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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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KEYWORDS

Fibrate; Fish oil; n-3 Long chain polyunsaturated fatty acids; Lipids; Lipoprotein particle size; 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 Z 0.048, respectively) and increased HDL cholesterol concentrations (0.13 _ 0.21 mmol/L, P Z 0.013, and 0.10 _ 0.18 mmol/L, P Z 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, PZ 0.013). Fenofibrate reduced concentrations of soluble endothelial selectin (sE-selectin) (_4.1 _ 7.5 ng/mL, P Z 0.032), but increased those of macrophage chemoattractant protein 1 (MCP1) (28 _ 55 ng/mL, P Z 0.034). Fish oil had no effects on these markers.

Conclusion: Although n-3 LCPUFA and fenofibrate can both activate PPARa, 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-grade systemic inflammation, while fenofibrate had more profound effects on plasma lipids and markers for vascular activity compared to fish oil.

INTRODUCTION

Drugs of the fibrate class, such as fenofibrate, are potent activators of Peroxisome Proliferator Activated Receptor a (PPARa) [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 PPARa 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 polyunsaturated fatty acids (n-3 LCPUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) preferentially bind to and activate PPARa [1]. However, these n-3 LCPUFA can also activate PPARg and PPARd, two other PPAR isoforms [1]. As fibrates, dietary n-3 LCPUFA have potent

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hypotriglyceridemic 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 PPARa 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.

MATERIAL AND METHODOLOGY

Subjects

With a BMI of at least 27 kg/m2 were recruited between the end of March and the end of August of 2024, 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/m2, 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 stanolenriched 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.

After the screening of 34 subjects, 26 subjects m *et al*l 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.

Table 1: Baseline characteristics of the participants.

Table 1 Baseline characteristics of the participants.[a]

	All (n = 20)	Females (n = 10)	Males (n = 10)
Age (years)	52 ± 12	51 ± 14	54 ± 10
BMI (kg/m^2)	33 ± 5	34 ± 5	31 ± 5
Waist circumference (cm)	117 ± 12	116 ± 11	118 ± 13
Systolic blood pressure (mmHg)	131 ± 14	122 ± 9	141 ± 10
Diastolic blood pressure (mmHg)	91 ± 8	85 ± 7	96 ± 5
Total cholesterol (mmol/L)	6.23 ± 1.18	5.89 ± 1.45	6.59 ± 0.78
LDL cholesterol (mmol/L)	3.97 ± 1.09	3.54 ± 1.23	4.41 ± 0.75
HDL cholesterol (mmol/L)	1.52 ± 0.44	1.67 ± 0.46	1.38 ± 0.39
Triglycerides (mmol/L)	1.63 ± 0.59	1.51 ± 0.52	1.76 ± 0.65
Glucose (mmol/L)	5.34 ± 0.73	5.22 ± 0.54	5.45 ± 0.88
Criteria metabolic syndrome (n)[b]	2.2 ± 1.0	1.6 ± 0.7	2.7 ± 1.1
Diagnosis metabolic syndrome (n)[b]	7	1	6

[a] Values are expressed as mean ± SD.
[b] According to the National Cholesterol Education Program Adult Treatment Panel III guidelines.

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Study design

The study had a randomized, double-blind, placebo controlled, cross over 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].

Blood sampling and analyses

Blood sampling

In weeks 5 and 6 of each intervention period, subjects arrived in the morning after an overnight fast and after abstinence from drinking alcohol the preceding day. Venous blood was sampled in BD vacutainer tubes (Becton Dickinson Company, NJ, USA). Serum was obtained by clotting the blood for 30 min, followed by 30 min centrifugation at 2000g. EDTA, NaF and heparin plasma were obtained by centrifugation at 2000g for 30 min at 4° C, directly after sampling. Serum and plasma aliquots were snap frozen and stored at 80° C until analysis.

Clinical safety parameters

Serum concentrations of markers of liver and kidney function (total bilirubin, aspartate aminotransferase (ASAT), alanineaminotransferase (ALAT), alkaline phosphatase (ALP), gglutamyl transpeptidase (g-GT), ureum, and creatinine) from week 6 of each intervention period were determined.

