

## Levels of IGF-1 and Their Relationship with Bone Mineral Density in the Premenopausal Women with Fibromyalgia Syndrome

*Fibromiyalji Sendromlu Premenopozal Kadınlarda IGF-1 Düzeyleri ve Kemik Mineral Yoğunluğunun İlişkisi*

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### Abstract

**Objective:** The present study aims to compare bone mineral density (BMD) of healthy female patients with that of females with fibromyalgia syndrome (FMS), as well as to determine the relationship between insulin-like growth factor-1 (IGF-1) and BMD.

**Materials and Methods:** Twenty-seven premenopausal women with FMS and 21 age-matched female controls were included in the study. Body mass index (BMI), IGF-1 and osteocalcin levels were assessed for all the cases. BMD measurements of the femoral neck and lumbar spine were done by using dual-energy X-ray absorptiometry.

**Results:** Lumbar and femoral bone mineral density were significantly lower in FMS patients compared with controls ( $p < 0.001$ ). Serum concentrations of IGF-1 were significantly lower in FMS than those in healthy females ( $p < 0.01$ ). There was a significant correlation between IGF-1 and BMD (trochanteric and lumbar spine) in FMS patients. No difference was found between the groups with respect to serum osteocalcin levels.

**Conclusions:** The results of the present study shows that routine BMD measurements should be done in premenopausal FMS patients, especially who have low levels of IGF-1.

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**Key words:** Fibromyalgia, IGF-1, osteoporosis

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### Özet

**Amaç:** Bu çalışmanın amacı, Fibromiyalji sendromlu (FMS) kadınlarla sağlıklı kadınların Kemik mineral yoğunluğunu (KMY) karşılaştırmak, aynı zamanda KMY ile insulin-like growth faktör-1 (IGF-1) arasındaki ilişkiyi tanımlamaktır.

**Yöntem ve Gereçler:** Yirmi yedi premenopozal kadın ve aynı yaş grubunda 21 sağlıklı kadın çalışmaya alındı. Çalışmaya alınan tüm olguların vücut kitle indeksleri (VKİ), IGF-1 ve osteokalsin düzeyleri değerlendirildi. Dual enerji X-Ray absorpsiyometri yöntemi ile femür boyun, trokanterik bölge ve lomber bölge (L 1-4 ön-arka) KMY ölçümleri yapıldı.

**Bulgular:** Lomber ve femoral bölge KMY' ları kontrol grubu ile karşılaştırıldığında FMS' lu hastalarda anlamlı düzeyde azdı ( $p < 0.001$ ). IGF-1 serum konsantrasyonu FMS' lu kadınlarda sağlıklı kadınlardan önemli derecede daha düşük düzeyde idi ( $p < 0.001$ ). Fibromiyalji sendromlu hasta grubunda IGF-1 ile KMY (trokanterik ve lomber bölge) arasında anlamlı pozitif bir korelasyon vardı. Gruplar arasında serum osteokalsin düzeyleri farklı bulunmadı.

**Sonuç:** Bu çalışmanın sonuçları özellikle düşük IGF-1 düzeyine sahip premenopozal FMS' lu hastalarda rutin KMY ölçümlerinin yapılması gerektiğini gösterdi (*Romatizma 2008; 23: 118-23*)

**Anahtar sözcükler:** Fibromiyalji, IGF-1, osteoporoz

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### Introduction

Fibromyalgia syndrome (FMS) is a chronic painful condition of unknown etiology that affects the quality of life of female population for about 3.4% (1, 2). The typical patient is a middle-aged woman, although fibromyalgia

can occur in men and children and is the second most common condition seen by rheumatologists (3).

Despite the large population suffering from this condition the basic pathophysiologic mechanisms in FMS are unknown. It has been proposed that the low serum GH levels in these patients is due to the impairment in pituitary

GH secretion secondary to a state of altered neurosecretory regulation of GH-releasing hormone (GHRH) and somatostatin (4-9).

Growth hormone secreted by the pituitary acts on the liver and other tissues to stimulate the production of (10) and is probably the cause of some morbidities (11). For instance, IGF 1 is a key factor in osteoblast proliferation and bone formation (12). There is also increasing evidence that serum insulin-like growth factor (IGF)-I levels are reduced in a substantial number of FM patients (5, 13,14).

