Clinical Research

Evaluation of PatientsWith Covid-19 Infection in Terms of Severity of Osteoprosis

Ayşe GÜÇ[1,a], Havva TALAY ÇALIŞ[1], Hanife ABAKAY[2], Esra YAPRAK TAŞ[1]

[1]*Kayseri City Hospital, Physical Medicine and Rehabilitation Clinic, Kayseri, Turkey*
[2]*Kayseri University, School of Health Vocational School, Kayseri, Turkey*

ABSTRACT

Objective: Difficulty in accessing osteoporosis treatment during the Covid-19 pandemic period, social isolation, immobilization, steroids used and the inflammatory effects of Covid-19 may contribute to the development of osteoporosis. Therefore, in this study, we aimed to evaluate with quantitative data whether patients with Covid-19 infection pose a risk for the development of osteoporosis.
Material and Method: The study is single-centered. Patients whose Covid-19 infection were retrospectively screened. Bone mineral density measurements were performed before and after Covid-19 infection and female patients over the age of 18 were included in the study. A total of 55 patients were examined. The patients' age, medications used during the Covid-19 treatment process and the number of days spent in the service and/or intensive care unit (ICU) were recorded. Lumbar total T score, femoral neck T score and femur total T scores detected.
Results: A significant relationship was found between the patients ICU stay and the femoral neck T score ($p < 0.05$). As the length of stay of the patients in the ICU increased, a decrease in the femoral neck T score was detected. No significant relationship was detected in other parameters evaluated.
Conclusion: It was found that as the length of stay in the ICU of patients with Covid-19 increased, the femoral neck T score decreased. Keeping ICU stays as short as possible in patients infected with Covid-19 may be beneficial to reduce hip osteoporosis.
Keywords: *Osteoporosis, Covid-19, Corticosteroid, Bone Mineral Density.*

ÖZ

Covid-19 Enfeksiyonlu Hastaların Osteoporoz Şiddeti Açısından Değerlendirilmesi
Amaç: Covid-19 pandemi tedaviye erişimde zorluk, sosyal izolasyon, hareketsizlik, kullanılan steroidler ve Covid-19'un inflamatuar etkileri osteoporoz gelişimine katkıda bulunabilir. Bu nedenle, bu çalışmada, Covid-19 enfeksiyonu olan hastaların osteoporoz gelişimi için risk oluşturup oluşturmadığını nicel verilerle değerlendirmeyi amaçladık.
Gereç ve Yöntem: Çalışma tek merkezlidir. Covid-19 enfeksiyonu olan hastalar retrospektif olarak tarandı. Kemik mineral yoğunluğu ölçümleri Covid-19 enfeksiyonundan önce ve sonra yapıldı ve 18 yaş üstü toplam 55 kadın hasta çalışmaya dahil edildi. Hastaların yaşı, Covid-19 tedavi sürecinde kullandıkları ilaçlar ve serviste ve/veya yoğun bakım ünitesinde (YBÜ) geçirdikleri gün sayısı kaydedildi. Lomber total T skoru, femur boyun T skoru ve femur total T skorları kayıt edildi.
Bulgular: Hastaların yoğun bakım ünitesinde kalış süresi ile femoral boyun T skoru arasında anlamlı bir ilişki bulundu ($p < 0,05$). Hastaların yoğun bakım ünitesinde kalış süresi arttıkça femoral boyun T skorunda azalma tespit edildi. Değerlendirilen diğer parametrelerde anlamlı bir ilişki tespit edilmedi.
Sonuç: Covid-19'lu hastaların yoğun bakım ünitesinde kalış süresi arttıkça femoral boyun T skorunun azaldığı bulundu. Covid-19'lu hastalarda yoğun bakım ünitesinde kalış süresinin mümkün olduğunca kısa tutulması kalça osteoporozunu azaltmak için faydalı olabilir.
Anahtar Sözcükler: *Osteoporoz, Covid-19, Kortikosteroid, Kemik Mineral Yoğunluğu.*

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ORCID IDs: A.G. 0000-0003-2552-1403, H.T.Ç. 0000-0002-8897-8921, H.A. 0000-0003-4047-7965, E.Y.T. 0000-0003-1214-4901.

Osteoporosis is a chronic condition that reflects decreased bone strength and the associated increased risk of fractures. Etiology includes age, gender, low body mass index, fragility fracture history, corticosteroid (CS) use, immobilization, smoking, alcohol use, endocrine pathologies, inflammatory and infectious pathologies (1, 2).

