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Original Article

The Effect of Short-term Treatment with Fennel on Bone Density in Postmenopausal Women: A Randomized Controlled Trial

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Objectives: The goal of this study is to assess the effect of fennel on bone density.
Methods: This was a double-blind, randomized, placebo-controlled trial, which studied sixty eligible postmenopausal women, who were randomly assigned to fennel and placebo groups. Then, the dual energy X-ray absorptiometry was utilized to measure bone mineral density (BMD) and bone mineral content (BMC) of the spine, femoral neck, intertrochanter, and trochanter at the baseline and after three-month follow-up.
Results: The mean BMD and BMC at lumbar spine (P = 0.14, P = 0.504), total hip femoral (P = 0.427, P = 0.471), trochanter (P = 0.075, P = 0.07), intertrochanter, (P = 0.864, P = 0.932) and femoral neck (P = 0.439, P = 0.641) was not significantly different between the fennel and placebo groups.
Conclusions: The results of this study did not approve the effect of fennel on bone density in post-menopausal women. However, to gain deeper insights, further studies with longer durations and larger sample sizes are recommended. **(J Menopausal Med 2017;23:124-130)**

Key Words: Bone density · Foeniculum · Postmenopause

Introduction

Osteoporosis is a leading cause of disability and death among elderly women which imposes huge economic costs on the society.[1,2] Estrogens are integral to skeletal homeostasis, with ovarian hormone deficiency acting as critical risk factors of osteoporosis. There are strong evidences on bone-related benefits of raloxifene and hormone replacement therapy (HRT).[3,4] However, short-term estrogen use can lead to vaginal bleeding, while long-term use can increase the risk of breast cancer, stroke and cardiovascular disease.[5] The main side effects of raloxifene are vein thromboses and pulmonary embolism. As a result, many postmenopausal women favor compounds that contain non-hormonal materials like phytoestrogens as a safer option.[6~9] Phytoestrogens are plant substances with a structure and function similar to estradiol, which is responsible for estrogenic effect.[10] Phytoestrogens have been the subject of growing attention for

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their bone-sparing properties.[3] Foeniculum vulgare is used to treat liver obstruction, spleen and gall bladder, to alleviate digestive problems such as indigestion, colic, nausea, flatulence and bronchodilation, and to enhance memory.[11,12] It also includes phenolic compounds such as flavonoids (flavonoid glycosides and flavonoid aglycones), phenolic acids, hydroxycinnamic acids, coumarins and tannins.[13] The results of in vitro studies have revealed the osteoprotective effect of Foeniculum vulgare extract.[14] Another recent in vitro cell culture demonstrated that Foeniculum vulgare Miller seed (FvMs) could potentially prevent bone loss in postmenopausal osteoporosis by mitigating osteoclast differentiation and function.[15] Nonetheless, to the best of our knowledge, the effect of Foeniculum vulgare on bone mineral content (BMC) and bone mineral density (BMD) has not been examined in human studies.

Materials and Methods

This is part of a study that assessed the effect of fennel on lipid profile and bone density in Iranian postmenopausal women. It is a randomized, double-blind, placebo-controlled clinical trial intended to compare the effectiveness of Foeniculum vulgare on bone density in menopausal women. The study was conducted in accordance with the principles of Declaration of Helsinki and approved by Ethics Committee of the Mashhad University of Medical Science.

All participants were recruited in the medical center of Imam Reza Hospital in Mashhad, Iran. Inclusion criteria were: 1) postmenopausal status, which was defined as an age of over 40 years with no vaginal bleeding for one year; 2) no regular ingestion of phytoestrogen or soy-based products (which was defined as consumption more than once a week) and 3) a normal mammogram in the last year. Exclusion criteria were: 1) use of any fluoride or bisphosphonates; 2) diseases or medications affecting bone metabolism; 3) current (or over past 6 months) use of estrogen or calcitonin; 4) history of endometrial or breast cancer; 5) any fracture, and 6) regular physical exercise or allergy to Foeniculum vulgare.

In the next step, informed consent forms were signed by participants along with verbal reassurance that participation was on a voluntary basis and that they could abandon the trial at any time. In addition, all participants were ensured about the confidentiality of information during and after the study. Sixty participants were randomly assigned to Foeniculum vulgare or placebo groups at the baseline. All participants were asked to take soft capsule three times a day – (in the morning, in the midday, and at night). Each 100-mg fennel soft capsule contained 30% fennel (Standardized to 21-27 mg anethole) combined with sunflower oil. Active ingredients of each capsule were Trans-anthol, Methyl chavicol, fenchone and stragol. Placebos were in identical shape and size, but filled with sunflower oil. These capsules were provided by Barij Essence Company. The sequence of allocation was based on a random number table. For the purpose of allocation concealment, a numbered sealed opaque plastic bottle was used, which contained enough treatment for 30 days. The allocation sequencing and packing was implemented by an employee of Barij Essence Pharmaceutical Company, who was not directly engaged in the study. In this study, participants and research team were blind to the treatment assignment.