It has been known that patients with FMS have abnormal sleep patterns involving stages 3 and 4 of non-REM sleep (15). Growth hormone is maximally secreted during stages 3 and 4 of non-REM sleep and this led to notion that patients with FMS may have impaired GH secretion (16, 17). Interestingly, clinical symptoms of FMS are similar to those described by patients with adult GH deficiency syndrome (18-20).

Recent studies report that there is a significant correlation between BMD and IGF-1 levels as a result of their research into the relationship between IGF-1 and metabolism of the bone (21, 22, 23). In addition, some authors have suggested that patients with fibromyalgia syndrome may have a tendency to osteopenia or osteoporosis (24). However, a study which evaluates the relationship between FMS and osteopenia in FMS patients has not been encountered to date.

The aim of this study was to compare bone mineral density (BMD) of healthy females and females with fibromyalgia syndrome (FMS) and to assess the relationship between bone mineral density (BMD) and the level of insulin like growth factor in the serum of these patients.

## Materials and Methods

The present study was carried out in Department of Physical Therapy and Rehabilitation in Eskisehir Osmangazi University Hospital. 27 premenopausal patients achieving criteria issued by American College of Rheumatology in 1990 for fibromyalgia were included in the study (2). The mean age of these patients 39.48±6.80 years and the mean body mass index was 25.63±3.14 kg/m<sup>2</sup>. These criteria include;

- 1) Widespread pain for at least 3 months, on both sides of the body and above and below the waist, and pain at 11 of 18 tender points on digital palpation (cervical spine or anterior chest or thoracic spine or low back pain) and
- 2) The presence of at least 11 tender point sites (2).

All patients were premenopausal. Exclusion criteria for both patients and controls included; diseases well-known to affect bone metabolism (Cushing's, hyperthyroidism, hypothyroidism, hyperparathyroidism, renal disease and ethanol abuse), any medication known to affect bone turnover such as glucocorticoids, low IGF 1 levels known to associate with diabetes mellitus, obesity (Body Mass Index

30 and over) and liver disease. Patients were also excluded from the study for any of the following reasons: if they had taken calcium supplementation >1500 mg/day, vitamin D supplementation >800 IU/day, anabolic steroids, parathyroid hormone, calcitonin, estrogen, androgens or bisphosphonates within the previous 12 months from study entry. Furthermore, exclusion criteria for FMS patients and normal controls were a recent or past history of psychiatric disorders, such as depressive disorder, schizophrenic or paranoid disorder, personality disorders and somatoform disorders .

For control group, 21 premenopausal healthy women without FMS were selected. The mean age of the controls was 35.7±7.2 years and the mean body mass index was 25.24±3.42kg/m<sup>2</sup>.

The ethics committee of Medical School of Eskisehir Osmangazi University approved this study and informed consents were obtained for all the patients taken to the study. Afterwards, the subjects gave their medical histories and then underwent a physical examination, including tender point evaluation. Finally, they filled in a questionnaire comprised of selected questions regarding their lifestyle, medication, and history. One of factors concerning lifestyle was smoking, according to which the subjects were sorted out smokers and non-smokers. A structured history was taken with details of weight, height, age of menarche, calcium intake and family history of osteoporosis.

A physical function score, known as sub-score of the Medical Outcomes Study Short Form-36 Questionnaire (SF-36) was made in FMS and control groups. The SF-36 is designed to measure health status in eight domains: Physical Functioning; Physical Role; Bodily Pain; General Health; Vitality; Social Functioning; Emotional Role; Mental Health. Each domain was scored independently from 0 (lowest level of functioning) to 100 (highest level of functioning). The SF-36 is a validated instrument and has been widely applied (25, 26).

## Laboratory Tests

### Biochemical Measurements

Routine hematological and biochemical test were performed in all patients. In addition, cortisol, free T3, T4, and thyroid stimulating hormone levels were measured in venous blood using routine clinic laboratory methods, 24-h urinary calcium, phosphate, and creatinine levels were also measured. Serum intact parathyroid hormone (PTH) was measured using electrochemiluminescence immunoassay with the original kit (Modular Analytics E170, Roche Diagnostics, Basel, Switzerland). For the quantitative determination of 25-OH vitamin D in human serum: immunodiagnostik® enzyme-immuno-assay (EIA) kit was used. This test kit was a competitive protein binding assay for the measurement of 25-OH Vit D.

