Isoflavone Rich Soy Protein Supplementation For Postmenopausal Therapy

G Radhakrishnan, Rashmi, N Agarwal, N Vaid

Citation

Abstract
Synopsis: Supplementation of Soy protein isolate containing phytoestrogens in postmenopausal women significantly decreases total and low density cholesterol and improves menopausal symptoms as compared to placebo.

Objective: To examine effects of 6 months supplementation of isoflavone rich soy protein on symptoms, lipid profiles and bone density in postmenopausal women. Methods: In this double blind, placebo controlled trial, hundred healthy postmenopausal women not taking Hormone Replacement Therapy, were randomly assigned to consume either 25gm soy protein isolate containing 75 mg isoflavones(study group) or 25 gm casein protein(control group) daily. Monthly assessment for acceptability & side effects, 3 monthly for menopausal symptoms(Kupperman Menopausal Index; KMI) and serum lipid-profile, 6 monthly for Follicular stimulating hormone, Estradiol levels, vaginal cytology, endometrial thickness and bone density were done. T-test, analysis of variance (ANOVA) and chi square tests were employed.

Results: Significantly higher number of cases reported improvement in hot-flashes, joint-pains and vaginal-dryness on soy treatment(p<.05). Soy supplement was significantly superior to placebo in reducing KMI(p<.05). Soy group showed 7.7% decrease in total cholesterol and 14% decrease in LDL-cholesterol(significantly different from control group p<.05) while no effect was seen on HDL cholesterol, Blood pressure, sex hormones, vaginal cytology, uterine endometrium & bone densitometry.

Conclusion: 25gm soy supplement containing 75mg of isoflavones may be an effective alternative therapy for menopausal symptoms and may offer a benefit to cardiovascular-system by altering lipid-profile favorably.

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INTRODUCTION
Estrogen replacement therapy is highly effective for relief of climacteric symptoms in post menopausal women [1] as well as for the prevention of osteoporosis and cardiovascular disease [1]. Recently publication of results from two large prospective studies, Women’s Health Initiative [1] and Heart and Estrogen/ Progestin Replacement Therapy (HERS) [1] indicating increased risk of breast cancer, stroke and coronary artery disease with hormone replacement therapy (HRT) has reduced the use of HRT for menopausal symptoms. Also HRT is no longer recommended for asymptomatic postmenopausal women [1]. Due to fear and dislike of adverse effects, as well as possible long term risk of HRT, there is increasing interest in effective & safe alternatives to HRT for menopausal problems.

Plant derived substances structurally related to estrogens that have been shown to bind to estrogen receptors, commonly termed phytoestrogens are currently used by many women as alternatives to HRT [1]. Of these, isoflavones which are primarily found in soy beans and their by products are most widely used and studied class. Interest in the use of soy and its derivatives for treatment of menopausal symptoms has been encouraged by observation of a lower prevalence of menopausal symptoms like hot flashes, breast cancer, cardiovascular morbidity & mortality in the inhabitants of Pacific Rim where soy is an important component of traditional diet [1]. Following these epidemiological observations, many clinical studies have shown that diet with supplementation of soy isoflavones is beneficial in decreasing menopausal symptoms [1]. However other studies have failed to demonstrate a reduction of menopausal symptoms with isoflavone supplements in postmenopausal women [1]. As regards potential role in reducing cardiovascular mortality & osteoporosis risk in postmenopausal population, many studies have shown favorable effect of soy proteins with isoflavones on lipid profile [1] and bone density [1], while others have
reported minimal or no effect \cite{15}. The results so far have been conflicting with some studies showing improvement while others reported no effect. So far no study has been published on the effect of soy isoflavone supplements in postmenopausal women in India. Dietary supplements containing isoflavones are being marketed without any sound evidence. Therefore this double blind, randomized, placebo controlled study was designed to evaluate the effect of supplementation of soy protein isolate preparation containing isoflavones on the postmenopausal symptoms, lipid profile and bone densitometry in postmenopausal women in Indian community.

