The effect of orlistat on the fatty acid composition of serum lipid fractions in obese subjects

Objective: **To determine whether there are any changes in the fatty acid composition of serum triglycerides, cholesterol esters, and phospholipids induced by administration of orlistat three times a day compared with placebo as combined with a low-fat hypocaloric diet.**

Methods: **After 4 weeks of placebo administration, 75 obese subjects were randomized to receive either one capsule (120 mg) of orlistat or placebo three times a day with meals for 1 year in conjunction with a nutritionally balanced hypocaloric diet. Food records were kept to estimate the nutrient intake. The fatty acid composition of serum lipids were analyzed with gas chromatograph. The molar percentage proportions of fatty acids in serum lipid fractions were calculated.**

Results: **Compared with placebo, there was a significant decrease in the proportion of linoleic acid in triglycerides, cholesterol esters, and phospholipids in the orlistat group, even after the effect of the decrease in the linoleic acid dietary intake (percent of energy), weight change, and gender were taken into account. However, the use of orlistat explained only 9% to 13% of the decrease in the proportion of linoleic acid in serum cholesterol esters, triglycerides, and phospholipids.**

Conclusion: **The long-term treatment with orlistat may result in a small decline in the proportion of diet-derived fatty acids in serum lipid fractions when used in conjunction with low-fat diet. (Clin Pharmacol Ther 1999;66:315-22.)**

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Restriction of the intake of fat and energy is the first line treatment for obesity, but dietary means often fail in the long run and therefore other treatment modalities are warranted. Pancreatic lipase is the primary enzyme responsible for the hydrolysis and subsequent absorption of dietary fat from the small intestine. Orlistat (Xenical) is a potent inhibitor of gastric and pancreatic lipase activity, exerting its effect within the gastrointestinal tract by binding covalently to the serine residue of the active site of gastric and pancreatic lipase. Inhibition of pancreatic lipase has been shown to partially inhibit the hydrolysis of triglycerides, reducing the subsequent absorption of monoglycerides and free fatty acids.[1] Orlistat selectively reduces the absorption of dietary fat,[2-4] with maximal inhibition of 30% of dietary fat in doses from 100 to 400 mg given three times daily with meals.[5] Based on the mechanism of action of orlistat, one can speculate that it could modify the absorption of different fatty acids, especially that of long-chain fatty acids, but no human long-term studies are available that examine the effect of orlistat in this respect. Because fatty acid composition of serum lipids reflects the long-term intake (and absorption) of dietary fatty acids, the aim of this study was to determine whether there are any changes in the fatty acid composition of serum triglycerides, cholesterol esters, and phospholipids during a 1-year period induced by administration of 120 mg orlistat three times a day compared with placebo, as combined with a low-fat hypocaloric diet. The study was a part of a multicenter international 2-year study to examine the efficacy and tolerability of orlistat in promoting weight loss and preventing weight regain during 104 weeks of therapy.[6]

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Table I. Characteristics of the study subjects

	Orlistat	*Placebo*
N	37	38
Sex		
Men	7	8
Women	30	30
Age (y)	43.0 ± 6.3	43.3 ± 6.5
Weight (kg)	97.2 ± 12.1	98.8 ± 15.0
Body mass index (kg/m^2)	35.1 ± 3.3	35.8 ± 4.1
Serum lipids (mmol/L)		
Total cholesterol	5.6 ± 1.2	5.2 ± 0.8
LDL cholesterol	3.7 ± 1.0	3.5 ± 0.8
HDL cholesterol	1.2 ± 0.3	1.2 ± 0.3
VLDL cholesterol	0.7 ± 0.4	0.6 ± 0.3
Total triglycerides	1.6 ± 0.9	1.6 ± 0.8

Data are mean values ± SD.
LDL, Low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein.

