# Benefits of Soy Isoflavone Therapeutic Regimen on Menopausal Symptoms

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**OBJECTIVE: To examine the change in menopausal symptoms and cardiovascular risk factors in response to 4 months of daily 100-mg soy isoflavone in postmenopausal women.**

**METHODS: In this double-blind, placebo-controlled study, 80 women were randomly assigned to isoflavone ($n = 40$) and placebo ($n = 40$) treatment. The menopausal Kupperman index was used to assess change in menopausal symptoms at baseline and after 4 months of treatment. Cardiovascular risk factors were assessed by evaluating plasma lipid levels, body mass index, blood pressure, and glucose levels in the participants. To examine the effects of this regime on endogenous hormone levels, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and 17$\beta$-estradiol were measured. Transvaginal sonography was performed to quantify endometrial thickness.**

**RESULTS: The data showed a decrease in menopausal symptoms ($P < .01$, paired $t$ test, two-tailed, between baseline and isoflavone groups, and $P < .01$, unpaired $t$ test, between placebo and isoflavone groups). Total cholesterol and low-density lipoprotein decreased significantly in the isoflavone group compared with the baseline or placebo group ($P < .001$, paired $t$ test, two-tailed, between baseline and isoflavone groups, and $P < .01$, unpaired $t$ test, between placebo and isoflavone groups). The isoflavone treatment appeared to have no effect on blood pressure, plasma glucose, and high-density lipoprotein and triglyceride levels.**

**CONCLUSION: This study suggests that isoflavone 100-mg regime treatment may be a safe and effective alternative therapy for menopausal symptoms and may offer a benefit to the cardiovascular system. (Obstet Gynecol 2002;99: 389–94. © 2002 by the American College of Obstetricians and Gynecologists.)**

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*We would like to thank Dr. Mercedes C. Panizzi; Marcos G. Mandarino and Dr. Akio Kikuchi (Brazilian Research Institute of Agriculture [EMBRAPA], Brasilia, Brazil); Dr. Tai W. Kwon and Dr. Sung R. Kim (Korea Food Research Institute, Seoul, Korea); Dr. Dong K. Yim (Food Technology of Campinas-[ITAL]), Campinas, Brazil; and Dr. Myoung K. Park (Life Science Research Center of Eugenbio Inc., Seoul, Korea) for their priceless efforts and cooperation in our study.*

Estrogen replacement therapy is well established for the relief of climacteric symptoms in postmenopausal women as well as for the prevention of osteoporosis and cardiovascular disease. Estrogen replacement therapy after menopause improves a woman's health and quality of life.[1–3] However, prolonged exposure to unopposed estrogens stimulates growth of endometrium, thus increasing the risk of endometrial hyperplasia and neoplasia.[3] Progestagen associated with estrogen, used to decrease these risks, can cause severe side effects in some patients.[4,5] The identification of an alternative agent, which has the beneficial effects of estrogen but has low cancer risk and side effects, would, therefore, be of considerable value.

Isoflavones are a group of biologically active compounds that have estrogenic and antiestrogenic effects depending on the target tissue.[6–10] Clinical studies have shown that diet with supplementation of soy isoflavone is beneficial in decreasing menopausal symptoms such as hot flashes.[7,11–14] However, other studies have failed to demonstrate a reduction of menopause symptoms using 80 mg or more of isoflavone per day in postmenopausal patients.[15–17] The effect of isoflavones on cardiovascular risk factors is also controversial.[18–21]

This study was designed to evaluate changes in menopausal symptoms in response to 4 months of 100 mg per day of soy isoflavone treatment and to analyze the impact of this therapeutic regimen on cardiovascular risk factors in postmenopausal women.

## MATERIALS AND METHODS

This study was a randomized, double-blind, placebo-controlled trial designed to investigate the extent to which isoflavone 100 mg per day (Eugenbio Co. Ltda, Seoul, South Korea) decreased menopausal symptoms as well as affected cardiovascular risk and endogenous hormone levels. Subjects for the present study consisted of women aged 45–55 years who attended screening and baseline visits and were subsequently enrolled in the isoflavone program in the Division of Endocrinological



0029-7844/02/$22.00
PII S0029-7844(01)01744-6

Gynecology and Climacterium at the Department of Gynecology of the Federal University of Sao Paulo/ Escola Paulista de Medicina. To be eligible for this study, women had to be in menopause at least 12 months, not on any type of hormonal treatment during the previous 12 months, and not currently using lipid-lowering drugs, antidiabetic medications, soybean-derived products, or herbal supplements. Other inclusion criteria were an intact uterus, follicle-stimulating hormone (FSH) levels in blood serum exceeding 25 U/L, estradiol levels less than 20 pg/mL, and presence of hot flashes. Women with a history of uncontrolled hypertension, stroke or transient ischemic attack, cancer diagnosed less than 5 years ago, or previous myocardial infarction were excluded from the study. The length of the study was from August 1999 to February 2000. All patients gave informed consent for their participation in the study after reading the protocol of this experiment and receiving information about isoflavone treatment. The Institutional Review Board of Federal University of Sao Paulo approved this study.