**SUBJECTS AND METHODS**

This prospective, randomized, double blind, placebo controlled six months clinical trial was conducted at the Deptt of Obstetrics & Gynecology, University College of Medical Sciences & Guru Teg Bahadur Hospital, Delhi. A staggered enrolment of participants was continued over a period of 1 year. Hundred postmenopausal women requesting treatment for various symptoms (post menopausal or non specific symptoms) in gynecological OPD were recruited for the study. Inclusion criteria were last menstruation at least 12 months back or 6 weeks since bilateral oophorectomy, FSH level > 40 mIU/ml, unwillingness or intolerance to take HRT and not currently using lipid lowering drugs, antidiabetic medications or herbal supplements. Exclusion criteria were: unexplained vaginal bleeding, hypertension, diabetes, liver dysfunction, renal or cardiac disease, active thromboembolic disease, deep vein thrombosis, coronary artery disease, cerebrovascular accident or past h/o thromboembolic disease associated with estrogen use, present or past estrogen dependent malignancy such as breast or endometrial carcinomas, known peanut/legume allergy. Women who had discontinued HRT more than 3 months back were eligible to be included in the study.

Study was approved by the ethical committee of the institution and informed written consent was obtained from all the participants selected for the study.

The initial evaluation consisted of detailed history, general physical & gynecological examination and cervical cytology. Data included information on age, time since menopause, type of menopause (natural or surgical), weight, height and arterial blood pressure measurement. The cases were then randomly assigned to either the study (soy) group or the control (placebo) group as per computer generated randomized numbers in blocks of ten. Intervention or placebo groups in blocks of ten. The intervention consisted of the study group receiving coded sachets containing 25 g of isoflavone rich soy protein isolate containing 75 mg of isoflavones in powder form, sweetened with aspartame with mild vanilla flavour. The control group received placebo sachets containing 25 g of milk protein which looked & tasted identical to the soy supplement. Both the supplement powders contained equal amounts of elemental calcium (900mg) and other trace elements and vitamins. Each sachet weighed 36.5 gm and provided 130 Calories of energy. Precoded sachets were provided by the DUPONT Protein Technology International. Participants were instructed to consume contents of one sachet per day in 2-3 divided doses dissolved in water, milk or juice. Participants were provided monthly supply of 30 sachets every month by the staff not directly involved with clinical follow up of cases. Treatment duration was 6 months. Participants & investigators were blinded to treatment assigned until the conclusion of the trial. At the completion of the study decoding was provided by the Dupont Protein Technology International.

Baseline evaluation: The cases were evaluated at baseline, mid (3 months) and completion (6 months) of the study. At baseline visit detailed history was taken regarding presence and severity of individual symptoms and Kupperman Menopausal Index (KMI) was calculated. This index is the sum of the severity scores (from 0:absent to 3:most severe) given to 11 of the most common menopausal complaints (hot flashes, paraesthesia, insomnia, nervousness, melancholy, vertigo, weakness, arthralgia, headaches, palpitation & formation). Paraesthesia, insomnia & nervousness are multiplied by 2 while hot flashes is multiplied by 4 \cite{25}. Mean number of hot flashes per day during previous week were recorded as Hot Flash score

Vaginal smears were taken from lateral fornix and evaluated cytologically for hormonal effects. Karyopyknotic index (percentage of superficial cells found in the total population of squamous cells examined) and Maturation Value (total number of superficial cells + half of the intermediate cells) were calculated. Transvaginal ultrasonography was performed to evaluate endometrial thickness and was considered normal if less than 5 mm.

Laboratory investigations included measurements of Serum triacylglycerols (TG), total cholesterol (TC), HDL & LDL cholesterols. Fasting (more than 12 hours) blood samples were collected and were analyzed for serum lipid profile by enzymatic chemical method. Serum estradiol and follicle
stimulating hormone concentrations were measured by enzyme linked immuno fluorescence assay. Bone densitometry measurement was done by DEXA scan (Dual Energy X-ray Absorptiometry) to measure the mineral density at two sites (femur neck and lumbar spine).

