University of Groningen

Change in saturated fat intake is associated with progression of carotid and femoral intima-media thickness, and with levels of soluble intercellular adhesion molecule-1

Bemelmans, W.J.; Lefrandt, Joop; Feskens, E.J.; Broer, J.; Tervaert, J.W.; May, J.F.; Smit, Andries J.

Published in:
ATHEROSCLEROSIS

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2002

[Link to publication in University of Groningen/UMCG research database](#)

Change in saturated fat intake is associated with progression of carotid and femoral intima-media thickness, and with levels of soluble intercellular adhesion molecule-1

Wanda J.E. Bemelmans [a],*, Johan D. Lefrandt [b], Edith J.M. Feskens [c], Jan Broer [d], Jan Willem Cohen Tervaert [e], Johan F. May [f], Andries J. Smit [g]

[a] *Department of General Practice, University of Groningen, Anton Deusinglaan 4, 9713 AW, Groningen, The Netherlands*
[b] *Department of Internal Medicine, Groningen University Hospital, Groningen, The Netherlands*
[c] *National Institute for Public Health and the Environment, Bilthoven, Groningen, The Netherlands*
[d] *Municipal Health Services Agency Groningen, Groningen, The Netherlands*
[e] *Department of Immunology, University of Maastricht, The Netherlands*
[f] *Department of Cardiology, Groningen University Hospital, Groningen, The Netherlands*
[g] *Department of Internal Medicine, Groningen University Hospital, Groningen, The Netherlands*

Abstract

Background: A high saturated fat (SFA) intake may stimulate progression of atherosclerosis, and may be positively associated with expression of adhesion molecules. *Methods:* In moderately hypercholesterolaemic participants of a dietary intervention study ($n = 103$; 55 ± 10 years), we examined associations between reported changes in SFA intake and changes in carotid and femoral intima-media thickness (IMT) and soluble intercellular adhesion molecule-1 (sICAM-1) levels after 2 years. The carotid and femoral IMT was assessed by high-resolution B-mode ultrasound images. *Results:* After 2 years, dietary intake of SFA decreased with $1.8 \pm 2.6\%$ of energy ($P < 0.01$). In the lowest quintile of change in SFA intake ($-5.9 \pm 1.4\%$ of energy), changes in carotid and femoral IMT were $+0.03$ mm (SEM 0.03) and -0.09 mm (SEM 0.07), respectively, versus $+0.10$ mm (SEM 0.03), $+0.17$ mm (SEM 0.07) in the top quintile ($+1.6 \pm 0.7\%$ of energy) (P linear trend 0.07 (carotis), 0.02 (femoralis)). Changes in sICAM-1 were -19.0 ng/nl (SEM 5.6) in the lowest quintile, versus $+8.6$ ng/ml (SEM 5.3) in the top quintile (P linear trend < 0.001), adjusted for baseline level, SFA intake, body mass index, age, changes in intake of fruit, polyunsaturated fat, and dietary cholesterol. Adjustments for changes in established risk factors did not alter these results. *Conclusions:* Decreased SFA intake may reduce progression of atherosclerosis, as assessed by IMT, and is associated with reduced levels of sICAM-1 after 2 years. Further research using randomised placebo-controlled trials is necessary to exclude potential confounding variables and to confirm causality. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

1. Introduction

There is convincing evidence that the intake of saturated fatty acids (SFA) is associated with increased coronary artery disease incidence and mortality [1,2]. A diet low in total fat and SFA has been shown to retard the overall progression of coronary artery disease [3], but the impact on progression of peripheral atherosclerosis is less well known. The mechanisms by which a decrease in SFA intake may retard atherosclerotic progression include lowering of the concentration of total and LDL cholesterol [4]. Furthermore, recent research showed that fatty acids influence the expression of intercellular and vascular adhesion molecules in vitro [5,6]. The level of soluble intercellular adhesion

---

* Corresponding author. Tel.: +31-50-363-2951; fax: +31-50-363-2964.

E-mail address: w.bemelmans@med.rug.nl (W.J.E. Bemelmans).

molecule-1 (sICAM-1) has been independently associated with risk of myocardial infarction [7]. Further, the adhesion molecules play a crucial role in the attachment of leucocytes to the endothelium [8], which may be an initial phase in the atherosclerotic process. An inverse association has been shown between the number of double bonds of the fatty acids and the expression of the adhesion molecules [6]. Hence, it is expected that the dietary substitution of SFA (no double bonds) with polyunsaturated fatty acids (more than one double bond) decreases the expression of adhesion molecules.

