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The evaluation of hormonal and psychological parameters that affect bone mineral density in postmenopausal women

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Abstract. – OBJECTIVE: In this study we aimed to investigate the relationships between serum levels of DHEAS, reproductive hormones and low bone mineral density (BMD) in postmenopausal women. We also examined the relationship between psychological status of patients and their BMD results.

PATIENTS AND METHODS: This study included postmenopausal female patients. BMD measurements were performed with dual-energy X-ray absorptiometry (DEXA). Psychological assessments of all cases were performed using the Hamilton Anxiety and Hamilton Depression scales. All patients provided fasting venous blood samples in order to determine serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and DHEAS.

RESULTS: There were 33 cases (45.2%) with normal BMD levels and 40 cases (54.8%) with abnormal BMD levels (osteopenia and osteoporosis). DHEAS levels did not show any statistically significant difference according to BMD results (p = 0.431). The Hamilton Anxiety and Depression scores also did not show statistically significant differences in accordance with the BMD results (p = 0.889 and p = 0.706, respectively).

CONCLUSIONS: According to our results, anxiety, depression and circulating DHEAS levels are not significantly associated with low levels of BMD, particularly at osteopenic levels. So these parameters are not useful for clinical practice in patients with low BMD in the middle-aged postmenopausal women.

Key Words:
Postmenopausal women, Dehydroepiandrosterone sulfate, Anxiety, Depression, Low bone mineral density.

Introduction

Osteoporosis and osteopenia are skeletal system diseases that show increasing incidences with age[1]. The World Health Organization (WHO) describes osteoporosis as a structural degeneration that causes a loss in bone mass leading to an increased risk for fracture in bone tissue[2]. During the last two decades, some studies have focused on the relationship between low bone mineral densitometry values and psychological alterations such as anxiety and depression; these studies have shown associations between low bone mineral density (BMD) values and depression and anxiety[3]. There are still limited number of studies that have investigated the relationship between anxiety levels and low BMD levels.

Some studies have claimed that patients with depression have lower BMD levels, which could be related to increased osteoclastic activity in these patients[4]. It was concluded that women with osteoporosis have difficulty practicing daily activities, and this caused a deterioration in their quality of life and self-esteem, thus, resulting in a state of reactive depression[5]. Also reduced levels of blood dehydroepiandrosterone sulfate (DHEAS) as well as rapid declines in estrogen levels have been blamed in the etiology of postmenopausal osteoporosis[6].

We investigated the relationships of anxiety and depression with low BMD during the postmenopausal period. Additionally, we aimed to determine possible variables related with postmenopausal osteoporosis (PMO) by doing a comprehensive evaluations that included determining levels of DHEAS and various reproductive hormones.

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Patients and Methods

Patients

This study was conducted in Dumlupınar University Evliya Çelebi Training and Research Hospital, Obstetrics and Gynecology Clinic between July 2013 and July 2014. This study was in accordance with the principles outlined in the Declaration of Helsinki. Ethical committee approval was received from the local Human Research Ethics Committee, and written informed consent was obtained from all patients. A total of 91 postmenopausal women were included in the study. Patients who had systemic diseases that could cause secondary osteoporosis, such as diabetes mellitus, primary hyperparathyroidism, thyrotoxicosis, hypogonadism, rheumatoid arthritis, and inflammatory bowel disease were excluded from the study. Additionaly excluded from the study were those patients who used medications and that could lead to secondary osteoporosis such as steroids, heparin, lithium, carbamazepine, phenytoin and serotonin reuptake inhibitors (SSRIs)[7]. Smokers and alcohol users were also excluded from the study.

BMD Measurements

BMD was measured in the left hip (femoral neck measurements) and the spine (vertebrae, L1-L4). BMD measurements were performed with a General Electric LUNAR DPX-NT (Madison, WI, USA) device. Bone screening was performed using the dual-energy X-ray absorptiometry (DEXA) method. This method is based on the beaming of photons through various areas of the body scan. BMD was measured in each of the three measurement parameters for two areas. The T score cut-off values were between -1 and -2.5 for osteopenia, and for osteoporosis, the cut-off score was ≤ -2.5[2,3].

Psychological Assessments

Psychological assessments of all cases were performed by the same psychiatrist using the Hamilton Anxiety Rating Scale (HARS)[8] and the Hamilton Depression Rating Scale (HDRS)[9]. Turkish reliability and validity studies of the HARS and HDRS were conducted by Yazici et al[10] and Akdemir et al[11], respectively. The HARS consists of 14 items designed to assess the severity of a patient's anxiety. The HDRS contains 17 items, however, four other questions are not added to the total score but are used to provide additional clinical information.

