Blood lipid and oxidative stress responses to soy protein with isoflavones and phytic acid in postmenopausal women

Heather M Engelman, D Lee Alekel, Laura N Hanson, Anumantha G Kanthasamy, and Manju B Reddy

ABSTRACT
Background: Postmenopausal women are at risk of cardiovascular disease (CVD) as a result of unfavorable blood lipid profiles and increased oxidative stress. Soy protein consumption may help protect against these risk factors.

Objective: Our objective was to ascertain the effect of the soy protein components isoflavones and phytate on CVD risk in postmenopausal women.

Design: In a double-blind 6-wk study, 55 postmenopausal women were randomly assigned to 1 of 4 treatments with soy protein (40 g/d) isolate (SPI): low phytate/low isoflavone (LP/LI); normal phytate/low isoflavone (NP/LI); low phytate/normal isoflavone (LP/NI); or normal phytate/normal isoflavone (NP/NI). Blood lipids (total, LDL, and HDL cholesterol and triacylglycerol) and oxidative stress indexes (protein carbonyls, oxidized LDLs, and 8-iso-prostaglandin-F2α) were measured at baseline and 6 wk.

Results: The oxidative stress indexes were not significantly affected by either phytate or isoflavones. Phytate treatment had a minimal but nonsignificant effect in reducing protein carbonyls and 8-iso-prostaglandin-F2α; the reductions were 6–8% and 4–6% in the NP/LI and NP/NI groups and 1–4% and 3–4% in the LP/LI and LP/NI groups, respectively. Similarly, circulating lipids were not significantly affected by either phytate or isoflavones. The decline in total (6%–7% compared with 2%–4%) and LDL (10%–11% compared with 3%–7%) cholesterol did not differ significantly between the normal- and low-isoflavone groups, respectively.

Conclusion: In postmenopausal women, neither phytate nor isoflavones in SPI have a significant effect of reducing oxidative damage or favorably altering blood lipids. Am J Clin Nutr 2005;81:590–6.

KEY WORDS Postmenopausal women, oxidative stress, cardiovascular disease, soy protein, isoflavones, phytate, blood lipids

INTRODUCTION
Men are usually at higher risk than are women of developing cardiovascular disease (CVD). After menopause, the risk for women becomes similar to that for men. The postmenopausal lack of estrogen may be responsible for affecting antioxidant defenses, as well as lipid and lipoprotein concentrations (1), both of which are implicated in the pathogenesis of CVD (2, 3). Soy protein consumption has been shown to significantly decrease serum concentrations of total and LDL cholesterol and triacylglycerols (4, 5). Many components associated with soy protein, eg, isoflavones (6), saponins (7), and β-conglycinin (7S globulin) protein fractions (8), are reported to have a lipid-lowering effect. Adding isoflavone-rich soy protein to a low-fat diet for 3 mo in hyperlipidemic men and postmenopausal women significantly reduced total and LDL-cholesterol concentrations (6). Conversely, a 6-mo study with perimenopausal women found that isoflavone-rich soy protein had no effect on serum lipid concentrations (9). Conflicting results may be due to subject selection, large interindividual variation, and varied doses of isoflavones. Hence, the effect of isoflavones on serum lipids in humans remains unclear. Soy isoflavones may also possess antioxidant properties that protect against LDL oxidation (5, 10) and improve total antioxidant status (11). The antioxidant effect of isoflavones may be due to their ability to donate hydrogen atoms to free radicals, which makes the radicals less reactive (12). Although it is unclear whether this free radical quenching happens in vivo, another possible mechanism of isoflavones may be the enhancement of antioxidant defenses by increasing antioxidant enzyme concentrations, as was shown in a mouse model (13).

Phytate, another component of soy, was originally considered an antinutrient, but it may be beneficial in some conditions. Phytate may have a stronger ability to quench free radicals than do isoflavones because of its metal-chelating ability, which renders the prooxidant metal iron unavailable to participate in the Fenton reaction and to catalyze hydroxyl radical formation in vitro (14). Thus, phytate may prevent oxidative damage, such as lipid peroxidation (15, 16) and may thereby decrease the formation of atherosclerotic lesions. Although phytate is absorbed in rats (17), its absorption in humans is very low (18); nevertheless, it is possible that even small amounts of phytate may protect against oxidative stress. In addition to its antioxidant activity, phytate has shown a lipid-lowering effect in rats (19). Reducing the ratio of zinc to copper (20) may be the mechanism by which...
phytate lowers lipid concentrations (21); however, human data in this area are limited. The overall hypothesis of the current study was that soy protein would reduce the risk of CVD—specifically, that soy isoflavones would favorably alter blood lipid concentrations and that phytate would decrease oxidative stress indices.

