Effect of fats high in individual saturated fatty acids on plasma lipoprotein[a] levels in young healthy men

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Abstract Plasma lipoprotein[a] (Lp[a]) is associated with atherogenesis and thrombogenesis. We examined how plasma Lp[a] in healthy young men was affected by fats high in stearic (C18), palmitic (C16), and lauric + myristic (C12 + C14) acid (experiment I, 15 subjects), and by fats high in myristic (C14) and palmitic (C16) acid (experiment II, 12 subjects). Strictly controlled isocaloric diets with 36% of energy from test fats were served in random order for 3 weeks separated by wash-out period(s). Diets high in C18 gave significantly higher levels of Lp[a] (51(12–560) mg/L) than diets high in C16 (38(12–533 mg/L) (P = 0.020) and C12 + C14 (34(12–534) mg/L) (P = 0.002). These differences were observed in several of the subjects in experiment I. In experiment II we saw no difference in plasma Lp[a] after diets high in C16 and C14. Our observations suggest that a fat high in stearic acid might affect Lp[a] in a different way than fats high in palmitic and myristic + lauric acid. Lp[a] concentrations were not associated with changes in tissue-plasminogen activator (t-PA) activity, factor VII coagualant activity, or plasma LDL cholesterol.—**Tholstrup, T., P. Marckmann, B. Vessby, and B. Sandström.** Effect of fats high in individual saturated fatty acids on plasma lipoprotein[a] levels in young healthy men. *J. Lipid Res.* 1995. **36:** 1447–1452.

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Lipoprotein[a] (Lp[a]) is a strong risk factor of coronary heart disease. Plasma Lp(a) is generally believed to be an independent risk factor. It does not seem to be affected by diet (1) and anthropometric variables (2). The Lp[a] concentration remains rather constant throughout life (3). Lp[a] levels in humans are usually below 150 mg/L and it has been discussed whether there are such thing as safe Lp[a] values. It has been suggested that a plasma Lp[a] level above 200–300 mg/l implies a 2- to 3-fold increase in the relative risk of myocardial infarction (4). Values above 400 mg/L are considered a strong risk factor of coronary heart disease (CHD) (3) and in patients with familial hypercholesterolemia an increased Lp[a] level is a supplementary risk factor of CHD (5).

Lp[a] is a low density lipoprotein (LDL) that contains a lipid core and an apolipoprotein B subunit. Lp[a] differs from LDL, as it also contains an apolipoprotein[a] subunit, apo[a]. This subunit is very similar to plasminogen. The homology between apo[a] and plasminogen (Pg) indicates that Lp[a] may be involved in the regulation of fibrinolysis. In this way Lp[a] is suggested to suppress normal fibrinolytic activity. In vitro studies have demonstrated that Lp[a] competes with plasminogen for various binding sites and inhibits plasmin generation by several Pg activators (6).

The physiological role of Lp[a] is unknown (4). Lp[a] concentrations are resistant to most forms of LDL-lowering therapy (7, 8). An example is HMG-CoA reductase inhibitors that either increase or do not affect Lp[a] level (9). An exception is the antihyperlipidemic drug, niacin, that decreases Lp[a] as well as LDL cholesterol (10). Lp[a] is produced predominantly (or perhaps only) by the liver. Lp[a] originates in the liver where its production rate thus determines the relative concentration of the Lp[a] (4). Apart from this, our knowledge of its metabolism is rather scarce.

Although it has been generally accepted that Lp[a] is mainly under genetic control and therefore hardly sensitive to dietary change, a few studies show that specific dietary fatty acids do affect the Lp[a] concentration. Nestel et al. (7) showed that elaidic acid (a *trans*-isomer to oleic acid) raised Lp[a] concentration more than oleic acid, palmitic acid and butter. Mensink et al. (11) reported that substitution of saturated fatty acids (SFAs) for oleic acid and *trans*-fatty acids caused the Lp[a] concentration to rise (higher after *trans*-FAs than oleic

Abbreviations: Lp[a], lipoprotein[a]; apo[a], apolipoprotein[a]; t-PA, tissue-plasminogen activator; Pg, plasminogen; CHD, coronary heart disease; LDL, low density lipoprotein; FA, fatty acid; SFA, saturated fatty acid; BMI, body mass index; CV, coefficient of variation.

