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The Comparison of Tibolone and Hormone Replacement Therapy on Bone Densitometry and Bone Turnover in Postmenopausal Women

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Background: Osteoporosis is a prevalent disease related to menopause, and causes an increasing health problem.
Objectives: Our aim was to compare the effects of conventional estrogen replacement therapy and tibolone on the bone mineral density (BMD) and bone turn over in postmenopausal women.
Patients and Methods: A total of 150 healthy non-surgical postmenopausal women in Iran were enrolled in a randomized controlled clinical trial. Fifty women received 2.5 mg tibolone plus one calcium + D tablet (500 mg Ca and 200 IU vitamin D) daily; 50 women received 0.625 mg conjugated equine estrogen and 2.5 mg medroxy progesterone acetate (CEE/MPA) plus one calcium + D tablet daily; 50 women received only one calcium + D tablet and served as a control group. Bone densitometry (DAX) of the lumbar spine and the proximal femoral neck and also bone turnover markers (serum alkaline phosphates (ALP) and urine Ca/Cr ratio) measured at baseline and after the nine months of entering into the study.
Results: After the treatments, ALP reduced significantly in the CEE/MPA and tibolone groups (P = 0.02, P = 0.002), but increased in the control group (P = 0.03) in comparison with the baseline. After the treatments with respect to femoral BMD, significantly increase occurred only in the tibolone group in comparison with the baseline (0.95 ± 0.13, 0.97 ± 0.12, P = 0.004).
Conclusions: Tibolone may be considered as an alternative for preventing of osteoporosis in postmenopausal women.

Keywords: Menopause; Tibolone; Bone Density; Bone Remodeling

1. Background

Osteoporosis is a prevalent disease related to ageing and menopause, and cause an increasing health and socio-economic problem. The treatment of advanced disease is often disappointing, and early intervention before fractures occur is valuable. The basic goals of hormone replacement therapy (HRT) are the prevention of cardiovascular diseases, osteoporosis and the improvement of quality of life (QoL). The capability of HRT in the prevention of postmenopausal bone loss has been established in terms of minimizing loss, increasing bone mass and reducing the number of fractures (1-4); however, bone mineral density decrease in is sometimes observed in clinical practice in patient in spite of treated with HRT (5).

Tibolone is a steroid substance, structurally related to 19-nortestosterone derivatives, such as norethisterone. Following oral administration tibolone is metabolized to three active agents: 3-alpha hydroxyl-tibolone; 3-beta-hydroxy-tibolone; and -tibolone. Data indicate that tibolone and its metabolites display oestrogenic, progestogenic or androgenic activity, depending primarily on the target tissue. Tibolone has been introduced as an alternative to estrogen replacement therapy for the treatment of climacteric complaints and postmenopausal bone loss while not having harmful effects on the endometrium and the breast (6-12).

2. Objectives

In this study, our aim was to compare the effects of conventional estrogen replacement therapy and tibolone on BMD and bone turnover in postmenopausal women.

3. Patients and Methods

This study was an open single blind randomized trial, conducted during 2010 and approved by the Ethics Committee of the Tarbiat Modares University. All participatnce were aware if the study and informed consent was obtained. Since there was no information relevant to this subject in the literature, a pilot study was undertaken. Assuming a β value of 0.2 and an α value of 0.05,a

Implication for health policy/practice/research/medical education:
Osteoporosis is a common disease associated with ageing and menopause, and is becoming an increasing health and socio-economic problem. In this study, our aim was to compare the effects of conventional estrogen replacement therapy and tibolone on the bone mineral density (BMD) and bone turnover in postmenopausal women.

sample size of 45 patients for each arm was calculated. To allow for possible losses to follow -up, by simple random sampling a total of 150 healthy non-surgical postmenopausal women, aged 45 to 60 years old were enrolled to the study. The subjects were referred from several private, educational and governmental hospitals in Tehran, Iran, when they had attended to seek medical advice regarding their menopause. Postmenopausal status was defined as amenorrhea for at least 12 months and estradiol level lower than 35 pg/mL. None of the women were currently or previously taken hormone therapy or any drugs which can effect on bone densitometry such as bisphosphonate, calcitonin, triparatide etc. within the past six months. Women who smoke; those with diabetes, cancer, and thyroid, parathyroid, liver, renal, or hematologic disorders; and those with other medical disorders with contra-indication for HRT were excluded. After the process of screening, the women were randomized to three groups according to a computer-generated randomization table.

