Polyunsaturated Fatty Acids May Impair Blood Glucose Control in Type 2 Diabetic Patients

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Fifteen patients with Type 2 diabetes were given two diets rich in either saturated fat or polyunsaturated fat in alternate order over two consecutive 3-week periods on a metabolic ward. Both diets contained the same amount of fat, protein, carbohydrates, dietary fibre, and cholesterol. The proportions of saturated, monounsaturated and polyunsaturated fatty acids in the saturated fat diet were 16, 10, and 5 %-energy and in the polyunsaturated fat diet (PUFA) 9, 10, and 12 %-energy. The PUFA diet contained a high proportion of n-3 fatty acids. Metabolic control improved significantly in both dietary periods, due to both qualitative dietary changes and a negative energy balance. The serum lipoprotein concentrations decreased on both diets but the serum lipids were significantly lower after the PUFA diet (serum triglycerides −20 %, $p=0.001$; serum cholesterol −5 %, $p=0.03$; VLDL-triglycerides −29 %, $p < 0.001$; and VLDL-cholesterol −31 %, $p=0.001$) than after the saturated fat diet. Average blood glucose concentrations during the third week were significantly higher fasting (+15 %, $p < 0.01$), and during the day at 1100 h (+18 %, $p < 0.001$) and 1500 h (+17 %, $p=0.002$) on PUFA than on the saturated fat diet. Significantly higher blood glucose levels were also recorded with a standard breakfast, while the sum of the insulin values was lower (−19 %, $p=0.01$). HbA_{1c} did not differ significantly between the two dietary periods. The present study suggests that an increased content of polyunsaturated fatty acids, especially long-chain n-3 fatty acids, in a low fat diet may have beneficial as well as adverse effects in the management of Type 2 diabetes.

KEY WORDS **Dietary fat Polyunsaturated fatty acids Diabetes Lipids**

Introduction

Dietary modification is the basis of management of diabetes. The aim is to normalize not only the blood glucose concentrations but also the other metabolic abnormalities, including the lipid disorder commonly seen in Type 2 diabetes. It is generally agreed that diabetic patients should eat a fat-restricted diet with an increased content of fibre-rich carbohydrates.[1,2] However, little is known about how the fat quality as such influences metabolic control in diabetes. The present study was undertaken to evaluate the effects of an isolated change of fat quality, within the framework of a diabetic diet of adequate nutritional composition, on carbohydrate and lipid metabolism in Type 2 diabetic patients.

Patients and Methods

Patients

Fifteen patients with poorly controlled Type 2 diabetes, 5 men and 10 women, age 63 (range 39–86) years, body weight 72.1 (range 62.9–99.2) kg with BMI 26.1 (range 21.8–32.0) kg m^{-2}, were included in the study. All patients had received dietary advice earlier and most of them were on treatment with anti-diabetic drugs, which were kept unchanged throughout the study. Other medication, such as digitalis glycosides, glyceryl trinitrate, selective β-adrenergic-blocking drugs, and diuretics, was also kept unchanged. No patient suffered from thyroid disease or nephropathy.

All patients had given their informed consent before entering the study and the protocol was approved by the Ethical Committee of the Medical Faculty of Uppsala University, Uppsala, Sweden.

Study Design

The patients were given two isoenergetic diets for two consecutive 3-week periods on a metabolic ward. Seven patients started with the diet rich in saturated fat, eight with the diet with a high content of polyunsaturated fat. One of the latter did not complete the saturated fat period due to intercurrent illness. Thus the comparison at the end of the two treatment periods is restricted to the 14 patients who completed both treatment periods.

All patients had diets with an individually calculated energy content in an effort to ensure stable body weight throughout the study. Thus, the female patients received 30 kcal (125 kJ) per kg body weight and the male patients 35 kcal kg^{-1} (145 kJ kg^{-1}). The relative content of

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nutrients was identical at different levels of energy intake. Admission and change of diet took place on the same day of the week. The blood glucose concentrations were measured after an overnight fast and at 1100 h and 1500 h 3 days a week (Monday, Wednesday, Friday). Similarly, the glucose concentration in 24-h urine samples was measured three times a week.