Infectious causes are among the rarer causes of osteoporosis. Along with infectious and inflammatory diseases in the body, proinflammatory cytokines, especially TNF-α and interleukin IL-17A made by T cells, have pro-resorptive effects (3). For example, in patients with chronic HIV infection, hepatitis B and C infection, a decrease in bone mass is observed with the effect of IL-17 (3-5). Bone resorption increases with proinflammatory cytokine increase in rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, periodontitis and multiple myeloma. In fact, in postmenopausal osteoporosis, the increase in proinflammatory cytokines with the withdrawal of estrogen is

[a]Yazışma Adresi: Ayşe GÜÇ, Kayseri City Hospital, Physical Medicine and Rehabilitation Clinic, Kayseri, Turkey
Tel: 0551 694 0038 e-mail: ayseatilabey@gmail.com
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associated with bone resorption (6).
Difficulty in reaching osteoporosis treatment during the pandemic period, social isolation, confinement to homes, immobilization with hospitalization and steroids used in the treatment, as well as the inflammatory effects of Covid-19 may contribute to the development of osteoporosis. However, as far as we know, there is no study on this subject in the literature. The studies of Covid-19 infection related to osteoporosis are in the form of how the osteoporosis follow-up of the patients should be during the pandemic period, how should the telerehabilitation practices in osteoporosis patients be (7, 8). Since there is no study that quantitatively evaluates whether the severity of osteoporosis increases in patients with Covid-19, we aimed to evaluate patients with Covid-19 infection with quantitative data whether they pose a risk for the development of osteoporosis.

MATERIAL AND METHOD

The study was conducted in accordance with the Declaration of Helsinki, and the necessary Ethics Committee approval was obtained from the Kayseri City Hospital Clinical Research Ethics Committee (decision No: 540).
The study was carried out in a single center at the Physical Medicine and Rehabilitation Clinic of Kayseri City Hospital. The data of patients whose Covid-19 infection was confirmed by polymerase chain reaction tests were retrospectively scanned from the hospital registry system. Afterwards, patients diagnosed with Covid-19 were examined for the development of osteoporosis. Patients who had dual-energy x-ray absorptiometry (DEXA) measurement for bone mineral density (BMD) before and after Covid-19 infection were included in the study (There are many methods of measuring BMD. DEXA is the most commonly used. Detected in DEXA T score is a parameter that shows the severity of osteoporosis (9). The hospital database was reviewed retrospectively when selecting patients. Between August 2020 and July 21, two separate excel files were created for the identification numbers of 17686 patients who had DEXA measurements and 31487 patients who had Covid-19 infection. Then, 536 patients with common identification numbers in both excel files were selected in the computer environment. Of these patients, 18 years old, female patients who were hospitalized for Covid-19, had two DEXA measurements before and after Covid-19, 9-15 months between two DEXA measurements, and whose second DEXA was done at least one month after Covid-19 infection were included in the study. Patients under the age of 18, male, who had a diagnosis other than Covid-19 infection that would affect bone metabolism between the dates of two DEXA shots before and after Covid-19, and who used any other drug other than Covid-19 treatment that would affect bone metabolism were not included in the study. The majority of patients who met the inclusion criteria for our study were postmenopausal women, and the number of male patients was very small. Therefore, we included only female patients in our study. The study was completed with a total of 55 patients who met the inclusion criteria. Thoracic computed tomography has been frequently used in studies evaluating bone mineral density in Covid-19 (10-11). According to our current literature review, we did not find any studies evaluating DEXA in bone mineral density measurement before and after Covid-19, as in our study. Therefore, we evaluated our study as a pilot study and did not perform a power analysis.
The age, additional diseases, medications used, medications used during the Covid-19 treatment process, and the number of days hospitalized in the service and/or ICU of the 55 patients included were recorded retrospectively. Lumbar total T score (lumbar 1-4 vertebra T scores), femoral neck T score and femur total T scores determined in DEXA before and after Covid-19 were compared. Is there an increase in the severity of osteoporosis of patients after Covid-19? Is there a relationship between the treatments given and osteoporosis? Is there a relationship between being treated in the intensive care unit (ICU) or service and the severity of osteoporosis? answers were sought.
The descriptive statistics of the data obtained at the end of the evaluations, with number (n) and percentage (%) values for qualitative data; For quantitative data, the mean, standard deviation (SD), and minimum and maximum values were shown. The conformity of the variables to the normal distribution was tested with Histogram Analysis, coefficient of variation, skewness-kurtosis (skewness and kurtosis), Kolmogorov-Smirnov Test, and "Normal Q-Q Plot" and "Detrended Normal Q-Q Plot". In addition, the relationships between continuous variables were examined by Spearman correlation analysis. In Spearman correlation analysis, r <0.001 (no relation), r =0.01-0.29 (low relation), r =0.30-0.70 (moderate relation), r =0.71-0 Reference ranges were taken as .99 (high correlation) and r =1.00 (excellent relationship). The 'IBM SPSS Statistics Version 22' program was used for all statistical analyzes and the statistical significance level was accepted as $p < 0.05$.

