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Bone mass and bone turnover in premenopausal women with fibromyalgia syndrome

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Abstract

In this study, we aimed to compare osteoporosis (OP)-related bone mineral density, and bone turnover (markers of formation, and resorption) between patients with Fibromyalgia Syndrome (FMS) and degenerative disc disease, and to determine the relationship of these parameters with clinical, functional and emotional evaluation outcomes in FMS. Fifty premenopausal women with FMS and 50 premenopausal female control patients with degenerative disc disease were enrolled. The patient and physician's global assessment of disease were assessed on a visual analog scale (VAS). Disease severity was determined with the Fibromyalgia Impact Questionnaire (FIQ). For the evaluation of fatigue The Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS) were used. The quality of life of all patients was evaluated using Nottingham Health Profile (NHP), Oswestry Disability Index (ODI), and QUALEFFO-41. The emotional state of all patients with chronic pain was evaluated with Hospital Anxiety and Depression Scale (HADS). Bone turnover markers [serum bone-specific alkaline phosphatase (bALP) and serum osteocalcin as markers of bone formation, serum â-isomerized Carboxy-terminal telopeptide of collagen type I (â-CTX) and urine hydroxyproline (OH-Pro) as markers of bone resorption], serum parathyroid hormone (PTH) and 25-hydroxyvitamin D [25(OH)D] levels, lumbar spine and left proximal femur bone mineral density (BMD) and T scores were measured in both groups. The FIQ, MFIS, FSS, NHP, ODI, QUALEFFO-41, HADS-A and HADS-D scores were statistically significantly higher in the FMS group relative to the patient control group. A significant difference between FMS and patient control group as for bone formation (bALP and osteocalcin) and resorption (â-CTX ve OH-Pro) markers was not detected. In the FMS group lumbar spine and left proximal femur BMD and T score values were significantly lower when compared with the patient control group. In the FMS group significant correlations were found between serum 25(OH)D and â-CTX values and VAS scores evaluated by the patient and physician, SS scale, FIQ, MFIS, ODI, QUALEFFO-41 and NHP scores. In conclusion many factors including depression and anxiety attacks, the presence of widespread pain and a decline in physical activity level and quality of life in FMS patients make them more prone to osteoporosis. In patients with FMS, osteoporosis is a major cause of morbidity and should not be neglected.

Keywords: Fibromyalgia, low back pain, Dual-energy X-ray absorptiometry (DXA), disability, bone metabolism

Introduction

Fibromyalgia Syndrome (FMS) is a chronic painful condition of a musculoskeletal system whose etiology is not known completely and characterized by the presence of tender points, widespread pain, tender muscles and fatigue. Somatic and psychologic symptoms as fatigue, morning stiffness, poor sleep, psychologic distress, cognitive difficulties, irritable bowel, bladder dysfunction and Raynaud's phenomenon frequently accompany the disease [1]. FMS is prevalently seen between ages of 30 and 60. The majority (85-90%) of the patients is female and its incidence in the population, in general, is nearly 1-4 % [2]. The most important symptom of the disease is a chronic widespread musculoskeletal pain. The pain is localized at the right and left the side of the body (it may be more severe at one side), upper and lower half of the body and axial skeleton. In FMS patients low back pain is prevalent and it is one of the most important causes of disability which induces dysfunction [1].

Osteoporosis (OP) is a disease of bone metabolism characterized by decreased bone mass and impairment of microarchitecture of bone resulting in bone fragility [3]. Menopause, aging, deficient calcium and vitamin D intake, smoking, alcohol use, immobility, drugs, hormonal and renal diseases have been suggested for the etiology of OP [4-6]. In recent years major depression has been also demonstrated as a risk factor in the development of OP [7-11].

It has been reported that in the fibromyalgia syndrome decreased mobility causes decrease in bone mineral density (BMD). Contradictory data are available on the risk of development of OP in patients with FMS. In some studies decrease in BMD in FMS patients has been indicated while some others suggested a lack of any correlation [12-17]. Patients with fibromyalgia syndrome have a lower exercise tolerance because of widespread musculoskeletal pain and especially low back pain and they lead a sedentary life

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which predisposes the patients to OP and decreases in BMD. At the same time depression which accompanies FMS patients constitutes an additional risk factor for FMS patients.

