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Influence of a healthy Nordic diet on serum fatty acid composition and associations with blood lipoproteins – results from the NORDIET study

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Abstract

Background: The fatty acid (FA) composition of serum lipids is related to the quality of dietary fat intake.
Objective: To investigate the effects of a healthy Nordic diet (ND) on the FA composition of serum cholesterol esters (CE-FA) and assess the associations between changes in the serum CE-FA composition and blood lipoproteins during a controlled dietary intervention.
Design: The NORDIET trial was a 6-week randomised, controlled, parallel-group dietary intervention study that included 86 adults (53 ± 8 years) with elevated low-density lipoprotein cholesterol (LDL-C). Serum CE-FA composition was measured using gas chromatography. Diet history interviews were conducted, and daily intake was assessed using checklists.
Results: Food and nutrient intake data indicated that there was a reduction in the intake of fat from dairy and meat products and an increase in the consumption of fatty fish with the ND. The levels of saturated fatty acids in cholesterol esters (CE-SFA) 14:0, 15:0, and 18:0, but not 16:0, showed a significant decrease after intake of ND compared to the control diet ($p < 0.01$). Also, a significant increase in serum 22:6n – 3 was observed compared with the control diet ($p < 0.01$). The changes in CE-SFA 14:0, 15:0, and 18:0 correlated positively with changes in LDL-C, HDL-C, LDL-C/HDL-C, ApoA1, and ApoB ($p < 0.01$), respectively, whereas the changes in polyunsaturated fatty acids in cholesterol esters (CE-PUFA) 22:6n – 3 were negatively correlated with changes in the corresponding serum lipids.
Conclusions: The decreased intake of saturated fat and increased intake of n-3 PUFA in a healthy ND is partly reflected by changes in the serum CE-FA composition, which are associated with an improved serum lipoprotein pattern.

Keywords: *serum cholesterol esters*; *plasma cholesterol*; *stearoyl-CoA desaturase-1*; *saturated fat*; *n-3 polyunsaturated fatty acids*

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The quality of dietary fat is recognised as an important factor affecting blood lipids. In the NORDIET study (in which the experimental diet was mainly based on healthy traditional Nordic foods), an improved blood lipid profile in hypercholesterolemic subjects was reported (1). Compared to a Swedish reference population, the intake of dairy and meat products was reduced and the intake of fish, eggs, and vegetable fat and oil was increased (2) among the participants randomly assigned to this healthy Nordic diet (ND).

The fatty acid (FA) composition of serum lipids is known to partially reflect the dietary FA intake over the preceding days and weeks (3), but the FA composition is also influenced by *de novo* lipogenesis and the endogenous elongation and desaturation of FAs (4, 5). In general, the essential dietary polyunsaturated fatty acids (PUFA) 18:2n – 6 (linoleic acid) and 18:3n – 3 (α-linolenic) of plant origin and the long-chain n-3 FAs 20:5n – 3 (eicosapentaenoic acid) and 22:6n – 3 (docosahexaenoic acid) of marine origin are good biomarkers of their intake (6). Saturated fatty acids (SFA) with even carbon chain numbers, such as 14:0 (myristic acid), 16:0 (palmitic acid), and 18:0 (stearic acid), are weaker biomarkers of intake, partly due to their *de novo* lipogenesis. Stearoyl-CoA desaturase-1 (SCD-1) is an enzyme that converts SFA, that is, 16:0 and 18:0, to their monounsaturated fatty acid (MUFA) counterparts, that is, 16:1 (palmitoleic acid) and 18:1 (oleic acid), respectively, especially when the exposure to SFA

is high. Two SFA with odd carbon numbers, 15:0 (pentadecanoic acid) and 17:0 (heptadecanoic acid), are good biomarkers of milk fat intake, as they cannot be synthesised in the human body (5).

The aim of this study was to investigate the effects of a healthy ND on the FA composition of serum cholesterol esters (CE-FA) and to investigate associations between the changes in serum CE-FA composition during the intervention and changes in the blood lipoproteins that are relevant to cardiovascular risk.

