

Beneficial Effects of Soy Phytoestrogen Intake in Postmenopausal Women With Type 2 Diabetes

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OBJECTIVE — Phytoestrogen consumption has been shown to reduce risk factors for cardiovascular disease. Type 2 diabetes confers an adverse cardiovascular risk profile particularly in women after menopause. The aim of this study was to determine whether a dietary supplement with soy protein and isoflavones affected insulin resistance, glycemic control, and cardiovascular risk markers in postmenopausal women with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 32 postmenopausal women with diet-controlled type 2 diabetes completed a randomized, double blind, cross-over trial of dietary supplementation with phytoestrogens (soy protein 30 g/day, isoflavones 132 mg/day) versus placebo (cellulose 30 g/day) for 12 weeks, separated by a 2-week washout period.

RESULTS — Compliance with the dietary supplementation was >90% for both treatment phases. When compared with the mean percentage change from baseline seen after 12 weeks of placebo, phytoestrogen supplementation demonstrated significantly lower mean values for fasting insulin (mean \pm SD $8.09 \pm 21.9\%$, $P = 0.006$), insulin resistance ($6.47 \pm 27.7\%$, $P = 0.003$), HbA_{1c} ($0.64 \pm 3.19\%$, $P = 0.048$), total cholesterol ($4.07 \pm 8.13\%$, $P = 0.004$), LDL cholesterol ($7.09 \pm 12.7\%$, $P = 0.001$), cholesterol/HDL cholesterol ratio ($3.89 \pm 11.7\%$, $P = 0.015$), and free thyroxine ($2.50 \pm 8.47\%$, $P = 0.004$). No significant change occurred in HDL cholesterol, triglycerides, weight, blood pressure, creatinine, dehydroepiandrosterone sulfate, androstenedione, and the hypothalamic-pituitary-ovarian axis hormones.

CONCLUSIONS — These results show that dietary supplementation with soy phytoestrogens favorably alters insulin resistance, glycemic control, and serum lipoproteins in postmenopausal women with type 2 diabetes, thereby improving their cardiovascular risk profile.

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Cardiovascular diseases (CVDs), especially coronary heart disease and cerebrovascular disease, are the leading causes of death in women (1). Type 2 diabetes increases the risk of death from CVD by two- to fourfold (2), and women with diabetes are four times more likely to die from CVD than men (3). Post-

menopausal estrogen depletion (4) and increased insulin resistance (5) may contribute to the high risk of accelerated CVD in women with type 2 diabetes.

Epidemiological data suggest that in Japanese-Americans in Seattle, WA, the prevalence of type 2 diabetes is four times that in Japanese in Tokyo (6,7). Despite

very similar degrees of hyperglycemia, the Japanese-Americans with type 2 diabetes showed significantly higher levels of plasma insulin after a 75-g oral glucose tolerance test (OGTT) than Japanese with diabetes (6,8), and BMI correlated with insulin levels only for the Japanese-American men (8). This observation suggested a greater degree of insulin resistance among the Japanese-Americans and that factors other than BMI were responsible for the difference in plasma insulin levels between the two groups (9). Soy is a staple in the diet of the Japanese population, and consumption of soy has been shown to have an inverse relationship with mortality from CVD. These legumes contain complex carbohydrates, vegetable protein, soluble fibers, oligosaccharides, minerals, and phytoestrogens, particularly the isoflavones genistein and daidzein, that may be beneficial in the management of diabetes (10). In vitro studies have shown isoflavones to have antidiabetic properties such as inhibiting intestinal brush border uptake of glucose, having α -glucosidase inhibitor actions, and also demonstrating tyrosine kinase inhibitory properties (11–13). Diets containing soy protein rich in isoflavones have been shown to improve insulin resistance in ovariectomized cynomolgus monkeys (14) and to reduce insulin levels in healthy postmenopausal women (15,16). Previous studies on the effects of using a soy-based diet in individuals with diabetes (17–20) have been performed on a heterogeneous population using differing soy preparations, and there are few data focusing specifically on the effect of soy phytoestrogens on postmenopausal women with type 2 diabetes. This double-blind, cross-over, placebo-controlled study was undertaken to determine the effect of dietary supplementation with 30 g of soy proteins containing 132 mg of phytoestrogen on indexes of glycemic control, insulin resistance, and cardiovascular risk in postmenopausal women with diet-controlled type 2 diabetes.

