ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Comparison of Vitamin D Levels of Postmenopausal Osteoporotic Female Patients with and Without Fibromyalgia

Fibromiyaljisi Olan ve Olmayan Postmenopozal Osteoporotik Kadın Hastaların D Vitamini Düzeylerinin Karşılaştırılması

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ABSTRACT Objective: To investigate the relationship between the frequency of fibromyalgia and vitamin D levels in postmenopausal female patients diagnosed with osteoporosis. Material and Methods: The participants' demographic data were first taken, including age, sex, education level, occupation, marital status and body mass index (BMI), age of menopause and menarche, drugs used, chronic diseases, and data on any osteoporotic fractures. The patients were then evaluated according to the fibromyalgia-syndrome 2016 American College of Rheumatology criteria, and those with and without fibromyalgia syndrome were identified. Blood 25(OH) vitamin D levels of all patients were recorded in their files. Results: Of the 68 women in the study, 23 had fibromyalgia (33.8%). Vitamin D levels were lower than 20 ng/mL in 40 of the patients (58.8%). No significant differences were noted in the age, height, weight, education level, marital status, BMI, age of menopause and menarche, or the total bone mineral density (BMD) values in L1-L4 and the femurs of those diagnosed and not diagnosed with fibromyalgia (p>0.05). No significant association was found between low vitamin D levels and the frequency of fibromyalgia (p=0.806). Significant differences were noted between the femur neck T-scores and femur neck BMDs of those diagnosed and not diagnosed with fibromyalgia. The femoral neck T score was found to be higher in patients with fibromyalgia. Conclusion: There was a greater prevalance of fibromyalgia in patients with osteoporosis in the present study, although no significant association was identified between vitamin D levels and the presence of fibromyalgia in the patients with osteoporosis.

Keywords: Postmenopausal osteoporosis; fibromyalgia; vitamin D; chronic pain ÖZET Amaç: Bu araştırmanın amacı, osteoporoz tanısı alan postmenopozal kadın hastalarda fibromiyalji sıklığı ile D vitamini düzeyleri arasındaki ilişkinin araştırılmasıdır. Gereç ve Yöntemler: Katılımcıların öncelikle yaş, cinsiyet, eğitim düzeyi, meslek, medeni durum ve beden kitle indeksi (BKİ), menopoz ve menarş yaşı, kullandıkları ilaçlar, kronik hastalıkları, vertebra ve vertebra dışı osteoporotik kırık bilgileri kaydedildi. Hastaların daha sonra fibromiyalji sendromu "2016 American College of Rheumatology" kriterlerine göre değerlendirilerek, fibromiyalji sendromu olan ve olmayanlar belirlendi. Tüm hastaların kan 25(OH) D vitamini düzeyleri dosyalarına kaydedildi. Bulgular: Çalışmaya katılan 68 postmenopozal osteoporotik kadının 23'ünde (%33,8) fibromiyalji saptandı. Hastaların 40'ında D vitamini düzeyi 20 ng/mL'nin altında saptandı (%58,8). Fibromiyalji tanısı alan ve almayanların yaş, boy, kilo, eğitim düzeyi, medeni durum, BKİ, menopoz ve menarş yaşı veya L1-L4 ve femur toplam kemik mineral yoğunluğu (KMY) değerlerinde anlamlı farklılık saptanmadı (p>0,05). Düşük D vitamini düzeyi ile fibromiyalji sıklığı arasında anlamlı ilişki bulunamadı (p=0,806). Fibromiyalji tanısı alan ve almayanların femur boynu T skorları ile femur boynu KMY'leri arasında anlamlı fark saptandı. Femur boynu T skoru değeri fibromiyalji sendromu eşlik eden hastalarda daha yüksek bulundu. Sonuc: Bu çalışmada, osteoporoz tanılı kadın hastalarda fibromiyalji görülme sıklığı daha yüksek bulunmasına rağmen osteoporoz tanılı hastalarda D vitamini düzeyleri ile fibromiyalji varlığı arasında anlamlı bir ilişki saptanmadı.

