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Efficacy of soy Isoflavones on bone mineral density and estradiol levels among postmenopausal women

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Abstract
Postmenopausal women were more prone to osteoporosis due to the declined levels of the female hormone, estradiol. The reduced levels attenuates bone mass with the corresponding decrease in bone mineral density. The present study is planned to minimize the risk of osteoporosis and maintain bone health through supplementation of 60mg of soy Isoflavones along with 500mg of calcium and 250 IU of vitamin D and of course a glass of milk (200ml). The findings implicated significant improvement in bone mineral density and serum estradiol levels. Whereas this beneficial effect was not noticed in case control group who were not provided with any form of supplementation. The continued bone loss was noticed among postmenopausal women due to age-related bone loss which would be minimized through appropriate intervention strategy. The findings thus proved the efficacy of soy isoflavone capsules in combination with calcium and vitamin D. Further adopting healthy lifestyle will be helpful in restoration of bone mass effectively.

Keywords: Osteoporosis, postmenopausal women, Bone health, Bone Turnover

Introduction
Osteoporosis is characterized by a reduction in bone density and strength to the extent that fractures occur after minimal trauma. It is well known that estrogen deficiency as in postmenopause and ovariectomy leads to acceleration of bone resorption and rapid bone loss, resulting in the development of osteoporosis. Current therapies recommended for postmenopausal osteoporosis (PMO) treatment include supplementation with estrogen or hormone replacement therapies (ERT or HRT). Estrogen is the most potent inhibitor of bone resorption and the most widely recommended therapy to reduce the rate of postmenopausal bone loss. However, available evidence appears to suggest that the long-term use of ERT has numerous side effects. Currently, natural alternatives with estrogen-like activities such as soy isoflavones are being investigated as possible alternatives for HRT.

Women are more susceptible to osteoporosis than men. Hormone replacement therapy has been shown to have the most protective effect against osteoporosis and osteopenia in postmenopausal women. However, the first Woman's Health Initiate Study showed that long-term hormone supplementation increased the risk of several side effects (endometrial cancer, breast cancer, ovarian cancer, and vinous thrombosis). The number of postmenopausal women is expected to increase considerably due to the prolongation of the life span and postmenopausal osteoporosis is therefore expected to become a great socioeconomic problem with increase in both mortality and morbidity. New strategies for preventing and treating postmenopausal osteoporosis are thus of interest and increased attention has been focused on soy bean-derived isoflavones [1].

Soy isoflavones are naturally found as inactive glycosides. Following oral ingestion, complex enzymatic metabolic conversions take place in the gastrointestinal tract, resulting in the formation of heterocyclic phenols structurally similar to 17β-estradiol. Absorbed by the enterocytes, isoflavone metabolites reach the peripheral circulation and are excreted in 7 to 8 hours. Aglycones (genistein, daidzein and glycitein) are the active forms which are actually absorbed. Absorption rate ranges from 20 to 55 percent. The concentrations of the different isoflavone metabolites, as well as their clinical effects, vary widely from individual to individual even when a controlled quantity is administered. Therefore, it is difficult to determine the ideal dosage. Some recommend from 30 mg to 100 mg/day

Isoflavones are found in soy foods both with and without a sugar molecule attached. Soy isoflavones are nonsteroidal molecules which are structurally and functionally related to 17-β estradiol. The two primary isoflavones in soybeans are diadzein and genistein and their respective glucosides, genistein and diadzin.

Estrogen replacement has been the mainstay of therapy for the prevention and treatment of

osteoporosis in the estrogen–deficient population of postmenopausal women. However, longterm compliance with estrogen therapy generally is poor, and there are numerous concerns regarding its safety. The phytoestrogens are non-steroidal plant – derived compounds that exhibit estrogen activity at several sites. The isoflavones are one such class of phytoestrogens derived largely from soy – based products. International popularity for menopausal therapy regimens containing isoflavones is growing rapidly [2].

