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Soy isoflavones, inulin, calcium, and vitamin D3 in post-menopausal hot flushes: an observational study

A. Cianci[1], N. Colacurci[2], A.M. Paoletti[3], A. Perino[4], E. Cicinelli[5], S. Maffei[6], M. Di Martino[7], R. Daguati[7], M. Stomati[8], M. Pilloni[3], S.G. Vitale[1], E. Ricci[7], F. Parazzini[7]

[1] University of Catania, Catania; [2] University of Naples Federico II, Naples [3] University of Cagliari, Cagliari
[4] University of Palermo, Palermo; [5] University of Bari Aldo Moro, Bari
[6] CNR Pisa, Institute of Clinical Physiology of CNR Pisa, Pisa
[7] University of Milan, Department of Clinical and Community Sciences, University of Milan, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan; [8] «D. Camberlingo» Hospital, Francavilla Fontana, Brindisi, A.S.L. Brindisi Presidio Ospedaliero Camberlingo, Francavilla Fontana (BR) (Italy)

Summary

Purpose of investigation: To evaluate the effect of soy isoflavones and inulin (SII) on hot flushes (HF) and quality of life in a clinical setting, the authors conducted an observational study. *Materials and Methods:* The authors performed an observational, prospective, multicentric study on women in peri-/post-menopause treated or untreated with a product present on the Italian market, consisting in a mixture of calcium (500 mg), vitamin D3 (300 IU), inulin (3 g) and soy isoflavones (40 mg). *Results:* A total of 135 patients, 75 (55.6%) in the SII group and 60 (44.4%) in the untreated group entered the study. After three months, the mean number of HF declined of 2.8 (SD 3.7) in the SII group and 0.0 in the untreated one. The corresponding values after six months were –3.7 (SD 2.7) in the SII group and –0.9 (SD 5.3) in the control group ($p = 0.02$). *Conclusion:* This observational trial suggests a possible beneficial effect of a dietary soy supplement containing 40 mg of isoflavone/day plus inulin in the management of menopausal symptoms such as hot flashes.

Key words: Menopause; Hot flushes; Inulin; Isoflavone.

Introduction

Peri-menopausal and post-menopausal women frequently experience vasomotor symptoms (VMS); if severe, they may remarkably worsen the woman's quality of life. Hormone therapy (HT) is the therapy of choice, but it has potential long term risk [1].

In recent years it has been suggested that phytoestrogens may represent an effective alternative, providing a weak estrogen-like activity sufficient to improve VMS [2], glucose homeostasis [3], and reducing bone turnover [4]. Additionally, inulin has been shown to enhance soy isoflavones absorption [5].

In order to evaluate the effect of soy isoflavones and inulin (SII) on hot flushes (HF) and quality of life in a clinical setting, the authors observed a unselected population of Italian women with VMS, not taking HT, treated with soy isoflavones and inulin, in comparison with an untreated group with similar characteristics.

Materials and Methods

The authors performed an observational, prospective, multicentric study on women in peri-/post-menopause treated or untreated with a product present on the Italian market, consisting in a mixture of calcium (500 mg), vitamin D3 (300 IU), inulin (3 g), and soy isoflavones (40 mg).

All peri- and post-menopausal women referring to the participating Menopause Clinics in the study period (beginning of study: January 2012), aged 45-60 years, with at least three hot flushes a day, not requiring HT and/or therapy for osteopenia/osteoporosis, and not on HT in the last month, were eligible for the study. They were asked to give their informed consent to the study. The study was approved by the Institutional Review Committee of IRCCS Policlinico of Milan.

As this is an observational study, the choice of therapy was entirely up to the individual physicians and patients in each center. As by clinical practice, women were proposed soy isoflavones and inulin and calcium therapy. Those who accepted were included in the treatment group, those who did not in the untreated group. General characteristics and anamnesis were collected and patients fulfilled the MenQOL questionnaire [6]. Follow-up visits were scheduled after three and six months and information about HF frequency and adverse events was recorded. The MenQOL questionnaire was administered at each visit.

