Lipoprotein(a) and dietary proteins: casein lowers lipoprotein(a) concentrations as compared with soy protein[1–3]

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ABSTRACT

Background: Substitution of soy protein for casein in the diet decreases LDL cholesterol and increases HDL cholesterol. How the 2 proteins affect lipoprotein(a) [Lp(a)], an independent risk factor for coronary artery disease, is unknown.

Objective: We compared the effects of dietary soy protein and casein on plasma Lp(a) concentrations.

Design: Nine normolipidemic men were studied initially while consuming their habitual, self-selected diets, and then, in a crossover design, while consuming 2 liquid-formula diets containing either casein or soy protein. The dietary periods lasted 45 d (n = 7) or 33 d (n = 2). Fasting total cholesterol, LDL-cholesterol, HDL-cholesterol, triacylglycerol, and Lp(a) concentrations were measured throughout.

Results: After 30 d of each diet, the mean concentration of Lp(a) was not significantly different after the soy-protein and self-selected diets. However, Lp(a) decreased by an average of 50% ($P < 0.001$) after the casein diet as compared with concentrations after both the soy-protein and self-selected diets. Two weeks after subjects switched from the self-selected to the soy-protein diet, Lp(a) increased by 20% ($P = 0.065$), but subsequently decreased to baseline. In contrast, the switch to the casein diet did not cause an increase in Lp(a), but instead a continuing decrease in mean concentrations to 65% below baseline ($P < 0.0002$). Total cholesterol, LDL cholesterol, and HDL cholesterol were significantly lower ≥30 d after both the casein and soy-protein diets than after the self-selected diet ($P < 0.001$). HDL cholesterol was 11% higher after the soy-protein diet than after the casein diet ($P < 0.002$), but LDL cholesterol, total cholesterol, and triacylglycerol were not significantly different after the casein and soy-protein diets.

Conclusion: These findings indicate that soy protein may have an Lp(a)-raising effect, potentially detrimental to its use in antiatherogenic diets. *Am J Clin Nutr* 1999;69:419–25.

KEY WORDS Lipoprotein(a), plasma lipoproteins, dietary proteins, soy protein, casein, liquid-formula diets, coronary artery disease, men, Denmark

INTRODUCTION

Elevated plasma concentrations of lipoprotein(a) [Lp(a)] are associated with obstructive disease of the coronary (1, 2), carotid (3, 4), and peripheral (5) arteries. Lp(a) and LDL both contain apolipoprotein (apo) B-100, but Lp(a) contains apo(a), whereas LDL does not (6). The LDL-like moiety of Lp(a) suggests atherogenic properties, whereas the homology of apo(a) to plasminogen suggests competitive inhibition of plasminogen activation and thus interference with clot lysis and with control of arterial smooth muscle proliferation and migration (7).

Lp(a) concentrations, although fairly stable in a given individual (8), vary markedly between individuals from <1 to >1000 mg/L, mainly because of variations in the *APOA* gene (9, 10). Most whites have concentrations <100 mg/L, whereas the threshold for increased risk of coronary artery disease may be 200–300 mg/L (11). The strong and independent association between high Lp(a) concentrations and risk of coronary artery disease in most (12–19), but not all (20–22), prospective studies, has led to a search for diets and drugs to lower elevated concentrations.

Diets low in saturated fat and cholesterol had no effect on Lp(a) concentrations (23), and studies of increased or decreased intakes of cholesterol and saturated and polyunsaturated n−6 and n−3 fatty acids similarly showed no or only marginal effects on Lp(a) (24, 25). Certain dietary fatty acids may, however, affect Lp(a) concentrations. *Trans* monounsaturated fatty acids constituting 5–10% of total energy intake increased Lp(a) by 20–70% (26, 27), whereas *trans* fatty acids contributing 4% of energy had insignificant effects (28). Fish oil, in a long-term study, lowered Lp(a) by 15% in normolipemic individuals with Lp(a) concentrations >200 mg/L (29) and by 37% in hypertriglyceridemic patients (30). Plasma Lp(a) concentrations were 25–33% lower when the subjects consumed a diet containing either palmitic acid or myristic + lauric acids than when they consumed a diet containing stearic acid (31).

