Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology-Obstetrics and Neonatology

ÖZGÜN ARAŞTIRMA / ORIGINAL ARTICLE

DOI: 10.38136/jgon.1587956

Relationship between bone mineral density and inflammatory markers in postmenopausal patients

Postmenopozal hastalarda kemik mineral yoğunluğu ile inflamatuar belirteçler arasındaki ilişki

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ABSTRACT

Aim: This study aimed to determine the effects of acute-phase reactants and other factors on osteoporosis in postmenopausal women and to investigate inflammation markers that can be used in early diagnosis.

Materials and Methods: This study included 200 postmenopausal patients aged 40-65. Patients were divided into two groups: those with a bone mineral densitometry T-score below -2.5 (osteoporosis-positive) and above -2.5 (osteoporosis-negative). Patient demographics (age, parity, height, weight, body mass index (BMI - kg/m^2), duration of menopause, education level [<University vs. ≥University], and occupation status [Working vs. Housewife/ Pensioner]), complete blood count (hematocrit, white blood cell (WBC) count, neutrophil-to-lymphocyte (NLR) ratio), and serum biochemistry (low-density protein (LDL), vitamin D, and C-reactive protein (CRP)) levels were compared between the two groups.

Results: The mean lumbar T-score in the osteoporosis-positive group was significantly lower than in the osteoporosis-negative group (-2.9±0.4 vs. -0.8±1.0, p<0.01). Age, height, duration of menopause, and occupation status did not differ between the groups. However, mean parity, weight, and BMI were significantly higher in the osteoporosis-negative group (p<0.01). Blood Htc, WBC, NLR, and serum CRP and vitamin D levels showed no significant differences, but serum LDL levels were significantly lower in the osteoporosis-positive group (p=0.03). Binary logistic regression indicated low parity (OR: 0.65; p=0.02) and high educational level (OR: 0.42, p=0.01) were independently associated with a reduced risk of osteoporosis.

Conclusion: In our study, postmenopausal osteoporosis was not associated with serum inflammatory markers, and inflammatory markers were not valuable in predicting osteoporosis. However, postmenopausal osteoporosis was found to be closely related to parity, education level, weight and BMI.

Keywords: Acute-Phase Proteins, osteoporosis, postmenopausal, body mass index, parity

ÖZ

Amaç: Bu çalışmanın amacı, postmenopozal kadınlarda akut faz reaktanlarının ve diğer faktörlerin osteoporoz üzerindeki etkilerini belirlemek ve erken tanıda kullanılabilecek inflamasyon belirteçlerini araştırmaktır.

Gereç ve Yöntemler: Bu çalışmaya 40-65 yaş aralığında 200 postmenopozal hasta dahil edildi. Hastalar iki gruba ayrıldı: Kemik mineral dansitometrisi T skoru -2,5'in altında ve -2,5'in üzerinde olanlar. Hastaların yaşı, vücut kitle indeksi (VKİ (kg/m^2)), parite, doğum şekli (sezaryen veya vajinal doğum), demografik özellikleri, tam kan sayımı sonuçları (hematokrit (Htc), beyaz kan hücresi (WBC), nötrofil/lenfosit oranı (NLR)), düşük yoğunluklu protein (LDL), D vitamini düzeyleri ve CRP düzeyleri iki grup arasında karşılaştırıldı.

Bulgular: Ortalama parite, kilo ve VKİ, osteoporoz negatif grupta osteoporoz pozitif gruba göre anlamlı derecede daha yüksekti (P <0,01). Gruplar, kan Htc, WBC sayısı, NLR ve serum CRP ve D vitamini seviyelerine göre farklılık göstermedi. Ancak, serum LDL seviyeleri osteoporoz pozitif grupta osteoporoz negatif gruba göre anlamlı derecede düşüktü (P = 0,03). İkili lojistik regresyon analizi, düşük paritenin (OR: 0,65; P = 0,02) ve yüksek eğitim düzeyinin (OR: 0,42, P = 0,01) bağımsız olarak düşük osteoporoz riski ile ilişkili olduğunu ortaya koydu.

Sonuç: Çalışmamızda, postmenopozal osteoporoz serum inflamatuar belirteçleri ile ilişkili değildi ve inflamatuar belirteçler osteoporozu tahmin etmede değerli değildi. Ancak, postmenopozal osteoporoz parite, eğitim düzeyi, kilo ve BKİ ile yakından ilişkili olarak saptandı.

Anahtar Kelimeler: Akut faz proteinleri, osteoporoz, postmenopozal, vücut kitle indeksi, parite

Cite as: Halilzade Mİ, Taş EE. Relationship between bone mineral density and inflammatory markers in postmenopausal patients. Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi 2024;21(4):335–339.

