Alcohol-Extracted, but Not Intact, Dietary Soy Protein Lowers Lipoprotein(a) Markedly

Hans Meinertz, Karin Nilausen, Jørgen Hilden

Abstract—We previously found that dietary soy protein produces higher lipoprotein(a) [Lp(a)] plasma concentrations than does casein. This study tested the hypothesis that soy protein contains Lp(a)-raising alcohol-removable components. Twelve normolipidemic women and men consumed, in a crossover design, liquid-formula diets containing casein, soy protein, or alcohol-extracted soy protein. Dietary periods of 32 days were separated by washout periods on self-selected diets. Fasting lipid and Lp(a) levels were measured throughout. Median Lp(a) concentration was >2-fold greater after 28 to 32 days on a soy protein diet than after an extracted soy protein diet ($P<0.001$). Lp(a) concentrations after casein and extracted soy protein diets were virtually identical. Women and men responded similarly. When the switch was made from a self-selected to a soy protein diet, median Lp(a) concentration increased 16% after 1 week ($P<0.001$) and subsequently decreased toward baseline; extracted soy protein and casein diets never exhibited increased median Lp(a) levels, and after 28 to 32 days, these levels were decreased >60% below baseline ($P<0.001$ and $P<0.01$, respectively). Low density lipoprotein cholesterol concentrations were not different after the 3 experimental diets. The data indicate that (1) dietary soy protein can increase Lp(a) concentrations, (2) this effect is eliminated after alcohol extraction, and (3) high Lp(a) concentrations may be markedly reduced by diet. (Arterioscler Thromb Vasc Biol. 2002;22:312-316.)

Key Words: lipoprotein(a) ■ plasma lipoproteins ■ dietary soy protein ■ dietary casein ■ liquid-formula diets

Substitution of soy protein in the diet for animal protein can lower plasma cholesterol, LDL cholesterol (LDL-C), and triglycerides$^1$ and can increase HDL cholesterol (HDL-C).$^2$ Although the lipemic response to soy protein is variable,$^4,5$ many individuals react favorably, particularly hyperlipidemic patients, especially when the intake of soy protein is high.$^1$ But despite the favorable effects on both atherogenic and protective lipoproteins, soy protein is not generally accepted for use in antiatherogenic diets. One reason for this is the question of safety. Therefore, the Nutrition Committee of the American Heart Association has recommended that potential risks of a high soy protein intake be examined before guidelines for the use of soy protein in antiatherogenic diets are developed.$^6$ How dietary soy protein affects plasma lipoproteins remains unknown. A recent study comparing intact with ethanol-extracted soy protein in rhesus monkeys has suggested that alcohol-extractable soy protein components have favorable effects on plasma total cholesterol and VLDL+LDL cholesterol in males and females, on HDL-C in females, on triglycerides in males, and on Lp(a) in females.$^7$ These findings suggest that extractable components of soy protein play an important role in the lipemic response of humans to soy protein diets. However, this is not to say that alcohol-treated protein itself is without beneficial effects, because human studies have shown significant LDL-C reductions in hypercholesterolemic patients after an intake of soy protein devoid of alcohol-extractable components.$^8$

Lp(a) is a unique cholesterol-rich lipoprotein that is found almost exclusively in primates. It consists of an LDL moiety plus a high molecular weight glycoprotein, apo(a), attached to apoB-100 of the LDL by a disulfide bridge.$^9$ Circulating Lp(a) levels have a skewed distribution with considerable scatter and are largely controlled by the apo(a) gene, with the concentration being negatively related to the size of apo(a).$^{10}$ Although diet generally has modest effects on Lp(a),$^9$ we recently found that dietary soy protein produces markedly higher Lp(a) concentrations than does casein.$^{11}$ This might be due to an Lp(a)-elevating effect of soy protein or an Lp(a)-lowering effect of casein. Because high Lp(a) plasma concentrations appear to be a strong independent risk factor for premature coronary artery disease (see review$^{12}$), especially in combination with other lipid and nonlipid risk factors,$^{12}$ it seemed important to examine whether soy protein affects Lp(a) levels in an adverse manner. If this proved to be the case, it furthermore seemed important to characterize the component of soy preparations responsible for the Lp(a) elevation. Therefore, the aim of the present study was to examine whether dietary soy protein raises Lp(a) levels and whether this putative effect resides with alcohol-extractable components or with the extracted protein.