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Abbreviations: CVD, cardiovascular disease; HOMA-IR, insulin resistance measured by Homeostasis Model Assessment; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

Subjects

A total of 40 postmenopausal women with type 2 diabetes were screened for inclusion in the study. Women were considered postmenopausal if menstrual periods had been absent for >1 year and follicle-stimulating hormone level was elevated. Women with a fasting venous plasma glucose concentration >7.0 mmol/l or a 2-h postprandial concentration >11.1 mmol/l after a 75-g OGTT were recruited for the study. Exclusion criteria included any secondary cause of hyperglycemia, current or previous (in the preceding 6 months) use of estrogen therapy, treatment with insulin or oral hypoglycemic agents, untreated hypothyroidism, history of drug or alcohol abuse, and history of breast or uterine cancer.

A total of 33 subjects were eligible for inclusion in the study: age (mean \pm SD) 62.5 ± 6.77 years, BMI (kg/m^2) 32.2 ± 5.0 , time from diagnosis of type 2 diabetes 2.6 ± 2.7 years. All subjects received advice on a diabetes diet from a registered dietitian before randomization. At the randomization visit, all subjects were advised to maintain their diabetes diet and level of physical activity throughout the study and were also instructed by interview and through an information leaflet to minimize ingestion of soy and soy-based products for the entire duration of the study. This advice was reinforced at all subsequent visits. One subject was withdrawn from the study after 5 months following the diagnosis of a myocardial infarction, and these data were excluded because there was less than the minimum of two paired data for analysis. None of the patients had complications of diabetes. One subject was started on 10 mg/day of simvastatin during the placebo arm of the trial. Her data were omitted from the lipid analysis. In three subjects, antihypertensive medication was altered during the course of the study. In one subject, bendroflumethiazide 2.5 mg/day was added to her medication regimen during the phytoestrogen treatment phase. In another subject, amlodipine 10 mg/day was changed to felodipine 10 mg/day during the placebo phase. In the third subject, the dose of atenolol was increased from 50 to 100 mg/day during the phytoestrogen treatment phase and doxazosin 2 mg/day changed to diltiazem 180 mg/day

during the placebo phase. The blood pressure readings for these women were excluded from the analysis.

Study design

A randomized, double-blind, placebo-controlled cross over study was undertaken. A total of 17 women were initially assigned to placebo and 16 women were assigned to soy for 12 weeks. After a 2-week washout period, the participants received the alternative treatment for an additional 12 weeks. The soy preparation (Essential Nutrition, Brough, U.K.) contained 30 g of isolated soy protein with 132 mg of isoflavones. The proportions of genistein, daidzein, and glycitein averaged 53, 37, and 10%, respectively, with 95% of the isoflavones present as their glucoside conjugates. The product was completely devoid of soluble fiber and each sachet provided 243 kcal. The control supplement consisted of an identical sachet containing 30 g of pure microcrystalline cellulose (Emcocel; Penwest Pharmaceuticals, Patterson, NY) of no significant calorific content. Patients were instructed to maintain an isocaloric diet. The randomization was performed by the supplying company with a random number generating table. A copy of the randomization code was kept secure by the hospital pharmacy and was available to the investigator only in emergency. All subjects gave their written informed consent and the protocol was approved by the Hull and East Riding Local Research Ethics Committee.

