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Research Article

The Relationship between Reproductive Hormone Levels and Osteoporosis

Semra Eroglu,[1] Gulsah Karatas[2]

[1]Department of Obstetrics and Gynecology, Baskent University, Konya, Turkey
[2]Department of Physical Medicine and Rehabilitation, Karabuk University, Karabuk, Turkey

Abstract

Objectives: Changes in serum levels of follicle-stimulating hormone (FSH) and estradiol (E2) due to menopause are the some of the most important factors for osteoporosis (OP). The aim of this study was to evaluate the relationship between bone mineral density (BMD) and reproductive hormone levels in postmenopausal women.

Methods: A total of 144 postmenopausal women were divided into two groups according to their BMD, as obtained using dual-energy X-ray absorptiometry; 72 patients with low BMD and 72 healthy subjects. Fasting blood samples were obtained from all participants for serum hormone levels, which were compared between the two groups.

Results: The FSH levels were significantly higher in the low BMD group (49.76±27.61 IU/L vs. 57.30±24.83 IU/L, p=0.001), and serum E2 levels were statistically lower in the low BMD group (39.25±22.11 pg/mL vs. 30.12±18.16 pg/mL, p=0.046). The time elapsed after the onset of menopause was longer in the low BMD group (p=0.002).

Conclusion: The low E2 and high FSH levels after the onset of menopause were associated with low BMD in postmenopausal women. According to these findings, considering the higher risk of OP in patients with low E2 and high FSH levels, randomized-prospective studies should be conducted to determine whether prophylactic treatment should be given to this group.

Keywords: FSH, estradiol, osteoporosis

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Osteoporosis (OP) is a metabolic bone disease characterized by a decrease in bone strength and increase in bone fragility, and usually arises in the postmenopausal period. OP is a highly important public health issue due to the increased risk of bone fracture in affected individuals.[1] Moreover, OP-associated fractures can lead to death, disability or loss of functions.[2] It has been suggested that about 50% of postmenopausal women will likely be affected by OP-associated fractures.[3] Therefore, the main risk factors predisposing to OP should be kept in mind in order to reduce its incidence and morbidity. The main underlying reasons for the development of OP are as follows: genetic, hormonal, and environmental factors including duration of menopause, age at menarche, nutritional factors, lifestyle, pregnancy, and lactation.[4–6]

Changes in hormone levels during the perimenopausal period have a critical role in the development of OP, such as estradiol (E2), follicle-stimulating hormone (FSH), and testosterone.[3] Bone mass and quality generally reaches the maximum level at around 30 years of age in women; however, an indolent resorption in bones begins thereafter. In the menopausal period, bone resorption shows

Address for correspondence: Gulsah Karatas, MD. Karabük Universitesi, Fiziksel Tip ve Rehabilitasyon Bolumu, Karabuk, Turkey
Phone: +90 506 287 43 66 **E-mail:** gulsah2206@gmail.com

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acceleration and reaches the top level at the age of 50 years, with the highest risk of osteoporotic fracture.[7] E2, which is known to be the best hormone at stimulating bone growth, plays a crucial role in maintaining bone mass in women. Therefore, decreased levels of post-menopausal E2 levels increase the risk of developing OP proportionate to this decrease.[8]

The association between bone loss and hormone levels in perimenopausal patients has been demonstrated in a variety of prospective studies.[9, 10] Herein, we aimed to analyze the relation of blood E2 and FSH levels in women with normal and low BMD.

Methods

Study Subjects

This controlled study was performed between January 2018 and July 2018. The study comprised 144 women aged between 40 and 60 years who were diagnosed as menopausal through clinical and laboratory tests and who had undergone BMD tests previously. The laboratory tests were requested by the physical medicine and rehabilitation clinic because X-ray images were suggestive of osteoporosis in patients with low back pain or other bone who had no other etiologic cause before performing the BMD test. The study was approved by the Non-invasive Clinical Research Ethics Committee (Decision number: 1/28, in 2017). All procedures in this study were conducted in accordance with the recommendations of the Declaration of Helsinki.

The following parameters were determined as the exclusion criteria: active hepatic or renal dysfunction; smoking history; active systemic infectious or comorbid disease such as diabetes mellitus, collagen tissue disease, rheumatoid arthritis, hypogonadism, severe heart failure, thyroid dysfunction, malabsorption syndrome; history of drug use associated with OP (steroids, thiazides, anti-dyslipidemic medications, warfarin, chemotherapy); previous treatment for OP; immobility; and current hormone replacement therapy. In total, 144 subjects were eligible for the study, consisting of 72 women with normal BMD and 72 with low BMD. All subjects participating in the study gave approval with written informed consent.

