Soy inclusion in the diet improves features of the metabolic syndrome: a randomized crossover study in postmenopausal women[1–3]

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ABSTRACT

Background: Little evidence exists regarding the effects of soy consumption on the metabolic syndrome in humans.

Objective: We aimed to determine the effects of soy consumption on components of the metabolic syndrome, plasma lipids, lipoproteins, insulin resistance, and glycemic control in postmenopausal women with the metabolic syndrome.

Design: This randomized crossover clinical trial was undertaken in 42 postmenopausal women with the metabolic syndrome. Participants were randomly assigned to consume a control diet (Dietary Approaches to Stop Hypertension, DASH), a soy-protein diet, or a soy-nut diet, each for 8 wk. Red meat in the DASH period was replaced by soy-protein in the soy-protein period and by soy-nut in the soy-nut period.

Results: The soy-nut regimen decreased the homeostasis model of assessment-insulin resistance score significantly compared with the soy-protein (difference in percentage change: -7.4 ± 0.8; $P < 0.01$) or control (-12.9 ± 0.9; $P < 0.01$) diets. Consumption of soy-nut also reduced fasting plasma glucose more significantly than did the soy-protein ($-5.3 \pm 0.5\%$; $P < 0.01$) or control ($-5.1 \pm 0.6\%$; $P < 0.01$) diet. The soy-nut regimen decreased LDL cholesterol more than did the soy-protein period ($-5.0 \pm 0.6\%$; $P < 0.01$) and the control ($-9.5 \pm 0.6\%$; $P < 0.01$) diet. Soy-nut consumption significantly reduced serum C-peptide concentrations compared with control diet (-8.0 ± 2.1; $P < 0.01$), but consumption of soy-protein did not.

Conclusion: Short-term soy-nut consumption improved glycemic control and lipid profiles in postmenopausal women with the metabolic syndrome. *Am J Clin Nutr* 2007;85:735–41.

INTRODUCTION

The metabolic syndrome is a clustering of metabolic abnormalities that occurs in individuals with impaired insulin sensitivity (1, 2). Existing data suggest that the incidence of the metabolic syndrome is rising at an alarming rate (3, 4). In Tehran, Iran, it has been estimated to affect >30% of adults (5), a prevalence significantly higher than that of most developed countries (6). The etiology of this syndrome is largely unknown; genetic, metabolic, and environmental factors, including diet, are thought to play a major role (7). In previous investigations, intakes of unsaturated fatty acids (8), n–3 fatty acids (9), dairy products (10), and whole grains (11) appeared to influence the prevalence of this syndrome, either positively or negatively, but little emphasis has been placed on the specific therapeutic diets that control the metabolic syndrome. In choosing a therapeutic diet, high amounts of vegetables, fruits, legumes, whole grains, low-fat dairy foods, and low amounts of saturated fat and salt have been used in previous studies (12–15). Foods that improve insulin sensitivity might also modulate the metabolic abnormalities linked with insulin resistance (16).

Many studies have reported beneficial effects of soy consumption on human health, but most of these investigations have been conducted among type 2 diabetic or hypercholesterolemic patients (16–19), or healthy subjects (20). Although some studies have reported effects of soy consumption on the metabolic syndrome in animals (21, 22), to our knowledge no reports are available regarding the effects of soy intake on features of the metabolic syndrome in humans. Soy consumption could reduce the risk of the metabolic syndrome through its beneficial components, including complex carbohydrates, unsaturated fatty acids, vegetable protein, soluble fiber, oligosaccharides, vitamins, minerals, inositol-derived substances such as lipintol and pinitol, and phytoestrogens, particularly the isoflavones genistein, diadzein, and glycitein (23–28). However, the amount and kind of these components may vary in different kinds of soy products; ie, textured soy-protein or soy-nut. We evaluated the effects of soy consumption (in the form of soy-protein and unsalted soy-nut) on features of the metabolic syndrome, including plasma lipids, lipoproteins, insulin resistance, and glycemic control, in postmenopausal women with the metabolic syndrome.

