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ORIGINAL ARTICLE

EFFECT OF SOY PROTEINS Vs SOY ISOFLAVONES ON LIPID PROFILE IN POSTMENOPAUSAL WOMEN

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ABSTRACT

Soy isoflavones and soy proteins are being considered as possible alternatives to postmenopausal hormone replacement therapy. This study was undertaken to evaluate effects of these two preparations on symptoms and lipid profile in postmenopausal women. The study was done in 75 postmenopausal women with FSH levels = 30 mIU/ml. These women were randomly divided into 3 groups (n=25). Study group I was given soy proteins 30gm/day containing 60 mg soy isoflavones. Study group II was given soy isoflavones (60 mg/day). The control group was given casein protein 30 gm/day. The menopausal symptoms were assessed by Kupperman Index. Fasting blood samples were analyzed for serum lipid profile, apolipoprotein A1 and B, Leutenizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) at the beginning of therapy, 4 and 12 weeks after initiation of therapy. A highly significant improvement in postmenopausal symptoms was observed in both the study groups. A highly significant improvement was seen in serum lipid profile and Apolipoprotein A1 and B in women taking soy proteins whereas women taking soy isoflavones demonstrated significant improvement in serum triglycerides only. Both soy proteins and soy isoflavones are helpful in alleviating postmenopausal symptoms but soy proteins offer a greater health advantage due to their beneficial effect on serum lipid profile.

KEY WORDS

Soy proteins, Soy isoflavones, Lipid profile, Kupperman Index, Apolipoproteins, Postmenopausal symptoms.

INTRODUCTION

Menopause is a normal life transition in a woman's life when reproductive capacity ceases due to loss of ovarian function resulting in a decrease in circulating estrogen levels (1). It is an objective hormonal event associated with subjectively perceived endocrine transition, resulting in various short-term vasomotor (hot flashes, mood swings, depression, nervousness, irritability) and urogenital symptoms (recurrent vaginitis, dysuria etc) and long-term sequelae- osteoporosis, Alzheimer's disease and Coronary Artery disease (CAD) (2).

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Due to increased longevity and awareness, most women seek help of the clinicians for these symptoms. Estrogen therapy has been recommended to postmenopausal women for alleviation of symptoms and long-term benefits (3).

However, recent evidence from studies of Women's Health Initiative showed that the combined estrogen and progestin therapy increased risks of coronary heart disease, stroke, pulmonary embolism and breast cancer (4). Recently, estrogen-like compounds from plants like soy proteins provide a new nutritional dimension to the management of short-term as well as long term effects of estrogen deficit (5). Epidemiological data suggest and indicate that only 25% of Japanese women complain of climacteric symptoms compared with 85% North American women and this difference has been attributed to soy protein consumption in Asian countries (6).

The beneficial effects of soy protein have been attributed to its active component - the phytoestrogens or the isoflavones

(7). These act on estrogen receptor owing to their structural similarity to estrogen or independently influence cell proliferation and cell differentiation process (8). Initial reviews on complementary and alternative medicine for menopausal symptoms indicate that soy protein is more effective than isoflavones for menopausal symptoms (9). Also soy proteins with increased concentration of isoflavones have a beneficial effect on lipid profile and osteoporosis in postmenopausal women (10). In another study on phytoestrogens supplementation, it is observed that soy protein as a whole appears to be required for the hypocholesterolemic effect as compared to its isoflavone alone, although phytoestrogens may have other beneficial effects on CVS as improvement in arterial compliance (11).

Hence a study was undertaken in North Indian postmenopausal women to study the role of soy protein as a whole and soy isoflavones in alleviating menopausal symptoms and urogenital problems, their effect on serum lipid and apolipoprotein levels and atherogenic index.

MATERIALS AND METHODS

The experimental design was that of a randomized placebo controlled, double blinded phase III trial. A total of 75 postmenopausal women, presenting with vasomotor or genito -urinary complaints were included in the study after a written, informed consent. Age 40-60 years, either surgically or naturally menopausal with FSH levels ≥ 30mIU/ml. Surgical menopausal women were those who had undergone hysterectomy with bilateral salpingo-oophorectomy for some benign disease of uterus and adenexa. They were included in the study after their histopathology report was negative for malignancy. The natural menopausal group consisted of those women who had their last menstrual period at least 1 year earlier but not more than 10 years.