The extent of (subclinical) atherosclerosis can be estimated by the intima-media thickness (IMT) of larger arteries, which is associated with the development of cardiovascular symptoms [9]. A cross-sectional study observed a positive association between SFA content of the cholesteryl ester and carotid IMT, independent of LDL and HDL cholesterol [10]. However, longitudinal data that assess the impact of changes in dietary SFA intake on IMT are limited. Within the context of a dietary intervention project, among subjects with elevated risk at developing cardiovascular diseases, we investigated associations between reported changes in SFA intake and changes in carotid and femoral IMT after 2 years of follow-up. Furthermore, we measured sICAM-1 levels as a marker of expression of ICAM-1 on different cells that play a pathophysiological role in atherosclerosis, such as endothelial cells, macrophages, T cells, and smooth muscle cells [11].

2. Methods

2.1. Study design

This study was part of a dietary prevention project for high-risk groups in The Netherlands, the so-called MARGARIN study. The design of the MARGARIN study is described in extensu elsewhere [12]. The present study includes the subjects from the intervention group since the IMT was assessed only in this group (38 men, 65 women; 55 ± 10 years). The intervention group received nutritional education in groups, and specific nutritional guidelines consisted of a daily intake of 5–7 slices of bread, 400 g of vegetables, 2 pieces of fruit, 2–3 lean dairy products, 0–2 consumptions of alcohol (if already a regular consumer), fish at dinner twice a week, less red meat, less fat cheese, and fewer eggs. Furthermore, the intervention group received margarine with a high content of polyunsaturated fat (composition: 60% PUFA; 20% SFA) that could be used ad libitum for 2 years. The study design was approved by the medical ethical committee of the Groningen University Hospital, and written informed consent was obtained from each participant.

2.2. Participants

Eligible subjects were 30–70 years old, had a serum total cholesterol concentration between 6.0 and 8.0 mmol/l (mean of two separate measurements) and at least two of the following cardiovascular risk factors: high blood pressure (diastolic ≥ 95 mmHg and/or systolic ≥ 160 mmHg) or use of anti-hypertensive medication, body mass index ≥ 27 kg/m^2, smoking, history of cardiovascular disease or a family history of onset of cardiovascular disease before the age of 60. The exclusion criteria were diabetes mellitus, hypothyroidism, and use of acetylsalicylic acid, anti-coagulants, or cholesterol lowering drugs.

2.3. Measurements

A standardised questionnaire was used to establish smoking habits and the presence of a family history of cardiovascular disease. Body weight was measured without shoes and heavy clothing. Sitting blood pressure was measured after rest by automatic device (Dinamap; Critikon Inc.,Tampa FLA, USA).

In fasting samples, serum total and HDL cholesterol, and triglycerides (without blanking) were determined by enzymatic methods on a Vitros 950 (Ortho-Clinical Diagnostics, Rochester NY, USA). HDL cholesterol was isolated by precipitation of LDL and VLDL with dextran sulphate and magnesium chloride (coefficient of variation (CV) 2.8–3.5%; CV_{inter} 3.3–6.3%). Serum LDL cholesterol was calculated with the Friedewald formula, excluding persons with serum triglyceride level above 5.0 mmol/l. Plasma fibrinogen was measured by Clauss assay on a STA coagulation analyser (CV 3.6% for a sample containing 2.8 g/l). Levels of sICAM-1 were measured by capture ELISA (HBT, Uden, The Netherlands) using a monoclonal antibody to sICAM-1 (HM.2) as capture antibody and a biotin-labelled anti-ICAM-1 as detection antibody as described earlier [13]. Dietary intake was assessed by a food frequency questionnaire (FFQ) [12], which was validated using a 3-day 24-h recall method as gold standard. Pearson correlation coefficients between assessment by the FFQ and by the 24-h recall method were as follows: energy intake ($r = 0.76$), total fat as percentage of energy ($r = 0.66$), and saturated fat ($r = 0.51$) ($P < 0.05$ for all).

