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Interactions among Lp(a) phenotypes, Lp(a) concentrations and lipoprotein response to fat-modified diets

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Lipoprotein(a) (Lp(a)), an LDL-like particle containing apo(a), a highly glycosylated protein, is a significant genetic risk factor for coronary heart disease (CHD). Lp(a) phenotypes are characterized into single-band and double-band phenotypes according to electrophoretic mobility compared to that of apo B-100. The first goal was to assess whether Lp(a) phenotype influences the concentrations and metabolism of other serum lipoproteins. A second focus was to evaluate the effect on Lp(a) concentrations of substituting medium chain saturated fat for a polyunsaturated, baseline diet. In this two-way cross-over study 18 females ate a baseline, polyunsaturated fat diet (Poly/Sat en% ratio = 10.5/11.9) for 1 week, and then a high saturated fat diet for 4 weeks (Poly/Sat en% ratio = 3.4/19.8) providing either 14 energy % medium chain triglycerides (MCT) 8:0 + 10:0 or 12:0, whereas monounsaturated fat was held constant. Subjects with double-band Lp(a) phenotypes had higher (P = 0.000) Lp(a) levels on the baseline diet compared to single-band phenotypes. Both diets decreased serum Lp(a) concentration about 30% (P < 0.05) but raised serum LDL-C about 11%. On the baseline diet, Lp(a) polymorphism did not affect serum LDL-cholesterol levels or receptor-mediated uptake and degradation of LDL. In a two-way ANOVA 8:0 + 10:0 and 12:0 had significantly different effects on change in serum HDL-C concentrations and LDL receptor activity in MNC, but Lp(a) polymorphism had no effect on the variables measured in this study. These results suggest that the response of LDL and Lp(a) levels to the two saturated fat diets were independent of each other. Lp(a) polymorphism did not seem to influence LDL metabolism. (J. Nutr. Biochem. 9:106–113, 1998) © *Elsevier Science Inc. 1998*

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Introduction

Lipoprotein (a), usually referred to as Lp(a), was first demonstrated by Berg[1] as a specific lipoprotein genetic variant in human blood and was subsequently associated with an increased risk for coronary heart disease (CHD)[2–7] and cardiovascular disease (CVD).[8–12] Lp(a) is different from low density lipoprotein (LDL) in that it contains an apolipoprotein (a) (apo(a)) as well as an apoprotein B-100.[13–15] Apo(a) is a highly glycosylated protein with a size varying from 300 kDa to 800 kDa[16–18] due to the different numbers of kringle-4-like repeats in the apo(a) molecule.[19] Most plasma Lp(a) is probably derived from liver.[20]

A high Lp(a) lipoprotein level is considered a significant and independent genetic risk factor for CHD because Lp(a) does not interfere with the LDL receptor pathway, and there is no significant difference between normal and hypercholesterolemic patients with respect to Lp(a) lipoprotein uptake by cells.[21] Reportedly, a high level of Lp(a) interferes with thrombosis-thrombolysis in arteries that are becoming atherosclerotic, and binding of cholesterol-rich Lp(a) particles at the sites of vessel damage may contribute to the development of atherosclerosis.

Lp(a) occurs in several heterogeneous forms that may be related to the molar ratio of apo(a) to apoB in the lipoprotein, the size of apo(a) and the existence of mixed apo(a) isoforms.[16] Lp(a) phenotypes are categorized according to relative electrophoretic mobilities compared with apoB-100 as F (faster than apoB-100), B (similar to apoB-100), S1,

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S2, S3, and S4 (slower than apoB-100), and as their respective double-band (heterozygous) phenotypes.[18] Researchers have identified at least 34 different isoforms,[22] which seem to be governed by one single Lp(a) locus on chromosome 6[23] on which the plasminogen gene also is located.[24,25] An inverse relation between apo(a) size and serum Lp(a) levels was suggested by Utermann et al.[18] Although it has been demonstrated that polymorphism of certain apolipoproteins, e.g., apoprotein E, influences lipoprotein metabolism,[26] the effect, if any, of different Lp(a) phenotypes on lipid metabolism has not been studied.