Study measurements

After an overnight fast, weight and blood pressure were measured and blood samples were collected at screening, baseline, and then every 6 weeks for each phase of the trial. Compliance checks and dietary reinforcement were performed at each visit after randomization. Compliance was monitored based on counting returned medication. Fasting venous blood samples were collected into serum gel, EDTA, and fluoride oxalate tubes. Samples were separated by centrifugation at 2000g for 15 min at 4°C, and the aliquots stored at -20°C within 1 h of collection. Sitting blood pressure was measured after 10 min of rest using an automated device (NPB-3900; Nellcor Puritan Bennett, Pleasanton, CA). Total cholesterol, triglyceride, and HDL cholesterol levels were measured enzymatically using a

Synchron LX20 analyzer (Beckman-Coulter, High Wycombe, U.K.). LDL cholesterol was measured using the Friedewald equation. Plasma glucose was measured using a Synchron LX20 analyzer (Beckman-Coulter), and serum insulin was assayed using a competitive chemiluminescent immunoassay performed using the DPC Immulite 2000 analyzer (Euro/DPC, Llanberis, U.K.). The coefficient of variation of this method was 8%, calculated using duplicate study samples. The analytical sensitivity was 2 $\mu\text{U}/\text{ml}$, and there was no stated cross-reactivity with proinsulin. The insulin resistance was calculated using the Homeostasis Model Assessment method ($\text{HOMA-IR} = (\text{Insulin} \times \text{glucose})/22.5$) (21). Serum luteinizing hormone, follicle-stimulating hormone, testosterone, estradiol, triiodothyronine, free thyroxine, and thyroid-stimulating hormone were measured on an Architect analyzer (Abbott Laboratories, Maidenhead, U.K.). Sex hormone-binding globulin was measured using the DPC Immulite 2000 analyzer (Euro/DPC) and HbA_{1c} was measured on a Diabetes Control and Complications Trial (DCCT)-aligned HA-8140 analyzer (A. Menarini Diagnostics, Berkshire, U.K.) using the manufacturer's recommended protocol. Routine biochemistry and liver function tests were performed at each visit using standard methods.

Statistical analysis and sample size calculation

Results from subjects who completed both treatment phases were included in the analysis. Mean percentage changes obtained at the end of the soy treatment phase were compared with the results at the end of the placebo phase, using the paired Student's *t* test for biochemical data and the Wilcoxon's signed-rank test for clinical observations. The Wilcoxon's signed-rank test was applied to biochemical data that violated the assumptions of normality when tested using the Kolmogorov-Smirnov test. The period and the carryover effect that may have occurred from the cross-over design were tested using the appropriate Student's *t* test.

Using two-sided 5% significance level, a sample of 33 patients per group was needed, assuming a 10% drop-out rate. This gave the study 80% power to detect a 12% difference in LDL between treatments (assuming a common SD of

16) and an 18% difference in fasting insulin between treatments, given a common standard deviation of 25 (22).

The results were considered significant if the two-tailed *P* value was <0.05. nQuery version 4 was used for sample size determination. Statistical analysis was performed using SPSS for Windows NT version 9.0 (SPSS, Chicago, IL)

RESULTS— A total of 32 postmenopausal women with diet-controlled diabetes completed the entire cross-over study. No period effect or carryover effects were identified for any of the observed results. Both the soy preparation and placebo were well tolerated, and the overall compliance was 93% during the soy phase and 91% during the placebo phase. Side effects were similar during both treatment phases and were predominantly gastrointestinal. Heartburn developed in three subjects during the study, two in the soy phase and one while on placebo. Six subjects complained of feeling bloated on both soy and placebo. One subject had self-limiting mouth ulcers during the placebo phase and one subject had a myocardial infarction during the soy phase and was withdrawn from the study.