2.4. Assessment of intima-media thickness

High-resolution B-mode ultrasound images (ACU-SON 128 XP, Mountain View, CA, USA) with a 7.0 MHz linear array transducer were used to measure the IMT. All scans were performed in the supine position by the same sonographer, unaware of the clinical status of the patient. The right and left common carotid, carotid bulb, and the internal carotid arterial wall

segments were imaged from a fixed lateral transducer angle. The common femoral and the superficial femoral arterial segments were imaged from a fixed anterior transducer angle. The scans were analysed blindly by an independent image analyst. The arterial segments were defined as following: the common carotid arterial wall segment as 1 cm proximal to the carotid dilatation; the carotid bulb as the segment between the carotid dilation and the carotid flow divider; the internal carotid segment as a 1 cm long arterial segment distal to the flow divider; the common femoral arterial segment as a 1 cm arterial segment proximal to the femoral dilatation; and the superficial femoral artery as the 1 cm arterial segment distal to the femoral flow divider. The arterial walls most distant from the transducer were imaged (far walls).

Scans of each arterial segment were stored in real time mode on S-VHS videotapes for offline analysis. From the B-mode images, single video frames were selected by the analyst for IMT measurements. The IMT is defined as the distance between the lumen/the intima and the media/adventitia interfaces. Image analysis procedures and software are described elsewhere [14]. An IMT measurement of approximately 10 mm along the arterial wall was performed manually, by positioning markers along predefined edges of the near and far wall double line patterns. The computer program subsequently drew lines through the markers.

The carotid and femoral arteries were investigated bilaterally at various segments. The IMT data are given as the mean distance between the two interfaces of the far wall of the left and the right side divided by two, and the standard deviations. The data on combined IMT of the carotid and femoral artery were calculated by adding means of the various segments divided by three for the carotid artery and two for the femoral artery (mean mean = Mmean).

2.5. Statistics

Changes in cardiovascular risk factors and dietary intake during the study when compared to baseline were analysed with paired student's t-test. At baseline, associations between variables and IMT were analysed with Pearson correlation coefficients or partial correlation coefficients to adjust the confounding variables. Univariate and multivariate linear regression models were used to examine the predicting variables of changes in IMT and sICAM-1. Analysis-of-covariance techniques (quintiles of change in SFA intake) were used to examine associations with IMT and sICAM-1, adjusted for confounding variables and corrected for multiple testing (indicated in the text and Table 4). The analyses were performed on an intention-to-treat basis using the statistical package SPSS 8.0 (SPSS Inc., Chicago, USA).

3. Results

3.1. Characteristics of study population

Table 1 shows the characteristics of the study population at baseline and changes after 2 years of follow-up. The mean carotid IMT increased with 0.05 (SD = 0.11) mm ($P < 0.01$; $n = 92$) and mean femoral IMT with 0.04 (SD = 0.26) mm (NS). The average level of sICAM-1 decreased with 2 (SD = 26) ng/ml (NS). After 2 years, dietary intake of SFA decreased with 1.8% (SD = 2.6) of energy ($P < 0.01$; $n = 80$), and there were non-significant changes in the intake of total fat (-0.8 en%), dietary cholesterol (-11 g/day), dietary fibre ($+0.6$ g/day), and fruit ($+30$ g/day) (Table 2).

3.2. Baseline associations between risk factors and intima-media thickness

At baseline, Mmean carotid IMT was positively associated with age ($r = 0.49$; $P < 0.01$), level of sICAM-1 ($r = 0.29$; $P < 0.01$; adjusted for age, gender, smoking), and diastolic and systolic blood pressure ($r = 0.23$ and 0.22, respectively; age adjusted; $P < 0.05$). Men had a higher carotid IMT (0.87 mm; SE = 0.02) than women (0.80 mm; SE = 0.02), when adjusted for age ($P < 0.05$). The Mmean femoral IMT was positively associated with age ($r = 0.35$; $P < 0.01$), and men had a higher

Table 1

Characteristics of the study population at baseline and after 2 years of follow-up [a]

