The Effect of Dietary Soy Supplementation on Hot Flushes

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Objective: To assess the effect of daily dietary supplementation of soy protein isolate powder on hot flushes in postmenopausal women.

Methods: We carried out a double-blind, parallel, multicenter, randomized placebo-controlled trial of 104 postmenopausal women. Fifty-one patients (age range 48–61 years) took 60 g of isolated soy protein daily and 53 patients (age range 45–62 years) took 60 g of placebo (casein) daily. The study lasted 12 weeks. Using analysis of covariance, we analyzed changes from baseline in mean number of moderate to severe hot flushes (including night sweats) during treatment.

Results: Soy was significantly superior to placebo ($P < .01$) in reducing the mean number of hot flushes per 24 hours after 4, 8, and 12 weeks of treatment. In particular, women taking soy had a 26% reduction in the mean number of hot flushes by week 3 and a 33% reduction by week 4 ($P < .001$ by the Wilcoxon exact test). By the end of the 12th week, patients taking soy had a 45% reduction in their daily hot flushes versus a 30% reduction obtained with the placebo ($P < .01$). The overall rates of adverse effects were similar for soy and casein-placebo. Twenty-five patients dropped out of the study: 11 in the soy group and 14 in the placebo group. Gastrointestinal side effects were the most common cause of premature withdrawal from the study (seven patients in each group).

Conclusion: Soy protein isolate added daily to the diet substantially reduced the frequency of hot flushes in climacteric women. (Obstet Gynecol 1998;91:6–11. © 1998 by The American College of Obstetricians and Gynecologists.)

Hormone replacement therapy (HRT) is the most effective treatment to date for the relief of climacteric symptoms. However, recent data on the effects of long-term HRT on the risk of breast cancer[1] and on venous thromboembolism[2] have reinforced fears and reservations that many women and their physicians have about this form of treatment. Moreover, there are women for whom HRT is contraindicated, and there is currently little to offer for the relief of climacteric symptoms for these patients.

Epidemiologic data indicate that less than 25% of Japanese climacteric women complain of hot flushes[3] compared with 85% of North American women.[4] Furthermore, Japanese women eating a traditional diet have a low incidence of estrogen-dependent cancers such as breast cancer[5] compared with Western women. This incidence increases once Asian women westernize their diet.[6]

Soy is a staple ingredient in the traditional Asian diet. This plant is rich in phytoestrogens. These compounds have both estrogenic and antiestrogenic activity and have been shown in vitro and in vivo to have an anticancerous effect,[7] particularly on the breast.[8]

We assessed the short-term efficacy of a soy-enriched diet on severe hot flushes in a randomized, double-blind, placebo-controlled pilot study.

Materials and Methods

The patients were all postmenopausal women requesting treatment for severe hot flushes. In all cases, at least 6 months had passed since the last menstrual period or at least 6 weeks had passed since bilateral oophorectomy was performed. To be eligible for the study, the patients had to have a minimum number of seven moderate to severe hot flushes (including night sweats) per 24 hours during at least the last 2 weeks of the 4-week prestudy period. Moderate hot flushes were defined as a warm sensation associated with sweating,

which left the patient able to continue her daily activity. Severe hot flushes were defined as a hot sensation associated with sweating so intense that the patient had to stop her activity. Patients also were required to have a baseline FSH concentration greater than 50 IU/L and a serum estradiol concentration less than 35 pg/mL. Hormone replacement therapy or any other drug used for the treatment of climacteric symptoms, such as vitamin E, clonidine, and veralipride, were not allowed throughout the study period. Tamoxifen was not considered to be contraindicated. Patients who had received HRT in the past had to have stopped treatment at least 6 weeks before starting the prestudy period. All patients gave written informed consent, and the study was approved by the Ethical Committee of Ferrara University Hospital. All eligible subjects were included in the study and the enrollment period lasted 7 months.

This was a 12-week, double-blind, randomized, multicenter parallel trial. After the prestudy period, the patients were assigned randomly in equal numbers to receive daily either 60 g of isolated soy protein (Supro Brand; Protein Technologies International Inc., St. Louis, MO) or 60 g of casein (placebo). The 60 g of isolated soy protein contained 40 g of proteins and 76 mg of isoflavones (aglycone units). The 60 g of casein contained 40 g of proteins but no isoflavones. Both soy and casein were in powder form, supplied by the manufacturer as identically appearing, coded sachets of 30 g each. After selection according to the inclusion-exclusion criteria, patients were assigned a progressive number. On confirmation of entry criteria at the end of the baseline period, patients received the first available randomization number that assigned them to one of the two treatment groups. The manufacturer provided a balanced computer-generated randomization list for each of the two centers. A 1:1 treatment allocation was used. The investigator site personnel were blinded to the trial codes, which became available only after the completion of the trial and the final data review.