Effects on glycemic control

Serum insulin, HOMA-IR, and HbA_{1c} decreased significantly during the soy phase of the trial and returned to baseline during the placebo phase. This was the same for both group A, which received placebo for the first 12 weeks and then soy for an additional 12 weeks, and group B, which received soy first and then placebo (Fig. 1). Compared with baseline at the start of the treatment phase, 12 weeks of soy supplementation reduced fasting insulin by 8.09% (14.5 ± 6.58 vs. 16.7 ± 8.13 μ IU/ml), HOMA-IR by 6.47% (4.94 ± 2.94 vs. 5.54 ± 3.40 units), and HbA_{1c} by 0.64% (6.78 ± 0.61 vs. 6.83 ± 0.64 %). Compared with the change seen during the placebo phase, insulin, HOMA-IR, and HbA_{1c} were significantly lower with soy (*P* = 0.006, 0.003, and 0.048, respectively). The mean fasting venous glucose did not change with either soy or placebo treatment (Table 1).

Effects on lipids

Compared with baseline at the start of the treatment phase, total cholesterol decreased with soy by 4.07% (5.52 ± 0.92

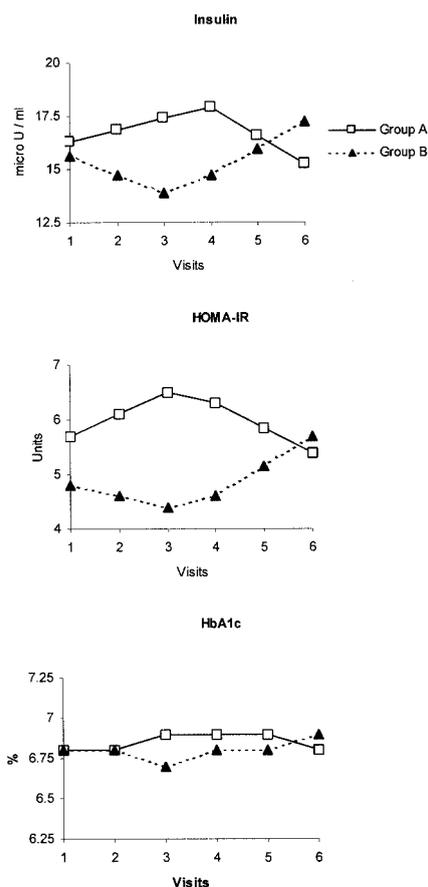


Figure 1—A schematic representation of the changes seen in the indexes of glycemic control over both placebo and phytoestrogen during the two treatment phases. Group A represents the study subjects who received placebo first followed by phytoestrogens, and group B represents the study subjects who received phytoestrogen first followed by placebo. The periods between visits 3 and 4 represent the washout period.

vs. 5.78 ± 1.02 mmol/l) and was significantly lower compared with placebo (*P* = 0.004). LDL cholesterol decreased by 7.09% and the total cholesterol-to-HDL cholesterol ratio decreased by 3.89% after the soy phase compared with baseline (3.35 ± 0.85 vs. 3.63 ± 0.91 and 4.43 ± 1.26 vs. 4.64 ± 1.37 mmol/l, respectively). These changes were also significantly lower with soy than with placebo treatment (*P* = 0.001 and 0.015, respectively). No changes were seen in either HDL or triglyceride levels during and between the two treatment phases (Table 1).

Other effects

There was no difference in either weight or blood pressure between treatment

phases (Table 1). There were no changes in routine biochemistry, including renal function (as measured by serum creatinine), and liver function tests. Serum free thyroxine decreased by 2.5% during the soy phase compared with baseline, and this difference was significant when compared with placebo (*P* = 0.004). However, soy did not affect either serum thyroid-stimulating hormone or triiodothyronine. No effects were seen for estradiol, follicle-stimulating hormone, luteinizing hormone, sex hormone-binding globulin, testosterone, dehydroepiandrosterone sulfate, and androstenedione (Table 2).

