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ORIGINAL ARTICLE

Evaluation of C-Reactive Protein to Albumin Ratio and Systemic Inflammation in Postmenopausal Osteoporosis

Postmenopozal Osteoporozda C-Reaktif Protein/Albümin Oranı ve Sistemik İnflamasyonun Değerlendirilmesi

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ABSTRACT

Aim: We aimed to evaluate systemic inflammation in patients with postmenopausal osteoporosis using C-reactive protein (CRP)/albumin ratio, blood neutrophil/lymphocyte ratio (NLR), and prognostic nutritional index (PNI) and to determine its relationship with bone mineral density (BMD).
Methods: Our study has a retrospective design. A total of 363 postmenopausal female patients admitted to physical medicine and rehabilitation outpatient clinics were evaluated. Patients were divided into three groups: osteoporosis, osteopenia, and normal BMD. Demographic data, femoral neck, and lumbar total T scores, BMD values, complete blood count parameters, CRP, and albumin results were recorded. CRP/albumin ratio, NLR, and PNI were calculated.
Results: Osteoporosis was found in 102, osteopenia in 167, and normal BMD in 94 patients. In the osteoporosis group, albumin, CRP and CRP/albumin ratio were lower than the normal BMD group ($p = 0.017$; $p < 0.001$; $p = 0.032$, respectively). In the osteoporosis group, PNI was lower than the other groups ($p < 0.001$). NLR was higher in the osteoporosis group than the other groups, but not statistically significant ($p = 0.723$). We found a positive correlation between BMD with albumin and PNI.
Conclusions: The effect of inflammatory response in postmenopausal osteoporosis is not prominent. CRP/albumin ratio does not seem to be an appropriate index for osteoporosis. In light of our data, nutritional factors seem to be more effective on osteoporosis.

Keywords: Albumin, CAR, inflammation, osteoporosis, PNI

ÖZ

Amaç: Postmenopozal osteoporoz tanılı hastalarda sistemik inflamasyonu; C-reaktif protein (CRP)/albümin oranı, kan nötrofil/lenfosit oranı (NLO) ve prognostik nütrisyonel indeks (PNİ) ile değerlendirmek ve kemik mineral yoğunluğu (KMY) ile ilişkisini saptamak amaçlandı.
Gereç ve Yöntemler: Çalışmamız retrospektif bir tasarıma sahiptir. Fiziksel tıp ve rehabilitasyon polikliniklerine başvuran 363 postmenopozal kadın hasta değerlendirilmeye alındı. Hastalar osteoporoz, osteopeni ve normal KMY olarak üç gruba ayrıldı. Hastaların demografik verileri, femur boyun ve lomber total T skorları ile KMY değerleri, tam kan sayımı ölçümü parametreleri, CRP ve albümin sonuçları kaydedildi. CRP/albümin oranı, NLO ve PNİ hesaplandı.
Bulgular: Hastaların 102'sinde osteoporoz, 167'sinde osteopeni ve 94'ünde normal KMY saptandı. Osteoporoz grubunda; albümin, CRP ve CRP/albümin oranı, normal KMY grubundan düşüktü (sırasıyla $p = 0,017$; $p < 0,001$; $p = 0,032$). Osteoporoz grubunda; PNİ diğer gruplardan daha düşüktü ($p < 0,001$). NLO ise osteoporoz grubunda diğer gruplardan yüksek olmakla beraber istatistiksel olarak anlamlı değildi ($p = 0,723$). KMY ile albümin ve PNİ arasında pozitif korelasyon saptadık.
Sonuçlar: Postmenopozal osteoporozda inflamatuar yanıtın etkisi ön plana çıkmamaktadır. CRP/albümin oranı, osteoporoz için uygun bir indeks olarak görünmemektedir. Verilerimiz ışığında daha çok nütrisyonel faktörler osteoporoz üzerinde etkili görünmektedir.