The patients first were seen at the screening visit and then were assessed 4 weeks later, before randomization, and then again at treatment weeks 4, 8, and 12. Patients were asked to record each day, throughout the entire period, including the prestudy period, the number of moderate to severe hot flushes (including night sweats). Patients were asked to record any occurrence of bleeding during treatment. At each visit, diaries were checked and the presence and severity of menopausal symptoms were assessed using the Kupperman[9] index, which represents the sum of the numeric conversion of the 11 most common menopausal complaints (hot flushes, paresthesia, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia, headaches, palpitation, and formication) to a figure based on severity (from 0 = absent to 3 = most severe). The Kupperman index was calculated without multiplying for additional correcting factors.

Weight and blood pressure also were measured. We assessed compliance by asking the patients to record the number of sachets taken each day during the trial. The number of unused sachets that each patient returned was accounted for at every visit.

A sample size of at least 35 patients per group was required to detect, with a 90% power, a difference between treatment of three hot flushes per 24 hours, assuming a standard deviation of 3.8 hot flushes per day. The test was performed two-sided at a significance level of $\alpha = .05$. The primary efficacy criterion was the change from baseline of the mean number of daily moderate and severe hot flushes (including night sweats) in each month of treatment.

Data were analyzed according to an intention-to-treat approach. We included in the analysis all randomized patients with data about hot flushes for at least 10 days during the last 2 weeks before assessment. The patients were randomized only if they met all the study criteria.

The average number of hot flushes per day during treatment was adjusted by subtracting this number from the average number of hot flushes per day at baseline. Improvements were expressed as negative values, ie, reduction from baseline, with a positive number reflecting worsening symptoms. We performed analysis of covariance with day of treatment used as covariate and treatment and center used as factors. Nonparametric tests (Wilcoxon rank sum, χ^2, and Fisher exact tests) were used when necessary. A linear regression analysis was used to study the relationship between compliance and decrease in hot flushes during treatment. All P values are two-tailed. A significance level of 5% was applied.

Results

Initially, two groups of 46 patients each were randomized to receive either 60 g of isolated soy protein or 60 g of placebo (casein) at two university hospitals in Italy. However, given the high dropout rate, 12 more patients were entered into the study following a reserve randomization list provided for each center by the manufacturer. The reserve list had a 1:1 treatment ratio. Therefore, a total of 104 patients met the study criteria: 51 patients who took soy and 53 patients who took casein.

These patients were well balanced with respect to baseline characteristics and there was no statistically significant difference between baseline values in the two groups (Table 1) or between centers. Forty patients taking soy and 39 patients taking casein completed the

Table 1. Baseline Characteristics

Characteristic	Soy group (n = 51)	Casein group (n = 53)
Age (y)	53.3 ± 0.45 (48–61)	52.4 ± 0.47 (45–62)
Body mass index	25.9 ± 0.51 (18–36)	25.9 ± 0.53 (18–36)
Duration of menopause (mo)	46.8 ± 7.2 (4–163)	46.2 ± 5.8 (5–221)
FSH (IU/L)	75.2 ± 3.41 (51–120)	83.5 ± 4.5 (50–150)
Estradiol (pg/mL)	18.8 ± 1.8 (2–35)	19.6 ± 1.6 (4–34)
No. of hot flushes per 24 h	11.4 (10.7–12.7)	10.9 (10.2–11.8)

Data are presented as mean ± standard error of the mean (range) or mean (range). None of the differences were statistically significant.

12-week study. At baseline, the median number of hot flushes was 11.4 (range 10.7–12.7) for the group taking soy and 10.9 (range 10.2–11.8) for the placebo group. During the first 4 weeks of the treatment period, the soy significantly decreased the frequency of hot flushes. The effect became significant after the first 2 weeks of treatment. In particular, women taking soy had a 26% reduction in the mean number of hot flushes compared with baseline by week 3 and a 33% reduction by week 4 ($P < .001$ by the Wilcoxon exact test).

Figure 1 shows the variation of hot flushes during the 3 months of treatment in the two groups. The estimated differences between treatments and the associated 95% confidence intervals and P values are summarized in Table 2. The estimated treatment difference after 12 weeks was −1.59, showing that treatment with 60 g of isolated soy protein reduced by 1.59 the mean number of moderate to severe hot flushes per 24 hours compared with baseline. This was calculated after subtract-

ing the effect of placebo. A significant treatment difference in favor of soy starts after 15 days, persists over time, and is highest after 12 weeks (−1.59). Figure 1 also shows an unexpected finding: there appeared to be a substantial decrease in the effect of soy at the 8th week of treatment. After noting this phenomenon, we looked at compliance, which was indicated by the number of sachets that women declared to have taken in their diary charts. A marked decrease in daily compliance by the soy group was found by the middle of the 2nd month of treatment. Of 51 patients taking soy, 24 were on their 2nd month of treatment between July and August, when most Italians commonly take their vacations away from home. A linear regression analysis has shown a strong influence of compliance on the number of flushes (b = −12; $P < .001$).