SUBJECTS AND METHODS

The original study population consisted of 683 obese men and women who participated in a 2-year, double-blind, randomized placebo-controlled study in 15 European centers. A detailed description of the study and the selection of the participants have been published elsewhere.[6] This study is an analysis of fatty acid composition of 75 subjects (60 women and 15 men) in two centers during the first year. The characteristics of the subjects are shown in Table I. In brief, patients meeting the inclusion criteria entered a 4-week placebo lead-in period. The patients received advice for a hypocaloric diet, and food records were kept two times during the lead-in period. After 4 weeks of placebo administration, the patients were randomized to receive either orlistat (n = 37) or placebo (n = 38) for 1 year in conjunction with a nutritionally balanced hypocaloric diet. Patients were asked to take one capsule (120 mg) of orlistat or placebo three times a day with meals. Patients visited the clinic every 2 weeks during the placebo lead-in period and during the first 3 months of the randomized treatment for the assessment of tolerability, efficacy, and dietary monitoring. Patients then came to the clinic once a month from week 17 to the end of the first year.

Dietary regimen was a nutritionally balanced hypocaloric diet that contained approximately 30% of energy as fat (10% saturated, 10% monounsaturated, and 10% polyunsaturated), 50% as carbohydrate, and 20% as protein, as well as a maximum of 300 mg/day cholesterol. Alcohol consumption was limited to no more than 150 g alcohol per week. The energy content of the prescribed diet was based on an estimate of the subject's initial maintenance energy needs minus 600 kcal/d between the lead-in period and week 24. At the end of week 24, the diet was readjusted: the energy intake was reduced by 300 kcal per day until the end of year 1. The subjects were asked to distribute the diet into three meals a day and, if desired, a low-fat snack was allowed.

The patients kept 4-day food and beverage diaries. At each follow-up visit the patients met the dietitian to reinforce the diet to achieve the prescribed caloric level. A food record was kept during the week that preceded the clinic visit on a weekly basis during the first 2 weeks of the placebo lead-in period, then every other week during the placebo lead-in period and the first month of treatment, and then once a month until the end of the study. The days were consecutive 2 weekdays and 2 weekend days. The patients were provided with booklets for records and with digital weighing machines for portion-size estimations. Food intake records were analyzed with a local database (Nutrica, Helsinki, Finland) to estimate the average daily energy intake and the intake of fat, carbohydrate, protein, alcohol, and dietary cholesterol.

Height was measured at the beginning of the lead-in period only. Body weight was measured by electronic scales at every visit during the lead-in period, then every 2 weeks for the first 3 months, and then monthly thereafter throughout the study, with the patients wearing light clothing and no shoes. Body mass index was calculated as follows: weight (kg)/height^2 (m). For this study, serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and triglycerides were measured at the beginning of the lead-in period, at randomization, and at the 1-year examination. Fatty acid composition of serum lipids were measured four times: at the beginning of the lead-in period and at the end of months 3, 9, and 12. All measurements were done in the morning after an overnight fast, and blood samples were taken after the fast before breakfast and before medication for the analysis of serum lipids and the fatty acid composition of serum lipid fractions.

Serum lipids were analyzed after ultracentrifugation (92,500*g* for 18 hours at 5°C) and precipitation by enzymatic methods[7-9]: the CHOD-PAP method (HiCo cholesterol reagents, Boehringer Mannheim, Mannheim, Germany) for cholesterol and HDL cholesterol and the GPO-PAP method (Boehringer Mannheim) for triglycerides. For the determination of the fatty acid composition of serum lipids, the samples were extracted with chloroform-methanol and the lipid fractions were separated by solid-phase extraction with aminopropyl columns. The fatty acids of triglycerides, cholesterol esters, and phospholipids were transmethylated with

Table II. Reported nutrient intakes of the study subjects during the lead-in period and after 1 year*

	Orlistat (n = 37)		*Placebo (n = 38)*	
	Lead-in period	*1 year*	*Lead-in period*	*1 year*
Energy (kcal)	1649 ± 504	1343 ± 305	1521 ± 578	1264 ± 338
Protein (E%)	19.5 ± 3.1	20.6 ± 3.9	18.9 ± 3.9	20.1 ± 3.5
Carbohydrates (E%)	42.0 ± 6.9	48.0 ± 5.9	41.5 ± 6.1	48.2 ± 6.7
Fat (E%)	35.2 ± 6.9	29.1 ± 5.3	36.0 ± 5.8	28.8 ± 4.9
SAFA (E%)	14.0 ± 3.6	10.9 ± 2.7	14.7 ± 3.6	10.5 ± 2.5
MUFA (E%)	12.6 ± 3.3	9.6 ± 2.2	12.7 ± 2.3	9.9 ± 2.2
PUFA (E%)	5.6 ± 1.5	5.0 ± 1.4	5.6 ± 1.5	5.1 ± 1.2
C18:2n6 (E%)	4.4 ± 1.3	3.8 ± 1.1	4.4 ± 1.4	4.0 ± 1.1
C18:3n3 (E%)	0.7 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.1
P/S value	0.43 ± 0.17	0.48 ± 0.15	0.40 ± 0.13	0.52 ± 0.17
Cholesterol (mg)	268 ± 110	187 ± 80	244 ± 102	173 ± 77
Alcohol (E%)	3.2 ± 4.8	2.3 ± 3.0	3.5 ± 5.0	2.8 ± 4.7