Anahtar Kelimeler: Postmenopozal osteoporoz; fibromiyalji; D vitamini; kronik ağrı

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Osteoporosis (OP) is characterized by reduced bone mass, resulting in bone weakness and increased susceptibility to fractures. Bone mineral density (BMD) assessment is used to diagnose low bone mass and OP.¹Postmenopausal OP and fragility fractures reduce health-related quality of life to varying degrees in women.²

Fibromyalgia syndrome (FMS) commonly manifests in young or middle-aged females as chronic widespread pain, stiffness, fatigue, disrupted unrefreshing sleep, and cognitive difficulties. FMS often coexists with a number of other unexplained symptoms, anxiety and/or depression, and functional impairment of daily living activities. Fibromyalgia typically causes broad pain that affects both sides of the body with numerous "tender points". Despite having incapacitating physical pain, FMS is not accompanied by tissue inflammation, tissue damage, or deformity. The exact pathophysiological mechanism behind fibromyalgia remains undefined, though it is likely multifactorial in origin including abnormal cortical processing, reductions in inhibitory pain modulatory mechanisms and molecular changes to the pain pathway.³

Vitamin D deficiency is associated with various health issues, including defects in bone mineralization, an increased risk of diabetes, immune defects and cardiovascular diseases.⁴

A large body of evidence indicates that vitamin D (250HD) deficiency may be related to an enhanced risk of FMS. Accordingly, clinical studies showed that individuals with FMS display lower 250HD circulating levels compared to controls. The vitamin D receptor is widely expressed in muscles, providing a direct regulatory role in this tissue.⁵

Fibromyalgia is the third most frequent musculoskeletal condition, and its prevalence increases with age.⁶The complex interaction between sex hormones and pain has been widely explored by multiple authors, ranging from basic science studies examining the changes in pain neurobiological pathways and pain-related gene expression modification in patients with different hormonal profiles. Although some controversial results have been found, a literature review of published studies implies that estrogens have important effects regulating pain by acting on intracellular receptors, modifying gene expression and Gcoupled proteins distributed along the central and peripheral nervous systems.⁷

Clinically, associations between FMS and OP have been shown in the literature. Since the earlier works published in the 90s, FMS has been suggested in a number of studies to be associated with an increased risk of OP. In a meta-analysis, BMD at the lumbar spine was decreased in FMS compared with normal individuals, stressing that the risk assessment of OP should be systematically performed.⁸

For these reasons, our aim in this study is to investigate the relationship between the frequency of fibromyalgia and vitamin D levels in postmenopausal female patients diagnosed with OP.

MATERIAL AND METHODS

It was planned to include patients, aged between 50-80, diagnosed with OP and admitted to the physical medicine and rehabilitation outpatient clinic. This descriptive-cross sectional study were 68 postmenopausal osteoporotic women diagnosed with OP based on dual-energy X-ray absorptiometry, according to the World Health Organization criteria (T score <-2.5), who matched the study criteria and who agreed to participate in the study. Patients with any neurogenic or myogenic disease, using any drug that affects the central nervous system and muscle strength, and patients with metastatic bone disease were not included in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study had local Ethics Committee approval (Kütahya Health Sciences University Non-Invasive Clinical Research Ethics Committee, date: October 1. 2019; number: 41997688-402.03.01-). The participants' demographic data were first taken, including age, sex, education level, occupation, marital status and body mass index (BMI), age of menopause and menarche, drugs used, chronic diseases, and data on any osteoporotic fractures in the vertebrae and other bones (were self-reported by participants). The patients were then evaluated according to the fibromyalgiasyndrome 2016 American College of Rheumatology criteria, and those with and without FMS were identified. According to the fibromyalgia 2016 diagnostic criteria, a widespread pain index (WPI) of 7 or higher and a symptom severity scale (SSS) of 5 and above, or a WPI of 46 and an SSS of 9 and above; the presence of pain in at least 4 of the predetermined five regions (chin, chest and abdomen excluded); and the presence of symptoms for at least 3 months are required for a diagnosis of fibromyalgia. The presence of another clinical diagnosis is not considered a reason for the exclusion of fibromyalgia. When calculating WPI, pain in the 19 predetermined regions within the previous week is questioned, while SSS is calculated based on the responses of the patient to questions about fatigue, wakening without feeling rested and cognitive symptoms, scored as none, mild, intermediate or severe. The patients are also asked about the presence of any headache, abdominal pain, cramps or depression within the last 6 months. Blood 25(OH) vitamin D levels are checked in all patients presenting to the outpatient clinic with a diagnosis of OP as a matter of routine. The vitamin D levels of all patients, tested in blood as ng/mL, were recorded on the patient registration form. The present study assesses the frequency of fibromyalgia and other associated factors in patients with OP, and evaluates any association between the fibromyalgia frequency and vitamin D levels.

