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The effect of dietary soy supplementation compared to estrogen and placebo on menopausal symptoms: A randomized controlled trial

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ABSTRACT

Objectives: To compare the effects of daily ingestion of dietary soy supplementation, low-dose hormone therapy (HT) and placebo on psychological, somatic and urogenital symptoms in postmenopausal women.
Study design: A double-blind, randomized, controlled trial. Sixty healthy, symptomatic, postmenopausal women of 40–60 years of age were allocated to use dietary soy supplementation (containing 90 mg of isoflavone) or HT (1 mg estradiol and 0.5 mg norethisterone acetate) or placebo. Main outcome measures: the Menopause Rating Scale (MRS) was used to assess menopausal symptoms at baseline and after 16 weeks of treatment. Intention-to-treat analyses were performed using the chi-square test, Fisher's exact test, the Kruskal–Wallis non-parametric test and analysis of variance (ANOVA).
Results: No statistically significant differences were found between the groups with respect to baseline clinical and sociodemographic characteristics. The psychological, somatic and urogenital symptoms analyzed in the MRS improved during treatment in all the groups, except for urogenital symptoms in the placebo group in which no significant changes were detected. Comparison between groups revealed a statistically significant improvement in somatic symptoms (hot flashes and muscle pain) in the users of HT (−45.6%) and dietary soy supplementation (−49.8%). Urogenital symptoms (vaginal dryness) improved significantly in HT users (−38.6%) and in users of the dietary soy supplementation (−31.2%). There was no statistically significant difference between the groups with respect to overall MRS score or to scores obtained in the psychological symptoms subscale.
Conclusion: Dietary soy supplementation may constitute an effective alternative therapy for somatic and urogenital symptoms of the menopause.

1. Introduction

Approximately 80% of menopausal women experience climacteric symptoms that negatively affect their quality of life [1]. A population-based study conducted in Brazil reported a prevalence of hot flashes of approximately 70% in perimenopausal and postmenopausal women [2]. Hormone therapy (HT) has been well-established for the treatment of climacteric symptoms in postmenopausal women; however, recent reports have shown that exposure to hormone therapy may increase women's risk of breast cancer, coronary heart disease, stroke and pulmonary embolism [3]. Therefore, since the risks of hormone therapy for the relief of postmenopausal symptoms may outweigh the benefits in some cases, alternatives to HT are being investigated. In Brazil, a recent evaluation of the Women's Health Initiative (WHI), which assessed the medical knowledge of gynecologists with respect to the menopause and the treatment of symptomatic women, and the repercussions of this knowledge on their attitudes and practice, reported that 46.3% of gynecologists had begun to prescribe isoflavone and other natural therapies for menopausal symptoms [4]. Many women consider the risk associated with hormone therapy to be unacceptable and request non-hormonal alternatives for the management of their vasomotor symptoms.

Interest has arisen concerning isoflavones, found in abundance in soy products, for the treatment of hot flashes [5]. Although many factors may contribute to the low prevalence of vasomotor symptoms in postmenopausal women in some Asian cultures, one possible explanation may be a diet high in phytoestrogens, plant compounds with estrogen-like properties [6]. Soy is a rich source of the isoflavones genistein, daidzein and glycitein. Isoflavones are structurally similar to estradiol and have a high binding affinity for the beta-estrogen receptor. The diphenolic structure of lignans and isoflavones is similar to that of 17β-estradiol and these compounds are believed to have estrogenic or antiestrogenic effects, depending on circulating estrogen levels, i.e. they act as antiestrogens when estrogen levels are high and as estrogens when

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estrogen levels are low as in the case of postmenopausal women [7].

Clinical studies have shown that a soy isoflavone extract successfully improved menopausal symptoms [8]. However, other studies have failed to demonstrate any improvement in menopausal symptoms with daily isoflavone doses of 80 mg or more in postmenopausal patients [9]. Studies indicating an inconclusive effect on symptoms have also often shown a bias in methodology; for example, in some studies the populations consisted of both perimenopausal and postmenopausal women [10]; some studies used soy powders that were found to provoke gastrointestinal side effects, resulting in high dropout rates [10,11]; not all studies were placebo-controlled and others failed to control phytoestrogen intake from other food sources, leading to potential contamination [10–12].

Therefore, the purpose of this study was to determine the effects of a single soy protein dietary supplement containing 90 mg of isoflavone on psychological, somatic and urogenital symptoms in postmenopausal women, and to compare the results with the effects of low-dose hormone therapy and placebo.

2. Methods

2.1. Study participants

Sixty participants were recruited from two menopause outpatient clinics situated at the Center for Women's Integrated Healthcare of the University of Campinas (UNICAMP), Campinas, São Paulo, Brazil, and at the *Leonor Mendes de Barros* Maternity Hospital in São Paulo, Brazil to participate in a 16-week double-blind, randomized, placebo-controlled trial designed to examine the effects of a dietary soy isoflavone supplementation on menopausal symptoms.

