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Camelina sativa oil, but not fatty fish or lean fish improved serum lipid profile in subjects with impaired glucose metabolism – a randomized controlled trial

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Abbreviations: AIRG, acute phase insulin response to glucose; ALA, alpha-linolenic acid; AUC, area under the curve; CRP, C-reactive protein; CSO, camelina sativa oil; CVD, cardiovascular disease; DHA, docosahexaenoic acid; DI, disposition index; EPA, eicosapentaenoic acid; FF, fatty fish; FSIGT, frequently sampled intravenous glucose tolerance test; hs, high sensitivity; ICAM, intracellular adhesion molecule; IFG, impaired fasting glucose; IS, insulin sensitivity; ISI, index of insulin sensitivity; LF, lean fish; LGI, low grade inflammation; OGTT, oral glucose tolerance test; Ra, receptor antagonist; T2DM, type 2 diabetes.

Keywords: Alpha-linolenic acid, fish, glucose metabolism, inflammation, lipid

The study is registered in Clinicaltrials.gov (NCT01768429)

ABSTRACT

Scope: The aim of the study was to examine whether lean fish (LF), fatty fish (FF) and camelina sativa oil (CSO), a plant-based source of alpha-linolenic acid (ALA), differ in their metabolic effects in subjects with impaired glucose metabolism.

Methods and results: Altogether 79 volunteers with impaired fasting glucose, BMI 25–36 kg/m^2, age 43–72 years, participated in a 12-week randomized controlled trial with four parallel groups, i.e. the FF (4 fish meals/week), LF (4 fish meals/week), CSO (10 g/day ALA) and control (limited intakes of fish and source of ALA) groups. The proportions of EPA and DHA increased in plasma lipids in the FF group, and the proportion of ALA increased in the CSO group ($P < 0.0001$ for all). In the CSO group total and LDL-cholesterol (C) concentrations decreased compared with the FF and LF groups, LDL-C/HDL-C and ApoB/ApoA-I ratios decreased compared with the LF group. There were no significant changes in glucose metabolism or markers of low-grade inflammation.

Conclusions: A diet enriched in CSO improves serum lipid profile as compared with a diet enriched in FF or LF in subjects with impaired fasting glucose, with no differences in glucose metabolism or concentrations of inflammatory markers.

1 INTRODUCTION

The consumption of fish is promoted in dietary recommendations based on its health benefits, especially regarding cardiovascular health [1,2]. The data are derived mainly from cohort studies. Fish consumption has been associated with lower rates of all-cause mortality and adverse cardiac outcomes [3], and with reduced progression of atherosclerosis in women with coronary heart disease (CHD) [4,5]. Most of the controlled studies related to fish are fish oil supplementation studies and data on effects of fish consumption are limited. Fatty fish (FF) intake has improved insulin sensitivity (IS) as compared with red meat in young women [6]. In addition to fatty fish, cod protein is beneficial regarding IS [7]. Four meals of lean fish (LF) per week have been shown to be beneficial to blood pressure in subjects with coronary heart disease [8]. The bioavailability of eicosapentaenoic acid (C20:5,n-3, EPA) and docosahexaenoic acid (C22:6,n-3, DHA) from fish is also better than from supplements [9].

The effects of the sources of the essential n-3 fatty acid (FA) of plant origin, alpha-linolenic acid (ALA, C18:3 n-3), on serum lipid profile and glucose metabolism have been less studied and are controversial [10]. ALA can be metabolized to EPA and DHA. The degree of this process varies depending on e.g. sex, age and the n-3-to-n-6 FA status in the body [11-13]. In a recent systematic review, the proportion of ALA in serum lipids was inversely associated with the risk of cardiovascular diseases (CVD) [10]. The association of either ALA intake or the proportion of ALA in plasma lipids or membranes of red blood cells with type 2 diabetes (T2DM) is controversial [10,14]. In a recent study, higher proportion of ALA in adipose tissue was inversely associated with insulin resistance. This association was more pronounced in subjects with normal waist circumference [15].

Low-grade inflammation is an important phenomenon in the pathogenesis of CVD and T2DM [16-18]. Fish consumption has been shown to be more beneficial for the concentrations of the markers of low-grade inflammation than fish oil supplements [19]. Studies regarding the effect of sources of ALA are very scarce [10].

