

## The Hypoglycemic Effects of Soy Isoflavones on Postmenopausal Women

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### ABSTRACT

**Objectives:** Soy isoflavones have many effects similar to those of estrogen and have become popular among postmenopausal women as an alternative for hormone replacement therapy (HRT). The purpose of this study was to determine the effects of soy isoflavones on glucose, insulin, and lipid profiles in postmenopausal Taiwanese women.

**Methods:** We conducted a randomized, double-blind, active placebo-controlled clinical trial to compare the effects of isoflavones with estrogen replacement therapy (ERT) on blood glucose, insulin, and lipid profiles in postmenopausal Taiwanese women. Thirty postmenopausal Taiwanese women were randomly assigned to two groups, and each received treatment for 6 months. The isoflavone group received 100 mg isoflavone soft capsules, 300 mg calcium, and a blank vitamin capsule per day. The estrogen active control group received 0.625 mg conjugated estrogen, 300 mg calcium, and blank isoflavone soft capsules per day. We measured baseline levels of fasting blood sugar, insulin, lipid profiles, and isoflavone concentrations prior to the study and repeated the same measurements every 3 months for a total duration of 6 months.

**Results:** Two-way ANOVA revealed that fasting glucose ( $p < 0.001$ ) and insulin ( $p < 0.005$ ) levels were significantly affected by estrogen and isoflavone treatments after 6 months. For the isoflavone group, the average blood genistein concentration was 6–10 times higher than those of the estrogen group. Within the same periods, the fasting blood glucose was reduced to 83% and 85% of the baseline levels, and insulin was reduced to 56% and 67% of the baseline levels, respectively, in the estrogen and isoflavone groups.

**Conclusions:** Soy isoflavones (100 mg) and 0.625 mg conjugated estrogen equally lower fasting blood glucose and insulin levels in postmenopausal women.

### INTRODUCTION

**P**HYTOESTROGENS ARE NATURALLY OCCURRING substances and are classified into isoflavones, coumestans, and lignans. Isoflavones are chemically and structurally similar to estradiol ( $E_2$ ), but

the physiological effect is  $10^2$ – $10^5$  less than that of  $E_2$ .<sup>1</sup> Small-scale studies have demonstrated that isoflavones can relieve menopausal symptoms, lower total cholesterol (TCHO) and low-density lipoprotein (LDL), prevent osteoporosis, and concomitantly lower the rate of high-risk mammo-

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graphic parenchymal patterns.<sup>1-4</sup> Among the various effects of isoflavones, the role of LDL reduction seems to be well documented; however, other metabolic effects, such as blood glucose control, are rarely investigated.

As unopposed estrogen can improve insulin resistance and hyperinsulinemia,<sup>5</sup> we hypothesize that isoflavones can cause the same effect.

## MATERIALS AND METHODS

### *Participants*

Thirty postmenopausal women participated in the study through the department of family medicine outpatient clinic in April 2002. The inclusion criteria were aged 48–75-years; postmenopausal without menstrual cycle for at least 1 year, which was documented by serum E<sub>2</sub>, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) levels; body mass index (BMI) >18.5 kg/m<sup>2</sup> and <30 kg/m<sup>2</sup>; Hb A1C <10%; and willing to comply with the protocol and sign the written informed consent. The exclusion criteria were vegetarian; undiagnosed vaginal bleeding; significant or pathological endometrial hyperplasia; IUD user; neurological diseases; known cardiovascular, cerebrovascular, or peripheral vascular disorders; uncontrolled hypertension with blood pressure >180/100 mm Hg; uncontrolled hypothyroidism; any renal disease with serum creatinine >1.5 mg/dl; abnormal liver function, with serum alanine aminotransferase (SALT) and serum alanine aminotransaminase (SAST) value >2-fold upper limits; mentally retarded; alcoholic; smoker; on hypoglycemic agents; on lipid-lowering agent or taking hormone replacement treatment (HRT) or SERM or phytoestrogens in the 3 months before the study; and past history of malignancy.

### *Study design*

Our study was a randomized, double-blind, active placebo-controlled human clinical trial. It lasted for 6 months. All participants were randomly assigned to one of two groups. The randomization procedure was based on a random number table that had an allocation ratio and was performed by the study assistant, who was also blinded. The isoflavone group was given 25-mg isoflavone soft capsules (4 pills per day), a blank vitamin capsule, and 300 mg calcium per day. The

estrogen active control group was given blank isoflavone soft capsules (4 pills per day), 0.625 mg conjugated equine estrogen (CEE), and 300 mg calcium per day. Fasting blood samples were drawn from all the participants before initiation of the study, and baseline levels of glucose, insulin, TCHO, LDL cholesterol (LDL-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and genistein were measured.