Data are mean values ± SD.
E%, Percent of energy; SAFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; P/S, polyunsaturated fatty acids/saturated fatty acids.
*NS between the groups.

boron-trifluoride in ethanol.[10] Fatty acid methyl esters were analyzed with gas chromatograph (HP 5890 Series II, Hewlett-Packard Company, Waldbronn, Germany) equipped with a HP-FFAP capillary column. The molar percentage proportions of fatty acids in serum lipid fractions were calculated.

All calculations were performed with use of the SPSS/WIN programs (version 6.0, SPSS Inc, Chicago, Ill). Normal distribution of variables was checked with Kolmogorov-Smirmov test before further analyses. All variables were normally distributed. Multivariate analysis of variance for repeated measurements (MANOVA) was used to determine the difference in the proportions of fatty acids of serum lipid fractions within and between the two groups.[11] If there were significant differences, the means of the fatty acid proportions at the beginning of the placebo lead-in period and after 1 year were compared with the Student *t* test for paired samples. The sample means of age, weight, body mass index, and nutrient intake and the changes in the nutrient intake and serum lipids were compared with the Student *t* test for independent samples. The stepwise multiple regression analysis was used to investigate the independent association of the changes of linoleic acid in serum lipid fractions during the orlistat versus placebo treatments; other factors in the model were the change percent of energy (E%) of the linoleic acid dietary intake, weight change during the study, and gender. The results are presented as mean values ± SD.

RESULTS

At baseline the ages, weights, and body mass indices were comparable in the study groups (Table I). The mean weights after 1 year in subjects in the orlistat and placebo groups were 84.6 ± 13.0 kg and 91.2 ± 16.6 kg, respectively. The mean weight reduction was significantly greater in subjects in the orlistat group than in the placebo group (12.0 ± 8.2 kg versus 7.8 ± 6.0 kg; $P = .01$).

There were no significant differences in the intake of nutrients between the study groups at any time points (Table II). The goals of the diet were well achieved; the intake of energy and the intake of fat remained low in both study groups. At the end of the study, the intake of linoleic acid was lower (E%) in both the orlistat and placebo groups compared with that at the lead-in period, but there were no significant differences in the magnitude of the changes in the intake between the two study groups. The intake of linoleic acid was 8.2 ± 3.8 g/d during the lead-in period and 5.3 ± 2.0 g/d ($P < .001$) after 1 year in the orlistat group and 7.5 ± 5.4 g/d and 5.9 ± 2.7 g/d ($P = .102$), respectively, in the placebo group.

There were no significant differences in serum total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, or serum total triglyceride concentrations between the study groups either before or after the study. In the orlistat group, HDL cholesterol increased significantly (1.2 ± 0.3 versus 1.3 ± 0.3 mmol/L at the beginning of the lead-in period versus after 1 year; $P = .023$). Furthermore, total cholesterol (5.6 ± 1.2 versus 5.2 ± 1.4 mmol/L), LDL cholesterol (3.7 ± 1.0 versus 3.4 ± 1.2 mmol/L), VLDL cholesterol (0.7 ± 0.4 versus 0.6 ± 0.4 mmol/L), and serum total triglycerides (1.6 ± 0.9 versus 1.4 ± 1.0 mmol/L) tended to decrease with orlistat, but the differences were not significant. In the placebo group, there were no significant changes

Table III. The fatty acid composition (mol% of total) of serum triglycerides during the lead-in period and after 1 year in the study groups