RESULTS

A total of 55 female patients were examined in our study. The median age of the patients participating in our study was 62 (min:47, max:86). Of the patients included in our study, 40 (73%) patients were followed only in the service. 15 (27%) patients were followed up in the ICU (all of our patients with ICU hospitalizations were also hospitalized in the service). The mean age of the patients followed in the ward was not statistically different from the mean age of the patients followed in the ICU ($p > 0.05$).
Two DEXA measurements of patients before and after Covid-19 infection were compared. Lumbar total T score difference, femoral total T score difference and

femoral neck T score difference in two DEXAs were taken.

Thirty of 55 patients had corticosteroid (CS) use. In our study, no statistically significant difference was found in lumbar total T score (p =0,906), femur total T score (p =0,966) and femoral neck T scores (p =0,477) between CS users and non-users (Table 1).

Table 1. *Comparison of CS use and DEXA scores.*

	Median (min-max) or Mean±SD		
	CS*** use + (n*=30)	CS*** use - (n*=25)	p value
Lumbar total T score difference	-2,10 (-3,80-0,80)	-1,90 (-3,80-3,20)	0,906
Femur total T score difference	-0,90 (-2,60-1,30)	-1,10 (-2,20-1,30)	0,966
Femoral neck T score difference	0,11±1,06	0,19±0,67	0,477

:number, **:standart sapma, *: corticosteroid.*

The amount of CS used by the patients during the hospitalization was converted to the equivalent of methylprednisolone, and the total amount of use was calculated. The total methylprednisolone equivalent used was calculated as a minimum of 32 mg and a maximum of 1000mg. The median amount of CS used by patients treated only in the service was 280mg methylprednisolone equivalent, while the median amount of CS used by patients receiving ICU treatment was equivalent to 304mg methylprednisolone. There was no significant difference in the amount of CS used between the patients followed in the service and ICU (p =0,420).

The relationship between the lumbar total T score, femur total T score, and femur neck T score obtained from DEXA scans before and after Covid-19, and the number of days of service treatment, ICU treatment, and the total amount of corticosteroids used for Covid-19 infection, was examined. A significant correlation was found between ICU stay duration and femur neck T score (p =0,003). As the duration of ICU stay of the patients increased, a decrease in the femur neck T score (indicating an increase in osteoporosis severity) was observed. There was no significant difference observed between the total amount of corticosteroids used and the lumbar total T score, femur total T score, and femur neck T score (Table 2).

Table 2. *The relationship between DEXA scores and the number of days hospitalized in the service, the number of days treated in the ICU and the total amount of CS used during the hospitalization period.*

		Lumbar total T score difference	Femur total T score difference	Femoral neck T score difference
Number of days in service	rr	0,18	0,01	0,134
	pp	0,19	0,94	0,333
Number of days in ICU*	rr	0,03	0,01	**-,396****
	pp	0,83	0,95	**0,003**
Total amount of CS** used	rr	0,07	0,04	-0,111
	pp	0,60	0,74	0,420

**: intensive care unit, **: corticosteroid.*

All patients examined in our study were given calcium and vitamin D supplements during their stay in the service and ICU as part of the Covid-19 treatment. Of the 55 patients examined, 28 were not receiving any osteoporosis treatment other than calcium and vitamin D given during their hospitalization. The remaining 27 patients were using antiresorptive or anabolic agents. There was no statistically significant relationship between lumbar total T score (p =0,208), femoral total T score (p =0,462) and femoral neck total T score (p =0,784) between those who use antiresorptive or anabolic agents and those who do not (Table 3) (p >0.05).