The aim of this study was to examine for the first time in a randomized controlled setting whether FF, LF and camelina sativa oil (CSO), a source of ALA, differ in their effects on serum lipid profile, glucose metabolism, and inflammatory markers in subjects with impaired fasting glucose.

2 MATERIALS AND METHODS

2.1 Subjects

The subjects were recruited in Kuopio area by newspaper advertisements and contacting the subjects who had participated in previous interventions of the Department and given a permission to contact them for coming interventions. The main inclusion criterion was fasting plasma glucose concentration 5.6–6.9 mmol/l. The 2-h glucose concentration in the oral glucose tolerance test (OGTT) had to be ≤11.0 mmol/l. Other inclusion criteria were: BMI 25–36 kg/m^2, age 40–75 years, concentrations of fasting serum total cholesterol ≤7.0 mmol/l, LDL cholesterol ≤5.0 mmol/l and total triglycerides ≤4.0 mmol/l. The main exclusion criteria included any chronic disease, a condition hampering the ability to follow the dietary intervention protocol, alcohol abuse (> 40 g/d), weight loss of ≥5 % during the preceding 6 months and fish allergy.

Altogether 153 Caucasian subjects were screened of which 96 fulfilled the inclusion criteria. Before the randomization, eight subjects dropped out leaving 88 subjects to be randomized; 21 in the FF and control groups, and 23 in the LF and CSO groups. Nine subjects dropped out within the first three weeks during the study. Altogether 79 subjects completed the intervention (**Figure 1**).

The baseline characteristics of the subjects are presented in **Table 1**. The drop outs did not differ from those participants who completed the study.

2.2 Ethical approval

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the Ethical committee of the Hospital District of Northern Savo (55/2012). Written informed consent was obtained from all subjects.

2.3 Study design

During the 4-week run-in period the subjects followed their conventional diet and were not allowed to use any oil supplements or products enriched in plant stanols or sterols. After this phase, the subjects were randomly assigned into one of the four parallel groups: CSO, LF, FF or control for 12 weeks. The randomization was conducted by the study nurse based on a randomization table by matching the subjects according to gender, median of age, and use of statins. From every division of

randomizing factors (gender-> age-> use of statins) it was possible to end up to any of the four groups.

The instructions to the subjects were given orally and in writing by a clinical nutritionist. The subjects visited the study clinic at 0, 2, 4, 8 and 12 weeks. At each visit body weight and blood pressure were measured. The major visits were at 0 wk and 12 wk. Physical activity, alcohol intake, smoking, and use of medication known to affect the parameters measured were instructed to be kept constant during the study. These data were recorded by a questionnaire at 0 wk and 12 wk.

2.4 Study diets

The study diets were isocaloric, and they were based on the nutrient recommendations current at the onset of the study [2,20] excluding fish and ALA intakes. The FF group consumed 4 fish meals of FF (e.g. salmon, rainbow trout) per week to provide approximately 1 g EPA+DHA per day. The LF group consumed 4 fish meals of LF (e.g. saithe, cod, pike, perch, pike perch) per week. The CSO group ingested CSO 30 ml (i.e. 27 g) per day in order to get 10 g ALA per day. The control and CSO groups were allowed to eat a fish meal per week and consumed mainly lean meat and poultry. The FF, LF and control groups were not allowed to use ALA containing vegetable oils, i.e. canola, flaxseed or camelina sativa oils. The subjects kept 4-day food records (consecutive predefined days including one weekend day, checked by a clinical nutritionist at return) prior to the intervention and at 3, 7 and 11 weeks during the intervention. The food records were analyzed by AivoDiet nutrient calculation software (v. 2.0.2.1, Aivo Finland, Turku, Finland) based on national and international analyses, and international food composition tables (fineli.fi). The subjects also kept daily consumption records regarding the intake of fish (number of meals and type of fish). The CSO group recorded also the intake of CSO.