Sample Collection and Measurement of Biochemical Parameters

Serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), and DHEAS were analyzed. After fasting overnight, venous blood samples were collected into an evacuated serum separator clot activator tube (Vacuette® Z Serum Sep Clot Activator, GreinerBio-One, Kremsmunster, Austria) at 9-10 a.m. All blood samples were centrifuged at 1500 ×g for 10 minutes at 4 ºC within 1 hour after collection. Hormone concentrations were measured in serum samples without delay. Serum hormone concentrations were measured on a Beckman Coulter UniCel DxI 800 immunoassay analyzer (Beckman Coulter, Miami, FL, USA) by chemiluminescent immunoassay (CLIA) using original assay reagents (Beckman Coulter, Miami, FL, USA).

Statistical Analysis

Statistical analyses were carried out on NCSS (Number Cruncher Statistical System) 2007 (Kaysville, UT, USA) statistics software. Besides descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum), quantitative data were compared using Student's *t*-tests for comparisons of normally distributed variables, and Mann-Whitney U tests for comparison of non-normally distributed variables between two groups. Qualitative data were compared using the Fisher-Freeman-Halton test. Associations between variables were determined with Spearman's correlation analysis. The statistical level of significance was accepted as $p < 0.05$.

Results

This study was conducted on 91 postmenopausal women. Demographic properties and patient characteristics, BMD status and T scores of the patients are summarized in Tables I and II, respectively. Levels of DHEAS, FSH, LH and E2 did not show any significant differences according to BMD results ($p = 0.431$, $p = 0.153$, $p = 0.153$, $p = 0.814$, respectively).

The anxiety and depression levels in 84 cases with known According to evaluation of total anxiety levels, 13.1% (n = 11) of the cases did not have anxiety, whereas 35.7% (n = 30) had minor anxiety and 51.2% (n = 43) had major anxiety. Of the 86 cases with known Hamilton depression

Table I. Distribution of demographical properties and patient characteristics.

	N	Min-Max	Mean ± SD	Median
Age (years)	91	36-58	51.73 ± 6.64	52
Age at menopause (years)	91	35-52	46.24 ± 6.07	47
Weight (kg)	91	45-114	75.57 ± 13.15	75
Height (cm)	91	146-171	158.27 ± 5.51	160
BMI (kg/m^2)	91	19.6-41.8	30.20 ± 5.33	30.3
Waist circumference (cm)	91	66-119	95.95 ± 11.80	98.5
Hip circumference (cm)	91	90-150	115.93 ± 12.56	117
Waist/hip ratio	91	0.7-1.1	0.83 ± 0.07	0.83
Number of children	90	0-9	2.72 ± 1.50	2

levels, 5.8% (n=5) did not have depression, whereas 9.3% (n=8) had minor depression, 68.6% (n=59) had moderate depression and 16.32% (n=14) had severe depression. Hamilton psychic anxiety and somatic anxiety levels did not show any significant difference according to BMD results (p = 0.670 and p = 0.338, respectively). Hamilton anxiety and depression levels also did not show any significant difference according to BMD results (p = 0.889 and p = 0.706, respectively). The comparisons of BMD results with hormonal and psychological status are summarized in Table III.

Discussion

Our main aim in this study was to investigate the relationship of depression, anxiety, DHEAS and reproductive hormones levels with BMD in postmenopausal women. Previous studies have demonstrated an association between depression and low BMD, and these same studies have demanded further research into the relationships of BMD with anxiety and stress[12-14]. Aging in women is characterized by a progressive decline of circulating DHEAS. Stomati et al[15] suggested that DHEAS treatment modulates the neuroendocrine control of pituitary beta-endorphin secretion, which may support the therapeutic efficacy of the DHEAS on behavioral symptoms in postmenopausal women. In some cases related to menstruation such as amenorrhea, late age of menarche and early menopause have been shown to be risk factors of osteoporosis in previous studies[16,17]. There are also distinguishable relationships between androgen deficiencies. Specifically, these deficiencies in women include those with clinical conditions such as premature ovarian failure, hypothalamic-pituitary abnormalities, iatrogenic menopause (chemotherapy, radiation, and bilateral oophorectomy), signs and symptoms including osteopenia or osteoporosis, decreases in lean body mass, loss of pubic hair, dysphoria, and other mood disorders[18]. Besides osteoporosis, other endocrine systemic diseases that are associated with depression include clinical and subclinical hypercortisolism, hypothalamic hypogonadotropism, and anorexia nervosa[19,20].

A two-way relationship between depression and BMD that involves different pathways has been identified[3]. Also, there are various associations that have been described for depression and

Table II. Distribution of the BMD Satatus and T Scores.

