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Phytoestrogens for menopausal vasomotor symptoms: efficacy of soybean isoflavones supplements for alleviating menopausal symptoms is positively related to hot flushes frequency

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Summary

Purpose of investigation: This study was designed to measure the beneficial effects of a combination of nutraceutics containing soy isoflavones (80 mg) and to evaluate the effect of soy isoflavones on hot flushes (HF) and quality of life in a clinical setting, as the authors conducted an observational study. *Materials and Methods:* This study was conducted on 92 patients with complaints of hot flashes, divided into two groups of 46 each. Group 1 received no therapy and group 2 received 80 mg of isoflavones daily for six months. The patients were interviewed to calculate hot flashes, global and depression scores and were rescored after 2, 4, 8, 12 and 24 weeks. The primary outcome measure was a change in the HF score from baseline. *Results:* A total of 92 patients, 46 (50%) in the treated group and 46 (50%) in the untreated group, entered the study. Extracts containing high levels of genistein (a substance derived from soy) appeared to reduce the number of daily HF and need to be investigated further. No indication suggested that discrepant results were due to the amount of isoflavones in the active treatment arm, the severity of vasomotor symptoms or trial quality factors. Also, no evidence indicated that these treatments caused oestrogenic stimulation of the endometrium or of the vagina or other adverse effects when used for up to one year. *Conclusions:* This observational trial suggests a possible beneficial effect of a dietary soy supplement containing 80 mg of isoflavones/day in the management of menopausal symptoms such as HF.

Key words: Neurovegetative symptoms; Menopause; Isoflavones.

Introduction

Hormone therapy (HT) is an effective treatment for controlling the most common menopausal symptoms: hot flushes (HF) and night sweats [1-4]. However, it is now recommended only in low doses given for the shortest possible time because of concerns about increased risk of some chronic diseases [7-10].

Vasomotor symptoms, such as HF and night sweats, are very common during the menopausal transition. HT has traditionally been used as a highly effective treatment but concerns about increased risk of some chronic diseases have markedly increased the interest of women in alternative treatments. Some of the most popular of these treatments are foods or supplements enriched with phytoestrogens plant-derived chemicals that have estrogenic action [5, 6].

This meta-analysis of clinical trials suggests that composite and specific phytoestrogens supplementations were associated with modest reductions in the frequency of HF and vaginal dryness, but no significant reduction in night sweats [4, 10].

Phytoestrogens are plant compounds with estrogen-like biological activity and have been proposed as a replacement to estrogen deficiency consecutive to menopause [1-14]. For several years a large volume of controversial scientific literature has been dealing with the efficacy of phytoestrogens in menopausal treatment [6]. While postmenopausal HT has been shown to be effective in the treatment of climacteric symptomatology and in the prevention of osteoporotic fractures, its efficacy in the prevention of cardiovascular disease is still debated [3, 8, 12].

There are three main classes of phytoestrogens: isoflavones, coumestans, and lignans, which are found in either plants or their seeds. A single plant often contains more than one class of phytoestrogens. The major isoflavones, genistein, and daidzein, commonly exist as inactive glucosides [9].

Soy has received attention as an alternative to conventional hormone replacement therapy (HRT) largely because it is an unique dietary source of isoflavones. Isoflavones are diphenolic compounds that have both hormonal and

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non-hormonal properties and are considered to be selective estrogen receptor modulators [10].

To assess the efficacy, safety, and acceptability of food products, extracts, and dietary supplements containing high levels of phytoestrogens when compared with no treatment, for the amelioration of vasomotor menopausal symptoms (such as HF and night sweats) in perimenopausal and postmenopausal women [1-14].

Materials and Methods

To investigate the efficacy of nutraceuticals containing 80 mg amounts of isoflavones (72 mg of genistein), 30 mg of cimicifuga racemosa, 40 mg of ascorbic acid (vitamin C), 6 mg of vitamin E, 12.5 mcg of vitamin D3, 1 mg of resveratrol, 25 mg of passiflora incarnata L., 10 mg of borrago officinalis L., and 1 mg of crocus sativus L. on the number and severity of vasomotor symptoms (HF and night sweats) in peri- and postmenopausal women.

A randomized, controlled, clinical trial was conducted. A total of 92 women reporting vasomotor symptoms at baseline were randomized into one of two groups.