SUBJECTS AND METHODS

Study design

In this 6-wk double-blind study, 55 free-living postmenopausal women were randomly assigned to 1 of 4 soy protein isolate (SPI) treatments provided by The Solae Company (St Louis, MO): low-phytate/low-isoﬂavone (LP/LI; n = 14), normal-phytate/low-isoﬂavone (NP/LI; n = 13), low-phytate/normal-isoﬂavone (LP/NI; n = 14), or normal-phytate/normal-isoﬂavone (NP/NI; n = 14) treatment. The 2 treatments containing isoflavone concentrations that are referred to as “normal” are in fact rich in isoflavones because their isoflavone content per gram protein is twice that found in typical SPIs. The Solae Company prepared the low-isoﬂavone and low-phytate SPIs by using alcohol extraction and phytase hydrolysis, respectively. The phytate and isoﬂavone (aglycone) contents, respectively, of each treatment per 40 g soy protein were as follows: LP/LI treatment, 0.22 g and 1.2 mg; NP/LI treatment, 0.64 g and 1.2 mg; LP/NI treatment, 0.22 g and 85.8 mg; and NP/NI treatment, 0.78 g and 84.6 mg. All subjects were white except one Asian woman. The women were supplied with protein in a powder form in two 20-g packets/d (84 total packets), and they were given recipes for incorporating the powder into fruit smoothies or other foods. Beginning 2 wk before and continuing throughout the intervention, subjects were required to avoid all supplements, including vitamins, minerals, and herbal remedies. Subjects were also provided with a list of foods that are phytate rich (ie, cereals, legumes, and nuts; 22, 23) or isoﬂavone rich (ie, primarily legumes; 24) and were instructed to avoid these foods during the intervention.

The study protocol, consent form, and subject-related materials were approved by Human Subjects Review Committee of Iowa State University (Institutional Review Board ID #02–351). Written informed consent was obtained from all subjects.

Subject selection

Postmenopausal women were recruited throughout central Iowa from April through November 2002 by means of campus and local newspaper advertisements and a television feature story. Approximately 300 women responded, and the potential participants were screened by telephone interviews to ensure that they met the inclusion and exclusion criteria. Health status with respect to chronic diseases (ie, arthritis, cancer, CVD, diabetes, or gastrointestinal, kidney, liver, parathyroid, and pulmonary disease) and menopausal state was assessed before a woman’s inclusion in the study with the use of a health and medical history questionnaire. Women were included in the study if they were postmenopausal (last menses ≥12 mo before intervention) and healthy (no chronic disease or medication use) and if they had a body mass index (BMI; in kg/m²) of 19–34. Women were excluded if they had a chronic disease, had undergone a hysterectomy, had taken hormone therapy ≤12 mo before the intervention, or had used cigarettes or hormone creams ≤6 mo before the intervention. On the basis of these criteria, 57 women were qualified to participate. Two of these women withdrew because of intolerable gastrointestinal side effects. The remaining 55 women completed the 6-wk intervention with minimal or no gastrointestinal side effects.