At the end of each treatment period, the blood glucose and serum insulin concentrations were measured fasting and after a standard breakfast (see below). All other laboratory tests were performed fasting as indicated below during the last 2 days of each diet period, with the exception of blood lipid concentrations which were also measured at 1100 h (before lunch) and 1900 h (after dinner).

Diets

Diets were based on 1-week menus. The calculated nutrient composition of the two diets is given in Table 1. Data from the Swedish Food Composition Tables [3] were used for the calculation.

The total fat content and the fatty acid composition of the two diets were analysed for each day after homogenization of the food and extraction with chloroform–methanol. The total fat content was determined by weighing after evaporation to dryness of an aliquot of the chloroform phase while another aliquot was used for determination of the fatty acid composition by gas–liquid chromatography as earlier described.[4] The analysed fatty acid composition of the two diets is given in Table 2. The content of saturated, monounsaturated, and polyunsaturated fatty acids in the saturated fat diet corresponded to 15.6, 10.3, and 5.1 %-energy and in the PUFA diet to 8.5, 10.4, and 12.2 %-energy.

Both diets were composed of ordinary Swedish food. Most of the dishes were similar or identical in the two menus, except for the type of fat used for cooking, as dressing and as spread on the bread. A high content of polyunsaturated fat in the PUFA diet was achieved by using a margarine rich in linoleic acid, low-fat milk, meat products with a low content of fat, and vegetable oils with a high ratio between polyunsaturated and saturated fatty acids as a dressing. For breakfast, in addition to porridge or cereals with milk, bread, coffee and tea, the patients were given some marinated herring in an effort to increase the content of n-3 fatty acids. This menu comprised six fish meals (of 14), mainly including fat fish such as mackerel, herring or salmon, in ordinary amounts. Thus, the content of n-3 fatty acids in a 1600 kcal day^{-1} diet amounted to 4–5 g, 75 % of which originated from long chain (20 carbon atoms or more) polyunsaturated fish fatty acids.

In the saturated fat diet the patients received breakfasts containing similar foodstuffs, but with cheese instead of herring on the bread. For cooking, a margarine containing less polyunsaturated fat was used and the bread was spread with butter. This menu contained fish for two main meals. These dishes, however, contained lean fish with a very low fat content. For the main dishes, more beef and pork was included than in the PUFA diet. The content of n-3 fatty acids in this diet was approximately 1.5 g per 1600-kcal, exclusively derived from linolenic acid (18:3 n-3).

The blood glucose, serum insulin, and plasma C-peptide concentrations were studied before and after a standard breakfast at the end of the two treatment periods. The breakfast contained approximately 350 kcal (1.5 MJ) with a nutrient composition corresponding to 16–17 %-energy from protein, 28–31 %-energy from fat and 53–56 %-energy from carbohydrates. The main difference

Table 1. Calculated nutrient composition of the diabetic diet enriched in polyunsaturated fatty acids (PUFA diet) and that containing a high proportion of saturated fatty acids

	PUFA diet	Saturated fat diet
Protein (%-energy)	16 ± 0	16 ± 1
Fat (%-energy)	31 ± 1	31 ± 1
Carbohydrates (%-energy)	56 ± 1	56 ± 1
Dietary fibre (g day^{-1})[a]	30.4 ± 0.6	30.1 ± 1.0
Cholesterol (mg day^{-1})[a]	180 ± 86	185 ± 113
P/S ratio[b]	1.45 ± 0.04	0.22 ± 0.01

Mean ± SD calculated on a 7-day menu.
[a]Calculated on a diet containing 1600 kcal (6.8 MJ) per day.
[b]Ratio between polyunsaturated and saturated fatty acids in the diet.