	Orlistat (n = 37)		*Placebo (n = 38)*		
Fatty acid	*Lead-in period*	*1 year*	*Lead-in period*	*1 year*	*MANOVA*
Myristic (14:0)	2.90 ± 0.77	2.84 ± 0.97	2.69 ± 1.01	2.84 ± 1.21	NS
Palmitic (16:0)	28.68 ± 3.00	29.64 ± 5.07	29.75 ± 3.81	29.42 ± 4.70	NS
Palmitoleic (16:1n7)	4.49 ± 1.50	5.11 ± 1.47	4.80 ± 1.66	4.72 ± 1.43	NS
Stearic (18:0)	4.17 ± 0.87	3.88 ± 0.76	4.18 ± 0.99	4.17 ± 1.12	NS
Oleic (18:1n9)	38.53 ± 2.96	38.34 ± 4.24	37.36 ± 4.04	37.52 ± 4.12	NS
Octadecanoic (18:n7)	2.80 ± 0.60	2.73 ± 0.53	2.73 ± 0.61	2.67 ± 0.49	NS
Linoleic (18:2n6)	14.56 ± 2.70	12.97 ± 2.26**	14.45 ± 3.42	14.08 ± 3.22	.031
γ-Linolenic (18:3n6)	0.30 ± 0.13	0.33 ± 0.12	0.29 ± 0.15	0.35 ± 0.24	NS
α-Linolenic (18:3n3)	1.37 ± 0.31	1.31 ± 0.30	1.25 ± 0.34	1.44 ± 0.45*	.030
Dihomo-γ-linolenic (20:3n6)	0.19 ± 0.06	0.21 ± 0.05	0.20 ± 0.05	0.21 ± 0.07	NS
Arachidonic (20:4n6)	0.83 ± 0.28	0.97 ± 0.28	0.91 ± 0.40	0.94 ± 0.38	NS
Eicosapentaenoic (20:5n3)	0.32 ± 0.20	0.40 ± 0.20	0.36 ± 0.30	0.43 ± 0.31	NS
Docosatetraenoic (22:4n6)	0.27 ± 0.14	0.33 ± 0.14	0.24 ± 0.15	0.28 ± 0.18	NS
Docosahexaenoic (22:6n3)	0.71 ± 0.45	1.16 ± 0.80	1.01 ± 0.85	1.18 ± 0.97	NS

Data are mean values ± SD.
MANOVA, Multivariate analysis of variance for repeated measurements.
**$P \leq .01$, Student *t* test for paired samples.
*$P \leq .05$, Student *t* test for paired samples.

Table IV. The fatty acid composition (mol% of total) of serum cholesterol esters during the lead-in period and after 1 year in the study groups

	Orlistat (n = 37)		*Placebo (n = 38)*		
Fatty acid	*Lead-in period*	*1 year*	*Lead-in period*	*1 year*	*MANOVA*
Myristic (14:0)	1.22 ± 0.31	1.34 ± 0.44	1.19 ± 0.53	1.20 ± 0.37	NS
Palmitic (16:0)	13.15 ± 1.43	14.30 ± 1.65***	13.22 ± 1.50	13.73 ± 1.15	.028
Palmitoleic (16:1n-7)	4.38 ± 1.36	4.69 ± 1.42	4.59 ± 1.74	4.16 ± 1.55*	.002
Stearic (18:0)	1.36 ± 0.38	1.28 ± 0.36	1.30 ± 0.52	1.35 ± 0.40	NS
Oleic (18:1n-9)	19.80 ± 2.49	21.16 ± 2.21***	19.49 ± 2.90	19.73 ± 1.92	.032
Octadecanoic (18:1n-7)	1.09 ± 0.25	1.23 ± 0.20	1.08 ± 0.32	1.18 ± 0.20	NS
Linoleic (18:2n-6)	50.60 ± 5.35	46.40 ± 4.85***	50.31 ± 5.85	49.30 ± 4.67	.006
γ-Linolenic (18:3n-6)	0.76 ± 0.27	0.77 ± 0.29	0.75 ± 0.32	0.67 ± 0.29	NS
α-Linolenic (18:3n-3)	0.71 ± 0.18	0.76 ± 0.22	0.68 ± 0.24	0.80 ± 0.17	NS
Dihomo-γ-linolenic (20:3n-6)	0.56 ± 0.13	0.59 ± 0.14	0.59 ± 0.11	0.58 ± 0.13	NS
Arachidonic (20:4n-6)	4.71 ± 1.12	5.30 ± 1.05	5.02 ± 1.40	5.05 ± 1.17	NS
Eicosapentaenoic (20:5n-3)	1.16 ± 0.51	1.52 ± 0.63	1.25 ± 0.61	1.58 ± 1.00	NS
Docosahexaenoic (22:6n-3)	0.50 ± 0.22	0.66 ± 0.26	0.52 ± 0.24	0.67 ± 0.30	NS

