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Obstructive Sleep Apnea Syndrome May Be a Risk Factor for the Development of Osteoporosis in Men at an Early Age?

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Abstract

Objective: Chronic intermittent hypoxia due to respiratory events occurring during sleep and sleep fragmentation due to arousals in obstructive sleep apnea syndrome (OSAS) may affect bone mineral density (BMD) directly or may be by causing a change in BMD through effects on hormones. We aimed to investigate whether any BMD change or any change in the level of hormones [growth hormone (GH), insulin-like growth factor-1 (IGF-1), free testosterone, total testosterone, and sex hormone-binding globulin (SHBG)], which may be related to BMD, occurs in middle-aged male patients with OSAS and compare the same with normal individuals.
Material and Methods: Blood samples were collected from the participants in the morning (07.00–08.00 AM) after applying polysomnography for diagnosis. GH, IGF-1, total testosterone, and SHBG levels were measured using the enzyme-linked immunosorbent assay method, whereas the free testosterone level was measured using the radioimmunoassay method. BMD was measured at the femoral neck and lumbar vertebra using the Dual energy X-ray absorptiometry (DEXA) method.
Results: Between the two groups of hormones levels and T-score values statistically significant difference was not obtained. There was a statistically significant positive relationship between age and T-score femur ($p<0.001$) and T-score vertebra ($p=0.017$) and between rapid eye movement sleep time and T-score femur ($p=0.032$) in the OSAS group. Although patients who have BMD <-2.5 in the OSAS group (5/24) was detected to be higher than the control group (0/22), the difference was not statistically significant ($p=0.05$).
Conclusion: In this study, we demonstrated that OSAS may not be a risk factor in the development of osteoporosis in middle-aged male patients. In addition, there was no direct relation between BMD and chronic intermittent hypoxia, apnea–hypopnea index, or excessive sleepiness. Furthermore, we could not obtain any distinct relationship between OSAS and hormonal parameters that affects BMD.
Keywords: Obstructive sleep apnea syndrome, osteoporosis, GH, IGF-1, testosterone, SHBG

Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by recurrent complete (apnea) or partial (hypopnea) obstruction attacks in the upper respiratory tract during sleep and by oxygen desaturations developing because of these respiratory events, and it is often accompanied by alertness reactions in the brain (arousal) (1). It is reported to be seen, particularly among middle-aged men in the society (2). Desaturations occurring during night cause chronic intermittent hypoxia (CIH), and arousals cause normal night's sleep to be disturbed and excessive daytime sleepiness (EDS). Moreover, respiratory events lead to sympathetic tonus increase during night (3). It is reported that hypoxia can cause changes in the hypothalamic–pituitary axis and peripheral endocrine glands (4). In addition, CIH can create systemic inflammation, oxidative stress, and endothelial dysfunction and directly cause bone cell dysfunction (5,6). Disturbed sleep can induce impaired sleep-controlled endocrine

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rhythms and accordingly induce endocrine and metabolic abnormalities. Negative effects of OSAS on many systems, particularly on cardiovascular and metabolic systems, are well known (7).

There are some studies suggesting that obstructive sleep apnea syndrome causes a decrease in growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels (8,9) and androgen and sex hormone-binding globulin (SHBG) levels (10-12). It has been demonstrated that decreased IGF-1 levels are associated with osteoporosis among middle-aged males (13,14). Moreover, the relationship between the decrease in androgen levels and early osteoporosis in men has been known for years (15). SHBG is a glycoprotein that specifically binds to testosterone and estradiol. The increase and decrease in SHBG levels are controlled in delicate balance. Their levels are reduced when insulin, IGF-1, and androgen levels increase. In addition, SHBG levels increase when GH, estrogen, and thyroxine levels increase (16).