Data on side effects were obtained monthly when patients returned to the clinic for their interviews. When a patient reported more than one side effect we took into account only the one that in her opinion was the most bothersome (Table 3). Gastrointestinal side effects were the most often reported. Constipation affected approximately half of the women in both groups and was the most common side effect (48%) that led to premature withdrawal from the study. A total of 25 patients stopped the trial prematurely, 11 in the soy group and 14 in the casein group. Fifteen of the 25 patients who dropped out reached the 1st month of treatment and then stopped. The remaining patients withdrew within the 1st month. Gastrointestinal side effects and food intolerance were the major cause of dropout for 14 patients, seven in each group. Lack of efficacy induced three women in the casein group and
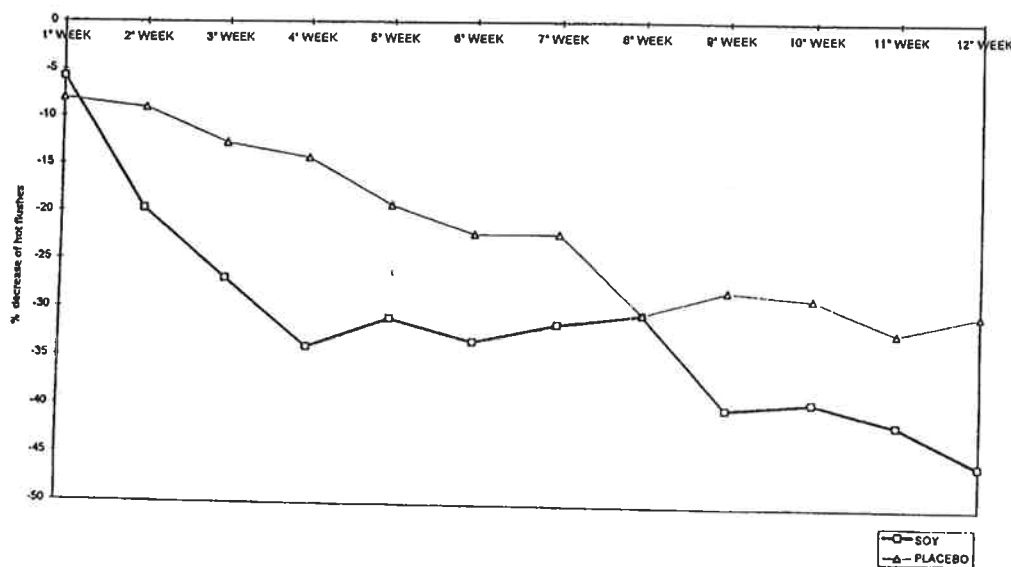

Figure 1. Weekly decrease in number of hot flushes; score expressed as percentage. The difference between soy and placebo was always significant after week 2, with the exception of week 8.

Table 2. Change in Number of Hot Flushes With Respect to Baseline Values (Intention-to-Treat Analysis)

	Weeks 1 and 2	Weeks 6 and 7	Weeks 11 and 12
Soy group mean (%)	−1.46 (−12.7)	−3.72 (−32.4)	−5.01 (−43.6)
Casein group mean (%)	−0.93 (−8.52)	−2.43 (−22.15)	−3.42 (−31.3)
Treatment group contrast			
Mean estimated value	−0.53	−1.29	−1.59
95% confidence interval	−1.03, −0.03	−1.47, −1.12	−1.95, −1.2
P	.09	<.01	<.01

Data were obtained with the analysis of covariance with day of treatment used as covariate and treatment and center used as factors. P values refer to analysis of covariance. Percentages are percent variation in relation to baseline values. Mean estimated values were obtained by subtracting mean values for casein from mean values for soy. The 95% confidence interval refers to the confidence interval of mean estimated values.

one woman in the soy group to leave the study; lack of compliance, defined as complete abandonment of treatment for more than a week, resulted in the withdrawal of one patient in each group. Two patients in each group were lost to follow-up and one patient in the casein group stopped for other reasons. However, a large portion (24%) of the 25 patients who withdrew from the study had difficulty with the amount of powder that they were instructed to take and with food intolerance, namely constipation, bloating, nausea, and vomiting. These two factors were the most common causes of both discontinuation and lack of compliance.