STATISTICAL ANALYSIS

Descriptive statistics of data; are given as mean, standard deviation, frequency and percentage values. The normality assumption of the quantitative data was checked with the Shapiro-Wilk test. In the comparison of the two groups, the independent sample t-test was used for the variables with normal distribution, while the Mann-Whitney U test was used for the variables that did not provide the normality assumption. The relationships between categorical variables were examined with the Pearson chi-square test. Logistic regression analysis was performed to understand whether age, marital status, education level, BMI, BMD are risk factors for the development of fibromyalgia in postmenopausal osteoporotic women. Statistical analysis IBM SPSS Statistics 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) package program. The level of significance was determined as 0.05 in all analyzes.

RESULTS

Of the 68 postmenopausal osteoporotic women in the study, 23 had fibromyalgia (33.8%). The mean age of the patients was 63.82 ± 10.154 years. 25 patients had chronic disease (hypertension n=13, diabetes mellitus n=10, asthma n=1, Vogt-Koyanagi-Harada syndrome n=1) The sociodemographic data of the patients are summarized in Table 1.

The mean femoral T score of the patients was -1.90 ± 0.840 , vertebral fractures were present in 11.8% (n=8) of the patients, and vitamin D levels were lower than 20 ng/mL in 40 of the patients (58.8%), between 20 and 30 ng/mL in 23 (33.8%) and above 30 ng/m in 5 (7.4%).

No significant differences were noted in the age, height, weight, education level, marital status, BMI, age of menopause and menarche, or the total BMD values in L1-L4 and the femurs of those diagnosed and not diagnosed with fibromyalgia (p>0.05). Significant differences were noted between the femur neck T-scores and femur neck BMDs of those diagnosed and not diagnosed with fibromyalgia (Table 2). The femoral T score was found to be higher in patients with fibromyalgia.

Furthermore, no significant difference was noted in the age, height, body weight, education level, mar-

TABLE 1: Sociodemographic data of patients.		
	n=68 (%)	
Age	63.82±10.154	
Marital status		
Married	54 (79.4)	
Single	14 (20.6)	
Job		
Active worker	3 (4.4)	
Not worker	65 (95.6)	
Education		
Not education	12 (17.6)	
Primary school	46 (67.6)	
High school	10 (14.7)	
Chronic disease		
Yes	25 (36.8)	
No	43 (63.2)	

	FMS-(X±SD)	FMS+(X±SD)	All patients (X±SD)	p value
Age (years)	64.89±10.91	61.74± 8.32	63.82 ±10.15	0.229
Height (meters)	1.56± 0.07	1.57±0.06	1.56±0.06	0.310
Weight (kg)	64± 10.09	62.78± 7.02	63.59 ±9.13	0.607
BMI	26.46± 4.27	25.42±3.04	26.11± 3.91	0.321
Menopause age	48.02±6.21	47.39± 4.93	47.81± 5.78	0.528
Menarche age	12.67±1.10	12.83±1.26	12.72±1.15	0.494
25OHD (ng/mL)	20.22±10.05	18.26± 6.14	19.56± 8.92	0.943
L1-L4 T score	-2.27±1.82	-2.16±1.24	-2.23 ±1.63	0.541
L1-L4 BMD	0.85± 0.11	0.91± 0.10	0.87± 0.11	0.082
Femoral neck T score	238±0.60	-2.0±0.62	-2.25 ±0.63	0.016*
Femoral neck BMD	0.71± 0.08	0.76± 0.08	0.73±0.09	0.018*
Femur total T score	-2.03±0.73	-1.64±0.98	-1.90 ±0.84	0.157
Femur total BMD	0.77±0.19	0.84±0.20	0.79± 0.20	0.063