Table 2. Analysed fatty acid composition of the two diabetic diets

Fatty acid	PUFA diet	Saturated fat diet
10:0–14:0	5.4 ± 1.0	15.3 ± 0.5
16:0	15.2 ± 1.0	24.2 ± 1.0
16:1	2.3 ± 0.8	2.2 ± 0.1
18:0	6.7 ± 0.9	10.4 ± 0.3
18:1	31.3 ± 2.8	31.0 ± 1.0
18:2 n-6	31.2 ± 4.9	13.7 ± 0.8
18:3 n-3	1.9 ± 0.4	2.8 ± 0.2
20:4 n-6	0.1 ± 0.2	0.1 ± 0.1
20:5 n-3	2.4 ± 1.6	0.1 ± 0.1
22:5 n-3	0.2 ± 0.3	0.0
22:6 n-3	3.4 ± 2.5	0.0
saturated	27.4 ± 1.6	50.2 ± 1.1
monounsaturated	33.4 ± 2.2	33.1 ± 1.1
polyunsaturated	39.2 ± 1.8	16.6 ± 0.8
n-6/n-3	5.2	4.8
P/S ratio	1.44 ± 0.11	0.33 ± 0.02

Mean ± SD of a 7-day menu, three analyses per day.
Fatty acid composition is given in % of total fatty acids analysed.
P/S ratio, ratio between polyunsaturated and saturated fatty acids; n-6/n-3, ratio between fatty acids of the n-6 and n-3 series.

between the two breakfasts was, as indicated above, that the breakfast containing more unsaturated fatty acids included marinated herring, the breakfast containing more saturated fat included cheese. The average fatty acid compositions of the two breakfasts are given in Table 3.

Laboratory Methods

Blood and urinary glucose concentrations were determined by a glucose oxidase method.[5] Serum insulin assays were performed by the Phadebas Insulin Test (Pharmacia, Uppsala, Sweden).[6] Haemoglobin A_{1c} was determined with fast-performance liquid chromatography (normal range 3.5–6.0 %).[7]

An intravenous insulin tolerance test was performed by injection of unmodified insulin, 0.1 U kg-bodyweight^{-1}. Blood glucose concentrations were followed every 5 min up to 45 min. Insulin sensitivity was expressed as the rate constant for glucose disappearance (k_{IVITT}).[8] A glucagon stimulation test was carried out as described by Madsbad *et al.* [9] with 0.5 mg of glucagon. Plasma C-peptide was measured according to Heding.[10]

Lipoprotein lipid concentrations were determined in serum after an overnight fast. Very low density (VLDL), low density (LDL), and high density lipoproteins (HDL) were isolated with a combination of preparative ultracentrifugation [11] and precipitation with a sodium phosphotungstate and magnesium chloride solution.[12] Triglyceride and cholesterol concentrations were determined in serum and in the isolated lipoprotein fractions by enzymatic methods using Boehringer-Mannheim (Mannheim, Germany) kits, modified for use in a Multistat III F/LS apparatus (Instrumentation Laboratories, Lexington, MA, USA).

Table 3. Analysed fatty acid composition (%) of the standard breakfast meals given at the end of the PUFA and saturated fat diet periods, respectively

Fatty acid	PUFA diet	Saturated fat diet
10:0–14.0	9.5	9.2
16:0	15.5	17.1
16:1	2.8	0.5
18:0	6.5	8.3
18:1	35.1	37.3
18:2 n-6	21.4	24.3
18:3 n-6	0.0	0.0
18:3 n-3	3.6	3.2
20:3 n-6	0.0	0.0
20:4 n-6	0.0	0.0
20:5 n-3	2.7	0.0
22:4 n-6	0.0	0.0
22:5 n-3	0.0	0.0
22:6 n-3	3.0	0.0

Mean of three analyses.

The concentrations of serum apolipoproteins (apo) B, A-I, and A-II were determined by turbidimetry in the Multistat III F/LS apparatus using monospecific polyclonal antibodies against apo B, A-I, and A-II, respectively. Before assay the samples were preincubated with triglyceride lipase as suggested by DaCol and Kostner.[13] The coefficients of variation in the apolipoprotein assays for apo B, A-I, and A-II were 2.5, 2.4, and 4.2 %, respectively.