The metabolic regulation of LDL and Lp(a) concentrations in blood may differ.[27,28] Pharmacological interventions that reduce LDL, e.g. inhibitors of 3-hydroxy-3-methyglutaryl coenzyme A, cholestyramine, or fibric acid derivatives, did not influence Lp(a) levels in many studies[29–33] although the Lp(a) response to drug therapy may be dependent on the initial Lp(a) levels in hypercholesterolemic patients,[34] and some drug interventions may reduce Lp(a) levels.[35,36] Dietary lipid modification often is used to lower serum LDL concentrations, at least modestly, but it was believed that dietary modification does not affect Lp(a) lipoprotein levels. In several recent studies Lp(a) concentrations increased on diets high in trans fatty acids,[37–39] which tend to mimic the effects of saturated rather than unsaturated fats on lipoprotein metabolism.[40] Tholstrup et al.[41] showed that saturated fatty acids do not have identical effects on Lp(a). Diets high in stearic acid (18:0) but not palmitic acid (16:0) or a mixture of 14:0 + 12:0 caused Lp(a) to increase. The effect of lower chain saturated fatty acids on Lp(a) has not been investigated. The study described in this paper was designed to assess the effects of two saturated fat diets, one with medium chain fatty acids (capric (8:0) + caprylic (10:0) and a 12-carbon fatty acid (lauric acid) on Lp(a) concentrations and the influence of Lp(a) polymorphism on cholesterol metabolism.

Method and materials

Subjects

Eighteen healthy premenopausal women were randomized into this two-period crossover study, the minimum number needed to detect a 10 percent mean difference with an eight percent standard deviation by a power of 0.9. Because one subject left the study after period one, 17 subjects consumed the medium chain fatty acid (MCT) (C8:0 + C10:0) diet and 18 subjects finished the lauric acid diet (C12:0). The average age of all subjects was 24 ± 4 years (mean ± SEM), range, 19 to 33 years; the average weight was 62.2 ± 11.7 kg, range 40.5 to 91.8 kg; and the average height was 161.9 ± 7.7 cm, range, 147.9 to 176.5 cm. The fasting serum cholesterol concentration at screening was 4.33 ± 0.57 mmol/L (mean ± SEM) with a range between 3.70 and 6.13 mmol/L. The health of subjects was verified by blood chemistry and a health questionnaire. Anyone taking medications influencing lipid metabolism was not recruited into this study. The Lp(a) phenotype was not known before the study. Ethnic background of subjects was 10 Caucasians, 7 Asians, and 1 African-American. Each subject signed a consent form approved by The Ohio State University Biomedical Human Subjects Committee.

Design

In this two-period and two sequence design involving 18 subjects, nine subjects ate the MCT diet in the first period, and the other nine received the lauric acid diet. Then, in the second period, all subjects consumed the alternate diet. To standardize nutrient intake before the experimental treatments and provide a comparison base, the subjects were given a baseline diet designed to be higher in polyunsaturated fatty acids (PUFAs) and lower in saturated fatty acids than the treatment diets for the initial week of each period. The experimental diets were given during the following 4 weeks. A 7-week washout period was held between periods. The study was designed so that blood samples were obtained at the same phase of each subject's menstrual cycle. Blood samples were collected twice during the last three days of baseline and twice during the last three days of experimental feeding, and the two data points were averaged. After the blood drawing, serum and MNC (mononuclear cells) were obtained by centrifuging at 500 × g and 800 × g, respectively, for 20 min. Some serum samples were used immediately for procedures requiring fresh blood. The remaining samples were frozen at −80°C for later analysis.

Diets

According to the nutrient analysis by Food Processor II software (ESHA Research, Salelm, OR), the baseline diet contained 40 en% total fat, 11.9 en% saturated fat, 14.9 en% monounsaturated fat, and 10.5 en% PUFA, and 323 mg cholesterol (*Table 1*). The 8:0 + 10:0 and 12:0 diets provided 40 en% total fat, 19.8 en% saturated fat, 14.8 en% monounsaturated fat, and 3.4 en% PUFA, and 316 mg cholesterol (*Table 1*). Commercial miglyol or trilaurin (42% of the fat blend), obtained from HULS America Inc. (Piscataway, NJ USA), was the main fat in the experimental fat blends. Food Processor II software was used to calculate the components of the diets by adding data on fatty acid composition in each menu to the softwear data base (*Table 1*). The specific fatty acid composition of 1-day composites of each menu was analyzed by gas liquid chromatography (GLC) (*Table 1*).