	Baseline (mean (SD))	2 years (mean (SD))
Serum total cholesterol (mmol/l)	6.8 (0.7)	-0.4 (0.9)**
Serum LDL cholesterol (mmol/l)	4.6 (0.8)	-0.6 (0.9)**
Ratio total/HDL cholesterol	5.7 (1.5)	-0.8 (0.9)**
Serum triglycerides (mmol/l)	2.1 (1.1)	$+0.1$ (0.8)
Systolic blood pressure (mmHg)	146 (22)	0 (16)
Diastolic blood pressure (mmHg)	87 (14)	$+3$ (14)
Body mass index (kg/m²)	29.7 (3.8)	$+0.6$ (1.2)**
Present smoking (%)	46	-3
Mean carotid IMT (mm)	0.83 (0.16)	$+0.05$ (0.11)**
Mean femoral IMT (mm)	0.80 (0.27)	$+0.04$ (0.26)
sICAM-1 (ng/ml)	86 (35)	-2 (26)
Use of medication (%):		
Lipid-lowering	0	$+13$
Antihypertensive	60	$+2$

** $P < 0.01$, when compared to baseline; LDL = low-density lipoprotein; HDL = high-density lipoprotein; IMT = intima-media thickness; sICAM = soluble intercellular adhesion molecule.

[a] Only subjects included with both measurements, men ($n = 35$), women ($n = 60$) (55 ± 10 years).

Table 2
Changes in dietary intake at 2 years of follow-up [a]

	Baseline (mean (SD))	Changes at 2 years (mean (SD))
Nutrients		
Energy (MJ/day)	9.9 (2.9)	−0.6 (2.3)*
Energy/body weight (kJ/kg)	116 (34)	−7 (26)*
Total fat (% of energy)	37.7 (6.6)	−0.8 (6.2)
Saturated fat (% of energy)	14.1 (2.8)	−1.8 (2.6)**
Monounsaturated fat (% of energy)	12.5 (2.4)	−1.3 (2.3)**
Polyunsaturated fat (% of energy)	8.7 (2.6)	+2.9 (3.1)**
Dietary cholesterol (mg/day)	214 (67)	−11 (67)
Dietary fibre (g/day)	26.8 (7.9)	+0.6 (7.7)
Alcohol (% of energy)	3.1 (4.0)	−0.4 (2.4)
Foods		
Fruit (g/day)	278 (185)	+30 (192)
Total added fat (g/day)	51 (25)	−5 (24)*
Margarine (g/day)	20 (22)	+19 (27)**

Men: ($n = 31$); women: ($n = 50$). *$P < 0.05$; **$P < 0.01$ when compared to baseline.
[a] Only subjects included with both measurements.

age-adjusted value (0.88 mm; SE = 0.04) than women (0.75 mm; SE = 0.03) ($P < 0.05$).

3.3. Predictors of changes in intima-media thickness and sICAM-1

In univariate regression analysis, changes of the carotid IMT were predicted by baseline carotid IMT, and changes in the intake of SFA and fruit (Table 3). Changes of the femoral IMT were predicted by baseline femoral IMT, age, baseline BMI, and change in the intake of dietary cholesterol. Changes in levels of sICAM-1 were predicted by baseline level and BMI. Changes in dietary intake of energy, total fat, vegetables, and fatty fish did not predict changes of IMT and sICAM-1 (data not shown).

In multivariate analysis, progression of femoral IMT was predicted by baseline femoral IMT, SFA intake and BMI. Changes in sICAM-1 level were predicted by baseline level of sICAM-1 and SFA intake, and changes in SFA intake. Although not significant, changes in SFA intake were consistently positively associated with changes in IMT (Table 3).

3.4. Quintiles of change in saturated fat intake and intima-media thickness

Table 4 shows (changes) in risk factors and dietary intake for quintiles of change in SFA intake. The intake of the research margarines was similar among the quintiles (data not shown). An increased SFA intake was associated with increased progression of the femoral IMT ($P = 0.02$), and tend to increase the progression of

Table 3
Predictors of change in IMT and soluble intercellular adhesion molecule-1 after 2 years, in univariate (UV) and multivariate (MV) regression analysis (standardized betas)