The visible sources of dietary fats, i.e. spreads, cooking fats/oils and oils for salad dressings, were provided for the subjects. The vegetable oil based spread and liquid margarine were rich in unsaturated FAs, but low in ALA. The CSO group received canola oil to be used for cooking because CSO was instructed to be used unheated. Olive oil was given for the other groups for cooking and salad dressings. Fish consumption was reimbursed according to consumption.

2.5 Methods

The samples were coded and the laboratory personnel was unaware of the randomization. Blood samples were drawn after a 10-hour overnight fasting from an antecubital vein. Concentrations of serum total, LDL and HDL cholesterol and serum triglycerides were analyzed using commercial kits (981813, 981656, 981823 and 981786, respectively) and Thermo Fisher Konelab 20XTi Analyzer (Thermo Electron Corporation, Vantaa, Finland). Apo A-I and ApoB were analyzed by immunoturbimetric method (340 nm) using Konelab 20Xti Clinical Chemistry Analyzer and Konelab System Reagents (Apolipoprotein A1 and Apolipoprotein B, Thermo Fisher Scientific, Finland). The within-run deviations (CV) for total, LDL and HDL cholesterol, triglycerides, and Apo A-I and ApoB were 3.9 %, 3.3 %, 1.9 %, 3.4 %, 1.9 % and 1.4 %, respectively. The respective between-run CVs were 1.8-2.6 %, 2.9-3.2 %, 2.7-3.6 %, 2.8-3.6 %, 1.4 % and 1.1 %.

OGTT with 75 g D-glucose and frequently sampled intravenous glucose tolerance test (FSIGT) were performed as previously described [21,22]. Due to technical problems, FSIGT data were available for 76 subjects. The Matsuda index of insulin sensitivity (Matsuda ISI) and the disposition index 30 (DI_{30}), were used as surrogate indices of the first/early-phase insulin secretion and peripheral IS, respectively. Matsuda ISI was calculated as: 10 000 / square root of (fasting glucose x fasting insulin x [arithmetic mean of glucose x arithmetic mean insulin during an OGTT at 0, 30, and 120 min]) and disposition index (DI_{30}) was calculated as the product of the ratio of total insulin area under the curve (AUC) and total glucose AUC during the 0-30min OGTT (Glu AUC_{30} / Ins AUC_{30}) multiplied by the Matsuda ISI [23,24]. The insulin sensitivity index (ISI) and acute phase insulin response to glucose (AIRG) were calculated by the MINMOD Millennium software [25] based on the FSIGT. The DI from the FSIGT was calculated by multiplying AIRG by ISI.

High sensitivity C-reactive protein (hs-CRP) was analyzed by enhanced immunoturbimetric assay using the Cobas 6000 automated analyzer (Hitachi High Technology Co, Tokyo, Japan) and C-reactive Protein High Sensitive Assay reagent (Roche Diagnostics GmbH, Mannheim, Germany). The within-run and between-run CVs were 0.5 % and 5.1 %, respectively. Serum interleukin receptor 1 antagonist (IL1Ra), intercellular adhesion molecule 1 (ICAM-1), hs-IL1beta, omentin-1 and IL-18 were analyzed by ELISA (R&D Systems, Minneapolis, MN, USA). The within-run and between-run CVs were 3.7-7.3 % and 6-11 % for IL1Ra, 3.6-4.9 % and 5.5-8.6 % for ICAM-1, 4.3-10.2 and 7.3-10.4 % for hs-IL1beta, 3.2-4.1 % and 4.4-4.8 % for omentin, and 2.5-3.1 and 7.9-8.7

% for IL-18, respectively. Three subjects (one subject in CSO, LF and control groups) were excluded from the analyses due to hs-CRP above 10 mg/dl either at baseline or/and at week 12.

As an objective measure of compliance proportions of plasma FAs in triglycerides, cholesteryl esters and phospholipids were measured by gas chromatography as previously described [26] with an exception of using C19:0 as an internal standard instead of C17:0.