Data collection

Health and medical history, nutrition history, and soy food intake data (25) were obtained at baseline by using interviewer-administered questionnaires. Usual dietary intake was also assessed at baseline with the use of a food-frequency questionnaire from Block Dietary Data Systems (Berkeley, CA). Overnight-fasted blood samples were collected at baseline and week 6 and were frozen at −80 °C until they were used. A standard reference laboratory (Quest Diagnostics, St Louis, MO) analyzed serum and plasma for the blood lipid profile (total, LDL−, and HDL− cholesterol and triacylglycerol concentrations) and other blood chemistry analytes. Indexes of oxidative stress [ie, protein carbonyls, oxidized LDL (oxLDL), and 8-iso-prostaglandin-F2α (PGF2α)] were measured in our laboratory at Iowa State University. Protein carbonyls were measured by using a slight modification of the procedure described in Reznick et al (26). Briefly, plasma was mixed with dinitrophenylhydrazine dissolved in hydrochloric acid, accompanied by blanks in hydrochloric acid alone. Protein was then precipitated with 20% (wt:vol) trichloroacetic acid and washed once with 10% trichloroacetic acid and 3 times with 5 mL of a 1:1 mixture of ethanol and ethyl acetate. Finally, precipitates were dissolved in a solution of 6 mmol guanidine-hydrochloric acid/L. The absorbance was measured spectrophotometrically at 380 nm. Plasma oxLDL concentrations were determined by using an enzyme-linked immunosorbent assay kit from ALPCO Diagnostics (Windham, NH), and serum PGF2α (free + esterified) concentrations were determined by using an enzyme-linked immunosorbent assay kit from Stressgen Biotechnologies (Victoria, Canada). The overall CVs for protein carbonyls, PGF2α, and oxLDL were <1%, 8%, and 6%, respectively.

Statistical analysis

Statistical analysis was performed with SAS software (version 8.0; SAS Institute, Cary, NC) with significance set at P ≤ 0.05. The sample size per group was based on a pooled SD of 22 mg/dL and 80% power (P < 0.05) to detect a reduction in LDL cholesterol of 15 mg/dL, which is biologically significant enough to reduce CVD risk. Analysis of variance with Tukey’s multiple comparison was used to test the differences in baseline values among the treatments. To ascertain whether baseline-adjusted differences (6 wk − baseline) between isoﬂavone and phytate treatments differed significantly, we used two-way analysis of covariance with the respective baseline values as covariates. Pearson’s product-moment correlation analysis was used to determine the relation among the risk factors at baseline.

RESULTS

Compliance

Compliance was based on the number of packets returned at the week 6 visit. Most of the women consumed 100% of their packets. However, 4 subjects returned 2, 3, 4, and 8 packets, respectively, and 2 subjects requested 3 and 4 extra packets,
TABLE 1
Baseline characteristics of subjects

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>LP/LI (n = 14)</th>
<th>NP/LI (n = 13)</th>
<th>LP/NI (n = 14)</th>
<th>NP/NI (n = 14)</th>
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<tr>
<td>Age (y)</td>
<td>56 (49–70)</td>
<td>59 (53–69)</td>
<td>58 (47–72)</td>
<td>60 (50–70)</td>
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<tr>
<td>Weight (kg)</td>
<td>71 (58.2–93.6)</td>
<td>72.7 (59.0–96.8)</td>
<td>72.7 (55.2–92.5)</td>
<td>69.2 (52.3–92.4)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.7 (1.5–1.8)</td>
<td>1.6 (1.5–1.7)</td>
<td>1.7 (1.6–1.7)</td>
<td>1.7 (1.6–1.7)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>25.9 (18.6–32.9)</td>
<td>27.9 (21.2–33.9)</td>
<td>26.5 (19.9–32.0)</td>
<td>25.3 (21.3–33.6)</td>
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</tbody>
</table>

1 All values are x; range in parentheses. LP/LI, low phytate/low isoflavone; NP/LI, normal phytate/low isoflavone; LP/NI, low phytate/normal isoflavone; NP/NI, normal phytate/normal isoflavone; α-TE, α-tocopherol equivalents; RE, retinol equivalents. There were no significant differences between the treatment groups (ANOVA).

2 Selected nutrients were assessed by using a food-frequency questionnaire.

respectively. These subjects were evenly distributed across the treatment groups. Compliance was also checked by randomly analyzing isoflavone excretion in urine before and after intervention (n = 4 per treatment). The subjects in the LP/NI and NP/NI treatment groups excreted 2239 and 29 μmol isoflavone/L, and the subjects in the LP/LI and NP/LI treatment groups excreted 1.6 and 2.8 μmol isoflavone/L, respectively. The graduate research assistant was in contact with these women on a regular basis. Fifteen of the 55 subjects reported intermittent constipation; we provided guidelines to increase fluid intake, which corrected the problem and apparently did not affect compliance.

Subject characteristics

The subjects ranged in age from 47 to 72 y. The time since menopause ranged from 1 to 20 y (x = 6.4 y). Thirteen subjects had smoked in earlier years, 6 subjects had experienced cancer (skin, n = 4; breast, n = 1; and cervical, n = 1), but all 6 were in remission, and 1 subject had 2 previous minor strokes that were not related to atherosclerotic CVD. There were no other reported cardiovascular events and no diagnoses of CVD.