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**TABLE 1. Baseline Values of Subjects**

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>30±13</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.5±2.0</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td></td>
</tr>
<tr>
<td>Total plasma</td>
<td>4.2±0.7</td>
</tr>
<tr>
<td>LDL</td>
<td>2.1±0.5</td>
</tr>
<tr>
<td>HDL</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.9±0.4</td>
</tr>
<tr>
<td>Lp(a), mg/L</td>
<td></td>
</tr>
<tr>
<td>At start of study</td>
<td>47 (12, 293)</td>
</tr>
<tr>
<td>Before start of diet</td>
<td></td>
</tr>
<tr>
<td>Casein diet</td>
<td>65 (17, 373)</td>
</tr>
<tr>
<td>Soy protein diet</td>
<td>57 (13, 313)</td>
</tr>
<tr>
<td>Extracted soy protein</td>
<td>56 (16, 294)</td>
</tr>
</tbody>
</table>

BMI indicates body mass index. Values are mean±SD, except Lp(a) concentrations, which are given in terms of median and antilog (mean±SD on logarithmic scale); n=12 (6 women +6 men).

**Methods**

**Subjects**

Table 1 shows baseline characteristics of the normolipidemic participants (6 women and 6 men, mostly medical students). Their ages varied from 22 to 29 years (women) and from 22 to 35 years (men) plus 1 subject aged 68 years (man), and their body mass index values ranged from 18.6 to 24.0 kg/m² (women) and from 21.7 to 25.9 kg/m² (men). With the exception of 1 woman and 1 young man, they had plasma cholesterol concentrations <5.2 mmol/L, which is considered desirable by National Cholesterol Education Program (NCEP) guidelines. Overall, Lp(a) concentrations showed the well-known skewed distribution; the female median Lp(a) concentration (201.4 mg/L) happened to be substantially higher than that of the males (33.9 mg/L) but with considerable overlap of individual values. All had normal liver, kidney, and thyroid function as well as normal fasting glucose concentrations. None used medications regularly, and none of the women used hormone preparations. The subjects gave informed consent, and the local ethics committee approved the protocol.

**Study Design**

In a crossover design, the participants consumed 3 liquid-formula diets containing (1) casein, (2) soy protein, and (3) ethanol-extracted soy protein. The dietary periods lasted 32 days and were separated by washout periods on self-selected solid-food diets. Initially, all subjects ate the casein diet, another 4 ate the soy protein diet, and the last 4 ate the extracted soy protein diet; subsequently, they switched to the other diets. Immediately before they began the casein diet, 8 subjects had been on a self-selected washout diet for 70±36 (mean±SD) days (range 33 to 120 days), and before the start of the soy protein diet and the extracted soy protein diets, the washout periods of 8 subjects were 39±13 days (range 18 to 59 days) and 28±11 days (range 18 to 46 days), respectively. The duration of the washout periods appeared adequate to eliminate carryover effects of the preceding liquid diet because the plasma levels of all components (Tables 1 and 2) immediately before the start of the liquid diets were insignificantly different.

Fasting blood samples were drawn for measurement of plasma Lp(a) and lipids. Two samples were drawn immediately before the start of the liquid diets, and 8 were drawn after the consumption of these diets for 7, 14, 21, 28, 29, 30, 31, and 32 days.