SUBJECTS AND METHODS

Participants

A total of 120 postmenopausal women were screened for inclusion in the study. The study was conducted in Tehran in 2005. Women were considered postmenopausal if menstrual periods had been absent for >1 y and follicle-stimulating hormone, serum luteinizing hormone, testosterone, and estradiol concentrations confirmed their status (29). The metabolic syndrome was defined according to Adult Treatment Panel (ATP) III guidelines (30): *1*) abdominal adiposity (waist circumference >88 cm); *2*) low concentrations of serum HDL cholesterol (<50 mg/dL); *3*) hypertriglyceridemia (≥150 mg/dL); *4*) elevated blood pressure (≥130 mm Hg systolic blood pressure and ≥85 mm Hg diastolic blood pressure); and *5*) impaired glucose homeostasis (≥110 mg/dL). To be enrolled in the study, patients had to have ≥3 of the above-mentioned criteria to be classified as having metabolic syndrome. Exclusion criteria were any secondary cause of hyperglycemia, current or previous (in the preceding 6 mo) use of estrogen therapy, treatment with insulin or oral hypoglycemic agents, untreated hypothyroidism, smoking, kidney or liver diseases, and breast malignancy or breast cancer. Finally, a total of 42 postmenopausal women who had 5 components of the metabolic syndrome and met the inclusion criteria were included in the present study. All participants provided informed written consent. The present study was approved by the research council and ethical committee of the National Nutrition and Food Technology Research Institute of Shaheed Beheshti University of Medical Sciences.

Study procedures

We used a randomized crossover design. After 3 wk of run-in on a usual diet (55% of energy from carbohydrate, 15% of energy from protein, and 30% of energy from fat), we randomly assigned women to consume the control diet (Diet A = red meat-DASH diet), DASH diet with soy-nut (Diet B = soy-nut period), or DASH diet with soy-protein (Diet C = soy-protein period); each one for 8 wk. Each patient received all 3 diets and had 2 washout periods (each washout for 4 wk) between the 3 diets. We set 6 different sequence of diet intakes (ABC, ACB, BCA, BAC, CBA, and CAB) with 2 washouts in each model; patients randomly followed one of these sequences. The randomization was conducted at the end of the run-in.

Measurements were obtained before run-in, after run-in, after each diet, and after each washout. Baseline measurements were performed at the beginning of each dietary period. The participants were free-living during the study period and they prepared their own meals. Only soy products were given to them during the different phases of the study. The participants were asked not to change their habitual physical activity level for the duration of the study. The patients recorded their physical activities for 3 days each month.

Diets

We used 3 diets. *1*) Control diet: this diet was a DASH diet. The general recommendation for macronutrient composition of the DASH diet was the following: 50–60% of energy as carbohydrate, 15–20% of energy as protein, and <30% of energy as total fat. This diet had one serving of red meat (red meat-DASH) and was rich in fruit, vegetables, whole grains, and low-fat dairy

TABLE 1
Nutrient composition of soy protein and soy nut used in the intervention[1]

Nutrients	Soy protein	Soy nut
Protein (g)	15	11.3
Fat (g)	0.3	7
Fiber (g)	10	9
Sodium (mg)	9	10
Total phytoestrogens (mg)	84	102
Glycitein (mg)	8	9
Genistein (mg)	43	53
Diadzein (mg)	33	40

[1] Amounts are per 30 g.

products and was low in saturated fat, total fat, cholesterol, refined grains, and sweets. The sodium intake was 2400 mg/d (31). Sodium intake was determined according to the Iranian Food Composition Table. We prescribed little added salt during cooking (only 1 tsp) and no table salt. *2*) Diet with soy-nut: this diet was the same as the control diet, but we replaced red meat with soy-nut. Every 30 g soy-nut was considered 1 serving of red meat (32). *3*) Diet with soy-protein: this diet was the same as the control diet, but we replaced red meat with soy-protein. Every 30 g soy-protein was considered 1 serving of red meat (32). Soy-nut was produced by Toos manufacturer in Mashhad, Iran, and soy-protein has produced by Sobhan manufacturer in Behshahr, Iran. The nutrient compositions of the soy-nut and soy-protein consumed by the study participants, based on our analysis, are shown in **Table 1**. Soy-composition data was determined by biochemical analysis. No significant differences were found between the results of the analysis and those that were calculated with the food-composition tables. The amount of soy isoflavones consumed was 84 mg/d (8 mg glycitein, 43 mg genistein, and 33 mg diadzein) during the soy-protein period and 102 mg/d (9 mg glycitein, 53 mg genistein, and 40 mg diadzein) during the soy-nut period. The patients received education in how they could prepare their meals with soy-protein. A nutritionist explained to the participants how to wash the soy-protein products, soak them for 30 min, and then cook them in boiling water with turmeric, lemon juice, and tomato paste for 10 min.

The calorie requirements of each participant were calculated individually on the basis of equations suggested by the Institute of Medicine, Food and Nutrition Board (33). Weight loss was not a goal, and patients were not on a weight-reducing diet.

The participants were visited every 2 wk for 45–60 min per patient. They were in touch with the study nutritionist daily by phone. For measuring food intake, 3-d diet records were used at baseline and during the intervention for each month. Every participant had to bring her 3-d diet record and physical activity records every month when they were reviewed by the study staff; these records were used for checking diet compliance. Each food and beverage in the diet records was then coded according to the prescribed protocol and analyzed for content of energy and the other nutrients by using NUTRITIONIST III software (version 7.0; N-Squared Computing, Salem, OR), which was designed for Iranian foods. Physical activity records were activities in MET-h/d.