Biochemical procedures

Lp(a) Concentration. Serum Lp(a) concentrations were measured by ELISA (MACRA™ Lp(a) EIA Kit from Strategic Diagnostics Industries, Inc. Newark, USA).

Lp(a) phenotype. Lp(a) phenotypes were identified by SDS-PAGE followed by Western blot analysis of apo(a) isoforms according to Taddei-Peters.[42] The membrane blotted with protein was incubated with mouse-anti-human apo(a) as first antibody (clone 4F3, RP-070, Perimmune, Inc. Rockville, MD USA). A peroxidase-labeled goat-anti-mouse IgG conjugate (Sigma) was used as a second antibody to bind the first antibody. To determine apo(a) isoforms, human apo(a) phenotype standards (RP-155, Perimmune, Inc) were compared with those of samples.

Serum lipoprotein cholesterol. Total cholesterol, free cholesterol, LDL-cholesterol, total HDL-, HDL_2- (by difference) and HDL_3-cholesterol and TG concentrations were determined as in previous studies.[43,44] Data for cholesterol and TG concentrations from two pre- and two post-period measurements were averaged. The coefficients of variation, evaluated for the assay using previously frozen pool samples, were 0.9% for total cholesterol, 1.2% for total HDL-cholesterol, 3.2% for HDL_3-cholesterol and 1.6% for TG levels.

Apolipoprotein concentration. Apolipoprotein A-1 and B were assayed by a turbimetric procedure (Raichem, San Diego, CA

Table 1 Daily energy and nutrient intake on baseline and experimental diets (mean ± SEM)

Dietary variable	Baseline (n = 35)	MCT (n = 17)	Lauric acid (n = 18)
Energy (MJ)*	8.1 ± 0.1	8.3 ± 0.1	8.4 ± 0.1
Protein (g)*	72 ± 0 (15)	73 ± 0 (15)	73 ± 0 (15)
Carbohydrate (g)*	225 ± 2 (46)	230 ± 3 (46)	231 ± 3 (46)
Total fat (g)*	86 ± 1 (40)	89 ± 1 (40)	89 ± 1 (40)
Fatty acids (g)†			
8:0 + 10:0 (MCT)	1.8 ± 0.0 (0.8)	30.1 ± 0.5 (13.6)	1.0 ± 0.0 (0.5)
12:0	3.6 ± 0.0 (1.7)	2.1 ± 0.0 (0.9)	31.4 ± 0.5 (14.1)
14:0	2.3 ± 0.0 (1.0)	1.4 ± 0.0 (0.6)	1.4 ± 0.0 (0.6)
16:0	8.2 ± 0.1 (3.8)	5.9 ± 0.1 (2.7)	5.9 ± 0.1 (2.7)
18:0	7.9 ± 0.1 (3.7)	2.9 ± 0.1 (1.3)	2.9 ± 0.1 (1.3)
SFA	25.7 ± 0.5 (11.9)	43.9 ± 0.6 (19.8)	44.1 ± 0.7 (19.8)
MUFA	32.0 ± 0.4 (14.9)	32.8 ± 0.4 (14.8)	32.9 ± 0.5 (14.8)
PUFA	22.6 ± 0.3 (10.5)	7.5 ± 0.1 (3.4)	7.5 ± 0.1 (3.4)
Cholesterol (mg)*	323 ± 1	316 ± 1	316 ± 1

Values in parentheses are calculated values for percent of food energy provided by the nutrient.
* Analyzed from daily dietary records using Food Processor II Analyses Software (ESHA Research, Salelm, OR USA)
† As determined by gas liquid chromatography
SFA—saturated fatty acid. MUFA—monounsaturated fatty acid. PUFA—polyunsaturated fatty acid.

USA) in one pre- and one post-period serum sample. The coefficient of variation of two control sera provided in the kits was 2.9% and 1.9% for apolipoprotein A-I and 2.5% and 2.5% for apolipoprotein B.

LDL receptor activity. LDL binding and degradation mediated by LDL receptors in MNC of ^{125}I-LDL were determined as in previous studies.[43,44] The composition of LDL was assumed to be constant throughout the whole study.