Of the women included, 50 women received 2.5 mg tibolone (Tibofem, Mfd, Cipla Ltd) plus one calcium+Vitamin D tablet (500 mg Ca and 200 IU vitamin D) daily; 50 women received 0.625 mg conjugated equine estrogen and 2.5 mg medroxy progesterone acetate (CEE/MPA) plus one calcium+Vitamin D tablet daily; 50 women received only one calcium+Vitamin D tablet and served a control group. Dual-energy X-ray absorptiometry (DEXA: Lunar DPX-L system, Lunar Radiation Corporation, Madison, WI) was used to evaluate bone mineral density (BMD) of the lumbar spine (vertebra Ll- L4, AP) and the proximal femoral neck. Subjects considered to be at risk of excessive loss of BMD were withdrawn from the study and recommended to approve therapies to prevent additional bone loss. These subjects were defined as these with BMD more than 2.5 SD below the age-matched normal level. Serum total alkaline phosphates as an indicator of bone formation was measured by a kinetic colorimetric test using an automated analysis according to the recommendations of International Federation of Clinical Chemistry. Urinary calcium as an indicator of bone resorption was measured turbidometrically. Value of urinary calcium was corrected for excretion of creatinine (Ca/Cr mg/dL).

The study duration was nine months. Bone densitometry and bone turnover markers measured at baseline and were repeated after the nine months of entering into the study. Morning fast blood and urine sampling were performed in all patients for biochemical assessments.

3.1. Statistical Analysis

Standard statistical methods were used to calculate means and standard deviations. As all parameters had normal distribution, we used parametric statistical tests. The Tukey adjustment for the comparison of means (ANOVA), and χ^2 test were done to assess the differences among groups at baseline and after the nine months. Paired T test was used to assess differences within groups at two different times. The significant level was set at $P < 0.05$.All reported P values were 2-tailed.

4. Results

A total of 150 women entered the study, but 12 did not complete the trial due to vaginal bleeding (n = 6), fear of breast cancer (n = 3) and breast tenderness (n = 3). Finally, 138 women were analyzed. There were no significant differences among the groups before the treatment for any patient's characteristics, biochemical turnover markers and BMD measurements (Table 1).

After nine months of the treatments, ALP reduced significantly in the CEE/MPA and tibolone groups (P = 0.027, P = 0.002), but increased in the control group (P = 0.032) in comparison with the baseline.

Table 1. The Comparison of Some Demographic and Clinical Data Among the three Groups Before the Treatments [a], [b]

	Tibolone Group (n = 46)	CEE/MPA Group (n = 44)	Control Group (n = 48)	P Value
Age, y [c]	51.45 ± 3.08	50.98 ± 4.50	51.69 ± 4.52	> 0.05
Menopausal age, y [d]	48.73 ± 2.81	48.25 ± 2.32	48.73 ± 2.16	> 0.05
Gravidity				> 0.05
< 3	8 (17.4)	5 (15.2)	8 (18.4)	
3-5	38 (82.6)	39 (84.8)	40 (81.6)	
BMI [c]	27.73 ± 3.58	28.34 ± 3.44	27.91 ± 3.15	> 0.05
ALP, IU/L, [c]	186.06 ± 68.72	176.56 ± 57.30	177.50 ± 84.27	> 0.05
Ca/Cr, mg/dL [c]	1.06 ± 0.99	0.96 ± 1.81	0.84 ± 1.14	> 0.05
Spine BMD, g/cm^2 [c]	0.99 ± 0.18	0.98 ± 0.15	0.96 ± 0.23	> 0.05
Femoral BMD, g/cm^2 [c]	0.95 ± 0.13	0.89 ± 0.12	0.93 ± 0.12	> 0.05

[a] Abbreviations: ALP, alkaline phosphates; BMD, bone mineral density; BMI, body mass building; CEE/MPA, conjugated equine estrogen and medroxy progesterone acetate
[b] Data are presented in mean ± SD.
[c] ANOVA (Tukey) test
[d] $\chi 2$ test

Table 2. The Comparison of BMD and Bone Turnover Markers Among the Three Groups [a]

	Tibolone Group A (n = 46)			CEE/MPA Group B (n = 44)			Control Group C (n = 48)			P Value [b]		
	Before	After	P Value [c]	Before	After	P Value [c]	Before	After	P Value [c]	A and B	A and C	B and C
ALP, unit/L [c]	186.06 ± 68.72	166.89 ± 51.92	0.002	176.56 ± 57.30	161.31 ± 38.72	0.027	177.50 ± 84.27	197.79 ± 66.46	0.03	NS	0.01	< 0.01
Ca/Cr, mg/dL [c]	1.06 ± 0.99	1.11 ± 1.04	NS	0.96 ± 1.81	0.87 ± 2.08	NS	0.84 ± 1.14	0. 84 ± 1.16	NS	NS	NS	NS
Spine BMD, g/cm^2 [c]	0.99 ± 0.18	1.01 ± 0.13	NS	0.98 ± 0.15	0.97 ± 0.16	NS	0.96 ± 0.23	0.95 ± 0.13	NS	NS	NS	NS
Femoral BMD, g/cm^2 [c]	0.95 ± 0.13	0.97 ± 0.12	0.004	0.89 ± 0.12	0.89 ± 0.12	NS	0.93 ± 0.12	0.91 ± 0.10	NS	0.03	0.05	NS