Serum osteocalcin (OC) levels, a marker of bone formation, were measured with commercially available ELISA kits (Trinity Biotech). IGF 1 levels were determined in the

Department of Biochemistry by using the method of chemiluminescent by means of Immulite One.

**BMD Measurements**

The standardized BMD measurements in lumbar spine (L1-4), femoral neck and trochanteric region (L1-4, anterior-posterior) were performed by using dual-energy X-ray absorptiometry (DEXA) equipment (Hologic QDR, 4500) in fibromyalgia and control groups. Bone mineral density was expressed as standard deviation scores, which compare individual BMD determinations to those of young (T) and age-sex matched (Z) normal populations.

**Statistical Methods**

Statistical analyses were performed using SPSS version 11.5. Results were reported as mean±SD. Student's unpaired t test was used for the comparison of the differences between the groups. In FMS patients, Pearson's correlation analysis was performed to assess the association between IGF 1 and BMD and age. Differences were considered significant if the p values were less or equal to a level of 5% and all results were expressed with 95% confidence interval.

**Results**

27 patients with FMS and 21 healthy women were included in the study. Parameters of age, weight, height and body mass index, menarche age, the number of smokers, and physical functional scores were similarly distributed between the two groups (p>0.05) (Table 1).

Levels of IGF 1 in patients with FMS and healthy control subjects are presented in Table 2. IGF 1 levels were determined between normal ranges in subjects in control group, while it was below the normal range in about 26% of patients with fibromyalgia. The serum concentrations of IGF 1 were significantly lower in FMS patients as compared with the control group (p<0.01) (Table 2). On the other hand, there were no significant differences in physical function score (p>0.05) (Table 1) and osteocalcin levels (p>0.05) (Table 2) between the two groups.

In patient group with fibromyalgia syndrome, the average t scores in lumbar spine (L1-4), femoral neck and trochanteric region were found -1.28±0.19,-1.66±0.27,-1.22±0.17 respectively. Bone mineral densities of lumbar spine and femoral neck and trochanteric region were significantly lower in FMS patients compared with control group (p<0.001, p<0.01, p<0.001, respectively) (Table 2).

**Table 1.** Baseline characteristics of patients with FMS and healthy control subjects

	Group 1 (n=27) (mean ± SD)	Group2 (n=21) (mean ± SD)	P
Age (yr)	39.48±6.80	35.71±7.23	>0.05
Height (Height) (cm)	160.60±4.59	162.33±6.17	>0.05
Weight (kg)	66.07±8.45	66.29±7.90	>0.05
BMI ( kg/m <sup>2</sup> )	25.63±3.14	25.24±3.42	>0.05
Age at menarche (yr)	12.41±1.37	12.19±1.33	>0.05
Daily cigarette consumption	3.33 ± 5.67	4.76±6.21	>0.05
Physical function score	80.93±10.29	86.43±11.85	>0.05
Calcium (mg/dl)	9.13±1.76	9.66±0.52	>0.05
Phosphorus (mg/dl)	3.54±0.51	3.62±0.56	>0.05
24 hr urinary calcium (mg/dl)	165.75±14.3	163.56±15.42	>0.05
25 Hydroxy Vitamin D (ng/ml)	59.09±37.54	78.42±36.50	>0.05
Parathormone (pg/ml)	46.40±24.06	47.23±15.16	>0.05

**Table 2.** Bone mineral density and biochemical parameters of study subjects

	Group 1 (n=27) (mean ± SD)	Group2 (n=21) (mean ± SD)	P
L1-L4 spine BMD (g/cm <sup>2</sup> )	-1.28±0.19	-0.14±0.17	<0.001
Trochanteric BMD (g/cm <sup>2</sup> )	-1.22±0.17	0.19±0.24	<0.001
Femoral neck (g/cm <sup>2</sup> )	-1.66±0.27	-0.45±0.25	<0.01
IGF-1 (ng/ml)	134.89±48.44	181.47±42.51	<0.01
Osteocalcin (ng/ml)	2.98±2.25	2.50±1.37	<0.05

A positive correlation was determined between BMD and IGF-1 levels in the lumbar (L1-4) and trochanteric regions of patients with FMS ( $r=0.401$ ,  $p<0.05$  and  $r=0.385$   $p<0.05$ , respectively) (figure 1, figure 2). However, no correlation could be determined between BMD and IGF-1 levels in the femoral neck ( $r=0.130$   $p>0.05$ ).