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acid). A higher Lp[a] was seen after *trans* fatty acids compared to stearic and linoleic acid, which did not differ (11). Finally Hornstra and co-workers (12) have demonstrated that ingestion of palm oil causes the serum Lp[a] concentration to fall to levels below those achieved with a habitual diet.

Recently we have shown that individual saturated fatty acids (SFAs) differ in their effect on blood lipids, lipoproteins, and hemostatic variables (13). Replacement of a diet high in palmitic or in myristic and lauric acid for a diet high in stearic acid resulted in a lowering affect on plasma LDL cholesterol and factor VII coagulant activity (13). In a second experiment substitution of a diet high in palmitic acid by a diet high in myristic acid increased HDL cholesterol, decreased the LDL/HDL cholesterol ratio, and increased factor VII activity (14). In this paper the effect of the individual SFAs on the Lp[a] concentrations in the two experiments is reported. The possible association between the initial concentrations of Lp[a] and its responsiveness to dietary change was also evaluated.

MATERIALS AND METHODS

Subjects

Young apparently healthy Danish men, (Caucasian male students), with a moderate physical activity level and BMI no greater than 27.5 (kg/m^2) were recruited for the studies. The level of their physical activity remained constant throughout the trial. Characteristics of subjects are shown in **Table 1.** Effects of the experimental diets on plasma lipids and lipoproteins are shown in our previous studies (13, 14).

Diets

Diets containing different test fats were served in randomized order for 3 weeks each. The intervention periods were separated by a period on habitual diet (lasting 1–2 months).

Ninety percent (36E%) of total fat of the experimental diets was derived from the test fat, the remaining from other food items, which were constant and identical in the experimental diets. Further details of calculation of individual energy intake and duplicate portions have been described previously (13). All food was prepared and weighed in individual servings in the experimental kitchen of the department. On weekdays lunch was served at the department. All other food was provided daily as a package with guidelines for its preparation. Meals for the weekend were provided on Fridays. Body weight without heavy clothing was recorded three times a week. The energy intake was adjusted so that each subject maintained his body weight constant throughout the study. If there was weight loss or hunger, the subjects were allowed muffins with the same fat energy composition as the rest of the diet. No extra foods and drinks, including alcohol, were allowed during the test periods, but coffee and tea in the same amounts as during habitual diet were permitted, as was mineral water in small quantities. During the study, the subjects could live normally with habitual physical activities, which, however, should be identical in the three periods. The subjects kept daily records of their physical activity, noting how many minutes were spent on sports, etc. They reported any sign of illness, medication used, coffee and tea and mineral water intake, and deviation from the diet. The subjects were highly motivated during the whole study.

TABLE 1. Characteristics of subjects in the two experiments

	Experiment I	Experiment II
n	15	12
Age	24 (21–26)	23 (21–28)
Body weight (kg)	79 (66-92)	81 (68-101)
BMI (kg/m^2)	23.5 (20.2–25.7)	24 (21-26)
Lp[a] (mg/L)	69 (< 12-611)	[a]
Total cholesterol (mmol/L)	4.00 ± 0.12	3.70 ± 0.12
LDL cholesterol (mmol/L)	2.87 ± 0.12	2.47 ± 0.13
HDL cholesterol (mmol/L)	0.97 ± 0.04	1.01 ± 0.04
Total triglycerides (mmol/L)	0.79 ± 0.08	0.90 ± 0.07

Values are means and ranges or ± SEM, except for Lp[a] which is median and ranges.

[a]Habitual values of Lp[a] concentration were not measured in experiment II.