CONCLUSIONS— The phytoestrogen preparation used in this study reduced insulin resistance, improved glycemic control, and reduced total cholesterol primarily through a reduction in LDL cholesterol, leading to an improvement in the ratio of total cholesterol to HDL cholesterol. These data show that soy supplementation has a therapeutic effect for both glycemic control and for cardiovascular risk markers, at least in the short term, for postmenopausal women with type 2 diabetes. Based on these data, high soy intake may explain the epidemiological observation of lower insulin levels in Japanese compared with Japanese-Americans (6–9). The therapeutic potential of soy for diabetes was first suggested in 1910 (23). The few small studies of the effect of soy on glycemic control in diabetes have shown inconsistent results that have been primarily attributed to the soluble fiber content of soybean preparation (18–20). In a small study of 14 women and 6 men, 6 weeks of treatment with soy protein (50 g/day), isoflavones (165 mg/day), and cotyledon fiber (20 g/day) compared with placebo (casein 50 g/day and cellulose 20 g/day) showed an improvement in lipid parameters but no difference in glucose, insulin, or HbA_{1c} (17). A modest improvement in blood glucose attributed to fiber intake from soybeans has been reported previously in individuals with type 2 diabetes, in both acute and some longer studies (18,19), although this was not found by others (20). In vitro studies suggested several mechanisms for a direct pharmacological action of soy on glycemic control, including a tyrosine kinase inhibitory action, changes in insulin receptor numbers and affinity, intracellular phosphorylation, and alterations in glucose transport

Table 1—Subject characteristics at the start of and after 12 weeks of treatment

	Soy			Placebo			Treatment difference (P value)
	Baseline (n = 32)	12 weeks (n = 32)	% Change	Baseline (n = 32)	12 weeks (n = 32)	% Change	
Weight (kg)	81.2 ± 13.1	81.7 ± 12.7	+0.77 ± 1.81	81.6 ± 13.1	81.7 ± 13.1	+0.19 ± 1.91	0.369
Fasting glucose (mmol/l)	7.29 ± 1.49	7.37 ± 1.63	+1.14 ± 10.8	7.23 ± 1.37	7.57 ± 1.93	+4.31 ± 12.7	0.340
HbA _{1c} (%)	6.83 ± 0.64	6.78 ± 0.61	-0.64 ± 3.19	6.82 ± 0.66	6.88 ± 0.59	+1.08 ± 3.90	0.048
Fasting insulin (μU/ml)	16.7 ± 8.13	14.5 ± 6.58	-8.09 ± 21.9	15.5 ± 7.26	17.3 ± 10.7	+9.92 ± 29.1	0.006
HOMA-IR	5.54 ± 3.40	4.94 ± 2.94	-6.47 ± 27.7	5.14 ± 3.04	6.09 ± 4.82	+14.7 ± 32.1	0.003
Cholesterol (mmol/l), n = 31*	5.78 ± 1.02	5.52 ± 0.92	-4.07 ± 8.13	5.62 ± 1.05	5.75 ± 1.07	+2.83 ± 8.70	0.004
LDL cholesterol (mmol/l), n = 31	3.63 ± 0.91	3.35 ± 0.85	-7.09 ± 12.7	3.47 ± 1.06	3.62 ± 1.07	+5.35 ± 15.2	0.001
HDL cholesterol (mmol/l) n = 31*	1.32 ± 0.33	1.32 ± 0.34	+0.69 ± 10.1	1.30 ± 0.30	1.31 ± 0.30	+1.29 ± 8.78	0.787
Cholesterol/HDL ratio, n = 31*	4.64 ± 1.37	4.43 ± 1.26	-3.89 ± 11.7	4.54 ± 1.35	4.61 ± 1.35	+2.23 ± 12.1	0.015
Triglycerides (mmol/l), n = 31*	2.20 ± 1.21	2.01 ± 1.03	-1.58 ± 31.2	2.18 ± 1.62	2.19 ± 1.51	+2.81 ± 24.9	0.624
Systolic blood pressure, n = 29†	146.9 ± 18.8	144.7 ± 14.6	-0.76 ± 9.63	147.2 ± 15.2	149.5 ± 17.2	+1.65 ± 7.46	0.325
Diastolic blood pressure, n = 29†	81.5 ± 8.78	80.7 ± 8.78	-0.41 ± 10.4	82.6 ± 7.8	82.2 ± 8.73	-0.23 ± 8.83	0.991

Data are means ± SD. All serum results are obtained from fasting variables. % change, percent difference compared with baseline. P value was calculated using Wilcoxon's signed-rank test. *One subject was removed from the analysis of the lipid effects because they were started on a statin drug during the trial period; †three subjects were removed from the analysis of the effects on blood pressure because their medications were changed during the trial period.