In this study we aimed to compare OP-related bone mineral density and bone turnover (markers of formation and resorption) between patients with FMS and degenerative disc disease and to determine the relationship of these parameters with clinical, functional and emotional evaluation outcomes in FMS. In conclusion the importance of disease severity, emotional status and quality of life on the development of osteoporosis was investigated in FMS patients.

Material and methods

A total of 50 premenopausal women with low back pain who met 1990 and 2010 American College of Rheumatology (ACR) criteria for the classification of FMS [18,19] and 50 premenopausal female control patients with degenerative disc disease were enrolled. The study was approved by the local ethics committee and written informed consent forms were obtained from all participants.

Patients aged < 18, and > 56 years, patients with whom sociocultural rapport cannot be established, postmenopausal patients, those with systemic inflammatory rheumatismal disease, patients under anti-depressant treatment, taking muscle relaxants or analgesics at least 3 weeks before the study, patients suffering from a disease affecting bone metabolism (hypogonadism, hyperthyroidism, hyperparathyroidism, multiple myeloma, diabetes mellitus etc.), those with a history of medication known to cause osteoporosis (methotrexate, glucocorticoids, aluminum- and magnesium-containing anti-acid etc.), those who were immobile for an extended period, who had spinal surgery or any fracture, and smokers and alcohol users and pregnant women were not included in the study.

Clinical assessments

All patients including patients with FMS and control patients with degenerative disc disease were requested to complete a structured form which evaluated age, height, body weight, body mass index (BMI), duration of chronic pain, widespread pain and associated symptoms. All clinical evaluations were performed by a blinded physician who did not know diagnosis of the patient. The patient and physician's global assessment of disease were assessed on a visual analog scale (VAS) (0–100 mm). Patients were also screened for characteristic symptoms of FMS (fatigue, sleep disorders, headache, paresthesia, irritable bowel syndrome, bladder dysfunction, sicca symptoms, orthostatic intolerance, Raynoud's phenomenon).

A mechanical algometer was used for the pressure pain threshold (PPT) measurements of patients. The same doctor, who was blind to FMS and degenerative disc disease, clinical variables and diagnosis, carried out all of the measurements and the tests throughout the study. Patients were informed of the procedure before the measurements. "Pain threshold" was clarified as the amount of pressure that induces discomfort and it was also emphasized that the aim was to determine "pain threshold" but not "pain tolerance". Eighteen tender points (TPs) and three control points (CPs) were evaluated using previously defined methods [20, 21]. A positive TP was described as a point that the subject had mild (or great) pain with <4 kg/cm2 pressure. The mid-forehead, the two-thirds distal portion of the dominant forearm and the dominant thumbnail were the three control points. The sum of the PPTs of 21 points (18 TPs and 3 CPs) was considered as the total myalgic score (t-MS in kg). All of tender and control points were examined by firm palpation with the thumb, and tenderness was graded on a four-point scale: 0=no pain; 1=mild tenderness; 2=moderate tenderness; and 3=wince or withdrawing. The sum of these tenderness scores (in 21 points) was calculated to obtain total pain score (t-PS).

Disease severity was determined with the Turkish version of the Fibromyalgia Impact Questionnaire (FIQ) [22] in both patient groups. For the evaluation of fatigue, The Modified Fatigue Impact Scale (MFIS) and Fatigue Severity Scale (FSS) were used. For all patients, Widespread Pain Index (WPI) and Symptom Severity (SS) scale which were included in 2010 FMS classification criteria were used. The quality of life of all patients was evaluated using Nottingham Health Profile (NHP), osteoporosis-related quality of life (Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO-41) and functional index of low back pain Oswestry Disability Index (ODI). The emotional state of all patients with chronic pain was evaluated with Hospital Anxiety and Depression Scale (HADS). The validity and reproducibility of the Turkish version of all of the questionnaires have been examined in previous reports. The Nottingham Health Profile section (pain, physical mobility, social isolation, emotional reaction, sleep, and energy) scores were obtained in both patient groups.