The fasting fatty acid composition of the plasma cholesterol esters were determined by gas liquid chromatography as described earlier.[14]

Statistical Analysis

Results were analysed by analysis of variance with main factors for diets, patients, and time-periods. The interaction between diets and time-period was included in the model. Hypotheses of interest were tested by contrasts in the combination of factors. No significant carry-over or order effect could be demonstrated. Thus the combined data for the two periods are presented together irrespective of the order of treatment. The difference between the polyunsaturated and the saturated fat diets was also tested at the end of the two treatment periods by paired *t*-test.

Results

Both diets were well accepted by the patients. There was a significant ($p < 0.01$) mean body weight reduction of the same magnitude during both treatment periods. The average body weight reduction during treatment was 0.8 kg. The mean body weight at the end of the two treatment periods was identical (Table 4).

Blood Glucose and Serum Insulin Levels

The fasting blood glucose concentrations were significantly lower at the end of treatment periods with both diets, despite unchanged drug therapy, when compared with baseline (Table 4, $p < 0.001$). However, the blood glucose reduction was more pronounced on the saturated fat diet than on the PUFA diet. During the third week of treatment, the mean blood glucose concentrations (mean of 3 days during the last week) fasting before breakfast (0700 h), and before (1100 h) and after (1500 h) lunch were significantly higher on the PUFA diet than on the saturated fat diet (Figure 1). Urinary glucose excretion was 21 mmol day^{-1} on the saturated fat diet and 39 mmol day^{-1} on the PUFA diet ($p < 0.001$).

HbA_{1c} was also lower on both diets compared with baseline, but was identical between diets (Table 4). The rate constant for blood glucose disappearance during the insulin tolerance test (k_{IVITT}) increased significantly with both diets but was not different between diets (Table 4). There were no significant differences in insulin or

Table 4. Body weight, blood glucose control, and results of provocation tests at baseline and at the end of the two dietary periods

	Baseline	PUFA diet	Saturated fat diet	Difference between diets	*p*-value for difference
Body weight (kg)	72.8 ± 9.2	72.0 ± 9.5[a]	72.0 ± 9.1[a]	−0.0 ± 0.9	NS
Fasting blood glucose (mmol l^{-1})	11.9 ± 2.9	9.3 ± 2.8[b]	7.7 ± 2.3[b]	−1.6 ± 1.5	0.003
HbA_{1c} (%)	8.9 ± 2.0	7.9 ± 1.8[b]	7.8 ± 1.5[b]	−0.0 ± 0.7	NS
k_{IVITT} (% min^{-1})	1.88 ± 0.90	2.78 ± 1.76[a]	2.82 ± 1.05[a]	0.04 ± 1.40	NS
IV glucagon stimulation test					
Serum insulin (mU l^{-1})					
0 min	10.0 ± 8.3	10.6 ± 10.9	9.1 ± 7.9	−1.5 ± 4.3	NS
6 min	29.7 ± 20.3	24.5 ± 10.7	24.7 ± 12.9	0.3 ± 2.5	NS
Plasma C-peptide (nmol l^{-1})					
0 min	0.6 ± 0.4	0.6 ± 0.4	0.7 ± 0.3	0.1 ± 0.2	NS
6 min	1.1 ± 0.7	1.2 ± 0.8	1.2 ± 0.8	0.0 ± 0.2	NS

Mean ± SD.
[a]$p < 0.01$; [b]$p < 0.001$ compared with baseline.
n = 12–14.

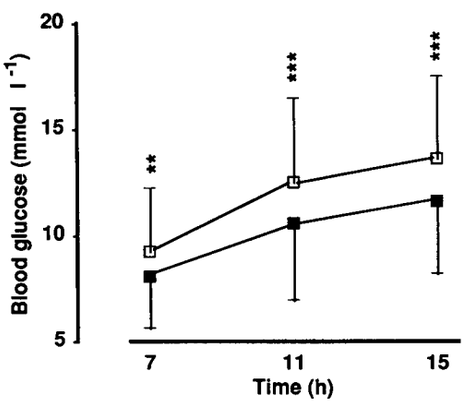

Figure 1. Mean blood glucose concentrations through the day during the third week of treatment on the diet rich in saturated (filled squares) and polyunsaturated (PUFA)(open squares) fatty acids, respectively; ** $p < 0.01$, *** $p < 0.001$

C-peptide concentrations fasting or after IV glucagon stimulation (Table 4).