Anahtar Kelimeler: Albümin, CAR, inflamasyon, osteoporoz, PNİ

Introduction

Osteoporosis is a progressive systemic disease characterized by a decrease in bone mass, deterioration of bone microstructure, increased bone fragility, and susceptibility to fractures (1). With the aging of the global population, osteoporosis and the fractures it causes have become a significant cause of mortality and morbidity. Due to the social and economic burdens this imposes, the causes, prevention, treatment, and follow-up of osteoporosis are of great importance (2).

In postmenopausal osteoporosis (PMOP), estrogen withdrawal indirectly leads to bone resorption; additionally, it is thought that low-level chronic inflammation is also effective in this resorption (3). It is stated that estrogen loss increases permanent inflammation and is effective in the development of osteoporosis (4). With the term osteoimmunology, which has come to the agenda in recent years; the effects of the immune system, inflammatory cytokines, and chronic inflammatory response on bone turnover are being tried to be explained (5). The increase in various inflammatory cytokines;

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by inducing osteoclast differentiation, activates bone turnover toward destruction and leads to a decrease in bone mineral density (BMD). In addition, these inflammatory cytokines stimulate C-reactive protein (CRP) synthesis in hepatocytes (6). Although studies have shown that increased CRP causes a decrease in BMD, the literature remains contradictory on this issue (2, 7). Albumin is a negative acute-phase protein produced in hepatocytes, and its low levels indicate an inflammatory state (8). The CRP/albumin ratio (CAR) is a recent inflammatory marker that indicates nutritional status in addition to inflammatory status. CAR is considered a more reliable marker for assessing low-level chronic inflammation than CRP or albumin alone (9). The prognostic nutritional index (PNI) has been used to predict perioperative complications in patients undergoing cancer surgery, but recently, its association with the activity levels of various rheumatic diseases has been shown (10). It also provides information about the immune and nutritional status of patients (10, 11).

The older age group, where postmenopausal osteoporosis is more common, appears to be a risky population in terms of low-level chronic inflammation and inadequate nutrition. There are differences in the results of studies evaluating inflammation and nutritional status in PMOP patients with various parameters (2, 12, 13). We did not find any study in the literature examining CAR and PNI, which could provide insight into both inflammation and nutritional status in PMOP patients.

We aimed to evaluate the systemic inflammatory response and nutritional status in PMOP patients using CAR, PNI, and the blood neutrophil/ lymphocyte ratio (NLR) and to determine their relationship with BMD.

Materials and Methods

Our study has a retrospective design. Postmenopausal patients who presented to the physical medicine and rehabilitation department between 01/03/2021 and 01/01/2023 were screened. Postmenopausal women between the ages of 45 and 80, whose demographic information, BMD measurement, routine biochemical values, and complete blood count data were available, were included in the study.

Patients with active infection, previous hip and spine surgery, inflammatory rheumatic disease, autoimmune disease, hematological disease, malignancy, steroid use, or chronic kidney and liver failure were excluded from the study.

The patients' ages, femoral neck and lumbar total (L1-4) BMD values, and T scores were recorded. BMD was measured using dual-energy X-ray absorptiometry (Lunar Prodigy Primo). According to the criteria of the World Health Organization, a T score below −2.5 standard deviations (SD) is defined as osteoporosis; a T score between −2.5 and −1 SD is defined as osteopenia; and a T score of −1 SD and above is defined as normal BMD (14). In light of this definition, patients were evaluated in three groups: osteoporosis, osteopenia, and normal BMD according to their T scores.