Laboratory assessments

Erythrocyte sedimentation rate (ESR), serum calcium (Ca), phosphate (P), magnesium (Mg), alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-hydroxyvitamin D [25(OH) D] and bone turnover markers [serum bone-specific alkaline phosphatase (bALP) and serum osteocalcin as markers of bone formation, serum β-isomerized Carboxy-terminal telopeptide of collagen type I (β-CTX) and urine hydroxyproline (OH-Pro) as markers of bone resorption] were measured in both groups. For analysis of bone turnover markers, blood samples were retrieved before 9:00 AM. For measurement of serum osteocalcin, CTX and PTH electrochemiluminescence immunoassay (ECLIA) method was used. Laboratory reference values were as follows: osteocalcin, 13-46 ng/mL; CTX, ≤0.29 ng/mL and PTH, 19.8-74.9 pg/mL. Measurement of serum bALP was realized using radioimmunoassay (RIA) (reference range, 2.9-14.5 ug/L). Spot urine OH-Pro and serum 25(OH)D were measured with tandem mass spectrometry (LC-MS/MS) method and their reference ranges were 19-36 mg/mgkr, 20-50 mcg/L during summer and 10-75 mcg/L during winter months.

Bone Mineral Density Measurements

World Health Organization (WHO) criteria established for osteoporosis in women was used for the diagnosis of osteoporosis [23]. Lumbar spine and left proximal femur bone mineral density (BMD) were measured using Dual-energy X-ray absorptiometry (DXA) on a Hologic DPX densitometer (Hologic Corp., Waltham, Massachusetts, USA). Values for results of DXA measurements were expressed as BMD (g/cm2) and T score of young adult healthy reference population, as supplied by the manufacturer. Patients were classified as follows: normal=patients whose T score was ≥ 1 SD on L2–4, femur neck or total femur with normal BMD;

osteopenia=patients with T score between –1 and –2.5 SD in these regions; osteoporosis=patients with T score less than –2.5 SD on L2–4, femur neck or total femur.

Statistical Analysis

Data were analyzed using the IBM Statistical Package for Social Sciences v20 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked using Kolmogorov-Smirnov test. Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of questionably normal distribution. Independent-samples t-test and Mann-Whiney U-test were used to compare independent groups. Categorical data were analyzed by the Chi - square test. To calculate correlation coefficients, Spearman correlation analysis was used. All differences associated with a chance probability of 0.05 or less were considered statistically significant. Continuous data were presented as mean±standard deviation or median [minimum-maximum], as appropriate.

Results

Mean ages of the fibromyalgia and the patient control (degenerative lumbar pain) group were 37.42±7.00, and 39.22±6.56 years, respectively. Mean BMIs in the FMS and the patient control groups were 25.08±3.12, and 28.79±4.71 respectively. Body weights and BMI values of the FMS patients were significantly lower than those of the patient control group. Demographic and clinical data of both groups are shown in Table 1. A significant difference between FMS and patient control group as for the duration of the disease and the degree of strain at work was not detected (p>0.05). However global VAS scores evaluated by the patient and the physician was higher in the FMS group when compared with the patient control group (Table 1).

Table 1. Comparisons of demographic and clinical parameters between fibromyalgia patients and control patients with degenerative disc disease

		FMS Group (n:50)	Patient Contol Group (n:50)	p
Age (years)		37.42±7.00 (24–54)	39.22±6.56 (23–53)	0.152
Height (cm)		161.10±5.47 (150–175)	160.04±6.73 (147–180)	0.199
Weight (kg)		65.32±9.37 (48–96)	73.44±12.17 (56–100)	<0.001
BMI (kg/cm2)		25.08±3.12(18.70–33.20)	28.79±4.71(20.80–38.30)	<0.001
Disease duration (years)		3.06±1.73 (1–8)	3.045±2.53 (0.25–10)	0.305
The degree of strain in work (%)		55.8±18.19 (30–90)	46.6±14.22 (20–80)	0.110
Patient's global assessment (0-100 mm VAS)		5.716±1.71 (2.2–8.8)	4.378±1.72 (2–8.1)	<0.001
Physician's global assessment (0-100 mm VAS)		5.558±1.62 (2.4–8.2)	4.352±1.66 (2–8)	<0.001
Tender point count (0-18)		12.32±1.36 (11-16)	6.16±1.99 (2-10)	<0.001
Control-PPTS (kg/cm2)		31.7±1.68 (27.5–35)	32.28±2.3 (27.25–36.25)	0.132
t-MS (kg/cm2)		109.87±7.28 (84.25-123.75)	128.05±7.29 (114.75-147.0)	<0.001
Control-PS (0-3)		0±0 (0–0)	0.02±0.14 (0–1)	0.317
t-PS (0-3)		22.34±6.62 (11-49)	8.02±3.26 (2-17)	<0.001
FIQ (0-100)		47.04±22.32 (14.2–86.4)	25.4±15.4 (5–69.4)	<0.001
MFIS (0-84)		42.14±21.71 (11–79)	25.04±13.34 (11–71)	<0.001
FSS (1-7)		28.52±13.84 (10–56)	18.4±10.1 (9–51)	<0.001
WPI (0-19)		10.92±2.92 (5–16)	3.9±1.6 (2–7)	<0.001
SS scale (0-39)		6.4±1.26 (5–10)	3.58±1.69 (1–8)	<0.001
NHP (0-600)	**Pain**	43.45±24.61 (12.5–87.5)	26.75±18.21 (0–75)	<0.001
	Physical mobility	43.05±24.43 (12.5–87.5)	21±18.97 (0–75)	<0.001
	Energy	37.84±29.32 (0–88)	7.66±15.24 (0–55)	<0.001
	Sleep	38.8±27.82 (0–100)	11.3±19.5 (0–60)	<0.001
	Social isolation	36.98±28.42 (0–80)	9.2±19.04 (0–60)	<0.001
	Emotional reactions	38.16±28.54 (0–80)	9.82±19.35 (0–66)	<0.001
Oswestry disability index (0-50)		25.48±12.41 (8–47)	15.46±9.28 (0–40)	<0.001
QUALEFFO-41 (0-100)		35.176±17.9 (10–76)	19.68±13.06 (6–58)	<0.001
HADS-A (0-21)		6.34±2.75 (1–11)	2.7±2.66 (0–9)	<0.001
HADS-D (0-21)		6.34±3.03 (1–11)	2.72±2.81 (0–10)	<0.001