Geliş/Received: 19.11.2024 • **Kabul/Accepted:** 12.12.2024

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Çevrimiçi Erişim/Available online at: https://dergipark.org.tr/tr/pub/jgon

INTRODUCTION

Osteoporosis is a disease with high morbidity, resulting in increased bone fragility due to low bone mass and deterioration of bone tissue (1). Vertebral fractures are the most common type of fractures associated with osteoporosis. Osteoporosis is particularly common in postmenopausal women and is associated with serious life-threatening vertebral fractures (2). Estrogen deficiency is the main cause of osteoporosis in postmenopausal women. Estrogen acts as a hormone that regulates bone mineral density. However, as it decreases during menopause, osteoporosis accelerates (3).

Pregnancy and lactation have been shown to be associated with osteoporosis in women. Pregnancy and lactation are conditions in which there is a high need for calcium, leading to significant physiological changes in bone mass. However, these changes have been shown to reverse after lactation (4). Despite this, studies have reported that the number of pregnancies is associated with osteoporosis and that osteoporosis increases with parity increases (5). Owing to these risk factors, early diagnosis and treatment of osteoporosis before vertebral fractures occur in women is very important.

Bone mineral density (BMD) measurement is the most important test used for the diagnosis of osteoporosis (6). According to the World Health Organization definition, osteoporosis is diagnosed as a T-score < –2.5 SD at any site (7). However, early and inexpensive methods for diagnosing osteoporosis remain a subject of research. It is known that systemic inflammation negatively affects BMD in patients with autoimmune chronic diseases such as rheumatoid arthritis, regardless of corticosteroid use (8). Therefore, it is suggested that acute-phase reactants, which are markers of inflammation, may be associated with osteoporosis. A large population study showed that C-reactive protein (CRP) values were inversely correlated with BMD scores in both men and women (9). Similarly, some studies have reported an inverse relationship between neutrophil to lymphocyte ratio (NLR) and BMD in postmenopausal women (2). However, some studies have reported that CRP is not an indicator of low BMD, bone loss, or fractures in postmenopausal women (10).

The fact that acute-phase reactants are affected by many diseases as inflammation markers and the conflicting results regarding their relationship with osteoporosis indicate that further studies are needed on this subject. This study aimed to determine the effects of acute-phase reactants and other factors on osteoporosis in postmenopausal women and to investigate inflammation markers that can be used for early diagnosis.

METHODS

This study included 200 postmenopausal patients in the Gynecology and Obstetrics Clinic of our hospital, which is a tertiary center, between 2019 and 2024. Approval from the local ethics committee was obtained from the same hospital (Ankara Bilkent City Hospital Ethics Committee no. 2, Approval No: 24-637). This study was a retrospective, cohort study.

Female patients aged 40-65 who entered menopause naturally were included in the study. Menopause was defined as patients who had not menstruated for two years or more. Patients with surgical menopause or early menopause (under 40 years of age) were excluded from the study. In addition, patients with parathyroid diseases that cause osteoporosis, thyroid disease, malignancy, rheumatological diseases, and infections were excluded. Patients who were started on medication for osteoporosis, who were using regular medication, and who were using hormone replacement therapy were not included in the study.

Patients were divided into two groups: those with a bone mineral densitometry T-score below -2.5 and above -2.5. Those with a BMD T score of 2.5, standard deviations (SD), or more below the mean BMD of the young adult reference population at any site were defined as having osteoporosis. Patients' age, body mass index (BMI (kg/m^2)), parity, delivery type (cesarean or vaginal delivery), and demographic characteristics were retrospectively investigated and recorded. Complete blood count results (hematocrit (Htc), white blood cell (WBC), lymphocyte count, NLR), low-density protein (LDL), vitamin D levels, and CRP levels were compared between the two groups. These markers (Htc, WBC, NLR) were tested automatically as part of a standard complete blood count. Bone mineral densitometry readings of the patients were obtained from the measurements recorded by the DXA method using a Hologic brand QDR 4500W device (Hologic Inc., Bedford, MA, USA) in the bone densitometer unit of the radiology department. The total BMD changes of the lumbar vertebrae were considered using T-scores (since osteoporosis is most commonly seen in the vertebrae (2)).

Data were expressed as mean±standard deviation. The independent samples t-test was used to compare parametric data between the groups. Categorical variables are expressed as numbers and percentages, and the groups were compared using the chi-square test. Variables with $P<0.05$, including parity, weight, BMI, education level, and serum LDL levels were included in the binary logistic regression analysis to identify independent factors associated with osteoporosis. Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 21.0 (IBM, SPSS Corp.; Armonk, NY, USA). Odds ratios (ORs) and 95.0% confidence intervals (CIs) were calculated, and statistical significance was set at $P<0.05$.