Blood analysis

Morning blood samples were taken once before the study and on the days 14, 19, and 21 (in exp. I) and on the last day (in exp. II) of each dietary period. The subjects had fasted for at least 12 h overnight and had rested supine for 10 min; they had not engaged in heavy physical activity or taken alcohol for at least 24 h. Plasma for lipoprotein analysis was frozen and stored at –80°C. The concentrations of plasma Lp[a] were measured by the Pharmacia Apo[a] immunoradiometric assay, RIA method (Pharmacia Diagnostics AB, Uppsala, Sweden). This procedure is based on the direct sandwich technique in which two monoclonal antibodies are directed against separate antigenic determinants on the apolipoprotein[a] in the sample. The concentration is expressed in units/L (U/L) which refer to the protein fraction of Lp[a]. One unit of apo[a] is approximately equal to 0.7 mg Lp[a] according to the manufacturer. The coefficient of variation (CV) is the same magnitude (less than 6%) over the whole range of apo[a] concentration. Apo[a] (U/L) was converted to (mg/L) by multiplying by 0.7.

Blood sampling and analysis for lipids, lipoproteins, and hemostatic variables has been described in previous publications (13, 14).

Experiment I (stearic vs. palmitic vs. myristic/lauric acid)

Fifteen young men participated. Their ages ranged from 22 to 30 years (mean 24.9 yr), body weights from 67.2 to 87.4 kg (mean 74.8 kg), and body mass index from 20.4 to 26.4 kg m^{-2} (mean 23.2 kg m^{-2}).

Natural fats and blends of natural fats were used to achieve differences in fatty acid composition. Shea butter (the kernel fat of the "shea butter tree," *Butyrospermum parkii, Sapotaceae*), a cooking fat in Nigeria, was used for diet S (high in stearic acid). Further details on the shea butter are given in ref. 13. Palm oil, "Palmotex," a commercial oil by Aarhus Oliefabrik A/S, was used for diet P (high in palmitic acid). Diet ML (high in myristic and lauric acids) contained fat that was a mixture of palm-kernel oil and high-oleic sunflower oil. The mixture was especially made for this study. The fatty acid composition of each test fat was determined by liquid gas chromatography (**Table 2**). The fats were provided by Aarhus Oliefabrik A/S, Oils and Fats Division, R&D, Aarhus, Denmark.

Experiment II (myristic vs. palmitic acid)

Twelve young men were recruited for the study. Their ages ranged from 21 to 26 years (mean 23.8 yr), body weights from 66.3 to 91.8 kg (mean 78.7 kg), and body mass index from 20.2 to 25.7 kg m^{-2} (mean 23.5 kg m^{-2}).

A synthetic fat and a natural fat were used to achieve the desired differences in fatty acid composition. The high myristic acid test fat was a synthetic fat especially made for this study by interesterifying trimyristin, (a commercial fat containing 98.2% of myristic acid, Dynasan 114 by Hüls, Marl, Germany), with high-oleic sunflower oil (a commercial fat, TRISUN 80, Eastlake, OH). Palm oil, (Palmotex), a commercial oil, from Aarhus Oliefabrik A/S, Aarhus, Denmark was used as the test fat high in palmitic acid. The fatty acid composition of each test fat was determined by gas–liquid chromatography (Table 2). All test fats were provided by Aarhus Oliefabrik A/S.

Ethics

The protocol and the aim of the study were fully explained to the subjects, who gave their written consent. The research protocol was approved by the Scientific Ethics Committee of the municipalities of Copenhagen and Frederiksberg.

Statistical analysis

A non-parametric test, Friedman's two-way ANOVA test, was performed to allow for the skewness of the Lp[a] concentrations measured. Dietary effects on the hemostatic variables were compared by Wilcoxon's matched-pairs, signed-rank test. Statistical analysis of plasma LDL cholesterol was based on the calculated mean value of the three samplings (days 14, 19, and 21) which were not statistically significantly different. When the analysis indicated that the LDL levels for diets were different, a paired *t*-test was used to compare the individual diets. Associations in differences between ML-diet and S-diet were tested by linear regression analysis. For calculations, we used SPSS PC program, (SPSS Inc., Chicago, IL).