**FOLLOW UP**

During monthly visits participants were interviewed regarding acceptability of the therapy and side effects. Acceptability was scored as 0 = not acceptable because of taste, odor or bulk of the preparation, 1 = neutral response and 2 = acceptable. Subjective feeling of well-being was also recorded. Compliance was assessed by self report of packets of products missed. Blood pressure and weight variations were monitored during therapy.

Evaluation of presence & severity of menopausal symptoms including calculation of KMI and measurement of serum lipid profile was monitored after 3 & 6 months of therapy. Hormonal evaluations including vaginal smears, endometrial thickness and bone densitometry was reassessed after 6 months of therapy.

We planned to recruit a total of 100 participants, 50 for each group. This was based on conventional assumptions of \( \alpha = 0.05 \) and \( \beta = 0.2 \) and a 20% withdrawal rate from both groups, so as to detect 7% decrease in cholesterol (as reported in literature). Statistical tests were performed by using SPSS version 10.0. Descriptive statistics expressed as means and standard deviations were determined for the baseline characteristics. Differences in the baseline characteristics and acceptability between the two groups were examined by using unpaired student’s ‘t’ test. Baseline difference in categorical variable (type of menopause) was tested by using Chi-square test. Repeated measures of ANOVA with Tukey adjustment at significance level 5% was used to determine the effect of treatment on body weight, systolic and diastolic blood pressure, Kupperman’s index, hot flush score lipid profile, hormonal assays, vaginal indices (maturation value and Karyopyknotic index), and bone densitometry results. Individual symptoms improvement between two groups was compared by using Chi-square test (number of cases reporting improvement) out of total number of symptomatic cases. Symptomatic feeling of well being on treatment was also compared using Chi-square test (number of subjects reporting well being on treatment). A p-value of <0.05 was considered as significant for all the statistical tests.

**RESULTS AND OBSERVATIONS**

We recruited 100 postmenopausal women satisfying inclusion criteria for the study and randomly assigned them to study and control groups ( 50 each). A total of 15 cases stopped the trial prematurely, 6 in the study group and 9 in control group during initial 2 months and were unable or unwilling to participate in a final visit. These cases were excluded from final analysis. Eighty five cases were included for analysis. All of the participants reported using at least 80% of the packets provided. Both preparations were found to be equally acceptable to postmenopausal women (acceptability score p=0.540). Generally acceptability for the protein supplement was better if taken with milk than water in both the groups.

Baseline characteristics of the subjects are shown in Table I. Apart from the duration of years since menopause other characteristics were statistically comparable between the study and control group.

**Figure 1**

Table I: Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (n=50)</th>
<th>Soy group (n=44)</th>
<th>Significance (Student ‘t’ test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>49.71(7.27)</td>
<td>48.07(5.44)</td>
<td>0.241</td>
</tr>
<tr>
<td>Years since menopause</td>
<td>6.30(5.7)</td>
<td>3.99(3.91)</td>
<td>0.031*</td>
</tr>
<tr>
<td>Surgical menopause</td>
<td>18 cases</td>
<td>19 cases</td>
<td>0.561</td>
</tr>
<tr>
<td>Weight</td>
<td>57.78(12.24)</td>
<td>57.14(10.72)</td>
<td></td>
</tr>
<tr>
<td>Body Mass index</td>
<td>25.42(4.18)</td>
<td>25.53(4.7)</td>
<td>0.931</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>122.05(10.91)</td>
<td>112.14(10.52)</td>
<td>0.560</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80.68(7.14)</td>
<td>79.95(6.59)</td>
<td>0.142</td>
</tr>
<tr>
<td>Serum estradiol (pg/ml)</td>
<td>14.53(6.9)</td>
<td>13.6(3.5)</td>
<td>0.157</td>
</tr>
<tr>
<td>Serum FSH (IU/ml)</td>
<td>68.7(28.8)</td>
<td>71.9(26.9)</td>
<td>0.708</td>
</tr>
</tbody>
</table>

*Significant difference between two groups

Commonest symptoms seen in the postmenopausal women in this study were joints pains and hot flashes (Figure 1).
Kupperman menopausal index and hot flash scores showed a significant reduction in both the groups (Figure 2 & 3). Improvement in Kupperman index was significantly more in soy supplement group (Figure 2).