2.6 Statistical analyses

SPSS statistical software (v. 21, IBM Corp., Armonk, NY) was used for statistical analyses. The data are reported as mean $\pm$ SD unless otherwise indicated. Skewed distributions were normalized using logarithmic values. Comparisons between study subjects and dropouts were performed using independent samples t-test or Mann Whitney's U test. Categorical variables were compared using χ^2 test. Repeated measures general linear model was used to analyze differences in dietary intake among the groups. Fold changes were calculated dividing the 12 wk concentrations with the concentrations at baseline (0 wk). Fold changes among the intervention groups were compared using ANCOVA adjusted for age, gender and baseline concentration and Bonferroni-corrected post hoc tests. Analyses for serum total and lipoprotein lipids were additionally adjusted for the use of statins. Changes within the groups (0 wk vs. 12 wk) were analyzed using paired samples t-test. $P < 0.05$ was considered as statistically significant.

The power calculation was based on differences in DHA in serum phospholipids, a valid biomarker of dietary intake [27] (n=18 per group, difference of 1.2 mol%, when alpha<0.05 and beta>0.9). This parameter was chosen due to modern methodology to be used in further analyses, e.g. lipidomic and metabolomic profiles, for which it is not possible to select certain variables and determine clinically relevant changes.

3 RESULTS

3.1 Dietary intake and compliance

The compliance of the subjects was good as indicated by the food consumption records, food records and the FA composition of serum lipids. Average numbers of fish meals per week during the study were 4.4 ± 0.4, 4.3 ± 0.5, 0.9 ± 0.4 and 0.9 ± 0.4 in the FF, FF, CSO and control groups,

respectively. The consumption of CSO was 25.7 ± 2.7 g/d in the CSO group. The nutrient intake is reported in **Table 2**. The intake of ALA was significantly higher during the intervention in the CSO group as compared with the other groups ($P < 0.05$). The intake of EPA and DHA was higher in the FF group as compared with the LF and control groups ($P < 0.05$ for both).

There was a significant increase in the proportion of ALA in plasma triglycerides, cholesteryl esters and phospholipids in the CSO group ($P < 0.001$) as compared with the other groups. The proportion of EPA and DHA increased in the FF group in all three lipid fractions as compared with the other groups ($P < 0.01$), except in the post hoc tests EPA did not differ from the CSO group in triglyceride and phospholipid fractions (**Figure 2**).

There was no difference in leisure time or every day physical activity among the groups during the intervention ($P = 0.965$ and $P = 0.576$, respectively, Kruskall Wallis test) or between the time points (0 vs. 12 wk, $P = 0.969$, Wilcoxon Signed ranks test).

3.2 Serum total and lipoprotein lipids

The changes in serum concentrations of total and lipoprotein lipids and apolipoprotein A-I and B within the groups are presented in **Figure 3**. In the post hoc tests the change in serum total and LDL cholesterol concentrations in the CSO group differed significantly compared with the FF group ($P = 0.008$ for total cholesterol, $P = 0.022$ for LDL cholesterol) and the LF group ($P = 0.032$ for total cholesterol, $P = 0.005$ for LDL cholesterol). Furthermore, the changes of the LDL-to-HDL ratio and the ApoB-to-ApoA-I ratio in the CSO group differed significantly compared with the LF group ($P = 0.001$ for both).

3.3 Glucose metabolism and inflammatory markers

The intervention resulted in no differences in fasting or post load plasma glucose or serum insulin concentrations in the OGTT or FSIGT among the groups (**Table 3**). Adjustment for the use of statin resulted in similar results (data not shown).

There were no differences in concentrations of hs-CRP, IL-1Ra, hs-IL-1 beta, omentin, IL-18 or ICAM-1 among the study groups ($P > 0.10$ for the group effect) (**Table 4**).

4 DISCUSSION

The aim of the present study was to examine whether FF, LF and CSO, the source of plant derived n-3 FA (ALA), differ in their effects on serum lipid profile, glucose metabolism, and inflammatory markers in subjects with impaired fasting glucose. Previous controlled comparisons between fish and CSO or other sources of plant derived n-3 FAs do not exist. A diet enriched in CSO improved serum lipid profile as compared with a diet enriched in FF or LF, whereas no significant differences were found in glucose metabolism or concentrations of markers of low-grade inflammation.