[a] Data are presented in mean ± SD.
[b] ANOVA (Tukey) test
[c] Paired t-test

There were not any significant differences in urine Ca/Cr ratio after the study in comparison with the baselineWith respect to femoral BMD, significantly increase occurred in the tibolone group in comparison with the baseline (0.95 ± 0.13, 0.97 ± 0.12, P = .004). There were not any differences with respect to BMD of the lumbar spine after the treatment in comparison with the baseline in the three groups. In the comparison among the three groups after the treatments, Alp and femoral BMD were difference between the tibolone and control groups. Tibolone significantly increased femoral BMD in comparison with CEE/MPA (P = 0.03) and Cal/D only consumption (P = 0.05). Also HRT and tibolone significantly reduced Alp in comparison to Cal/D only consumption (P = 0.01, P = 0.0) (Table 2).

5. Discussion

Biochemical markers of bone metabolism are separated into two groups of formation and resorption markers. Bone turnover is a dynamic process, which increases in postmenopausal period. After the menopause, the bone formation rate is less than the resorption rate, which results in a negative remodeling balance. Biochemical markers reflect acute changes in bone metabolism. Therefore, they may be useful for subsequent bone mineral density changes prediction after various treatments (12, 13). The potential use of bone markers in clinical practice may be categorized as follows: monitoring effectiveness of therapy and compliance; prediction of bone loss and fracture risk; and selection of patients for antiresorptive therapy. The oldest bone formation marker is total alkaline phosphatase (ALP). It is proposed to participate in the initiation of bone mineralization. Postmenopausal women have higher levels of total ALP in respect of bone isoenzyme than premenopausal women have. On the other hand, urinary Ca/Cr measurement is the cheapest bone resorption marker with acceptable sensitivity (14). In our study we used the two mentioned bone turnover markers. BMD measurement is considered as the worthy approach for screening individuals with risk of osteoporosis. However, BMD cannot evaluate the actual bone turnover and are not particularly valuable in identifying individuals who rapidly lose their bone mass equal to postmenopausal women. In the present study, we used biochemical markers of bone turnover to evaluate acute changes. Since these markers measurements cannot replace BMD measurement, therefore, we used bone markers in combination with BMD to monitor the therapies.

Hormone replacement therapy (HRT) is increasingly accepted as an aim of preventing osteoporosis and improvement climacteric symptoms in postmenopausal women (1-4). However, some women do not accept the adverse effects of conventional HRT. Alternatives are, therefore, obviously needed. Tibolone is mainly used to treat women with a climacteric complaint for whom

bleeding is unacceptable, or have experienced side effects during conventional HRT. The estrogenic characteristics of tibolone therapy apply an estrogen-like effect on bone as well. The objective of the present study was, therefore, to evaluate and compare the bone-preserving effects of tibolone and HRT. Our results suggest that tibolone is suitable as any HRT to prevent bone loss. It decreased ALP and increased femoral BMD in comparison with the baseline. This findings is in the way of several clinical and preclinical data that show tibolone inhibits bone loss similarly to estrogens (6, 9-13). Our study have several limitations and some methodological questions required discussion in our study. Firstly, the use of total ALP and not the bone-specific isoform of the enzyme. However, it has been shown that, unless there is a significant increase of hepatic isoenzyme, total ALP maintains an acceptable capacity to evaluate bone turnover, and that a high correlation exists between lost the bone-specific ALP and total ALP (14). In our study we had not any elevation in hepatic isoenzyme. Secondary, period of this study was nine months and this might be regarded as insufficient period for consideration of all BMD measurements. However, Gallagher et al. conducted two randomized, placebo-controlled, dose finding studies to identify the lowest dose of tibolone with optimal effect on bone loss prevention in postmenopausal women within 1-4 years. They found tibolone 1.25 mg per day to showa positive change in BMD of spine and femoral neck at first year (10). Our study has the major strengths: First; the relatively acceptable sample size, second; the randomized and controlled design, and third; the use of bone turnover markers which reflect acute changes in bone metabolism and DEXA as a reliable method for assessing long term changes in BMD. In the present study, we compared the conventional HRT with tibolone and our data suggest that tibolone may be considered as an alternative for osteoporosis prevention in postmenopausal women. However, clinical recommendations regarding the effects of tibolone on bone densitometry must await the performance of additional long-term studies with clinical end points.

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Authors' Contribution

Heidari Zinab, student proposal; Ziaei Saeideh, designer; Faghihzadeh Soghrat, statistical analysis

Financial Disclosure

Our study had no competing interest.

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