LCAT and CETP activity. Endogenous cholesterol esterification (lecithin-cholesterol acyl transferase, LCAT) and transfer (cholesterol ester transfer protein, CETP) were measured by an isotopic method[45] as in a previous study.[44]

Statistical Analysis

Differences between the baseline and experimental values were analyzed by paired t-test set at $\alpha = 0.05$ (MINITAB). The differences between variables among different Lp(a) phenotypes on the baseline diet was determined by one-way ANOVA ($P < 0.05$). Significance level was set at $\alpha = 0.05$ to evaluate the main effects of diet and Lp(a) phenotype and the interaction between phenotype and diets by two-way ANOVA (SAS). Relationships among relevant variables were determined by Pearson correlation analysis.

Results

Influence of Lp(a) phenotype on lipoprotein metabolism

After SDS-PAGE and Western blot analysis of plasma obtained from the 18 subjects, the following Lp(a) phenotypes were identified: four S3, eight S4, one S1/S2, three S2/S3, one S2/S4, and one null phenotype (no detected band) (*Figure 1*). The subject with the null phenotype had the lowest Lp(a) level (0.016 g/L) among all subjects.

Our first goal was to assess whether Lp(a) phenotype influences serum lipoprotein concentrations and lipoprotein metabolism when subjects consumed a constant (baseline) diet. To do this we analyzed the variables of interest at the end of each of the two baseline periods and stratified the data according to phenotype. The double band phenotypes, all of which included S2, were combined into one group. The other two groups were comprised of single band S3 and

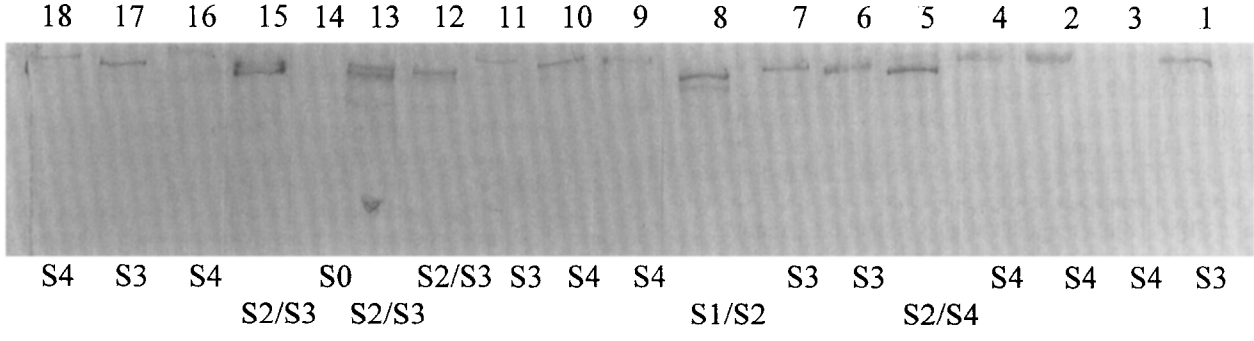

Figure 1 Lp(a) phenotypes by Western blot after gel electrophoresis for four hours at 80 V of 18 subjects. Because of the low Lp(a) concentration of subject 3, the phenotype of Lp(a) is hardly seen. However, after gel electrophoresis for seven hours at 80 V, the Lp(a) phenotype of subject 3 was detected to be S4 on other membranes.

Table 2 Comparison of serum lipoprotein cholesterol metabolic parameters (mean ± SEM) on the baseline diet among different Lp(a) phenotypes