**Diet**

After enrollment, the subjects were asked to continue their habitual diets until the first liquid-diet period and during the washout intervals. The self-selected diets contained, as evaluated from food records, 16.8±2.3% protein (mean±SD of total energy), 58.9±8.4% carbohydrate, 23.3±8.6% fat (10.2±6.0% saturated, 9.4±3.3% monounsaturated, and 3.8±1.4% polyunsaturated), 1.1±2.5% alcohol, and 242±131 mg/d cholesterol.

The composition of the liquid-formula diets has been described.2 Protein constituted 20% of the energy intake. Calcium caseinate (Casec, donated by Mead Johnson Laboratories, Evansville, Ind) was 94% pure, and the soy protein isolates (Supro 670HG and Supro 670IF, donated by Protein Technologies International, St. Louis, Mo) were 88% and 96% pure, respectively. The intact protein (Supro 670HG) contained 63 mg lipid and 2.39 mg isoflavone (aglycone) per gram protein, whereas the extracted protein (Supro 670IF) contained 8.2 mg lipid and 0.11 mg isoflavone per gram protein. The mean daily protein intake per kilogram body weight was the same for the 3 diets. A cornstarch hydrolysate (Maltodextrin 01915, Cerestar) constituted 55% of the energy, whereas the fat component (25% of the energy) was the high oleate variant of safflower oil (Oleinate 181, Pacific Vegetable Oil Corp). Slightly more cholesterol (USP, Sigma Chemical Co) was added to the soy diets than to the casein diet to compensate for the cholesterol content of the casein; the daily cholesterol intake was 55 mg/MJ (236 mg/1000 kcal). Calcium lactate was added to the soy diets to compensate for the calcium content of the caseinate, and sodium lactate was added to the casein diet to compensate for the lactate. After the addition of salts and vitamins, the diets fulfilled “recommended dietary allowances.”13 The subjects were allowed energy-free beverages and were asked not to drink alcohol.

The subjects were weighed regularly and were asked to modify their intake of formula to maintain body weight. The mean body weights were not different at the start of the 3 dietary periods: 67.8±12.0 kg (mean±SD) for the casein diet, 68.5±11.9 kg for the soy protein diet, and 68.9±12.6 kg for the extracted soy protein diet. After 32 days on casein and soy protein diets, the subjects had insignificant mean reductions of 0.6 and 0.4 kg, respectively, whereas the extracted soy protein diet caused a formally significant weight loss of 1.0 kg (P<0.05).

**Lipid and Lipoprotein Analyses**

After the subjects had fasted for 12 hours and after they had spent at least 15 minutes in a recumbent position, blood samples were collected, and EDTA-plasma was immediately separated by centrifugation (2000g for 30 minutes at 4°C). HDL was isolated after precipitation of LDL and VLDL with MgCl₂ and dextran sulfate.14 VLDL was separated from LDL+HDL by ultracentrifugation for 20 hours at 100 000 g, at a density of 1.006 g/mL, and at 4°C in a 50.3 Beckman rotor, and the fractions were recovered after tube slicing. Crude LDL-C was calculated as the difference between the cholesterol content of the >1.006 g/mL-density fractions before and after precipitation of LDL; to correct for Lp(a) cholesterol, plasma Lp(a) mass (in milligrams per deciliter)×0.3 was subtracted from crude LDL-C (in milligrams per deciliter).15 Plasma and lipoprotein fractions were stored at −20°C; all samples were assayed after each subject had completed the study. Cholesterol and triglycerides were analyzed by enzymatic methodology (Boehringer-Mannheim).