Plasma lipids, lipoproteins and glucose

Plasma EDTA samples from weeks 5 and 6 were analyzed separately for concentrations of serum total cholesterol (ABX Diagnostics, Montpelier, France), HDL cholesterol (precipitation method; Roche Diagnostics Corporation, Indianapolis, IN), and triglycerides corrected for free glycerol (Sigmae Aldrich Chemie, Steinheim, Germany). Serum LDL cholesterol concentrations were calculated with the formula of Friedewald *et al*. [7]. After analysis, values of weeks 5 and 6 were averaged. The free EPA and DHA content in plasma as a compliance marker, was determined with LC-MS methodology (TNO, Zeist, the Netherlands) as described [8] in heparin plasma of week 6 from each period. The plasma lipoprofile (number and size op lipoprotein particles) was analyzed by NMR (NMR LipoProfile test, Liposcience Inc., Raleigh, NC, USA) in a pooled sample from weeks 5 and 6 of each treatment period. NaF plasma samples from weeks 5 and 6 were analyzed for free fatty acids (FFA) with the Wako Nefa C test kit (Wako Chemicals, Neuss, Germany) and plasma glucose with the hexokinase method (LaRoche, Basel, Switzerland), and values were averaged.

Markers of inflammation and vascular activity

Plasma EDTA samples from weeks 5 and 6 of each intervention period were pooled prior to the analysis of plasma markers of inflammation and vascular activity. High sensitive CRP (hsCRP) was measured with a immunoturbidimetric assay using commercially available kit (Kamiya Biomedical Company, Seattle, WA, USA). The MS2400 Human Vascular Injury II Assay (Meso Scale Discovery, MD, USA) was used for analysis of soluble Vascular Cell Adhesion Molecule-1 (sVCAM1) and soluble Intracellular Adhesion Molecule-1 (sICAM1). Tumor Necrosis Factor a Receptors (TNFR) 1 and 2 were measured with the MS2400 TNFR1 and TNFR2 ultrasensitive assay (Meso Scale Discovery, MD, USA). Plasma concentrations of

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Macrophage Chemoattractant Protein 1 (MCP1) were measured with the MA2400 Human MCP1 ultrasensitive assay (Meso Scale Discovery, MD, USA). Soluble endothelial selectin (sE-selectin) concentrations were measured by enzyme-linked immunosorbent assay (ELISA) as described [9]. Plasma Tumor Necrosis Factor a (TNFa) and interleukin 6 (IL6) were measured with an ELISA kit from R&D systems (Abingdon, UK). All samples from one subject were analyzed in the same analytical run in duplicate. The intra- and inter-assay variation coefficients were below 10% for all measured parameters.

Statistics

The power to detect a true difference of 0.20 mmol/L in triglyceride concentrations between treatments after adjustment for multiple comparisons was 80%. Normality was checked visually and tested with the ShapiroeWilk test. Glucose and sE-selectin concentrations were log transformed to achieve normality. Differences in fasting levels at the end of the intervention periods were compared with a General Linear Model for Univariate ANOVA with treatment as fixed factor and subject number as random factor. Since there were no significant interactions between treatment and gender, and treatment and body weight on the outcome parameters, these parameters were not included in the final model. To adjust for multiple comparisons, a Tukey Honestly Significantly Difference (HSD) procedure was carried out. A $P < 0.05$ was considered to be statistically significant. Data are presented as mean _ SD. Statistical analysis was performed using SPSS 15.0 for Windows.

Table 2: Effects of fish oil and fenofibrate on serum lipid concentration and plasma glucose concentration.[a]

Table 2 Effects of fish oil and fenofibrate on serum lipid concentrations and plasma glucose concentrations.[a]

	Placebo	Fenofibrate	Fish oil
Total cholesterol (mmol/L)	6.01 ± 1.32	5.42 ± 1.20[c]	6.29 ± 1.42[d]
LDL cholesterol (mmol/L	3.74 ± 1.14	3.30 ± 1.09[c]	4.08 ± 1.24[c, d]
HDL cholesterol (mmol/L)	1.44 ± 0.41	1.58 ± 0.42[c]	1.54 ± 0.48
FFA (μM/L)	396 ± 236	368 ± 237	357 ± 209
Glucose (mmol/L)[b]	5.3 ± 0.7	5.4 ± 0.7	5.6 ± 0.7

[a] Values are expressed as mean ± SD.
[b] Log transformed concentrations were used for statistical analysis.
[c] $P<0.05$ versus placebo period.
[d] $P<0.05$ versus fenofibrate period.