According to the World Health Organization (WHO), osteoporosis is accepted as a silent and epidemic disease characterized by increased risk of fracture and tendency of bone fragility because of the impairment in the microstructure of the bone tissue and bone mass. It is generally perceived as a woman's disease. Because a hormonal change is not seen in men, like in women, early osteoporosis is not expected for them and age-related osteoporosis develops over the age of 70 years in men (17). Based on the hormonal changes mentioned above, it can be considered that OSAS can lead to changes in bone mineral density (BMD). This study aimed to investigate the presence of any change in BMD and in GH, IGF-1, free testosterone, total testosterone, and SHBG levels and determine whether related clinical parameters differ from normal values in middle-aged male patients with OSAS. To exclude the effects of age, fat distribution, obesity, and smoking on hormones and osteoporosis, patient and control groups were compared with regard to age, waist circumference, body mass index, and smoking. The obtained data will demonstrate both the changes in GH, IGF-1, testosterone, and SHBG levels in OSAS and the relationship of OSAS with a disease such as osteoporosis, which has some important impacts on public health.

Material and Methods

Patients

Male patients between the ages of 40 years and 68 years, who had 1 or more complaints of snoring, excessive daytime sleepiness, and nocturnal witnessed apnea and who were referred to our clinic with the pre-diagnosis of OSAS, were scanned on the basis of detailed physical examination and medical history in terms of inclusion and exclusion criteria. Anthropometric measurements were performed during the physical examination. Body mass index (BMI) was calculated by dividing the body weight (in kilograms) by the height (in meters) squared. Neck circumference was measured at the level of the cricoid membrane, and waist circumference was measured around the widest part of the waist with a tape measure. Blood pressure was evaluated using a sphygmomanometer (ERKA, Chemnitz, Germany) as soon as the patients woke up in the morning. To rule out comorbid diseases in the participants, PA chest radiography, respiratory function test, fasting blood glucose analysis, liver function test, and analyses of urea, creatine, and blood lipids were performed.

Patients having 1 of following features were excluded from the study: patients with any systemic disease such as diabetes mellitus (FBG>126 mg/dL), moderate–severe hypertension (those who were previously diagnosed and had blood pressure level above 140/90 mmHg), chronic renal failure, cancer, and hypercholesterolemia (those who received lipid-lowering drugs or had serum triglyceride level of ≥150 mg/dL and/or high-density lipoprotein-cholesterol (HDL-C) level of ≤40 mg/dL); those who were younger than 40 years or older than 68 years old; those with severe chronic obstructive pulmonary disease or clinical findings for asthma (postbronchodilatator FEV_1<70% according to the expected value); those having osteoporosis, hypogonadism, hypothyroidism, hyperparathyroidism, and Cushing syndrome; those receiving hormone replacement therapy; those using Ca, D vitamin, bisphosphonate, and proton pump inhibitors; and those whose BMI values were above 35.

As a result, of 287 patients, 46 male patients between the ages of 40 and 68 years, who accepted to participate in the study and did not have exclusion criteria, were included in the study. Patients with apnea–hypopnea index (AHI) value<5 were defined as the control group (n=22), and other patients with AHI value≥6 were included in the OSAS group (n=24).

For evaluating excessive daytime sleepiness, the Turkish validated version of the Epworth Sleepiness Scale (ESS) was applied. This test includes questions regarding the likelihood of falling asleep in eight situations, and a value is obtained between the scores of 0 (not sleepy) and 24 (excessively sleepy). The values of 10 and above are considered for making the diagnosis of EDS (18).

All patients in the study underwent polysomnography for diagnosis, and their serum samples were collected in the morning. GH, IGF-1, SHBG, total testosterone, and free testosterone values were evaluated, and BMD was measured in the regions of lumbar vertebra and femur neck.

The ethical approval for the study was obtained from the Ethics Committee of Selçuk University Meram Medical Faculty with the decision number of 2009/048. Written informed consent was obtained from the patients who participated in the study.

Polysomnography

The participants were subjected to full-night polysomnography (PSG) procedure, and the results were recorded using a digital polysomnographic system (VIASYS Healthcare GmbH, Germany). Physiological changes were essentially recorded. Electroencephalography, electrooculography, and submental electromyography (EMG) were performed for the evaluation of sleep. For monitoring respiration, an oro-nasal thermocouple or thermistor was placed in the nose to measure the airflow. Thoracic and abdominal motions were recorded with a thoracoabdominal effort sensor. In addition, hemoglobin oxygen saturation and heart rate were followed up using a pulse oximeter. The