Plasma Lp(a) concentrations were measured by radioimmunoassay (Pharmacia Diagnostics AB) using 2 monoclonal anti-apo(a) antibodies; one was used as a trapping antibody bound to sepharose microbeads, and the other reporting antibody was radioiodinated. Samples and standards were incubated in excess of both antibodies, and the antigen bound to the beads was isolated by centrifugation for counting in a gamma counter. Each sample was analyzed in duplicate and measured from a standard curve constructed for that particular run. The intra-assay and the interassay coefficients of variation were 3.4% and 7.8%, respectively. All samples from each subject were analyzed in the same run. The plasma samples for Lp(a) determination were stored at −80°C for <1 year before analysis and were thawed only at the time of analysis. A comparison of this procedure with an immunonephelometric analysis (Dade Behring) showed a close correlation of Lp(a) concentrations (r=0.95), and values obtained by the present procedure were, on average, 5% higher than the nephelometric measurements. Lp(a) standards for the 2 analytical procedures were provided by Pharmacia and Dade Behring, respectively.
TABLE 2. Plasma Lipid Concentrations at Start (Self-Selected Diet) and After Consuming the Liquid-Formulas Diets for 28 to 32 Days

<table>
<thead>
<tr>
<th></th>
<th>Casein (Before Casein)</th>
<th>Casein Diet</th>
<th>Extracted Soy Protein (Before Extracted Soy Protein)</th>
<th>Extracted Soy Protein</th>
<th>Soy Protein (Before Soy Protein)</th>
<th>Soy Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total plasma</td>
<td>4.02 ± 0.87</td>
<td>3.15 ± 0.43*</td>
<td>4.16 ± 0.64</td>
<td>3.25 ± 0.37*</td>
<td>4.15 ± 0.86</td>
<td>3.39 ± 0.34*</td>
</tr>
<tr>
<td>LDL</td>
<td>2.05 ± 0.60</td>
<td>1.65 ± 0.35†</td>
<td>2.17 ± 0.52</td>
<td>1.71 ± 0.41†</td>
<td>2.16 ± 0.50</td>
<td>1.61 ± 0.36*</td>
</tr>
<tr>
<td>HDL</td>
<td>1.54 ± 0.49</td>
<td>1.27 ± 0.23‡</td>
<td>1.56 ± 0.43</td>
<td>1.34 ± 0.22</td>
<td>1.58 ± 0.49</td>
<td>1.40 ± 0.19§</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.87 ± 0.30</td>
<td>0.74 ± 0.20</td>
<td>0.92 ± 0.34</td>
<td>0.66 ± 0.14‡‡</td>
<td>1.00 ± 0.43</td>
<td>0.83 ± 0.22‖</td>
</tr>
</tbody>
</table>

Values are mean ± SD for 12 subjects. Baseline concentrations (on self-selected diet) were measured twice before the start of each experimental dietary period, and the values were pooled. The experimental concentrations were measured after the subjects had consumed the liquid-formula diets for 28, 29, 30, 31, and 32 days, and the values were pooled.

*P < 0.001, †P < 0.01, and ‡P < 0.05 vs corresponding baseline values (self-selected diet); §P < 0.05 and ||P < 0.05 for corresponding liquid diet values.

Statistical Analysis
Mean concentrations obtained during the last 5 days of each dietary period were used for statistical analysis of the dietary effects. In the case of cholesterol and triglycerides, this was performed by parametric repeated-measures ANOVA, and pairs of diets were evaluated by the Bonferroni multiple comparisons test. Similar procedures were used to compare lipid concentrations at baseline with those observed after the liquid-formula diets. The dietary effects on Lp(a) concentrations (Figure) were assessed (1) by the Friedman nonparametric repeated-measures ANOVA and multiple comparisons by the Dunn test, (2) by pooling days 28 through 32, (3) by pooling each subject’s 2 preliquid diet measurements, and (4) by pooling the sexes.

Results
Consumption of the liquid-formula diets for 28 to 32 days reduced plasma cholesterol and LDL-C 20% (P < 0.001) compared with baseline (Table 2), indicating excellent dietary compliance. In addition, the extracted soy protein diet caused lower triglyceride levels (P < 0.01), and the casein diet caused lower HDL-C levels (P < 0.05) than at baseline. However, comparison of plasma lipid levels after an 1-month intake of the 3 liquid diets showed insignificant differences in total cholesterol and LDL-C; thus, compared with the casein diet, neither of the soy protein diets reduced LDL-C, presumably because of the low baseline values.1 But the extracted soy protein diet produced lower triglyceride levels (P < 0.05) and the casein caused lower HDL-C levels (P < 0.05) than did the soy protein diet.