Anthropometric data

BMD was measured by using a Dual-Energy X-ray Absorptiometry (DEXA) (Norland, XR-600TM, USA). In accordance with the World Health Organization (WHO) recommendations, a bone mineral density showing a T-score ≤ -2.5 was considered as OP. Osteopenia was defined as T-scores between -1.0 and -2.5. T-scores > -1.0 were considered as normal.[11] Those with osteopenia and OP were included in the low BMD group. Patient demographic characteristics including age, body weight and height, body mass index (BMI), the age at menopause onset, the pregnancy count, and breastfeeding history were recorded. BMI was calculated by dividing body weight (in kilograms) by body height (in meters squared) [weight/(height)^2] and expressed as kilograms per square meter.

Laboratory Measurements

Fasting blood samples were taken from each subject from the median cubital vein in the morning; each sample contained 5 mL blood. Serum hormone levels including FSH, luteinizing hormone (LH), thyroid-stimulating hormone (TSH), testosterone (T), and E2 were measured using an Advia Centour XP. Serum vitamin D levels (ng/mL) were measured using a Siemens Advia 1800.

Statistical Analysis

The conformity of the variances to normal distribution was assessed using the Kolmogorov–Smirnov test and the Shapiro–Wilk test. Variances showing normal distribution were given average standard variance [mean±standard deviation (SD)] levels. Mean and SD values of parameters were used to describe scale variables. As the data was normally distributed, independent sample t-tests were conducted to compare the parameters among groups and Pearson's correlation test was used for correlation between variables. The data were examined using 95% confidence levels, and $p<0.05$ was considered as significant. The Statistical Package for the Social Sciences (SPSS) for Windows, Version 21.0 software package (IBM, Armonk, New York, USA) was used for statistical analyses.

Results

The mean age was 54.51 in the low BMD group and 52.41 in the normal BMD group. There was no statistically significant difference between the groups. The mean age was 48.4±3.4 years and the mean BMI was 29.82±5.2 kg/m^2. There were no significant differences between the two groups in terms of age, BMI, obstetric characteristics, and infertility type. The average gestation count was 2.8±1.3. The cumulative mean time of breastfeeding was 38.4±10.4 months. The time elapsed after the onset of menopause was significantly higher in the low BMD group ($p=0.002$). However, there was no statistically significant difference in BMI, number of births, duration of breastfeeding, and serum TSH, T, and vitamin D levels between the groups (Table 1). Serum E2 levels were lower in the low BMD group than in the normal BMD group, with a statistically significant difference (30.12±18.16 pg/mL, $p=0.046$ vs. 39.25±22.11 pg/mL, $p=0.046$). Serum FSH levels were significantly higher

in the low BMD group (57.30±24.83 pg/mL vs. 49.76±27.61 pg/mL, p=0.001). The LH levels were higher in the low BMD group, but this difference was not statistically significant (33.25±13.12 pg/mL vs. 31.36±14.03, p=0.237). The clinical and laboratory characteristics of the participants are listed in Table 1. Receiver operating characteristic (ROC) curve analysis was used to identify the significance of the FSH and E2 levels. The corresponding values for the ROC curve area were found to be 0.782 and 0.509, respectively, which were considered as significant for low BMD (osteopenia and osteoporosis). The cut-off value for FSH level was found as 40.5 IU/L (Fig. 1). Age and BMI had no correlation with BMD (Table 2). The age of menopause was inversely correlated with femoral neck BMD (r=-0.22, p=0.01) and femoral total BMD (r=-0.17, p=0.04). E2 was slightly correlated with lumbar spine (L1-L4)* BMD (r=-0.20, p=0.01). FSH was inversely correlated with lumbar spine (L1-L4) BMD (r=-0.25,