The blood glucose concentrations during the breakfast test were lower by the end of both diet periods, but significantly higher on the PUFA than on the saturated fat diet (Figure 2). The fasting serum insulin concentrations did not differ between the diets but the sum of the insulin concentrations at the six time-points was significantly lower on the PUFA diet than on the saturated fat diet (−19 %, p=0.01). The C-peptide concentrations fasting, at 60, and at 120 min after breakfast were 0.62 ± 0.43 (±SD), 1.07 ± 0.70, and 1.23 ± 0.90 nmol l^{-1} on the PUFA diet and 0.64 ± 0.43, 1.20 ± 0.78, and 1.46 ± 1.13 nmol l^{-1} on the saturated fat diet (all NS between diets).

Lipid and Apolipoprotein levels

The fasting lipoprotein lipid profile was improved with both diets compared with baseline (Table 5). The VLDL

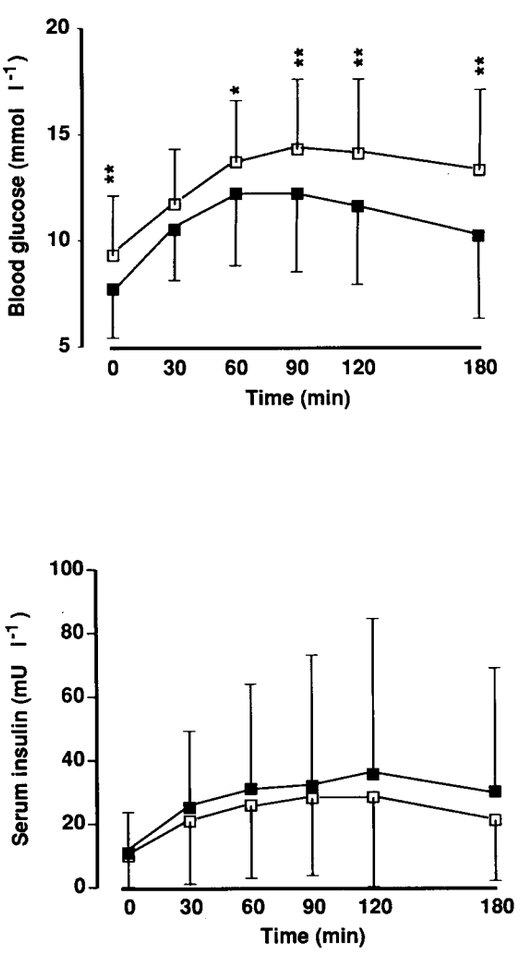

Figure 2. Blood glucose (top panel) and serum insulin (bottom panel) concentrations before and after a standard breakfast (eaten between 0 and 30 min) after the diet rich in saturated (filled squares) and polyunsaturated (PUFA) (open squares) fatty acids, respectively; * $p < 0.05$, ** $p < 0.01$

Table 5. Serum lipoprotein (mmol l^{-1}) and apolipoprotein (g l^{-1}) concentrations at baseline and at the end of the two dietary periods