Of the hypolipemic drugs, only neomycin sulfate and niacin decreased Lp(a) concentrations substantially (32–34), whereas statins and bile acid sequestrants either had no effect or increased Lp(a) (35–37). Fibrates appeared to lower Lp(a) to a

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modest degree (38–40); acipimox had no effect (34). Hormonal preparations have been shown to affect Lp(a) concentrations. Sex hormones and related compounds—estrogen (41), progestin (42), estrogen-progestin combinations (43), testosterone (44), anabolic steroids (45), tamoxifen (46), raloxifene (47), and corticotropin and dexamethasone (48)—have all been found to lower Lp(a); growth hormones have been shown to increase Lp(a) (49).

Of the dietary proteins, plant proteins (particularly soy protein) have been found to lower atherogenic lipoproteins and sometimes increase antiatherogenic HDL as well (50, 51). A meta-analysis of human studies showed significant reductions in plasma total cholesterol, LDL cholesterol, and triacylglycerol after soy protein intakes (52); we found previously that normolipemic women and men had lower LDL- and higher HDL-cholesterol concentrations after a soy-protein than after a casein diet (53). Because no one to our knowledge has described the effects of dietary proteins on Lp(a) in humans, the present study compared the effects of casein and soy protein on Lp(a) concentrations in normolipemic men.

SUBJECTS AND METHODS

Subjects

Nine active, healthy, normolipemic men—friends and acquaintances of the laboratory staff—volunteered to participate. Baseline characteristics are shown in **Table 1**. Participants ranged in age from 21 to 64 y and their body mass indexes (in kg/m^2) ranged from 21.7 to 25.1. At entry, all subjects were normolipemic by standard clinical criteria, ie, individual plasma lipid and lipoprotein-cholesterol concentrations were within the 5th–95th percentile of the adult Danish population. All subjects had normal liver, kidney, and thyroid function as well as normal fasting plasma glucose concentrations and none were taking medications regularly. The composition of the subjects' self-selected diets, evaluated by a questionnaire covering 3-d dietary intakes, showed that roughly one-half of the subjects ate a prudent diet, whereas the other half had a more traditional intake of saturated fat and cholesterol. Subjects gave informed consent and the protocol was approved by the scientific-ethical committee of the municipalities of Copenhagen and Frederiksberg.

Study design

All participants were studied while consuming 3 different diets in a crossover design: a self-selected, solid-food diet (baseline); liquid-formula, casein diet; and liquid-formula, soy-protein diet. In most cases, the subjects were studied initially while consuming their habitual, self-selected diet; subsequently, they were switched to the liquid-formula diets (either the soy-protein or the casein diet) for 45 d ($n = 7$) or 33 d ($n = 2$), so that 4 subjects consumed the casein diet before the soy-protein diet and 5 subjects consumed the diets in the reverse order. The 3 dietary periods were separated by washout periods, during which time the subjects ate a self-selected diet, lasting for 44 ± 17 d ($\bar{x}$ ± SD) before the casein-diet period and 66 ± 47 d before the soy-protein diet period. The duration of the washout period appeared adequate to eliminate any carryover effects of the preceding liquid diet because plasma concentrations of total cholesterol, triacylglycerol, LDL cholesterol, HDL cholesterol, and Lp(a) immediately before the start of the 2 liquid-formula diet periods were not significantly different [by repeated-measures analysis of variance (ANOVA)] from those observed at the start of the self-selected diet. Thus, the mean (±SD) Lp(a) concentration at the start of the self-selected dietary period was 123.2 ± 85.7 mg/L, whereas concentrations were 121.5 ± 92.3 and 123.8 ± 91.7 mg/L immediately before the start of the soy-protein and casein diets, respectively. Subsequently, during the self-selected dietary period, Lp(a) concentrations dropped (NS) to a mean range of 94.1–87.4 mg/L. One reason for this change might have been that the subjects modified their self-selected diet in both quantity and composition in the days immediately preceding the start of the dietary periods.