RESULTS

Compliance, dietary intake, body weight and blood pressure

The calculated main daily capsule intake was 93% during the fish oil period, 95% during the fenofibrate period and 95% during the placebo period, indicating a good compliance. This was confirmed for the fish oil period, as plasma free EPA and DHA concentrations increased by 358% ($P < 0.001$) and 105% ($P < 0.001$) compared to the placebo period, and by 463% ($P < 0.001$) and 157% ($P < 0.001$) compared to the fenofibrate period, respectively. Total energy intake and the proportions of energy from fat, carbohydrates and protein, and the amounts of fiber, alcohol and cholesterol in the diet did not differ between the treatment groups (data not shown). Furthermore, body weight and blood pressure did not change between the treatment periods (data not shown).

Effects on serum lipids and lipoprofile and plasma glucose

Compared to placebo, fenofibrate reduced serum total cholesterol and LDL cholesterol by respectively 9% (_0.59 mmol/L, P Z 0.001) and 11% (_0.45 mmol/L, P Z 0.004; Table 2). Fish oil tended to increase the concentration of total cholesterol (PZ0.099) and increased that of LDL cholesterol by 10% (0.34 mmol/L, P Z 0.035)

Compared to placebo. Both fenofibrate and fish oil effectively reduced serum triglyceride concentrations by respectively 27% (_0.61 mmol/L, $P < 0.001$) and 13% (_0.34 mmol/L, PZ 0.048) compared with placebo (Fig. 1). HDL cholesterol concentrations increased by 11% (0.13 mmol/L, P Z 0.013) after fenofibrate treatment, whereas fish oil tended to increase HDL cholesterol (P Z 0.076) compared to placebo. Compared with fenofibrate

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treatment, HDL cholesterol (PZ0.737) and triglyceride concentrations (PZ0.133) were comparable after fish oil intake, but total cholesterol (0.91 mmol/L, P < 0.001) and LDL cholesterol (0.78 mmol/L, P<0.001) were increased. Concentrations of free fatty acids were not affected by either treatment. Fish oil tended to raise fasting plasma glucose concentrations compared to placebo (0.24 mmol/L, P Z 0.056) and fenofibrate treatment had no effect (P Z 0.721) compared to placebo. At the end of the intervention period, glucose concentrations between fish oil and fenofibrate treatment (P Z 0.250) did not differ.

Compared to placebo, fenofibrate significantly reduced total VLDL particle numbers (_23 nmol/L, P Z 0.001), in particular large (_2.4 nmol/L, P Z 0.003) and medium VLDL particles (_14 nmol/L, P Z 0.001). Fish oil reduced the number of large VLDL particles (_3.0 nmol/L, P < 0.001), although the total number of VLDL particles was not affected. It increased however the total number of LDL particles (224 nmol/L, P Z 0.005), but decreased the number of IDL particles (_28 nmol/L, P Z 0.016). For HDL, fenofibrate decreased HDL size (_0.11 nm, P Z 0.025) and increased the number of medium HDL particles (3.1 mmol/ L, PZ0.011). Fish oil had no overall effect on HDL size, but increased the number large HDL particles (1.5 mmol/L). Fish oil treatment resulted in higher particle numbers of (1.8 nmol/L, P Z 0.004 and 0.14 nm, P Z 0.004, respectively). The number of medium HDL particles was smaller after fish oil treatment compared to fenofibrate treatment (_4.8 nmol/L, P < 0.001).