Subjects with history of major medical illnesses like myocardial infarction, stroke, congestive heart failure, hepatitis or a history of malignant disease of breast or known or suspected estrogen dependent tumors, myomas or endometrial carcinoma. Women receiving any treatment for menopausal symptoms were excluded. All women with high triglyceride level ≥ 500 mg/dl and those who were receiving anti-hyperlipidemic drugs were excluded from the study.

All the seventy five women were randomly divided into 3 groups including 2 study groups and one control group. Study Group I included 25 women who were given soy protein (powder) 30 gm/day containing 60 mg of isoflavones. Study Group II included 25 subjects who were given soy isoflavones 60mg/ day (tablet). Control Group included 25 subjects who were given casein protein 30 gm/day. Detailed history of the patients was taken for any major illness, drug intake or malignancy. They underwent routine clinical examination including examination of breast. Women with intact uterus were subjected to ultrasonogram lower abdomen and PAPS smear at the beginning and end of 12 weeks of therapy to rule out any premalignant/ malignant changes in uterus and adenexa and to assess the endometrial thickness.

Evaluation of menopausal symptoms was done by menopausal index devised by Kupperman and Blatt (12), which includes eleven variables as vasomotor symptoms, paresthesias (numbness, tingling sensation and temperature changes), insomnia, nervousness, melancholia, weakness and fatigue, myalgia and arthalgia, headache, palpitations, formication and vertigo. Vasomotor complaints were given a score of 4, paresthesias, insomnia and nervousness were given a score of 2 each and the rest were scored at 1 each. Each symptom was graded 0 to 3 depending on severity.

Venous blood sample was taken after an overnight fast and analysed for blood glucose, renal function tests, liver function tests, lipid profile (serum cholesterol, triglycerides, high density lipoprotein (HDL) and low-density lipoprotein (LDL), Very Low density Lipoprotein (VLDL) and Apolipoprotein A1 and B (immunoturbidimetric) on Synchron CX5 Clinical Chemistry Autoanalyser (Beckman) using standard reagents and kits from Randox (UK). All the tests were carried out at the beginning and 4 and 12 weeks after supplementation. Atherogenic index was calculated for each patient by dividing proatherogenic lipid fractions by anti-atherogenic fractions. (Total Cholesterol-HDL) x Apoliporotein-B/ Apolipoprotein A1 x HDL. Serum LH and FSH were measured by ELISA using commercial kits. All the women were re-evaluated at 4 and 12 weeks. The follow-up included detailed history of menopausal symptoms, evaluation of urogenital symptoms, routine hematological and biochemical profile, lipid profile, hormonal assays-LH and FSH and evaluation of endometrial thickness by pelvic ultrasound.

Continuous variables were expressed as mean ± Standard Error of Mean. The Student's 't' or Mann–Whitney U test, depending on the shape of the distribution curves, was used for evaluation of differences in continuous variables. For paired samples, Wilcoxon- signed rank test was used. A two-tailed $P<0.05$ was considered statistically significant and those less than 0.01 were considered highly significant. Statistical analysis was carried out using SPSS for windows 10.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

The patients selected for the study were comparable for age, parity, Body Mass Index and time since menopause and no statistically significant difference was found between the three groups (Table1). When all the groups were considered together, 88% of the postmenopausal women presented with vasomotor symptoms. Weakness with fatigue, arthralgia and myalgias were the commonest complaints found in all women followed by paresthesias, which were complained by 96% women. Mean Kupperman Index reduced by 44% in Study Group I, 42.6% in study group II and 24.9% in the control group. Changes in Study Group I and Study Group II were highly significant whereas in the control group the changes were significant.

Table 1: Comparable clinical parameters in the study group I and II and Control Group

	Study Group I (soy Protein) (Mean ±SEM)	Study Group II (soy Isoflavones) (Mean ±SEM)	Control Group (Mean ±SEM)
Age (Years)	51.21 ± 1.10	51.23 ± 1.12	50.96 ± 2.4
Parity	2.92 ± 0.16	2.92 ± 0.13	3.28 ± 0.21
BMI (Kg/m^2)	23.25 ± 0.52	23.50 ± 0.66	23.56 ± 0.55
Time since menopause (yrs)	2.20 ± 0.22	2.88 ± 0.25	2.52 ±0.25

Improvement in different vasomotor symptoms with therapy is shown in Table 2. Amongst the genito-urinary symptoms, the most common complaint was frequency of micturition (73% women), followed by urgency (68%) and dysuria (52%). In the soy protein group maximum improvement was seen in urgency (33%) followed by frequency (27.7%). Similarly, in soy isoflavone group urgency showed marked relief in 29.48% patients followed by frequency (25%). Women on soy proteins reported maximum relief in dyspareunia (44%) women as compared to soy isoflavones (37.5%). These findings could be related to increased vaginal maturation index observed in women on soy proteins and soy isoflavones.