Venous blood samples taken in the morning were used for CRP, albumin, and complete blood count measurements. Albumin levels were measured photometrically using the bromocresol method on the Beckman Coulter AU 5800 biochemical autoanalyzer. A complete blood count was performed on the Beckman Coulter DxH 800 autoanalyzer. Cellular analysis was based on flow cytometry principles. Platelet count was determined using the impedance (aperture impedance, DC) method, and hemoglobin measurement was carried out using a photometric method. Lymphocyte and neutrophil subgroups were evaluated using VCSn (volume, conductivity, scatter, and neutrophil lobularity) technology. CRP levels had been measured using the nephelometric method on the Beckman Coulter Image 800 system. PNI value; Calculated according to the formula 10 x serum albumin value (g/dL) + 0.005 × peripheral lymphocyte count (/mm3) (15). Low PNI values indicate the risk of malnutrition (11). CAR was calculated. High CAR values indicate increased inflammation and poor nutritional status (9). Blood NLR was calculated. NLR is calculated from complete blood count parameters and its increase indicates the systemic inflammatory response (16).

Patients were evaluated after approval was obtained by the Local Yozgat Bozok University Ethics Committee of Yozgat Bozok University (Decision No: 2017-KAEK-189, Date: 28/.04/.2023). The study was conducted under the principles of the Declaration of Helsinki.

Statistical Analysis

The data obtained were evaluated statistically

using the Statistical Package for the Social Sciences, version 20 package program (SPSS Inc., Armonk, NY, USA). The normality of numerical data distribution was examined using the Kolmogrov-Smirnov test. As descriptive statistics, variables with normal distribution were expressed as mean±standard deviation, and variables without normal distribution were expressed as median and interquartile range (25%-75%). The Mann-Whitney U test was utilized for data without normal distribution in comparison between groups; the independent test was applied to parametric data. In the correlation analysis, the appropriate Spearman or Pearson correlation tests were used. It was considered statistically meaningful when p<0.05.

Results

Three hundred sixty-three postmenopausal female patients were included in the study. According to T scores, 102 patients had osteoporosis, 167 had osteopenia, and 94 patients had normal BMD. Table 1 summarizes the age, BMD, and T scores of the groups.

Table 1. Age and bone mineral density analysis of the patients

	Normal BMD	Osteopenia	*Osteoporosis*	p-value
Age, years	55.83±8.59	61.23±8.41*	67.83±10.03 *†	< 0.001
Lumbar total T score (SD)	0.05 (-0.6 / 1)	-1.6 (-2.10 / -1.0) *	-3.0 (-3.3 / -2.7) *†	< 0.001
Femoral neck T score (SD)	0.10 (-0.33 / 0.8)	-1.3 (-1.70 / -0.9) *	-2.1 (-2.7 / -1.5) *†	< 0.001
Lumbar total BMD (gr/ cm^2)	1.17 (1.09 / 1.27)	0.99 (0.92 / 1.06) *	0.81 (0.77 / 0.85) *†	< 0.001
Femoral neck BMD (gr/ cm^2)	1.00 (0.95 / 1.09)	0.82 (0.77 / 0.89) *	0.73 (0.66 / 0.78) *†	< 0.001

BMD: Bone mineral density, SD: Standard deviation *Osteopenia-Normal BMD, †Osteopenia-Osteoporosis

Lumbar total and femoral neck BMD and T scores were lower in the osteoporosis group than in the osteopenia and normal BMD groups (p < 0.001). The average age was found to be higher in the osteoporosis group than in the other two groups (p < 0.001).

Biochemical data of the patients included in the study are summarized in Table 2. CRP, albumin, and CAR values were lower in the osteoporosis group than in the normal BMD group (respectively, p = 0.017; p < 0.001; p = 0.032). PNI was lower in the osteoporosis group than in the other two groups (p < 0.001). NLR was higher in the osteoporosis group but not statistically significant (p = 0.723). Hemoglobin values were also lower in the osteoporosis group than in the other groups (p < 0.002).