Predictors	Dependent variable					
	Change in carotid IMT		Change in femoral IMT		Change in sICAM-1	
	UV	MV	UV	MV	UV	MV
Baseline level	−0.22*	−0.21	−0.48**	−0.36**	−0.42**	−0.49**
Age	0	0.19	−0.28**	0.19	0.07	0.14
Gender	0.08	0.12	−0.07	−0.04	0.07	0.01
Baseline smoking	0.07	0.07	0.10	0.20	0.07	0.12
Baseline systolic blood pressure	−0.02	0.06	−0.11	−0.07	0.01	0.06
Baseline serum LDL cholesterol	0.04	0.07	−0.20	−0.06	−0.06	−0.09
Baseline body mass index	−0.17	−0.19	−0.23*	−0.25*	0.21*	0.14
Baseline sICAM-1	−0.06	−0.11	0.13	0.14	–	–
Baseline intake saturated fat	−0.15	0.19	0.12	0.31*	0.07	0.27*
Change in systolic blood pressure	0.14	0.14	0.16	0.17	0.04	0.07
Change in serum LDL cholesterol	−0.14	0.03	0.18	0.08	0.01	−0.09
Change in body mass index	0.06	0.05	0.12	0.07	0.06	0.13
Change in sICAM-1	0.05	−0.16	−0.02	−0.02	–	–
Change in intake of saturated fat	0.26*	0.24	0.18	0.21	0.06	0.44**
Change in intake polyunsaturated fat	−0.11	−0.18	−0.17	−0.30*	−0.07	0.01
Change in intake of cholesterol	0.09	0.01	0.23*	0.15	−0.07	−0.19
Change in intake of fruit	−0.23*	−0.14	−0.02	0.13	0.13	0.22
Change in intake of alcohol	−0.03	−0.10	−0.05	−0.05	0	−0.14

*$P < 0.05$; **$P < 0.01$; IMT = intima-media thickness, LDL = low-density lipoprotein; sICAM-1 = soluble intercellular adhesion molecule 1.

Table 4
Risk factors and changes during the study for quintiles of changes in saturated fat intake after 2 years (mean (SEM))

Quintiles		1 (n = 16)	2 (n = 16)	3 (n = 17)	4 (n = 16)	5 (n = 16)	P trend [a]
Change in saturated fat intake (en%) (mean (SD))		−5.9 (1.4)	−2.7 (0.4)	−1.7 (0.3)	−0.3 (0.5)	+1.6 (0.7)	
Age (years)		55.3 (9.6)	56.6 (9.0)	51.8 (11.1)	58.2 (9.4)	54.1 (9.3)	
Male sex (%)		44	38	35	44	31	
Serum total cholesterol (mmol/l)		7.0	6.6	6.6	7.0	6.8	
Serum LDL cholesterol (mmol/l)		4.8	4.4	4.4	4.8	4.5	
Baseline	Intake of saturated fat (% of energy)	16.9 (2.4)	14.7 (1.8)	13.8 (1.8)	13.0 (2.0)	12.0 (3.3)	<0.01
	Carotid intima-media thickness (mm) [b]	0.84 (0.03)	0.82 (0.03)	0.84 (0.03)	0.80 (0.03)	0.81 (0.03)	
	Femoral intima-media thickness (mm) [b]	0.88 (0.06)	0.76 (0.06)	0.80 (0.06)	0.73 (0.07)	0.80 (0.06)	
	sICAM-1 (ng/ml)	82.3 (10.2)	72.8 (7.8)	92.1 (6.5)	82.6 (8.3)	97.3 (10.9)	
Changes in	Carotid IMT (mm) [c]	0.03 (0.03)	0.02 (0.03)	0.03 (0.03)	0.09 (0.03)	0.10 (0.03)	0.07
	Femoral intima-media thickness (mm) [c]	−0.09 (0.07)	0.02 (0.06)	0.04 (0.06)	0.12 (0.06)	0.17 (0.07)	<0.05
	sICAM-1 (ng/ml) [c]	−19.0 (5.6)	−12.7 (4.9)	−2.0 (4.8)	+5.6 (5.0)	+8.6 (5.3)	<0.001
	Serum LDL cholesterol (mmol/l) [d]	−0.5 (0.2)	−0.6 (0.2)	−0.7 (0.2)	−0.9 (0.2)	−0.7 (0.2)	
	Systolic blood pressure (mmHg) [e]	−2 (3)	−5 (3)	−2 (3)	+4 (4)	+8 (4)	<0.05
	Body mass index (kg/m²) [f]	+0.2 (0.3)	+0.6 (0.3)	+0.7 (0.3)	+1.3 (0.3)	+0.1 (0.3)	<0.05(quadr.)
	Dietary intake of PUFA (en%)	+2.5 (0.9)	+2.7 (0.9)	+2.9 (0.8)	+2.9 (0.5)	+3.6 (0.8)	
	Dietary intake of cholesterol (mg/day)	−59 (16)	−13 (19)	+9 (11)	−10 (10)	+18 (20)	<0.01
	Dietary intake of fruit (g/day)	+101 (48)	+119 (52)	+51 (34)	−49 (41)	−74 (48)	<0.01

en% = percentage of energy intake; sICAM-1 = soluble intercellular adhesion molecule 1; LDL = low-density lipoprotein; PUFA = polyunsaturated fat.