During the study, all subjects visited the outpatient clinic and received their monthly quota of medications on schedule every month. Body height and weight were measured at each visit. Blood samples were collected every 3 months, and measurements of glucose, insulin, TG, TCHO, LDL-C, HDL-C, and genistein were repeated. Subjects were advised not to eat food rich in isoflavones, such as soybean. They were instructed to report any problems and side effects associated with the medication. All subjects provided written informed consent.

### *Supplements*

Isoflavone soft capsules with the ingredients originally from Novasoy (Archer Daniels Midland, Decatur, IL) were provided by Multipower Enterprise Corp. (Taipei, Taiwan). Each capsule contained evening primrose oil, daidzein, and genistein (w/w ratio 1:1:3) in conjugated form, with an equivalent of 25 mg isoflavones. The genistein and daidzein content was verified using high-performance liquid chromatography (HPLC) according to the method of Thomas et al.,<sup>6</sup> with some modifications. All capsules were stored at ambient temperature after manufacture. The estrogen we used was 0.625 mg CEE (Premarin; Sheng-Da Pharmaceutical, Taipei, Taiwan), manufactured in Taiwan.

### *Blood analyses*

Serum TG, TCHO, and LDL-C measurements were performed in the department of laboratory medicine at National Taiwan University Hospital, using enzymatic assays and Vitros 950 Chemistry Analyzer (Johnson & Johnson, New Brunswick, NJ). Serum HDL-C was calculated according to the formula:

$$\text{HDL (mmol/L)} = \text{TCHO} - \left( \frac{\text{TG}}{2.2} \right) - \text{LDL-C}$$

Serum glucose and insulin measurements were performed in Nan Chang Medical Laboratory

Center (Taipei, Taiwan), using commercial reagents and the Hitachi 7070 automatic analyzer and Roche-ELESCYS 2010 for enzymatic assay and immunoassay, respectively.

Plasma genistein was extracted and quantified using HPLC according to the method of Thomas et al.,<sup>6</sup> with some modifications.

### Statistical analysis

Descriptive data are presented as means  $\pm$  standard deviation (SD). Statistical analysis was performed with PC SAS for Windows software (version 8.2, Cary, NC). The difference in baseline characteristics was assessed using Student's *t* test. The main effects of treatment and time on lipid profile and glucose, insulin, and genistein concentrations were assessed by two-way ANOVA. Differences among treatment and time groups were assessed by Duncan's multiple range test after controlling the baseline glucose and LDL-C levels using forward multiple regression analysis. A *p* value  $< 0.05$  was considered statistically significant.

## RESULTS

### Participants

There were 30 subjects enrolled in the study and 28, completed the study, 17 (94%) in the isoflavone group and 11 (91%) in the estrogen group. One subject withdrew from the study because of abdominal pain, and one subject discontinued because of vaginal bleeding. The baseline characteristics are shown in Table 1. The subjects in the isoflavone group were slightly older, shorter, and lighter than those in the estrogen replacement group, although the differences were not significant. The fluctuation of BMI

in both groups was also not significant during the study period.

### Blood genistein

The baseline level of blood genistein averaged 0.48 and 0.46  $\mu\text{mol/L}$  for the estrogen and the isoflavone groups, respectively, and there was no significant difference between the two groups. Treatment significantly affected the blood genistein concentration ( $p = 0.031$ ), and the isoflavone group had significantly higher levels than the estrogen group after 3 and 6 months of intervention (Table 2). For the estrogen group, the average blood genistein concentration decreased to 0.11  $\mu\text{mol/L}$  after 3 months and to 0.07  $\mu\text{mol/L}$  at 6 months. For the isoflavone group, the average blood genistein concentration increased to 0.74  $\mu\text{mol/L}$  after 3 months and to 0.85  $\mu\text{mol/L}$  at 6 months.

