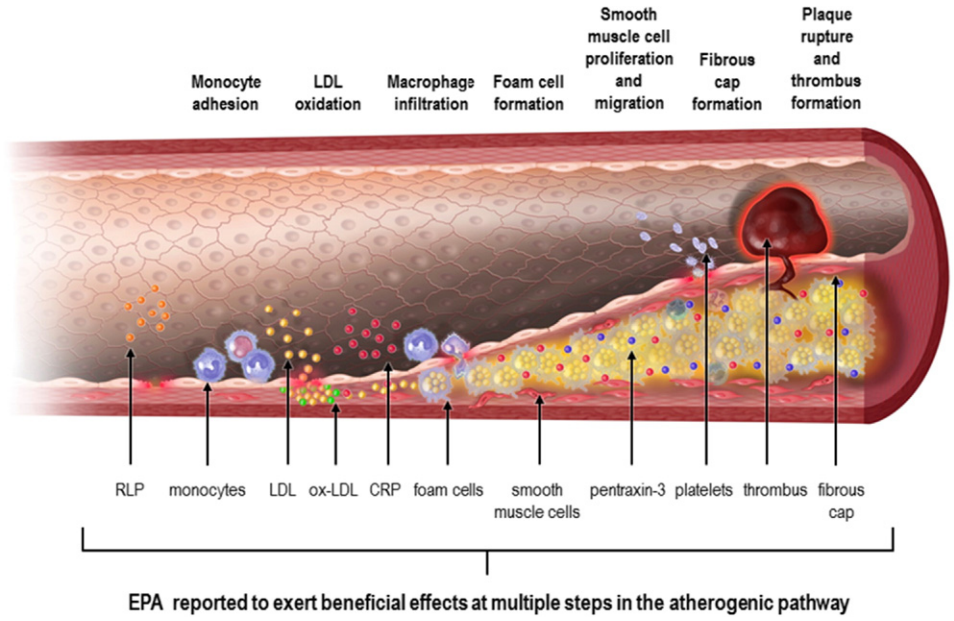

Fig. 1. Atherosclerosis is a multistep process ranging from endothelial dysfunction to plaque development, progression, and rupture, leading to thrombus formation and cardiovascular events. EPA has been reported to have beneficial effects on many of these steps. CRP, C-reactive protein; EPA, eicosapentaenoic acid; LDL, low-density lipoprotein; ox-LDL, oxidized low-density lipoprotein; RLP, remnant-like particle.
Adapted with permission from Lamon and Hajjar [3].

mechanisms associated with the causal pathway of atherosclerosis and the occurrence of CV events has been recognized more recently [2,4].

Eicosapentaenoic acid (EPA) is an omega-3 polyunsaturated fatty acid that is incorporated into membrane phospholipid bilayers [4]. EPA lowers the plasma levels of atherogenic parameters such as triglycerides, non-high-density lipoprotein cholesterol (non-HDL-C), remnant-like particle cholesterol (RLP-C), and oxidized low-density lipoprotein particles (ox-LDL) without raising low-density lipoprotein cholesterol (LDL-C) [4–6]. EPA has been shown to have a number of potential beneficial effects on atherosclerotic plaque factors, including antioxidant effects, anti-inflammatory effects, improved endothelial function, decreased adhesion of monocytes, decreased macrophage accumulation, decreased foam cell accumulation, increased fibrous-cap thickness, and an increase in a class of pro-resolving lipid mediators called resolvins [4,5,7,8].

Low serum levels of EPA have been associated with an increased presence of lipid-rich atherosclerotic plaques [9]. Patients with acute coronary syndrome (ACS) have been shown to have significantly lower EPA serum levels versus patients without ACS, and plaques in patients with low EPA levels had a significantly higher percent lipid volume and significantly lower percent fibrous volume versus plaques in patients with high EPA levels [9]. In addition, low serum EPA levels in patients receiving statin therapy have been associated with a greater extent of plaque involvement and more vulnerable plaque characteristics [10]. In an Infarction Prognosis Registry analysis of 508 patients who had an acute myocardial infarction (MI), low plasma EPA, but not low docosahexaenoic acid (DHA), was predictive of all-cause and CV mortality at 16 months of follow-up [11]. Likewise, in a multicenter study of 1144 patients with acute MI, the concentration of EPA, but not DHA, in erythrocytes predicted the incidence of in-hospital death after acute MI [12].

EPA has been reported to be incorporated rapidly into atherosclerotic plaques and to a greater extent than DHA [13]. In a randomized study of patients undergoing carotid endarterectomy (n = 121) who consumed omega-3 polyunsaturated fatty acids (omega-3 PUFAs) or placebo prior to surgery, the proportion of EPA in carotid plaques was significantly higher in patients who consumed omega-3 PUFA versus placebo; however, DHA concentrations were not significantly higher [13]. Within the plaque itself, EPA has been reported to exert anti-inflammatory and other potentially beneficial effects [4]. EPA can also partition into atherogenic apolipoprotein B (ApoB)–containing particles. Oxidation of such particles plays an important role in atherosclerosis, and EPA has been shown to inhibit the oxidation of ApoB-containing particles such as low-density lipoprotein (LDL), small dense LDL, and very-low-density lipoprotein particles [14]. EPA has also been shown to improve the anti-oxidant, anti-inflammatory, and cholesterol efflux properties of high-density lipoprotein (HDL) particles from patients with coronary risk factors, thereby improving HDL functionality [15]. Here we review preclinical and clinical research on the effects of EPA on atherosclerotic plaques and discuss the potential effects of EPA on CV outcomes.

2. Preclinical studies of EPA effects on atherosclerotic plaques

The effects of EPA on atherosclerotic plaques have been evaluated in animal models. In a study of apolipoprotein E– and LDL-receptor–deficient mice (mouse model of hyperlipidemia), EPA suppressed the development of atherosclerotic lesions and increased the cellular content of omega-3 PUFAs, without increasing total cholesterol or HDL content (Fig. 2) [16]. The atherosclerotic plaques of mice treated with EPA had a stable morphology, including less lipid deposition, decreased accumulation of macrophages, increased smooth muscle cells, and greater collagen content. In addition, EPA had an anti-inflammatory effect on endothelial cells inhibiting the expression of adhesion molecules and monocyte chemoattractant protein-1 (MCP-1) and by inhibiting production of matrix metalloproteinase by macrophages. A recent study utilized ApoE*3 Leiden transgenic mice as an animal model to examine the effects of the EPA-derived resolvin E1 on atherosclerotic lesion progression. The mice were fed a hypercholesterolemic diet for 9 weeks and then treated for 16 weeks with either resolvin E1 (low dose or high dose), atorvastatin, or the combination of low-dose resolvin E1 and atorvastatin. Compared with vehicle control, resolvin E1 (low dose or high dose) and atorvastatin decreased atherosclerotic lesion area by 35% and 27%, respectively (all $P < 0.05$); the combination of resolvin E1 and atorvastatin reduced atherosclerotic lesion area by 51% ($P < 0.001$) [17].