In the present study the concentration of total cholesterol decreased in the CSO group. There were no changes in the concentration of triglycerides in any of the intervention groups. Previous studies have usually compared fish oils and PUFA from vegetable oils [10]. Overall, no differences in these comparisons have been found in serum total or HDL cholesterol concentrations [10]. Regarding concentration of serum total triglycerides some studies show no difference [28-30], whereas others show a beneficial effect of fish oil as compared with other sources of PUFA [31-34]. The amount of fatty acids and the type of subjects studied including the baseline concentration of total triglycerides are very variable in these studies [13]. Regarding PUFA of plant origin there is clear evidence that consumption of non-tropical vegetable oils while replacing sources of saturated fat are beneficial regarding serum/plasma lipid profile [10,35]. One of the potential mechanisms is that PUFAs increase and the saturated fatty acids decrease the activity of LDL receptor in the liver [36].

In the present study, LDL cholesterol concentration decreased in the CSO group, but did not change in the fish groups. In previous studies, there are differences in the effects of PUFA on serum LDL cholesterol concentration depending on the source of PUFA. Some studies show no difference [29,30,32,34], whereas other studies show that fish oil increases the concentration of LDL cholesterol as compared with PUFA from plant sources [28,31,33].

An increase in HDL cholesterol concentration was observed in the FF group. In an intervention study comparing FF and LF the intake of FF decreased HDL cholesterol concentration but did not affect plasma glucose concentration in healthy normal-weight subjects [37]. In a meta-analysis salmon intake increased HDL cholesterol concentration by 0.08 mmol/l and decreased triglyceride concentration by 0.16 mmol/l [38].

The concentration of serum LDL cholesterol concentration, LDL-C-to-HDL-C ratio and ApoB-to-ApoA-I ratio decreased significantly also in the control group, not just in the CSO group. The reason for this might be that the intake of MUFA increased by 1.2 E% in the control group during the study. All the subjects were given the sources of visible fats, i.e. a vegetable oil-based spread for bread, vegetable oil for cooking and salad dressings, and liquid margarine for cooking. The most common spread for bread in Finland is a butter-vegetable oil mixture [39], which was not allowed during the study. Therefore, the quality of dietary fat improved in the control group during the study.

To our knowledge there are no comparisons of sources of ALA and fish intakes regarding glucose metabolism. There are few comparisons of plant-derived n-3 FAs and fish oils [28,31]. No differences were found in the study of Griffin et al. [31] comparing diets with a differing n-6-to-n-3 ratio whereas in a study by Tahvonen et al. [28] fish oil resulted in a lower plasma glucose concentration as compared with black currant seed oil in young healthy females. Increased intake of long chain n-3 PUFA of marine origin has been found to be associated with an increased risk of T2DM [40-42]. Wallin et al. [43] found this association in the studies conducted in the United States, but not in studies conducted in Europe, Asia or Australia. In the Atherosclerosis Risk in Communities study, the proportion of ALA in plasma phospholipids but not in cholesteryl esters was inversely associated with the risk of T2DM [44], whereas most of the studies have shown no association [45-47].

No differences in markers of inflammation were observed among the groups in this study. Data from clinical trials on the effect of EPA+DHA intake on inflammation are conflicting and for ALA, scarce [10,48]. The anti-inflammatory effect of ALA may depend on the background diet in dyslipidemic subjects [49]. Furthermore, even though >1 g/d of EPA + DHA has been reported to have anti-inflammatory effects, most of the studies have not replicated this finding [48]. A recent study showed that DHA has a more potent anti-inflammatory effect than EPA [50] in subjects at risk for CVD. In intervention studies, increase in the intake of FF has not affected circulating CRP concentrations [51-53].

An omega-3 index of ≥ 8 % has been proposed to be cardioprotective [54]. In the present study, omega-3 index (EPA + DHA in red blood cells) was relatively high at baseline, >8 % for all groups (CSO: 9.3 ± 1.7, FF: 8.9 ± 1.5, LF: 8.5 ± 1.3, control: 9.2 ± 1.5, $p = 0.289$ between the groups), which may have diluted the effects and partly explain some of the non-significant results. The

strengths of the present study are the randomized controlled design and careful monitoring of the diet by both repeated food records and consumption records regarding the key food items. A relevant biomarker, i.e. the FA composition of plasma phospholipids, was used. The results indicate good compliance. FSIGT and the other laboratory methods used have been in long-term use and are considered high-quality methods, except the methodology for the analysis of inflammatory cytokines, which still has high intra- and inter-assay variations. Other weaknesses are the sample size, which could have been larger especially regarding glucose metabolism and low-grade inflammation, and the unblinded nature of the study. However, it is very difficult to carry out a blinded study on the effects of fish. The study subjects had impaired fasting glucose, so the results are not directly generalizable to subjects with normal glucose metabolism or T2DM.