Fasting blood samples were drawn for measurement of plasma Lp(a), cholesterol, triacylglycerol, LDL-cholesterol, and HDL-cholesterol concentrations. Two samples were drawn in the days immediately before the liquid-formula diets started; 3 samples were drawn 2, 3, and 4 wk after these diets started; and 6 samples were drawn >30 d after these diets started, at which time plasma concentrations were presumed to be stable: in 7 subjects after 31, 35, 38, 40, 42, and 45 d and in 2 subjects after 31, 32, and 33 d.

TABLE 1
Baseline values of the normolipidemic male subjects[1]

Age (y)	37 ± 16.8
BMI (kg/m^2)	22.9 ± 1.8
Total plasma cholesterol (mmol/L)	5.12 ± 0.89
LDL cholesterol (mmol/L)	3.17 ± 0.90
HDL cholesterol (mmol/L)	1.44 ± 0.36
Total plasma triacylglycerol (mmol/L)	0.93 ± 0.49
Plasma lipoprotein(a) (mg/L)	112 ± 82.7

[1] $\bar{x}$ ± SD; $n = 9$.

Diets

The composition of the liquid-formula diets was described previously (53). Briefly, the protein preparations were >90% pure, and protein constituted ≈20% of the energy intake. Casein was provided as calcium caseinate (Casec; Mead Johnson Laboratories, Evansville, IN) and the soy protein was a protein isolate (Supro 660; Protein Technologies International, St Louis). The mean (±SD; $n = 7$) daily intake of soy protein was 154 ± 7.9 g and that of casein was 154 ± 33 g. The mean daily intake was calculated as follows: g protein/L diet × (total amount of formula given to the subjects over the entire study period − amount of formula returned unused)/number of days in the diet period. The carbohydrate in both diets was a cornstarch hydrolysate (Maltodextrin 01915; Cerestar, Haubourdin, France) constituting ≈55% of energy; the fat component was a high-oleate variant of safflower oil (Oleinate 181; Pacific Vegetable Oil Corporation, San Francisco) constituting ≈25% of energy. Slightly more cholesterol (USP; Sigma, St Louis) was added to the soy-protein diet than to the casein diet to compensate for the cholesterol content of the casein; the cholesterol content of both diets was 55 mg/MJ. To compensate for the high calcium content of the casein diet, an equivalent amount was added to the soy diet in the form of calcium lactate. To compensate for lactate, an equivalent amount was added to the casein diet in the form of sodium lactate. The diets were supplemented with salts and vitamins to meet recommended dietary allowances (54). Subjects were allowed to drink energy-free beverages, but were specifically asked not to drink alcohol.

Subjects were asked to weigh themselves daily and to increase or decrease the intake of formula to maintain their body weights.

Mean (±SD) body weights were not significantly different ($P > 0.5$) at the start of the 3 dietary periods: 72.6 ± 7.0 kg (self-selected diet), 72.1 ± 8.0 kg (casein diet), and 72.9 ± 8.0 kg (soy-protein diet). After consuming the casein and soy-protein diets for 30 d, the subjects had lost 1.63 ± 1.65 and 1.67 ± 1.32 kg, respectively (NS).

Lipid and lipoprotein analyses

After subjects had fasted for ≥12 h and spent ≥15 min in a recumbent position, blood samples were collected into tubes containing potassium EDTA. Plasma was immediately separated by low-speed centrifugation at 2000 × *g* for 30 min at 4°C. HDL was isolated for cholesterol measurement after precipitation of LDL and VLDL with $MgCl_2$ and dextran sulfate (55). VLDL was separated from LDL + HDL by ultracentrifugation for 20 h at 100 000 × *g* and 4°C in a 50.3 Ti rotor (Beckman, Palo Alto, CA), and the fractions were recovered after tube slicing. Plasma and lipoprotein fractions were frozen at −20°C and stored so that all assays were performed after each subject had completed the study. Cholesterol and triacylglycerol were analyzed with an enzymatic method (Boehringer Mannheim, Mannheim, Germany). Plasma Lp(a) concentrations were determined by radioimmunoassay (Pharmacia Diagnostics AB, Uppsala, Sweden) using 2 different monoclonal anti-apo(a) antibodies: a trapping antibody bound to sepharose microbeads and a reporting antibody that was radioiodinated. Samples and standards were incubated in an excess of both antibodies, and the antigen bound to the beads was isolated by centrifugation (1500 × *g* for 10 min at room temperature) for counting in a gamma counter. Each sample was analyzed in duplicate and measured from a standard curve constructed for that particular run. All samples from each subject were analyzed by using reagents from the same batch. Plasma samples from the first 6 subjects were stored at −80°C for ≤3 y until analyzed, whereas those from the last 3 subjects were stored at −20°C for ≤1 y. Because the dietary effects on Lp(a) concentrations were similar regardless of storage conditions, the results were combined.