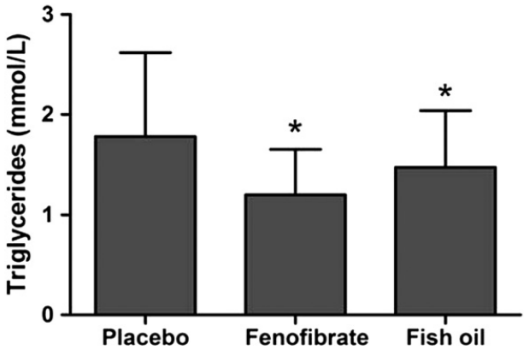

Figure 1 The effects of fish oil and fenofibrate treatment on serum triglyceride concentrations. Data are presented as mean ± SD. An asterisk indicates a significant effect compared to placebo ($P < 0.05$).

Table 3: Effects of fenofibrate and fish oil consumption on plasma NMR lipoprofile. [a]

Table 3 Effects of fenofibrate and fish oil consumption on plasma NMR lipoprofile.[a]

	Placebo	Fenofibrate	Fish oil
Particle numbers			
Total VLDL	63 ± 28	40 ± 24[b]	56 ± 40[c]
Large VLDL	4.9 ± 3.7	2.4 ± 2.6[b]	1.8 ± 3.2[b]
Medium VLDL	26 ± 17	12 ± 9[b]	26 ± 24[c]
Small VLDL	32 ± 18	26 ± 15	28 ± 18
Total LDL	1484 ± 554	1374 ± 548	1708 ± 679[b, c]
IDL	55 ± 62	40 ± 47	27 ± 43[b]
Large LDL	523 ± 252	439 ± 176	571 ± 292[c]
Small LDL	906 ± 614	895 ± 497	1110 ± 727[c]
Medium small LDL	191 ± 139	190 ± 118	223 ± 145
Very small LDL	714 ± 496	705 ± 382	887 ± 586[c]
Total HDL	36 ± 8	38 ± 6	36 ± 8
Large HDL	7.1 ± 4.4	6.7 ± 3.9	8.6 ± 5.3[b, c]
Medium HDL	4.5 ± 5.4	7.6 ± 6.0[b]	2.8 ± 3.4[c]
Small HDL	25 ± 6	24 ± 7	25 ± 6
Particle sizes			
VLDL	56 ± 16	53 ± 10	48 ± 8[b]
LDL	21 ± 1	21 ± 1	21 ± 1
HDL	8.9 ± 0.5	8.7 ± 0.4[b]	8.9 ± 0.5[c]

[a] Values are means ± SD ($n = 20$). Particle numbers are expressed in nmol/L, except for HDL particles, which are expressed in μmol/L. Particle sizes are expressed in nm.
[b] $P<0.05$ versus placebo period.
[c] $P<0.05$ versus fenofibrate period.

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Effects on plasma makers of inflammation and vascular activity

Concentrations of TNFR1, TNFR2 hsCRP, TNFa, IL6, sICAM1 and sVCAM1 did not differ between the treatments (Table 4). Compared with placebo, the chemokine MCP1, however, increased upon fenofibrate treatment (28 ng/mL, PZ0.034), but remained unaffected after fish oil treatment (P Z 0.204) (Table 4). Further, fenofibrate significantly lowered sE-selectin concentrations compared to both placebo (_4.1 ng/mL, P Z 0.034) and fish oil (_5.7 ng/mL, P Z 0.014), whereas fish oil treatment had no effect compared to placebo (PZ0.932).

Table 4: Effects of fenofibrate and fish oil treatment on market of inflammation and vascular function. [a]

Table 4 Effects of fenofibrate and fish oil treatment on markers of inflammation and vascular function.[a]