At the screening visit, women responded to a standardized questionnaire, which ascertained information about demographic characteristics including age, ethnicity, and education level. Women were also queried about menopausal symptoms covered by the Kupperman menopausal index,[22] gynecologic history, including age at menopause, the use of selected medications, cigarette smoking history, frequency of alcohol use, physical activity, education status, and dietary and nutritional habits. Medication use was validated by examination of prescriptions or pills brought to the clinic for that purpose. After fasting for 12 hours, blood samples were obtained by venipuncture to measure FSH, luteinizing hormone (LH), 17$\beta$-estradiol, glucose, total lipid levels, and lipoprotein levels. FSH and LH were measured by fluoroimmunometric assays and 17$\beta$-estradiol by radioimmunoassay. Plasma glucose was measured by a glucose oxidase assay. Plasma total cholesterol and triglyceride levels were measured using enzymatic techniques, and lipoproteins were determined according to the National Institutes of Health lipid research clinics method. The baseline visit occurred 1 month after the screening visit and confirmed the menopausal symptoms. Height and weight were measured with subjects wearing lightweight clothing and no shoes; body mass index (calculated as kg/m$^2$) was used as an estimate of obesity. Blood pressure was measured with a mercury sphygmomanometer after the participant had been seated quietly for at least 5 minutes. Transvaginal sonography was performed to evaluate the endometrial cavity, using a Toshiba SAL-38B real-time sonography fitted with a mechanical 5.0-MHz probe (Tochigi, Japan). It was measured in the anteroposterior direction from the echogenic interface of the endometrium-myometrium junction on both sides in the most endometrial thickness area in the 1/3 of the uterine body. The operator who performed all examinations did not know the patient's clinical data.

After initial screening, 82 women were assigned to the two different treatments in a sequence determined by a computerized random-number generator. All patients received a numerical randomized envelope, with a letter inside labeled #1 or #2, corresponding to placebo and isoflavone 100 mg per day, respectively. During the study, the subjects and study personnel were not informed about the order of treatments. To avoid compromising the double-blind design, the occurrence of side effects or physical changes such as menstrual bleeding was recorded by an independent gynecologist. In addition, at the study entry, subjects were informed that menstrual bleeding could occur regardless of the type of treatment received. Study drugs were packaged in 30-day flasks (90 capsules). The patients were instructed to take one capsule of corresponding number 8/8 hours during the study. The follow-up was conducted by a gynecologist who did not participate in the screening part of this study or the distribution of the drugs. In the isoflavone group, the concentration of each capsule was 83.3 mg and composed of soy protein 50.3 mg (60%) and isoflavone 33.3 mg (40%). The specific amount of genistein, daizein, and glycitein in aglycone form in each capsule was 23.3 mg, 6.2 mg, and 3.8 mg, respectively. In the placebo group, the concentration of each capsule was 83.3 mg and composed of purified soy protein 50.3 mg (without any kind of isoflavones) and glucose 33.3 mg. A total of 80 patients completed the 5-month study (including screening, baseline, and 4 months of treatment). Two patients dropped out of this study (one from each arm) because of "poor response" ($n = 1$) and nausea ($n = 1$). None of the women showed abnormal bleeding or side effects after the treatment period. At the end of the study, menopausal symptoms were assessed, height/weight, blood pressure, lipid, and hormone levels were measured, and transvaginal sonography was performed for comparison with baseline data. One month after completing the study, patients were examined for physical disturbances and informed about the received treatment.