Serum cholesterol, triglycerides, HDL, LDL, VLDL and apolipoprotein A1 and B levels were estimated for each patient at the beginning of the study and were found to be similar in all the 3 groups (Table 3). At the end of 3 months, a highly significant improvement was seen in serum Lipid Profile, Apolipoprotein A1 and B levels in patients taking soy proteins whereas in the women taking soy isoflavones only Triglyceride levels were found to improve. In the control group, no-significant changes were seen in the lipid profile and Apolipoprotein A1 and B during the study period. Atherogenic indices in all the three groups were comparable at the beginning of the therapy. In the women taking soy proteins, it showed a highly significant decrease at 4 weeks (3.160) and 12 weeks (2.657) as compared to baseline (4.168). No change was observed in the control group and the soy isoflavone group during the study period.

The mean changes in serum LH and FSH levels are shown in Table3. A decrease was observed in serum LH levels in all the three groups but it was significant only in the soy protein group (P=0.013) at the end 0f 12 weeks of therapy. Serum FSH levels did not vary significantly in both the study groups. However, in the control group a very highly significant increase was observed. Endometrial thickness did not vary significantly in all the three groups before and after therapy. The most commonly observed side effects were bloating, abdominal pain and constipation observed in approximately 20% of the patients taking soy proteins and soy isoflavones. Other minor side effects were nausea and vomiting observed in one patient in each group.

DISCUSSION

The ovary is the only endocrine organ that stops its functioning before the final stages of life resulting in unpleasant symptoms. The present double-blinded clinical study was done to evaluate the short-term effects of soy-proteins and soy isoflavones as compared to placebo in postmenopausal women. The average age of the women included in this study was approximately 51 years with average time since menopause ranging from 2.2 to 2.8 years. The age at menopause in our study was similar to the earlier studies which have reported menopause at 43 to 49 years in developing countries (13, 14).

In the present study, 88% women presented with mild vasomotor symptoms and 3% complained of severe hot flushes. All 75 women complained of weakness and fatigue. In women taking soy proteins and soy isoflavones the decrease in Kupperman Index after 3 months of therapy was highly significant (44% in study group I and 42.6% in study group II as compared to the control group, where 24.9% decline in Kupperman Index was seen). Our findings are in contrast to earlier report by Germain etal where no improvement in menopausal index was seen with either soy proteins or soy isoflavones after 24 weeks (15). However, Murkies et al have demonstrated significant decrease in menopausal symptoms in soy supplemented group with in 6 weeks as compared to wheat flour group (16). In women taking placebo significant improvement was seen in hot flushes, insomnia, paresthesias

Table 2 : Comparative study of soy proteins, soy isoflavones and placebo on menopausal symptoms by Kuppermann Index