When number of cases reporting improvement in individual symptoms were compared between two groups, significantly higher number of cases reported improvement in hot flushes, joint pains and vaginal dryness (Figure 4) on soy treatment as compared to the placebo group. No treatment effect was seen on urinary symptoms.

*Significantly different from baseline value within group (p<0.05)
†Significantly different between groups (p<0.05) (ANOVA)
Feeling of well-being as assessed subjectively was reported by equal number of patients in both the groups (19/41 in control group and 20/44 in Soy group). One case with complaint of loss of libido at the start of therapy reported significant improvement on soy supplement. No change in weight or blood pressure was observed in either group during the study.

In laboratory investigations, significant effect was seen on lipid profile. In the subjects on soy supplementation significant fall in the serum total cholesterol levels and LDL cholesterol levels was observed during therapy as compared to placebo group (Figure 5). The decrease was significant after 3 months of soy therapy and the effect was even more pronounced after 6 months of therapy. Though slight fall was seen in the subjects in control group as well, the effect was not significant. There was no significant change in HDL cholesterol levels in either group (Figure 5). As regards triacylglycerol levels there was a trend towards decreasing levels in the soy group though it was not statistically significant (Figure 5).

**Figure 6**
Figure 5: Comparison of the total cholesterol, LDL cholesterol, HDL cholesterol and Triglycerides values among the patients of the soy group (n=44) and the placebo group (n=41) (mean±standard deviation)

We did not find any effect of either preparation on vaginal cytology as measured by Maturation Index, and Karyopyknotic Index, estradiol & FSH values as well as endometrial thickness (Table 2). Bone densitometry measurement was done in 66 subjects (31 controls and 35 soy group). BMD improved in both the groups after 6 months of protein supplementation but no significant effect of either preparation was detected.(Table 2).

**Figure 7**
Table 2: Effect on Bone Densitometry, Genitourinary Tract & Sex Hormones

<table>
<thead>
<tr>
<th></th>
<th>Soy group (n=44)</th>
<th>Control group (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD/D (cm²)</td>
<td>0.80±0.12</td>
<td>0.88±0.12</td>
</tr>
<tr>
<td>BMD/D (g/cm²)</td>
<td>0.84±0.10</td>
<td>0.85±0.29</td>
</tr>
<tr>
<td>Endometrial thickness</td>
<td>4.07 (1.7)</td>
<td>4.29 (1.51)</td>
</tr>
<tr>
<td>Thickness on TVS (mm)</td>
<td>34.5 (7.4)</td>
<td>3.90 (0.99)</td>
</tr>
</tbody>
</table>

We did not find any effect of either preparation on vaginal cytology as measured by Maturation Index, and Karyopyknotic Index, estradiol & FSH values as well as side effects were commonly gastrointestinal in both the groups (Table 3). Three cases had postmenopausal bleeding while on therapy – 2 cases in soy group and 1 in control group. Endometrial thickness was <5 mm in all these cases. Dilatation and curettage was done no abnormality was detected on histopathology.

**Figure 8**
Table 3: Incidence of side effects

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Control (n=41)</th>
<th>Study (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea / vomiting</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Fullness / abdominal distention</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Generalized itching</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bruising counts</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Severe weakness</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Acceptability score (n=85)</td>
<td>4.89±0.24</td>
<td>5.2±4.02</td>
</tr>
</tbody>
</table>

Fifteen patients dropped out of the study after recruitment due to various reasons. Gastro intestinal side effects and food intolerance were the major causes of drop out for 5 cases (3 in control and 2 in Soy group). Three cases in each group were lost to follow up and couldn't be traced. One case in control group had severe palpitations on treatment
and was excluded from the study after 1 month though no cardiac problem was found. Two cases in control group took therapy for one month and then decided to switch over to HRT. One case in the study group stopped treatment after 1 month when she met an accident. However, majority of the cases 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