Data are mean values ± SD.
***$P \leq .001$, Student's *t* test for paired samples.
*$P \leq .05$, Student's *t* test for paired samples.

in the values of serum total cholesterol (5.2 ± 0.8 versus 5.2 ± 0.9 mmol/L), HDL cholesterol (1.2 ± 0.3 versus 1.2 ± 0.3 mmol/L), LDL cholesterol (3.5 ± 0.8 versus 3.4 ± 0.8 mmol/L), VLDL cholesterol 0.6 ± 0.3 versus 0.6 ± 0.3 mmol/L), or total triglycerides (1.6 ± 0.8 versus 1.3 ± 0.8 mmol/L).

The levels of fatty acids in the serum triglycerides, cholesterol esters, and phospholipids at the beginning of the lead-in period did not differ between the study groups (Tables III, IV, and V). After 1 year, the proportions of palmitic and oleic acids in cholesterol esters increased significantly in the orlistat group compared with those before the lead-in period, whereas significantly decreased values of linoleic acid in triglycerides, cholesterol esters, and phospholipids and stearic acid in phospholipids were observed in this group. Com-

Table V. The fatty acid composition (mol% of total) of serum phospholipids during the lead-in period and after 1 year in the study groups

	Orlistat (n = 37)		*Placebo (n = 38)*		
Fatty acid	*Lead-in period*	*1 year*	*Lead-in period*	*1 year*	*MANOVA*
Myristic (14:0)	0.83 ± 0.21	0.83 ± 0.39	0.75 ± 0.16	0.76 ± 0.15	NS
Palmitic (16:0)	32.54 ± 2.56	33.58 ± 1.68	32.79 ± 1.39	32.89 ± 1.80	NS
Palmitoleic (16:1n7)	0.96 ± 0.22	1.00 ± 0.36	0.97 ± 0.24	0.91 ± 0.23	NS
Stearic (18:0)	14.00 ± 1.07	12.98 ± 1.00***	13.77 ± 1.32	13.59 ± 1.24	<.001
Oleic (18:1n9)	9.83 ± 1.29	10.62 ± 2.68	9.57 ± 1.25	9.45 ± 1.00	NS
Octadecanoic (18:1n7)	1.52 ± 0.30	1.55 ± 0.32	1.50 ± 0.31	1.55 ± 0.30	NS
Linoleic (18:2n6)	21.25 ± 3.04	18.60 ± 2.39***	20.99 ± 2.33	20.38 ± 2.81	.002
γ-Linolenic (18:3n6)	0.18 ± 0.22	0.14 ± 0.07	0.12 ± 0.07	0.12 ± 0.08	NS
α-Linolenic (18:3n3)	0.36 ± 0.19	0.35 ± 0.14	0.30 ± 0.10	0.35 ± 0.11	NS
Dihomo-γ-linolenic (20:3n6)	3.11 ± 0.68	3.13 ± 0.66	3.18 ± 0.65	3.02 ± 0.60	NS
Arachidonic (20:4n6)	6.43 ± 1.29	6.97 ± 1.13**	6.90 ± 1.41	6.83 ± 1.17	.035
Eicosapentaenoic (20:5n3)	1.20 ± 0.51	1.44 ± 0.52	1.27 ± 0.49	1.51 ± 0.82	NS
Docosatetraenoic (22:4n6)	0.15 ± 0.08	0.18 ± 0.06	0.16 ± 0.06	0.15 ± 0.05	.039
Docosapentaenoic (22:5n3)	0.61 ± 0.20	0.64 ± 0.16	0.54 ± 0.11	0.61 ± 0.13	NS
Docosahexaenoic (22:6n3)	3.40 ± 0.94	4.35 ± 1.34***	3.72 ± 0.83	4.15 ± 1.10**	.012
Lignoserinoic (24:0)	0.66 ± 0.19	0.63 ± 0.19	0.59 ± 0.13	0.61 ± 0.14	NS
Nervonic (24:1n9)	1.72 ± 0.42	1.80 ± 0.60	1.72 ± 0.54	1.87 ± 0.46	NS

