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Comparison of the effects of n-3 long chain polyunsaturated fatty acids and fenofibrate on markers of inflammation and vascular function, and on the serum lipoprotein profile in overweight and obese subjects

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Inflammation;
Peroxisome proliferator activated receptor;
Obesity

Abstract *Background and aims:* To compare the effects of n-3 long chain polyunsaturated fatty acids (n-3 LCPUFA), with those of fenofibrate, on markers of inflammation and vascular function, and on the serum lipoprotein profile in overweight and obese subjects.
Methods and results: Twenty overweight and obese subjects participated in a randomized, double-blind, placebo-controlled intervention trial and received 3.7 g/d n-3 fatty acids (providing 1.7 g/d EPA and 1.2 g/d DHA), 200 mg fenofibrate or placebo treatment for 6 weeks separated by a 2 weeks wash-out period. Fish oil and fenofibrate treatment reduced triglyceride (-0.61 ± 0.81 mmol/L, $P < 0.001$, and -0.34 ± 0.85 mmol/L, $P = 0.048$, respectively) and increased HDL cholesterol concentrations (0.13 ± 0.21 mmol/L, $P = 0.013$, and 0.10 ± 0.18 mmol/L, $P = 0.076$), as reflected by a decrease of large very VLDL particles and increases of large HDL particles and medium size HDL particles. Fish oil increased serum LDL cholesterol concentrations (0.34 ± 0.59 mmol/L, $P = 0.013$). Fenofibrate reduced concentrations of soluble endothelial selectin (sE-selectin) (-4.1 ± 7.5 ng/mL, $P = 0.032$), but increased those of macrophage chemoattractant protein 1 (MCP1) (28 ± 55 ng/mL, $P = 0.034$). Fish oil had no effects on these markers.
Conclusion: Although n-3 LCPUFA and fenofibrate can both activate PPARα, they have differential effects on cardiovascular risk markers. In overweight and obese subjects fenofibrate (200 mg/d) or n-3 LCPUFA (3.7 g/d) treatment for 6 weeks did not improve markers for low-

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grade systemic inflammation, while fenofibrate had more profound effects on plasma lipids and markers for vascular activity compared to fish oil.

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Introduction

Drugs of the fibrate class, such as fenofibrate, are potent activators of Peroxisome Proliferator Activated Receptor α (PPARα) [1]. These lipid-lowering drugs effectively reduce triglyceride, moderately reduce low density lipoprotein (LDL) cholesterol, and elevate high density lipoprotein (HDL) cholesterol [2]. Furthermore, fibrates may exert anti-inflammatory effects and improve vascular function [3]. Therefore, targeting PPARα can be an effective way to improve features belonging to the metabolic syndrome and to reduce cardiovascular risk. As PPARs can be seen as lipid sensors, dietary n-3 fatty acids deserve attention in this respect. Especially the marine n-3 long chain poly-unsaturated fatty acids (n-3 LCPUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) preferentially bind to and activate PPARα [1]. However, these n-3 LCPUFA can also activate PPARγ and PPARδ, two other PPAR isoforms [1]. As fibrates, dietary n-3 LCPUFA have potent hypo-triglyceridemic effects and can increase HDL cholesterol [4]. Furthermore, the suggested beneficial effects on inflammation and endothelial function may further contribute to a reduction in cardiovascular risk. Stalenhoef et al. have compared in hypertriglyceridemic subjects gemfibrozil with n-3 LCPUFA and showed that both treatments had favorable effects on serum lipid concentrations and lipoprotein particle heterogeneity [5]. However, in that study markers reflecting low-grade systemic inflammation and endothelial function were not examined.

To establish the relevance of a dietary component as a subtle, PPAR agonist with that of a strong, synthetic PPARα agonist, we decided to compare side-by-side the effects of n-3 LCPUFA with those of fenofibrate on inflammatory parameters, vascular function, and the serum lipoprotein profile in overweight and obese subjects, who are at increased risk to have or to develop the metabolic syndrome.

Methods

Subjects

Caucasian subjects with a BMI of at least 27 kg/m^2 were recruited between the end of March and the end of August of 2007 via posters in the university and hospital buildings, and via advertisements in local newspapers. Subjects came to the university for a screening visit. On this visit, fasting blood was sampled for analyses of serum lipids and lipoproteins. In addition, height and body weight were determined. Furthermore, subjects had to complete a medical and general questionnaire. Exclusion criteria were BMI below 27 kg/m^2, impairment of kidney (creatinine $>$ 150 mmol/L) and liver function (ALAT, ASAT, ALP, GGT or total bilirubine $>$ 2 times upper limit of normal), serum total cholesterol above 8 mmol/L, serum triglycerides above 4 mmol/L, taking medication that could influence the study outcome or could interfere with fenofibrate treatment, use of fish oil supplements, consumption of plant sterol or stanol-enriched food products, having donated blood within 1 month prior to the start of the study, having a diagnosis of any long-term medical condition (e.g. diabetes, cardiovascular diseases, epilepsy) or experiencing strong symptoms of allergy. Subjects received oral and written information about the nature and risk of the experimental procedures before their written informed consent before the start of the study. The study was approved by the Medical Ethical Committee of Maastricht University.

After the screening of 34 subjects, 26 subjects met all our inclusion criteria and started the study. After inclusion, 6 subjects dropped out (1 man underwent surgery for an aneurysm, 1 woman had complained about vapors during the placebo period, 1 man and 1 woman did not regularly attend appointments and were excluded, 1 man had a work-related reason, and 1 man had personal reasons). Thus, ten men and ten women completed the trial. Baseline characteristics are presented in Table 1.

Study design

The study had a randomized, double-blind, placebo-controlled, crossover design. Each subject enrolled in random order in a fish oil, a fenofibrate and a placebo period for 6 weeks with a wash-out period of at least 2 weeks between the intervention periods. During the fish oil intervention, subjects had to consume daily 8 fish oil capsules (Marinol C-38™, Lipid Nutrition, Wormerveer, the Netherlands), providing approximately 3.7 g/d n-3 LCPUFA (1.7 g/d EPA and 1.2 g/d DHA,) and 2 capsules placebo-matching fenofibrate (200 mg/d cellulose). During the fenofibrate period, subjects consumed 2 capsules providing 200 mg/d micronized fenofibrate (Lipanthyl®, Fournier Laboratories, Dijon, France) and 8 placebo-matching fish oil capsules (containing 80% High Oleic Sunflower Oil (HOSO)). During the placebo period, subjects received 8 HOSO capsules and 2 cellulose capsules. Subjects had to ingest half of the capsules before breakfast and the other half before dinner with a glass of water. Subjects were restricted in their fish consumption to a maximum of one portion a week. During the study, subjects recorded any symptom of illness, visits to physician, medication used, alcohol consumption, and any deviations from the protocol in diaries. Body weight was recorded at weeks 0, 5 and 6 of each intervention period and blood pressure was monitored using a sphygmomanometer (Omron M7, CEMEX Medische Techniek BV, Nieuwegein, the Netherlands). At the end of each intervention period, energy and nutrient intakes of the previous 4 weeks were estimated using a food frequency questionnaire (FFQ) [6].