RESULTS

Experiment I (stearic vs. palmitic vs. myristic/lauric acid)

The concentration of Lp[a] on habitual and after experimental diets and differences between them is given **Table 3.** Diet S resulted in a 25% higher Lp[a]

TABLE 2. Fatty acid composition of test fats in experiments I and II

Fatty Acid[a]		Test Fat in Experiment I			Test Fat in Experiment II	
		Shea Butter	Palm Oil	Palm Kernel Oil + High Oleic-Sunflower Oil	"Myristic Acid Fat"	Palm Oil
		% of total test fat			*% of total test fat*	
	≤10:0			5.2		
Lauric acid	12:0	0.1	0.8	29.8	0.1	0.3
Myristic acid	14:0	0.1	1.2	10.4	43.0	1.0
Palmitic acid	16:0	3.9	43.3	6.8	2.4	42.9
Stearic acid	18:0	42.1	4.7	3.1	2.5	4.3
Oleic acid	18:1	45.0	38.3	39.9	40.4	40.7
Linoleic acid	18:2	6.4	10.4	4.8	10.5	9.5
Linolenic acid	18:3	0.2	0.3	< 0.05	0.1	0.2
	≤ 20:0	2.2	0.7	1.0	0.9	0.6

[a]Designations are given as the number of carbon atoms constituting the structural chain of the fatty acid molecule: the number of double bonds within the carbon chain.

TABLE 3. Plasma Lp[a] concentrations in subjects on habitual diet and after test diets high in myristic and lauric acid (ML), high in palmitic acid (P), and high in stearic acid (S) in 15 healthy young men

Diet	Lp[a]				*P* Value Friedman Two-Way ANOVA
	Habitual[a]	ML[b]	P[c]	S[d]	
			mg/L		
Final	69 (12–611)[e]	34 (12–534)[f]	38 (12–533)[f]	51 (12–560)[e]	0.001
Difference between habitual and experimental diet		28 (1–102)	32 (–65–108)	8 (–33–58)	

Values are given as medians and range (in parentheses).
[a]Habitual, n = 15, one sampling before the study.
[b]ML, diet high in myristic acid, n = 15, mean of three samplings.
[c]P, diet high in palmitic acid, n = 15, mean of three samplings (except for two cases, as three samples deriving from two different persons were excluded).
[d]S, diet high in stearic acid, n = 15, mean of three samplings.
[e,f]Values with different superscripts are significantly different, $P < 0.05$.

concentrations ($P = 0.020$) than diet P and a 34% higher Lp[a] concentration than diet ML ($P = 0.002$). The difference between diet S and ML was 16 (0–52) mg/L and between diet S and P 11 (–32–59) mg/L, (median and ranges). **Fig. 1** shows individual effect of experimental diets on Lp[a] concentrations in 15 persons (means of three samplings and standard errors of the mean). No significant differences were observed between diets P and ML with regard to Lp[a]. The difference between the habitual and diet P was 32 (–65–108) mg/L, median and ranges ($P = 0.028$) and between the habitual diet and diet ML 28 (1–102) mg/L, ($P = 0.002$). **Table 4** shows that there was a positive (borderline significant) association between habitual Lp[a] levels and changes in Lp[a] for subjects on diet S and ML. We did not observe any associations between dietary change in Lp[a] and dietary change in plasma LDL-cholesterol, t-PA activity and factor VIIc either when using baseline data or for experimental levels (Table 4).

Exp II (myristic vs. palmitic acid)

The Lp[a] concentration after diet P was 12 (12–1012) mg/L and after diet M 27(12–912) mg/L. Values are median and ranges. Diet P and diet M did not affect plasma Lp[a] differently.

DISCUSSION

A main finding of this study was that a test fat high in stearic acid resulted in significantly higher levels of Lp[a] than fats high in palmitic and myristic + lauric acid. In addition it was demonstrated that the difference in Lp[a] levels associated with diets enriched with stearic or myristic/lauric acid was primarily seen in those individuals with the higher initial Lp[a] concentrations.