Table 1. PSG and demographic features of the OSAS group and control group

	OSAS (n=24)	Control (n=22)	
	Mean±SD	Mean±SD	p
BMI (kg/m^2)	29.13±3.60	27.81±3.30	0.205
SE (%)	87.04±6.36	84.64±7.77	0.256
REM time (%)	14.17±5.60	15.23±8.80	0.981
	Median (min–max)	Median (min–max)	
AHI (event/h)	45.2 (15–84.2)	3.4 (0.7–5)	0.000*
Minimum SaO_2 (%)	76 (44–88)	89 (69–91)	0.000*
Mean SaO_2 (%)	92 (54–94)	94 (91–97)	0.000*
SaO_2≥90% time	84.7 (0.4–98.4)	98.2 (79.7–100)	0.000*
NREM3 time (%)	5.3 (0–17.1)	7 (2–25)	0.708
EDS	11	2	0.000*
Smoking (pack/year)	20 (0–40)	7 (0–40)	0.119
Age (year)	48.50 (40–68)	44.50 (40–59)	0.079

BMI: body mass index; SE: sleep efficiency; %REM time: the ratio of REM sleep time to total sleep time; AHI: apnea hypopnea index; mean SaO_2 (%): the mean oxygen saturation measured during night; SaO_2≥90% time: the ratio of time spent with the saturation rate of 90% and above to total sleep time; NREM3 time (%): the ratio of NREM3 sleep time to total sleep time; EDS: excessive daytime sleepiness

Table 2. Biochemical analysis and bone mineral density (BMD) values of the OSAS and control groups

	OSAS (n=24)	Control (n=22)	p
	Mean±SD	Mean±SD	
IGF-1 (ng/mL)	126.91±33.09	135.26±49.91	0.504
Free testosterone (pg/mL)	6.12±2.49	5.01±2.89	0.170
SHBG (nmoL/lt)	25.07±9.16	22.60±7.27	0.320
T score AP	–0.683±1.36	–0.536±0.94	0.676
T score femur	–0.567±1.32	–0.241±1.290	0.404
	Median (min–max)	Median (min–max)	
GH (ng/mL)	0.99 (0.50–1.33)	0.50 (0.50–0.801)	0.113
Total testosterone (ng/dL)	309.5 (120–569)	337.5 (171–757)	0.904

SD: standard deviation; SHBG: sex hormone-binding globulin; GH: growth hormone; IGF-1: insulin-like growth factor-1; OSAS: obstructive sleep apnea syndrome

leg movements were recorded through an EMG sensor placed on the anterior tibilais muscle of a single leg. Sleep stages were manually scored in accordance with the standard scoring criteria of the American Academy of Sleep Medicine (AASM) (1). The AHI value was calculated by dividing the number of total apnea and hypopnea episodes (hour) by the duration of sleep. Patients with AHI values above 5 were evaluated to have OSAS. In total, 24 patients diagnosed with OSAS were included in the study group, and 22 adult patients without OSAS (AHI<5) were included in the control group.

For all patients, the following data included in their polysomnography reports were recorded to be used in our study: AHI; minimum oxygen saturation (min SaO_2): the lowest oxygen saturation level during sleep; mean oxygen saturation (mean SaO_2): the mean value of oxygen saturation recorded during night; time spent with saturation at the rate of 90% and above (SaO_2≥90% time): during sleep, the ratio of time spent with the saturation rate of 90% and above to the whole duration of sleep; sleep efficiency (SE): the ratio of sleeping time to the time spent in bed; duration of %NREM3: the ratio of deep sleep period (NREM3) to the whole sleeping time; and duration of % REM: the ratio of REM sleeping time to the whole sleeping time.

Sample Collection

Following 8–12-h fasting, venous blood samples were collected from the participants in the patient and control groups between 07.00–08.00 a.m. in the morning after polysomnography was performed. The collected blood samples were centrifuged at 4000 rpm/min for 10 min, and their serums were separated. For biochemical analyses, sufficient amount of serum samples were separated and stored in a deep-freezer at –80°C until analysis.

Biochemical Analysis

All serum samples were kept at room temperature and analyzed simultaneously. The measurement of serum GH, IGF-1, total testosterone, and SHBG levels was performed using the chemiluminescence method in the Immulite system (Immulite 2000, Siemens, UK). Free testosterone levels were evaluated using the radio immunoassay (RIA) method with the free testosterone kit, Free Testosterone-RIA-CT (DIAsource Immunoassays, Belgium).