Intake of the liquid diets for 28 to 32 days showed marked differences between intact and extracted soy protein on Lp(a) concentrations. The Lp(a) responses of individual subjects to the liquid formulas are presented in the Figure. Although an intact soy protein diet produced insignificant changes of Lp(a) levels, from a median concentration at baseline of 57.0 mg/L to a final value of 50.0 mg/L, the extracted soy protein diet reduced median Lp(a) concentration by >60%, from 56.0 mg/L at baseline to 21.5 mg/L (P < 0.01); the casein diet, similarly, reduced it from 65.0 to 21.0 mg/L (P < 0.001), so that Lp(a) levels after casein and extracted soy protein diets were virtually identical and below one half of the final median for the intact soy protein diet. As judged on the logarithmic scale of the Figure, there were no significant interactions of diet and sex or of diet and period (first, second, and third course). Nor did the relative changes (logarithmic scale) appear to depend on initial levels (of course, absolute changes were larger, the larger was the individual’s general level).

After 7 days on the intact soy protein diet, there was an increase in Lp(a) concentrations in all but 1 subject (Figure), whose level was low and unchanged, so that the median concentration increased from 57.0 mg/L at baseline to 66.0 mg/L (P < 0.01). No such pattern of increase after 7 days was seen for the extracted soy protein and casein diets; in fact, the tendency was the opposite. After the initial Lp(a) increase at day 7 during consumption of the intact soy protein diet, the Lp(a) elevation continued for a variable period of time in individual subjects (Figure). Roughly two thirds of the subjects maintained high levels throughout the period, whereas the levels for the remaining subjects slid down to varying extents after the first week. After 28 to 32 days, when Lp(a) levels had stabilized, the extracted soy protein and the
casein diets had lowered Lp(a) in all subjects, with a single exception, whereas the intact soy protein diet produced small and variable responses.

**Discussion**

The aim of the present study was to examine whether the Lp(a)-raising effect of dietary soy protein, compared with that of casein, was due to an alcohol-extractable component. We found, as previously noted, 11 that intact soy protein produced higher Lp(a) concentrations than did casein. In addition, we found that soy protein, after extraction, produced the same low Lp(a) levels as did casein. Thus, the findings appear to agree with our working hypothesis that intact soy protein contains an Lp(a)-elevating constituent that may be removed by alcohol extraction. However, eventual verification of that suggestion will require isolation of this putative factor and demonstration of its Lp(a)-raising effect. Alternative mechanisms might be that extracted soy protein or casein lowers Lp(a) or that the extraction process modifies constituents of the soy preparation to alter their effect on Lp(a) concentrations. However, 2 observations appear to favor our hypothesis. First, intact soy protein increased Lp(a) concentrations significantly after switching from the self-selected to the experimental diet; with time, this increase evened out toward baseline values, suggesting that intact soy protein and self-selected diets contain Lp(a)-raising components. Second, preliminary observations on the effects of a soy protein extract, containing (besides soy protein) soy lipids and isoflavones, showed the following: when this extract was added to a self-selected diet, Lp(a) concentrations remained unaffected, but when it was added to the casein diet, after the diet had been consumed for 5 weeks, whereby Lp(a) levels were reduced to 60% of baseline, the extract increased Lp(a) to baseline levels within 4 to 5 weeks.