(11,13,24,25). In this study, the improvement in insulin concentration and insulin resistance noted after the active treatment phase was not only significant when compared with the change seen after the placebo phase but also when compared with baseline ($P = 0.005$ and 0.032 , respectively). The 8% decrease in fasting insulin and the corresponding decrease in insulin resistance without a change in weight seems to support a direct pharmacological effect of soy in these patients, although information on the effect of soy on body fat distribution is required to be more certain of this. Nevertheless, the changes seen here are comparable to the reported insulin-lowering effect of some oral hypo-

glycemic agents (26). This action of soy isoflavones in reducing insulin resistance without a change in weight seems, therefore, to be independent of the action of soy fiber that enhances satiation and thus would cause an improvement in insulin resistance secondary to weight loss (10). It seems that the washout period between the two treatment phases was adequate, because the insulin levels and insulin resistance in the group receiving the active medication first returned to baseline before the start of the placebo phase.

Some of the metabolic effects of soy seem to be specific to women and influenced by menopausal status. A worsening of endothelial function in men but not in

women was reported after soy treatment (27), and a primate study showed that soy improved vascular reactivity in female but not in male monkeys (28). Whether a sex effect is evident for glycemic control and insulin resistance is unclear. However, an improvement in insulin sensitivity and glucose effectiveness occurred in ovariectomized healthy female cynomolgus monkeys given a soy-based diet but not in male diabetic monkeys in whom only the lipid parameters were improved (14,29). Determination of response to soy by menopausal status is suggested by studies showing that soy protein (containing 132 mg of isoflavones per day) decreased serum insulin significantly in healthy post-

Table 2—Effects of soy supplementation versus placebo on plasma hormone concentrations and creatinine

	Soy			Placebo			Treatment difference (P value)
	Baseline (n = 32)	12 weeks (n = 32)	% Change	Baseline (n = 32)	12 weeks (n = 32)	% Change	
LH (IU/l)	28.4 ± 14.8	25.9 ± 12.6	-4.28 ± 20.6	28.8 ± 14.5	28.3 ± 13.8	+0.30 ± 21.8	0.866
FSH (IU/l)	48.7 ± 18.7	44.6 ± 16.1	-5.23 ± 16.8	49.2 ± 18.6	47.9 ± 18.3	-2.29 ± 13.1	0.443
Catradial (pmol/l)	103.7 ± 51.2	137.4 ± 60.4	+42.7 ± 55.6	117.6 ± 58.1	140.0 ± 78.4	+29.2 ± 76.8	0.079
Testosterone (nmol/L), n = 31*	2.16 ± 0.85	1.77 ± 0.77	-15.8 ± 32.8	2.19 ± 0.84	1.90 ± 0.97	-11.4 ± 35.9	0.970
SHBG (nmol/l)	39.3 ± 16.4	36.4 ± 14.7	-4.98 ± 16.9	39.1 ± 17.1	36.0 ± 16.0	-6.88 ± 14.9	0.985
Androstenedione (nmol/l)	4.25 ± 2.25	3.97 ± 1.60	+3.65 ± 36.3	4.73 ± 3.59	4.08 ± 1.88	+8.31 ± 52.3	0.722
DHEAS (μmol/l)	2.09 ± 1.17	2.01 ± 1.03	-0.35 ± 21.3	2.02 ± 1.04	2.07 ± 1.28	+0.40 ± 22.5	0.889
Creatinine (μmol/l)	77.6 ± 15.8	75.3 ± 15.9	-2.53 ± 9.45	76.2 ± 16.1	78.2 ± 18.6	+2.95 ± 11.7	0.072
TSH (mU/l)	2.15 ± 1.08	2.27 ± 1.35	+9.32 ± 36.4	2.18 ± 1.08	2.26 ± 1.18	+9.48 ± 46.1	0.739
Free thyroxine (pmol/l)	14.1 ± 1.53	13.7 ± 1.65	-2.50 ± 8.47	13.8 ± 1.75	14.4 ± 1.87	+4.26 ± 9.22	0.004
Free triiodothyronine (pmol/l)	3.18 ± 0.46	3.23 ± 0.50	+2.55 ± 15.3	3.26 ± 0.63	3.29 ± 0.58	+3.69 ± 25.7	0.970