Then, dual-energy X-ray absorptiometry (DXA; Hologic QDR-2000 Inc., Bedford, MA, USA) was utilized to measure BMD and BMC of the spine, femoral neck, intertrochanteric, and trochanter at the baseline and after three months.[16] The subject screening was performed every 4 weeks to check for any side effect and compliance. To ensure compliance, patients were asked to bring their medication bottle to each visit to count the pills.

Statistical tests

The normal distribution of data was examined using the Kolmogorov-Smirnov test of normality. Paired t-tests (intra group) was used to draw a comparison between the baseline and three-month follow-up, and Student's t-test (inter groups) was used to compare the two treatment groups, Statistical tests were two-sided, and a P values of less than 0.05 were considered to indicate statistical significance.

Results

The two groups were similar in variables such as age, history of hysterectomy, body weight, body mass index (BMI)

and duration of menopause at the baseline, as shown in Table 1. Side effects were observed in 6 subjects in the fennel group and 3 subjects in the placebo group. In the fennel group, subjects complained of allergic rash (n = 1), weight gain (n = 1), hypertension (n = 1) and vaginal bleeding (n = 2). Only one patient in placebo group complained of stomachache. The fennel was different from placebo in term of the mean BMD and BMC at lumbar spine (P = 0.14, P = 0.504), total hip femoral (P = 0.427, P = 0.471), trochanter (P = 0.075, P = 0.07), intertrochanter (P = 0.864, P = 0.932) and femoral neck (P = 0.439, P = 0.641) (Table 2). Also, no significant difference was observed in both groups at the baseline and three-month follow-up in terms of mean BMD and BMC at lumbar spine, total hip femoral, trochanter and intertrochanter (the data is not shown in the Table)

Discussion

To the best of our knowledge, this is the first study to assess the effects of Foeniculum vulgare on BMC and BMD at the lumbar spine, femoral neck, trochanter, intertrochanter and hip femoral in post-menopausal women. According to results, Foeniculum vulgare did not have any significant positive effect on BMD and BMC over a three-month period.

Despite our efforts, no human study about the effects of Foeniculum vulgare on bone density was found. Nevertheless, considering that phytoestrogen is an active biological compound in fennel, we referred to studies that evaluated the effect of phytoestrogen on BMC and BMD. Phytoestrogens are plant compounds with properties that resemble those of estrogen. There are four main groups of phytoestrogens: isoflavones, lignans, flavonoids and coumestans.[10] Isoflavones are found in soy and red clover extracts; soy isoflavones are mainly composed of genistein and daidzein, but red clover isoflavones consist of formononetin and biochanin.[2] Lignans are commonly found in flaxseed[11] and Foeniculum vulgare is considered as a major source of flavonoids.[13] Although the positive effect of soy isoflavone has been demonstrated in a number of studies[17,18] other studies have not reported any beneficial effect (Table 3).[18~21] We found three studies assessing the effect of red clover on bone density. The first study was by Atkinson according to which red clover isoflavones enriched with biochanin had a beneficial effect on spine BMD and BMC, but not on hip BMD and BMC over a 24-month follow-up.[3] In the second study by Clifton-Bligh, no significant difference was observed in BMD loss in the spine, hip and forearm after 24 months of treatment with red clover isoflavones enriched with formononetin.[22] The third trial by Thorup showed that 150 mL/day red clover could improve bone status.[23]

A systematic review of five trials by Abdi revealed an increase in BMD and bone turnover after genistein administration in postmenopausal women. They also found that it was impossible to make conclusive statements about the effect of soy on BMD in postmenopausal women due to heterogeneity in formulation, phytoestrogen content, and dosage of supplement.[24]

The results of an in vitro study showed that Foeniculum vulgare extract in the range of 5 to 50 μg/mL might have

Table 1. Baseline characteristics of subjects in the group

Variables	Fennel group	Placebo group	*P* value
Age (years)	56.1 ± 6.5	56.2 ± 4.7	0.933
Height (cm)	15.3 ± 5.57	1.51 ± 4.71	0.206
Weight (kg)	68 ± 25	72.03 ± 11.5	0.206
Duration of menopause (months)	97 ± 81	86 ± 59	0.587
No. of children	4.29 ± 1.9	3.7 ± 1.7	0.334
History of hysterectomy (yes)	1 (4.0%)	4 (14.8%)	0.354
Smoking status (yes)	2	0	

The data is presented as mean ± standard deviation or number (%)