Serum & MNC parameter	Lp(a) S3 (n = 8)	Lp(a) S4 (n = 16)	Lp(a) S1/S2, S2/S4, S2/S3 (n = 9)	Probability
Lp(a) concentration (g/L)	0.15 ± 0.04—a	0.04 ± 0.01—b	0.24 ± 0.04—c	S (P = 0.000)
Total cholesterol (mmole/L)	4.03 ± 0.14	4.27 ± 0.16	3.95 ± 0.11	NS
LDL-cholesterol (mmole/L)	2.24 ± 0.26	2.43 ± 0.17	2.22 ± 0.17	NS
HDL-cholesterol (mmole/L)	1.48 ± 0.17	1.45 ± 0.08	1.48 ± 0.09	NS
HDL_2-cholesterol (mmole/L)	0.58 ± 0.12	0.48 ± 0.07	0.50 ± 0.06	NS
HDL_3-cholesterol (mmole/L)	0.90 ± 0.07	0.97 ± 0.03	0.97 ± 0.05	NS
TG concentration (mmole/L)	0.67 ± 0.02—ab	0.85 ± 0.07—a	0.57 ± 0.06—b	S (P = 0.02)
Apo A-I concentration (g/L)	1.62 ± 0.11	1.72 ± 0.07	1.58 ± 0.06	NS
Apo B concentration (g/L)	0.61 ± 0.08—ab	0.76 ± 0.06—a	0.59 ± 0.03—b	S (P = 0.021)
LCAT activity (μmol/L/hr)	50.03 ± 4.31—ab	54.99 ± 4.22—a	42.83 ± 3.14—b	S (P = 0.046)
CETP activity (μmol/L/hr)	27.00 ± 1.81	27.82 ± 2.88	22.02 ± 1.50	NS
Receptor-mediated degradation of ^{125}I-LDL (ng/10^6 MNC/hr)	12.28 ± 2.04	12.05 ± 1.00	15.61 ± 3.00	NS
Nonspecific degradation of ^{125}I-LDL (ng/10^6 MNC/hr)	8.34 ± 1.41	5.59 ± 0.72	5.58 ± 1.16	NS
Receptor-mediated ^{125}I-LDL binding (ng/10^6 MNC)	16.81 ± 1.12	16.17 ± 1.31	20.88 ± 1.69	NS

Values with different letters within a column are significantly different ($P < 0.05$).

S4 phenotypes. The possibility that the single band phenotypes were heterozygous for the null phenotype cannot be excluded.[18] The results suggest that the double band phenotype group, all members of which had at least one lighter Lp(a) component than the S3 and S4 groups, had higher (60%–500%) mean concentrations of Lp(a) than S3 and S4 while S3 had a higher (300%) mean level of Lp(a) than S4 (*Table 2*; *Figure 2*).

In this study, Lp(a) phenotype did not influence serum concentrations of total cholesterol, LDL-cholesterol, or HDL-cholesterol but it did appear to affect concentrations of triglycerides and apoB on the baseline diet because S4, the phenotype group with the least mobile Lp(a) band, had higher levels of both variables (P = 0.02) (*Table 2*).

We also noted that the Lp(a) phenotype had no effect ($P > 0.05$) on LDL-receptor variables including LDL binding or LDL degradation. However, there were significant differences among the phenotype groups in one parameter of reverse cholesterol transport (RCT) (*Table 2*), e.g. the double band phenotype group had lower lecithin acyl cholesterol transferase (LCAT) activity (P = 0.046) in plasma than the other phenotype groups although there are no known mechanisms of action of Lp(a) that would explain an effect on LCAT activity.

Influence of diet on serum Lp(a) concentration

A second focus of this study was to evaluate the effect on Lp(a) concentrations of substituting diets with 8:0 + 10:0 and 12:0 for a polyunsaturated baseline diet. Both saturated fat diets reduced serum Lp(a) concentrations (P = 0.014 for 8:0 + 10:0 and P = 0.05 for 12:0) (*Figure 3*). The correlation of Lp(a) concentrations between the two baseline periods and between the two treatment periods was strong (r = 0.967 for baseline, and 0.868 for treatment), meaning that subjects with the highest Lp(a) values maintained the highest values regardless of diet. Although Lp(a) levels decreased in all Lp(a) phenotype groups, on both

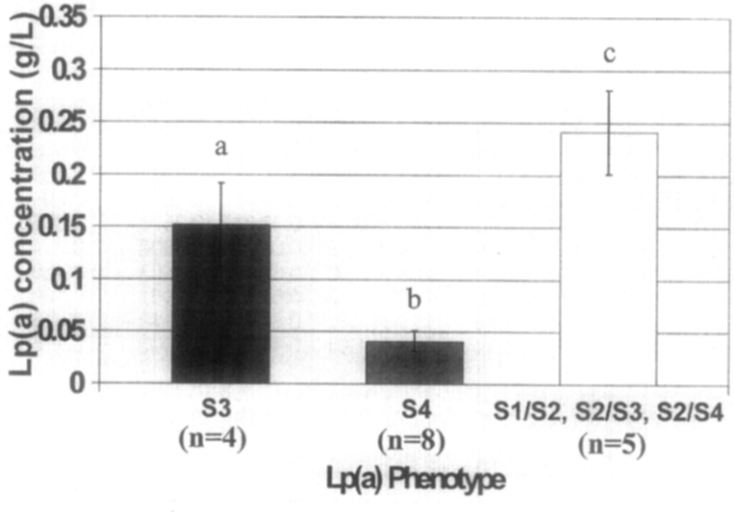

Figure 2 Lp(a) concentration among different Lp(a) phenotypes on the baseline diet (a, b, c denotes a significant difference $P < 0.05$). One subject with null Lp(a) phenotype was not included in this figure (Lp(a) levels was 0.016 g/L).