The elevated Lp[a] concentration after the high stearic acid fat intake contrasts with the significantly lower LDL cholesterol levels and factor VII activity achieved with that fat relative to the fats high in myristic + lauric acid (ML diet) (13). Similar differences were observed between effect of a high stearic fat and high palmitic fat (P diet) (13). LDL cholesterol concentrations were 3.07 ± 0.17 (mmol/L) (mean ± SEM) after ML diet, 2.96 ± 0.14 after P diet, and 2.18 ± 0.12 after S diet (13). Experiment I showed a borderline significant positive association between habitual Lp[a] and dietary change in Lp[a] concentration. This observation is in agreement with results by Mensink et al. (11), but was not observed by others (10). In our study, changes in Lp[a] concentrations were not related to changes in LDL cholesterol concentrations. This confirms earlier observations (10, 11). As suggested (10, 11) it is therefore likely that Lp[a] is regulated in a different way than LDL cholesterol. We did not observe any association between changes of Lp[a] and factor VIIc. This may indicate that, although factor VIIc and Lp[a] both respond to change in SFAs, the effect is not mediated by the same mechanism.

Lp[a] is suggested to inhibit in vivo fibrinolysis because of homology with plasminogen. Therefore, it could be speculated whether changes in Lp[a] could be associated with changes in individual fibrinolytic vari-

TABLE 4. Univariate regression coefficients β, SEM of β, and *P* values of difference between ML diet (diet high in myristic and lauric acid) and S diet (diet high in stearic acid) in 15 healthy young men

	Δ Lp[a]		
	β	SEM β	*P*
		mg/L	
Habitual Lp[a]	0.06	0.03	0.053
Δ t-PA activity (IU/L)	1.348	7.80	0.862
Δ LDL chol. (mmol/L)	–0.002	0.004	0.498
Δ Factor VIIc (%)	0.10	0.12	0.408