The study nutritionist explained the benefits of each diet for patients. Patients also received education in using an exchange list of foods and in writing food diaries. The diets were individually prescribed by using a calorie count system, and an exchange

list was given to each patient for exchanging the food items and calculating calories. A 7-d menu cycle at 6-calorie levels (1800, 1900, 2000, 2100, 2200, and 2300 calories) was developed for each diet. Subjects were free-living and they provided their own meals.

To maximize treatment fidelity, group discussions, in which the food items that should be eaten were emphasized, were performed monthly. Patients also received education on the methods of preparing soy-protein according to their menu and were encouraged to follow their diets. The investigators randomly took part in the counseling sessions and controlled the messages that nutritionist was giving to each group. Patient adherence was assessed by analyzing the 3-d food record diaries monthly and by the attendance at the meetings and monthly visits.

Measurements

Body weight was measured while the subjects were minimally clothed without shoes by using digital scales and recorded to the nearest 0.1 kg. Height was measured in a standing position, without shoes, by using a tape meter while the shoulders were in a normal state. Waist circumference (WC) was measured to the nearest 0.1 cm at the narrowest level over light clothing, with the use of an unstretched tape measure, without any pressure to body surface. Blood pressure was measured twice after the participants sat for 15 min.

Twelve-hour fasting blood samples were collected into tubes containing 0.1% EDTA and were centrifuged at 4 °C and 500 × g for 10 min to separate the plasma. Blood glucose was measured on the day of blood collection by an enzymatic colorimetric method by using glucose oxidase. Serum total cholesterol and triacylglycerol concentration were measured with commercially available enzymatic reagents (Pars Azmoon, Tehran, Iran) adapted to a Selectra autoanalyzer (Vital Scientific, Spankeren, Netherlands). HDL cholesterol was measured after precipitation of the apolipoprotein B–containing lipoproteins with phosphotungstic acids (34). Inter-and intraassay CVs were both <5% for all measurements. Serum insulin concentrations were measured by using an enzyme-linked immunosorbent assay (ELISA; Diagnostic Biochem Canada Inc, Montreal, Canada). The CV, which was calculated by using duplicate study samples, was <10%; the analytic sensitivity was 2 μU/mL. Insulin resistance was calculated by using the homeostasis model of assessment-insulin resistance (HOMA-IR) (35). Serum luteinizing hormone and follicle-stimulating hormone were measured by radioimmunoassay; testosterone and estradiol were measured by ELISA. C-peptide was also measured by ELISA (Diagnostic Biochem Canada Inc) (36). Plasma phytoestrogens were measured by HPLC according to Franke et al (37, 38). Serum concentrations of apolipoprotein B 100 (apoB-100) and apoA-I were determined by ELISA (Diagnostic Biochem Canada Inc). We used standard and control solutions for all measurements, all laboratory measurements were standardized, and standard curves were plotted for all of them. Soy-derived phytoestrogens were measured by HPLC to determine the patients' adherence (38).

Statistical analysis

We used 3 methods of analyses to be confident that the results were similar. First, we used general linear models to compare the means of the metabolic variables at the end of the soy-nut, soy-protein, and control phases. Then, we used Tukey's test as a post-hoc test for comparing the end of treatment values of each group with each other group. The percentage change for each variable was also calculated by the formula [$(E - B)/B$] × 100, where E is the end of treatment value and B is the baseline value. We compared groups using the percentage change in both repeated-measures analysis of variance and paired t test analyses. We also determined the mean percentage change differences, which were derived by calculating the differences in percentage change for each variable in pair-wise group comparisons. This parameter gives the most direct estimate of the difference in response in comparing groups. Interactions between soy intake and weight were not significant for any of the metabolic features. Period and treatment order effects were tested by using the appropriate general linear models.

For skewed variables (apoA-I and fasting insulin concentration), we used log-transformed values in all analyses and reported the geometric means. Pearson correlation coefficients were used to evaluate the relation between soy-derived phytoestrogens intake (calculated from self reported soy intake in 3-d diet records) and plasma phytoestrogen concentrations. All results were considered significant if the two-tailed P value was < 0.05. Statistical analysis was performed by using SPSS for WINDOWS version 13.0 (SPSS, Chicago, IL) and SAS version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

All participants (42 postmenopausal women with the metabolic syndrome) completed the entire crossover study. Calculated nutrient content and food group servings of 3-d diet records according to the patients' report is shown in **Table 2**. Both the soy-nut and soy-protein diets were well tolerated. Only one person complained of feeling bloated during the soy-protein period. The activity level of the subjects remained the same across all study periods [$\bar{x}$ (±SE) physical activity in control period: 2.38 ± 0.19 MET-h/d; in soy-protein period: 2.50 ± 0.26 MET-h/d; and in soy-nut period: 2.44 ± 0.26; $P = 0.10$).