Evaluation of Bone Mineral Density

Bone mineral density was measured using the whole body DEXA scanning method (Lunar DPX, NT+A40G5-252PG-6N5NO-O26GA, USA) at the levels of the femur neck and lumbar vertebra (L1–L4). BMD was provided in g/cm^2. The T score was expressed as standard deviation (SD) from the mean BMD of young healthy individuals of the same gender (20–35 years, young adult). The diagnosis of osteoporosis was established when the T score, which was measured for the femur or vertebra, was lower than –2.5 SD (19).

Statistical Analysis

The data of the patient and control groups were statistically evaluated using SPSS 17.0 (Statistical Package for the Social Sciences, Armonk, NY, USA) software. Because %NREM3 time, min SaO_2, mean SaO_2, SaO_2≥90% ratio, AHI, GH, and total testosterone values did not demonstrate parametric distribution, Mann–Whitney U test was used for the comparison of 2 independent groups. For other variables, an independent t-test was employed. For revealing any relationship between the waist

Table 3. The correlation between biochemical parameters and bone mineral density (BMD) values and PSG and demographic data in patients with OSAS

	GH	IGF-1	Total testosterone	Free testosterone	SHBG	Vertebral T score	Femoral T score
	r	r	r	r	r	r	r
	p	p	p	p	p	p	p
Age	0.177	0.071	0.072	0.103	0.337	–0.350	–0.531
	–0.240	0.640	0.637	0.495	0.022	0.017	<0.001
BMI	–0.230	0.036	–0.204	0.016	–0.153	–0.018	–0.073
	0.124	0.814	0.174	0.917	0.310	0.906	0.630
AHI	0.245	0.167	0.003	0.152	0.114	–0.199	–0.177
	–0.101	0.267	0.982	0.312	0.450	0.185	0.240
NREM3 time	0.305	0.069	–0.175	–0.046	–0.196	0.108	0.152
	–0.039*	0.649	0.245	0.761	0.193	0.476	0.315
REM time	–0.021	0.154	0.168	–0.027	0.002	0.167	0.317
	0.892	0.307	0.266	0.861	0.991	0.269	0.032*
Minimum SaO_2	–0.124	0.098	–0.032	–0.145	0.097	0.179	0.229
	0.413	0.518	0.831	0.336	0.523	0.235	0.125
Mean SaO_2	–0.109	0.125	–0.038	–0.146	–0.235	0.008	0.082
	0.471	0.409	0.800	0.332	0.116	0.958	0.590
SaO_2≥90% time	–0.160	0.028	–0.060	–0.206	0.265	0.142	0.139
	0.294	0.855	0.694	0.174	0.079	0.353	0.363
ESS	0.063	–0.072	–0.101	0.043	–0.205	–0.084	0.045
	0.675	0.634	0.505	0.778	0.172	0.581	0.766

BMI: Body mass index; AHI: apnea hypopnea index; NREM3 time: the ratio of NREM3 sleep time to total sleep time; REM time: the ratio of REM sleep time to total sleep time; Mean SaO_2 (%):the mean oxygen saturation measured during night; SaO_2 ≥%90 time: the ratio of time spent with the saturation rate of 90% and above to total sleep time; ESS: Epworth sleepiness scale; SHBG: sex hormone-binding globulin; IGF-1: insulin-like growth factor-1; GH: growth hormone

Table 4. The correlation of biochemical parameters and bone mineral density (BMD) values in patients with OSAS

		GH	IGF-1	Total testosterone	Free testosterone	SHBG
T score,	r	–0.059	0.193	0.244	0.250	0.042
Vertebra,	p	0.698	0.198	0.102	0.094	0.782
T score,	r	–0.178	0.273	0.013	0.035	–0.181
Femur,	p	0.236	0.067	0.934	0.816	0.227

SHBG: Sex hormone-binding globulin; GH: growth hormone; IGF-1: insulin-like growth factor-1

circumference, neck circumference, BMI, and % REM time and IGF-1, free testosterone, SHBG, vertebral T score, and femoral T score levels, Pearson correlation test was employed. In addition, Spearman correlation test was used to determine a relationship between AHI, %NREM3 time, min SaO_2, mean SaO_2, and SaO_2≥90% ratio and the GH and total testosterone levels. In the OSAS group, multiple regression analysis was used with T scores of the femur and vertebra and correlated values. The values below the p value of 0.05 were accepted to be statistically significant.