The Kupperman index is a numerical conversion index and covers 11 menopausal symptoms: hot flashes (vasomotor), paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia or myalgia, headache, palpitations, and formication. Each symptom on the Kupperman index was rated on a scale from 0 to 3 for no, slight, moderate, and severe complaints. To calculate the Kupperman index, the symptoms were weighted as

**Table 1.** Characteristics of Study Participants by Treatment

| | Placebo ($n$ = 40) | Isoflavone ($n$ = 40) |
|---|---|---|
| Age (y, mean ± SEM) | 49 ± 1.3 | 48 ± 1.1 |
| Postmenopausal status (y, mean ± SEM) | 2 ± 0.3 | 1.8 ± 0.2 |
| Race | | |
| Black (%) | 55 | 62.5 |
| White (%) | 35 | 32.5 |
| Asian (%) | 10 | 5 |
| Education status | | |
| Graduate school (%) | 20 | 30 |
| High school (%) | 2.5 | 5 |
| Primary school (%) | 77.5 | 65 |
| Smoker (%) | 30 | 20 |
| Stress urinary incontinence (%) | 30 | 30 |
| Diabetes mellitus type 2 (%) | 2.5 | 2.5 |

SEM = standard error of the mean.

follows: hot flashes (×4), paresthesias (×2), insomnia (×2), nervousness (×2), and all other symptoms (×1). The highest potential score is thus 51. The score of hot flashes was based on number of complaints per day: slight (more than 5), moderate (5–10), and severe (more than 10).

The natural pairing of observations (baseline and after treatment) in the same group was compared with a Student paired, two-tailed $t$ test. A Student unpaired, two-tailed $t$ test was used for comparison of between-group data. A preliminary exploratory study showed that the data were fit for parametric procedures. Of note for the Kupperman score statistical analysis, nonparametric analyses (Mann-Whitney and Wilcoxon paired rank tests) produced similar results (data not shown). All efficacy results reported are on an intent-to-treat basis in which the last observation was carried forward into all subsequent time points for patients who dropped out before the end of the study. An $\alpha$ error ($P$) of $<.05$ level was used. All values in the figures and text are expressed as mean ± standard error of the mean. All statistical tests were done using GraphPad Prism 3.00 for Windows (GraphPad Software, San Diego, CA).

## RESULTS

The epidemiologic and clinical characteristics of age, race, education, and social status, use of nicotine and dietary and nutritional habits, and clinical problems were similar in both groups (Table 1). Subjects reported no consumption of alcohol. All participants exercised less than three times per week.

To evaluate the menopausal symptoms, the menopausal Kupperman index questionnaire was applied. In the first visit, symptoms were similar between placebo and isoflavone groups (Table 2). During the treatment period, the menopausal symptoms of participants using isoflavone were significantly lower than placebo treatment and baseline (Table 2). No side effects or improvement on stress urinary incontinence were reported at the end of treatment.

To assess the impact of isoflavone treatment on cardiovascular disease risk, blood glucose and pressure, body mass index, lipids, and lipoproteins were analyzed. No differences in blood glucose, blood pressure, or body mass index were found during treatment (Table 3). Baseline serum total cholesterol, triglycerides, and lipoproteins were similar between groups before the treatment period (Table 3). The mean of absolute changes (mg/dL) in serum lipoprotein levels at the end of the

**Table 2.** Quantification of Menopausal Kupperman Index (Mean ± SEM)

| | Placebo ($n$ = 40) | | Isoflavone ($n$ = 40) | |
|---|---|---|---|---|
| | Baseline | Post-treatment | Baseline | Post-treatment |
| Vasomotor | 10 ± 0.4 | 9.9 ± 0.4 | 11.3 ± 0.2 | 8.2 ± 0.5* |
| Paresthesia | 4.9 ± 0.2 | 4.8 ± 0.3 | 5.2 ± 0.2 | 2.4 ± 0.3* |
| Insomnia | 4.6 ± 0.3 | 4.6 ± 0.3 | 5.5 ± 0.2 | 3.3 ± 0.3* |
| Nervousness | 4.7 ± 0.3 | 4.8 ± 0.3 | 5.1 ± 0.2 | 1.7 ± 0.3* |
| Melancholia | 2 ± 0.2 | 2.3 ± 0.2 | 2.6 ± 0.1 | 1.3 ± 0.2* |
| Vertigo | 2.2 ± 0.2 | 2.4 ± 0.1 | 2.5 ± 0.1 | 1.2 ± 0.2* |
| Weakness | 2.3 ± 0.2 | 2.5 ± 0.1 | 2.5 ± 0.1 | 1.4 ± 0.2* |
| Arthralgia and myalgia | 2.1 ± 0.2 | 2.4 ± 0.1 | 2.5 ± 0.1 | 1.4 ± 0.2* |
| Headache | 2.5 ± 0.1 | 2.7 ± 0.1 | 2.6 ± 0.1 | 1.3 ± 0.2* |
| Palpitation | 2.4 ± 0.2 | 2.4 ± 0.1 | 2.6 ± 0.1 | 1.6 ± 0.2* |
| Formication | 2.7 ± 0.1 | 2.7 ± 0.1 | 2.6 ± 0.1 | 1.5 ± 0.2* |
| Total | 40.3 ± 1.2 | 41.6 ± 1.1 | 44.6 ± 1 | 24.9 ± 1.7* |

Abbreviation as in Table 1.