	Placebo	Fenofibrate	Fish oil
Immune receptors			
TNFR1 (ng/mL)	3.4 ± 0.8	3.5 ± 0.7	3.4 ± 0.6
TNFR2 (ng/mL)	4.3 ± 1.1	4.6 ± 0.9	4.1 ± 1.0
Acute phase protein			
CRP (mg/L)	4.0 ± 2.8	3.6 ± 1.9	4.3 ± 3.7
Cytokines			
TNFα (pg/mL)	2.0 ± 0.8	2.0 ± 0.6	2.0 ± 0.7
IL6 (pg/mL)	2.8 ± 1.1	2.7 ± 1.1	2.7 ± 1.0
MCP1 (ng/mL)	257 ± 69	285 ± 87[c]	267 ± 64
Adhesion molecules			
ICAM (ng/mL)	275 ± 50	304 ± 105	267 ± 48
VCAM (ng/mL)	440 ± 102	451 ± 95	425 ± 86
E-selectin (ng/mL)[b]	76 ± 32	72 ± 32[c]	77 ± 34[d]

[a] Values are mean ± SD.
[b] Log transformed concentrations were used for statistical analysis.
[c] $P<0.05$ versus placebo period.
[d] $P<0.05$ versus fenofibrate period.

Side effects

Fish oil and micronized fenofibrate were well tolerated by all subjects. Fish oil had no significant effects on markers of liver and kidney function (Table 5) compared to placebo.

Table 5: Effects of fenofibrate and fish oil treatment on markers of kindly and liver function. [a]

Table 5 Effects of fenofibrate and fish oil treatment on markers of kidney and liver function.[a]

	Placebo	Fenofibrate	Fish oil	Reference values[b]
Total bilirubin (μmol/L)	14 ± 7	12 ± 3	14 ± 5	0–17
ALAT (IU/L)	28 ± 8	50 ± 52[c]	38 ± 27	5–45
ASAT (IU/L)	17 ± 7	30 ± 26[c]	22 ± 10	5–35
ALP (IU/L)	75 ± 24	67 ± 23[c]	73 ± 21	30–140
γ-GT (IU/L)	34 ± 10	58 ± 61	35 ± 10	2–50
Ureum (mmo/L)	5.0 ± 0.9	5.4 ± 1.3	4.8 ± 0.9	3–7
Creatinine (μmol/L)	78 ± 12	88 ± 16[c]	78 ± 13[d]	53–110

[a] Values are mean ± SD.
[b] Reference values from the department of Clinical Chemistry, University Hospital Maastricht, Maastricht, the Netherlands.
[c] $P<0.05$ versus placebo period.
[d] $P<0.05$ versus fenofibrate period.

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In contrast, fenofibrate slightly increased ALAT (22 IU/L, PZ0.043). For 5 out of the 20 subjects values were above the normal range Fenofibrate also increased ASAT (13 IU/L, P Z 0.016L) and decreased ALP concentrations compared to placebo (_8 IU/ L, P Z 0.019). Creatinine concentrations were higher after fenofibrate treatment compared to placebo (9.8 mmol/L, P < 0.001) and fish oil treatment (9.4 mmol/L, P < 0.001). Although g-GT did not change significantly (P Z 0.979), it slightly exceeded the normal range upon fenofibrate treatment compared to placebo for 4 out of 20 subjects.

DISCUSSION

Overweight and obese subjects are often characterized by a disturbed lipid and lipoprotein profile, low-grade systemic inflammation, and endothelial dysfunction. Away to improve these metabolic aberrations is by targeting PPARa. We hypothesized that a dietary intervention with n-3 LCPUFAs, as non-selective PPARa agonists, could be an alternative for a strong medicinal agonist. Therefore, we directly compared the effects of these n-3 LCPUFAs with those of fenofibrate on a broad range of biomarkers for cardiovascular disease. However, we found that fenofibrate (200 mg/d) and n-3 LCPUFA (3.7 g/d) treatment for 6 weeks did not improve markers for low-grade systemic inflammation and that fenofibrate had more profound effects on plasma lipids and vascular activity compared to fish oil in overweight and obese individuals.