The baseline characteristics of the study participants and the effects of the 3 diets on components of the metabolic syndrome, lipid profiles, and glycemic control are shown in **Table 3**. No significant differences in the baseline characteristics of the study participants were seen. Significant differences between the end values of control diet, soy-protein regimen, and soy-nut consumption for glycemic control indexes were seen. A post-hoc comparison of the diets showed a significant difference between the control and soy-protein diets with regard to LDL cholesterol, total cholesterol, fasting insulin, HOMA-IR, and apoB-100. Similar results were seen for fasting plasma glucose (FPG), LDL cholesterol, total cholesterol, fasting insulin, HOMA-IR, C-peptide, and apoB-100 in a comparison of the soy-nut and control diets. No significant effects of period or treatment order were observed. Compared with the control diet, plasma phytoestrogen increased significantly after the soy-nut regimen (percentage change: 64%; $P < 0.01$) and after the soy-protein diet (percentage change: 48%; $P < 0.01$).

DISCUSSION

We found that soy as a replacement for red meat in a DASH eating plan had beneficial effects on features of the metabolic syndrome, soy-nut being more effective than soy-protein. We

TABLE 2
Dietary intakes of the participants by intervention period[1]

Daily dietary intakes	Control[2] (n = 42)	Soy-protein[3] (n = 42)	Soy nut[4] (n = 42)	P[5]	Washout[6] (n = 42)
Soy protein (g)	0	30	0	—	0
Soy nut (g)	0	0	30	—	0
Nutrients					
Energy (kcal)	2055 ± 24[7]	2039 ± 23	2049 ± 21	0.62	2078 ± 20
Protein (% of energy)	17 ± 0.4	17 ± 0.3	17 ± 0.4	0.71	15 ± 0.4
Total fat (% of energy)	28 ± 0.6[a]	25 ± 0.7[b]	29 ± 0.5[a]	<0.05	31 ± 0.5
Saturated fat (% of energy)	7 ± 0.6	5 ± 0.6	5 ± 0.5	0.61	14 ± 0.5
Polyunsaturated fat (% of energy)	8 ± 0.6[a]	8 ± 0.5[a]	11 ± 0.6[b]	<0.05	7 ± 0.6
Monounsaturated fat (% of energy)	10 ± 0.5	10 ± 0.6	10 ± 0.6	0.73	9 ± 0.5
Cholesterol (mg)	189 ± 10	173 ± 8	175 ± 8	0.51	300 ± 7
Carbohydrate (% of energy)	55 ± 1	58 ± 2	57 ± 1	0.79	54 ± 2
Fiber (g)	25 ± 1[a]	32 ± 2[b]	33 ± 2[b]	<0.05	11 ± 2
Potassium (mg)	4395 ± 143	4416 ± 176	4426 ± 144	0.31	1546 ± 133
Calcium (mg)	1209 ± 71	1219 ± 77	1227 ± 88	0.49	750 ± 85
Food groups (servings)					
Fruit	5.5 ± 2	5.5 ± 3	5.5 ± 3	0.69	2.4 ± 3
Vegetable	5.0 ± 3	5.0 ± 3	5.0 ± 3	0.71	3.0 ± 2
Total grains	8.5 ± 0.2	8.5 ± 0.1	8.5 ± 0.1	0.77	11.0 ± 0.1
Whole grains	3.5 ± 0.1	3.4 ± 0.1	3.4 ± 0.1	0.73	1.0 ± 0.1
Low-fat dairy	2.5 ± 0.1	2.5 ± 0.1	2.5 ± 0.1	0.77	0.5 ± 0.1
Regular-fat dairy	0.5 ± 0.1	0.5 ± 0.1	0.50 ± 0.1	0.73	0.5 ± 0.1
Red meat	1.0 ± 0.1	0	0	0.21	1.6 ± 0.1
Poultry and fish	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.79	0.5 ± 0.1
Fat and oils	3.5 ± 0.1	3.5 ± 0.1	3.5 ± 0.1	0.78	7.9 ± 0.1
Sweets	2.5 ± 0.1	2.5 ± 0.1	2.5 ± 0.1	0.77	5.8 ± 0.1

[1] Means with different superscript letters are significantly different, $P < 0.05$ (Tukey's test).

[2] This diet provided one serving of red meat and was rich in fruit, vegetables, whole grains, and low-fat dairy products and was low in saturated fat, total fat, cholesterol, refined grains, and sweets. The sodium intake was 2400 mg/d [Dietary Approach to Stop Hypertension (DASH) pattern].

[3] This diet was the same as the control diet (DASH diet), but we replaced red meat with soy-protein. Every 30 g soy-protein was considered 1 serving of red meat.