### Glucose, insulin, and lipid profiles

For the estrogen group, the average glucose concentration was  $118 \pm 46$  mg/dl at baseline, which decreased markedly to  $94 \pm 20$  mg/dl after 3 months and to  $92 \pm 21$  mg/dl at 6 months. For the isoflavone group, the average glucose concentration was  $102 \pm 18$  mg/dl at baseline, which decreased to  $90 \pm 24$  mg/dl at 3 months and markedly to  $81 \pm 25$  mg/dl at 6 months. The duration of treatment significantly affected the glucose concentration ( $p = 0.001$ ) in both groups. For the estrogen group, the insulin level averaged  $11 \pm 9$   $\mu\text{U/ml}$  at baseline and decreased to  $6 \pm 7$  and  $6 \pm 11$   $\mu\text{U/ml}$  at 3 and 6 months, respectively. For the isoflavone group, the insulin level was  $12 \pm 12$   $\mu\text{U/ml}$  at baseline, which decreased significantly to  $4 \pm 3$   $\mu\text{U/ml}$  at 3 months and to  $5 \pm 8$   $\mu\text{U/ml}$  at 6 months. The duration of treatment significantly affected the insulin levels ( $p =$

TABLE 1. BASELINE CHARACTERISTICS OF POSTMENOPAUSAL WOMEN GIVEN EITHER ESTROGEN OR ISOFLAVONES FOR 6 MONTHS<sup>a</sup>

Treatment group	Estrogen group (n = 11)	Soy isoflavone group (n = 17)
Age, years	58.1 $\pm$ 6.0	60.9 $\pm$ 8.9
Height, meters	1.57 $\pm$ 0.05	1.54 $\pm$ 0.06
Weight, kilograms	57.3 $\pm$ 5.7	52.1 $\pm$ 6.5
Body mass index, kg/m <sup>2</sup>	23.2 $\pm$ 2.0	21.8 $\pm$ 2.6
LMP, years <sup>b</sup>	11.2 $\pm$ 8.2	16.1 $\pm$ 11.4

<sup>a</sup>The two groups were not significantly different as assessed by Student's *t* test.

<sup>b</sup>LMP, last menstrual period.

TABLE 2. EFFECTS OF ESTROGEN AND SOY ISOFLAVONE SUPPLEMENTATION ON BLOOD GENISTEIN, INSULIN, AND GLUCOSE CONCENTRATIONS IN POSTMENOPAUSAL WOMEN<sup>a,b</sup>

Blood parameters	Treatment groups and duration						p values from two-way ANOVA <sup>c</sup>	
	Estrogen group (n = 11)			Soy isoflavone group (n = 17)			Time	Treatment
	0 months	3 months	6 months	0 months	3 months	6 months		
Genistein, $\mu\text{mole/L}$	0.48 $\pm$ 0.76 <sup>a,b</sup>	0.11 $\pm$ 0.25 <sup>b</sup>	0.07 $\pm$ 0.22 <sup>b</sup>	0.46 $\pm$ 0.94 <sup>a,b</sup>	0.74 $\pm$ 0.65 <sup>a</sup>	0.85 $\pm$ 0.81 <sup>a</sup>	0.942	0.031
Glucose, mg/dl	118 $\pm$ 46 <sup>a</sup>	94 $\pm$ 20 <sup>b</sup>	92 $\pm$ 21 <sup>b</sup>	102 $\pm$ 18 <sup>a,b</sup>	90 $\pm$ 24 <sup>b</sup>	81 $\pm$ 25 <sup>b</sup>	0.001	0.154
Insulin, $\mu\text{IU/ml}$	11 $\pm$ 9 <sup>a</sup>	6 $\pm$ 7 <sup>a,b</sup>	6 $\pm$ 11 <sup>a,b</sup>	12 $\pm$ 12 <sup>a</sup>	4 $\pm$ 3 <sup>b</sup>	5 $\pm$ 8 <sup>a,b</sup>	0.005	0.940

<sup>a,b</sup>Different superscript letters in each row indicate significant difference by Duncan's multiple range test,  $p < 0.05$ .

<sup>c</sup>There was no significant interaction between time and treatment for all three parameters as tested by two-way ANOVA,  $p < 0.05$ .

0.005) in both groups. Both blood glucose and insulin levels shifted toward lower values after the intervention with either estrogen or soy isoflavone (Fig. 1).