		N	T scores min-max (median)	Mean ± SD
Femur neck BMD		73	-2.5-2.7 (-0.2)	-0.32 ± 1.08
Spinal BMD		73	-3.5-2.0 (-1.0)	-0.88 ± 1.13
		N	**%**	
BMD results (n = 73)	Normal	33	45.2	
	Osteopenia	36	49.3	
	Osteoporosis	4	5.5	

Table III. The comparisons of BMD results with hormonal and psychological status.

	BMD results				
	Normal		Abnormal		
	N	Mean ± SD (median)	N	Mean ± SD (median)	p
BMI (kg/m^2)	31	29.78 ± 5.54 (30.4)	35	29.82 ± 5.36 (29.6)	0.954[a]
DHEAS	30	125.48 ± 64.11 (103.5)	34	119.57 ± 66.82 (102.5)	0.431[b]
FSH	31	66.99 ± 32.09 (59)	39	61.27 ± 27.96 (56)	0.153[b]
LH	31	38.91 ± 15.05 (39)	38	36.70 ± 15.28 (36.1)	0.153[b]
E2	31	38.35 ± 60.84 (16)	38	37.48 ± 57.59 (17)	0.814[b]
Hamilton anxiety psychic	30	6.20 ± 3.01 (6.5)	39	6.42 ± 2.92 (7)	0.670[b]
Hamilton anxiety somatic	30	8.30 ± 5.04 (8)	39	8.94 ± 4.70 (9)	0.338[b]
	N	%	N	%	
Hamilton anxiety (n = 69)					
No anxiety	5	16.7	4	10.3	0.889[c]
Minor anxiety	11	36.7	14	35.9	
Major anxiety	14	46.7	21	53.8	
Hamilton depression (n = 71)					
No depression	3	9.7	2	5.0	0.706[c]
Mild depression	4	12.9	4	10.0	
Moderate depression	21	67.7	26	65.0	
Severe depression	3	9.7	8	20.0	

[a]Student's *t*-test; [b]Mann-Whitney U test; [c]Fisher-Freeman-Halton test.

low BMD, namely the physiological pathway, the behavioral pathway, and the medical pathway. The physiological pathway involves increased production of proinflammatory cytokines in depression, these include IL-6 and TNF-α, which act on bone turnover and cause increased osteoclastic activity and bone resorption[21,22]. The behavioral pathway is related with the negative effects of environmental factors such as smoking, excessive alcohol consumption, and reduced physical activity on BMD[1]. The medical pathway involves the negative effects of anti-depressants on BMD, as shown by recent studies[7]. However, women who had used SSRIs during the 2 years prior to our study were excluded.

In our study, there was no significant association between low BMD levels and depression scores in postmenopausal women. Bistrović et al[23] screened 130 postmenopausal and perimenopausal women who were 44 to 72 years old and had registered at the densitometry clinic. Their study had nearly the same design as our study; however, unlike our study, they used the Beck depression scale. As a result of their research, they suggested that self-reported depression is not associated with low BMD levels in perimenopausal and postmenopausal women[23]. There are some studies that are consistent with our findings[24,25]. In our study conducted with middle-aged postmenopausal women, there was no significant association between anxiety and low BMD. Erez et al[3] found a significant association between anxiety and low BMD. Their study included 128 patients with an average age of over 60 years. It is possible to evaluate their patient group as both postmenopausal and geriatric patients. These findings are different from the results of our study. However, it is difficult to make strict interpretations about correlations between low BMD levels and high depression or anxiety scores. Most of the previous studies have been conducted in different populations and countries. Low BMD is dependent on many factors including race, small body structure, alcohol, smoking, exposure to sunlight, and vitamin D intake[26].

Another finding in this study is that levels of DHEAS, FSH, LH and E2 did not show statistically significant difference according to BMD results of the patients. The study by Ghebre et al[27] which included 1,003 cases, was a large scale study that brought greater attention to this topic. During their 15-year follow-up period, this group measured BMD eight times for each case; they found that higher initial DHEAS levels were associated with less bone loss at the following

BMD measurements. However, this association was determined to be weakened every succeeding year. Nevertheless, they found BMD levels at the end of the 15-year follow-up time were higher in patients who had higher initial levels of DHEAS. DHEAS levels that are within the normal range may have varying effects on BMD. There are several studies that have found a positive association between DHEAS and BMD[28-30]. Conversely, Lambrinoudaki et al[31] did not find a statistically significant association between BMD and DHEAS levels.

Conclusions

According to our results, it could be said that there is not a significant association of anxiety and depression with low BMD, particularly at osteopenic levels. We also did not find a significant association between circulating levels of DHEAS and low BMD. So these parameters are not useful for clinical practice in patients with low BMD. Large-scale prospective studies performed in multicenters are necessary in order to investigate the association between DHEAS, reproductive hormones, psychiatric conditions, and low BMD levels.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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