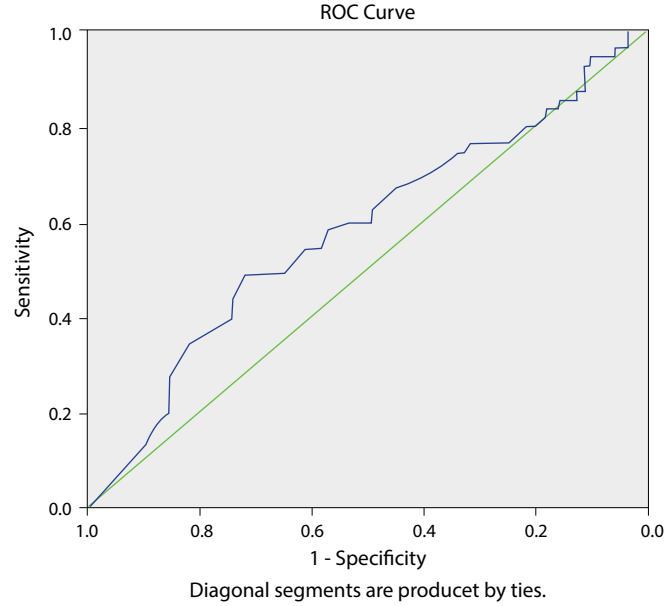

Figure 1. ROC analysis of the FSH level; (x), sensitivity; (y), specificity.

Table 2. The Spearman's rank correlation between BMD values and age, BMI, the age of menopause, E2, LH, FSH, testosterone, and Vitamin D

Variables	Lumbar spine BMD	Femoral neck BMD	Femoral Total BMD
Age (years)			
R	-0.14	-0.09	-0.14
P	0.07	0.25	0.07
BMI (kg/m²)			
R	0.38	0.10	0.16
P	0.07	0.23	0.05
The age of menopause			
R	-0.15	-0.22	-0.17
P	0.06	0.01*	0.04*
Estradiol			
R	0.20	0.16	0.10
P	0.01*	0.05	0.23
LH			
R	-0.19	-0.07	-0.05
P	0.01*	0.40	0.48
FSH			
R	-0.25	-0.20	-0.17
P	0.002*	0.14	0.03*
Testosterone			
R	0.18	0.14	0.19
P	0.07	0.16	0.05
Vitamin D			
R	-0.10	0.01	-0.003
P	0.91	0.86	0.97

p<0.05 statistically significant; BMD, bone mineral density; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SD, standard deviation.

Table 1. Demographic and laboratory characteristics of the participants according to BMD

Characteristic	Low BMD† (n=72)	Normal BMD† (n=72)	p*
Age (years), mean±SD	54.51±7.02	52.42±6.08	0.063
BMI (kg/m²) ‡, mean±SD	29.26±4.57	30.35±6.20	0.137
Time elapsed after the onset of menopause (years), mean±SD	7.42±7.44	4.49±4.18	0.002
Number of birth, mean±SD	3.0±1.5	2.71±1.2	0.189
Duration of breastfeeding (month), mean±SD	36.05±2.31	41.55±2.86	0.136
Vitamin D (ng/mL), mean±SD	12.93±6.1	12.65±6.1	0.897
TSH (UI/mL), mean±SD	2.36±0.94	2.12±1.02	0.620
FSH (IU/L), mean±SD	57.30±24.83	49.76±27.61	0.001*
LH (IU/L), mean±SD	33.25±13.12	31.36±14.03	0.237
Estradiol (pg/mL), mean±SD	30.12±18.16	39.25±22.11	0.046*
Testosterone (ıu/L), mean±SD	30.50±16.19	29.38±18.05	0.428

Values are presented as mean±standard deviation. P-values were calculated by using independent sample t-test. *p<0.05 statistically significant. †BMD: bone mineral density, ‡BMI: body mass index, §SD: standard deviation, FSH: follicle-stimulating hormone, TSH: thyroid-stimulating hormone, LH: luteinizing hormone.

p=0.002) and femoral total BMD (r=-0.17, p=0.03). LH had an inverse association with lumbar spine BMD (r=-0.19, p=0.01).