In conclusion, in this carefully conducted comparison of FF, LF and CSO, a source of ALA, a CSO diet improved serum lipid profile as compared with a diet enriched either in FF or LF in subjects with impaired fasting glucose, with no differences in glucose metabolism or concentrations of inflammatory markers.

Authorship

USS, MAL and ATE formulated research questions, designed and conducted the study. SK and DEL conducted the FSIGT. MAL, VDM and SM analyzed the data and performed statistical analyses. USS, MAL, ATE, VDM and SM wrote the paper USS having the main responsibility. DEL checked the language as a native speaker. KP was responsible for the analyses of the inflammatory markers. All authors have commented the manuscript.

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Conflict of Interest

None.

5 References

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Figure legends

Figure 1. Flow chart of the study. CSO, camelina sativa oil.

Figure 2. Proportions of (A) alpha-linolenic acid (ALA), (B) eicosapentaenoic acid (EPA) and (C) docosahexaenoic acid (DHA) in plasma phospholipids at 0 and 12 wk. Group effects between fold changes adjusted for age, gender and the proportion at baseline ([1]ANCOVA, [2]post hoc tests). CSO, camelina sativa oil; FF, fatty fish; LF, lean fish.

Figure 3. Concentrations of serum (A) total cholesterol, (B) LDL cholesterol, (C) total triglycerides (D) HDL cholesterol, (E) LDL-to-HDL cholesterol ratio and (F) apolipoprotein (Apo) B to ApoA-I ratio at 0 wk (solid bars) and at 12 wk (bars with lines). Group effects between fold changes adjusted for age, gender, use of statins and concentration at baseline ([1]ANCOVA, [3]post hoc tests), [2]paired t-test within the groups. CSO, camelina sativa oil; FF, fatty fish; LF, lean fish.

Table 1. Baseline characteristics of the subjects (n=79) and drop outs (n=17)

	Study subjects		**Drop outs**		
	Mean	SD	Mean	SD	p[a]
Age, y	58.9	6.5	57.9	8.1	0.893
Sex, female/male, *n*	39/40		11/6		0.251
BMI, kg/m^2	29.2	2.4	30.2	1.8	0.123
Fasting plasma glucose, mmol/l	6.1	0.4	6.0	0.5	0.352
Serum cholesterol, mmol/l					
Total	5.3	0.9	5.2	1.0	0.681
LDL	3.1	0.8	2.9	1.0	0.380
HDL	1.4	0.4	1.6	0.6	0.314
Serum triglycerides, mmol/l	1.4	0.6	1.6	0.9	0.784
Use of statins, *n*	18		4		0.947

[a] Independent samples t-test, Mann Whitney's U test or χ^2 test.

Table 2. Dietary intake at baseline and during the intervention[a,b]