Statistical analysis

Mean lipid and lipoprotein concentrations after ≥30 d of the 3 different diets were compared between diet groups with parametric, repeated-measures ANOVA with the Bonferroni multiple-comparisons test. Plasma concentrations between individual subjects, by diet group, were compared by one-way ANOVA. Nonparametric tests (Friedman and Kruskal-Wallis, as well as Dunn's multiple-comparisons test) yielded similar results. Because of the skewed distribution of Lp(a) concentrations in plasma, the values were log-transformed before statistical evaluation. Student's paired *t* test was used to compare baseline Lp(a) concentrations with those observed at different time points during consumption of the soy-protein and casein diets and to compare Lp(a) concentrations observed at the same time points during consumption of the diets. INSTAT software (version 2.0, 1993; Graph Pad, San Diego) was used for the statistical analyses.

RESULTS

We found previously that it takes ≥2–3 wk after a switch from a self-selected, solid-food diet to a liquid-formula diet before plasma lipid and lipoprotein concentrations stabilize (53). Plasma lipid and lipoprotein concentrations >30 d after consumption of the 3 diets are shown in **Table 2**. Plasma total cholesterol, LDL-cholesterol, and HDL-cholesterol concentrations after consumption of the 2 liquid-formula diets were significantly lower than those measured during consumption of the self-selected diet (baseline). This finding indicated excellent dietary compliance by all subjects. Total cholesterol, triacylglycerol, and LDL-cholesterol concentrations were not significantly different after the 2 liquid-formula diets, but HDL cholesterol was significantly greater after the soy-protein diet than after the casein diet (11%). However, individual responses of the subjects showed considerable variation. For example, 5 subjects had significantly lower plasma total cholesterol and LDL-cholesterol concentrations after the soy-protein diet than after the casein diet, whereas 8 subjects had significantly higher HDL-cholesterol concentrations after the soy-protein diet than after the casein diet (data not shown) (56).

Plasma concentrations of Lp(a) after the subjects had eaten the 3 diets for >30 d are shown in **Table 3**. Mean Lp(a) concentrations were not significantly different after the self-selected and soy-protein diets, whereas the mean concentration after the casein diet was only half of those measured after the self-selected and soy-protein diets ($P < 0.001$ for both). A comparison of the Lp(a) concentrations in each individual subject showed that concentrations after the casein diet varied from 22% to 68% ($\bar{x}$:49%) of those observed after the soy-protein diet. Thus, the casein diet resulted in significantly lower concentrations of Lp(a) than did the soy-protein diet in all 9 subjects and in significantly lower concentrations of Lp(a) than did the self-selected diet in 8 of 9 subjects. Lp(a) concentrations after the soy-protein diet were not significantly different from those after the self-selected diet in most subjects, but were higher in 3 subjects and lower in 1 subject. The degree of Lp(a) reduction after the casein diet correlated with the plasma concentrations observed with the self-selected diet ($r = 0.66$, $P = 0.05$); ie, the higher the baseline concentration, the greater the reduction in Lp(a) concentrations by the casein diet.