FMS: Fibromyalgia syndrome, BMI: Bone mineral density, VAS: Visual analog scale, PPTS: Pain pressure threshold score, tMS: Total myalgic score, PS: Pain score, FIQ: Fibromyalgia Impact Questionnaire, MFIS: The Modified Fatigue Impact Scale, FSS: Fatigue Severity Scale, WPI: Widespread Pain Index, SS: Symptom Severity, NHP: Nottingham Health Profile, QUALEFFO-41: Quality of Life Questionnaire of the European Foundation for Osteoporosis, HADS-A: Hospital Anxiety and Depression Scale-Anxiety, HADS-D: Hospital Anxiety and Depression Scale-Depression

Laboratory test results and DXA values were demonstrated in all patients of both groups are shown in Table 2. ESR, Ca, P, Mg, ALP, PTH and 25(OH) D values did not differ statistically significantly between both groups (p>0.05). Besides bone formation (bALP and osteocalcin), and resorption (β-CTX ve OH-Pro) markers did not differ statistically significantly between both groups (p>0.05) (Table 2).

All BMD and t-scores estimated for the patient control and fibromyalgia groups were statistically lower in the FMS group (p<0.001). When we examined OP classification recommended by WHO based on DXA test results, osteopenia was seen in 38 (76%) and osteoporosis in 2 (4%) patients in the FSM group, while 10 (20%) patients were normal. However in the patient control group osteopenia was seen in 6 (12%) patients, while 44 (88%) patients were not osteoporotic with a statistically significant intergroup difference (p<0.001) (Table 2).

Correlations between bone metabolism markers and clinical parameters are shown in Table 3. A significant positive correlation was found between bone formation marker osteocalcin and SS scale, FIQ, MFIS and ODI scores. In FMS patients a positive correlation was observed between bone resorption marker CTX and global VAS scores evaluated by the patients and physicians, SS scale, FIQ, MFIS, ODI, QUALEFFO-41, NSP-pain, NHP-physical mobility and NHP-sleep values (p<0.05). Besides in the FMS group significant correlations were found between PTH and global VAS scores evaluated by patients and physicians, WPI, SS scale, t-MS, FIQ, MFIS, FSS, HADS-A, HADS-D, ODI, QUALEFFO-41, NHP-Pain, NHP-Physical mobility, NHP-Energy and NHP-Sleep scores. Excluding 25(OH)D values and SS scale scores analyzed in patients with FMS significant correlations existed between 25(OH)D values and other clinical parameters shown in Table 3.

In the fibromyalgia group correlations between BMD values and clinical parameters analyzed are shown in Table 4. Significantly negative correlations were found between ODI values and Femur neck T, Femur total BMD and Femur total T values, between HADS-A values and L2-L4 BMD, Femur neck BMD, Femur neck T, Femur wards T, Femur total BMD and Femur total T values, between HADS-D values and L2-L4 BMD, Femur neck BMD, Femur neck T, Femur wards T, Femur total BMD and Femur total T values (p<0.05) (Table 4).

