Effects of Isoflavone Dietary Supplementation on Cardiovascular Risk Factors in Type 2 Diabetes

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A diet supplemented with soy protein and isoflavones has been shown to reduce cardiovascular risk factors in postmenopausal women with type 2 diabetes. However, it remains unclear which component is responsible for these effects. Our aim was to determine whether the addition of isoflavones alone modifies cardiovascular disease risk markers in this group of patients. Cardiovascular disease (CVD) is the leading cause of mortality in women in developed countries (1), and women with diabetes are four times more likely to die from CVD than men (2). Among other factors, postmenopausal estrogen depletion, greater insulin resistance, and dyslipidemia (3,4) may contribute to high risk of accelerated CVD.

Modification of lifestyle is important to reduce CVD risk factors and delay progression of type 2 diabetes–associated complications. In particular, the addition of oral supplements, such as soy products, as part of a healthy diet has attracted recent interest because of their beneficial effects on lipid profiles (5–10). However, scant information is available on the effects of soy in individuals with type 2 diabetes (11–13), who are at higher risk due to hyperlipidemia, lower HDL levels, and abnormalities in LDL/lipoprotein composition (14). It also remains unclear whether a beneficial effect can be attributed to the soy protein or isoflavones.

We have shown that soy protein combined with isoflavones can improve glycemic control, insulin resistance, and lipids in patients with type 2 diabetes (11). Therefore, our aim was to determine if this effect was due to the isoflavone component alone.

RESEARCH DESIGN AND METHODS

— This was a randomized, double-blind, placebo-controlled, crossover study with a 4-week washout period separating the placebo and active phases (12 weeks each). Subjects provided informed consent. Randomization was performed using a random number generator.

Thirty-two Caucasian, postmenopausal women with diet-controlled type 2 diabetes (according to World Health Organization criteria) (15) and amenorrhoa (for >1 year) were recruited. Exclusion criteria were breast/uterine cancer; uncontrolled hypothyroidism; and treatment with oral hypoglycemic agents, insulin, estrogens, or statins initiated <4 months before the trial.

Baseline characteristics are included in Table 1. Six subjects withdrew from the study: one required a cholecystectomy and one a coronary angioplasty, one had an acute attack of polymyalgia rheumatica requiring steroids, and three were unable to comply with study requirements.

Intervention

The soy preparation (Essential Nutrition) contained 132 mg isoflavones (53% genistein, 37% daidzein, and 10% glycitein). It was devoid of soluble fiber. The placebo was an identical tablet of microcrystalline cellulose. Compliance was monitored by counting returned medication.

Study measurements

Venous blood samples were collected at each visit after a 12-h overnight fast. A1C, glucose, and lipid levels were measured using standard methods. LDL cholesterol was calculated using the Friedewald equation and insulin resistance using the homeostasis model assessment of insulin resistance (HOMA-IR) method (16).

Statistical analysis

Mean percentage changes obtained at the end of isoflavone treatment were compared with those at the end of the placebo phase, using the paired Student's *t* test if they followed a Gaussian distribution or the Wilcoxon's signed-rank test if those changes violated the assumption of normality when tested using the Kolmogorov-Smirnov test (C-reactive protein and HOMA-IR data). The period effect (calculated by comparing the mean difference between placebo and isoflavone treatment in the group starting on placebo with that in the group starting on isoflavones) and the carryover effect (comparing baseline values for each treatment group) were tested using Student's *t* test. The results were considered statistically significant if the two-tailed *P* value was <0.05. Statistical analysis was performed using SPSS (version 15). *P* values are included in Table 1.

RESULTS

— A total of 26 patients completed the study. No period or carryover effects were detected. Both study preparations were well tolerated, with >90% compliance.

Effects on glycemic control and other effects

There were no significant differences detected in glucose, A1C, HOMA-IR, total

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Abbreviations: CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance.

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

Table 1—*Subject characteristics and effects on CVD risk at the start of the trial and after 3 months of treatment*