[4] This diet was the same as the control diet (DASH diet), but we replaced red meat with soy-nut. Every 30 g soy-nut was considered 1 serving of red meat.

[5] Differences between the 3 trial periods (repeated-measures ANOVA).

[6] In this period, patients consumed the same diet they consumed before the study.

[7] $\bar{x}$ ± SEM (all such values).

also found that soy consumption improved glycemic control and cardiovascular disease risk factors, at least in the short term, in postmenopausal women with the metabolic syndrome. Although some studies have assessed the effects of soy intake on the metabolic syndrome in animals (21, 22), to our knowledge this is the first study in which such an effect has been evaluated in humans.

Both soy-nut and soy-protein had beneficial effects on serum concentrations of total cholesterol, LDL cholesterol, triacylglycerol, and apoB-100. Such results have also been seen among subjects with different types of diseases (39, 40). Beneficial effects of soy consumption on blood lipids were the most consistently reported findings. In a meta-analysis of 38 controlled clinical trials, Anderson et al (18) showed significant reductions in total cholesterol (9%), LDL cholesterol (13%), and triacylglycerols (11%) with the consumption, on average, of 47 g soy-protein/d. Two recent meta-analyses concluded that the isoflavone content of soy may be responsible for its lipid-lowering effect (41, 42). Controversy still exists in the field regarding the relative contribution of potential mechanisms of action of soy-protein, isoflavones, and other soy components on blood lipids and lipoproteins.

Besides abnormalities in lipid metabolism, elevated blood pressure is another feature of the metabolic syndrome. Most studies showed no effect on blood pressure with consumption of soy-protein containing isoflavones (25, 43, 44). In the current study, neither soy-protein nor soy-nut consumption had significant effects on systolic or diastolic blood pressures compared with the control diet. It seems that the blood pressure-lowering effect of the overall DASH diet in the 3 periods of the study may be responsible for the changes in blood pressure during the soy-nut or soy-protein periods.

We also observed that soy consumption improved glycemic control. HOMA-IR decreased significantly at the end of the soy-nut diet compared with the soy-protein and control diets. This finding may support a direct pharmacologic effect of soy constituents. The hypothesis that soy isoflavones modulate glycemic control is not proven yet. We assumed that a higher level of isoflavones in combination with polyunsaturated fatty acids, pinitol, and protein might have beneficial effects on glycemic control.

In most studies, the phytoestrogens, amino acids, and fatty acid content of soy-nuts were suggested to be responsible for its favorable effects (16, 45–47). In the present study, soy-nut intake had more beneficial effects on metabolic risks than did soy-protein intake. The combination of higher amounts of unsaturated fat and isoflavones in soy-nut (48) may synergistically provide an optimum benefit. Polyunsaturated fatty acids and lecithin, which are the most common fats in soy-nut, have well-documented favorable effects on the metabolic syndrome risks (8, 9, 49). A 20% difference in protein content from soy-nut and

TABLE 3
Features of the metabolic syndrome at baseline and after 8 wk of intervention in postmenopausal women[1]