Apart from these correlations, among bone turnover markers analyzed in patients with FMS, a significantly negative correlation was detected between only osteocalcin and femur neck and wards BMD values (p<0.05). However such a correlation did not exist among other bone turnover parameters (p>0.05).

Table 2. Laboratory parameters and bone mineral densitometry values in patients with fibromyalgia and control patients with degenerative disc disease

	FMS Group (n:50)	Patient Contol Group (n:50)	p
ESR (mm/saat)	10.44±6.4 (2–27)	11.1±6.88 (2–31)	0.683
ALP (U/L)	70.28±20.69 (32–151)	72.08±18.66 (31–120)	0.377
Calcium (mg/dl)	9.54±0.44 (8.5–10.8)	9.41±0.41 (8.67–10.2)	0.136
Phosphorus (mg/dl)	3.54±0.51 (2.4–5.1)	3.57±0.47 (2.8–4.4)	0.748
Magnesium (mg/dl)	2.19±0.27 (1.3–2.8)	2.14±0.35 (1.1–3.5)	0.201
PTH (ng/L)	68.51±31.54 (9.2–143.7)	68.86±27.79 (28.1-149.3)	0.912
25(OH)D (ng/mL)	13.62±10.43 (1.1–42.8)	17.04±24.21 (2–145.7)	0.983
bALP	7.39±2.24 (1.16–12.98)	7.69±2.03 (4.73–12.44)	0.526
osteocalcin	16.61±16.18 (5.52–120.7)	15.34±7.87 (6.34–47.37)	0.926
β-CTX	0.3±0.44 (0.05–3.28)	0.28±0.15 (0.08–0.78)	0.230
Hydroxyproline	24.15±4.69 (9.65–34.6)	24.08±3.58 (17.85–33.7)	0.612
L2-L4 BMD (gr/cm2)	0.93±0.097 (0.74–1.2)	1.07±0.09 (0.93–1.31)	**<0.001**
L2-L4 T score	-1.24±0.8 (-3–0.6)	0.026±0.83 (-1.3–2.2)	**<0.001**
Femur neck BMD (gr/cm2)	0.74±0.09 (0.51–0.99)	0.85±0.09 (0.72–1.11)	**<0.001**
Femur neck T score	-0.77±0.6 (-2.6–0.6)	0.002±0.80 (-1.2–2.7)	**<0.001**
Femur wards BMD (gr/cm2)	0.63±0.11 (0.34–0.89)	0.74±0.11 (0.54–0.95)	**<0.001**
Femur wards T score	-0.75±0.59 (-2.5–0.4)	0.05±0.65 (-1.1–1.8)	**<0.001**
Femur total BMD (gr/cm2)	0.83±0.07 (0.62–1.02)	0.94±0.09 (0.79–1.26)	**<0.001**
Femur total T score	-0.86±0.62 (-2.2–0.6)	0.05±0.62 (-0.9–1.8)	**<0.001**
Normal n (%)	10 (20%)	44 (88%)	**<0.001**
Osteopenia n (%)	38 (76%)	6 (12%)	
Osteoporosis n (%)	2 (4%)	0 (0%)	

FMS: Fibromyalgia syndrome, ESR: Erythrocyte sedimentation rate, ALP: Alkaline phosphatase, PTH: Parathyroid hormone, 25(OH)D: 25-hydroxyvitamin D, bALP: bone-specific alkaline phosphatase, β-CTX: β-isomerized Carboxy-terminal telopeptide of collagen type I, L2-L4: 2. Lumbar and 4. Lumbar vertebrals, BMD: Body Mineral Density