	Fatty fish (n=20)				**Lean fish (n=21)**				**Camelina sativa oil (n=18)**				**Control (n=20)**				
	Baseline		Intervention		Baseline		Intervention		Baseline		Intervention		Baseline		Intervention		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P[c]
Energy, kJ	7931	2296	8765	2093	8506	2029	8985	1783	8413	2187	9270	2568	7866	1666	8111	1821	0.436
Fat, E%	35.7	6.4	39.0	5.1	34.8	5.6	34.5	3.2[d]	35.5	5.6	42.5	3.4	33.5	6.8	34.0	5.1[d]	**0.003**
SFA, E%	12.3	3.1	12.4	2.4	12.1	2.7	11.0	1.7	12.6	3.8	12.1	1.9	11.4	2.2	11.3	2.1	0.356
MUFA, E%	13.0	2.6	15.1	2.1	12.3	2.5	13.5	1.9	12.3	2.3	15.0	1.6	11.9	3.4	13.1	2.4	0.072
PUFA, E%	6.1	2.1	7.0	1.4[d]	5.8	1.1	6.2	0.8[d]	6.0	1.6	11.6	1.6	5.8	1.5	5.6	0.9[d]	**<0.001**
SFA/UFA	0.67	0.21	0.57	0.12	0.68	0.15	0.56	0.10	0.72	0.26	0.46	0.10	0.66	0.13	0.61	0.12	0.710
ALA, g	2.1	1.0	2.7	0.8[d]	2.0	1.0	2.8	1.0[d]	2.1	0.9	12.4	1.4	1.8	0.9	2.1	0.8[d]	**<0.001**
Linoleic acid, g	8.7	4.4	10.9	4.1	8.3	3.5	11.3	3.7	9.1	3.9	13.5	3.1	7.9	3.2	9.0	2.9	0.079
EPA, mg	105	109	526	248	190	239	89	141[e]	136	114	108	64	69	77	94	85[e]	**<0.001**
DHA, mg	215	207	1235	695	479	586	194	193[e]	386	338	280	175	205	224	273	246[e]	**0.002**
Cholesterol, mg	250	104	327	90	275	99	264	75	267	118	286	151	260	60	239	116	0.638
Protein, E%	17.9	2.5	18.6	2.1[d]	17.9	3.3	18.2	2.5	16.6	2.6	15.6	2.3	17.5	3.7	17.7	3.7	**0.030**
Carbohydrates, E%	38.0	8.5	34.2	6.4	41.6	5.9	41.9	4.2[e]	43.2	6.6	38.2	4.8	43.6	8.3	42.5	6.0[e]	**0.001**
Fiber, g	22.0	8.7	21.4	11.4	25.5	8.4	26.6	7.2	24.9	6.4	24.2	5.2	22.0	5.9	22.9	5.3	0.055
Alcohol, E%	5.4	6.5	5.7	6.4[d]	2.5	4.4	2.4	3.3	1.5	2.2	1.2	1.3	2.7	3.9	3.2	3.6	**0.014**
Vitamin D, µg	10.6	5.9	18.8	8.5[d]	13.4	9.1	17.2	8.3[d]	7.7	2.9	7.2	4.2	8.2	3.9	8.1	3.5[ef]	**<0.001**
Vitamin C, mg	135.5	63.7	106.9	46.1	138.3	77.5	127.6	50.2	150.5	57.8	133.3	49.5	137.6	75.0	122.5	45.9	0.364

[a] 4-d food record at baseline, mean of three 4-d food records during the intervention.

[b] ALA, alpha-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SFA, saturated fatty acids; UFA unsaturated fatty acids

[c] repeated measures general linear model

[d] vs. CSO, $P < 0.05$; [e] vs. fatty fish, $P < 0.05$; [f] vs. lean fish, $P < 0.05$

Table 3. Fasting and post load glucose and insulin concentrations and surrogate indices of insulin and glucose homeostasis according to the study group[a,b]

