

**Clinical Research**

## Investigation of Bone Mineral Density Loss in Patients with COVID-19

Türkan TUNCER<sup>1,a</sup><sup>1</sup>Fethi Sekin Şehir Hastanesi, Fiziksel Tıp ve Rehabilitasyon Kliniği, Elazığ, Türkiye**ABSTRACT**

**Objective:** Previous reports have documented the observation of altered bone metabolism following COVID-19 infection and during the recovery period. Our knowledge of the relationship between osteoporosis (OP) and COVID-19 is limited. In this report, we aimed to determine whether the inflammation due to COVID-19 infection negatively effects bone health.

**Material and Method:** Three hundred and thirteen patients were analyzed retrospectively. Bone mineral density loss was investigated by comparing dual-energy X-ray absorptiometry (DEXA) lumbar spine or femur neck T scores. The patients were examined in two main groups as newly diagnosed (n =104) and known osteoporosis (n =145) patients. Patients diagnosed with osteoporosis at the time of application constituted the newly diagnosed patient group. After the exclusion criteria, patients with known osteoporosis were subdivided according to their status of having COVID-19 infection (n =61), as well as worsening or healing in T scores. Initial and final T scores were compared in each group.

**Results:** In the newly diagnosed osteoporosis patient group, 22.9% of the patients (n =57) had been infected with COVID-19. In the patient group with known osteoporosis, this rate was 24.5% (n =61). While there was no significant difference between previous T-score values in the group with known osteoporosis with COVID-19, there was a statistical difference in final T-scores (p <0.001). When the group of patients with known osteoporosis were classified according to worsening or healing T-scores, those with COVID-19 infection had a worse final T-score (p <0.001). In the group with healing in the T score, the final DEXA values were better in the group without COVID-19 (p =0.004).

**Conclusion:** COVID-19 infection may affect bone metabolism, leading to progression of bone mineral density loss.

**Keywords:** Bone Mineral Density, COVID-19 Infection, Osteoporosis.

**ÖZ****COVID-19 Hastalarında Kemik Mineral Yoğunluğu Kaybının Değerlendirilmesi**

**Amaç:** Önceki raporlar, COVID-19 enfeksiyonu sonrası kemik metabolizmasında değişiklikler olduğunu belgelemiştir. Osteoporoz (OP) ve COVID-19 arasındaki ilişki hakkındaki bilgilerimiz sınırlıdır. Bu çalışmada COVID-19 enfeksiyonuna bağlı inflamasyonun kemik sağlığını olumsuz etkileyip etkilemediğini belirlemeyi amaçladık.

**Gereç ve Yöntem:** Üçyüzonüç hasta retrospektif olarak incelendi. Dual-energy X-ray absorpsiyometri (DEXA) lomber omurga veya femur boynu T skorları karşılaştırılarak kemik mineral yoğunluğu kaybı araştırıldı. Hastalar yeni tanı almış (n =104) ve daha önce OP tanısı olan hastalar (n =145) olmak üzere iki ana grupta incelendi. Başvuru anında OP tanısı alan hastalar yeni tanı OP hastaları grubunu oluşturdu. Dışlama kriterleri sonrası bilinen OP olan hastalar, COVID-19 enfeksiyonu geçirme durumlarının yanı sıra T skorlarında kötüleşme veya iyileşme durumlarına göre alt gruplara ayrıldı. Her grupta ilk ve son T skorları karşılaştırıldı.

**Bulgular:** Yeni tanı konulan OP hasta grubunda hastaların %22,9'u (n =57) COVID-19 ile enfekte olmuştu. Bilinen OP olan hasta grubunda bu oran %24,5 (n =61) idi. COVID-19 ile bilinen OP olan grupta önceki T-skoru değerleri arasında anlamlı fark bulunmazken, nihai T skorunda istatistiksel olarak anlamlı fark vardı (p <0.001). Bilinen OP olan hasta grubu, kötüleşen T skorlarına göre sınıflandırıldığında, COVID-19 enfeksiyonu olanların nihai T skoru daha kötüydü (p <0.001). T skorunda iyileşme olan grupta son DEXA değerleri COVID-19 olmayan grupta daha iyiydi (p =0,004).