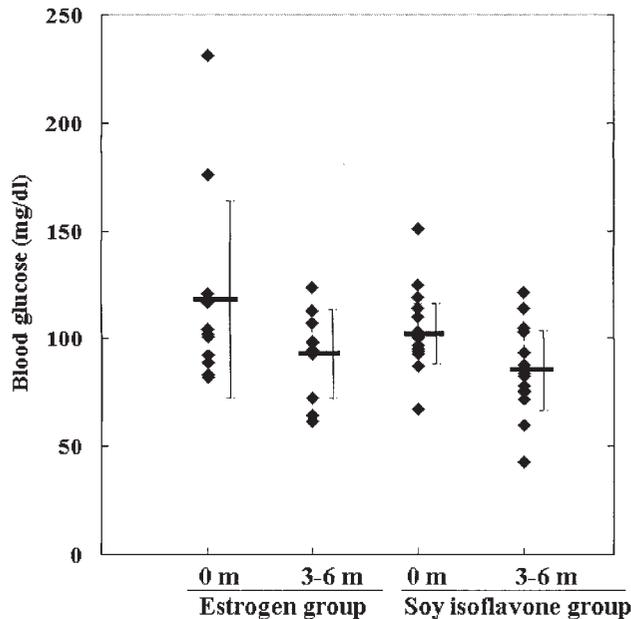
In contrast, the lipid profiles, including TG, TCHO, HDL-C, TCHO/HDL-C ratio, and LDL-C/HDL-C ratio, in both groups were not significantly changed by the intervention (Table 3), except that soy isoflavone-treated subjects showed a significant increase in LDL-C at 6 months.

## DISCUSSION

Cardiovascular disease (CVD) is the third leading cause of death for Taiwanese women. Apart from the close association with hypertension and hyperlipidemia, the rapidly increasing prevalence of diabetes is believed to be responsible. This has drawn the attention of both the medical field and the field of public health.

Compared to the west, acceptance of HRT is relatively low in Taiwanese women. Ever since

(A) Blood glucose



(B) Serum insulin

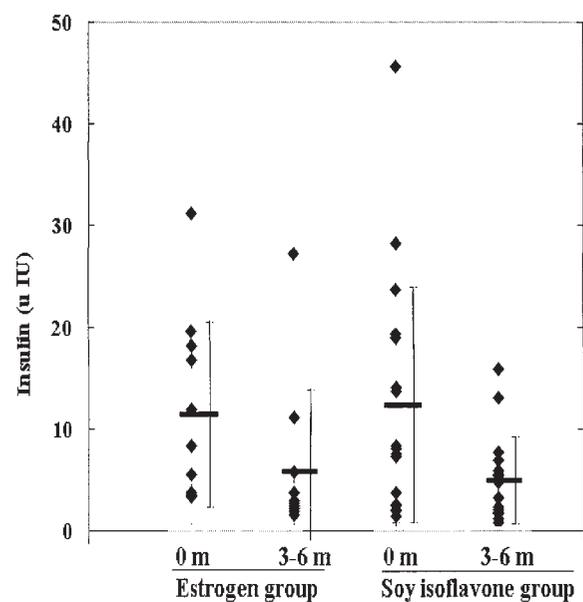


FIG. 1. Distribution pattern of blood glucose concentrations (A) and insulin levels (B) in postmenopausal women before and after estrogen or soy isoflavone supplementation for 6 months. Horizontal bar indicates group mean, and vertical line indicates 1 SD for the specified group.

TABLE 3. EFFECTS OF ESTROGEN AND ISOFLAVONE SUPPLEMENTATION ON BLOOD LIPID PROFILES IN POSTMENOPAUSAL WOMEN

Blood lipid profiles	Treatment groups and duration <sup>a</sup>					
	Estrogen group (n = 11)			Soy isoflavone group (n = 17)		
	0 months	3 months	6 months	0 months	3 months	6 months
Triglycerides, mmole/L	1.38 ± 0.59	1.66 ± 0.84	1.57 ± 1.21	1.26 ± 0.49	1.44 ± 0.83	1.28 ± 0.55
TCHO, mmole/L	5.56 ± 0.71	5.85 ± 0.99	5.69 ± 0.95	5.11 ± 0.83	5.50 ± 0.85	5.38 ± 0.84
LDL-C, mmole/L <sup>b,c,d</sup>	3.39 ± 0.75 <sup>b,c</sup>	3.40 ± 0.75 <sup>b,c</sup>	3.87 ± 0.89 <sup>b</sup>	2.75 ± 0.78 <sup>d</sup>	3.23 ± 0.62 <sup>c,d</sup>	3.48 ± 0.69 <sup>b,c</sup>
HDL-C, mmole/L	1.56 ± 0.37	1.71 ± 0.47	1.69 ± 0.44	1.84 ± 0.76	1.68 ± 0.59	1.70 ± 0.52
TCHO/HDL-C	3.7 ± 0.8	3.6 ± 1.0	3.5 ± 0.9	3.1 ± 1.1	3.6 ± 1.1	3.3 ± 0.8
LDL/HDL-C	2.3 ± 0.7	2.1 ± 0.7	2.4 ± 0.8	1.8 ± 0.9	2.1 ± 0.8	2.2 ± 0.7

<sup>a</sup>The main effects of treatment and duration on lipid profiles were not statistically significant as tested by two-way ANOVA,  $p < 0.05$ .