The menopause is characterized by complete cessation of menstruation and rapid reduction in the female hormone estradiol which is regarded as bone formation marker. As the onset of menopause is an unavoidable biological process efforts to enhance estrogen levels might be beneficial to certain extent in restoring bone mass. In view of this advantage, the present study was planned to improve the estradiol levels among osteopenic and osteoporotic postmenopausal women through soy isoflavone supplementation. The efficacy of the intervention was tested through pre-post test evaluation of serum estradiol levels as well as bone mineral density against case control study.

Materials and Methods

The study was conducted in Tirupati urban and slum areas of Chittoor district, Andhra Pradesh. Initially, preliminary screening test was organized to identify osteopenic and osteoporotic women aged 35 to 74 years through Quantitative Ultra Sound (QUS) bone densitometry. They were again grouped into four different age groups viz., 35 to 44 (n=60), 45 to 54 (n=80), 55 to 64 (n=80) and 65 to 74years (n=40) both from urban (n=260) and urban slum women (n=260).

The osteoporosis screening for women was carried out during free BMD campaigns who voluntarily participated to undergo bone mineral density testing. The six months intervention study was planned to supplement osteopenic and osteoporotic women (n=30) with 60mg of soy isoflavones in the form of capsule along with 500 mg of calcium and 250 IU of Vitamin D_3 (n=30). During this intervention period, the experimental group of selected women was also provided with 200ml of milk. The efficacy of the soy isoflavones was evaluated against case control those were not provided with any form of supplementation. Estradiol and bone mineral density testing were basically chosen for pre-post testing. As FDA has recommended the QUS method for screening purpose, dual energy X-ray absorptiometry (DEXA) method was used to test the effectiveness of the intervention. DEXA technique with a model of HOLOGIC – Discovery A (S/N 82730) available at Sri Venkateswara Institute of Medical Sciences (SVIMS), Tirupati was utilized to evaluate the changes in bone density and impact of soy isoflavones. The bone mineral density measured at Lumbar spine (AP) L_1-L_4 was employed for pre and post testing.

Results and discussion

Six months intervention programme was planned for postmenopausal women suffering from either osteopenia or osteoporosis identified by calcaneous quantitative ultrasound (QUS) bone densitometry during preliminary screening. One group of women who voluntarily participated to take 60mg of soy isoflavone capsule daily along with 500 mg of calcium and 250 IU of Vitamin D_3 (n=30) and 200ml of milk were included for the intervention study. The effectiveness of the study was compared against case control through pre-post test DEXA-BMD measures and serum estradiol. The data thus obtained was discussed further under the following sub-heads.

i) Efficacy of soy isoflavone capsule on BMD and BMD T-scores using DEXA bone densitometry

Food and Drug Administration (FDA) approved 'QUS' bone densitometry as only for screening the patients for osteopenia and osteoporosis but not for testing therapeutic practices and efficacy of therapeutic and curative intervention approaches. In this regard, the dual energy X-ray absorptiometry (DEXA) remains the golden standard method of assessing BMD, identifying disease condition and for treatment of the disease. Hence during the present research of pre-post test evaluation on bone mineral density of the experimental group against case control group was assessed by DEXA -Lumbar spine BMD measured at AP Site (L1- L4) and also expressed as BMD T-scores.

Table 1: Efficacy of Soy isoflavones capsule on 6-months supplementation among osteopenic and osteoporotic postmenopausal women: Pre and post test changes at Lumbar spine (AP) L1-L4 BMD

Group	DEXA-Lumbar spine BMD (AP): L1-L4		
	Pre-Treatment (Initial)	Post-Treatment	Calculated t-value
Soy Isoflavones (n=30)	0.70 ± (0.09)	0.83 ± (0.10)	11.04**
Control (n=30)	0.69 ± (0.08)	0.63 ± (0.07)	12.40**

Note: **=1 Percent level

The DEXA measurements obtained during an intervention study period denoted a significant improvement in the bone mineral density of soy isoflavone experimental group. Whereas in contrast, the bone density levels were significantly reduced who were not provided any supplemental benefit. The findings thus clearly supported the beneficial role of soy isoflavones along with calcium and vitamin D. The data clearly represented a definite deterioration and increased porosity levels of bone in control group of women as evidenced by lowered BMD.