Twenty-eight and 26 of the subjects reported their health to be good and excellent, respectively, whereas 1 subject reported her health to be fair. Education levels were high school (n = 16), college (n = 29), and graduate school (n = 10). Thirteen of the participants stated they had experienced iron deficiency at least once in the past as a result of malnutrition, pregnancy, menstruation, or the onset of menopause; however, only one woman had a baseline hemoglobin concentration < 12 g/dL. Thirty-six subjects (8–10/treatment) reported regular use of a multivitamin, and 2 subjects (LP/LI, n = 1; LP/NI, n = 1) reported regular use of iron supplements. Thirty-five subjects (7–11/treatment) reported they were consuming soy or soy products before the intervention, although most indicated that this consumption was irregular.

The subjects’ descriptive characteristics and daily nutrient intakes are reported in Table 1. None of the descriptive characteristics at baseline differed significantly between the treatment groups. Neither body weight nor BMI differed significantly among the treatment groups even at 6 wk (data not shown). The dietary intakes of macronutrients were within normal ranges and did not differ significantly among the treatment groups. Overall, intakes of selected antioxidants (vitamins A, C, and E) were within the recommended allowances in each treatment group. Although vitamin C intakes were higher in 2 treatments (NP/LI and LP/NI), the differences were not significant.

Oxidative stress indexes

Oxidative stress indexes before and after intervention and the mean changes for each treatment are shown in Table 2. The mean protein carbonyl concentration at baseline was very low (0.2 nmol/mg protein), and there were no significant differences among the treatment groups. Phytate treatment had a very modest (P = 0.15) and nonsignificant effect on protein carbonyl concentrations, which decreased by 6%–8% and 1%–4%, respectively, in the normal-phytate and low-phytate groups. At baseline, the PGF2α concentration in the NP/LI group was significantly (P = 0.05) different from that in the LP/LI group but not from that in the other 2 groups. Neither the phytate nor the isoflavone treatment had a significant effect on PGF2α concentrations. The reduction in PGF2α in the NP/LI group was 6%, and that in the other 3 groups was 3%–4%. The mean oxLDL concentration at baseline ranged from 66 to 81 U/L across the treatments. As was seen with PGF2α, there was a 5%–13% decline in oxLDL across the groups, but this reduction was not significantly affected by either phytate or isoflavone treatment. The reduction in oxLDL in the normal-isoﬂavone groups was 6–10 U/L, and that in the low-isoﬂavone groups was 4 U/L. No signiﬁcant phytate × isoﬂavone interaction was found for any of the above 3 oxidative stress indicators.

Blood lipid concentrations

Blood lipid values at baseline and 6 wk and the mean changes are shown in Table 2. Mean total cholesterol did not differ across
treatments at baseline, ranging from 223 to 235 mg/dL. Although both the normal- and low-isoflavone treatment groups experienced a modest decline in total cholesterol (6%–7% and 2%–4%, respectively) after 6 wk, the reductions did not differ significantly between the groups. Similarly, LDL cholesterol decreased with treatment in all groups, but the differences between low and normal treatments (phytate or isoflavones) were too small to detect significance. The reduction in LDL cholesterol was 10%–11% (14–16 mg/dL) in the normal-isoflavone and 3%–7% (4–9 mg/dL) in the low-isoflavone group. The mean baseline triacylglycerol concentration in the NP/LI group was significantly higher than that in the other treatment groups, but we found no significant effect of treatment. Similarly, HDL cholesterol did not respond to treatment. As we have noted with oxidative stress, phytate and isoflavones had no significant interactive effect on blood lipids.

Correlation of CVD risk factors

Correlations among baseline BMI, oxidative stress indexes, and blood lipid measures are shown in Table 3. The highest positive correlations ($P < 0.0001$) were observed between triacylglycerol and PGF$_{2\alpha}$, as well as between LDL cholesterol and oxLDL and between total cholesterol and oxLDL. In addition, BMI was highly correlated with triacylglycerol ($P < 0.001$), PGF$_{2\alpha}$ ($P < 0.05$), and oxLDL ($P < 0.05$). HDL cholesterol was negatively correlated with triacylglycerol ($P < 0.0001$), BMI ($P < 0.0001$), PGF$_{2\alpha}$ ($P < 0.001$), and oxLDL ($P < 0.05$).