<sup>b,c,d</sup>Different superscript letters in this row indicate significant difference by Duncan's multiple range test,  $p < 0.05$ .

the report by the Women's Health Initiative (WHI),<sup>7</sup> the prevalence rate of taking HRT is even lower; many Taiwanese women discontinued HRT and turned to alternative medicine. Among the various treatments, phytoestrogens is one of the most popular.

The majority of studies on isoflavones have concentrated on their effects on blood lipids. Studies that have shown decreases in serum LDL-C with soy proteins in humans generally have involved hypercholesterolemic subjects and inclusion of soy proteins in their treatment. Such an effect may be absent in a healthy population using purified isoflavones.<sup>8-14</sup> In our study, dietary advice was kept to a minimum to avoid any major changes in the subjects' habitual diets. The results were consistent with recent findings using phytoestrogens, which found that isoflavone supplement alone had no effect on lipid profiles during the 6-month intervention.

Recent studies have provided evidence that phytoestrogens may be beneficial in the management of diabetes. *In vitro* studies have shown isoflavones to have antidiabetic properties, such as inhibiting intestinal brush border uptake of glucose, having  $\alpha$ -glucosidase inhibitor action, demonstrating tyrosine kinase inhibitory properties and multiple action on insulin release from pancreatic islet cells, and acting as peroxisome proliferator-activated receptor (PPAR- $\alpha$  and PPAR- $\gamma$ ) agonists.<sup>15-19</sup> Human studies are few, but results are promising. Diets containing soy protein rich in isoflavones can reduce insulin levels in healthy postmenopausal women. Soy consumption also alleviates insulin resistance and

impaired glycemic control in postmenopausal women with type 2 diabetes.<sup>20</sup>

In our study, after 6 months of intervention, the average blood genistein concentration for the isoflavone group was 10 times higher compared with those of the estrogen group. Within the same period, the fasting blood glucose level was reduced to 83% and 85% of the baseline levels and the insulin level was reduced to 56% and 67% of the baseline levels, respectively, in the estrogen and isoflavone groups. The effects of both estrogen and genistein treatment observed in our study were greater than the 16% reduction in fasting insulin after 3 years of HRT in the Postmenopausal Estrogen/Progestogen Intervention (PEPI) trial.<sup>21</sup> This shows that isoflavones are as effective as estrogen in improving insulin resistance and glucose tolerance.

Two prior studies have reported phytoestrogen effects on glycemic control and insulin sensitivity in postmenopausal women. Jayagopal et al.<sup>22</sup> demonstrated that dietary supplementation with 30 g soy proteins containing 132 mg phytoestrogen for 12 weeks reduced fasting insulin by 8.09% in postmenopausal women with diet-controlled type 2 diabetes. Goodman-Gruen and Kritzer-Silverstein<sup>23</sup> examined the effects of usual, un-supplemented dietary isoflavones ranging from none to 13.9 mg/day, with an average of  $1.3 \pm 2.4$  mg/day, and observed a significant 20% reduction in fasting insulin in women consuming moderate to high isoflavones in their usual diet. In accordance with these studies, our results also support the insulin-reducing and hypoglycemic effects of soy isoflavones. These effects remained

significant after controlling the baseline LDL-C levels by forward multiple regression analysis in our study. The results in our study and in the study of Goodman-Gruen and Kritz-Silverstein<sup>23</sup> are similar in that insulin and glucose reduction occurred in the absence of any change in lipid profiles, including TCHO, HDL-C, TCHO/HDL-C ratio, and LDL-C/HDL-C ratio, thus demonstrating a differential effect of soy isoflavones on blood lipid and glycemic controls in postmenopausal women.

## CONCLUSIONS

As the dietary habits of Taiwanese women become more and more westernized, the increasing prevalence of obesity, hyperlipidemia, and hyperglycemia leads to a greater incidence of CVD. The accumulating evidence regarding the ability of phytoestrogens, especially isoflavones, to lower plasma lipid and blood glucose levels seems to provide postmenopausal women as alternative to HRT for potential cardioprotection. It also can foster a reappreciation of the benefits of the traditional diet.

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