Table 3. Correlations between bone metabolism markers and clinical parameters

	Osteocalcin		bALP		β-CTX		OH-Pro		PTH		25(OH)D	
	r	p	r	p	r	p	r	p	r	p	r	p
Patient's global assessment (0-100 mm VAS)	0.112	0.440	0.054	0.712	0.340	**0.016***	-0.022	0.878	0.481	**<0.001**	-0.708	**<0.001**
Physician's global assessment (0-100 mm VAS)	0.195	0.174	0.083	0.568	0.413	**0.003***	-0.084	0.562	0.527	**<0.001**	-0.624	**<0.001**
WPI	0.228	0.111	0.012	0.933	0.222	0.121	0.035	0.807	0.501	**<0.001**	-0.409	**0.003***
SS scale	0.427	**0.002***	-0.108	0.456	0.477	**<0.001**	-0.124	0.393	0.425	**0.002***	-0.274	0.054
t-MS	-0.238	0.096	-0.019	0.895	-0.252	0.078	0.021	0.885	-0.311	**0.028***	0.341	**0.015***
FIQ	0.303	**0.033***	-0.028	0.847	0.319	**0.024***	0.135	0.349	0.562	**<0.001**	-0.682	**<0.001**
MFIS	0.296	**0.037***	-0.093	0.520	0.315	**0.026***	0.154	0.286	0.576	**<0.001**	-0.684	**<0.001**
FSS	0.260	0.068	-0.047	0.744	0.259	0.069	0.136	0.348	0.576	**<0.001**	-0.662	**<0.001**
HADS-A	0.218	0.129	0.007	0.961	0.215	0.134	-0.030	0.838	0.288	**0.043***	-0.383	**0.006***
HADS-D	0.225	0.116	0.026	0.859	0.208	0.147	-0.061	0.672	0.306	**0.031***	-0.353	**0.012***
ODI	0.300	**0.034***	-0.112	0.439	0.335	**0.017***	0.135	0.348	0.548	**<0.001**	-0.619	**<0.001**
QUALEFFO-41	0.151	0.294	0.019	0.894	0.291	**0.041***	-0.069	0.632	0.411	**0.003***	-0.289	**0.042***
NHP-Pain	0.219	0.127	0.023	0.872	0.360	**0.010***	0.037	0.798	0.523	**<0.001**	-0.739	**<0.001**
NHP-Physical	0.248	0.083	0.016	0.910	0.375	**0.007***	0.031	0.831	0.522	**<0.001**	-0.727	**<0.001**
NHP-Energy	0.141	0.327	-0.061	0.674	0.259	0.069	0.045	0.757	0.502	**<0.001**	-0.647	**<0.001**
NHP-Sleep	0.168	0.245	-0.174	0.227	0.287	**0.044***	-0.005	0.975	0.393	**0.005***	-0.656	**<0.001**
NHP-Social	0.149	0.302	-0.066	0.657	0.215	0.134	-0.053	0.717	0.214	**0.135**	-0.450	**<0.001**
NHP-Emotional	0.131	0.364	-0.015	0.917	0.156	0.279	-0.071	0.624	0.232	**0.105**	-0.419	**0.002***

bALP: bone-specific alkaline phosphatase, β-CTX: β-isomerized Carboxy-terminal telopeptide of collagen type I, OH-Pro: Hydroxyproline, PTH: Parathyroid hormone, 25(OH)D: 25-hydroxyvitamin D, WPI: Widespread Pain Index, SS: Symptom Severity, tMS: Total myalgic score, FIQ: Fibromyalgia Impact Questionnaire, MFIS: The Modified Fatigue Impact Scale, FSS: Fatigue Severity Scale, HADS-A: Hospital Anxiety and Depression Scale-Anxiety, HADS-D: Hospital Anxiety and Depression Scale-Depression, ODI: Oswestry disability index, NHP: Nottingham Health Profile.
* $p < 0.05$

Table 4. Correlations between bone metabolism markers and clinical parameters

	Oswestry disability index		HADS-A		HADS-D	
	r	p	r	p	r	p
L2-L4 BMD (gr/cm2)	-0.212	0.139	-0.325	**0.021***	-0.316	**0.026***
L2-L4 T score	-0.166	0.248	-0.217	0.130	-0.227	0.114
Femur neck BMD (gr/cm2)	-0.158	0.272	-0.364	**0.009***	-0.344	**0.014***
Femur neck T score	-0.281	**0.048***	-0.375	**0.007***	-0.389	**0.005***
Femur wards BMD (gr/cm2)	-0.086	0.551	-0.121	0.403	-0.085	0.557
Femur wards T score	-0.272	0.056	-0.382	**0.006***	-0.389	**0.005***
Femur total BMD (gr/cm2)	-0.311	**0.028***	-0.392	**0.005***	-0.399	**0.004***
Femur total T score	-0.294	**0.038***	-0.410	**0.003***	-0.428	**0.002***

HADS-A: Hospital Anxiety and Depression Scale-Anxiety, HADS-D: Hospital Anxiety and Depression Scale-Depression, L2-L4: 2. Lumbar and 4. Lumbar vertebrals, BMD: Body Mineral Density.
* $p < 0.05$

Discussion

Although osteoporosis is a concern of all population it is an important health problem with multifactorial etiology which may affect the quality of life of individuals and it is especially more frequently seen in postmenopausal women. As is seen all over the world increase in the number of elder people every year and OP and development of OP-related complications inevitably will threaten public health.