**DISCUSSION**

The Food and Drug Administration approved the health claim that a daily intake of 25 g soy protein (27) reduces heart disease risk. In the current study, we chose to use 40 g soy protein/d to ascertain whether a higher intake would elicit beneficial effects on blood lipid profiles, as well as on oxidative stress indexes, in postmenopausal women, who are at high risk for CVD. This amount was also chosen on the basis of previous human studies that investigated health benefits of soy protein (9, 28–30). Moreover, because of phytate’s low absorption in humans, the subjects needed to consume 40 g soy protein/d to obtain enough dietary

<table>
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<td>Oxidative stress and blood lipid measures at baseline and 6 wk$^1$</td>
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<td>PC (nmol/mg)</td>
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<td>Baseline</td>
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<td>6 wk</td>
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<td>Change</td>
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<td>PGF$_{2\alpha}$ (pg/mL)</td>
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<td>oxLDL (U/L)</td>
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<td>LDL (mg/dL)</td>
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<td>HDL (mg/dL)</td>
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<td>Triacylglycerol (mg/dL)</td>
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$^1$ LP/LI, low phytate/low isoflavone; NP/LI, normal phytate/low isoflavone; LP/NI, low phytate/normal isoflavone; NP/NI, normal phytate/normal isoflavone; PC, protein carbonyl; PGF$_{2\alpha}$, 8-iso-prostaglandin-F$_{2\alpha}$; oxLDL, oxidized LDL. Mean baseline values with different superscript letters are significantly different (ANOVA).

$^2$ Baseline-adjusted differences (6 wk − baseline) were compared by using two-way analysis of covariance with respective baseline values as covariates.

$^3$ ± SD (all such values).

$^4$ Changes reflect 6 wk − baseline values.
Phytate to show beneficial effects. However, the amount of phytate provided daily from 40 g soy protein (ie, 0.64–0.78 g) was considerably lower than the amount used in an earlier human study, in which 8.8 g phytate/d was given to patients at risk of kidney stones (31).

Our results showing no significant effect of soy isoflavones on oxLDL do not agree with the results of a study by others that showed a positive correlation between reductions in oxLDL and serum daidzein, genistein, and total isoflavone concentrations after a 12-wk intervention with soy foods in postmenopausal women (5). Perhaps differences in response to treatment may depend on the menopausal status of the person at baseline and whether baseline values are taken into account in the analyses, as we have done. Women in our study were considered to have normal antioxidant status because the oxLDL concentration in only 1 woman was greater (170 U/L) than the reference range (26–117 U/L) specified by the assay kit manufacturer. However, our data indicate a strong correlation between oxLDL and blood lipids, which suggests that a response to treatment may also depend on the interaction between blood lipids and oxidative stress. Jenkins et al (10) showed that the consumption of 33 g soy protein/d for 1 mo significantly decreased oxLDL concentrations in hyperlipidemic subjects. Although 14 of 55 women in our study had LDL-cholesterol concentrations high enough that they could be classified as hyperlipidemic (LDL cholesterol >160 mg/dL; 32), the mean LDL-cholesterol concentrations were within the normal range (138–151 mg/dL). Thus, it is not surprising that no significant effect of isoflavone treatment on oxLDL concentrations was seen in these relatively normolipidemic women.

Dent et al (9) had results similar to ours, reporting no effect on circulating lipids in either normal or hyperlipidemic perimenopausal women fed isoflavone-rich soy protein for 24 wk. This lack of effect was attributed to the perimenopausal status of these subjects, whose hormonal milieu is typically erratic. Furthermore, Hsu et al (33) found that supplementing normal postmenopausal women with 150 mg isoflavones/d for 6 mo resulted in no significant change in plasma lipids. These data, similar to those for oxidative stress, suggest that the effect of isoflavones depends on the lipidemic state of each person. It has been reported that the consumption of 60 g soy protein/d for 12 wk had a more pronounced effect on blood lipids in hypercholesterolemic than in normolipidemic postmenopausal women (4). In addition, the consumption of isoflavone-rich soy food diets for 1 mo has been shown to reduce blood lipids and homocysteine concentrations in hyperlipidemic men and postmenopausal women (6).