Data are mean values ± SD.
***$P \leq .001$, Student *t* test for paired samples.
**$P \leq .01$, Student *t* test for paired samples.

pared with the values of the lead-in period, the orlistat group also had significant increases in the proportions of arachidonic acid and docosahexaenoic acid in phospholipids. Only the proportion of docosahexaenoic acid in phospholipids also increased significantly in the placebo group during the study.

When compared with the lead-in values the proportions of stearic and linoleic acids decreased and that of arachidonic acid increased significantly in phospholipids in the orlistat group, but no significant changes were observed in the placebo group (Fig 1).

To determine the impact of orlistat on the changes in serum lipid fatty acid composition and, in particular, on that of linoleic acid in serum triglycerides, cholesterol esters, and phospholipids, stepwise multiple regression analysis was carried out that included the treatment (orlistat versus placebo), the change (E%) in the linoleic acid dietary intake, weight change during the study, and gender. The use of orlistat explained 13% ($P = .0031$) of the decrease in the proportion of linoleic acid in cholesterol esters and 9% ($P = .0136$) in phospholipids. In triglycerides the use of orlistat accounted for 9% ($P = .0162$) and the weight change accounted for 15% ($P = .0326$) of the decrease of linoleic acid proportion.

DISCUSSION

Orlistat reduces the absorption of dietary triglycerides in a dose-dependent manner, but no information is available to clarify whether orlistat evenly reduces the absorption of all dietary fatty acids or whether it particularly reduces the absorption of certain dietary fatty acids. If orlistat did change the absorption of certain fatty acids more than others, this would be seen as a reduced proportion of these fatty acids in serum lipids in the long term. In this study of obese subjects, orlistat resulted in a small decrease of linoleic acid content of serum lipids.

The proportion of linoleic acid in serum lipids, especially that in cholesterol esters, has been reported to be a good indicator of its dietary intake.[12,13] It is well established that changes in dietary intake of linoleic acid result in changes in its proportion in serum lipids.[14-17] In line with this, a reduced proportion of linoleic acid in serum cholesterol esters was reported after 6 months in subjects who consumed a low-fat diet that included 3.9 ± 1.4 g/d linoleic acid (2.1 ± 0.5 E%).[14] In this study, the dietary intake of linoleic acid reduced during the study in both groups similarly (from 4.4 ± 1.3 E% to 3.8 ± 1.1 E% and from 4.4 ± 1.4 E% to 4.0 ± 1.1 E% in the orlistat and placebo groups, respectively). After 1 year the proportion of linoleic acid in serum lipids was significantly lower in the subjects in the orlistat group (Tables III through V), and this decrease was observed in phospholipids also after 3 and 9 months (Fig 1). A small decrease of linoleic acid proportion in phospholipids was observed in