Methods

The NORDIET trial was a 6-week randomised, controlled, parallel-group dietary intervention study that examined free-living subjects ($n = 88$). All subjects followed a 3-week rotating menu plan where all meals were provided. The study design and the participants are described in detail elsewhere (1). In summary, the participants were healthy men and women between 25 and 65 years of age (mean, 53 ± 8 years), with plasma low-density lipoprotein cholesterol (LDL-C) ≥ 3.5 mmol L^{-1} and body mass index ≥ 20 and ≤ 31 kg m^2. Diet history interviews were performed to assess the participants' intake of total dietary fat and FAs at baseline. At 6 weeks, a second diet history interview was completed for the control diet group, and compliance to the ND was evaluated from daily ND checklists (1). The intake of dietary fat and individual FAs at baseline and after 6 weeks in the control diet group and the ND group is presented as the mean $\pm$ SD relative percentage of total energy intake. The CE-FA composition was measured at baseline and after 6 weeks in all subjects and then determined using gas-liquid chromatography as previously described (7). The proportions of the individual CE-FAs are expressed as the percentage of the total CE-FAs analysed. The activity of SCD-1 was estimated by calculating the ratio between CE-16:1 and CE-16:0 (8). The plasma high-density lipoprotein (HDL-C) concentration was measured using the enzymatic peroxidase reaction with a Roche Diagnostics Ltd. Cobas® 6000 (c501module). Plasma LDL-C was calculated according to the Friedewald formula (9), and apolipoprotein A1 (ApoA1) and ApoB were determined using an immunoturbidimetric method (10). All subjects gave informed consent, and the study was approved by the Regional Ethical Board at Uppsala University.

Statistical analyses

Distributions of all variables were examined by visual inspection of histograms and after such inspection were considered to be normally distributed. Statistical analyses were based on per-protocol analysis. Comparisons between the control diet group and the ND group with respect to the changes observed during the intervention period were performed using Student's two-sample *t*-test. Changes within groups were analysed using Student's paired-sample *t*-test. Pearson correlation coefficients were calculated from the combined data of the ND and control diet groups, only on those CE-FAs that were significantly different between groups. All *p*-values were unadjusted. To avoid type I errors due to the large number of analyses performed, only *p*-values less than 0.01 were considered statistically significant. Statistical analyses were performed using SPSS.

Results

Of the 88 subjects randomly assigned to the two diets in the NORDIET study, two subjects were lost to follow-up providing 86 subjects for analysis. In the ND group, the total dietary SFA intake and the intake of 14:0, 16:0, and 18:0 decreased from baseline to the end of the study and was about one third that of baseline (Table 1). Table 1 also indicates a significant but minor relative decrease in dietary MUFA intake and a significant relative increase in total dietary PUFA. According to the intake of individual FAs, there was a significant but slight decrease in 18:2n – 6 and an increase in 18:3n – 3 (Table 1).

With respect to serum CE-FA, there were significant differences between the two groups in the changes from baseline to 6 weeks ($p < 0.01$) in 14:0, 15:0, 18:0 and 22:6n – 3 (Table 2). Otherwise, no differences between groups were observed.

Table 3 shows the correlations between the changes in CE-FA and blood lipids during the intervention period. The changes in saturated fatty acids in cholesterol esters (CE-SFA) 14:0 were positively correlated with the changes in LDL-C, HDL-C, LDL-C/HDL-C, ApoA1, and ApoB ($p < 0.01$), whereas the changes in the marker of dairy fat intake, 15:0, were positively associated with the changes in LDL-C and ApoB. CE-SFA 18:0 showed corresponding correlations with LDL-C, LDL-C/HDL-C, and ApoB. Polyunsaturated fatty acids in CE (CE-PUFA) 22:6n – 3 was negatively correlated with LDL-C, HDL-C, ApoA1, and ApoB but not with ApoB/ApoA1. The SCD-1 index was positively correlated with serum blood lipids, but the correlations were generally weaker than those of SFA (data not shown).

Discussion

The major observation in this sub-study of the controlled NORDIET trial was that compared with the control diet, the healthy ND reduced serum CE-SFAs, including 14:0, 15:0, and 18:0, and increased CE-PUFA 22:6n – 3, and that these changes were correlated with changes in blood lipoproteins. These results reflect concurrent decreases in the total dietary SFA intake by two thirds as well as a moderate increase in dietary PUFAs during ND.