Results

Polysomnographic and demographic features of patients with OSAS and the control group are presented in Table 1. In the study, the number of male adult patients was 24 in the OSAS group and 22 in the control group. The values of ESS, AHI, min SaO_2, mean SaO_2, and SaO_2≥90% time were significantly different between the 2 groups (for all values, $p<0.05$). In total, 11 patients from the patient group and 2 participants from the control group had 10 scores and above according to ESS, and they were found to be excessively sleepy. No statistically significant difference was found between the patient and control groups in terms of age, smoking, BMI, SE, %NREM3 time, and %REM time (Table 1).

In patients with OSAS, T scores of the femur and vertebra were detected to be lower than –2.5 SD in 5 participants (20.8%). On the other hand, in the control group, no participant had a T score below –2.5 SD (0%). In the evaluation through

Fisher's exact test, this situation was not statistically significant between the groups (p=0.05).

For the participants in the OSAS group and control group, biochemical analysis and BMD values are shown in Table 2. There was no statistically significant difference between 2 groups with regard to GH, IGF-1, free testosterone, total testosterone, SHBG, vertebral T score, and femoral T score values (Table 2).

The correlation between the biochemical parameters and BMD values and polysomnographic and demographic data is presented in Table 3 for the patients with OSAS. In the OSAS group, a statistically significant relationship was found between GH and %NREM3 time in the evaluation performed with Spearman's correlation test (p=0.039, r=0.305). In the OSAS group, a significant positive correlation was detected between the femoral T score and %REM time (p=0.032, r=0.317) and age (p<0.05, r=–0.531) (Table 3). Regression analysis revealed that REM time affected the femoral T score significantly (β=0.048, p=0.038) and the other parameter affecting the femoral T score was age (β=–0.091, p<0.001).

On the other hand, a significant negative correlation was found between the vertebral T score and age (p=0.017, r=–0.350), and regression analysis demonstrated that age had an effect on the vertebral T score (β=–0.054, p=0.022). No other parameter correlated with the vertebral T score.

The correlation between the biochemical parameters and BMD values of patients with OSAS is shown in Table 4. No significant relationship was found between the vertebral and femoral T scores and hormonal parameters in the correlation analyses (Table 4).

Discussion

In this study, hormonal disorders that were expected to be seen in OSAS patients were not found in patients with OSAS included in the study. No statistically significant difference was detected between the groups in terms of the means of vertebral and femoral T scores. The number of patients with BMD value below –2.5 was higher in the OSAS group (20.8%) than in the control group (0%). However, the difference between the groups was not statistically significant. In the study of Izumotani et al. (20), the rate of osteoporosis was found to be 9.5% based on the criterion of T score<–2.5 SD in healthy males between the ages of 40 and 59 years. The 3 most common causes of secondary osteoporosis among males are alcohol consumption, excess of glucocorticoids (Cushing syndrome or, more often, long-term glucocorticoid treatment), and hypogonadism (15). This study, which was conducted after ruling out the causes of secondary osteoporosis, suggested that OSAS had no extra contribution to osteoporosis. Consistent with other studies (21), it was found that age had important effect on the femoral and vertebral T scores. The presence of more participants that were over the age of 65 years may have been the cause of higher number of patients with low BMD in the OSAS group than in the control group. Contradictory results have been obtained from the clinical studies conducted on this topic to date. Tomiyama et al. (22) and Uzkeser et al. (23) reported that OSAS impaired BMD. In the study conducted by Mariani et al. (21) on obese patients, they found that OSAS did not affect BMD. In another study conducted on rats (24), it was demonstrated that CIH had no effect on BMD, which was consistent with this study. On the other hand, another study on elderly patients with OSAS (25) revealed increased BMD in OSAS patients, and this situation was attributed to the stimulation of mesenchymal cells in the bone by CIH.