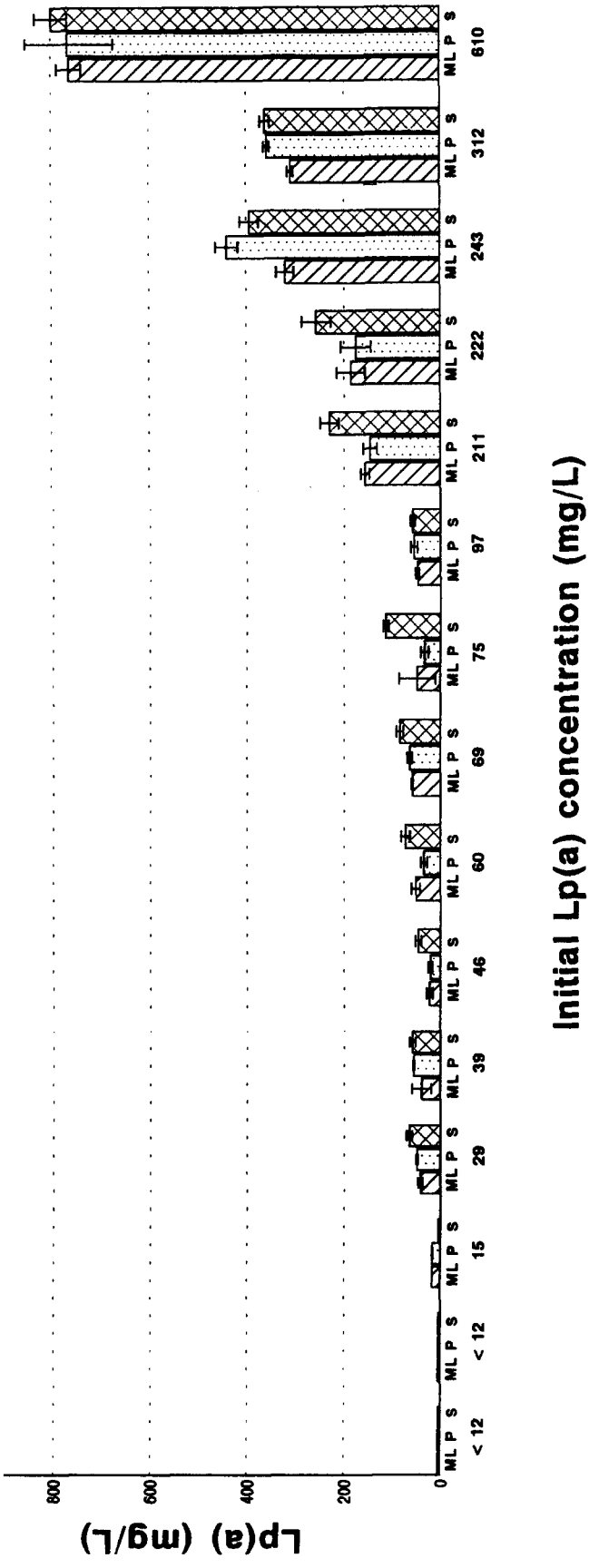

Fig. 1. Individual response in plasma Lp[a] concentrations in 15 subjects after ML diet (high in myristic and lauric acid), P diet (diet high in palmitic acid), and S diet (high in stearic acid) in experiment I. Values are means of three samplings and error bars are standard deviation of the mean. Subjects are ranked according to increasing individual habitual Lp[a] levels. For details of fatty acid composition, see Table 2.

ables. In this study there was no association between Lp[a] and t-PA activity. In order to better elucidate whether Lp[a] affects fibrinolysis in vivo, it might be useful to study the effect on some intermediary reaction products of fibrinolysis, such as plasmin-antiplasmin complex of fibrin degradation products.

As it is suggested that stearic acid may be desaturated, or partly desaturated (15, 16) into oleic acid in the organism, stearic acid and oleic acid may affect Lp[a] in a rather similar way. Our finding that the cholesterol raising SFAs resulted in a lower Lp[a] than the stearic fat is therefore partly in agreement with the results of Mensink et al. (11), who demonstrated that cholesterol raising SFAs produced a marginally lower Lp[a] than oleic acid. Nestel et al. (7) reported that the Lp[a] concentration was affected differently by the *trans*-isomer C18:1 elaidic acid to three other test diets (with oleic acid, palmitic acid, and butter, respectively), whereas oleic acid, palmitic acid, and butter did not differ in terms of their effect on Lp[a]. These different findings demonstrate that the mechanism by which Lp[a] is affected may be very complex. Furthermore, in our study the amount of the specific SFAs was much higher than in the other studies mentioned. Finally, non-glyceride components in shea butter might also have influenced degradation of Lp[a] by the liver. However, it should be pointed out that the median Lp[a] levels reported are far below the 200–300 mg/L threshold for cardiovascular risk.

The finding that Lp[a] may be affected by individual dietary fatty acids may suggest that plasma Lp[a] should be taken into consideration together with other dietary changeable risk factors of CHD. However, increase in Lp[a] levels took place only in about half of the subjects investigated (mainly in those with higher initial Lp[a] levels). This seems to indicate a different susceptibility to saturated fatty acids among individuals. It may therefore be essential to identify people with elevated Lp[a] levels who seem to respond more readily to changes in dietary fat as far as plasma Lp[a] is concerned as observed in this study and by others (11).

In hypercholesterolemic patients, an elevated Lp[a] is a supplementary risk factor of CHD (4). Proper dietary advice in this risk group is a quite complicated matter, because some FAs that increase LDL cholesterol will result in a lower Lp[a] and vice versa. Current knowledge about the effect of dietary FA on Lp[a] (7, 11)

would indicate that hypercholesterolemic patients with elevated Lp[a] should minimize their intake of *trans*-fatty acids because these acids raise Lp[a] and LDL cholesterol levels. As it may require a certain amount of FA to affect the Lp[a], a dose-response relationship between FAs and plasma Lp[a] should be established in order to monitor a threshold value for their effect. Thus, further research into the relationship between plasma Lp[a] and dietary FAs is required in order for us to be able to give proper dietary advice.

In conclusion, a shea fat diet, high in stearic acid that favorably affected blood lipids and factor VII coagulant activity, might increase Lp[a] levels in comparison with fats high in palmitic or myristic + lauric acid. Palmitic and myristic + lauric acid test fat had no different effect on plasma Lp[a]. Levels of Lp[a] were not associated with changes in t-PA activity, factor VIIc activity, or plasma LDL cholesterol.

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