**Sonuç:** COVID-19 enfeksiyonu, kemik metabolizmasını etkileyerek kemik mineral yoğunluğu kaybının ilerlemesine yol açabilir.

**Anahtar Sözcükler:** Kemik Mineral Yoğunluğu, COVID-19 Enfeksiyonu, Osteoporoz.

**Bu makale atıfta nasıl kullanılır:** Tuncer T. COVID-19 Hastalarında Kemik Mineral Yoğunluğu Kaybının Değerlendirilmesi. Fırat Tıp Dergisi 2025; 30(3): 144-149.

**How to cite this article:** Tuncer T. Investigation of Bone Mineral Density Loss in Patients with COVID-19. Fırat Med J 2025; 30(3): 144-149.

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In 2019-2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became widespread throughout the world. The clinical spectrum of coronavirus disease of 2019 (COVID-19) ranges from severe and critical to acute respiratory distress syndrome (ARDS) (1,2). Furthermore, COVID-19 patients can acquire pneumonia and recently, bronchiolitis has been commonly observed (3-5). In most of these patients, ARDS

and pneumonia are primary causes of poor prognosis and increased mortality/morbidity (6-8). Several reports have shown increased frequency of COVID-19 in those who have pre-existing conditions (e.g. heart disease, respiratory disease, and/or metabolic syndrome) (2, 9, 10). Interestingly, elderly people have an increased risk of severe complications from COVID-19, and studies have shown an accelerated rise in hospitaliza-

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Kabul Tarihi/Accepted: 11.04.2025

tion of those over 60 years of age with COVID-19 (11-13).

OP is common in the elderly, increases with age, and is characterized by a progressive alteration of bone mass with increased fracture risk often without trauma (14, 15). OP affects about 0.5 million men and 1.2 million women worldwide and is the third most common chronic complication behind hypertension and arthritis (16, 17). Studies have shown suggest that there are changes to bone metabolism following COVID-19 infection and during the recovery period (18, 19). Additionally, others have shown that there is a higher risk of fracture associated with COVID-19 (20, 21). Interestingly as well, those with some type of low bone mineral density (BMD) fractures may have higher susceptibility to SARS-CoV2 infection (22). Others observed an increase in severe clinical incidence in COVID-19 patients with lower BMD compared to those with higher BMD suggesting that scoring BMD levels may be a strong prognosticator of COVID-19 severity (23).

One potential consequence of COVID-19 is cytokine release syndrome, which contributes to acute inflammatory complications (24, 25). Reports have also shown that increased cytokines release not only causes ARDS, but also chronic inflammatory diseases including chronic pulmonary inflammation and arthritis, which contribute to 'long' COVID-19 complications (26-30). Additionally, the complications may be linked to accelerated bone loss, systemic OP, and increased fractures (31, 32). Previous reports have determined that chronic lung diseases like chronic obstructive pulmonary disease (COPD) and asthma have been linked to bone loss (33, 34). Despite evidence for long-term complications of COVID-19, there is still a lack of investigations on OP, COVID-19 and lung involvement. In this report, the main goals were to determine whether the hyper-inflammation caused by COVID-19 infection negatively effects bone health. Therefore, we investigated BMD loss, by comparing DEXA values and lung involvement, in patients with and without COVID-19 who were previously diagnosed with OP and followed up for 15 months in our polyclinic.