	Baseline	PUFA diet	Saturated fat diet	Difference between diets	Confidence interval for difference	p-value for difference
VLDL-triglycerides	3.24 ± 2.58	1.33 ± 0.66[b]	1.87 ± 0.95[b]	0.54 ± 0.43	(0.29; 0.79)	< 0.001
VLDL-cholesterol	1.51 ± 1.41	0.59 ± 0.26[b]	0.86 ± 0.45[a]	0.27 ± 0.24	(0.12; 0.40)	0.001
LDL-triglycerides	0.66 ± 0.19	0.56 ± 0.12[b]	0.54 ± 0.13[c]	−0.02 ± 0.05	(−0.05; 0.01)	NS
LDL-cholesterol	4.27 ± 1.36	3.80 ± 1.01[b]	3.75 ± 0.88[b]	−0.03 ± 0.41	(−0.27; 0.20)	NS
HDL-triglycerides	0.27 ± 0.12	0.23 ± 0.07	0.25 ± 0.11	0.02 ± 0.05	(−0.01; 0.05)	NS
HDL-cholesterol	0.93 ± 0.27	0.87 ± 0.17	0.86 ± 0.20	−0.01 ± 0.12	(−0.08; 0.06)	NS
Serum triglycerides	4.18 ± 2.69	2.13 ± 0.76[c]	2.67 ± 0.97[b]	0.54 ± 0.49	(0.26; 0.82)	0.001
Serum cholesterol	6.74 ± 1.30	5.26 ± 1.03[c]	5.50 ± 0.97[c]	0.25 ± 0.37	(0.04; 0.46)	0.03
Apo B	1.19 ± 0.31	1.00 ± 0.27[c]	1.04 ± 0.21[b]	0.05 ± 0.13	(−0.03; 0.12)	NS
Apo A-I	1.28 ± 0.25	1.02 ± 0.14[c]	1.08 ± 0.15[b]	0.06 ± 0.17	(−0.04; 0.16)	NS
Apo A-II	0.40 ± 0.09	0.29 ± 0.04[c]	0.33 ± 0.06[c]	0.04 ± 0.04	(0.02; 0.06)	0.002

Mean ± SD.
[a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.001$ compared with baseline.

lipid reduction was close to 60 % on the PUFA diet and 43 % on the saturated fat diets. When compared at the end of the two treatment periods (Table 5) the serum triglycerides and serum cholesterol concentrations were significantly lower on the PUFA than on the saturated fat diet (−20 and −5 %, respectively, $p=0.001$ and $p=0.03$) corresponding to significantly reduced levels of VLDL-triglycerides and VLDL-cholesterol. The LDL-cholesterol concentrations decreased to a similar extent with both diets. Apo B, apo A-I, and apo A-II were reduced on both diets but the only significant difference between the two periods concerned Apo A-II which was lower after the PUFA than after the saturated fat diet (−12 %, $p=0.002$) (Table 5).

The serum triglyceride and cholesterol concentrations were also measured at baseline and after the two diet periods at 1100 h and 1900 h. The average serum triglyceride and cholesterol concentrations were reduced by 33 and 21 % on the saturated fat and by 40 and 25 % on the PUFA diet at 1100 h and by 23 and 21 % on the saturated fat and by 32 and 22 % on the PUFA diet after dinner at 1900 h (all $p < 0.001$ compared with baseline). The serum concentration of triglycerides was significantly lower (−11 %, $p < 0.05$) after the PUFA than after the saturated fat diet at 1100 h.

Plasma Fatty Acid Composition

The diverging fat composition of the two diets was reflected in changes in the fatty acid spectrum of the plasma cholesterol esters. Compared with baseline there were limited changes at the end of the saturated fat period, while more pronounced effects were seen on the PUFA diet period. The fatty acid composition of the plasma cholesterol esters at the end of the two diet periods is shown in Table 6. There was a highly significant increase of 20:5 n-3 and 22:6 n-3 fatty acids with a reduction of the linolenic acid content (18:3 n-3) at the end of the PUFA diet compared with the saturated fat diet. Despite the high content of linoleic acid (18:2 n-6) in the diet the relative content was unchanged at the end of the PUFA diet while the content of 18:1 decreased.