The decreased dietary SFA after intake of ND that caused a significant relative decrease in CE-SFAs 14:0, 15:0, and 18:0 was presumably related to a change in the

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Table 1. Intake of total fat and fatty acids at baseline and after 6 weeks in the control diet group and the Nordic diet group, presented as a percentage of total energy intake (E%)

	Control diet group			Nordic diet group		
	Baseline[a] $n=42$	6 weeks[a] $n=42$	p^b	Baseline[a] $n=44$	6 weeks $n=44$[c]	p^b
Total fat[d]	34±4.9	34±5.0	0.20	34±5.0	27±0.9	<0.01
Saturated fatty acids[d]	13±3.0	13±3.0	0.40	14±3.1	5.2±0.4	<0.01
14:0 (myristic acid)	1.3±0.6	1.4±0.6	n.s.	2.0±1.0	0.3±0.0	<0.01
16:0 (palmitic acid)	6.8±2.2	6.8±2.2	n.s.	9.4±3.8	2.9±0.4	<0.01
18:0 (stearic acid)	2.8±0.9	2.8±0.9	n.s.	3.8±1.6	0.9±0.1	<0.01
Monounsaturated fatty acids[d]	12±2.3	12±2.3	0.32	12±2.1	11±0.5	<0.01
16:1 (palmitoleic acid)	0.6±0.2	0.6±0.2	n.s.	0.7±0.2	0.3±0.0	<0.01
18:1 (oleic acid)	11.0±3.6	11.1±3.6	n.s.	13.9±4.7	9.6±1.1	<0.01
Polyunsaturated fatty acids[d]	5.6±1.7	5.6±1.7	0.07	4.9±1.1	6.3±0.3	<0.01
18:2n − 6 (linoleic acid)	4.4±2.2	4.4±2.2	n.s.	4.6±1.5	3.7±0.5	<0.01
18:3n − 3 (α-linolenic)	0.8±0.5	0.8±0.5	n.s.	0.8±0.3	1.6±0.2	<0.01
20:5n − 3 (eicosapentaenoic acid)	0.1±0.1	0.1±0.1	n.s.	0.1±0.1 (0.17±0.14[e])	0.1±0.0 (0.24±0.05[e])	<0.01
22:6n − 3 (docosahexaenoic acid)	0.2±0.1	0.2±0.1	n.s.	0.2±0.1 (0.41±0.3[e])	0.2±0.0 (0.51±0.09[e])	0.027

Data are presented as mean±SD.
[a]Assessed from dietary history interviews.
[b]Difference within the group using paired sample *t*-test.
[c]Assessed using a daily study check-list.
[d]These data have been previously reported (1).
[e]Intake presented as gram.

intake of dairy and meat products (2). Despite the reported decreased intake of total SFA and 16:0 after intake of ND, the proportion of, 16:0, the major dietary SFA in the diet did not change in the serum CE. During controlled feeding trials involving reduced SFA intake by substitution for PUFAs or MUFAs, CE-16:0 usually decreases significantly, with a concomitant reduction in the SCD-1 index (16:1/16:0) (11–13). Indeed, the SCD-1 index appears to be a reasonable marker of SFA intake, perhaps reflecting reduced dietary 16:0 even better than changes in serum CE-16:0, which seem to be rather tightly regulated (8). The absence of a reduction in serum CE-16:0 despite the decreased intake in the present study might be explained by the inhibition of SCD-1 activity by ND, as indicated by a decrease in the estimated SCD-1 index by 10% at 6 weeks after initiating the ND. This decreased SCD-1 activity may in turn be secondary to the increased intake of PUFAs (8), which inhibit the activity of SCD-1, and/or to the reduced SFA intake (11, 12). Finally, reduced elongase activity, that is, the conversion of 16:0 to 18:0, might also have contributed to the lack of a reduction in serum 16:0.

There were no significant changes in the serum MUFAs, which is to be expected because these FAs are weak biomarkers of the MUFA intake. Moreover, in the traditional Swedish diet, dietary MUFAs are mainly derived from foods containing SFAs (14). Therefore, the decreased intake of dietary MUFAs in the ND group may reflect a decreased consumption of dairy and meat products rather than being related to changes in the consumption of plant oils such as rapeseed oil.

The relative increase in dietary PUFA intake was only reflected in a significant but moderately increased CE-22:6n − 3 and can probably be ascribed to an increased dietary intake of marine n-3 PUFAs from fatty fish. An increase in PUFA 22:6n − 3 in serum phospholipids was observed in a 24-week study of an ND (15). However, the relatively higher intake of dietary PUFAs in the ND was not reflected in the CE-PUFAs 18:2n − 6 or 18:3n − 3 in the current study. This observation might be explained by a rather moderate increase in the consumption of margarine and rapeseed oil, known to be rich in 18:2n − 6 and 18:3n − 3, respectively. The finding is also in line with the previously mentioned study on a healthy ND (15). However, this result stands in contrast to reports from strictly controlled feeding studies that involved replacing SFAs (mainly from high-fat dairy) with rapeseed oil, leading to increases in 18:2n − 6 and 18:3n − 3 in serum CE-FAs (11) and serum phospholipids (11, 16), respectively.