Discussion

This study showed that high FSH and low E2 levels were significantly slightly associated with low BMD in postmenopausal women. According to the ROC analysis, the cut-off values for FSH were 40.5 IU/L. In addition, regardless of the individuals' age, BMD values decreased as the time elapsed after the onset of menopause increased. We found no relationship between patient age and BMD. Similar to our study, Jiang reported no relationship between patient age and BMD, but found a positive relationship between patient age and BMI, concluding that age was not a risk factor in early postmenopausal period.[12] In contrast, age is known to be an important risk factor for OP and fractures in older women; some studies indicated that advanced age was linked with low BMD.[12–14] However, age is not the only risk factor for OP because some reproductive hormones may still be active in the early menopausal period. Also, in this study, the ages of the participants were quite similar to examine the effect of hormones in predicting the postmenopausal OP. In the present study, postmenopausal OP was not associated with patient age, but with the duration of menopause. The time elapsed after the onset of menopause was significantly higher in the low BMD group. Many studies have supported this finding.[13, 14] Similar to our findings, Demirtas and Terzi reported that the duration of menopause in multiparous women was an independent risk factor for OP.[15, 16] In our study, BMD values were significantly higher in patients who were overweight, but no significant difference were found between BMI and BMD. Similar results were reported in other previous studies. One study demonstrated that normal-weight women had 1.2 times higher prevalence of osteopenia than obese women,[17] suggesting that body weight might elevate BMD by increasing bone strength.[14, 17] Sharami reported that BMI >25 kg/m^2 was a protective factor against OP.[13] Moreover, Jiang stated that BMI <28 kg/m^2 could be an indicator for OP.[12] In another study conducted in women in perimenopausal period, weight gain was shown to increase lumbar spine BMD.[18]

E2 was significantly lower in the low BMD group. The results of Chinda support our findings.[19] Bravo showed that low serum E2 levels (<60 pg/μL) increased low BMD risk by 4.93 times.[20] Estrogen antagonizes the effect of parathyroid hormone (PTH) on bone resorption, increases osteoblast development through the release of local cytokines, increases calcium absorption from the gastrointestinal tract, and increases bone production by reducing renal calcium excretion.[3] During the menopausal transition (perimenopause), E2 levels decrease significantly (7-10 times). By contrast, age-adjusted correlation analysis by Pardhe showed no correlation between E2 levels and markers of bone destruction, but showed that E2 was in correlation with calcium levels.[8] We found that FSH levels were significantly higher in the low BMD group. Moreover, we found the cut-off value for FSH as 40.5 IU/L. We suggest that postmenopausal women with FSH values above 40.5 IU/L should be evaluated for BMD.

In the literature, there are some studies supporting the relationship between FSH level and OP.[21] Wu et al.[22] found that increased levels of FSH could accelerate the bone turnover rate and increase the risk of bone loss. In a study by Ahlborg, FSH concentrations were not found to be associated with OP before the age of 40 years or after the age of 50 years. However, a significant difference was found in BMI in patients with FSH <40 vs. FSH >40 IU/L between the ages of 40 and 50 years.[23] In our study, there was no correlation between the pregnancy count and BMD. The literature represents various results on this topic. Similar to our findings, Terzi and Lenora found no statistically significant difference between parity and BMD.[16, 24] Hillier found no association between parity and BMD.[25] In contrast, Okyay and Cure et al. found that increased parity number was protective against OP.[26, 27] Cure et al.[26] reported 4-fold increase in OP among nulliparous women. In the present study, breastfeeding did not affect the BMD in postmenopausal women. Different results were reported in previous studies. Similarly, Lenore divided patients into four groups according to the number of births. The number of births and duration of lactation were not associated with BMD in the postmenopausal period.[24] However, Jimenez reported that breastfeeding was 0.93-fold preservative for BMD.[28] In a study of 1694 postmenopausal women, women with no breastfeeding history were compared with those with a breastfeeding history >79 months, and long breastfeeding time was reported to be a risk factor for OP.[29] Okyay also found that the duration of breastfeeding for each child was the most important risk factor for OP, independent of the first breastfeeding age.[27] Some other studies also supported this finding.[14, 30] In conclusion, reproductive hormones may be useful in evaluating postmenopausal BMD. Annual E2 and FSH measurements can predict the change in BMD and be used as a screening method to prevent possible bone fractures. This study showed that the evaluation of postmenopausal hormone levels could be used as a marker in predicting osteoporosis. Measuring levels of FSH, LH, and E2 is a practical and cost-effective method. Bone loss during the peri- and post-menopausal period is a reproductive-hormone–dependent event. Hormonal therapies and FSH-blocking agents can be used to prevent

osteoporosis and fractures in early menopausal and postmenopausal women.

Disclosures

Ethics Committee Approval: Approval for the research was obtained from the Ethics Committee of Karabuk University (decision No: 1/28, 25 January 2017).

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Conflict of Interest: None declared.

Authorship Contributions: Concept – S.E.; Design – S.E.; Supervision –G.K.; Materials – S.E., G.E.; Data collection &/or processing – S.E.; Analysis and/or interpretation – G.K.; Literature search – S.E.; Writing – S.E.; Critical review – G.K.

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