The differential effects of the soy-protein and casein diets on Lp(a) were further illustrated by the time course of Lp(a) concentrations when the diet was changed from the self-selected, solid-food diet to a liquid-formula diet (**Figure 1**). Two weeks after the start of the soy-protein diet, Lp(a) concentrations were ≈20% ($P = 0.065$) higher than those after the self-selected diet (baseline); subsequently the concentration decreased to a concentration that

TABLE 2
Plasma concentrations of lipids and lipoproteins after >30 d of the self-selected, soy-protein, and casein diets[1]

	Diet		
	Self-selected	Soy-protein	Casein
	mmol/L		
Total cholesterol[2]	4.57 ± 1.14	3.48 ± 0.64[3]	3.54 ± 0.82[3]
LDL cholesterol[2]	2.63 ± 0.85	1.76 ± 0.54[3]	2.03 ± 0.79[3]
HDL cholesterol[2]	1.40 ± 0.20	1.23 ± 0.18[3,4]	1.10 ± 0.15[3]
Triacylglycerol	0.85 ± 0.36	0.76 ± 0.30	0.68 ± 0.22

[1] $\bar{x}$ ± SD.
[2] Significant variation among diets, $P < 0.0001$ (repeated-measures ANOVA).
[3] Significantly different from self-selected diet, $P < 0.001$ (Bonferroni multiple comparisons test).
[4] Significantly different from casein diet, $P < 0.01$ (Bonferroni multiple comparisons test).

was not significantly different from baseline. No increase in Lp(a) was observed with the casein diet. Instead, concentrations decreased significantly and continuously at all time points to values 65% below baseline after 5 wk. Lp(a) concentrations during consumption of the casein diet were significantly lower than those observed during the soy-protein diet at all time points.

DISCUSSION

This study of normolipemic, nonobese, healthy men showed marked differential effects of the 2 dietary proteins on plasma Lp(a) concentrations. With the soy-protein diet, Lp(a) concentrations were on average twice those observed with the casein diet. The magnitude of the change in Lp(a) concentrations due to the casein diet was directly correlated with baseline concentrations during the self-selected diet and was seen in all 9 subjects. Significant differential effects of the dietary proteins on HDL- and LDL-cholesterol concentrations were seen in 8 and 5 subjects, respectively.

To what extent the present findings can be generalized to the effects of normal, solid-food diets and to individuals with a wide range of Lp(a) concentrations remains to be seen. The number of subjects studied was small; none of the men had Lp(a) concentrations considered high enough to increase the risk of coronary artery disease and women were not included in this study. We believe, however, that some generalizations can be made. In a subsequent unpublished trial we found that plasma Lp(a) concentrations in young women responded to casein and soy protein in the same way as we described for men in the present study. We also found in this subsequent trial that individuals with Lp(a) concentrations up to 800 mg/L or more responded to dietary casein and soy protein in the same way as described in the present study. Furthermore, in agreement with the findings of the subsequent study, we found that the soy-protein diet, as early as 1 wk after the switch from the self-selected diet, increased Lp(a) concentrations by 50% above baseline ($P = 0.035$), whereas the casein diet at the same time point decreased Lp(a) concentrations by 30% ($P = 0.065$). Despite these observations, our findings have important limitations. The number of subjects studied was not large, the study may have been too short, and the compositions of liquid-formula diets used were markedly different from the composition of the self-selected diet. Further studies are necessary to show to what extent our findings can be generalized to the long-term effects of solid-food diets.

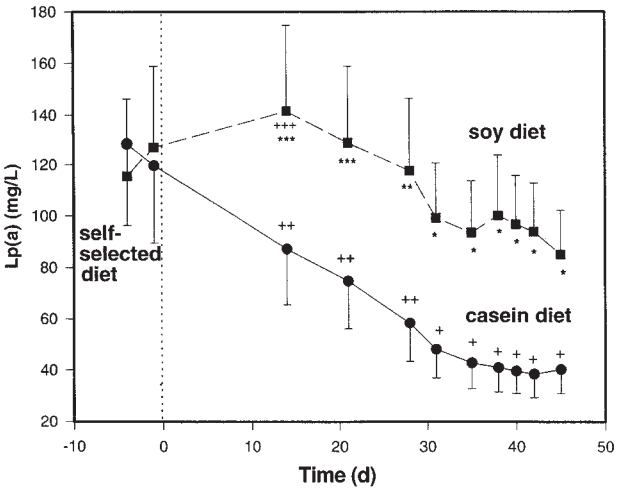

FIGURE 1. Mean (±SEM) lipoprotein (a) [Lp(a)] concentrations over time when healthy male subjects switched from a self-selected, solid-food diet to a liquid-formula diet containing either casein (●) or soy protein (■). $n = 9$ for day −4 to day 31 and $n = 7$ for days 35–45. Differences between means of 2 baseline concentrations (self-selected diets) and experimental values (casein and soy-protein diets): $^{+}P < 0.0002$, $^{++}P < 0.025$, $^{+++}P = 0.065$. Significantly different from the casein diet after the same number of days: $^{*}P < 0.002$, $^{**}P < 0.007$, $^{***}P < 0.03$.