Statistical analysis

Descriptive statistics (mean±standard deviation, SD), median (interquartile range, IQR), and frequency (%) were used to describe the study population. Women were evaluated at study entry and after three and six months. Primary endpoint was the mean change in the number of HFs/day; secondary endpoints were the mean change in the domains of the MenQOL validated question-

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Table 1. — *Baseline characteristics of women enrolled in the observational study.*

Variable	Soy isoflavones and inulin (n.: 75) mean (SD)		No treatment (n.: 60) mean (SD)		*p*
Age (years)	53.7	4.4	53.7	4.0	0.96
Age at menopause (years)	49.3	4.0	48.8	3.7	0.57
Hot flushes (n. / day)	5.9	4.3	5.8	6.8	0.89
Previous therapy for menopausal symptoms (n.%)	11	14.7%	5	8.3%	0.23
MenQOL score					
Vasomotor domain	4.4	2.1	3.9	1.9	0.16
Psychosocial domain	3.1	1.5	3.3	1.6	0.51
Physical domain	3.0	1.0	3.2	1.2	0.34
Sexual domain	3.9	2.0	3.7	2.1	0.60

naire. Univariate analysis of variance was used to test changes from the baseline.

Sample size

The authors foresaw to include into the study 200 subjects. They interrupted the trial when the recruitment reached 135 women due to the low recruitment rate during the last period of the study. With this sample size, they were able to identify a decrease of two HF per day (SD 4). This decrease may be considered the minimum clinically important change from baseline in the treated group as compared to the not treated one.

Results

A total of 135 patients, 75 (55.6%) in the SII group and 60 (44.4%) in the untreated group entered the study. General characteristics are shown in Table 1. Baseline characteristics were comparable by group: no statistically significant difference was present, in particular the two groups were comparable in terms of baseline values of mean number of HF and of the considered domains of the MenQOL questionnaire.

A total of 19 women in the SII were lost to follow up (16 in the first three months of treatment and three in the three to six months period). The corresponding numbers in the no treatment group were six and 22.

Out of the 69 women in the SII group who were seen at three- or six- month visit, nine (13.0%) stopped the treatment: they were not considered in the HF and MenQOL analysis. After three months, the mean number of HF declined of 2.8 (SD 3.7) in the SII group, but in the control group it was unchanged ($p = 0.0009$). The corresponding values after six months were –3.7 (SD 2.7) and –0.9 (SD 5.3) ($p = 0.02$, Table 2).

Considering the MenQOL questionnaire, after three-month follow up, the mean changes from baseline showed a favourable effect of SII as compared to no treatment in the vasomotor and sexual domain. At six-month follow-up, these improvements were statistically significant in all the domains.

Adverse events are considered in Table 3. A total of nine women stopped the treatment due to adverse effects. Nausea and vomiting were more commonly reported in the SII group than in the untreated one, but the differences were not statistically significant. Women reported having felt bloating less frequently in the treatment group than in the not treated group: 33.3% versus 54.4% ($p = 0.02$).

Table 2. — *Vasomotor symptoms and MenQOL scores at three- and six-month visits.*

Variable	Soy isoflavones and inulin mean (SD)		No treatment mean (SD)		*p*
Three-month follow-up	(n. = 59)		(n. = 54)		
Hot flushes (n. / day): change from baseline	-2.8	3.7	0.0	4.0	0.0009
MenQOL scores: change from baseline					
Vasomotor domain	-0.7	0.8	-0.3	1.4	0.04
Psychosocial domain	-0.4	0.6	-0.2	1.2	0.29
Physical domain	-0.3	0.6	-0.2	0.9	0.22
Sexual domain	-0.8	1.1	0.1	1.6	0.003
Six-month follow-up	(n. = 56)		(n. = 32)		
Hot flushes (n. / day): change from baseline	-3.7	2.7	-0.9	5.3	0.02
MenQOL scores: change from baseline					
Vasomotor domain	-1.5	1.3	-1.2	1.9	0.006
Psychosocial domain	-0.9	1.1	-0.5	1.5	0.008
Physical domain	-0.9	0.7	-0.5	1.4	0.006
Sexual domain	-1.3	1.5	-0.4	2.0	0.0001