* $P < .01$ for baseline vs post-treatment comparison in the isoflavone group (paired $t$ test, two-tailed) and placebo and isoflavone treatment in post-treatment period (unpaired $t$ test, two-tailed).

**Table 3.** Evaluation of Cardiovascular Disease Risk (Mean ± SEM)

| | Placebo ($n$ = 40) | | Isoflavone ($n$ = 40) | |
|---|---|---|---|---|
| | Baseline | Post-treatment | Baseline | Post-treatment |
| BMI (kg/m$^2$) | 24.2 ± 0.5 | 24.4 ± 0.5 | 25.6 ± 0.6 | 25 ± 0.6 |
| MinBP (mm Hg) | 84 ± 2 | 84 ± 1 | 84 ± 1 | 85 ± 1 |
| MaxBP (mm Hg) | 133 ± 3 | 133 ± 2 | 131 ± 2 | 131 ± 1 |
| Total cholesterol (mg/dL) | 226.6 ± 7.7 | 226.8 ± 8.1 | 225.6 ± 6.2 | 199 ± 5* |
| HDL cholesterol (mg/dL) | 40 ± 1.3 | 43.9 ± 1.6† | 40.2 ± 1.4 | 44.3 ± 1.6† |
| LDL cholesterol (mg/dL) | 133.5 ± 6.4 | 139 ± 5.2 | 133.6 ± 5.3 | 120.3 ± 4.3‡ |
| VLDL cholesterol (mg/dL) | 49 ± 3 | 46.5 ± 3.3 | 46.7 ± 5.5 | 37.7 ± 3.2 |
| Triglycerides (mg/dL) | 175.8 ± 23.3 | 186.1 ± 6.2§ | 204.3 ± 23.3 | 210.8 ± 15.8§ |
| Glucose | 96.8 ± 1.7 | 93.9 ± 1.4 | 95.6 ± 1.5 | 97.4 ± 1.4 |

BMI = body mass index; MinBP = minimum blood pressure; MaxBP = maximum blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein. Other abbreviation as in Table 1.

* $P < .001$ for baseline vs post-treatment comparison in the isoflavone group (paired $t$ test, two-tailed) and placebo and isoflavone treatment in post-treatment period (unpaired $t$ test, two-tailed).

† $P < .005$ for baseline vs post-treatment comparison in both placebo and isoflavone groups (paired $t$ test, two-tailed).

‡ $P < .001$ for baseline vs post-treatment comparison in the isoflavone group (paired $t$ test, two-tailed) and placebo and isoflavone treatment in post-treatment period (unpaired $t$ test, two-tailed).

§ $P < .05$ for baseline vs post-treatment comparison in both placebo and isoflavone groups (paired $t$ test, two-tailed).

study for each treatment group is shown in Table 3. Total cholesterol and low-density lipoproteins (LDL) decreased significantly in the isoflavone group compared with the baseline or placebo group. The high-density lipoproteins (HDL) and triglycerides increased in both groups after treatment.

To evaluate isoflavone effects on endogenous hormones and estrogen target tissue, this study was complemented by measuring blood FSH, LH, 17$\beta$-estradiol, and endometrial thickness. Although estrogen levels rose after isoflavone treatment, they were not enough to produce a proliferative effect on endometrium. No differences between placebo and isoflavone treatment groups in blood FSH, LH, and endometrial thickness were detected (Table 4).

## DISCUSSION

Some critics might question the optimal daily dose required to recognize a clinical response. Some authors cited a per capita estimated intake of 50–200 mg of iosflavone daily in an Asian diet.[23,24] Also, others may consider the length of time on the soy isoflavones as too short to elicit a clinical response.[16] However, it has been determined that genistein and diadzein plasma concentrations peak 6–8 hours after ingestion.[25] These data endorse our choice of 33.3 mg 8/8 hours per day as adequate.