*p<0.05 value was considered significant, Mann-Whitney U test; FMS: Fibromyalgia syndrome; SD: Standard deviation; BMI: Body mass index; BMD: Bone mineral density.

ital status, BMI, age of menopause and menarche, or total BMD values at L1-L4 and the femurs of those with low (<20 ng/mL) and normal (>20 ng/mL) vitamin D levels (p>0.05). All eight patients identified with osteoporotic fractures had low recorded vitamin D levels (Table 3).

No significant association was found between low vitamin D levels and the frequency of fibromyalgia (p=0.806) (Table 4). Furthermore, no significant difference was found between those with vitamin D levels of >30 ng/mL, 20-30 ng/m and <20

TABLE 3: Comparison of the data of those with normal and low vitamin D levels.				
2	5OHD>20 ng/mL	25OHD<20 ng/mL	p value	
Age	62.18±10.90	64.98±9.57	0.267	
Height	1.57±0.08	1.56±0.05	0.583	
Weight	65.64±10.38	62.15±7.97	0.121	
BMI	26.85±4.92	25.59±2.97	0.529	
Menopause age	47.36±6.54	48.13±5.25	0.970	
Menarche age	12.75±1.35	12.70±1.02	0.969	
L1-L4 T score	-2.08±1.41	-2.34±1.79	0.296	
L1-L4 BMD	0.89±0.10	0.85±0.12	0.231	
Femoral neck T score	-2.33±0.62	-2.20±0.65	0.625	
Femoral neck BMD	0.72±0.09	0.74±0.09	0.376	
Femur total T score	-1.99±0.66	-1.84±0.95	0.667	
Femur total T BMD	0.81±0.28	0.78±0.11	0.400	
Osteoporotic fracture	0	8 (%20)	0.012*	

*p<0.05 value was considered significant, Mann-Whitney U test; BMI: Body mass index; BMD: Bone mineral density.

TABLE 4: Comparison of fibromyalgia frequency between those with normal and low vitamin D.			
250HD (ng/mL)	FMS-n (%)	FMS+n (%)	
Normal (>20 ng/mL)	19 (42.2)	9 (39.1)	
Low (<20 ng/mL)	26 (57.8)	14 (60.9)	

Pearson-chi-square p=0.806; FMS: Fibromyalgia syndrome.

in terms of the incidence of fibromyalgia (p=0.794) (Table 5).

The factors affecting FMS were evaluated using the logistic regression and Stepwise regression (backward) methods, and the femoral neck T score was found to be significant in predicting the presence of FMS (p=0.028; odds ratio=2.688), with a one-unit increase in femoral neck T score leading to a 2.68-fold increase in the risk of development of FMS.

DISCUSSION

FMS is a chronic pain syndrome characterized by widespread, persistent pain that lasts more than 3 months without an evident organic lesion. FMS has been considered controversial throughout history due to its validity as a diagnosis being constantly in question. Most patients diagnosed with FMS are females. FMS has been associated with multiple conditions, including irritable bowel and psychiatric disorders. Pathogenesis of FMS involves both genetic and environmental factors.⁹

TABLE 5: Comparison of vitamin D level and the presence of fibromyalgia.			
25OHD (ng/mL)	FMS-n (%)	FMS+n (%)	
<20 ng/mL	26 (57.8)	14 (60.9)	
20-30 ng/mL	15 (33.3)	8 (34.8)	
>30 ng/mL	4 (8.9)	1 (4.3)	

Pearson-chi-square p=0.794; FMS: Fibromyalgia syndrome.