Table 2: Analysis of biochemical data of the patients

	Normal BMD	Osteopenia	*Osteoporosis*	p-value
Albumin (g/ dL)	4.24±0.24	4.18±0.25	4.12±0.22*	0.001
C-reactive protein (mg/ dL)	0.43 (0.3-0.7)	0.45 (0.27-0.74)	0.36 (0.21-0.54)†	0.017
CAR	0.10 (0.07-0.17)	0.11 (0.07-0.19)	0.09 (0.05-0.14) †	0.032
PNI	52.65 (50.5-56.35)	52.7 (50.05-55.2)	50.85 (48.5-53.95) *†	0.001
NLR	1.81 (1.42-2.47)	1.76 (1.5-2.38)	1.98 (1.45-2.44)	0.723
Neutrophil ($\times10^3$/µl)	3.9 (2.98-4.83)	3.8 (3.05-4.7)	3.6 (2.9-4.58)	0.369
Lymphocyte ($\times10^3$/µl)	2.1 (1.78-2.6)	2 (1.75-2.55)	1.8 (1.43-2.48)	0.029
Platelet ($\times10^3$/µl)	252.5 (224-286.25)	252 (217-296)	246 (211-281.25)	0.405
Hemoglobin (g/dL)	13.6 (12.88-14.4)	13.5 (12.85-14.2)	13.2 (12.3-13.8) *†	0.002

CAR: C-reactive protein/albumin, PNI: Prognostic nutritional index, NLR: Neutrophil/lymphocyte ratio

*Osteoporosis-normal BMD

†Osteopenia-Osteoporosis

Correlation analyses between systemic inflammatory parameters and BMD are summarized in Table 3. We found a positive correlation between albumin, PNI, and hemoglobin values with BMD. There was a negative correlation between age and BMD. We found a positive correlation between femoral neck BMD with CRP and CAR.

Discussion

Postmenopausal osteoporosis is mostly seen in advanced age and causes serious morbidities. In recent years, studies investigating systemic inflammation in the etiology of osteoporosis have increased (17, 18). In our study, we evaluated the systemic inflammatory response and nutritional status in PMOP patients with CAR, PNI, and NLR parameters. Albumin, CRP, CAR, and PNI were significantly lower in the PMOP group. Although the low levels of albumin and PNI in the PMOP group support a nutritional deficiency, the low levels of CRP and CAR in the PMOP group do not support an increase in systemic inflammation. NLR, another inflammatory parameter, was higher in the PMOP group, but not statistically significant. Contradictory results on inflammatory markers make it difficult to conclude the effect of systemic inflammation in PMOP.

A study evaluating NLR, platelet/lymphocyte ratio

Table 3: Correlation analysis between bone mineral density and inflammatory parameters

		Lumbar Total T Score	Femoral Neck T Score	Lumbar Total BMD	Femoral Neck BMD
Albumin (g/dL)	rho	0.141	0.183	0.136	0.179
	p-value	0.007	0.001	0.009	0.001
C-reactive protein (mg/dL)	rho	0.1	0.136	0.097	0.129
	p-value	0.056	0.011	0.066	0.015
CAR	rho	0.088	0.119	0.085	0.113
	p-value	0.095	0.026	0.108	0.033
PNI	rho	0.160	0.151	0.153	0.152
	p-value	0.002	0.005	0.004	0.005
Lymphocyte (×10³/µl)	rho	0.131	0.110	0.128	0.120
	p-value	0.013	0.041	0.016	0.025
Age (years)	rho	-0.370	-0.462	-0.357	-0.456
	p-value	0	0	0	0
Hemoglobin (g/dL)	rho	0.167	0.177	0.164	0.164
	p-value	0.002	0.001	0.002	0.002
NLR	rho	-0.026	-0.025	-0.03	-0.033
	p-value	0.621	0.646	0.567	0.541

CAR: C-reactive protein/albumin, PNI: Prognostic nutritional index, NLR: Neutrophil/lymphocyte ratio, BMD: Bone mineral density