Studies on fenofibrate have shown inconsistent results regarding effects on low-grade inflammation and vascular activity [10e12]. We found that fenofibrate reduced sE-selectin concentration compared to placebo and fish oil treatment in overweight and obese subjects. This finding corresponds to that of Hogue *et al*., who found in type 2 diabetic patients, that micronized fenofibrate (200 mg/d) for 6 weeks reduced plasma sE-selectin, but did not affect concentrations of hsCRP, sICAM1 and sVCAM1 [11]. In contrast, Ryan *et al*. showed in an obese population, that fenofibrate reduced sVCAM1, sICAM1, TNFa, IL6, IL1b, but did not affect sE-selectin concentrations [12]. The reduced sE-selectin concentration as we observed suggests beneficial effects of fenofibrate on vascular activity, since E-selectin is involved in the adherence of leukocytes in the process of atherosclerosis [13]. However, this seems to contradict the observed increase in MCP1 concentrations after fenofibrate treatment compared to placebo, since this chemokine is responsible for attracting monocytes to the injured endothelium [13]. For fish oil, human intervention studies using doses ranging between 1.1 and 6.6 g/d n-3 LCPUFAs are inconsistent and do not often report beneficial effects on inflammatory markers and cellular adhesion molecules [14,18]. In that respect, our results agree with those of other studies in obese men [17,18] and healthy middle-aged individuals [19], although our sample size may have been too limited to detect statistically significant changes in IL6 and TNFa.

The main well-established effects of fenofibrate and fish oil on plasma lipids are their hypotriglyceridemic effectsm [4,20]. Indeed, we also found that both treatments similarly lowered serum triglyceride concentrations and the number of large triglycerideerich VLDL particles. These effects have been ascribed to an increased hepatic lipolysis and decreased lipogenesis [21,22], pathways which are under control of PPARa [2]. We demonstrated a small increase in HDL cholesterol concentrations after fenofibrate and fish oil treatment, reflected by increases in medium size and large size HDL particles. The increased delivery of surface remnants from the catabolism of VLDL particles, together with a PPARa-induced expression of apoA1 and apoA2, the main apolipoproteins of HDL, may contribute to the raise in HDL cholesterol [23]. Furthermore, PPARa may stimulate reverse cholesterol transport via induction of ATP Binding Cassette protein A1 (ABCA1) [24]. Regarding the effects of fish oil and fenofibrate on triglycerides and HDL cholesterol, it is important to note that the degree of these effects largely depend on baseline plasma lipid levels [4,25,26]. In contrast to fenofibrate, fish oil increased LDL cholesterol concentrations. Others have also reported that high dose supplementation of EPA and DHA can raise LDL cholesterol by 5e10% [26]. In this respect, some groups of subjects may be more sensitive than other groups and it has been suggested that this variability in LDL cholesterol response is related to the apoE4 variant of apolipoprotein E [27]. For fenofibrate and fish oil treatments, it has been reported that the LDL particle size changes into a more buoyant type, which may be less atherogenic [5]. In our study, however, this could not be confirmed. Fish oil increased large, small and very small LDL compared to fenofibrate. These findings seem inconsistent in relation to our observed reduction in triglycerides and increase in large HDL

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particles. When plasma triglycerides are reduced, the proportion or concentration of small LDL particles is expected to be reduced and that of large HDL increased [28]. We do not have an explanation for these unexpected results.

Finally, we observed a non-significant increase of fasting plasma glucose after fish oil treatment. This agrees with a meta-analysis by Balk *et al*. [26], who reported a very small and non-significant average net increase in fasting plasma glucose after treatment with n-3 LCPUFAs.

In summary, although n-3 LCPUFAs and fenofibrate can both activate PPARa, this study in overweight and obese subjects showed that both fenofibrate (200 mg/d) and fish oil (7.2 g/d, providing 1.7 g/d EPA and 1.2 g/d DHA) treatment for 6 weeks have different effects on cardiovascular risk markers. Both interventions equally lowered serum triglycerides and raised HDL cholesterol, which agrees with few other human studies that have compared side-by-side the effects of fibrates with those of n-3 LCPUFAs [5,29,30] Also, as in several other studies [26], fish oil treatment increased LDL cholesterol. Both treatments, however, did not improve markers for low-grade systemic inflammation, while fenofibrate had more profound, but apparently conflicting, effects on markers for vascular activity compared to fish oil. Still, like fenofibrate [30], LCPUFAs may lower cardiovascular risk through beneficial effects on other cardiovascular risk factors such as blood pressure, arrhythmias and platelet function [31,32].

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