In recent years the relationship between chronic rheumatismal diseases and OP has gained importance. In the development of OP depression, decreased physical activity and muscular condition encounters us as risk factors. In FMS various psychiatric disorders

as depression, anxiety and somatoform disorders can be seen. Depression is one of the most frequently associated psychiatric symptoms [24-26]. Many OP-related factors are detected in patients with FMS including depression, decreased physical activity and especially sedentary lifestyle. However whether they are independent risk factors for OP in patients with FMS is not a clear-cut issue.

In this study the relationship between FMS and osteoporosis and factors effective on bone mineral density and bone metabolism were evaluated in FMS. In this study as the control group, patients with low back pain who had degenerative disc disease which can cause pain and disability similar to FMS were selected and a patient control group was formed. By comparing with a patient control group in this way, the importance of osteoporosis-related risk factors in FMS has been investigated. BMIs and body weights of the patients in our patient control group were higher than those of the FMS patients and these increased BMI values were also risk factors for degenerative disc disease. Unequal BMI values in our patient groups were essentially a limitation of our study. In our study disease duration and the degree of strain at work did not differ between groups. Parameters which evaluate the severity of pain and widespread pain especially patients' and physicians' global VAS scores, the number of tender points and t-MS values were significantly higher but t-PS values were lower in the FMS group when compared with the degenerative disc disease group. (Table 1). These findings demonstrate that pain is more severe and widespread in the patients with FMS.

In a study performed by Aktekin et al. [26] significantly higher VAS-widespread pain, VAS-sleep, FIQ, and Beck Depression Inventory (BDI) scores were detected in FMS patients when compared with healthy controls and in conclusion the authors asserted that social adaptation of the patients was disrupted because of variations in symptomatology of FMS. The authors suggested that patients with FMS who were evaluated more frequently in pain polyclinics should receive psychiatric support in case of need. Similarly in our study significantly higher FIQ, MFIS, FSS, WPI, SS, NHP, ODI, QUALEFFO-41, HADS-A and HADS-D scores which reflect disease severity, quality of life, disability and emotional disorder were found in the FMS group (<0.001) (Table 1). Also in patients with fibromyalgia we detected a negative correlation between DXA values (excepting L2-L4 T-score and femur wards BMD) and measurements of anxiety and depression (HADS-A and HADS-D) and ODI scores (Table 4). According to these findings patients with FMS were feeling more pain and fatigue and were suffered from more depression and anxiety. Therefore it can be said that the patients with FMS are more unhappy people accompanied by pain, depression, disability and with deteriorated quality of life. At the same time we may say that depression, anxiety and disability may predispose these patients to osteoporosis. We think that depression and OP comorbidity which are frequently overlooked in FMS patients is very important for diagnosis and treatment. Many studies have investigated the association between fibromyalgia syndrome and OP and also risk factors of development of OP in patients with FMS [12-17, 27]. In a study by Tander et al. [12] based on ACR criteria of diagnosis 50 premenopausal female patients diagnosed with FMS and 40 premenopausal healthy women were subjected to FIQ, BDI and VAS tests and BMDs of the lumbar spine and femoral neck were measured. As a result in patients with fibromyalgia bone mineral density of lumbar spine was found to be lower than in the control group, however in these patients depression did not effect BMD. In a study by Erdal et al., [27] lumbar and hip BMDs were compared between premenopausal patients with FMS and healthy controls and lower BMDs were measured in patients with FMS about control subjects. The authors indicated that necessary nutritional support (calcium/vitamin D), appropriate exercise programs and in the case of need medical treatment should be considered at an early stage as for the management of OP. In our study DXA measurements of the lumbar spine and femoral region (neck, wards, and total) were lower in FMS patients than patients with degenerative disc disease (<0.001) (Table 2). Besides osteopenia and osteoporosis were seen in 76 and 4% of FMS patients. While in patient control group (degenerative disc disease) osteopenia was seen in 12% of the patients, osteoporosis was not observed in any patient with a significant intergroup difference ($p<0.001$) (Table 2). Based on these findings one can say that in FMS patients osteopenia and OP were more frequently encountered when compared with another patient group (degenerative disc disease) with pain and disability and also BMD was more severely affected.

