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Treatment with omega-3 fatty acid ethyl-ester alters fatty acid composition of lipoproteins in overweight or obese adults with insulin resistance

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ABSTRACT

Introduction: The effects of dietary fatty acid supplementation on lipoprotein fatty acid composition have rarely been described.
Patients and methods: Sixty-one overweight and obese adults with dyslipidemia and insulin resistance were randomized to placebo, 2 g/day extended-release nicotinic acid (ERN), 4 g/day prescription omega-3 fatty acid ethyl ester (P-OM3), or combination therapy for 16 weeks. Lipoprotein fatty acid composition was analyzed by gas chromatography pre- and post-treatment.
Results: Treatment with P-OM3 or combination, but not ERN, increased proportions of eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid, and reduced those for arachidonic acid in all lipoprotein fractions, with greatest impact in the high-density lipoprotein fraction. P-OM3-induced changes in eicosapentaenoic acid within low-density lipoproteins and very low-density lipoproteins were associated with beneficial effects on mean arterial pressure and pulse pressure.
Conclusions: P-OM3 supplementation, with or without ERN, was associated with differentially altered lipoprotein fatty acid composition and improved blood pressure parameters.

1. Introduction

Changes in lipoprotein concentration and composition play a role in the development of atherosclerosis and cardiovascular disease events [1]. Increased circulating levels of very low-density lipoproteins (VLDL; particularly VLDL remnants) and low-density lipoproteins (LDL) contributes to atherosclerosis and cardiovascular disease by promoting ectopic lipid accumulation, particularly of cholesterol [2]. Decreased levels of high-density lipoproteins (HDL) can in theory slow reverse cholesterol transport, and result in loss of their anti-inflammatory, anti-oxidative and anti-atherogenic effects [3–7].

In addition to lipoproteins, omega-6 (n6) and omega-3 (n3) fatty acids play important mechanistic roles in cardiovascular health [8,9]. Linoleic acid (LA), found in vegetable oils, accounts for 85–90% of dietary n6 fatty acids and can be converted (sparingly) into arachidonic acid (AA), which is the precursor for many proinflammatory and anti-inflammatory eicosanoids and promotes platelet aggregation [8]. Eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA) are n3 fatty acids derived almost exclusively from seafood ingestion and have demonstrated protective and therapeutic effects against cardiovascular disease [10]. Supplementation of long-chain n3 fatty acids, primarily EPA and DHA, in fish oil has demonstrated the following effects: improved arterial endothelial function, reduced platelet aggregation, decreased circulating triacylglycerols, improved blood pressure, and reduced risk of cardiac death after an acute myocardial infarction [11–17]. Additionally, the fatty acid composition of lipoproteins has long been associated with lipoprotein oxidizability [18] and more recently with the activity of associated proteins such as paraoxonase [19], suggesting indirect means whereby fatty acids might impact lipoprotein metabolism. Although these are promising biochemical effects, the potential clinical benefit of dietary fatty acid supplementation is clouded

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by more recent studies, which did not support a cardioprotective effect of fish oil supplementation [20–23]. Amidst these controversies, there is a lack of literature about the effects of fish oils on the fatty acid compositions of the various lipoprotein fractions (HDL, VLDL, and LDL) and plasma.

Similar to dietary fatty acid supplementation, nicotinic acid favorably modulates lipoprotein concentrations, but there is much debate regarding its use in the prevention and treatment of cardiovascular disease [20–22,24–26]. Nicotinic acid is thought to reduce cardiovascular disease events by increasing HDL-C while decreasing LDL-C and triacylglycerols [27,28], but recent data indicate that increasing HDL-C may not confer cardioprotective benefits [25,26]. At present, there is no reason to believe that nicotinic acid would alter fatty acid profiles, but no data on that question currently exist.

Here, we describe the biochemical effects of n3 fatty acid supplementation (Lovaza®) alone or in combination with extended-release nicotinic acid (Niaspan®) on the fatty acid content of lipoproteins. We also explored whether these changes could be associated with changes in blood pressure or vascular function.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled clinical trial of 4 g/day prescription n3 fatty acid ethyl ester formulation (Lovaza®, GSK; P-OM3), and 2 g/day of extended-release nicotinic acid (Niaspan, Abbott; ERN), for the treatment of cardiovascular disease risk in overweight and obese adults with dyslipidemia. The effects on the primary endpoints have been published [29]. A 6-week, single-blind run-in period to control for lifestyle changes and non-compliance preceded a baseline visit, at which time subjects were randomized to a 16-week treatment arm (placebo, ERN alone, P-OM3 alone, or combination). Lipid and vascular outcomes were measured at baseline (pre-intervention) and week 16 (post-intervention). A cohort of healthy subjects was included at baseline as a comparator group. The study was carried out by Sanford Research/USD in conjunction with the Sanford Clinic Clinical Research Services in Sioux Falls, SD. The study was approved by the local IRB and written informed consent was obtained from each subject prior to participating in the trial. The trial was registered with clinicaltrials.gov (#NCT00286234).