As people age, their bones become less dense and bone fractures occur more easily. Estrogen helps to maintain bone health in younger women, but after about 30 years of age, estrogen levels begin to decrease and then fall sharply after menopause. Estrogen replacement therapy is effective at maintaining bone, but because of its side effects, it is no longer recommended for this purpose. Many women who are looking for "natural" ways to promote bone health use phytoestrogens. Phytoestrogens are naturally occurring estrogen analogues, which are found in soy products [3]. The present study levels also confirmed the beneficial role of soy isoflavones in restoration of bone mass.

Table 2: Efficacy of Soy isoflvones capsule on 6-months supplementation among osteopenic and osteoporotic postmenopausal women: Pre and post test changes at Lumbar spine (AP) L1-L4 BMD T-Score

Group	DEXA-Lumbar spine BMD T-Score (AP): L1-L4		
	Pre-Treatment (Initial)	Post-Treatment	Calculated t-value
Soy Isoflavones (n=30)	-2.53 ± (0.78)	-2.06 ± (0.93)	6.19**
Control (n=30)	-2.61 ± (0.86)	-3.03 ± (0.83)	18.59**

Note: **=1 Percent level

The BMD T-Scores in both the groups were at osteoporotic score (BMD T-score: ≤ -2.5) during baseline study. The post test results after six months intervention with soy isoflavones significantly enhanced the bone mass and strength as observed by the shift in BMD T-score from osteoporotic condition to osteopenic condition. But the condition was reversed in control group with significant reduction in BMD T-score which was much worsened towards still higher osteoporotic score. The condition addressed the necessity of minimizing age-related bone loss.

The data highlighted a definite deterioration and increased porosity levels of bone in control group of women who's BMD T-scores found to be much deviated with ageing process due to continuous bone age-related bone loss. The results were well proved the necessity of supplementation for all the postmenopausal women to arrest the rate of bone loss and to restore bone health and to avoid risk of osteoporosis. Supplementation with 60mg of soy isoflavone capsules proven to be a better intervention approach for postmenopausal women and also might be for all the women after 45 years of age who attained or going to attain menopause.

The meta-analysis study results with a range of 47 to150 mg soy isoflavones from 1240 menopausal women for 6-12 months significantly increased spine BMD compared to controls. No significant effects on femoral neck, hip total and trochanter BMD were found. Soy isoflavone extract supplements increased lumbar spine BMD in menopausal women. The present study results also demonstrated the beneficial effects of soy isoflavone capsule supplement on bone restoration in postmenopausal women for six months period providing 60 mg isoflavones [4].

In the present study, supplementation of soy isoflavones demonstrated a positive and beneficial role in improving the bone density levels of post-menopausal osteopenic and osteoporotic women. Supplementation of 6 months duration demonstrated sufficient post time effect on restoration of bone mass from osteoporotic level to osteopenic condition. May be further and continuous supplementation definitely help women in improving the bone density. Soy isoflavones helped in improving the bone density along with calcium and Vitamin D_3 supplementation to avoid calcium and Vitamin D deficiency otherwise may further aggravate resorption of bone. Thus, the present study on supplementation of soy isoflavones (60 mg) proved to be the good intervention step in the treatment of osteopenia and osteoporosis conditions.

ii) Efficacy of soy isoflavone capsule on Serum Estradiol levels

Isoflavones which are phyoestrogens with diphenolic ring structure resembling those of endogenous estrogens and have been shown to exert estrogenic normal effects. Estradiol is the biologically active estrogen that is most often associated with maintenance of skeletal homeostasis [5]. The phytoestrogens, isoflavones which mimic the chemical structure of estradiol may influence the levels of estradiol by increasing its value in the serum by their ingestion. In view of the effectiveness of soy isoflavones, an intervention study was planned with 60mg of soy isoflavones along with calcium and vitamin D and tested against case control sample. The results obtained were denoted in the table no-3 along with calculated t-values for pre-post test results.