In our study, no difference was found between the groups in terms of hormone levels, but there was a significant relationship between the GH level and %NREM3 time in the OSAS group. This is consistent with the finding of a relationship between sleep-controlling mechanisms and GH secretion in the literature. It has been reported that the secretion of GH in adults occurs more rapidly at night (20) and somatotropic secretion increases during sleep, particularly in slow-wave sleep (NREM3). Moreover, it has been reported that 70% of GH pulse at night is related to the slow-wave sleep (NREM3) time (26). In OSAS, qualitative and quantitative sleep changes are well defined. Superficial sleep time (NREM stage 1, 2) is increased, but the deep sleep (NREM stage 3) period is decreased (27). There are some studies demonstrating that these changes are associated with decreased GH/IGF-1 secretion (28), and both GH and IGF-1 secretions are increased with CPAP treatment (9). Ursavas et al. (29) found that IGF-1 levels decreased in OSAS patients and there was an inverse relationship between this decrease and AHI, apnea–hypopnea time, arousal index, mean desaturation, and oxygen desaturation index as well as sleep stages.

The relationship between GH and %NREM3 time, which was found in our study, is consistent with these literature findings. However, in our study, %NREM3 times were low both in the OSAS group and in the control group, and no significant difference was detected. Therefore, it was thought that there may be no difference between the groups in terms of GH levels in this study. In our study, the mean BMI values in the OSAS and control groups demonstrated that most patients were overweight and obese (BMI≥25 kg/m^2) (30) and all were above 40 years old. In the literature, it has been reported that sleep is disturbed in obese patients despite the absence of OSAS (31-33) and increased age can reduce NREM3 sleep time (32). In a study conducted on obese and nonobese patients, whose sleep patterns were polysomnographically monitored, GH, IGF-1, and sleep times were found to be decreased in obese patients, although they did not have OSAS (33). Similar to our study, Ghigo et al. (34) found basal GH levels of obese patients with OSAS to be similar to those in patients with simple obesity and to be lower than those in normal cases. On the other hand, in the study of Gianotti et al. (35), a remarkable difference was shown between obese patients with and without OSAS in terms of the functional profile of the GH/IGF-1 axis. However, similar to our study, no difference was found between the groups when basal GH and IGF-1 levels were corrected according to age.

In our study, no significant difference was detected between the groups with regard to free testosterone, total testosterone, and SHBG levels. In the literature, compared with the control group patients whose age and BMI were matched, both total and free testosterone levels were revealed to be lower in obese

male patients with OSAS and a negative correlation was demonstrated between the severity of OSAS and testosterone levels (36). It is suggested that the main affecting factor for low serum testosterone levels is hypoxia that occurs because of apnea and hypopnea episodes (37, 38). In our study, Spearman's correlation analysis revealed a weak relationship between SHBG and $SaO_2 \geq 90\%$ time in the OSAS group.

It is unclear whether the presence of OSAS decreases testosterone levels alone or OSAS patients with advanced age, obesity, insulin resistance, metabolic syndrome, and diabetes mellitus are more prone to hypogonadal testosterone levels. In our study, no significant difference was found in the hormone levels of the groups matched for BMI and comorbid diseases.

However, there was a significant positive relationship between the femoral T score and REM sleep time in OSAS patients. Luboshitzky et al. (39) reported in their study that the interruption of sleep prevented the intra-day change in testosterone levels and decreased an increase at night that was associated with the first REM sleep period. On the other hand, in our study, no significant relationship was found between REM sleep time and testosterone level. Therefore, no finding was detected for explaining how REM sleep time affected BMD. However, because no significant difference was found between the patient group and control group with regard to the rates of REM time, this relationship may have been the reason for the absence of any difference in femoral T scores between the groups. The short REM time, which was one of the polysomnographic features of patients with OSAS, was also available in randomly selected patients of the control group. Furthermore, it has been reported that the first-night effect of the polysomnography procedure can impair the sleep pattern (26). Therefore, it was suggested that the REM time of the control group could actually be longer.

Conclusion

It can be suggested that age is effective in BMD, but there is no tendency of early osteoporosis in male patients with OSAS. Moreover, no apparent relationship could be revealed between hormonal parameters that were investigated in this study and BMD. Similar sleep patterns of the patient and control groups in the study may have hindered the identification of a hormonal abnormality that could be associated with sleep pattern disorder. Moreover, not examining activity shortage, D vitamin deficiency, and insufficient calcium intake, which can lead to osteoporosis, is a limitation of this study. Further larger prospective controlled studies are required for shedding light on this topic.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Selçuk University Meram Faculty of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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