TABLE 3
Plasma concentrations of lipoprotein(a) after >30 d of the self-selected, soy-protein, and casein diets[1]

Subject	Diet		
	Self-selected	Soy-protein	Casein[2]
	mg/L		
1	182.8 ± 30.3	151.2 ± 19.5	103.4 ± 7.2[3]
2	10.6 ± 2.5	17.6 ± 2.9[3]	10.1 ± 0.4
3	32.1 ± 3.5	37.4 ± 7.3	14.1 ± 2.2[3]
4	170.7 ± 18.7	182.0 ± 24.6	75.3 ± 4.9[3]
5	80.6 ± 25.8	128.6 ± 12.4[3]	27.7 ± 2.6[3]
6	167.1 ± 21.8	111.1 ± 14.4[3]	65.0 ± 5.2[3]
7	30.5 ± 13.0	27.2 ± 4.3	15.6 ± 0.9[3]
8	103.5 ± 4.7	102.7 ± 10.1	59.3 ± 7.5[3]
9	50.6 ± 17.6	83.7 ± 6.1[3]	31.7 ± 3.6[4]
All	92.1 ± 67.1[5]	93.5 ± 57.2[5]	44.7 ± 32.5

[1] $\bar{x}$ ± SD.
[2] All values significantly different from the soy-protein diet, $P < 0.001$ (Bonferroni multiple comparisons test).
[3,4] Significantly different from the self-selected diet (Bonferroni multiple comparisons test): [3] $P < 0.001$, [4] $P < 0.01$. For all subjects, the variation among diets was significant, $P < 0.0001$ (repeated-measures ANOVA). For individual subjects, the variation among diets was significant for subjects 1, 2, 3, 4, 5, 6, 8, and 9 ($P < 0.0001$) and for subject 7 ($P < 0.0018$) by parametric one-way ANOVA.
[5] Significantly different from the casein diet, $P < 0.001$ (Bonferroni multiple comparisons test).

How dietary proteins affect Lp(a) concentrations remains unknown. Both apo(a) production rates, Lp(a) assembly rates, and Lp(a) catabolism rates may be affected. Because plasma Lp(a) concentrations are controlled primarily by the rate of synthesis rather than by the rate of clearance (57, 58), the differential effects of dietary proteins on Lp(a) production may be the most likely explanation. This notion is supported by studies of dietary factors and drugs affecting Lp(a) concentrations. Estrogen treatment of postmenopausal women lowered plasma Lp(a) by decreasing Lp(a) production by ≈30%, whereas the fractional catabolic rate was not affected significantly (59). Testosterone treatment of healthy men lowered Lp(a) concentrations (44) and studies of these hormones in transgenic mice expressing human apo(a) complementary DNA showed that apo(a) plasma concentrations are regulated by both estrogen (60) and testosterone (61) at the hepatic messenger RNA level. Niacin treatment lowered Lp(a) by 33% without affecting the fractional catabolic rate, whereas the synthetic rate was reduced by 29% (34). Oral neomycin lowered Lp(a) plasma concentrations (32) and reduced the release of apo(a) from cultivated baboon hepatocytes (62). Although these findings suggest a reduction in apo(a) production as a cause of the decrease in Lp(a) in vivo during neomycin treatment, it remains to be shown whether poorly absorbed neomycin achieves sufficient hepatic concentrations in vivo to affect apo(a)

release. In cynomolgus monkeys, both monounsaturated and polyunsaturated dietary fatty acids resulted in lower Lp(a) concentrations than did the saturated lauric and myristic acids. The fact that hepatic apo(a) messenger RNA abundance decreased significantly while the animals were consuming the monounsaturated diet means that dietary monounsaturated fatty acids decreased hepatic apo(a) transcription and thus decreased apo(a) production. How the polyunsaturated fatty acid diet lowered Lp(a) remains unexplained, but the authors hypothesized that up-regulation of LDL receptors may have increased the rate of catabolism (63). Up-regulation of LDL receptors, however, whether by dietary polyunsaturated fatty acids (24) , 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (36, 37), or bile acid–sequestering agents (35), did not result in a decrease in Lp(a) concentrations in humans.