Inclusion criteria consisted of postmenopausal women between 40 and 60 years of age who had their last menstrual period more than 12 months previously, had follicle-stimulating hormone (FSH) levels >30 mUI/ml and estradiol levels <20 pg/ml, who were having more than 8 hot flashes in 24 h, had not been using any form of hormonal treatment during the previous 6 months and were not currently using any lipid-lowering drugs, antidiabetic drugs, soybean derived products or herbal supplements. The exclusion criteria consisted of: previous hysterectomy, chronic gastrointestinal disorder, any contraindication to hormone therapy or patients participating in a conflicting clinical trial. Finally, women were excluded if they had a known allergy or hypersensitivity to soy or cow milk or were not willing to cease consumption of soy products for the 16 weeks of the study. The study was conducted between January and October 2007. The Internal Review Board of the institution approved the protocol, and all participants signed an informed consent form.

2.2. Randomization and blinding

After initial recruitment, 60 women were successfully screened and randomly assigned to one of the three different treatment groups in a sequence determined by a computer-generated randomization list. A numerically randomized envelope containing a label that indicated #1, #2 or #3, corresponding to the patient's allocation to the hormone therapy, isoflavone 90 mg per day or placebo groups, respectively, was opened for each patient. For the duration of the study, the subjects and study personnel remained blinded with respect to the treatment modality. Study drugs were packaged in bottles containing sufficient treatment for 30 days. A gynecologist who did not participate in the screening process of this study or in dispensing the drugs conducted the patient follow-up.

2.3. Intervention

The three treatment groups consisted of the following therapies:

- Hormone therapy ($n = 20$): one tablet containing 1 mg of estradiol and 0.5 mg of norethisterone acetate (Activelle®, Medley Pharmaceuticals, Campinas, São Paulo, Brazil), in addition to 2 portions/day of placebo powder.
- Soy group ($n = 20$): one placebo tablet plus 2 portions/day of dietary soy supplementation powder containing 45 mg of isoflavone per portion, making a total of 90 mg of isoflavone/day (Previna®, Sanavita Functional Foods, Piracicaba, São Paulo, Brazil).
- Placebo group ($n = 20$): one placebo tablet and 2 portions/day of placebo powder.

The dietary soy supplement (Previna®, Sanavita Functional Foods, Piracicaba, SP, Brazil) consisted of 20 g portions of a food powder containing 12 g of soy protein and a total of 45 mg of isoflavones (26.5 mg aglycons) to be mixed with 200 ml of water. The soy supplement contained approximately 8 mg of total daidzein, 15 mg total genistein and 3.5 mg total glycitein. The placebo powder (Sanavita Functional Foods) contained 20 g of maltodextrin, was identical in appearance to the soy powder and contained the same nutrients and calories except for the isoflavones and soy protein. Both supplements also contained 488 mg of calcium carbonate and 1.2 mg of hydrolyzed collagen per portion. The supplement was taken twice a day for a total of 16 weeks.

The placebo tablet was taken once a day. It was identical in appearance to the hormone therapy tablet and was produced by Medley Pharmaceuticals.

2.4. Measurements

At the screening visit, women completed a standardized questionnaire designed to obtain information on their demographic characteristics including age, ethnicity, education level and social status. Women were also queried about their reproductive history, age at menopause, time since menopause, use of medication, history of cigarette smoking and frequency of alcohol consumption.

In all three groups, data were collected at baseline and after 16 weeks of use of the respective medication. To examine the effects of the regime on endogenous hormone levels, follicle-stimulating hormone (FSH) and 17β-estradiol were measured. The Menopause Rating Scale (MRS) was used to evaluate menopausal symptoms at baseline and after 16 weeks of treatment. The MRS is composed of 11 items assessing menopausal symptoms and is divided into three subscales [13]:

- Somatic symptoms: hot flashes, heart discomfort, sleeping problems and muscle and joint problems (items 1–3 and 11, respectively).
- Psychological symptoms: depressive mood, irritability, anxiety, physical and mental exhaustion (items 4–7, respectively).
- Urogenital symptoms: sexual problems, bladder problems and vaginal dryness (items 8–10, respectively).

Each item is graded by the subject, scores ranging from zero (absent) to four (1 = mild; 2 = moderate; 3 = severe; 4 = very severe). The total score for each subscale is the sum of each item graded within that subscale. Total MRS score is composed of the sum of the scores obtained for each subscale.

Side effects were analyzed according to the occurrence or exacerbation of an adverse event during the treatment period. If the event was already present prior to admission to the study and either