		0 weeks	4 weeks	12 weeks
Vasomotor Complaints	Study Group I	7.36 ± 0.75	5.92 ± 0.70	4.48 ± 0.78**
	Study Group II	8.96 ± 0.18	7.68 ± 0.76	5.28 ± 0.76**
	Control Group	7.68 ± 0.76	7.04 ± 0.70	6.40 ± 0.73*
Paresthesias	Study Group I	5.12 ± 0.31	4.72 ± 0.30	3.28 ± 0.23**
	Study Group II	4.24 ± 0.31	3.52 ± 0.30	2.48 ± 0.24**
	Control Group	3.52 ± 0.17	3.44 ± 0.18	3.04 ± 0.26*
Insomnia	Study Group I	3.12 ± 0.55	2.56 ± 0.47	1.20 ± 0.23**
	Study Group II	2.48 ± 0.53	1.12 ± 0.39	0.96 ± 0.23**
	Control Group	1.92 ± 0.39	1.60 ± 0.35	1.28 ± 0.28*
Nervousness	Study Group I	2.16 ± 0.54	1.84 ± 0.46	0.48 ± 0.15**
	Study Group II	3.12 ± 0.55	2.40 ± 0.42	0.72 ± 0.16**
	Control Group	3.22 ± 0.55	2.56 ± 0.41	2.19 ± 0.17*
Depressed Mood	Study Group I	1.08 ± 0.28	1.00 ± 0.26	0.24 ± 0.09**
	Study Group II	1.36 ± 0.25	1.16 ± 0.21	1.00 ± 0.1*
	Control Group	0.88 ± 0.16	0.88 ± 0.16	1.00 ± 0.2*
Vertigo	Study Group I	0.84 ± 0.26	0.84 ± 0.26	0.84 ± 0.26
	Study Group II	0.92 ± 0.24	0.92 ± 0.24	0.84 ± 0.26*
	Control Group	0.92 ± 0.24	0.92 ± 0.24	0.92 ± 0.24
Weakness/ Fatigue	Study Group I	3.00 ± 0.00	2.64 ± 0.10	2.16 ± 0.10**
	Study Group II	2.80 ± 0.10	2.72 ± 0.11	2.48 ± 0.12**
	Control Group	2.60 ± 0.12	2.32 ± 0.13	2.08 ± 0.1**
Arthralgia + Myalgia	Study Group I	3.00 ± 0.00	2.64 ± 0.10	2.00 ± 0.13**
	Study Group II	2.68 ± 0.10	2.52 ± 0.10	1.96 ± 0.16*
	Control Group	2.20 ± 0.08	2.16 ± 0.09	1.96 ± 0.12
Headache	Study Group I	2.00 ± 0.20	2.00 ± 0.20	0.40 ± 0.13**
	Study Group II	1.36 ± 0.27	1.28 ± 0.26	0.32 ± 0.56**
	Control Group	1.32 ± 0.29	1.20 ± 0.24	1.12 ± 0.56
Palpitation	Study Group I	0.88 ± 0.25	0.88 ± 0.25	0.80 ± 0.24
	Study Group II	0.48 ± 0.21	0.44 ± 0.19	0.32 ± 0.14
	Control Group	0.32 ± 0.14	0.32 ± 0.14	0.32 ± 0.14
Formication	Study Group I	0.24 ± 0.12	0.24 ± 0.14	0.20 ± 0.13
	Study Group II	0.08 ± 0.06	0.08 ± 0.06	0.08 ± 0.06
	Control Group	0.08 ± 0.06	0.08 ± 0.06	0.08 ± 0.06
Mean KI	Study Group I	28.80 ± 1.89	25.28 ± 1.8	16.08 ± 1.25**
	Study Group II	28.48 ± 2.03	24.64 ± 1.49	16.32 ± 1.06**
	Control Group	24.56 ± 1.52	22.52 ± 1.27	18.44 ± 1.11*

*P< 0.05; **P<0.01

and weakness. However, unlike the study group, arthralgia, myalgia and mood did not improve significantly in the placebo group.

In soy protein supplementation group, a highly significant improvement was seen in atherogenic index due to decrease in serum cholesterol, triglycerides, Serum LDL and serum Apolipoprotein B and a highly significant increase in serum HDL. However, in the soy isoflavone and placebo group, no significant change was observed after 3 months. In women taking soy isoflavones, a significant decrease was observed in serum Apolipoprotein B and a highly significant decrease was seen in serum triglycerides. Numerous other clinical studies have shown that soy protein can cause significant reduction in serum total cholesterol, LDL-Cholesterol and triglycerides (17-19). Isoflavones as part of soy protein have been postulated to account for the hypocholesterolemic effect of soy protein (20-22). However, the present study challenges this theory since in the present study, the effect of isoflavones on serum cholesterol, LDL-Cholesterol was not significant, indicating that other components in soy proteins besides soy isoflavones may be responsible for the hypocholesterolemic effects of soy protein. Several other investigations also do not support the hypocholesterolemic role of soy isoflavones

Table 3: Comparative Effects of soy proteins, soy isoflavones and placebo on lipid profile, apolipoproteins, atherogenic index and hormones