## MATERIAL AND METHOD

For this single-center study, 313 patients, recruited from January 2021 to April 2022, were retrospectively reviewed for diagnosis of OP within the Hospital Information Management System (HBYS). All of the patients recruited were female with postmenopausal OP. Only newly and previously diagnosed patients who received treatment were included. The same device was used for bone mineral density measurements (Lunar prodigy, A (s/n 81461). During this time, patient data was also screened for positive COVID-19 test results and recorded as positive (with date) or negative; patients with and without COVID-19 were included in the study. Subsequently, those patients who were COVID-19 positive were subjected to a chest exam to

determine lung pathology based on the presence of pneumonia detected by thoracic CT. Patient demographics, co-morbidities, type(s) of OP drugs used, and previous DEXA values were recorded and used for the study. In addition, medical records from each patient were also evaluated for hospitalization or intensive care admission.

Exclusion criteria were as follows: 1- those with disease affecting the musculoskeletal system (pituitary gland disease, thyroid gland diseases, parathyroid gland disease, rheumatic disease history, and/or malignancy); 2- Those with a history of drug use that would affect the musculoskeletal system; and 3- those with OP who received medical treatment and had previous DEXA values that could not be determined. After exclusion criteria were considered, the study was completed with 249 female patients with postmenopausal OP and the absence or presence of COVID-19 infection. The current study was conducted according to the Helsinki Declaration, and approved by Ethical Committee of Firat University (approval code: 16.03.2022-357). The minimum number of patients to be included in the study was determined to be 313 to achieve 80% power at the significance level of  $\alpha=0.5$  with a medium effect size.

Patients were stratified into groups. The first group consisted of patients with new diagnosis of OP and COVID-19 positive (nDOP/COVID+) and new diagnosis OP and COVID-19 negative (nDOP/COVID-). The second group consisted of patients with known OP who were COVID-19 positive (kOP/COVID+) or COVID-19 negative (kOP/COVID-). Patients were followed up for 15 months after receiving medical treatment with biphosphonate or denosumab and previous (initial) DEXA values were compared to the final DEXA value T-Scores. For the kOP/COVID+ group, patients were categorized based on worsening DEXA value T-Scores (kOP/COVID+ W) or healing DEXA value T-Scores (kOP/COVID+ H). The kOP/COVID- cohort consisted of patients grouped based on worsening DEXA value T-Scores (kOP/COVID- W) or healing DEXA value T-Scores (kOP/COVID- H) (Table 1).

**Table 1.** Descriptive statistics.

Age	Mean $\pm$ SD 66.52 $\pm$ 11.84 Frequency (n)	Mean (min - max) 66 (50 - 76) Percent (%)
<i>COVID-19</i>		
Positive	118	47.4
Negative	131	52.6
<i>CT Involvement</i>		
Present	71	28.5
Absent	178	71.5
<i>New OP diagnosis</i>		
nDOP/COVID+	57	22.9
nDOP/COVID-	47	18.9
<i>Known OP diagnosis</i>		
kOP/COVID+	61	24.5
kOP/COVID+W (worsening DEXA value)	38	15.2
kOP/COVID+H (Healing DEXA value)	23	9.3
kOP/COVID-	84	33.7
kOP/COVID-W (worsening DEXA value)	44	17.6
kOP/COVID- H (Healing DEXA value)	40	16.06

### COVID-19 testing and lung involvement (CT):

For determination of COVID-19 infection, the date that patients were PCR positive was recorded via the public health management system. In the same system, the follow-up CT scans from individuals with COVID-19 infection were analyzed for lung involvement. CT examination was evaluated according to thorax CT reports obtained through the HIMS hospital system and clinical data information through the Public Health Management System.

### BMD scoring and diagnosis of OP:

Diagnosis of OP was determined in accordance to the International Society for Clinical Densitometry guidelines (35, 36). DEXA was used to calculate bone mineral density. A scoring system using the lowest BMD T-score was used and included the total lumbar spine (LS) L1-L4 or femur neck as recommended by the guidelines above. A T-score between +1 and -1 was considered normal, while a T-score within -1 and -2.5 was an indicator of low BMD; however, not enough to diagnose as OP. A DEXA value of -2.5 or lower was considered T-score indicative of OP and higher fracture risk (a greater negative value is directly proportional to OP severity).