Metabolic variables	Control[2]	Soy protein[3]	Soy nut[4]	Overall P[5]
Weight[6]				
Baseline	70.0 ± 0.9	70.0 ± 0.8	70.1 ± 0.8	0.98
End of trial	70.1 ± 0.9	70.7 ± 0.9	70.4 ± 0.8	0.57
Waist (cm)[6]				
Baseline	91.5 ± 0.7	91.4 ± 0.7	91.2 ± 0.8	0.60
End of trial	91.9 ± 0.8	91.5 ± 0.9	91.0 ± 1.0	0.19
SBP (mm Hg)[6]				
Baseline	136 ± 0.7	136 ± 0.7	136 ± 0.7	0.97
End of trial	131 ± 1.2	132 ± 0.7	131 ± 1.0	0.26
DBP (mm Hg)[6]				
Baseline	87 ± 0.1	87 ± 0.2	87 ± 0.2	0.16
End of trial	84.0 ± 0.5	85.0 ± 0.5	85.0 ± 0.5	0.85
FPG (mg/dL)[6]				
Baseline	120 ± 0.6	119 ± 0.6	118 ± 0.5	0.25
End of trial	112 ± 1.0[a]	111 ± 0.9[a]	103 ± 0.5[b]	<0.01
Triacylglycerols (mg/dL)[6]				
Baseline	219 ± 1.3	220 ± 1.1	218 ± 1.2	0.79
End of trial	213 ± 1.2	210 ± 1.7	212 ± 1.7	0.30
HDL cholesterol (mg/dL)[6]				
Baseline	31.0 ± 0.4	32.0 ± 0.4	32.0 ± 0.4	0.91
End of trial	33.3 ± 0.7	34.0 ± 0.7	33.3 ± 0.4	0.51
LDL cholesterol (mg/dL)[6]				
Baseline	143 ± 0.8	142 ± 0.6	137 ± 3.2	0.08
End of trial	134 ± 3.3[a]	127 ± 2.4[b]	118 ± 3.0[c]	<0.01
Total cholesterol (mg/dL)[6]				
Baseline	238 ± 1.0	239 ± 0.9	238 ± 0.9	0.37
End of trial	228 ± 0.9[a]	217 ± 0.5[b]	209 ± 0.6[c]	<0.01
Fasting insulin (μIU/mL)[7]				
Baseline	14.3 ± 0.09	14.2 ± 0.09	14.1 ± 0.09	0.73
End of trial	14.2 ± 0.09[a]	13.3 ± 0.04[b]	12.8 ± 0.09[c]	<0.01
HOMA-IR[6]				
Baseline	4.19 ± 0.03	4.20 ± 0.04	4.16 ± 0.06	0.65
End of trial	3.9 ± 0.04[a]	3.6 ± 0.03[b]	3.3 ± 0.03[c]	<0.01
C-peptide (ng/mL)[6]				
Baseline	2.09 ± 0.04	2.1 ± 0.03	2.1 ± 0.02	0.79
End of trial	1.92 ± 0.04[a]	1.86 ± 0.03[a]	1.77 ± 0.04[b]	<0.05
Apolipoprotein AI (g/L)[7]				
Baseline	1.33 ± 0.02	1.30 ± 0.02	1.32 ± 0.01	0.51
End of trial	1.32 ± 0.01	1.30 ± 0.01	1.31 ± 0.01	0.35
Apolipoprotein B100 (g/L)[6]				
Baseline	1.33 ± 0.02	1.28 ± 0.01	1.25 ± 0.01	0.61
End of trial	1.08 ± 0.03[a]	0.98 ± 0.03[b]	0.92 ± 0.04[b]	<0.01

[1] $n = 42$. SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting blood glucose; HOMA-IR, homeostasis model of assessment-insulin resistance. Means with different superscript letters are significantly different, $P < 0.05$ (Tukey's test). No significant period effect or interaction of period effect and treatment effect were observed for any of the variables.

[2] This diet provided one serving of red meat and was rich in fruit, vegetables, whole grains, and low-fat dairy products and was low in saturated fat, total fat, cholesterol, refined grains, and sweets. The sodium intake was 2400 mg/d [Dietary Approach to Stop Hypertension (DASH) pattern].

[3] This diet was the same as the control diet (DASH diet), but we replaced red meat with soy-protein. Every 30 g soy-protein was considered 1 serving of red meat.

[4] This diet was the same as the control diet (DASH diet), but we replaced red meat with soy-nut. Every 30 g soy-nut was considered 1 serving of red meat.

[5] Comparison of the 3 diet periods (repeated-measures ANOVA).

[6] Values are $\bar{x} \pm$ SE.

[7] Values are geometric $\bar{x} \pm$ SE.

soy-protein was observed, but studies have not focused on the effect of the amount of protein per se.

The amount of soy isoflavones consumed was 84 mg/d during the soy-protein period and 102 mg/d during the soy-nut period. This is lower than the doses used in previous effective trials (16, 40), but it is higher than the isoflavone content of diets commonly consumed in some Asian countries where soy is a staple food (20–80 mg/d) (47). In some situations, excessive soy-protein intake could do more harm than good; some evidence suggests that genistein can stimulate estrogen-receptor positive breast cancers to grow (50). We excluded any patients with breast malignancy or breast cancer from the present study, and we used textured soy-protein or soy-nut, which were food sources of isoflavones, rather than pure isoflavones or soy-protein pills.

The washout period of 4 wk between 2 treatment phases in our study seemed adequate, because the values of metabolic risk factors returned to baseline levels before the start of the next trial. A strength of the present study was the good compliance of our subjects, which was confirmed by the phytoesterogen concentrations in each period of the study. We did not evaluate the effects of soy-protein or soy-nut according to estrogen receptor genotype in our participants; in some studies, responses to isoflavone consumption have varied according to estrogen receptor genotype (51–53). Also, further studies may be warranted to assess the effect of soy consumption on features of the metabolic syndrome while taking the "equol producer" or "equol nonproducer" status into account (51–53). In conclusion, our findings suggest that short-term soy-nut consumption may reduce insulin resistance and improve glycemic control and lipid concentrations in postmenopausal women with the metabolic syndrome. ❦