Bianchi et al. reported in their study that 40% of all patients with OP had depressive symptoms.¹⁰ OP has been further linked to pain, fractures, deformities, functional loss, loss of social functioning (between the individual and their family) and lack of social communication, all of which can be associated with depression.¹¹

The prevalence of fibromyalgia in the general population is approximately 1 to 5%, with female predominance, and it is also more prevalent in patients over 50 years old.⁹ It can be suggested that the prevalence of fibromyalgia is increased in patients with OP (33.8%) when compared to the normal population in the our study. In a study similar to our study, while FMS was seen in 5% of women in the normal population, it was seen in 19% of postmenopausal osteoporotic women.¹²

A relevant number of epidemiological studies have suggested the potential role of vitamin D in order to maintain or improve muscle strength and function, physical performance and preserve independence in older people.¹³ Vitamin D levels were found to be lower in patients with postmenopausal FMS than in the control group in a previous study.¹⁴ Matthana reported in their study that 61 of 100 women with FMS had vitamin D deficiencies, and the symptoms improved after vitamin D replacement in 42 women when the blood level of 25(OH)D was above 30 ng/mL, with an even greater improvement in symptoms when the blood level of 25(OH)D was above 50 ng/mL.15 Quality of life was assessed using the SF-36 in a study of 74 patients with low vitamin D levels and fibromyalgia in a study in which one group was given a placebo and the other was given vitamin D, and quality of life improved considerably in the group given vitamin D.¹⁶

In a review suggests that vitamin D deficiency is frequently observed in FMS patients, and supplementation with vitamin D can be proposed to reduce musculoskeletal pain and improve the quality of life in vitamin D-deficient subjects with FMS.⁵ However, in the present study, an evaluation of the patients diagnosed with OP revealed no significant difference in the vitamin D levels of the patients with and without fibromyalgia.

Previous studies have shown that FMS is associated with low level of physical activity and exercise, which may lead to an increased risk of OP. However, studies of BMD in fibromyalgia have shown conflicting results. At lumbar spine (L2-L4), BMD is significantly decreased in patients with FMS compared with controls with pooled MD of -0.02 (95% confidence interval -0.03 to-0.01, p value=0.003, I²=0%). At femoral neck, BMD is not significantly decreased in patients with FMS compared with controls with pooled MD of 0.01 (95% confidence interval -0.02 to 0.01, p value=0.23, I²=0%).¹⁷

In another study, females with FM had lumbar spine and hip BMD results similar to controls who were matched with them for age, menopausal status and OP risk factors.¹⁸

Similarly, in the present study, while there was no difference in the total BMD values of L1-L4 or the femur, a significant difference was noted between the patients with and without fibromyalgia in femoral neck T scores and femoral neck BMD (femoral T score was found to be higher in patients with fibromyalgia).

In a study conducted among 1,311 communitydwelling older men and women of the Longitudinal Aging Study Amsterdam, an ongoing multidisciplinary cohort study. Serum 25(OH)D was determined using a competitive protein binding assay. Fractures were assessed during six years of followup. The data were analyzed using Cox proportional hazards model. Serum 25(OH)D levels below or equal to 12 ng/mL were associated with an increased fracture risk in persons aged 65-75 years.¹⁹ Similarly, all 8 patients with osteoporotic vertebral fractures were found to have low vitamin D levels in our study. The limitations of the study are the relatively small number of patients and the lack of re-evaluation after vitamin D replacement. Further studies involving larger numbers of patients who are reevaluated after undergoing vitamin D replacement therapy are required.

CONCLUSION

There was a greater prevalence of fibromyalgia in patients with OP in the present study, although no significant association was identified between vitamin D levels and the presence of fibromyalgia in the patients with OP. Considering the complexity of the etiopathogenesis of fibromyalgia, many factors other than vitamin D levels should be kept in mind.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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