RESULTS

This study included 100 postmenopausal patients with osteoporosis (osteoporosis-positive) and 100 postmenopausal patients without osteoporosis (osteoporosis-negative). The mean lumbar T-score in the osteoporosis-positive group was lower than that in the osteoporosis-negative group (-2.9±0.4 vs. -0.8±1.0), and the difference was significant (p<0.01).

The groups (osteoporosis-positive and osteoporosis-negative) did not differ in age, height, duration of menopause, or occupation status (p=0.58, 0.17, 0.10, and 0.17, respectively). However, the mean parity, weight, and BMI were significantly higher in the osteoporosis-negative group than in the osteoporosis-positive group (P <0.01).

The demographic characteristics of the osteoporosis-positive and osteoporosis-negative groups are presented in Table 1.

The groups (osteoporosis-positive vs. osteoporosis-negative) did not differ based on blood Htc, WBC count, NLR, and serum CRP and vitamin D levels (p=0.06, 0.20, 0.86, 0.60, and 0.63, respectively). However, serum LDL levels were significantly lower in the osteoporosis-positive group than in the osteoporosis-negative group (P =0.03). The laboratory characteristics of the osteoporosis-positive and osteoporosis-negative groups are presented in Table 2.

Binary logistic regression analysis revealed that low parity (OR: 0.65; P=0.02) and high educational level (≥university) (OR: 0.42, P=0.01) were independently associated with a low risk of osteoporosis (Table 3).

Table 1. The demographic characteristics of the osteoporosis-positive and osteoporosis-negative groups

Characteristics	Osteoporosis-positive (n=100)	Osteoporosis-negative (n=100)	P
Age (years)	57.8±6.4	57.3±7.2	0.58
Parity	1.9±0.8	2.4±1.1	<0.01
Height (cm)	159.8±5.8	160.0±5.4	0.17
Weight (kg)	66.1±10.5	73.4±14.1	<0.01
Body mass index (kg/m²)	25.9±4.2	28.9±5.8	<0.01
Duration of menopause (years)	8.9±5.3	7.7±5.8	0.10
Education degree			
<University	61 (30.5)	44 (22)	0.01
≥University	39 (19.5)	56 (28)	
Occupation status			
Working	34 (17)	27 (13.5)	0.17
Housewife/Pensioner	66 (33)	73 (365)	

Data are presented as the mean±standard deviation or n (%).

Table 2. The laboratory characteristics of the osteoporosis-positive and osteoporosis-negative groups

Characteristics	Osteoporosis-positive (n=100)	Osteoporosis-negative (n=100)	P
Hematocrit (%)	41.4±3.1	42.2±2.8	0.06
WBC count (x 103/µL)	6.6±1.8	7.0±1.8	0.20
NLR	1.9±0.9	1.9±0.8	0.86
CRP (mg/L)	2.4±1.8	7.0±1.8	0.60
D vitamin	49.8±23.4	48.1±26.4	0.63
LDL	127.8±32.7	140.2±48.2	0.03

Data are presented as the mean±standard deviation or n (%).
Abbreviations: CRP, C-reactive protein; LDL, low-density protein; NLR, neutrophil-to-lymphocyte ratio.

Table 3. Binary logistic regression analysis of risk factors associated with osteoporosis

	P-value	95% CI	OR
Parity	0.02	0.45–0.93	0.65
Weight (kg)	0.30	0.90–1.03	-
Body mass index (kg/m²)	0.78	0.83–1.15	-
Education level (≥university)	0.01	0.22–0.79	0.42
LDL	0.10	0.98–1.00	-

Abbreviations: CI, confidence interval; OR, odds ratio; LDL, low-density protein

DISCUSSION

In our study, we compared the demographic characteristics and laboratory parameters of patients with and without postmenopausal osteoporosis to understand the causes of postmenopausal osteoporosis and to find a simple and cost-effective method that can help in its early diagnosis. There were no differences between the groups in terms of Htc, WBC count, NLR, serum CRP, and vitamin D levels. However, the serum LDL levels were significantly lower in the osteoporosis-positive group than in the osteoporosis-negative group. We demonstrated that high parity and low education levels are independent variables for postmenopausal osteoporosis and increase the risk of osteoporosis.

Osteoporosis is more common in postmenopausal women than in premenopausal women and men. This is primarily due to the decrease in estrogen levels after menopause, which results in decreased bone accumulation and increased bone resorption, especially in weight-bearing bones (11). However, it has been shown that the risk of osteoporosis increases more in the presence of other accompanying factors. Studies have reported that a low educational level is associated with an increased risk of osteoporosis (12). In our study, we also found an increased risk of osteoporosis with a similarly low level of education. It is known that physical activity and increased muscle mass protect against osteoporosis and possible osteoporotic fractures (13). Therefore, low education level has been associated with not engaging in sports activities. However, there are also studies stating that a high educational level is associated with a higher risk of osteoporosis. These studies have suggested that people with a higher level of education do not have sufficient time to exercise (14). In our society, since it has been observed that exercise status increases with increasing education level (15), we think that patients with lower education levels exercise less and, therefore, have a higher risk of osteoporosis.