A negative correlation was determined in FMS patients with regarding to age and IGF-1 levels ( $r=-0.659$ ,  $p<0.01$ ) (figure 3), while no significant correlation could be found between age and IGF-1 levels in healthy controls ( $r=-0.417$ ,  $p>0.05$ ).

### Discussion

The aim of this prospective and controlled study was to determine the changes occurring in the bone mineral density in premenopausal women with FMS and to investigate the relationship between these changes and IGF-1 levels.

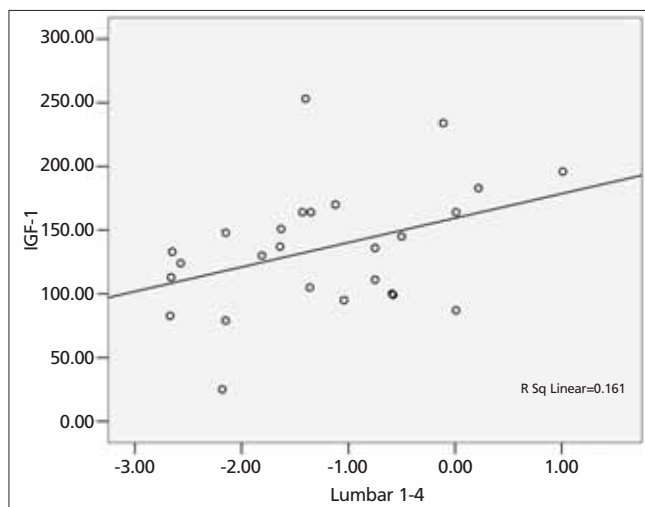


Figure 1. Positive association between serum IGF-1 levels and L1-L4 BMD (Group 1)

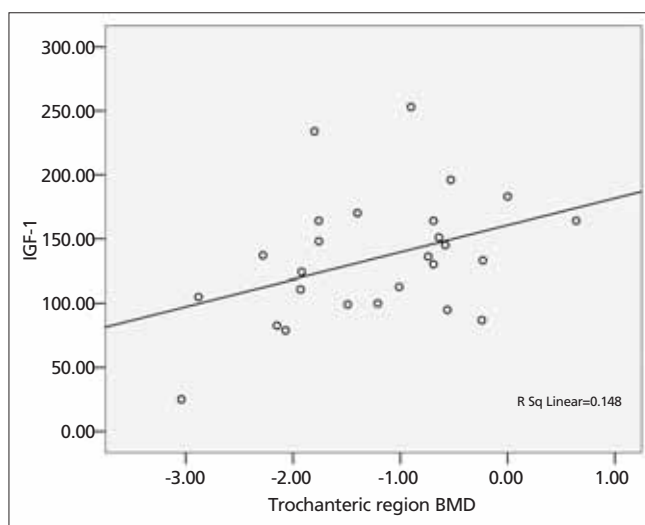


Figure 2. Positive association between serum IGF-1 levels and Trochanteric region BMD (Group 1)

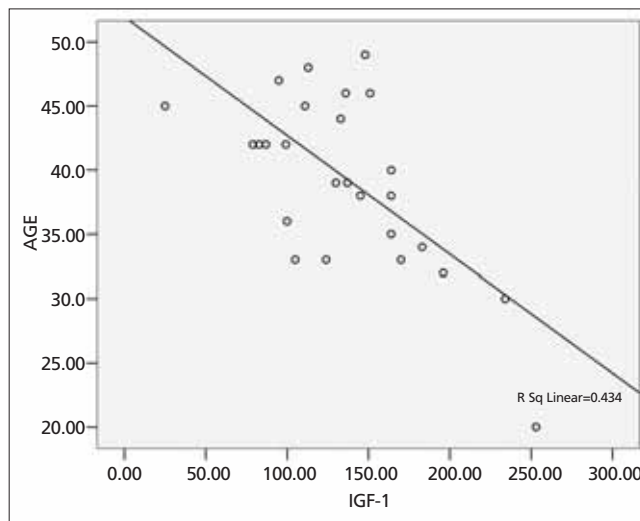


Figure 3. A negative correlation was determined in FMS between age and IGF-1 levels (Group 1)

However, studies of bone mineral density (BMD) in FMS have, to date, shown conflicting results some authors have suggested that patients with fibromyalgia syndrome may have a tendency to osteopenia. (24, 27, 28).