Data are means ± SD. P value was calculated using Wilcoxon's signed-rank test. *One patient was removed because the testosterone result was an extreme outlier (>3 SD from the mean of the group). % Change, percent difference compared with baseline; LH, luteinizing hormone; FSH, follicle-stimulating hormone; SHBG, sex hormone binding globulin; DHEAS, dehydroepiandrosterone sulfate; TSH, thyroid-stimulating hormone.

menopausal women (15) but not in healthy premenopausal women (30). To circumvent the possible confounding effects of sex and menopausal status, the current study was designed to include an all-female postmenopausal population. Antihypertensive medication is known to affect carbohydrate metabolism. In three women, blood pressure medication was changed during the study period. However, excluding these subjects from the analysis of the indexes of carbohydrate metabolism did not significantly alter the result.

The most consistently reported beneficial effect of soy has been on lipids, and a meta-analysis of 38 controlled human clinical trials using on average 47 g of soy protein daily showed significant reductions in total cholesterol (9%), LDL cholesterol (13%), and triglycerides (11%) (22). In the present study, we observed significant improvements in total cholesterol, LDL cholesterol, and cholesterol-to-HDL ratio but no change in triglyceride levels. In accord with others (22), HDL cholesterol was not affected by soy treatment. The mechanism of the lipid-lowering effect of soy is unclear. It has been suggested that soy may induce a hyperthyroid state (31), but our data did not support this because the mean free thyroxine levels decreased significantly with soy and serum thyroid-stimulating hormone and free triiodothyronine levels were unchanged. Obesity is a known important variable in carbohydrate and lipid metabolism, and it is important to determine whether the effect of phytoestrogens is influenced by the degree of obesity. In this study, however, only two subjects had BMI <25 kg/m²; therefore, no meaningful comparison could be made between the lean and obese groups. However, exclusion of these two lean subjects from the analysis did not significantly alter the results.

In this study, the soy preparation used was a combination of soy protein and isoflavones. In previous in vitro studies assessing the beneficial effect of soy in diabetes (11–13), isoflavones have been shown to act as α -glucosidase inhibitors, to inhibit intestinal brush border uptake of glucose, and to have tyrosine kinase inhibitory properties. Furthermore, the benefit of soy protein enriched with isoflavones ('whole' soy protein) on indexes of carbohydrate metabolism has also been previously proven in animal

studies (14) and in healthy postmenopausal women (15,16). It remains unclear which of these two components of soy are primarily responsible for the benefits seen or indeed whether both need to act synergistically for optimum benefit. The quantity of isoflavones needed to achieve a therapeutic benefit also remains unclear. The dose of isoflavones (132 mg/day) used in this study was based on the dose previously shown to reduce insulin levels in healthy postmenopausal women. This dose is higher than the isoflavone content in diets commonly consumed in some Asian countries (20–80 mg/day), where soy is a staple (32). Currently, foods such as bread enriched with soy isoflavones are available and can be used to supplement other natural sources. However, before definite dietary recommendations can be suggested, further information is needed from studies assessing the effects of lower doses of isoflavones on carbohydrate metabolism.

In summary, these data show that short-term dietary phytoestrogen supplementation reduces insulin resistance and improves glycemic control in postmenopausal women with type 2 diabetes, while also reducing their cardiovascular risk by lowering LDL cholesterol. Studies of longer duration are needed to determine whether these effects are sustained and have a beneficial effect on reducing cardiovascular events.

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