[a] When corrected for multiple testing the P for trend regarding sICAM-1 is <0.05.
[b] Adjusted for age, gender, systolic blood pressure.
[c] Adjusted for baseline level, intake saturated fat, body mass index, age, changes in intake of dietary cholesterol, fruit, polyunsaturated fat.
[d] Adjusted for lipid-lowering medication, baseline level.
[e] Adjusted for baseline level, smoking, change in body mass index.
[f] Adjusted for age, gender.

the carotid IMT ($P = 0.07$) (adjusted for baseline IMT, BMI, and SFA intake, age, and changes in intake of fruit, polyunsaturated fat and dietary cholesterol) (Fig. 1). For the carotid (data not shown) and femoral IMT, the linear trend was similar with additional adjustments for changes in LDL cholesterol ($P = 0.01$), BMI ($P = 0.01$), systolic blood pressure ($P = 0.02$), and sICAM-1 ($P = 0.01$).

3.5. Quintiles of change in saturated fat intake and soluble ICAM-1

Table 4 and Fig. 2 show the changes in sICAM-1 levels per quintile of change in SFA intake. In the lowest quintile, the sICAM-1 concentration decreased with 19.0 ng/ml (SEM = 5.6) versus an increase of 8.6 ng/ml (SEM = 5.3) in the top quintile (P for trend
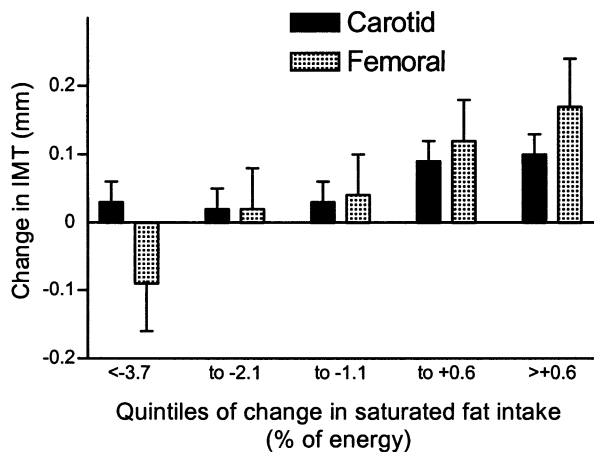
Fig. 1. Change in carotid and femoral IMT per quintile of change in saturated fat intake after 2 years ($n = 78$). Legend. *P* for trend 0.02 (femoral IMT) and 0.07 (carotid IMT); adjusted for baseline IMT, body mass index, and saturated fat intake, age, changes in intake of fruit, dietary cholesterol, polyunsaturated fat.

< 0.001; $n = 78$; adjusted for baseline sICAM-1 level, BMI and SFA intake, age, and changes in intake of fruit, polyunsaturated fat, and dietary cholesterol).

4. Discussion

In these moderately hypercholesterolaemic study participants, who had two other cardiovascular risk factors, we showed that decreasing the intake of SFA is associated with a reduced progression of the femoral and carotid IMT. The mechanism may involve the expression of ICAM-1, since we found a clear association between changes in SFA intake and sICAM-1. However, statistical adjustment for changes in sICAM-
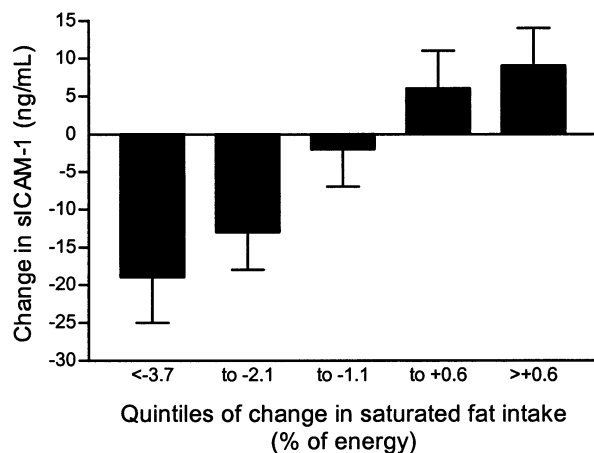

Fig. 2. Change in levels of soluble intercellular adhesion molecule-1 (sICAM-1) per quintile of change in saturated fat intake after 2 years ($n = 78$). Legend. *P* for trend < 0.001; adjusted for baseline sICAM-1, body mass index, and saturated fat intake, age, and changes in intake of fruit, dietary cholesterol and polyunsaturated fat.