The relationship between postmenopausal osteoporosis and BMI has been demonstrated in several studies. Low weight and BMI have been reported to increase the risk of osteoporosis (16,17). Bone strength is thought to be preserved in obese patients with a high BMI due to the protective effect of weight bearing on bone and estrogen secretion from fat tissue (18). In parallel, it has been concluded that the risk of osteoporosis is reduced in obese women with high serum LDL levels who are fed a high-fat diet (19). Similarly, in our study, we found that the risk of osteoporosis was higher in postmenopausal women with low weight, BMI, and LDL levels. However, some studies in mouse models have reported that low-grade systemic inflammation due to obesity induces bone loss (20,21). In addition, studies have reported that increased LDL levels support osteoclast formation and increase the risk of osteoporosis by causing increased bone destruction (22). Therefore, the relationship between BMI, LDL, and osteoporosis is still unclear and requires further research.

In our study, increased parity as an independent variable was associated with an increased risk of osteoporosis. However, the data on this issue in the literature are contradictory. Studies have reported that when maternal intestinal calcium absorption during pregnancy and lactation is not sufficient to meet the calcium requirement to support fetal skeletal development during pregnancy, the fetal system compensates by taking calcium from the mother's skeleton, which may increase the mother's long-term fracture risk by reducing bone mass (4). In contrast, other studies have reported that increased bone load and higher serum estrogen levels during pregnancy provide protection against maternal bone loss, and that the risk of osteoporosis and fractures decreases as parity increases (23). We believe that the effect of increased calcium requirement during pregnancy on maternal bone density is more effective than the protective effect of increased estrogen; therefore, the risk of osteoporosis increases with parity. In addition, we believe that the decrease in estrogen levels and continuation of calcium requirement during the lactation period after pregnancy also play an important role in increasing the risk of osteoporosis. When increasing parity is also considered to increase breastfeeding periods, the risk of osteoporosis may increase. However, a limitation of our study is that it was retrospective, and the required information of the patients (such as breastfeeding status) cannot be fully obtained.

The relationship between inflammatory markers and BMD has been investigated in previous studies, with conflicting results. As BMD has been shown to be negatively affected in chronic autoimmune diseases with systemic inflammation, the relationship between inflammatory markers and osteoporosis in postmenopausal women without comorbidities has been a matter of curiosity. Koh et al. investigated the relationship between baseline CRP levels and BMD in a study they conducted and demonstrated that high CRP levels were associated with an increased risk of osteoporosis in both premenopausal and postmenopausal women (7). In contrast, Berglundh et al. reported in their study on elderly women (75-80) that a single CRP measurement was not an indicator of low BMD, bone loss, or fracture; however, continuous CRP values ≥ 3 mg/L may be associated with bone loss (10). In addition, many authors have reported that NLR, another inflammatory marker, is closely associated with osteoporosis (24). Yılmaz et al. It has been stated that NLR can predict more than CRP values in postmenopausal women with osteoporosis (25). In addition, several studies have shown that elevated NLR is associated with poor prognosis in patients with osteoporosis (26, 27). Similarly, Lee et al. suggested that NLR is negatively associated with the mean lumbar BMD in postmenopausal patients with chorea. They reported that this is because inflammatory cytokines bind to stromal cells and activate osteoclast-mediated bone resorption by increasing the production of receptor activator of nuclear factor-kappa B (NF-$_{K}$B) ligand (RANKL) and macrophage colony-stimulating factor (28). In addition, a recent study observed that other inflammatory markers,

especially NLR, were negatively associated with BMD and positively associated with osteoporosis risk (29). However, we did not find a significant association between serum NLR and CRP values and BMD in our study. The NLR and CRP levels were not associated with osteoporosis in postmenopausal women. Our patients were women of the same age group, without any additional diseases, and were not very old. The absence of any additional conditions that could affect inflammatory markers is a strength of the present study.

In conclusion, we found that postmenopausal osteoporosis was not associated with serum inflammatory markers in our study. However, postmenopausal osteoporosis is closely associated with parity, education level, weight, and BMI. In particular, high parity and low education level were associated with a high risk of osteoporosis as independent factors.

Ethics Approval

For studies with human subjects include the following: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. Ethics committee approval was obtained from the Clinical Research Ethics Committee No. 2 of our hospital (24-637). Informed consent was obtained from all patients for being included in the study.

Authors' Contributions

MİH: Conceptualization, Writing – original draft, Methodology, Data curation, Resources, EET: Formal analysis, Writing – review & editing. All authors read and approved the final manuscript.

Conflicts of Interest/Competing Interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Funding Statement

None

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