	Fatty fish (n=20)[c]				Lean fish (n=21)				Camelina sativa oil (n=18)[d]				Control (n=20)[e]				
	0WK		12WK		0WK		12WK		0WK		12WK		0WK		12WK		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P[f]
Fasting glucose, mmol/l	5.94	0.40	6.09	0.52	6.05	0.41	6.01	0.42	6.06	0.41	6.11	0.52	6.15	0.62	6.24	0.74	0.330
Glucose 120 min, mmol/l	6.39	2.07	6.40	1.85	6.57	1.41	6.39	1.74	5.82	1.68	5.73	1.33	7.13	2.17	6.48	1.65	0.761
Fasting insulin, mU/l	9.75	4.53	10.23	4.56	9.85	5.31	10.72	5.70	10.86	4.53	11.54	3.65	11.42	6.63	11.52	6.42	0.770
Insulin 120 min, mU/l	48.4	30.5	53.2	47.8	85.7	141.2	61.1	85.1	58.0	40.0	70.0	55.2	87.3	88.4	61.1	48.5	0.702
Glu AUC_{30} / Ins AUC_{30}	25.7	14.3	26.7	15.9	26.0	18.7	25.5	12.2	33.0	22.5	33.4	17.9	30.9	21.9	30.7	28.0	0.521
Matsuda ISI	5.00	2.62	4.69	3.21	4.41	2.02	4.65	2.32	3.79	1.47	3.65	1.63	4.23	2.74	4.04	2.17	0.308
DI_{30}	109.2	57.9	102.3	55.7	93.9	40.0	98.1	40.9	110.0	44.3	107.5	38.2	94.6	38.2	90.7	36.9	0.612
AIRG, $[mU/l]^{-1} \times min^{-1}$	3.68	2.84	3.58	2.31	3.57	3.17	3.53	3.02	3.15	2.75	3.27	2.39	3.20	2.75	2.83	2.16	0.818
SI, $[mU/l]^{-1} \times min^{-1}$	3.22	1.80	3.17	1.64	3.41	2.03	4.00	2.14	3.60	1.28	3.43	1.63	3.16	1.85	3.65	1.39	0.616
DI	10.50	8.32	10.88	8.46	7.69	5.14	10.89	9.63	9.70	4.14	10.62	8.15	8.58	7.94	10.89	10.56	0.651

[a] Data are mean ± SD

[b] AIRG, acute insulin response to glucose from the frequently sampled intravenous glucose tolerance test (FSIGT); Glu AUC30 / Ins AUC30; ratio of total insulin area under the curve (AUC) and total glucose AUC during the 0-30min OGTT; DI, disposition index calculated as the product of the AIRG and SI. DI_{30}: disposition index calculated as the product of the Glu AUC30 / Ins AUC30 and the Matsuda ISI; ISI, insulin sensitivity index; SI, insulin sensitivity index from the frequently sampled intravenous glucose tolerance test (FSIGT).

[c] n=18, [d] n=16 and [e] n=17 for the FSIGT derived indices

[f] ANCOVA fold change of the variable adjusted for age, sex, and baseline measurement

Table 4. Concentrations of inflammatory markers at the beginning and at the end of the study[a,b]

	Fatty fish (n=20)		Lean fish (n=20)		Camelina sativa oil (n=17)		Control (n=19)		
	0WK	12WK	0WK	12WK	0WK	12WK	0WK	12WK	P[c]
hs-CRP, mg/l	2.00 (1.10; 2.90)	1.70 (1.40; 2.60)	1.55 (1.10; 2.25)	1.50 (0.83; 2.45)	1.50 (0.70; 2.55)	1.30 (0.70; 3.25)	1.60 (0.8; 2.6)	1.70 (1.0; 2.8)	0.42
IL-1Ra, pg/ml	284 (202; 397)	305 (204; 342)	210 (187; 415)	220 (185; 333)	278 (174; 339)	248 (207; 327)	221 (193; 284)	242 (194; 336)	0.12
hs-IL-1β, pg/ml	2.15 (0.12; 0.13)	2.15 (0.12; 0.16)	1.88 (0.12; 0.12)	2.15 (0.12; 0.12)	2.31 (0.12; 0.13)	2.15 (0.12; 0.15)	2.08 (0.12; 0.12)	2.15 (0.12; 0.12)	0.45
Omentin-1, ng/ml	311 (291; 241)	309 (225; 243)	316 (252; 272)	304 (262; 247)	329 (408; 423)	299 (388; 422)	294 (375; 368)	346 (385; 391)	0.85
IL-18, pg/ml	206 (158; 316)	200 (156; 280)	213 (176; 332)	206 (152; 315)	255 (198; 285)	245 (195; 279)	238 (192; 316)	260 (189; 295)	0.53
ICAM-1, ng/ml	181 (150; 241)	172 (142; 227)	199 (169; 217)	189 (156; 208)	200 (164; 261)	198 (160; 253)	184 (150; 234)	184 (144; 218)	0.70

[a] Data are median (IQR).

[b] CRP, C-reactive protein; hs, high sensitivity; ICAM, intercellular adhesion molecule 1; IL, interleukin; Ra, receptor antagonist.

[c] ANCOVA fold change of the variable adjusted for age, sex, statin use and baseline measurement.