### Statistics

Data were analyzed with IBM SPSS version 23. Conformity to normal distribution was evaluated by Shapiro Wilk and Kolmogorov-Smirnov tests. The Mann-Whitney U Test was used to compare the data that were not normally distributed according to the paired groups. Kruskal-Wallis H Test was used to compare the data that were not normally distributed according to groups of three or more, and multiple comparisons were examined with Dunn's test. Wilcoxon test was used to compare the before and after L1-L4 T-Scores that were not normally distributed within the groups. Analysis results were presented as mean  $\pm$  standard deviation (SD) and median (minimum (MIN)-maximum (MAX)) for quantitative data, and as frequency and percentage for categorical variables. A p-value of less than 0.05 was considered statistically significant.

## RESULTS

The present study included 249 female patients with postmenopausal OP. Table 1 shows the descriptive statistics for the patients. The mean age of the patients was  $66.52 \pm 11.84$  (min-max: 50-76). Of the 249 patients, 118 (47.4%) tested positive for COVID-19, while 131 (52.6%) were negative. Interestingly, lung involvement based on CT was observed in 71 (28.5%) out of 249 patients, while 178 of the total (71.5%) did not have any observable lung involvement. When considering only those patients who were positive for COVID-19, 71 (60.17%) of the 118 patients had CT involvement. Within newly diagnosed OP patients, 22.9% of the patients were grouped into nDOP/COVID+, whe-

reas the patient distribution for nDOP/COVID- was 18.9%. For known diagnosed OP patients, 24.5% of the patients were categorized into kOP/COVID+, while kOP/COVID- had 33.7%.

In table 2, patients with a known diagnosis of OP and receiving medical treatment were compared based on COVID-19 infection.

**Table 2.** Comparison of COVID-19 infection status and DEXA L1-4/L2-4 T-score values in patients with known OP.

	Previous L1-4/L2-4 T Score	Final DEXA L1-4/L2-4 T Score
<i>Known OP diagnosis</i>		
kOP/COVID+	-3.1 (-2.7 - 4)	-3.4 (-2.4 - -4.8) <sup>a</sup>
kOP/COVID-	-3.1 (-2.6 - 3.8)	-3.1 (-3.2 - 4.6) <sup>ac</sup>
p	0.364**	<0.001*

\*Kruskall-Wallis test, \*\*Mann-Whitney U test, median (MIN-MAX), a-c: no difference between groups with the same letter, \*\*\*: Not included in the comparison because there were no observations and the number of observations was low, median (MIN-MAX).

There were no statistical differences observed between the medians of the previous T-Scores in kOP/COVID+ and kOP/COVID- (p=0.364). However, a comparison between the medians of the final DEXA T-Scores in kOP/COVID+ and kOP/COVID- was statistically different compared (p <0.001).

In table 3, patients with a known diagnosis of OP and receiving medical treatment were grouped according to fixed/decreasing or worsening of their final DEXA values. A worsening of DEXA value T-scores was detected in 82 of the 249 total patient cohort (56.5%).

**Table 3.** Comparison of DEXA values of patients with known OP whose DEXA values were found to worsen based on COVID-19 infection.

	Previous L1-4/L2-4 T-Score	Final L1-4/L2-4 T-Score
kOP/COVID+ W (n=38)	-3.1 (-2.7 - 4)	-3.5 (-2.9 - -4.8)
kOP/COVID- W (n=44)	-2.9 (-2.4 - 3.8) <sup>b</sup>	-3.2 (-2.6 - -4.9)
p*	0.007	<0.001

\*Kruskall-Wallis test, \*\*Mann-Whitney U test, median (MIN-MAX).

For kOP/COVID+ W, 38 of the 82 patients (46.3%) were COVID-19 positive and had worsened DEXA values, while 44 of the 82 patients (53.6%) in kOP/COVID- W group had worse DEXA values. No significant difference was found between the previous DEXA values for both groups. However, there was a significantly worse (higher) final T-Score for those patients who had COVID-19 infection (kOP/COVID+ W) (p <0.001).