Dietary SFA 14:0 is known to raise LDL-C, ApoB, and even HDL-C (17). Similar findings were reached in the present study, as 14:0 was the sole CE-SFA associated with HDL-C and ApoA1 in addition to its association with LDL-C and ApoB. Despite its positive correlation with HDL-C and ApoA1, it should be noted that CE-SFA 14:0 was still directly linked to an increased

Table 2. Fatty acid composition in serum cholesterol esters (CE-FA) at baseline and after 6 weeks in the control diet group and the Nordic diet (ND) group

	Control diet group ($n=42$)				Nordic diet group ($n=44$)				
	Baseline	6 weeks	Change	p for change[a]	Baseline	6 weeks	Change	p for change[a]	p^b
CE-SFA									
14:0 (myristic acid)	0.805 ± 0.202	0.925 ± 0.269	0.121 ± 0.170	<0.01	0.844 ± 0.168	0.613 ± 0.178	−0.231 ± 0.208	<0.01	<0.01
15:0 (pentadecanoic acid)	0.198 ± 0.039	0.203 ± 0.046	0.005 ± 0.025	n.s.	0.192 ± 0.030	0.168 ± 0.029	−0.024 ± 0.025	<0.01	<0.01
16:0 (palmitic acid)	11.10 ± 0.69	11.34 ± 0.64	0.24 ± 0.44	<0.01	11.13 ± 0.62	11.30 ± 0.52	0.17 ± 0.62	n.s.	n.s.
18:0 (stearic acid)	0.814 ± 0.126	0.833 ± 0.156	0.020 ± 0.145	n.s.	0.797 ± 0.130	0.688 ± 0.202	−0.109 ± 0.230	<0.01	<0.01
CE-MUFA									
16:1 (palmitoleic acid)	2.78 ± 0.84	2.94 ± 0.95	0.15 ± 0.52	n.s.	3.07 ± 0.87	2.89 ± 0.86	−0.18 ± 0.70	n.s.	n.s.
18:1 (oleic acid)	21.11 ± 1.41	21.45 ± 1.55	0.34 ± 1.16	n.s.	21.40 ± 1.60	21.12 ± 1.61	−0.28 ± 1.22	n.s.	n.s.
CE-PUFA									
18:2n − 6 (linoleic acid)	51.01 ± 3.65	49.11 ± 3.83	−1.90 ± 2.68	<0.01	50.94 ± 2.85	50.11 ± 3.24	−0.83 ± 2.88	n.s.	n.s.
18:3n − 3 (α-linolenic)	0.911 ± 0.180	0.924 ± 0.257	0.013 ± 0.202	n.s.	0.886 ± 0.186	0.927 ± 0.219	0.040 ± 0.202	n.s.	n.s.
20:5n − 3 (eicosapentaenoic acid)	2.15 ± 0.97	2.85 ± 1.11	0.70 ± 0.99	<0.01	1.72 ± 0.56	2.63 ± 0.95	0.91 ± 0.92	<0.01	n.s.
22:6n − 3 (docosahexaenoic acid)	0.95 ± 0.17	1.05 ± 0.22	0.09 ± 0.15	<0.01	0.83 ± 0.23	1.14 ± 0.23	0.31 ± 0.22	<0.01	<0.01
Desaturase and elongase indices									
SCD-1 activty[c]	0.249 ± 0.068	0.258 ± 0.077	0.008 ± 0.042	n.s.	0.277 ± 0.081	0.256 ± 0.076	−0.021 ± 0.061	n.s.	<0.01
Elongase activity[d]	0.073 ± 0.011	0.074 ± 0.013	0.000 ± 0.013	n.s.	0.072 ± 0.011	0.061 ± 0.017	−0.011 ± 0.019	<0.01	<0.01
D6D activity[e]	0.015 ± 0.007	0.016 ± 0.007	0.001 ± 0.001	<0.01	0.017 ± 0.005	0.018 ± 0.005	0.000 ± 0.001	n.s.	n.s.
D5D activity[f]	9.37 ± 1.97	9.37 ± 2.13	0.00 ± 1.35	n.s.	8.96 ± 2.16	10.48 ± 2.68	1.52 ± 1.81	<0.01	<0.01

FAs are presented as a relative percentage of FAs analysed. Data are presented as mean ± SD.