Table 3: Efficacy of Soy isoflvones capsule on 6-months supplementation among osteopenic and osteoporotic postmenopausal women: Pre and post test changes of Serum Estradiol

Group	Serum Estradiol (pmol/l)		
	Pre-Test	Post-Test	Calculated t-value
Soy Isoflavones (n=30)	48.29 ± 8.46	60.07 ± 7.41	13.58**
Control (n=30)	42.46 ± 7.23	35.16 ± 7.06	43.86**

Note: **=1 Percent level

The results indicated a significant raise (P<0.01) in serum estradiol levels when the women were supplemented with soy isoflavones capsule supplementation along with calcium and Vitamin D for a period of six months. In case of control group, the serum estradiol levels seem to be declined continuously and resulted in significant (P<0.01) decrease in serum estradiol levels.

The investigation done on the effect of soy isoflavones as an alternative for estrogen replacement therapy using a postmenopausal osteoporotic rat model indicated that bone mineral (calcium and phosphorus) contents were increased in rats supplemented with 80 ppm soy isoflavones or the rats treated with only estrogen injection without soy isoflavones. Therefore, the effect of 80 ppm soy isoflavone supplementation was the same as estrogen injection but there was no beneficial effect from combining soy inflavones and estrogen injection. These results suggest the appropriate soy isoflavone supplementation prevents postmenopausal bone loss without estrogen injection and may have efficacy as an alternative to estrogen therapy [6]. The current research had proven the beneficial effect of soy isoflavones on reducing the post-menopausal bone loss by increasing the levels of serum estradiol which accelerates the bone formation and facilitates the bone mineral content.

The meta-analysis study was conducted on the effects of soy isoflavones on circulating hormone concentrations in post-menopausal women. The trials of soy or isoflavones for 4 or more weeks on estrogens are included. The results indicate a small increase in circulating total estradiol concentrations following soy isoflavone consumption, but not statistically significant [7]. Whereas in the present study the estradiol levels found to be increased significantly with the consumption of soy isoflavones capsules for six months. This probably due to comparatively longer duration and the effectiveness might be improved by the additional supplementation with 500mg of calcium and 250 IU of Vitamin D. Thus, it might be inferred that instead of supplementing solely with isoflavones in postmenopausal women, the combining intervention strategy with calcium and Vitamin D provided beneficial effect both in maintaining skeletal homeostasis, restoration of bone mass through positive impact on serum estradiol levels.

Conclusion

The menopausal status is an unavoidable biological process usually attained on an average of 45 years. There is a definite drop in estrogen levels with the cessation of menstruation from the onset of menopause and hence the age-related bone loss cannot be arrested with the ageing process. This particular situation certainly leads to the condition of continued bone loss even after 45 years and is impossible to expect the absolute retention of bone mass when compared against pre-menopausal women. The finding thus explains a

true risk associated with the menopausal condition and is one of the reasons for the most common bone metabolic problem of postmenopausal osteoporosis. However, adopting healthy life style patterns and inclusion of phyto-estrogenic rich foods such as soy, flax seeds may minimize the degree of menopausal risk status and helpful to reduce age-related bone loss and restore bone mass in women.

The intervention study planned with 60mg of soy isoflavone capsules for a period of six months with calcium, vitamin D and 200ml of milk as an integrated approach yielded beneficial results on bone health by enhancing bone mineral density measured by DEXA at lumbar spine as well as serum estradiol. This beneficial effect was not observed in case control group whose age-related bone loss found to be significantly lowered.

Osteoporosis can be prevented by simple life style modifications, for example, increased calcium intake (either from diet or supplement) can improve BMD. However, calcium alone is not sufficient in bringing favourable effect on bone. Calcitriol (1, 25-$(OH)_2$ Vitamin D), the physiologically active metabolite of Vitamin D is the main regulator of intestinal calcium absorption. In addition isoflavones, the major phytoestrogens modulate the estrogen levels in postmenopausal women. This interactive relationship is well evidenced in the present planned supplementation programme by the increased levels of both BMD as well as serum estradiol levels against the lower levels in the control group.

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