Table 3. — *Adverse events at three- and six-month visits.*

Variable	Soy isoflavones and inulin		No treatment		*p*
	N.	%	N.	%	
Nausea	17	24.6	5	8.8	0.02
Vomiting	10	14.5	6	10.5	0.50
Bloat	23	33.3	31	54.4	0.02

Ten patients in the soy isoflavones and inulin and three in the no treatment group did not attend the three-month visit but were seen at six-month visit: accordingly, overall period adverse events recorded were from 69 and 57 subjects, respectively.

Discussion

In this study, three-month supplementation with soy isoflavones and inulin was effective in reducing the mean number of hot flushes per day in peri- and post-menopausal women. Further significant changes in the quality of life score were observed in all the MENQOL domains after six months of treatment.

The results of this study are consistent with those reported in several studies [7-12] but not in others [13-15]. This inconsistency has been, although not entirely explained due to different and inadequate isoflavone doses [7].

In this study the authors used 40 mg of soy isoflavones plus inulin, that has been shown to enhance soy isoflavones absorption [5] and, potentially, the therapeutic effect.

To evaluate the quality of life at baseline and during the sixth-month follow-up, the 29-item MenQOL was used [6] It is a self-administered, health-related quality of life scale for menopausal women. It indicates the well being as regards four domains (vasomotor, psychological, physical, and sexual).

In the present study; after three months of treatment, the differences were not significant in the psychological and physical domains, whereas vasomotor and sexual improvement emerging. At the six-month follow-up, women still on treatment showed a consistent relief of discomfort in all the domains.

In a double-blind, randomized, controlled, intention-to-treat trial a treatment with 50 mg of lignans, 25 g of soy and 42 mg of isoflavones showed no significant effect of treatment on all quality-of-life domains measured with the MenQOL questionnaire [13]. It is difficult to interpret these different results. The observational design versus the randomized one should be considered, however it is conceivable that the association of isoflavones with inulin may enhance the clinical effect of isoflavones.

In the present study, gastrointestinal adverse events were more frequent, but in a non-statistically significant way, in the SII group. Nausea and vomiting were reported in about 25% of treated women and 15% of untreated ones, whereas feeling bloated was more frequent among women not receiving the treatment. This may be at least partially explained by a bias toward reporting adverse effects in women aware of taking an active treatment. Along this line, in several randomised studies reporting adverse effects in women taking soy isoflavones [8, 16, 17], the frequency of gastrointestinal complaints was much lower. In fact, for example, the higher figure was 7.3% in the active treatment and 8.6% in the placebo group, reported by in Ferrari [16] and similar by treatment arm, when patients were blind to the assigned treatment.

The main limitation of this study was the observational design. Being aware of the treatment can affect both the response to supplementation and the adverse event reporting. In fact, the proportion of women reporting nausea and vomiting was remarkably higher than in randomised, placebo controlled trial using similar interventions [8, 17].

In conclusion, this observational trial suggests a possible beneficial effect of a dietary soy supplement containing 40 mg of isoflavone/day plus inulin in the management of hot flushes. As alternative treatment, soy isoflavones plus inulin combination might represent an interesting and safe, at least in the medium term, alternative in women who do not accept conventional HRT, but are seeking relief for menopausal vasomotor symptoms.

References

[1] Rossouw J.E., Anderson G.L., Prentice R.L., LaCroix A.Z., Kooperberg C., Stefanick M.L.*, et al.:* "Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial". *JAMA*, 2002, *288,* 321.

[2] Taku K., Melby M.K., Kronenberg F., Kurzer M.S., Messina M.: "Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials". *Menopause*, 2012, *19,* 776.

[3] Ricci E., Cipriani S., Chiaffarino F., Malvezzi M., Parazzini F.: "Effects of soy isoflavones and genistein on glucose metabolism in perimenopausal and postmenopausal non-Asian women: a meta-analysis of randomized controlled trials". *Menopause*, 2010, *17,* 1080.