(PLR), and systemic immune inflammation index (SII) in patients with osteoporosis and normal BMD found no difference between the groups or correlation with T-scores (18). In another study evaluating NLR and SII in PMOP patients, NLR was found to be significantly higher in the PMOP group. Additionally, SII has been stated as a marker that can distinguish both PMOP diagnosis and osteoporotic fracture risk. In the same study, albumin was found to be significantly lower in the PMOP group (17). Moreover, in another study evaluating SII in patients with osteoporosis, SII was found to be higher in osteoporosis patients compared to the non-osteoporotic group (19). Furthermore, in a study evaluating the inflammatory content of the diet, an increase in the dietary inflammation index was found to be associated with a higher risk of osteoporosis in women (20). Although we found NLR to be high in the osteoporosis group, it was not statistically significant. Moreover, we did not detect any correlation between NLR and BMD values. In a study evaluating the relationship between the geriatric nutritional risk index (GNRI) and osteoporosis in type 2 diabetes; GNRI was found to be lower in osteoporosis patients, and it was stated that the osteoporosis group was at nutritional risk (21). Similarly, in a study investigating the relationship between albumin and BMD, albumin levels were found to be significantly lower in the osteoporosis group compared to the normal BMD group. Albumin has been considered a protective parameter against osteoporosis and osteoporotic fractures (22). Similar to these studies; we found albumin and PNI to be lower in the PMOP group. In addition, we detected a positive correlation between albumin and PNI with BMD; this supports a nutritional deficiency in PMOP patients. However, it is difficult to support the presence of systemic inflammation with our current data. Recent studies provide evidence supporting the role of inflammation in the development of osteoporosis; however, there are also studies in the opposite direction. Therefore, no consensus has yet been reached on this matter (17-19).

In a cohort study, CRP was negatively correlated with femoral neck BMD, and tumor necrosis factor-alpha was negatively correlated with lumbar vertebral BMD in premenopausal women. In postmenopausal women, a positive correlation was found between femoral neck BMD and CRP in the group receiving hormone therapy, while no correlation was found in the group not receiving hormone therapy. These contradictory results suggest that there is no definitive link between inflammation and BMD (12). In another study evaluating the relationship between serum inflammatory markers and BMD, CRP concentration was significantly higher in the low BMD group than in the normal BMD group. In the low BMD group, a negative correlation was found between BMD and CRP. In the same study, albumin values were similar between the two groups (6). The population of this study was younger compared to our study, and the groups were homogeneously distributed in terms of age. In our study, the age of the PMOP group was

significantly higher than that of the other groups. In our study, CRP, albumin, and CAR were lower in the PMOP group; we found a positive correlation between femoral neck BMD and CRP and CAR. These results do not support increased systemic inflammation and its association with BMD.

We detected no inflammatory changes in PMOP patients. CRP, in addition to reflecting the inflammatory state, can also be affected by the patient's nutritional status and liver function since it is synthesized in the liver. Whereas NLR was higher in the PMOP group, CAR, albumin, hemoglobin, and PNI values were lower. While NLR is a marker of bone marrow-derived marker; the fact that CRP, albumin, and CAR are liver-derived markers may explain this difference. These data suggest that nutritional deficiencies, rather than a chronic inflammatory condition, may play a primary role in PMOP. A more accurate evaluation of inflammation and nutritional status can be achieved through studies conducted in age-matched groups.

Limitations of our study include the heterogeneity between groups in terms of age, which prevented the exclusion of age-related effects on biochemical parameters. In addition, the lack of body mass index data can be considered a limitation given the impact of obesity on osteoporosis and inflammation. The strengths of our study include the large sample size and the first-time evaluation of CAR and PNI in PMOP, which had not been assessed before.

Conclusion

The effect of the inflammatory response does not appear to be prominent in PMOP. CAR does not currently seem to be a suitable index for PMOP. Our data suggest that nutritional factors have a greater impact on PMOP. Since the literature remains contradictory on this matter, prospective studies evaluating the asymptomatic inflammatory response and nutritional status in PMOP patients, alongside an age- and demographically matched control group are needed.

Conflict of interest

No conflicts of interest were reported between the authors.

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