		0 weeks	4 weeks	12 weeks
Serum Cholesterol (mg/dl)	Study Group I	191.37 ± 2.79	184.58 ± 3.12	169.71± 2.74**
	Study Group II	185.55 ± 4.0	187.44 ± 2.81	188.18 ± 4.91
	Control Group	181.31 ± 5.50	179.80 ± 5.34	180.35 ± 5.13
Serum Triglycerides (mg/dl)	Study Group I	155.40 ± 3.85	139.96± 3.86**	123.92± 3.67**
	Study Group II	153.28 ± 3.59	143.92± 4.15**	130.68± 4.40**
	Control Group	155.80 ± 3.03	157.04 ± 3.69	162.68 ± 4.28
Serum HDL (mg/dl)	Study Group I	40.82 ± 1.15	46.55 ± 0.97**	48.24 ± 1.63**
	Study Group II	43.58 ± 1.41	43.96 ± 1.52	44.84 ± 1.36
	Control Group	40.84 ± 1.22	39.52 ± 1.57	42.42 ± 1.42
Serum LDL (mg/dl)	Study Group I	119.48 ± 2.83	109.99 ± 3.04*	96.59 ± 3.28**
	Study Group II	110.95 ± 4.89	115.08 ± 3.53	107.56 ± 5.36
	Control Group	109.27 ± 5.88	108.72 ± 5.92	106.05± 5.65
Serum Apolipoprotein A1 (mg/dl)	Study Group I	128.56 ± 2.55	130.75 ± 2.87	131.24 ± 3.42
	Study Group II	129.76 ± 2.81	133.65 ± 2.62	137.17 ± 3.96
	Control Group	130.04 ± 1.28	130.96 ± 1.22	131.20 ± 1.40
Serum Apolipoprotein B (mg/dl)	Study Group I	139.52 ± 4.26	136.68± 4.34**	129.44 ±3.93**
	Study Group II	145.90 ± 3.79	142.44 ± 3.43	137.32 ±3.33*
	Control Group	141.72 ± 4.05	142.04 ± 4.00	142.08 ± 4.00
Atherogenic Index	Study Group I	4.17 ± 0.25	3.16 ± 0.15**	2.66 ± 0.21**
	Study Group II	3.87 ± 0.27	3.67 ± 0.20	3.47 ± 0.35
	Control Group	3.83 ± 0.22	3.65 ± 0.27	4.03 ± 0.28
Serum LH	Study Group I	36.72 ± 0.71	35.37± 0.75*	34.24 ± 0.65*
	Study Group II	35.64 ± 0.53	34.72 ± 0.50	34.40 ± 0.57
	Control Group	36.0 ± 1.26	36.32 ± 1.07	35.40 ± 1.39
Serum FSH	Study Group I	61.10 ± 2.32	61.61 ± 2.07	58.82 ± 1.95
	Study Group II	64.17 ± 1.37	61.61 ± 2.13	61.35 ± 1.95
	Control Group	67.04 ± 3.46	69.85 ± 3.85	83.0 ± 2.56**

**P<0.01; *P<0.05

(17, 23-27). Three recent meta-analyses have discussed this issue (28-30) and two concluded that isoflavones do not appear to have a lipid lowering effect (28, 29). The possible biological mechanisms of the effect of soy on blood lipid level may be associated with several of its components, including isoflavones, trypsin inhibitors, phytic acid, saponins, fiber, and small peptide fractions (31-33).

In the study Group I, serum LH levels showed a significant decline from 36.72 ± 0.71 IU/ml to 34.23 ± 0.64 IU/ml (P<0.05). In soy isoflavone group, although serum LH levels decreased from 35.64 ± 0.52 IU/ml to 34.40 ± 0.57 IU/ml, no statistical significance was observed. The control group did not show any significant changes throughout study from 0 to 12 weeks. Serum FSH levels showed a slight decrease in study group I and II (as seen in Table 3), however, these changes were not found significant for duration of the therapy. In contrast, in the control group, FSH levels showed a highly significant increase indicating the trend of declining estrogen levels in untreated patients. Foth and Naworth (34) also demonstrated minimal non-significant changes in hormone levels in women taking 20 g of soy protein containing 20mg soy isoflavones. The increased dose of soy protein (30 g) and soy isoflavones (60 mg) in this study elicited a significant decrease in LH levels in the soy protein group but not in the soy isoflavones group. In another study, even higher doses of isoflavones (114 mg) failed to elicit any changes in FSH and LH levels (35), thus indicating that these phytoestrogens may have a tissue specific/ receptor-specific action which needs further investigation. The most common side effects observed with soy proteins and isoflavones in the present study were abdominal bloating, pain and constipation. Similar side effects have been reported in an earlier study also (36). These harmless yet unpleasant symptoms are usually short-lived and may represent intolerance to proteins. Although comprehensive studies have yet to be completed, the preliminary results of soy protein testing indicate that it can be an invaluable resource for menopausal women from combating menopausal symptoms

to providing protection against menopause related dyslipidemia. Given the evidence, it may be advisable for women to take advantage of this health-promoting plant throughout life and especially in the menopausal years.

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