[4] Taku K., Melby M.K., Nishi N., Omori T., Kurzer M.S.: "Soy isoflavones for osteoporosis: an evidence-based approach". *Maturitas*, 2011, *70,* 333.

[5] Piazza C., Privitera M.G., Melilli B., Incognito T., Marano M.R., Leggio G.M.*, et al.:* "Influence of inulin on plasma isoflavone concentrations in healthy postmenopausal women". *Am. J. Clin. Nutr.*, 2007, *86,* 775.

[6] Hilditch J.R., Lewis J., Peter A., van Maris B., Ross A., Franssen E.*, et al.:* "A menopause-specific quality of life questionnaire: development and psychometric properties". *Maturitas*, 1996, *24,* 161.

[7] Burke G.L., Legault C., Anthony M., Bland D.R., Morgan T.M., Naughton M.J.*, et al.:* "Soy protein and isoflavone effects on vasomotor symptoms in peri- and postmenopausal women: the Soy Estrogen Alternative Study". *Menopause*, 2003, *10,* 147.

[8] Cancellieri F., De Leo V., Genazzani A.D., Nappi C., Parenti G.L., Polatti F.*, et al.:* "Efficacy on menopausal neurovegetative symptoms and some plasma lipids blood levels of an herbal product containing isoflavones and other plant extracts". *Maturitas*, 2007, *56,* 249.

[9] Crisafulli A., Marini H., Bitto A., Altavilla D., Squadrito G., Romeo A.*, et al.:* "Effects of genistein on hot flushes in early postmenopausal women: a randomized, double-blind EPT- and placebo-controlled study". *Menopause*, 2004, *11,* 400.

[10] D'Anna R., Cannata M.L., Atteritano M., Cancellieri F., Corrado F., Baviera G.*, et al.:* "Effects of the phytoestrogen genistein on hot flushes, endometrium, and vaginal epithelium in postmenopausal women: a 1-year randomized, double-blind, placebo-controlled study". *Menopause*, 2007, *14,* 648.

[11] Han K.K., Soares J.M Jr., Haidar M.A., de Lima G.R., Baracat E.C.: "Benefits of soy isoflavone therapeutic regimen on menopausal symptoms". *Obstet. Gynecol.*, 2002, *99,* 389.

[12] Faure E.D., Chantre P., Mares P.: "Effects of a standardized soy extract on hot flushes: a multicenter, double-blind, randomized, placebo-controlled study". *Menopause*, 2002, *9,* 329.

[13] Lewis J.E., Nickell L.A., Thompson L.U., Szalai J.P., Kiss A., Hilditch J.R.: "A randomized controlled trial of the effect of dietary soy and flaxseed muffins on quality of life and hot flashes during menopause". *Menopause*, 2006, *13,* 631.

[14] Nikander E., Kilkkinen A., Metsa-Heikkila M., Adlercreutz H., Pietinen P., Tiitinen A.*, et al.:* "A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients". *Obstet. Gynecol.*, 2003, *101,* 1213.

[15] Penotti M., Fabio E., Modena A.B., Rinaldi M., Omodei U., Vigano P.: "Effect of soy-derived isoflavones on hot flushes, endometrial thickness, and the pulsatility index of the uterine and cerebral arteries". *Fertil. Steril.*, 2003, *79,* 1112.

[16] Ferrari A.: "Soy extract phytoestrogens with high dose of isoflavones for menopausal symptoms". *J. Obstet. Gynaecol. Res.*, 2009, *35,*1083.

[17] Kotsopoulos D., Dalais F.S., Liang Y.L., McGrath B.P., Teede H.J.: "The effects of soy protein containing phytoestrogens on menopausal symptoms in postmenopausal women". *Climacteric*, 2000, *3,* 161.

Address reprint requests to:
F. PARAZZINI, M.D.
Department of Clinical and Community Sciences
University of Milano, Fondazione IRCCS
Ca' Granda Ospedale Maggiore Policlinico
Via Commenda 12, 20122 Milan (Italy)
e-mail: Fabio.Parazzini@unimi.it