REFERENCES

1. Lau DC, Yan H, Dhillon B. Metabolic syndrome: a marker of patients at high cardiovascular risk. Can J Cardiol 2006;22:85B–90B.
2. Das UN. Is metabolic syndrome X an inflammatory condition? Exp Biol Med 2002;227:989–97.
3. Cankurtaran M, Halil M, Yavuz BB, Dagli N, Oyan B, Ariogul S. Prevalence and correlates of metabolic syndrome (MS) in older adults. Arch Gerondol Geriatr 2006;42:35–45.
4. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. Diabetes Care 2004;27:2444–9.
5. Azizi F, Salehi P, Etemadi A, Zahedi-Asl S. Prevalence of metabolic syndrome in an urban population: Tehran Lipid and Glucose Study. Diabetes Res Clin Pract 2003;61:29–37.
6. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356–9.
7. Hollenberg NK. Genetic versus environmental etiology of the metabolic syndrome among male and female twins. Curr Hypertens Rep 2002;4:178.
8. Vessby B. Dietary fat and insulin action in humans. Br J Nutr 2000;83:591–6.
9. Connor W. Importance of n–3 fatty acids in health and disease. Am J Clin Nutr 2000;47:419–25.
10. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi F. Dairy consumption is favorably associated with metabolic syndrom in Tehranian adults. Am J Clin Nutr 2005;82:523–30.
11. Esmaillzadeh A, Mirmiran P, Azizi F. Whole-grain intake and the prevalence of hypertriglyceridemic waist phenotype in Tehranian adults. Am J Clin Nutr 2005;81:55–63.
12. Esposito K, Marfella R, Citotola M, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trail. JAMA 2004;292:1440–6.
13. Riccardi G, Rivellese AA. Dietary treatment of the metabolic syndrome–the optimal diet. Br J Nutr 2000;83:S143–8.
14. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi T, Azizi F. Beneficial effects of a Dietary Approach to Stop Hypertension (DASH) eating plan on features of metabolic syndrome. Diabetes Care 2005;28:2823–31.
15. Klimes I, Sebokova E. The importance of diet therapy in the prevention and treatment of manifestations of metabolic syndrome X. Vnitr Lek 1995;41:136–40 (abstract).
16. Jayagopal V, Albertazzi P, Kilpatrick ES, et al. Beneficial effects of soy phytoestrogen intake in postmenopausal women with type 2 diabetes. Diabetes Care 2002;25:1709–14.
17. Azadbakht L, Shakerhosseini R, Atabak S, Jamshidian M, Mehrabi Y,

18. Esmaill-Zadeh A. Beneficiary effect of dietary soy protein on lowering plasma levels of lipid and improving kidney function in type II diabetes with nephropathy. Eur J Clin Nutr 2003;57:1292–4.
18. Anderson JW, Johnstone BM, Cook-Newell ME. Meta-analysis of the effects of soy protein intake on serum lipids. N Engl J Med 1995;333:276–82.
19. Anderson JW, Blake JE, Turner J, Smith BM. Effects of soy protein on renal function and proteinuria in patients with type 2 diabetes. Am J Clin Nutr 1998;68(suppl):1347S–53S.
20. McVeigh BL, Dillingham BL, Lampe JW, Duncan AM. Effect of soy protein varying in isoflavone content on serum lipids in healthy young men. Am J Clin Nutr 2006;83:244–51.
21. Davis J, Iqbal MJ, Steinle J, et al. Soy protein influences the development of the metabolic syndrome in male obese ZDFxSHHF rats. Horm Metab Res 2005;37:316–25.
22. Dyrskog SE, Jeppesen PB, Colombo M, Abudula R, Hermansen K. Preventive effects of a soy-based diet supplemented with stevioside on the development of the metabolic syndrome and type 2 diabetes in Zucker diabetic fatty rats. Metabolism 2005;54:1181–8.
23. Wangen KE, Duncan AM, Xu X, Kurzer MS. Soy isoflavones improve plasma lipids in normocholesterolemic and mildly hypercholesterolemic postmenopausal women. Am J Clin Nutr 2001;73:225–31.
24. Merz-Demlow BE, Duncan AM, Wangen KE, et al. Soy isoflavones improve plasma lipids in normocholesterolemic, premenopausal women. Am J Clin Nutr 2000;1:1462–9.
25. Jenkins DJ, Kendall CW, Jackson CJ, et al. Effects of high- and low-isoflavone soyfoods on blood lipids, oxidized LDL, homocysteine, and blood pressure in hyperlipidemic men and women. Am J Clin Nutr 2002;76:365–72.
26. Kim JI, Kim JC, Kang MJ, Lee MS, Kim JJ, Cha IJ. Effects of pinitol isolated from soybeans on glycaemic control and cardiovascular risk factors in Korean patients with type II diabetes mellitus: a randomized controlled study. Eur J Clin Nutr 2005;59:456–8.
27. Crisafulli A, Altavilla D, Marini H, et al. Effects of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women. Menopause 2005;12:186–92.
28. von Post-Skagegard M, Vessby B, Karlstrom B. Glucose and insulin responses in healthy women after intake of composite meals containing cod-, milk-, and soy protein. Eur J Clin Nutr 2006 Feb 15. Epub ahead of print.
29. Rozenberg S, Bosson D, Peretz A, Caufriez A, Robyn C. Serum levels of gonadotrophins and steroid hormones in the post-menopause and later life. Maturitas 1988;10:215–24.
30. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
31. Karanja NM, Obarzanek E, Lin PH, et al. Descriptive characteristics of the dietary patterns used in the Dietary Approaches to Stop Hypertension trial. J Am Diet Assoc 1999;99:S60–8.
32. Mahan LK, Escott-stump S. Krauses food nutrition and diet therapy. 11th ed. Philadelphia, PA: WB Saunders, 2004:1267–8.
33. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intake for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: The National Academies Press, 2002.
34. Burstein M, Scholnick HR, Morfin R. Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. J Lipid Res 1970;11:583–95.
35. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
36. Welborn TA, Garcia-Webb P, Bonser AM. Basal C-peptide in the discrimination of type I from type II diabetes. Diabetes Care 1981;4:616–9.
37. Franke AA, Custer LJ, Tanaka Y. Isoflavones in human breast milk and other biological fluids. Am J Clin Nutr 1998;8(suppl):1466S–73S.
38. Franke AA, Custer LJ, Wang W, Shi CY. HPLC analysis of isoflavonoids and other phenolic agents from foods and from human fluids. Proc Soc Exp Biol Med 1998;217:263–73.

