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Original Article

Effects of n-3 fatty acid treatment on monocyte pheno types in humans with hypertriglyceridemia

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BACKGROUND: Hypertriglyceridemia increases risk for atherosclerotic cardiovascular disease and may contribute to atherosclerosis by changing circulating monocyte phenotypes. High-dose n-3 polyunsaturated fatty acids reduce blood triglyceride levels. Effects of triglyceride-lowering therapy on monocyte phenotypes are not well known.

OBJECTIVE: We examined effects of n-3 polyunsaturated fatty acid treatments (eicosapentaenoic acid [EPA] plus docosapentaenoic acid [MAT9001] vs EPA ethyl esters [EPA-EE]) on monocyte phenotypes in individuals with hypertriglyceridemia.

METHODS: Individuals with triglycerides 200 to 400 mg/dL were recruited. Subjects received 2 treatments in randomized order for 14 days each: MAT9001 and EPA-EE, at 4 g/d. At 2 days before the start of, and on the last day of, each treatment, nile red staining for lipids and phenotypes of each monocyte subset were examined by flow cytometry after an overnight fast and postprandially after a high-fat meal.

RESULTS: Treatment with MAT9001 or EPA-EE reduced fasting triglyceride levels and decreased proportions of intermediate monocytes. Only MAT9001 decreased postprandial blood triglyceride levels, lowered fasting nile red levels, indicating less lipid in classical and intermediate monocytes, and reduced postprandial CD11c levels on nonclassical monocytes. MAT9001 and EPA-EE each reduced fasting and postprandial CD11c and CD36 levels on classical and intermediate monocytes and postprandial CCR5 levels on intermediate and nonclassical monocytes, with no significant differences between the 2 treatments.

CONCLUSIONS: Treatment with MAT9001 in individuals with hypertriglyceridemia reduced fasting nile red staining for lipids in classical and intermediate monocytes. MAT9001 and EPA-EE each improved fasting and postprandial monocyte phenotypes, which could potentially help to protect against atherosclerosis.

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Introduction

Hypertriglyceridemia has been identified as an independent causal risk factor for atherosclerotic cardiovascular disease (ASCVD).[1–4] However, the mechanisms whereby hypertriglyceridemia contributes to ASCVD remain incompletely understood.

Atherosclerosis is an inflammatory disease characterized by accumulation of lipid-laden macrophages (foam cells) in arterial walls.[5–8] Monocyte infiltration from the circulation into arterial walls and differentiation into macrophages, which take up modified lipoproteins and become foam cells, are important steps in the development of atherosclerosis.[5,8,9] Monocytes are heterogeneous and include several subsets, which may exert differential roles in inflammation and atherosclerosis. Based on surface markers CD14 and CD16, human monocytes have been classified into $CD14^+/CD16^-$ classical, $CD14^+/CD16^+$ intermediate, and $CD14^{dim}/CD16^+$ nonclassical monocytes.[10–13] Under healthy conditions, classical monocytes are the dominant monocyte population, accounting for ~80% to 90% of total monocytes, while intermediate and nonclassical monocytes each account for 5% to 10% of total monocytes.[11,14] Nevertheless, results from most studies show that compared with $CD16^-$ classical monocytes, $CD16^+$, particularly intermediate, monocytes play more important roles in inflammation.[10,14]

While the traditional paradigm in atherosclerosis has focused on macrophage foam cell formation in arterial walls,[9] our studies and others have shown that hyperlipidemia also causes formation of foamy monocytes, monocytes with intracellular lipid droplets, in the circulation in both mice and humans.[15–22] Foamy monocytes infiltrate into arterial walls and contribute to atherosclerosis.[19,23] Hypertriglyceridemia in humans with obesity and metabolic syndrome is also associated with increased proportions of $CD16^+$ intermediate or nonclassical monocytes[12,24] and with phenotypic changes in monocytes and subsets, including upregulation of adhesion molecules, toll-like receptors, inflammatory molecules, and oxidative stress.[15,20,25–28] Moreover, postprandial elevations in triglyceride (TG) levels after a single high-fat meal promote monocyte (subset) phenotypic changes, particularly in subjects with elevated fasting TGs and metabolic syndrome.[20] Formation of foamy monocytes with phenotypic changes in hyperlipidemia may accelerate monocyte (subset) contributions to atherosclerosis and therefore serve as an important link between hypertriglyceridemia and the development of ASCVD.[19,21,23]

Because of the causal role of hypertriglyceridemia in ASCVD, reducing TG levels may be an important strategy for ASCVD prevention.[4,29] Treatment with large doses of n-3 polyunsaturated fatty acids (PUFAs; generally 2–4 g/d) reduces blood TG levels, including fasting and postprandial TG levels.[30,31] Eicosapentaenoic acid (EPA) and docosahexaenoic acid have been the most commonly used n-3 PUFAs for TG lowering.[32] More recently, supplementation with n-3 docosapentaenoic acid (DPA) revealed incorporation of DPA in various plasma lipid fractions, further reducing plasma TG levels.[33] Compared with EPA alone, EPA plus DPA resulted in greater reductions in fasting blood TG levels in subjects with hypertriglyceridemia.[34] Moreover, n-3 PUFAs may exert direct anti-inflammatory effects through several pathways independent of changes in plasma TG levels.[35] However, potential effects of n-3 PUFA treatment and reduced TG levels on monocyte (subset) lipid accumulation and phenotypes have not been well studied, particularly in individuals with hypertriglyceridemia. In the present study, we examined effects of treatment with EPA plus DPA, compared with EPA alone, on fasting and postprandial monocyte subset lipid accumulation and phenotypes in subjects with hypertriglyceridemia.

Subjects and methods

Study population and design

This was a substudy of a clinical trial (ClinicalTrials.gov identifier: NCT02310022) examining lipid effects of EPA plus DPA (MAT9001; Matinas BioPharma, Inc, Bedminster, NJ) vs EPA ethyl esters (EPA-EE) alone (VASCEPA, icosapent ethyl; Amarin Pharma, Inc, Bedminster, NJ) in subjects with hypertriglyceridemia.[34] The study was performed in a clinical research unit (Pharma Medica Research, Inc) located in Mississauga, ON, Canada, and has been detailed previously.[34] Briefly, the study included men and women aged 18 to 70 years, each with body mass index of 19.0 to 40.0 kg/m^2 and fasting TG levels of 200 to 400 mg/dL. Exclusion criteria included total cholesterol levels >300 mg/dL; nonstable use of statin therapy within 8 weeks before study drug; use of the highest recommended dose of any statin; use of TG-targeted drugs, or nonsteroidal anti-inflammatory drugs within 30 days before study drug; known history or presence of diabetes, CVD, impaired cardiovascular function, clinically significant gastrointestinal disease, or malabsorption; regular consumption of more than 1 meal containing fish or shellfish per week for 6 months before drug administration; or following a special diet within 30 days before the study.

The study had an open-label crossover design with two 14-day treatment periods (4 g/d MAT9001 vs 4 g/d EPA-EE) in randomized order, separated by a ≥35-day washout period. At 2 days before the start of each treatment and on the last day of each treatment, a postprandial study with a high-fat high-calorie breakfast was performed after a ≥12-hour fasting time. The total calorie content of the breakfast was 1241 kcal, of which 45% was from fat (Supplemental Table 1). Blood samples were collected by venipuncture before the breakfast (after fasting ≥12 hours) and at 4 and 6 hours after the breakfast.

The study protocol was approved by an ethics review board (Optimum Clinical Research Inc, Oshawa, ON, Canada). All subjects signed informed consent forms to participate in the study.

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