Others have examined the effects of intact versus alcohol-extracted soy protein on plasma Lp(a) concentrations. In human studies, supplementation of either the NCEP step I diet with 25 g soy protein daily 16 or a customary diet with 53 g soy protein daily 17 showed no difference between Lp(a) concentrations after the addition of intact or extracted soy protein. If our suggestion that the intact soy protein and the self-selected diets contain Lp(a)-raising constituents is correct, it is perhaps not surprising that the daily addition of 25 or 53 g extracted soy protein was unable to dilute such putative factors sufficiently to lower Lp(a). Based on the assumption that extracted soy protein (and casein), per se, lowers Lp(a), another explanation could be that the greater intake of soy protein and casein in the present study (mean 96 and 170 g/d for women and men, respectively), replacing other food components, had more of a potential to lower Lp(a) concentrations than did the 25- and 53-g supplementations of the cited trials. In contrast to our observations, studies in nonhuman primates, with the use of diets with soy protein as the only protein source, found that intact compared with alcohol-extracted preparations lowered Lp(a) by percentages ranging from 8% to 26%. 7,18 Whether the discrepant findings are due to species differences or to differences in experimental conditions remains unknown.

The effect of extracted soy protein, compared with the untreated preparation, was highly specific for Lp(a), inasmuch as the median concentration was more than halved, whereas neither total cholesterol, LDL-C, nor HDL-C was different, and only triglycerides were modestly affected. The uniformity of the relative response of Lp(a) to intact versus extracted soy protein over the range of Lp(a) concentrations suggests, inasmuch as plasma concentrations are inversely correlated with apo(a) isofom size, 10 that the soy factor affected Lp(a) levels regardless of apo(a) size. Because changes in Lp(a) concentrations usually are due to changes in Lp(a) production rates, 19 the observed effects may have been due to the effects on hepatic apo(a) production, directly or indirectly, by translational or posttranslational mechanisms. 20 One might speculate that alcohol-extractable soy lipids (or their fatty acid moiety) target hepatic peroxisome proliferator-activated receptors (PPARs) and thereby affect apo(a) transcription rates. Studies in monkeys have shown that gemfibrozil 21 and different dietary fatty acids, 22 known activators of PPARα, modify not only apo(a) production but also apo(a) mRNA abundance. Also, the marked Lp(a)-elevating effect in humans of troglitazone, 23 an activator of PPARγ, suggests that the present effects of dietary proteins on Lp(a) concentrations might involve interactions with nuclear PPAR receptors. Although alcohol extraction removes, besides lipids, estrogenic and antiestrogenic isoflavones from soy protein, it seems unlikely that the presence of isoflavones could explain the Lp(a)-elevating effect of intact compared with extracted soy, inasmuch as estrogen 24 and the antiestrogens tamoxifen 25 and raloxifene 26 decrease Lp(a) concentrations. Furthermore, comparison of isoflavones from clover and placebo detected no significant effect on Lp(a). 27

Major limitations of the present study, from the clinician’s or dietician’s point of view, were the short duration, the limited number of subjects, use of liquid-formula diets, and the high soy protein intake exceeding what is achievable in solid-food diets. Also, differences between women and men in baseline Lp(a) concentrations and age may make our findings less persuasive. However, the relative responses to intact versus extracted soy protein were similar despite differences in baseline Lp(a) levels, and the only elderly male participant responded in the same way as did the younger men and the women.

Because high Lp(a) concentrations may be an independent cardiovascular risk factor, attempts have been made to find ways to reduce elevated levels that are based on the assumption that Lp(a) plays a causal role. In agreement with that assumption, a recent study has suggested that lowering high (>250 mg/L) Lp(a) concentrations by estrogen-progestin treatment reduces the risk of recurrent coronary heart disease events in postmenopausal women. 28 Diet has generally had only a limited effect, 9 and although n-3 polyunsaturated fatty acids decreased Lp(a) considerably in some studies, 29–31 this effect was not always observed. 32 The present findings indicate that diet can lower elevated Lp(a) concentrations markedly. Three of our subjects with baseline levels of 343, 549, and 833 mg/L had their Lp(a) concentrations reduced 60% to 72% to acceptable levels (<250 mg/L) by our diets. As discussed above, we believe that the evidence suggests that high levels of Lp(a) are due in part to Lp(a)-elevating components of commonly consumed foods. If those components were identified and removed or avoided, effective Lp(a)-lowering solid-food diets might be developed.
Acknowledgments

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