Discussion

Few studies have evaluated the effects of a change of fat quality alone on carbohydrate and lipid metabolism in Type 2 diabetes. An increased content of polyunsaturated fatty acids of the n-6 series reduced lipoprotein lipid levels in patients with hyperlipoproteinaemia.[15] In the same study, the *k* value of the intravenous glucose tolerance test increased in patients with hypertriglyceridaemia, indicating a possible improvement of glucose tolerance, after increasing the amount of polyunsaturated fat in the diet. Improved glucose tolerance was also seen in women with Type 2 diabetes when they were given a diet with a high content of polyunsaturated fatty acids.[16] Heine and coworkers [17] compared the effects of a diet with a low P/S ratio (0.3) with that of a high P/S ratio (1.0) in Type 2 diabetic patients. Total- and LDL-cholesterol were lower after the diet with a high P/S ratio. There was a modest increase of insulin-mediated glucose disposal at physiological insulin levels but no influence was seen in blood glucose control or plasma insulin and C-peptide responses to mixed meals.

The present study was performed with ordinary Swedish food. Different fats were used for cooking, as dressing and as spread on the bread, with a high content of linoleic acid in the PUFA diet, while the total fat content in the diets was similar to that recommended for diabetic patients.[1,2] The amount of polyunsaturated fat exceeded 10 %-energy, which is usually regarded as a desirable

Table 6. Plasma cholesterol fatty acid composition (%) at the end of the two dietary periods

Fatty acid	Baseline	PUFA	Saturated fat diet	Difference between diets	*p*-value for difference
16:0	12.8 ± 1.1	12.8 ± 0.7	12.8 ± 0.7	0.0 ± 0.4	NS
16:1	3.8 ± 1.3	3.2 ± 0.8[a]	3.9 ± 1.2	0.8 ± 0.5	0.001
18:0	1.0 ± 0.2	0.8 ± 0.2[c]	1.0 ± 0.3	0.2 ± 0.2	0.004
18:1	17.9 ± 2.9	14.5 ± 1.4[c]	18.5 ± 1.8	4.0 ± 1.0	< 0.001
18:2 n-6	54.4 ± 5.6	54.4 ± 2.9	53.5 ± 3.3	−1.5 ± 2.0	0.01
18:3 n-6	0.8 ± 0.3	0.4 ± 0.1[c]	0.6 ± 0.2[c]	0.2 ± 0.1	< 0.001
18:3 n-3	0.7 ± 0.2	0.4 ± 0.0[c]	0.8 ± 0.1	0.4 ± 0.1	< 0.001
20:3 n-6	0.7 ± 0.2	0.5 ± 0.1[c]	0.8 ± 0.2	0.3 ± 0.1	< 0.001
20:4 n-6	5.6 ± 1.4	5.8 ± 0.9	5.9 ± 1.4	0.1 ± 0.7	NS
20:5 n-3	1.0 ± 0.4	5.0 ± 0.9[c]	1.2 ± 0.3	−3.8 ± 0.9	< 0.001
22:6 n-3	0.7 ± 0.4	1.6 ± 0.2[c]	1.0 ± 0.2	−0.6 ± 0.2	0.001

Mean ±SD.
[a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.001$ compared with baseline.

upper limit nowadays. The only extraordinary feature was that the PUFA diet contained considerably more fish than is usually eaten by most Swedes today. The fat fish was included in order to increase the content of long-chain polyunsaturated fatty acids of the n-3 series which have been reported to reduce triglyceride concentrations in hypertriglyceridaemia [18] and to prevent the development of insulin insensitivity in rats fed high-fat diets.[19]

As expected, metabolic control, which was poor on admission, improved significantly during both dietary periods when the patients received diabetic diets of adequate nutritional composition. The main aim of the study was, however, to compare the effects of the two strictly controlled diets. Although the differences were not very pronounced the average blood glucose concentrations were clearly significantly higher both during the day and after a standard breakfast on the PUFA than on the saturated fat diet. In spite of the high glucose values the insulin concentrations during the standard breakfast test were lower on the PUFA diet. This is compatible with the results from several recent studies, where addition of n-3 fatty acids, especially in Type 2 diabetic patients, has increased the blood glucose concentrations without a concomitant increase of insulin or C-peptide concentrations (review by Vessby[20]). This is the first study where similar effects have been demonstrated after addition of n-3 fatty acids as fat fish included in normal food as a part of an adequate diabetic diet. It has to be stressed that the PUFA diet in this study also contained a high content of polyunsaturated fatty acids of the n-6 series, which may have influenced blood glucose control, although this seems less likely in the light of earlier studies where such effects were not seen.[15–17]