1 did not alter the linear association between the changed SFA intake and IMT.

Our findings about an association between the reported SFA intake and sICAM-1 are compatible with the results of De Caterina and coworkers who found that fatty acids influence the expression of adhesion molecules in vitro [5,6]. Plasma levels of sICAM-1 have been shown to be significantly different between symptomatic and asymptomatic plaques, and risk factor-free age-matched controls. An increased expression of ICAM-1 may be involved in the conversion of carotid plaque to a symptomatic state [15]. Hence, when decreasing SFA intake would reduce the expression of ICAM-1, a component of the inflammatory pathway, this may not only influence the initiation of formation of plaques but also the conversion of plaques to a symptomatic or prothrombotic state.

With respect to other cardiovascular risk factors, we observed an increased systolic blood pressure and BMI among the quintiles of changes in SFA intake. At baseline, the blood pressure was associated with carotid IMT, and other research showed that an increased BMI of 1 kg/m² is associated with excess annual IMT progression by 0.013 mm/year [16]. However, statistical adjustments for changes in systolic blood pressure, BMI, and sICAM-1 did not alter the associations between changed SFA intake and IMT. This may be partly due to the small differences in BMI and blood pressure among the quintiles, and to the small number of participants in each quintile.

Other limitations of the study are acknowledged. The present investigation was conducted within the intervention group of a primary prevention project. Unfortunately, the IMT was not assessed in our control group due to budgetary reasons. Therefore, further research using randomised controlled trials is necessary to exclude the possibility of confounding variables and to confirm causality. For example, the IMT progression rate may also be predicted by dietary cholesterol [16]. In our study, statistical adjustment for dietary cholesterol did not alter the association between SFA and IMT, but dietary intakes of SFA and cholesterol are usually highly correlated (in our study $r = 0.42$). Since we found a clear association between SFA and sICAM-1, we hypothesize that the mechanism by which diet affects IMT progression includes the expression of ICAM-1, and SFA intake may be more important in influencing the progression of IMT than dietary cholesterol. Another dietary determinant of IMT progression can be a changed intake of fruit. However, as was the case with dietary cholesterol, statistical adjustment for changes in fruit intake did not affect the significance of the association between changes in SFA intake and IMT or sICAM-1. Finally, changes in SFA intake may merely reflect changes in dietary compliance, and hence perhaps changes in other health behaviours (like physi-

cal activity). In the present study this potential source of bias could not be controlled completely. It should be noted, however, that adjustments for changes in HDL-, LDL cholesterol, and BMI that may be determined by physical activity, did not alter our results.

The association between changes in SFA intake and femoral IMT remained significant after adjusting the changes in LDL cholesterol. Although this may seem surprising, it has been shown previously that the positive association between SFA intake and risk of developing CHD (RR = 1.11, 95%CI = 1.04–1.18) is not fully mediated by serum lipids [17]. Other studies showed that the level of sICAM-1 independently predicts the presence of ischaemic heart disease [7,18]. Further, the ARIC study found a cross-sectional association between SFA and carotid IMT, independent of age, smoking, and established cardiovascular risk factors [10]. Finally, it has been shown that atherosclerosis can also regress in persons without a decrease in LDL cholesterol [19].

The impact of dietary changes on coronary narrowing has been established. Intervention studies, using quantitative coronary angiographic measures, showed a 25–30% difference in the progression of the extent of coronary narrowing between the intervention group (low fat diet) when compared with usual care in patients with angina pectoris or myocardial infarction [3,20]. In our study population, which already had a high PUFA intake at baseline [12], the nutritional education combined with the free provision of PUFA-rich margarines decreased average dietary SFA intake by 1.8% of energy intake after 2 years. The intake of SFA in industrialized countries exceeds the guidelines for a healthy diet, which state as goal less than 10% of energy intake [21]. From a public health perspective, it is important to stimulate the replacement of products rich in SFA by products rich in unsaturated fatty acids. In persons having multiple risk factors the goal for reducing SFA intake is even lower (< 7% of energy) [22]. This is congruent with our findings that emphasise the need to reduce SFA intake in hypercholesterolaemic persons with elevated risk of developing CHD.