Although FMS patients do not have osteoporotic values, the results showed that t scores of the lumbar spine, femoral neck, and trochanteric regions were significantly lower in FMS patients as compared with controls.

Factors such as chronic and widespread pain, reduced exercise capacity, sedentary life and depression are risk factors for low BMD levels in FMS patients (29-31). In our study we excluded patients with a depression history.

However, It has been recognized that patients with FMS are relatively deconditioned, compared with normal subjects (32) as well as muscle strength and endurance have been shown to be lower than healthy age matched controls (32, 33). We could not observe a difference between healthy control and patients with FMS in terms of physical activity scores of SF-36. No difference was observed between healthy control group and patients with FMS in terms of physical activity scores of SF-36. Similarly, in a recent study, Jensen et al. investigated the relationship between physical activities and BMD levels in FMS patients, but they could not show a significant correlation (34). Depending on these results, the author suggested that this reduction in BMD levels might be related with the neuro-endocrine mechanisms which were responsible in the etiopathogenesis of FMS (34).

Research into etiology of FMS has explored the hypothesis that growth hormone (GH) deficiency is a significant feature of the syndrome (35). This theory is predicated on the observation that adult patients with a primary pituitary defect resulting in GH deficiency have similar clinical features, such as depressed mood, anxiety, reduced vitality, energy, reduced strength and exercise capacity (reduced vitality, energy, strength and exercise capacity),

cold intolerance (18). It is interesting that these features are also seen in patients with FMS. Furthermore, some other studies have reported growth hormone and IGF-1 levels to be lower in FMS (7, 36-38). In a review by Benett, it is suggested that low insulin-like growth factor-1 (IGF-1) levels are observed in approximately 30% of patients with fibromyalgia and is probably the cause of some morbidity (11). Similarly, we found that 26% of our patients with FMS have IGF1 levels below normal range in this study.

Growth hormone can sustain its effect upon skeletal muscle system through IGF-1 (12). Insulin-like growth factor I (IGF-I) is one of the most abundant growth factors present in bone that stimulates osteoblast activity, subsequently leading to bone matrix formation and inhibition of bone collagen degradation (39). IGF-1 is a stimulant factor for renal calcitriol synthesis and, enhanced intestinal calcium absorption, bone mineralization and stimulus for matrix protein synthesis (12).

Several studies have analyzed the relationship between IGF-I levels and bone mass, recent studies report that in different patient groups there is a significant correlation between BMD and IGF-1 levels as a result of research into the relationship between IGF-1 and metabolism of the bone (21, 22, and 23). There are also studies reporting that even patients with idiopathic osteoporosis have low levels of serum IGF 1 (21, 23).

In our study IGF-I levels in FMS patients were lower than those in with normal healthy control and a positive correlation was determined between BMD and IGF-1 levels in the lumbar (L1-4) and trochanteric regions of patients with FMS.

In addition, many previous studies had demonstrated that serum or bone IGF-I levels decreased with aging (40, 41, 42). It was also found that IGF-I levels decreased after menopause or with estrogen deficiency (43, 44). These studies, including the current one, suggested that age-related IGF-I decreasing correlated with age-related bone loss. In our study, the relationship between IGF-1 levels and age in control and FMS groups was evaluated. We found that there was a statistically significant negative correlation between age and IGF-1 levels in our FMS patients. Considering the fact that our FMS patients were premenopausal, and that there is a significant decrease in IGF-1 levels as compared with the control group, we may speculate that they would be candidates for some pathological losses in the postmenopausal stage.

In conclusion, although the results of our study may be somewhat limited by the small patient number, our results and the findings of the previous studies provides evidence that IGF 1 may play an important role on bone metabolism. As we know, this was the first study that looked into the relationship between BMD and IGF-1 levels in FMS patients. Based on our study results suggesting that FMS patients have a higher tendency to osteoporosis, we suggest that performing BMD measurements could be useful in premenopausal women, especially who had low IGF 1 levels.

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