The reason for increased glucose concentrations after addition of n-3 fatty acids has been discussed. Glauber *et al.* reported an increase in basal hepatic glucose output after dietary supplementation with n-3 fatty acids.[21] This may be due to an increased availability of gluconeogenic precursors or decreased hepatic sensitivity to insulin. A blunted C-peptide reponse to a mixed meal has been observed in patients with lipodystrophic diabetes on a diet enriched with n-3 fatty acids.[22] This could be one mechanism underlying the lower insulin response after the mixed meal on the PUFA than on the saturated fat diet. Although the increased fasting blood glucose concentrations are compatible with an increased basal hepatic glucose output, similar insulin/C-peptide ratios on the three diets do not indicate differences in the hepatic extraction of insulin. Rather, the results of this study and others [21,23] are compatible with the existence of an impaired insulin response to glucose after supplying a diet rich in n-3 fatty acids. The n-3 fatty acids are precursors of prostaglandins and leukotrienes. Prostaglandins are capable of augmenting as well as diminishing the pancreatic insulin release. Other possible regulating effects of eicosanoids on pancreatic islet function include modulation of islet blood flow and increased responsiveness, as recently reviewed.[24]

In this study the k_{IVITT}, which gives a good estimate of *in vivo* insulin action,[25] did not indicate any significant differences in peripheral insulin sensitivity between the dietary periods, although both diets were associated with improvements compared with baseline. Others have found an increased metabolic clearance rate of glucose after dietary supplementation of fish oils rich in n-3 fatty acids in Type 2 diabetic patients. This was interpreted as indicating improved insulin sensitivity.[26]

There were pronounced reductions of lipoprotein lipid concentrations during both dietary periods. These changes reflect the general improvement in dietary adherence during the hospital stay, including a decreased total fat content, an increased fibre content, and probably also a lower dietary cholesterol content than during the preceding outpatient treatment. A negative energy balance and the improved blood glucose control may also have contributed to the serum lipid and apolipoprotein

reductions. In spite of the reduced fat consumption and the high content of polyunsaturated fatty acids in the PUFA diet, there were no significant reductions of HDL-cholesterol levels. There was, on the other hand, a reduction of the apolipoprotein A-I and A-II levels in serum, which should probably be regarded as a step towards normalization of the lipoprotein composition. The significantly lower concentrations of serum cholesterol and serum triglycerides after PUFA than after the saturated fat diet are in accordance with what could be expected from earlier studies in non-diabetic subjects.[15] In contrast to the findings by Heine *et al.* [17] we could not demonstrate any differences with regard to the effects on LDL-cholesterol, probably due to the normal average levels of LDL-cholesterol in these patients.

In spite of a high content of n-6 fatty acids in the PUFA diet, there were no changes in the content of 18:2 n-6 in the cholesterol esters, while there were highly significant increases in the n-3 fatty acids with chain-lengths of 20 carbon atoms and more, similar to those reported earlier after addition of fish oil rich in n-3 fatty acids to an ordinary diabetic diet.[27] This is in accordance with the preferential incorporation of the n-3, rather than n-6, fatty acids in plasma lipids when both types of fatty acids are included in the diet.

It is at present too early to give a definite answer to the question of whether a high content of polyunsaturated fatty acids, and especially of n-3 fatty acids, is advantageous in the treatment of Type 2 diabetic patients. On the one hand there is a tendency to impairment of blood glucose concentrations, while on the other the effects on lipoprotein metabolism, the coagulation system and eicosanoid metabolism, may possibly outweigh this potentially negative effect with regard to the risk for atherosclerotic cardiovascular manifestations. Controlled studies during longer time-periods using ordinary foodstuffs are desirable. Also, the qualitative differences between the effects of n-3 and n-6 fatty acids on glucose homeostasis require further study.

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