2.2. Sample population

Subject inclusion/exclusion criteria have been published in detail [29]. Briefly, otherwise healthy men and women meeting the following criteria were eligible for randomization to the experimental groups: age 40–69 years, BMI 25–40 kg/m^2, fasting triacylglycerols (TG) 150–750 mg/dL, HDL >10 mg/dL, and the ratio of TG/HDL >3.5. A reference cohort of 14 healthy adults was also enrolled for baseline comparison purposes. This reference cohort was not randomized to treatment or evaluated beyond baseline.

2.3. Lipid, fatty acids and other measurements

A fasting (≥ 8 h) blood sample was obtained at baseline and after 16 weeks of treatment. Lipoproteins were purified by sequential flotation and fatty acid composition was determined by gas chromatography as described [30,31]. The following fatty acids in plasma and within each lipoprotein fraction are reported here as a proportion of the total fatty acid composition: linoleic acid (LA, C18:2n6), arachidonic acid (AA, C20:4n6), eicosapentaenoic acid (EPA, C20:5n3), docosapentaenoic acid (DPA, C22:5n3), and docosahexaenoic acid (DHA, C22:6n3). The analytic error for these measurements can be found in the study reported by Shearer et al., in which the same methodology was used [32]. Blood pressure was measured per standard clinical procedures.

2.4. Statistical analysis

Statistical analyses were performed using Stata12® software. Analysis of variance and chi-square tests were used to compare baseline characteristics among the treatment groups. Differences between baseline and follow-up lipoprotein fatty acid proportions within groups were determined using paired *t*-tests. The changes in proportions were compared among treatments and among lipoprotein fractions using two-sample *t*-tests with unequal variances. A Bonferroni correction (alpha=0.0125) was included to account for multiple comparisons across the four groups. Two-sample *t*-tests were conducted to compare the mean change of cardiovascular parameters with each treatment by fraction. Pairwise correlations between the changes cardiovascular parameters and the changes in lipoprotein fatty acid proportions by treatment group were performed.

3. Results

3.1. Baseline characteristics

The final trial cohort consisted of 61 insulin resistant subjects, with an additional reference cohort of 14 healthy subjects for baseline comparisons. At baseline, the insulin resistant subjects had higher BMI, blood pressure, and homeostatic model assessment of insulin resistance (HOMA-IR), as well as increased serum concentrations of triacylglycerols, non-HDL-C, glucose, and insulin compared to the healthy reference population. Additionally, insulin resistant subjects had lower HDL-C concentrations.

With a few exceptions, baseline fatty acid proportional compositions of lipoprotein fractions were similar between healthy controls and the experimental groups (Table 1). Compared to healthy controls, insulin resistant subjects had higher proportions of LA, AA, and DPA in the VLDL fraction and higher proportions of AA in the HDL and LDL fractions. Additionally, EPA and DHA were lower in whole plasma in the insulin resistant subjects compared to healthy controls.

As previously published [29], randomization of insulin resistant subjects to one of four treatment arms resulted in similar distribution of these baseline characteristics across treatment groups.

3.2. Changes in fatty acid proportional composition of lipoprotein fractions in response to treatment

Fig. 1 displays the treatment effects (change from baseline) on fatty acid proportion within each lipoprotein fraction. Assignment to placebo did not affect the fatty acid composition within any lipoprotein fraction compared to baseline. The only effect of ERN alone was a significant reduction in the proportion of DHA within the VLDL fraction compared to baseline. Treatment with P-OM3 or in combination with ERN significantly decreased AA and significantly increased EPA, DPA, and DHA in all fractions compared to baseline. These effects of P-OM3 or Combo were also significantly different than those of placebo or ERN alone. Additionally, Combo reduced LA in the HDL and VLDL fractions compared to baseline. This effect was greater than placebo in the VLDL fraction and greater than ERN alone in the HDL fraction.