Soy isoflavones have generated a lot of interest in last two decades as a natural approach to the management of menopause and many studies have been conducted with conflicting results using soy isoflavones either as a part of protein supplement or as purified tablet. In the present study we selected a supplement of phytoestrogens with soy proteins as treatment form as this is a more natural form and lipid profile changes, the most important benefit of soy derivatives is not generally seen with pure isoflavone extracts [8]. A quantity of 25 gm of soy protein was selected as this is recommended for cardiac protection [12]. Also higher quantities have not always resulted in greater benefits, while compliance definitely decreases [8]. In the present study, phytoestrogen (isoflavones) composition in soy protein isolate was well controlled and constant at 3mg/gm of protein providing 75 mg isoflavones per day (Protein Technology International). We selected a moderate amount of 75 mg for the present study as various studies have used the isoflavone quantity varying from 35-150 mg per day and there is no consensus as regards the optimum dosage.

Menopausal symptoms were mostly mild in severity in our population. In the present study, a reduction in the frequency of typical climacteric symptoms was demonstrated by the significant decrease in Kupperman Menopausal Index. Though a strong placebo effect, as reported in all the studies on menopausal symptoms [8], was seen in our study, the effect of isoflavone rich soy protein supplementation was significantly more than placebo. This is in accordance with many studies reporting improvement in menopausal symptoms using 35-150mg of isoflavones per day either as soy protein supplement or purified isoflavone extract in the form of tablets [8,9,10,11,12]. These effects have not been seen consistently with many studies finding no effect more than placebo[13,14]. Though no significant difference was found between two groups in hot flash score, there were significantly more responders for hot flashes improvement in soy category as compared to the placebo group. A placebo effect with any therapy for hot flashes may be caused by variability and spontaneous improvement that occurs over time or may simple be a result of monitoring or expectation, particularly in highly motivated women. Other symptoms that had higher number of responders in soy group were joint pains and dyspareunia. Similar improvement has been reported in a recent study [15], but others haven’t found these effects. The variable response seen in various studies may be not only because of various dosage and preparations used, but also because of variable metabolism, as intestinal flora can convert the soy isoflavones to equol, a more potent estrogenic isoflavone. The production of equol by intestinal bacteria is variable. This also may account for the variability of the clinical effects of soy and ultimately for the overall reduced efficacy of soy compared with estrogens on the hot flashes.

The most significant finding in the present study was the effect on lipid profile. There was significant reduction in total cholesterol (7.7%) and LDL cholesterol (14%) on soy treatment as compared to placebo. The effect was seen after 3 months of therapy and further improved by 6 months. This is important as research has documented that serum lipoproteins and lipoprotein subclasses are altered as a consequence of menopause, resulting in a more atherogenic lipid. A high blood concentration of LDL-C is an established risk factor for cardiovascular disease [8]. Of interest, based on mortality data from lipid research clinics study, 7% decrease in total cholesterol level would be expected to reduce coronary artery disease (CAD) risk by 14% suggesting a substantial impact on CAD primary prevention with dietary soy supplementation [16]. A meta analysis by Anderson et al indicated that a daily intake of average 47g of soy protein is associated with a 12.9% reduction in LDL-C [17] which is quite similar to our results. Since then various studies have found beneficial effects of soy supplements on non HDL-C in postmenopausal women using 20-60gm of soy protein with 34-160mg of isoflavones [18,19,20,21]. The effect has been seen more consistently in hypercholesterolemic subjects but also reported in normcholesterolemic women [22] as seen in our study. Though a recent meta analysis has found only small fall in TC & LDL-C and effect was not much in postmenopausal women [23]. The hypocholesterolemic effect of soy may be attributable to the soy protein or the high content of isoflavones. In our study effect was seen with soy protein isolate containing high dose of isoflavones. Studies designed to find the active component have not found lipid lowering
effect with isoflavones poor soy proteins or isoflavones extract [10,3] except for two recent studies [11,12]. Perhaps hypcholesterolemic effect of soy may not be attributable to any specific component but results from synergistic action of several components present in soy. The mechanism of soy effects on lipid profile remains unresolved; however, the response pattern doesn’t parallel that of estrogens. In contrast with effects of estrogens, in the present study there was reduction (11%) in triglycerides level on soy treatment though effect was not found to be statistically significant. This finding has been reported in few other studies as well [10,20]. The fall in triglycerides is encouraging, because there is increasing epidemiological evidence that elevated triglycerides independently increase vascular risk and emergency intervention data that suggests that reduction in triglyceride levels reduces vascular risk [13]. We didn’t find any treatment effect on HDL-C while few studies have reported improvement in HDL-C levels [19]. In contrast with few studies reporting fall in BP [11,20], we didn’t have any effect on blood pressure with soy supplementation.