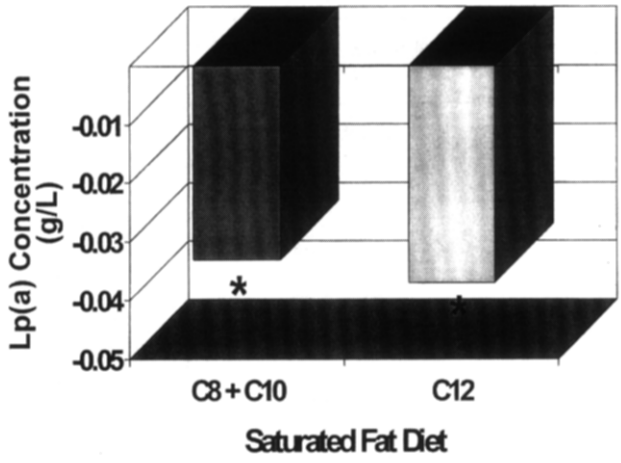

Figure 3 Lp(a) concentrations decreased significantly on the 8:0 + 10:0 and 12:0 diets.

saturated diets there were no significant differences among Lp(a) phenotypes in the change in concentration induced by feeding the saturated diets (*Table 3*).

Influence of Lp(a) phenotype on the lipoprotein response to the saturated fat diets and on lipoprotein metabolism

Several statistical analyses were used to evaluate the effect of Lp(a) phenotype. A paired *t*-test was used to assess significant changes from baseline within a phenotype and diet group. Two-way ANOVA assessed phenotype effects in an analysis of the combined test diet groups (*Table 3*). Some phenotype groups experienced a significant change from baseline when the saturated fat diets were consumed, whereas others did not. However, in this study in which there were small numbers of subjects in some phenotype groups in a two-way ANOVA, there were no significant main effects of phenotype on the responses to the saturated fat diets for any parameter of lipoprotein metabolism with one exception, serum apoA-I, which increased in the double band phenotype group and decreased in the other groups (*Table 3*). However, there is no known mechanism of action of Lp(a) that explains this effect.

Influence of Lp(a) phenotypes on LDL degradation and binding by MNC

The rate of receptor-mediated ^{125}I-LDL degradation in MNC increased on the 8:0 + 10:0 diet but decreased on 12:0 in all subjects. Diet but not Lp(a) phenotype significantly influenced the response of receptor-mediated LDL degradation and binding by MNC to the substitution of the saturated diets for the baseline diet (*Table 3*). There were no significant differences in nonspecific LDL degradation either between dietary treatments or among different Lp(a) phenotypes.

Discussion

The objective of this study was to determine the effect of Lp(a) polymorphism on 1) serum lipoprotein concentrations and metabolism and 2) the cholesterolemic response to a change from a baseline polyunsaturated diet to two saturated diets. The major findings were that 1) both 8:0 + 10:0 and 12:0 decreased serum Lp(a) concentrations compared with the baseline diet, 2) the metabolic regulation of Lp(a) was independent of LDL, 3) there was no compelling evidence that Lp(a) polymorphism influenced the cholesterolemic response to a change from a polyunsaturated fat to saturated diets although additional studies involving larger number of subjects would be desired. Significant diet effects on lipoprotein metabolism were noted in this study but their implications apart from Lp(a) polymorphism will be discussed elsewhere.