Isoflavones in SPI had no effect on HDL cholesterol, which contradicted a previous finding of a positive association between soy isoflavone intake and HDL-cholesterol concentrations in postmenopausal women (34). At baseline, the mean triacylglycerol concentration in the NP/LI group (ie, 100–112 mg/dL) was significantly higher than that in the other groups, and yet we found no effect of treatment in these women with normal triacylglycerol concentrations. Similarly, no change in triacylglycerol concentration was shown in a 24-wk study by feeding a diet with 30 or 50 g soy protein/d to men and women (35). Hence, the CVD risk protection of SPI in normolipidemic persons may not be due to the effect of isoflavones on increasing HDL cholesterol or reducing triacylglycerol.

Phytate is considered as an antioxidant because it has been shown in vitro to have a dose-dependent quenching effect on iron-induced free radical formation (14). The modest (P < 0.15) decline we found in protein carbonyl concentrations and the nonsignificant decline in lipid oxidation indicators with phytate treatment do not support the antioxidant potential of phytate, and no data are available to suggest the degree of reduction in oxidative stress that is biologically significant. Furthermore, our results indicating the lack of lipid-lowering effect of phytate do not support the findings in rat studies (19, 20). However, Jariwalla et al (19) used in rats a cholesterol-enriched diet with a considerably higher amount of phytate than our subjects consumed. Nonetheless, the lack of effect we report may be due either to insufficient amounts of phytate in the treatment or to phytate’s poor absorption in humans (18) compared with that in rats (17).

Oxidative stress indicators and the circulating lipids (except HDL cholesterol) declined in all 4 groups (albeit not significantly), but this decline in turn made the differences between the phytate and isoflavone groups very small and, indeed, too small.
to detect significance. For example, we based our study on detecting a 15 mg/dL difference in LDL, but the actual difference between the normal- and low-isoflavone groups was only 9.5 mg/dL (baseline-adjusted difference of 6.5 mg/dL). It is possible that other components in SPI might have an additional effect on the outcome variables. Beneficial effects on lipids and antioxidant status have been shown by other components of soy protein, such as saponins (7), 7S globulin (8), and arginine (36). Thus, a single component in SPI may not necessarily be responsible for protection against CVD, but rather multiple components of SPI may be protective through different mechanisms.

Although subjects were recruited throughout the summer and fall seasons, we could not document differences among the treatments at baseline or intervention-related changes in BMI, which suggests that seasonal variations in dietary intake had no effect on BMI. Moreover, because all subjects consumed the same amount of protein during the intervention, the differences in dietary intakes between the treatment groups were not expected. However, the positive correlation of BMI with the oxidative stress markers oxLDL and PGF$_{\alpha_2}$ (Table 3) is noteworthy. Vaiankari et al. (37) found a similar correlation between BMI and oxLDL, whereas Suzuoki et al. (38) found no correlation between these 2 markers. Baseline BMI was also negatively correlated with HDL cholesterol, much as was reported in another study (39). A negative correlation between HDL cholesterol and fat mass (40) suggests unfavorable HDL-cholesterol concentrations in overweight or obese persons. Thus, reducing BMI may help to reduce oxidative stress and maintain HDL cholesterol. However, confirmation of these results will require further study of the relation between fat mass and oxidative stress.

In contrast to the studies that examined only total antioxidant status (11, 30), our study included 3 oxidative stress indicators to assess specific damage to proteins and lipids, which may be a better indication of oxidative damage. Yet, we have not shown a significant effect on these 3 indexes by SPI that contained either phytate or isoflavones. Previous studies (6, 11) had led us to believe that a 6-wk intervention was sufficiently long to note significant effect on these 3 indexes by SPI that contained either phytate or isoflavones. Previous studies (6, 11) had led us to believe that a 6-wk intervention was sufficiently long to note beneficial effect of phytate or isoflavones in this study, but future studies with higher doses of these components and a greater number of subjects, perhaps including subjects with hyperlipidemia, may provide different results.

We thank Philip Dixon, Department of Statistics at Iowa State University, for statistical advice.

DLA and MBR participated in the study design. HME and LNH collected and analyzed the data. HME wrote the first draft of the manuscript, and DLA, AGK, and MBR provided advice and consultation on the final draft. None of the authors had any personal or financial conflicts of interest.

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