No significant change in vaginal epithelium was found on soy treatment even after 6 months. But as regards symptoms, more subjects reported improvement in the symptom of vaginal dryness on soy treatment as has also been seen in another study [14]. There is a lot of controversy over the beneficial effects of phytoestrogens on vaginal cytology. Studies of effects of isoflavones on the vaginal epithelium have reported conflicting results with few studies reporting improvement [15,16] while others have found no change [30,7].

Despite the fact that estrogen deficiency symptoms improved in present study, soy supplementation didn’t change serum hormonal levels of estradiol or gonadotrophins. It is in accordance with other studies reporting no effect on these hormones in postmenopausal women [12,20].

Bone densitometry improved in both the groups though no treatment effect of soy was found more than placebo. The improvement seen could be because of calcium supplementation which was part of both the supplements. Also 6 months is relatively a short period to detect any treatment effect on bone densitometry. Prolonged studies of 1-2 years should be planned to detect effect on bones. Few other studies studying effect of soy supplement on bone mineral density or markers of bone resorption have not found any effect [19]. Biochemical markers though more sensitive indicators of bone metabolism were not studied in the present study. Isolated reports of isoflavones as pure extract or with soy protein isolate have found positive effect on bone mineral density [20].

In the present work, no change in endometrial thickness as measured at transvaginal sonography was observed in both the groups. Other studies evaluating effect of isoflavones on endometrium have also shown no change in endometrial thickness [11,2]. Though phytoestrogens seemed to have an anti estrogenic & antiproliferative effect on endometrial thickness [38], studies showing proliferation & endometrial hyperplasia with isoflavones therapy [39,40] have raised concerns. Commonest side effects seen were gastrointestinal and were seen in both the groups. Because of difficulty in compliance because of GI side effects and not liking the form of treatment (bulky drink), 15% subjects dropped out of the study. Other researchers have also reported gastrointestinal side effects and food intolerance in both study and control groups in studies using soy protein supplementation [20]. These side effects have not been reported in studies using isoflavone extract tablets [11].

An important limitation of our study was that we didn’t measure concentrations of isoflavones as measure of compliance. Another potential limitation was the considerable interindividual variation in different parameters although randomization reduced the variability between two groups.

To conclude, present study confirms that 25 gm of soy supplementation with 75 mg of isoflavones in postmenopausal women improves estrogen deficiency symptoms and also improves lipid profile. Reduction in total and LDL-cholesterol without inducing hypertriglyceridemia is an advantage over estrogens. Soy proteins were found to have an added advantage of reduction in triglycerides in term of cardiovascular health. No estrogen effect on endometrium is a reassuring finding. But the adverse effects reported in other studies like increase in Lipoprotein a, effects on breast tissues and possibility of proliferative effect on endometrium after prolonged use need caution and further investigation. Also effectiveness needs to be matched with tolerance of the form of therapy to improve compliance.

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CONTRIBUTION OF AUTHORS TO MANUSCRIPT WORK

Gita Radhakrishnan: Author contributed significantly to the concept & design of the study, collections of data, analysis of
data & writing of manuscript

Rashmi: Author contributed significantly to the design of the study, collections of data, analysis of data & writing of manuscript

Neera Agarwal: Author contributed significantly to the design of the study, writing of manuscript and provision of significant advice & consultation

Neeam B Vaid: Author contributed significantly to the design of the study, writing of manuscript and provision of significant advice & consultation

There is no conflict of interest among all the above authors

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