Table 3 Least square mean (LSM ± STDERR) changes in lipoprotein metabolism by experimental diets among different Lp(a) phenotypes

	Lp(a) phenotype			Experimental diet		Main effects		Interaction
	S3	S4	S1/2, S2/3, S2/4	8:0 + 10:0	12:0	Pheno (*P* value)	Diet (*P* value)	Pheno × Diet (*P* value)
Lp(a) (g/L)	−0.07 ± 0.03	−0.01 ± 0.02	−0.04 ± 0.03	−0.03 ± 0.01	−0.04 ± 0.01	0.2826	0.4076	0.0890
TC (mmol/L)	0.33 ± 0.16	0.35 ± 0.12	0.56 ± 0.16	0.31 ± 0.13	0.52 ± 0.12	0.5374	0.2662	0.4647
LDL-C (mmol/L)	0.23 ± 0.15	0.31 ± 0.11	0.51 ± 0.15	0.31 ± 0.14	0.40 ± 0.13	0.4333	0.6445	0.2382
HDL-C (mmol/L)	0.06 ± 0.05	0.06 ± 0.03	0.07 ± 0.05	0 ± 0.04	0.12 ± 0.04	0.9771	0.0360	0.8084
HDL_2-C (mmol/L)	−0.01 ± 0.05	−0.04 ± 0.03	−0.01 ± 0.05	−0.10 ± 0.02	0.05 ± 0.02	0.8602	0.0004	0.5695
HDL_3-C (mmol/L)	0.08 ± 0.03	0.09 ± 0.02	0.08 ± 0.03	0.10 ± 0.03	0.07 ± 0.02	0.8589	0.4925	0.2993
TG (mmol/L)	0.08 ± 0.07	−0.03 ± 0.05	−0.03 ± 0.07	0.01 ± 0.05	0.00 ± 0.05	0.4742	0.9473	0.0866
Apo A-I (g/L)	−0.01 ± 0.06	−0.11 ± 0.04	0.22 ± 0.06	0.02 ± 0.10	0.04 ± 0.09	0.0023	0.8600	0.4644
Apo B (g/L)	0.11 ± 0.05	0.02 ± 0.04	0.05 ± 0.05	0.03 ± 0.04	0.09 ± 0.03	0.3761	0.2553	0.4538
LCAT (μmole/L/hr)	1.25 ± 4.50	5.79 ± 3.18	7.38 ± 0.05	2.63 ± 3.06	6.99 ± 2.83	0.6065	0.3151	0.1600
CETP (μmole/L/hr)	1.84 ± 2.04	1.86 ± 1.44	3.25 ± 2.04	−0.65 ± 1.48	5.29 ± 1.37	0.8410	0.0112	0.8162
Receptor-mediated LDL degradation ($ng/10^6$ MNC/hr)	−0.27 ± 1.61	1.33 ± 1.13	2.82 ± 1.61	4.73 ± 1.10	−2.14 ± 1.01	0.4189	0.0005	0.1150
Nonspecific LDL degradation ($ng/10^6$ MNC/hr)	−0.99 ± 2.70	2.77 ± 0.91	4.39 ± 2.70	−0.16 ± 2.02	4.27 ± 1.87	0.3678	0.1316	0.4365
LDL binding ($ng/10^6$ MNC)	0.11 ± 1.65	1.06 ± 1.17	1.77 ± 1.65	4.20 ± 2.03	−2.24 ± 1.87	0.7769	0.0364	0.7016

Diet affects Lp(a) concentration

According to many but not all previous human studies, diet does not influence Lp(a) concentrations in serum.[29,46–52] Recently, trans-monounsaturated[37–39] and partially hydrogenated fatty acids[40] were shown to raise Lp(a) levels, but the results were not consistent. Also, Tholstrup et al.[41] indicated that a diet high in C18 (stearic acid) increased plasma Lp(a) concentration but diets high in C16 (palmitic acid) and C14 (myristic acid) did not affect Lp(a) levels. In another study, n-3 fatty acids reduced Lp(a) levels compared with n-6 fatty acids.[53] Interestingly, in this study the 8:0 + 10:0 and 12:0 treatments decreased serum Lp(a) concentrations by at least 27%, whereas LDL-C concentrations increased by at least 12%.