Discussion

Our study shows that adding 60 g of isolated soy protein to the daily diet of climacteric women markedly diminishes moderate to severe hot flushes, thus supporting the conclusion from previous uncontrolled pilot trials.[10]

As has been well known since 1931, soybeans contain high amounts of isoflavones, particularly genistein and daidzein.[11] These are nonsteroidal weak estrogenic compounds that constitute a range of substances (phytoestrogens) to which anticancerous properties have been ascribed.[12] However, the concentration of estrogenic isoflavones varies in soy food depending on the variety of soybeans, growing conditions, soil, and other factors such as processing, just as naturally occurring

Table 3. Side Effects Experienced During Treatment

	Soy group (n = 51)	Casein group (n = 53)
Nausea	1 (1.9)	1 (3.6)
Vomiting	0	1 (3.6)
Bloating	6 (11.7)	7 (13.2)
Constipation	25 (49.0)	27 (50.9)
Other	3 (5.8)	9 (16.9)
Total	35	45

Data presented as n (%) or n. No statistical difference was found with Fisher exact test.

vitamins and minerals vary in plants.[13] In the 60 g of isolated soy protein that our patients were taking daily, there was 76 mg of isoflavones, the major substances being genistein (40 mg) and daidzein (28 mg). Phytoestrogens in such an amount produce an effect on hot flushes within 2 weeks from the start of diet supplementation that persists throughout the entire 3 months of treatment. This pattern is similar to that seen with estrogen replacement therapy. However, soy given in this amount reduces hot flushes by 45%, whereas estrogens produce a reduction of 83% in the hot-flushes score.[14] Nevertheless, the direct comparison of the effects of naturally occurring, plant-derived substances and pharmaceutic preparations might be improper. The lower efficacy of soy supplementation might be due to the variability of phytoestrogen concentration occurring in the dietary preparation used, rather than the specific potency of the phytoestrogens. In this study, we have tried to minimize as much as possible this potential source of bias, and the phytoestrogen composition present in isolated soy protein was controlled and constant at a quantity of 1.90 mg/g of protein (Protein Technologies International Inc. data sheet). However, after ingestion of soy by humans, intestinal bacteria play an important role in the transformation of the plant precursors: intestinal flora can convert the soy isoflavone to equol, a more potent estrogenic isoflavone that is absorbed along with the unconverted genistein and daidzein. The production of equol by intestinal bacteria is variable.[15] This also may account for the variability (0–50 hot flushes per day) of the clinical effects of soy and ultimately for the overall reduced efficacy of soy compared with estrogens[14] on hot flushes.

Soy does not appear to alter any of the other menopausal complaints such as anxiety, arthralgia, myalgia, headaches, and insomnia that compose a large part of the Kupperman index. In our study, the Kupperman index values as a whole did not change. Data on climacteric symptoms experienced by Japanese women include as among the most common shoulder stiffness, headache, lumbago (back pain), and insomnia.[3] Thus,

soy, even in Japanese women, does not appear to affect psychologic and arthalgic symptoms.

Our study period was too short to disclose any effect of phytoestrogens on the endometrium or on the breast. However, much of the literature has focused so far on the estrogenic and antiestrogenic effect of phytoestrogens on these tissues[15] that should occur with a mechanism similar to that of tamoxifen but with a more useful spectrum of estrogenic and antiestrogenic properties.[16]

In Japan, the consumption of phytoestrogens is estimated to be approximately 200 mg a day[17] and the incidence of hot flushes,[3] hormone-related cancers,[18] and osteoporosis[19,20] is reported to be one of the lowest in the world. We have tried to simulate an Asian diet by supplementing a typical Italian diet with approximately one-third (76 mg a day) of the average daily intake of phytoestrogens by Japanese women. This could be achieved only by adding, or substituting meals with, a large quantity of soy protein each day. The intrinsic difficulties that women faced while undergoing the trial are manifested by the number of women who dropped out and by the decrease in compliance. Compliance also was affected by the number of gastrointestinal side effects that patients experienced during treatment (Table 3) and the concomitance of the summer holidays. This was a time when even the most motivated of our patients had difficulty choosing a glass of "sticky powder" over a restaurant meal. However, it is reassuring that the effects of soy on hot flushes so closely relate to compliance.

If future, long-term studies are to be planned to assess the effects of phytoestrogen on major issues such as prevention of osteoporosis and of breast and endometrial cancer, two major difficulties must be resolved. First, further research needs to address the preparation of compounds with the same or greater concentration of phytoestrogens in a more user-friendly form. Second, the interindividual variability of phytoestrogens needs to be overcome. Estrogen is still the main form of treatment for the climacteric syndrome and in particular for hot flushes. The number of contraindications continues to be reduced,[21] and the increased risk of cancer, particularly that of the breast, in relation to long-term HRT use is controversial.[22] Patients were selected for this study only on the basis of the severity of their symptoms. However, among them were both women from whom HRT had been withheld because of contraindications and women who preferred to experience severe hot flushes rather than undergo treatment that even remotely might increase their chances of developing breast cancer. For these women, an alternative form of HRT, with less worrisome long-term negative effects, is desirable.

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