39. Hoie LH, Graubaum HJ, Harde A, Gruenwald J, Wernecke KD. Lipid-lowering effect of 2 dosages of a soy protein supplement in hypercholesterolemia. Adv Ther 2005;22:175–86.

40. Hermansen K, Hansen B, Jacobsen R, et al. Effects of soy supplementation on blood lipids and arterial function in hypercholesterolaemic subjects. Eur J Clin Nutr 2005;59:843–50.

41. Zhan S, Ho SC. Meta-analysis of the effects of soy protein containing isoflavones on the lipid profile. Am J Clin Nutr 2005;81:397–408.

42. Zhuo XG, Melby MK, Watanabe S. Soy isoflavone intake lowers serum LDL cholesterol: a meta-analysis of 8 randomized controlled trials in humans. J Nutr 2004;134:2395–400.

43. Hodgson JM, Puddey IB, Beilin LJ, et al. Effects of isoflavonoids on blood pressure in subjects with high-normal ambulatory blood pressure levels: a randomized controlled trial. Am J Hypertens 1999;12:47–53.

44. Hermansen K, Sondergaard M, Hoie L, Carstensen M, Brock B. Beneficial effects of a soy-based dietary supplement on lipid levels and cardiovascular risk markers in type 2 diabetic subjects. Diabetes Care 2001; 24:228–33.

45. Kris-Etherton PM, West SG. Soy protein with or without isoflavones: in search of a cardioprotective mechanism of action. Am J Clin Nutr 2005; 81:5–6.

46. Zhang X, Shu XO, Gao YT, et al. Soy food consumption is associated with lower risk of coronary heart disease in Chinese women. J Nutr 2003;133:2874–8.

47. Barnes S, Peterson TG, Coward L. Rationale for the use of genistein-containing soy matrices in chemoprevention trials for breast and prostate cancer. J Cell Biochem 1995(suppl);22:181-7.

48. Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M, American Heart Association Nutrition Committee. Soy protein, isoflavones, and cardiovascular health: an American Heart Association Science Advisory for professionals from the Nutrition Committee. Circulation 2006;113:1034–44.

49. Vergroes AJ. Dietary fat and cardiovascular disease: possible modes of action of linoleic acid. Proc Nutr sac 1972;31:323–9.

50. Willett WC, Skerrett PK. Eat, drink and be healthy. The Harvard Medical School Guide to healthy eating. New York, NY: Simon and Schuster Inc, 2005:130–1.

51. Setchell KD, Brown NM, Lydeking-Olsen E. The clinical importance of the metabolite equol-a clue to the effectiveness of soy and its isoflavon. J Nutr 2002;132:3577–84.

52. Kreijkamp-Kaspers S, Kok L, Bots ML, Grobbee DE, Lampe JW, van der Schouw YT. Randomized controlled trial of the effects of soy protein containing isoflavones on vascular function in postmenopausal women. Am J Clin Nutr 2005;81:189–95.

53. Hall WL, Vafeiadou K, Hallund J, et al. Soy-isoflavone-enriched foods and markers of lipid and glucose metabolism in postmenopausal women: interactions with genotype and equol production. Am J Clin Nutr 2006; 83:592–600.