Dietary treatments influenced Lp(a) levels in some studies of primates in a manner not entirely consistent with the human studies. Rainwater et al.[54] found that a diet high in cholesterol and saturated fat raised plasma Lp(a) levels. In addition, Brousseau et al.[55] observed that Lp(a) levels were significantly higher when the diet was enriched in saturated fat compared with diets rich in monounsaturated or PUFAs. Hepatic mRNA levels of apo(a) were also higher in monkeys fed saturated fatty acid compared to monounsaturated fatty acid. Although the saturated fat diet in the study of Brousseau et al. was rich in 12:0 (7.2 en%), the finding of increased Lp(a) levels was opposite to the results of this current study. One explanation may be the lower percentage of 12:0 (7.2 en% vs. 14 en% in this study) or a difference in metabolism between human and nonhuman primates. Although some studies indicated that Lp(a) levels are mainly a function of synthetic mechanisms,[56,57] the rate of clearance of apo(a) may also be a factor.

Association between LDL and Lp(a) metabolism

Metabolic regulation of Lp(a) may be independent of LDL because the correlation between diet-induced concentration changes in LDL-C and apoB ($r = 0.408$) was higher than that between Lp(a) and apoB ($r = -0.153$), which was in agreement with Albers et al.[27] In this study a negative small or moderate correlation was observed on the baseline diet between concentrations of either LDL-C ($r = -0.189$) or apoB ($r = -0.339$) and Lp(a), whereas there was a strong positive correlation between LDL-C and apo B ($r = 0.712$). These results were in agreement with Brown et al.[49] who did not find a significant correlation between increases in either LDL-C or apoB and Lp(a), nor between dietary-induced changes in LDL-C or apoB and Lp(a) in normolipidemic men subjected to short-term dietary cholesterol and fat modifications.

In contrast, some studies have indicated that Lp(a) binding to fibroblasts seems to be mediated by the cellular LDL receptor.[15,58] In addition, Lp(a) catabolism was increased in transgenic mice overexpressing the human LDL receptor.[59] Utermann et al.[60] found that Lp(a) levels were elevated in LDL receptor deficient patients with FH hypercholesterolemia. However, Ghiselli et al.[61] observed that there was no significant or consistent elevation of the Lp(a) levels detected in FH hypercholesterolemic patients. These results were in line with other studies that the LDL receptor activity only had small influence on Lp(a) metabolism.[62–66] Furthermore, Rader et al.[67] also found that radiolabeled Lp(a) was catabolized at a similar rate in the FH homozygous patients who have little or no functional LDL receptor activity as in normal subjects. The authors, therefore, concluded that LDL receptor is not necessary for normal Lp(a) catabolism. Finally, plasma Lp(a) levels were not decreased by administering the drugs that upregulate LDL receptor activity.[15,29,68,69] In summary, many but not all findings suggest that the metabolic regulation of Lp(a) is independent of LDL even though Lp(a) shares the same structural protein, apoB. Because in this study there was only a small association on the baseline diet between serum Lp(a) levels and specific LDL degradation ($r = 0.313$), LDL receptor activity is probably not a major determinant of serum Lp(a) levels as suggested by other reports.[61,67,70] Further studies are needed to verify the mechanism.

Lp(a) polymorphism and lipoprotein metabolism

There are some apolipoprotein polymorphisms that influence LDL and HDL metabolism and response to fat-modified diets, e.g. apolipoprotein E.[71–73] There is no compelling reason to suspect that Lp(a) variants have such an influence because their major effect on the atherogenic process seems to involve thrombosis-thrombolysis. Nevertheless, when the subjects in this study consumed the constant baseline diet, persons with different Lp(a) phenotypes had significantly different serum concentrations of apoB and triglycerides as well serum LCAT activity. However, there was little evidence that Lp(a) polymorphism influenced the changes that occurred in lipoprotein metabolism when the baseline diet was switched to a high saturated fat diet. Additional investigations involving larger numbers of subjects within specific Lp(a) phenotype groups and other saturated fatty acids, e.g. myristic, palmitic and stearic acid, would be desired.

Conclusion

This was the first piece of research to indicate that Lp(a) concentrations are reduced by diets with 8:0 + 10:0 and 12:0. However, these fats are not abundant in American food products. Although MCT diets could be used to treat patients with high Lp(a) levels, but normal LDL levels, genetic inheritance has a greater effect on this risk factor for CHD than diet. We also noted, as did other researchers, that concentrations of Lp(a) and LDL are regulated independently of each other despite their similar structure. In this investigation, Lp(a) polymorphism did not modulate the lipoprotein response induced by fat modification. This study can serve as a guideline for further research because the effects of dietary treatments have not been compared among different Lp(a) phenotypes. Additional studies are required involving larger groups of subjects and other fats.

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