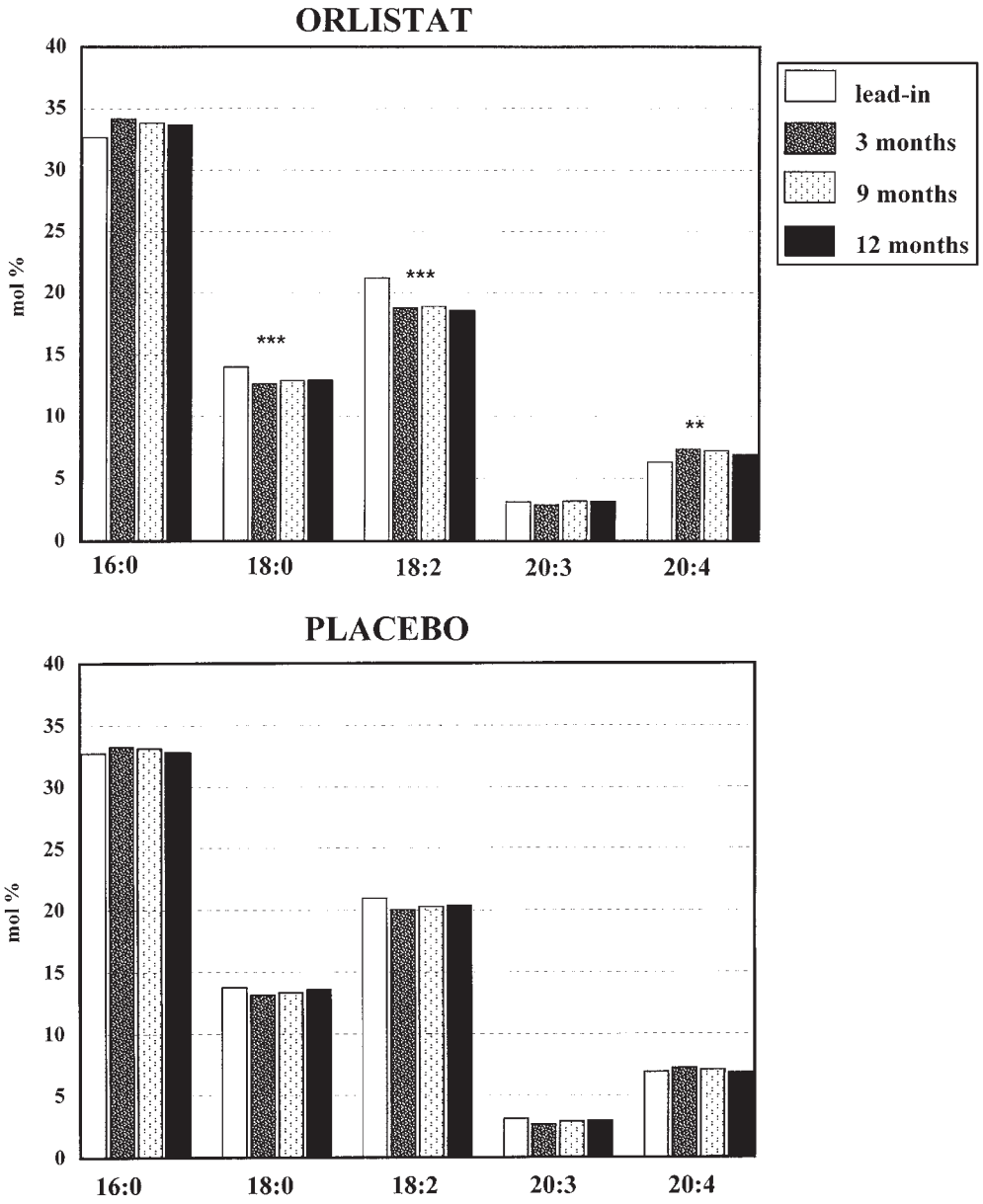

Fig 1. The proportion (mole % of total) of palmitic acid, stearic acid, linoleic acid, dihomo-γ-linolenic acid, and arachidonic acid of serum phospholipids during the lead-in period and after 3, 9, and 12 months in the study groups. ***$P \leq .001$, ANOVA; **$P \leq .01$, ANOVA.

the placebo group after 3 months but increasing after that close to the basic level. The intake of linoleic acid in the orlistat group after 1 year was 5.3 ± 2.0 g/d and in the placebo group 5.9 ± 2.7 g/d. However, assuming that an average of 30% of ingested fat is excreted in the feces at a dose of 120 mg orlistat three times a day,[5,18] the estimated absorbed amount of linoleic acid in the orlistat group was about 3.7 g/d. Therefore the observed decrease in the proportions of linoleic acid in serum lipids can be ascribed in part to the reduced absorption of linoleic acid in subjects in the orlistat group.