	Placebo			Isoflavones			*P* for between-treatment difference	*P* for period effect	*P* for crossover effect
	Baseline	3 months	Percent change between baseline and 3 months	Baseline	3 months	Percent change between baseline and 3 months			
BMI (kg/m^2)	31 ± 6.4	30.7 ± 5.5	0.01 (−0.55 to 0.59)	30.7 ± 5.5	30.7 ± 5.5	0.02 (−0.69 to 0.75)	0.97	0.1	0.7
Blood pressure (mmHg)									
Systolic	133 ± 15	137 ± 16	4.26 (−1.28 to 9.8)	130 ± 16	129 ± 12	0.69 (−3.44 to 4.8)	0.35	0.5	0.9
Diastolic	75 ± 10	76 ± 8	2.79 (−2.99 to 8.57)	73 ± 9	74 ± 9	−0.24 (−4.23 to 3.76)	0.38	0.5	0.7
A1C (%)	6.7 ± 0.6	6.8 ± 0.7	1.00 (−0.20 to 2.2)	6.7 ± 0.7	6.8 ± 0.6	1.56 (−0.43 to 3.5)	0.58	0.5	0.2
Plasma glucose (mmol/l)	7.0 ± 1.4	6.9 ± 1.3	−0.34 (−3.6 to 2.9)	6.9 ± 1.3	6.8 ± 1.2	−1.6 (−4.3 to 1.13)	0.59	0.1	0.1
Insulin (μU/ml)	14.1 ± 10	13 ± 6.9	−0.39 (−12 to 11.2)	12.8 ± 8.1	14.1 ± 9.2	−13.4 (−27.3 to 0.38)	0.15	0.4	0.5
HOMA-IR	4.6 ± 4.5	4.5 ± 2.5	−4.49 (−15.58 to 6.6)	4.03 ± 3.3	4.5 ± 3.8	−15.95 (−31.1 to 0.77)	0.24	0.5	0.7
Cholesterol (mmol/l)									
Total	5.4 ± 1	5.4 ± 0.9	2.14 (−7.54 to 3.25)	5.4 ± 1	5.5 ± 0.9	2.01 (−6.4 to 2.4)	0.96	0.3	0.9
LDL	3.4 ± 0.9	3.4 ± 0.8	3.6 (−10.5 to 3.1)	3.4 ± 0.8	3.5 ± 0.9	3.85 (−9.9 to 2.2)	0.97	0.2	0.7
HDL	1.2 ± 0.3	1.2 ± 0.3	0.37 (−3.69 to 4.4)	1.2 ± 0.3	1.2 ± 0.3	0.16 (−3.4 to 3.6)	0.93	0.8	0.4
Triglycerides (mmol/l)	1.8 ± 0.8	1.7 ± 0.7	−4.16 (−16.2 to −7.9)	1.9 ± 0.9	1.8 ± 0.9	−1.19 (−13,3 to 10.9)	0.74	0.8	0.2
CRP (mg/l)	5.1 ± 6.7	6.4 ± 10.1	24.4 (−46.5 to 2.21)	5.4 ± 8	6.2 ± 8	44 (−43.5 to 133)	0.40	0.3	0.4

Data are means ± SD or means (95% CI). The percentages of change in each group were compared to obtain the *P* values for the between-treatment difference. CRP, C-reactive protein.

cholesterol, triglycerides, or HDL and LDL cholesterol levels between isoflavone and placebo phases. Likewise, no significant differences were seen in BMI, blood pressure, or C-reactive protein between treatment and placebo phases.

CONCLUSIONS — This study showed that soy isoflavones alone do not confer significant cardiovascular protection or positive effects on glycemic control in this group of patients. This is in accord with studies with red clover isoflavones in diabetes that observed no change of plasma lipoproteins or glycated hemoglobin, although basal endothelial function (17) and arterial compliance (18) did alter. However, it is possible that effects mediated by the isoflavones are too modest to be detected over the 3-month study period.

Epidemiological studies (19,20) have indicated that there is no significant association between the standard western dietary intake of isoflavones (0.369 – 0.770 mg/day) and the reduction of cardiovascular events or lipid levels in different cohorts of postmenopausal women over prolonged periods of time (4–6 years). Our subjects received >150 times this amount, yet no significant changes were observed over a 3-month period. The dose of isoflavones given was the same we used with 30 g soy protein, which reduced these cardiovascular and glycemic parameters within the same time frame (11). In addition, supplementation with isoflavones alone (40–150 mg/day) in subjects without diabetes showed that there was no change in lipid profile in peri/postmenopausal women, both healthy and mildly hypercholesterolemic (18,21,22).

Conversely, isolated soy protein has been shown to reduce total cholesterol (9.3%), LDL cholesterol (12.9%), and triglycerides (10.5%) (23). The FDA recommends that 25 g soy protein/day may reduce CVD (24), since beneficial effects have also been observed with different combinations of soy protein and isoflavones in healthy or mildly hypercholesterolemic postmenopausal/perimenopausal women (9,10,25) and in men/postmenopausal women with type 2 diabetes (11,12).

In conclusion, isoflavones alone did not alter CVD markers over a 3-month period. This suggests that either the soy protein component alone or a synergistic effect between the protein with the isoflavones may be responsible for any CVD changes.

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