In a study performed by Köse [28] serum vitamin D levels and effectiveness of vitamin D treatment were investigated. In conclusion the authors indicated that vitamin D deficiency is frequently seen in patients with fibromyalgia and vitamin D treatment regressed symptoms of the patients. Çidem et al. [29] investigated the prevalence and risk factors of vitamin D deficiency in patients with widespread musculoskeletal pain. Their study demonstrated that vitamin D deficiency might be present in patients with widespread musculoskeletal system pain and it can be prevented by taking sun baths during summer months. In our study a significant difference was not detected between both groups as for vitamin D values, while vitamin D levels were found to be lower in both groups (Table 2). In the FMS group a negative correlation was found between vitamin D levels and patients and physicians' global VAS values, WPI, FIQ, MFIS, FFS, HADS-A, HADS-D, ODI, Qualeffo-41 and NHP scores, while a significantly positive correlation was detected between vitamin D levels and t-MS. These findings demonstrated that in patients with FMS serum 25(OH)D levels were decreased and also 25(OH)D levels are correlated with pain, fatigue, physical dysfunction and impaired quality of life. Therefore in FMS patients vitamin D levels should be investigated in terms of the development of osteoporosis and these patients should be supported with calcium and vitamin D.

Early diagnosis is important in osteoporosis. To this end densitometric examinations are being used and precise information about the actual bone mass can be obtained. However prognostic information cannot be obtained with densitometric measurements and also evaluation of treatment response requires a long-lasting process [30]. Therefore in addition to densitometric tests, specific biochemical markers which rapidly display bone metabolism, gain increasing importance. It is reported that these markers may outperform the techniques that show BMD changes in a single region in terms of showing bone loss occurring in the whole skeletal system [31]. In a study performed by Paker et al. [32] DXA, serum ALP, osteocalcin and CTX values were compared in 16 women with perimenopausal and 26 women with early postmenopausal period and no difference was found. Any correlation was not

seen between bone turnover markers and bone densities of the lumbar region and proximal femur in perimenopausal and early postmenopausal women. Gözaydın et al. [33] performed a study on healthy 46 premenopausal women (mean age, 30 ± 4 years) and 76 postmenopausal women (mean age, 58 ± 8 years) who did not receive treatment for osteoporosis. The postmenopausal group was investigated in 3 groups based on their BMD levels as a normal, osteopenic and osteoporotic group. The same group was divided into early or late menopausal subgroups. Serum CTX and osteocalcin levels of all patients were measured. CTX and osteocalcin levels in postmenopausal women were found to be significantly higher when compared with premenopausal women. Besides any difference could not be found among normal, osteopenic and osteoporotic groups as for both CTX and osteocalcin values. However lower CTX and osteocalcin values in the late postmenopausal group were detected about early postmenopausal group. Based on these findings authors concluded that during early postmenopausal period where bone turnover occurs rapidly and BMD changes can not yet be detected, monitorization of rates of bone turnover (i.e. bone formation and resorption) with biochemical markers may be useful in predicting the potential development of OP. However, in our study we found that all parameters of bone turnover did not differ between premenopausal FMS and the patient control group (Table 2).

Besides in the fibromyalgia group, a negative correlation existed only between osteocalcin and femoral neck and wards BMD values. These findings suggest that bone turnover in premenopausal FMS patients is not different from those of degenerative disc disease and does not affect BMD apart from osteocalcin. In FMS patients the relationship between bone metabolism markers and clinical parameters were studied and it was seen osteocalcin and CTX were correlated with SS scale, FIQ, MFIS ve ODI values and PTH was correlated with many clinical parameters (Table 3). Bone metabolism in FMS can thought to be affected by disease severity, pain, functional and emotional disturbance.

There are a few limitations in this study: number of participants in both of groups was not determined by power analysis before the study and an additional healthy control group was not included in the study.

Conclusion

In conclusion, many factors including more frequently seen depression and anxiety attacks, the presence of widespread pain, decrease in physical activity and quality of life in FMS patients make them more prone to osteoporosis. In this study we have observed that osteopenia and osteoporosis are more frequently seen in premenopausal FMS patients when compared with another disease (patients with degenerative low back pain) accompanied by pain and disability, and various clinical variables effected bone metabolism and bone density. Based on these findings, as a matter of consideration, osteoporosis and osteopenia may occur at a relatively early stage in patients with FMS. Therefore initiation of treatment at an early stage is recommended.

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