CE-SFA, saturated fatty acids in cholesterol esters; CE-MUFA, monounsaturated fatty acids in CE; CE-PUFA, polyunsaturated fatty acids in CE.

[a]p = Difference in change in fatty acid (FA) composition in CE (CE-FA) from baseline to 6 weeks after the control diet and the ND within group.

[b]p = Difference in change in CE-FA composition from baseline to 6 weeks after the control diet and the ND between groups.

[c]SCD-1, stearoyl-CoA desaturase-1 (16:1n − 7/16:0).

[d]Estimated elongase activity (18:0/16:0).

[e]D6D, estimated delta-6 desaturase activity (18:3n − 3/18:2n − 6).

[f]D5D, estimated delta-5 desaturase activity (20:4n − 6/20:3n − 6).

Table 3. Relationship between the difference in change for fatty acid composition in serum cholesterol esters (CE-FA) and blood lipoproteins after 6 weeks in the control diet and Nordic diet groups combined ($n = 86$)

	LDL-C		HDL-C		LDL-C/HDL-C ratio		ApoA1		ApoB		ApoB/A1 ratio	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
CE-SFA												
14:0	0.557	<0.01	0.413	<0.01	0.287	<0.01	0.594	<0.01	0.620	<0.01	0.162	n.s.
15:0	0.282	<0.01	0.169	n.s.	0.179	n.s.	0.191	n.s.	0.283	<0.01	0.056	n.s.
18:0	0.286	<0.01	0.036	n.s.	0.318	<0.01	0.137	n.s.	0.311	<0.01	0.183	n.s.
CE-PUFA												
22:6n − 3	−0.346	<0.01	−0.434	<0.01	−0.015	n.s.	−0.573	<0.01	−0.355	<0.01	0.098	n.s.

r = Pearson's correlation coefficient.

CE-SFA, saturated fatty acids in cholesterol esters; CE-PUFA, polyunsaturated fatty acids in CE.

LDL-C/HDL-C ratio, suggesting an overall unfavourable effect on blood lipids. Both CE-SFA 15:0 and 18:0 were directly correlated with LDL-C and ApoB but not with changes in HDL-C and ApoA1. However, the negative correlation between CE-PUFA 22:6n – 3 and LDL-C is not supported by controlled studies that have investigated the effects of fish oil supplementation on LDL-C concentrations (18). On the contrary, high doses of DHA alone from dietary supplements have been shown to increase HDL-C levels (19). Thus, the current correlations between DHA, LDL, and HDL should be interpreted cautiously and warrant further investigation. It should be noted that these associations persisted after making an adjustment for weight changes, in line with the weight-independent effects on blood lipids previously reported from this and other studies (15).

There are some limitations of this study. First, the CE-FA composition of the serum is given in relative amounts, which introduces the possibility that a result that appears to indicate an increase or decrease in a certain FA is secondary to a pronounced increase in one or several other serum CE-FAs present in high proportions. Another limitation is the usage of different dietary assessment methods for food intake at baseline and 6 weeks in the ND group, which prevented a direct comparison between food intake patterns before and after initiating the ND. The strengths of the study include the randomised controlled design and the fact that all food was provided in the ND group. The latter protocol allowed us to monitor dietary compliance both for nutrients and foods directly using a daily study checklist to record the uneaten foods; compliance in the ND group was high.

Conclusions

There was a pronounced decrease in dietary SFA intake and a moderate relative increase in dietary PUFAs intake in response to the ND during the 6-week period, which were reflected by changes in all measured CE-SFAs (except 16:0) and in the CE-PUFA 22:6n – 3. A low intake of dairy and meat products and a change to their low-fat counterparts, as well as an increased intake of fatty fish, might have contributed to these serum changes. The positive correlation in the whole group between CE-SFAs and most blood lipids was in this study mainly reflecting reduced CE-SFAs that was accompanied by reduced blood lipids during the ND. The change in CE-PUFA 22:6n – 3 was inversely related to both LDL-C and HDL-C. These results suggest that at least part of the lipid-lowering effects observed following the ND seems to be related to improved dietary fat quality, which is relevant to cardiovascular risk.

Authors' contributions

VA conceived the study and participated in the design, data acquisition, data analysis, and manuscript writing. BV conceived the study, participated in the design and data analysis, provided critical advice, and helped draft the manuscript. TC participated in the design, provided critical advice, and helped draft the manuscript. UR conceived the study, participated in the design and data analysis, provided critical advice, and helped draft the manuscript.

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Conflicts of interest and funding

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