Table 2. Effects of placebo and fennel on BMD and BMC

	Treatment (mean ± SD)	Placebo (mean ± SD)	Test		
			t-value	df	*P* value
BMD (g/cm^2)					
Spine (L1–L4)					
Baseline	0.820 ± 0.107	0.884 ± 0.120	-2.019	49	0.05
Post-treatment	0.839 ± 0.114	0.885 ± 0.11	-1.47	49	0.14
Change (%)	1.92	0.21	1.12	49	0.26
Total hip					
Baseline	0.816 ± 0.089	0.848 ± 0.123	-1.030	49	0.308
Post-treatment	0.834 ± 0.096	0.860 ± 0.132	-0.801	49	0.427
Change (%)	1.87	1.23	0.402	49	0.689
Femoral neck					
Baseline	0.67 ± 0.0.1	0.70 ± 0.103	-1.07	49	0.288
Post-treatment	0.683 ± 0.101	0.70 ± 0.104	-0.780	49	0.439
Change (%)	1.79	0.38	0.668	49	0.507
Trochanter					
Baseline	0.571 ± 0.061	0.608 ± 0.100	-1.56	49	0.124
Post-treatment	0.573 ± 0.062	0.613 ± 0.08	-1.81	49	0.075
Change (%)	0.37	1.12	-709	49	0.481
Intertrochanter					
Baseline	0.982 ± 0.113	1.01 ± 0.149	0.356	51	0.724
Post-treatment	1 ± 0.122	1 ± 0.154	-0.172	51	0.864
Change (%)	1.79	0.11	964	49	0.340
BMC (g)					
Spine (L1–L4)					
Baseline	46.30 ± 8.82	48.1 ± 11.45	-0.635	49	0.528
Post-treatment	46.90 ± 0.839	48.7 ± 10	-0.673	49	0.504
Change (%)	0.86	0.85	-0.5	49	0.960
Total hip					
Baseline	25.70 ± 3.11	27.6 ± 4.10	-1.51	49	0.137
Post-treatment	27.80 ± 4.10	28.5 ± 6.72	-0.418	49	0.471
Change (%)	6.2	2.8	0.446	49	0.446
Femoral neck					
Baseline	3.06 ± 0.53	3.25 ± 0.54	-1.16	49	0.25
Post-treatment	3.23 ± 0.515	3.30 ± 0.64	-0.469	49	0.641
Change (%)	1.79	0.38	0.668	49	0.507
Trochanter					
Baseline	5.30 ± 0.58	5.78 ± 1.30	-1.67	49	0.1
Post-treatment	5.44 ± 0.781	5.99 ± 3.19	-1.85	49	0.07
Change (%)	0.37	1.12	-709	49	0.48
Intertrochanter					
Baseline	17.65 ± 2.7	18.5 ± 4.1	-0.084	49	0.381
Post-treatment	19.16 ± 3.90	19.06 ± 5.4	0.086	49	0.932
Change (%)	1.34	0.35	0.43	49	0.43

BMD: bone mineral density, BMC: bone mineral content, df: degree of freedom

Table 3. Effects of soy on bone density

References	Duration	Type of intervention	Result
Kenny et al.[19]	1 year	Group1 = Soy protein + isoflavones, Soy protein + placebo, Control protein + isoflavones, Control protein + placebo	No significant differences among four groups in BMD.
Tai et al.[25]	2 years	Consumed 300-mg/day isoflavones (aglycone equivalents) or a placebo	A significant decrease in total lumbar spine both isoflavones and placebo groups. However, comparison of two group was not significant.
Wong et al.[26]	2 years	80 or 120 mg of soy hypocotyl aglycone isoflavones + calcium and vitamin D	80 or 120 mg of soy isoflavones + calcium and vitamin did not alter BMD and BMC.
Brink et al.[21]	1 year	Isoflavone-enriched products placebo	Isoflavone-enriched products had no effect on BMD at the lumbar spine.
Arjmandi et al.[27]	1 year	Consumption of soy-containing foods (providing 25 g protein and 60 mg isoflavones)	No significant changes in total hip BMD and BMC.
Ye et al.[20]	6 months	84 and 126 mg isoflavones	Mean percent changes increased in soy isoflavones group regarding BMD at the lumbar spine (P = 0.114) and femoral neck (P = 0.053).
Chi and Zhang[17]	6 months	isoflavone (90 mg/day) and with placebo	Both tibia bone density and limb bone density increased compared to at baseline. However it reach significant level only in tibia bone density.
Huang et al.[18]	1 year	100 mg/day isoflavone (IF100) and 200 mg/day isoflavone (IF200) groups	Soy isoflavone showed significant positive effect on spin BMD.

BMD: bone mineral density, BMC: bone mineral content

a positive effect on cell proliferation and mineralization. In another study on the effects of FvMs on the femurs bone, 32 female mice were randomly assigned to four groups as follows: Group 1 (n = 8) was sham; Group 2 (n = 8) was ovariectomized and treated with water; Group 3 (n = 8) was ovariectomized and treated with low-dose of FvMs 30 mg/kg, and Group 4 (n = 8) ovariectomized and treated with high dose of FvMs 100 mg/kg. Compared to the control group, the group treated with low and high doses of FvMs demonstrated improved BMD and BMC in the trabecular bone.[15] This is inconsistent with the findings of this study.

Limitations of the study

In this study, postmenopausal women were followed only for 12 weeks. Further studies can focus on longer durations and larger sample sizes to explore their beneficial effects.

Conclusion

Foeniculum vulgare did not have any significant effect on BMC and BMD at lumbar spine and total hip in post-menopausal women. Further studies with longer durations and larger sample sizes are recommended to validate the results of this study.

Acknowledgement

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Conflict of Interest

The Barij Essence Pharmaceutical Company supported this study by providing soft fennel capsules. However, the design of protocol, analysis, and research implementation were undertaken by the author.

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