No earlier studies have been published on the effect of orlistat on the absorption of fatty acids in humans. The inhibition of fat absorption by orlistat has been studied in acute and subchronic experiments in several animal species fed either single test meals or fat diets.[12,19-20] Absorption of oleic acid was inhibited only marginally, but absorption of triolein was markedly

reduced.[12,20] It is very unlikely that orlistat interferes with triglyceride absorption at the stages that follow lipolysis, incorporation to micelles, absorption at the brush border, reesterification, and release into the lymphatics. Linoleic acid has been noticed to absorb over a relatively short length of proximal intestine compared with another long-chain fatty acid, palmitic acid, which requires a greater length of intestine.[19] In addition, pancreatic lipase specifically catalyzes the removal of fatty acids from the 1 and 3 positions of triglycerides, producing free fatty acids and 2-monoacylglycerols. This is partly hydrolyzed to liberate glycerol and the remaining free fatty acid residue. In vegetable fats, linoleic acid prefer the 2 position of triglycerides. Because inhibition of pancreatic lipase by orlistat inhibits the hydrolysis of triglycerides, and one can speculate that the absorption of linoleic acid from the intestine may be reduced to some extent by this mechanism.

Unchanged[21,22] or reduced[23-25] linoleic acid content in serum lipids have been noticed in obese patients during weight reduction with very-low-calorie diets, depending on the amount of linoleic acid in the diet. In obese subjects during 4 weeks of treatment with a liquid diet that provided about 600 kcal (about 8 g/d linoleic acid), linoleic acid in serum phospholipids remained constant, whereas dihomo-γ-linolenic acid concentration decreased significantly despite supplementation of the diets with maize oil and safflower oil to provide 0.1 g/d γ-linolenic acid.[21] In addition, Tang et al[22] reported unchanged linoleic acid and dihomo-γ-linolenic acid values in serum triglycerides and phospholipids during the 3 to 5 months of weight loss with very-low-calorie diets that contained canola oil or linseed oil. Reduced linoleic acid values in serum lipids have been reported after very-low-calorie diets,[23,26] but lower linoleic acid content in plasma lipids[23] in obese patients compared with control subjects were also reported.

The proportion of arachidonic acid in phospholipids was significantly increased in the orlistat group after 3, 9, and 12 months but not in the placebo group (Fig 1), whereas the proportion of dihomo-γ-linolenic acid was decreased in both groups after 3 months and in the placebo group after 9 months, but in neither group after 12 months. In accordance with our results for the orlistat group, elevated arachidonic acid and reduced dihomo-γ-linolenic acid contents in serum lipids after short very-low-calorie diets have been reported.[21,23-25] Weight reduction has been reported to increase mobilization of arachidonic acid from tissues and to decrease desaturation and elongation of linoleic acid, and weight loss correlates with arachidonic acid composition in phospholipids.[21] In this study the weight reduction in the orlistat group was more marked than that in the placebo group. It can therefore be speculated that an increase of arachidonic acid content in serum lipids is derived from tissues rather than metabolized from linoleic acid.

In the orlistat and placebo groups the intake of fish and consequently the intake of eicosapentaenoic acid and docosahexaenoic acid increased similarly during the study. Therefore the proportion of n-3 fatty acids in serum lipids, especially in phospholipids, increased in both groups. The increase of n-3 fatty acids, especially that of eicosapentaenoic acid and docosahexaenoic acid, can result in a decrease in the proportion of linoleic acid because an increase in the proportion of some fatty acids takes place at the expense of another fatty acid in serum lipids and because the same enzymes produce the desaturation and elongation of α-linolenic, linoleic, oleic, and palmitoleic acids. The competition between the substrates may therefore partly explain the changes in the fatty acid composition of serum lipids. If the decreased proportion of linoleic acid in serum lipids was induced by increased proportions of eicosapentaenoic acid and docosahexaenoic acid, this should have been observed similarly in both study groups of this study.

In a stepwise multiple logistic analysis, only 9% to 13% of the decrease of linoleic acid proportion in serum lipids could be explained by the orlistat therapy. Furthermore, according to our results there is no risk of linoleic acid deficiency during the long-term use of orlistat provided the intake of this essential fatty acid is at the recommended level. As shown in many previous studies,[6] orlistat resulted in decreases of serum total and LDL cholesterol levels but, because of the relatively small number of subjects, these changes were not statistically significant.

In conclusion, we cannot entirely exclude the possibility that orlistat has some minor effect on the absorption of long-chain fatty acids (eg, linoleic acid). Although values for percentage proportion of linoleic acid in serum lipid fractions slightly decreased in the orlistat group, the levels remained within normal range.

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