Table 4 shows a comparison between patients with known OP, healing DEXA value T-scores and COVID-19 infection status.

**Table 4.** Comparison of patients with known osteoporosis and healing DEXA values based on COVID-19 infection.

	Previous L1-4/L2-4 T-Score	Final DEXA L1-4/L2-4 T-Score
kOP/COVID+ H (n =23)	-3.2 (-2,6 – -4.1)	-3.0 (-2.4 – -3.8)
kOP/COVID- H (n =40)	-3.4 (-2.5 – -4.6)	-2.7 (-2,5 – 3.0)
p*	0.089	0.004

\*Kruskall-Wallis test, median (MIN-MAX).

There were 63 total patients between the kOP/COVID+ H and kOP/COVID- H groups. The kOP/COVID+ H group made up 36.5% (n =23) of the total patients, while kOP/COVID- H made up 63.5% (n =40). There were no significant differences for previous DEXA T-Scores in either group. However, the final DEXA T score was found to be significantly lower in the group that did not have COVID-19 infection.

## DISCUSSION

In this report, we aimed to investigate whether COVID-19 had an effect on BMD by comparing DEXA values in patients previously diagnosed with OP with and without COVID-19 infection. We evaluated the efficacy of the BMD in the prediction of COVID-19 patients who underwent a chest CT scan. While there was no significant difference in the previous DEXA value T-Scores of patients with known OP (before COVID-19 positivity), there was a significant difference in DEXA value T-Scores that worsened following COVID-19 infection. These results suggest that COVID-19 infection leads to the potential progression of OP bone mineral density loss.

Low BMD has been shown to associate with poor survival in patients with pulmonary complications or respiratory infection (37, 38). Others have shown that patients with COVID-19 may be able to use low BMD as a predictor of severity or mortality (18, 21). Conversely, patients with low BMD fractures may have increased susceptibility to COVID-19 (19, 22). People with low BMD, like that of postmenopausal OP patients, should be aware of the potential increased risk of infection or even sepsis. Our data suggests that BMD

worsens in postmenopausal women following COVID-19 infection. These studies combined suggests that the low BMD is not only a potential prognostic factor in patients with COVID-19 but also a possible indicator of previous COVID-19 infection or 'long' COVID complications.

In our study, 118 (47.4%) of the 249 patients tested positive for COVID-19. CT determined lung involvement was observed in 71 (28.5%) of the total 249 patients enrolled in the study. When all patients who were positive for COVID-19 were considered, 60.17% had lung involvement. COVID-19 has been shown to contribute to lung complications (i.e., pneumonia or bronchitis) and the potential for severe complications like ARDS (39). Those with chronic lung diseases have a higher risk of severe complications resulting from COVID-19 (40). Interestingly, several reports have demonstrated a link between OP or osteopenia in patients with interstitial lung disease suggesting lung involvement can contribute to the risk of bone resorption complications (41, 42). Others have shown that OP may represent a common comorbidity of COPD (43, 44).

While our study has some strengths, there are several limitations that must be considered. Our study was a retrospective study design with follow-up data for only one year. Even though we enrolled 249 postmenopausal woman with and without COVID-19, our sample size was relatively small. In addition, lung involvement was confined to a broad category and did not include the specifics on the type of involvement (i.e., pneumonia, bronchitis, fluid retention etc). Also, we did not include any controls who were positive/negative for COVID-19 with no history of OP (or low BMD). Therefore, future studies are needed to investigate the findings of COVID-19 on worsening of BMD in OP patients in a larger population. Nevertheless, our study shows that COVID-19 infection results in the progression of BMD loss in patients with a known history OP. More research is needed to identify possible treatment options for improving bone health and preventing COVID-19 infection-related bone complications in the elderly.

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