The protein preparations used in this study were ≈90% pure; therefore, the differential effects of the 2 preparations on Lp(a) may have been due to the protein moieties or to nonprotein impurities. Studies in rabbits of dietary casein, casein hydrolysates, and casein amino acids indicate that essential amino acids, except for arginine, are largely responsible for the cholesterol- and LDL-elevating effects of dietary casein (64, 65), and the LDL elevation appears to be due both to decreased LDL receptor activity and to increased synthesis of apo B (66). The amino acid composition of a dietary protein might, therefore, also affect hepatic apo(a) production and thus Lp(a) plasma concentrations. Assuming that casein reduced Lp(a) concentrations by reducing apo(a) production, then casein would have to concomitantly increase the production of apo B and decrease that of apo(a).

Although the present observations suggest an Lp(a)-lowering effect of dietary casein, the possibility exists that the soy-protein and self-selected diets contained Lp(a)-elevating components that were lacking in the casein diet. Thus, the elevated Lp(a) concentrations, relative to those observed after the casein diet, may have been due to the soy polypeptides or to nonprotein impurities such as soy isoflavones or saponins. Isoflavones have weak estrogenic and antiestrogenic effects and Lp(a) concentrations are sensitive to both estrogen and to antiestrogenic tamoxifen. A recently published study of the effects of dietary soy protein on rhesus monkeys showed that soy-protein isolate with a high isoflavone content not only lowered LDL and VLDL cholesterol significantly in both sexes, but also decreased Lp(a) concentrations by 18% in females and by 8% (NS) in males when compared with ethanol-extracted soy protein containing minimal amounts of isoflavones and other alcohol-extractable constituents (67). The soy-protein isolates we used were not alcohol extracted and therefore contained isoflavones, although we do not know how much. If soy isoflavones and other alcohol-extractable impurities similarly affect Lp(a) concentrations in humans and rhesus monkeys, and if soy-protein impurities affect Lp(a) concentrations significantly, we would expect lower Lp(a) concentrations after a soy-protein than after a casein diet in humans because casein contains no isoflavones nor, presumably, any of the other ethanol-extractable components of soy protein. However, in the present study, Lp(a) concentrations increased transiently with the soy-protein diet but were not significantly different from baseline by the end of the study. Therefore, we conclude that either isoflavones have no significant effects on Lp(a) or that they affect Lp(a) differently in humans and in rhesus monkeys.

It is firmly established that a reduction in LDL cholesterol can prevent both new and recurrent coronary artery disease. An increase in HDL cholesterol in all likelihood is also beneficial, although the evidence for this is less firm. Whether a reduction in Lp(a) concentrations >200–300 mg/L will reduce the risk of coronary artery disease is unknown, although epidemiologic evidence and some (68), but not all (69), observations in transgenic mice suggest that it might. Several observations indicate that the risk associated with high Lp(a) concentrations depends on whether LDL-cholesterol concentrations are elevated, and, possibly on whether HDL-cholesterol concentrations are low (70, 71). Because dietary soy protein can lower LDL and increase HDL concentrations, these effects may counteract the putative undesirable effects of an elevated Lp(a) concentration. Note that the degree of Lp(a) elevation in the present study occurred with a soy protein intake constituting 20% of the total energy consumption. This intake exceeds by far the amount that could practically be incorporated into a therapeutic diet. Thus, more information is needed on the dose effect of dietary soy protein on Lp(a) and other plasma lipoproteins before conclusions can be drawn about the validity of these findings as they pertain to the use of soy protein in antiatherogenic diets.

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