This study demonstrated that 100 mg per day of isoflavone was effective in alleviating vasomotor symptoms, such as hot flashes, consistent with previous study results.[11–14] Additionally, our results showed a decrease of other subjective symptoms, which was not reported by other studies,[13,14] using less than 50 mg of genistein plus daizein. This effect may be a consequence of the daily 88 mg of genistein plus daizein or of the life quality improvement due to a decrease in hot flashes. In addition, some studies using similar concentration of isoflavones, found no effects on hot flashes; however, one used different percentages of genistein, daizein, and glycitein in aglycone,[15] or another used associated tamoxifen in 68% of breast cancer survivors.[16]

**Table 4.** Quantification of Gonadotropins, 17$\beta$-Estradiol, and Endometrial Thickness (Mean ± SEM)

| | Placebo ($n$ = 40) | | Isoflavone ($n$ = 40) | |
|---|---|---|---|---|
| | Baseline | Post-treatment | Baseline | Post-treatment |
| FSH (pg/mL) | 84.3 ± 0.5 | 65.4 ± 3.7* | 90.3 ± 3.3 | 67 ± 3.2* |
| LH (pg/mL) | 64.8 ± 3.1 | 67 ± 2.4 | 68.7 ± 3 | 66.8 ± 2.4 |
| 17$\beta$-Estradiol (pg/mL) | 9.6 ± 0.5 | 10.9 ± 0.6 | 9 ± 1.2 | 19 ± 2.2† |
| TVS (mm) | 2.6 ± 0.1 | 2.6 ± 0.1 | 3.3 ± 0.1 | 3.1 ± 0.1 |

FSH = follicle-stimulating hormone; LH = luteinizing hormone; TVS = transvaginal sonography. Other abbreviation as in Table 1.

* $P < .01$ for baseline vs post-treatment comparison in both placebo and isoflavone groups (paired $t$ test, two-tailed).

† $P < .001$ for baseline vs post-treatment comparison in the isoflavone group (paired $t$ test, two-tailed) and placebo and isoflavone treatment in post-treatment period (unpaired $t$ test, two-tailed).

Hot flashes are experienced in those periods of the female life when estrogen levels are low.[26] In our study, isoflavone reduces hot flashes, but its real mechanism of action is not known. One possible explanation for isoflavone effect on menopausal symptoms is through its action on the estrogen receptor, which is capable of binding several structurally diverse compounds such as natural estrogens and isoflavones.[18] Another explanation is that isoflavones act through their antioxidant effects. Genistein is an inhibitior of tyrosine protein kinases, which is seen to play a role in vascular endothelial activity.[27,28] Finally, the 17$\beta$-estradiol enhancement of the isoflavone-group patients suggests that isoflavone supplementation increases estrogen levels. It may have an indirect effect due to isoflavones acting on sex hormone-binding globulin.[29] Isoflavones might compete with estrogens to this protein. Another possibility is that participants in the isoflavone group had an increase in endogenous estrogen. However, these patients had similar estrogen levels on baseline compared with the placebo group. Regardless of the basis for the increase in estrogen levels, this enhancement was too small to account for the significant decrease in menopausal symptoms, although it might partially influence our results.

The changes in FSH and estradiol levels were unexpected in this study because other studies found slight or moderate effect of isoflavones on gonadotropin or steroids.[29,30] The FSH level increase may be related to soy protein because both the isoflavone and placebo groups had similar reduction of this gonadotropin. Transvaginal sonography data did not show any significant increase in endometrial thickness. These data suggest isoflavone treatment is not enough to produce a proliferative effect on endometrial tissue, regardless of estrogen levels.

Epidemiologic studies have shown a decrease in cardiovascular disease risk in postmenopausal women who daily consume soy-derived products.[18,19] Soy protein with isoflavones has been reported[31] to lower LDL cholesterol and to inhibit oxidizability of LDL.[32] Although our data showed a similar protective effect of isoflavone, such as a decrease in total and LDL cholesterol, the mechanisms have not been clearly defined. These effects may be attributed to weak estrogenic effects of isoflavones, which also possess antioxidant properties.[20] In addition, previous findings correlate this protection with soy protein but not with isoflavone supplements.[17] Furthermore, isoflavones from red clover with similar concentration did not show this effect.[20,21] Our data suggest that isoflavones may not be responsible for the enhancement of HDL and triglyceride levels, as a consequence of soy protein effect. The increase of triglycerides may be a negative effect of soy protein in postmenopausal women. In contrast, it has been reported to have a decrease in triglyceride levels and slight changes in HDL in women who consume soy protein daily.[17]

This preliminary study showed that isoflavone treatment regimen may be a safe and effective alternative therapy for postmenopausal symptoms without significant increase in endometrial thickness. Another benefit is a decrease in LDL levels, which suggests a positive effect on the cardiovascular system.

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*Received July 11, 2001. Received in revised form November 1, 2001. Accepted November 9, 2001.*