The study was conducted on outpatients according to a multicenter, randomized, double-blind, placebo-controlled, parallel-group design. A total of 92 patients in natural menopause suffering from at least seven HF per day were randomized to receive during six months either soy isoflavone extract (total of 80 mg per day) or placebo.

A total of 92 women were selected, with a 12-week duration of intervention, having selected postmenopausal and affected with HF attributed to the climacterium (without cancer background). The intervention to be evaluated was "no soy/placebo treatment" or "isoflavones concentrate" (72 mg genistein). The results were expressed as the number of HF, average score of vasomotor symptoms or average percent reduction in HF within a time unit (day, week, or month).

Results

The study period of 12 months was completed by 92 patients out of 92 enrolled (46 in the therapy group and 46 in the untreated group). The women completing the study had a mean age of 51.2 (range 41-56) years and a BMI of 26.7 (range 21.7-29.9) kg/m^2. The menopause mean age was 49.6 (range 45-56) years, and the mean duration of menopause 9.5 (range 1-27) years. By group, the mean age in treated group was 50.7 ± 5.3 years and the BMI 26.3 ± 2.2 kg/m^2. In the untreated group the mean age was 55.5 ± 4.5 years and the BMI 26.1 ± 1.5 kg/m^2.

The present study suggested that extracts with high (80 mg) levels of isoflavones (72 mg of genistein) and 30 mg of cimicifuga racemosa consistently reduced the frequency of HF.

The isoflavones treatment led to a progressive significant ($p < 0.01$) reduction of the number of HF in the group of geinstein treated patients. At week 12 the Kupperman index and HF score decreased significantly in all the treated group. A regular decrease of Kupperman index value and improvement of life quality were observed in the group of 46 postmenopausal treated women.

The present authors noted a decrease in the intensity and number of HF, diaphoresis ($p < 0.05$), diminished sleep disturbances ($p < 0.05$), decreased headache, dizziness, and arthrosis pain. Influence of genistein on the variability and moderation of depressive mood ($p < 0.05$) have been also positively evaluated by patients.

Discussion

A number of clinical trials of soy foods have been conducted in postmenopausal women, aimed at evaluating the effects on HF and vaginal cytology. Results and conclusions have been variable but promising with regard to estrogenic effects [2-5].

Estrogens deficiency is associated with significant alterations in lipoprotein metabolism, with serum cholesterol concentrations increasing markedly in the postmenopausal years. Animal studies have shown that substituting soy proteins for dietary animal proteins reduces serum total and LDL-cholesterol concentrations [8-14]. Only limited epidemiologic research has evaluated the impact of soy or isoflavones intake on depression, although several studies from China and Japan did find soy products intake was inversely related to risk of depression [9-13].

Some trials reported a slight reduction in HF and night sweats with phytoestrogens-based treatment. Extracts containing high levels of genistein (a substance derived from soy) appeared to reduce the number of daily HF and need to be investigated further. Overall no indication suggested that other types of phytoestrogens work any better than no treatment. No evidence was found of harmful effects on the lining of the womb, stimulation of the vagina or other adverse effects with short-term use [1-5]. The clinical and epidemiologic evidence suggests that isoflavones may offer a safe, well-tolerated option for management of depression. Furthermore, the intervention doses used in the clinical studies fall well within the dietary range [1-14]. The extant literature reveals key design features for future studies, which based upon the results of this study, are clearly warranted [8-11].

There is currently sufficient evidence to support the use of cimicifuga racemosa for menopausal symptoms. However, there is adequate justification for conducting further studies in this area. The uncertain quality of identified trials highlights the need for improved reporting of study methods, particularly with regards to allocation concealment and the handling of incomplete outcome data [6-8]. The effects of cimicifuga racemosa on other important outcomes, such as health-related quality of life, sexuality, bone health, night sweats, and cost-effectiveness also warrant further investigation [8, 10].

Conclusions

The present findings suggest that oral soy isoflavones and cimicifuga racemosa are effective to attenuate slight to moderate menopausal neurovegetative symptoms. In daily practice conditions, high doses of isoflavones, particularly genistein, and cimicifuga racemosa can be used for the management of HF in postmenopausal women not treated with HRT due to their superior efficacy to placebo and very good safety profile.

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