Acknowledgements

References

[1] Hu FB, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review. J Am Coll Nutr 2001;20:5–19.

[2] Hooper L, Summerbell CD, Higgins JP, et al. Dietary fat intake and prevention of cardiovascular disease: systematic review. BMJ 2001;322:757–63.

[3] Watts GF, Lewis B, Brunt JN, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in St Thomas' Atherosclerosis Regression Study (STARS). Lancet 1992;339:563–9.

[4] Caggiula AW, Mustad VA. Effects of dietary fat and fatty acids on coronary artery disease risk and total and lipoprotein cholesterol concentrations: epidemiologic studies. Am J Clin Nutr 1997;65(Suppl):S1597–610.

[5] De Caterina R, Libby P. Control of endothelial leukocyte adhesion molecules by fatty acids. Lipids 1996;31(Suppl):S57–63.

[6] De Caterina R, Liao JK, Libby P. Fatty acid modulation of endothelial activation. Am J Clin Nutr 2000;71(1):213–23.

[7] Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. Lancet 1998;351:88–92.

[8] Springer TA. Adhesion receptors of the immune system. Nature 1990;346:425–34.

[9] Veller MG, Fisher CM, Nicolaides AN, et al. Measurement of the ultrasonic intima-media complex thickness in normal subjects. J Vasc Surg 1993;17:719–25.

[10] Ma J, Folsom AR, Lewis L, Eckfeldt JH. Relation of plasma phospholipid and cholesterol ester fatty acid composition to carotid artery intima-media thickness: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 1997;65:551–9.

[11] Gearing AJH, Newman W. Circulating adhesion molecules in disease (review). Immunol Today 1993;14(10):506–11.

[12] Bemelmans WJE, Broer J, Vries de JHM, Hulshof KFAM, May JF, Meyboom-de Jong B. Impact of Mediterranean diet education versus posted leaflet on dietary habits and serum cholesterol in a high risk population for cardiovascular disease. Public Health Nutr 2000;3(3):273–83.

[13] Wolkerstorfer A, Laan MP, Savelkoul HFJ, et al. Soluble E-selectin, other markers of inflammation and disease severity in children with atopic dermatitis. Br J Dermatol 1998;138:431–5.

[14] de Groot E, Zwinderman AH, van der Steen AFW, et al. Variance components analysis of carotid and femoral intima-media thickness measurements. Ultrasound Med Biol 1998;24:825–32.

[15] DeGraba TJ, Sirén AL, Penix LR, et al. Increased endothelial expression of intercellular adhesion molecule-1 in symptomatic versus asymptomatic human carotid atherosclerotic plaque. Stroke 1998;29:1405–10.

[16] Markus RA, Mack WJ, Azen SP, Hodis HN. Influence of lifestyle modification on atherosclerotic progression determined by ultrasonographic change in the common carotid intima-media thickness. Am J Clin Nutr 1997;65(4):1000–4.

[17] Esrey KL, Joseph L, Grover SA. Relationship between dietary intake and coronary heart disease mortality: lipid research clinics prevalence follow-up study. J Clin Epidemiol 1996;49:211–6.

[18] Morisaki N, Saito I, Tamura K, et al. New indices of ischemic heart disease and aging: studies on the serum levels of soluble intercellular adhesion molecule-1 (ICAM-1) and soluble vascular cell adhesion molecule-1 (VCAM-1) in patients with hypercholesterolemia and ischemic heart disease. Atherosclerosis 1997;131:43–8.

[19] Baldassarre D, Veglia F, Gobbi C, et al. Intima-media thickness after pravastatin stabilizes also in patients with moderate to no

reduction in LDL–cholesterol levels: the carotid atherosclerosis Italian ultrasound study. Atherosclerosis 2000;151(2):575–83.

[20] Schuler G, Hambrecht R, Schlierf G, et al. Regular physical exercise and low-fat diet. Effects of progression of coronary artery disease. Circulation 1992;86(1):1–11.

[21] Report of the expert panel on population strategies for blood cholesterol reduction. A statement from the National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health. Circulation 1991;83:2154–32.

[22] Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA 2001;285:2486–97.