Table 3. *Changes in lumbar total T score, femur total T score, and femur neck T score between individuals using osteoporosis-targeted medications (antiresorptive, anabolic drugs) and those not using them.*

	Median (min-max) or Mean±SD		
	non-medicated	medicated	p value
Number of patient	(n*=28)	(n*=27)	
Lumbar total T score difference	-2,80 (-3,40--1,50)	-2,10 (-3,80-3,10)	0,208
Femur total T score difference	0,18 ± 0,49	0,19 ± 0,61	0,462
Femoral neck T score difference	0,21±0,82	0,29±0,89	0,784

**: number.*

Of 27 patients using antiresorptive or anabolic agents for osteoporosis, 6 were using alendronate, 5 were using zolendronate, 15 were using denosumab, and 1 were using teriparatide. No statistically significant difference was found between the drugs used for the development of osteoporosis (Table 4).

Tablo 4. *Change in lumbar total T score, femoral total T score and femoral neck T score according to the osteoporosis drug used.*

	alendronate (n*=6)	zoledronate (n*=5)	Denosumab (n*=15)	teriparatide (n*=1)	p value
Lumbar total T score difference	-0,15 ± 0,22	4,44 ± 0,84	0,12±0,53	0,20	0,456
Femur total T score difference	-0,11 ± 0,40	0,38 ± 1,13	0,21±0,47	0,10	0,462
Femoral neck T score difference	0,83 ± 0,58	0,5 ± 0,95	-0,04±1,14	-0,10	0,784

**: number.*

DISCUSSION

In this study, patients who had experienced a Covid-19 infection were evaluated for the development of osteoporosis, and a comparison was made between the two DEXA measurements conducted before and after Covid-19. A significant correlation was found between the duration of patients ICU stay and femur neck T score (p =0.003). As the duration of ICU stay increased, a decrease in femur neck T score (indicating an increase in osteoporosis severity) was observed. Among the examined patients, there were no statistically significant differences in lumbar total T score, femur total T score, and femur neck T score based on

corticosteroid (CS) usage, total amount of CS used, the number of days treated in the service and/or ICU, use of medications for osteoporosis, and the type of medication used for osteoporosis.

Studies evaluating the severity of osteoporosis in Covid-19 are very limited. Evaluating the impact of Covid-19 on osteoporosis is difficult due to the need for extensive human resources and time-consuming follow-up. Since the hospital where we conducted this study is a comprehensive pandemic hospital and the bed capacity is quite high, the patients were screened retrospectively.

Studies on osteoporosis in Covid-19 mainly focus on how to prevent and treat osteoporosis in Covid-19 patients (7, 8). These studies focus on telerehabilitation, the need for patients to go to the hospital less often, and treatments applied once a year, every 6 months, and every 3 months to reduce contact should be preferred. In our study, the rate of use of zoledronic acid and denosumab was high. We think that this is due to the choice of drugs under pandemic conditions.

A better understanding of the pathogenesis of Covid-19 causing bone loss and knowing whether it increases the severity of osteoporosis is important for the diagnosis, treatment and preventive measures of osteoporosis. Covid-19 infection exerts its effects on humans by binding to the angiotensin converting enzyme 2 receptor (ACE2) (9, 12). Covid-19 infection increases angiotensin 2 levels by blocking ACE2 receptors (11). Angiotensin 2 leads to activation of NF-kappa-B ligand (RANKL) receptor and osteoclasts (14). In addition, increased RANKL/osteoprotegenin ratio has been shown in the serum of patients with acute COVID-19 infection compared to healthy individuals (15). This situation brings to mind the question “Does Covid-19 infection trigger osteoporosis”?

Macrophages and neutrophils, whose levels increase in blood after Covid-19 infection, play a role in limiting osteoclast activation due to inflammation. However, if this inflammation cannot be limited, hyperinflammation and cytokine storm develop. As a result, both osteoclasts are activated and osteoclastogenesis is triggered. Thus, cytokine storm can result in bone loss (16).

In Covid-19 infection, CS have been frequently used to control the cytokine storm. CS may cause CS-related osteoporosis by decreasing osteoblast activation and increasing osteoclast activation (17). In order to consider CS induced osteoporosis, it is necessary to use a minimum of 7.5mg prednisone equivalent daily for at least 3 months (18). In our study, the longest CS use was 18 days. In a systematic review of hospital stays in Covid-19 infection, the length of stay in many clinics did not exceed 20 days. Only in China, lengths of stay of 53 days have been reported (19). For this reason, we think that CS will not cause CS induced osteoporosis since CS are used for a short time in Covid-19 infection. In our study, we did not find a significant relationship between the use of CS and the total amount of CS used, and the lumbar total T score, femoral total T score, and femoral neck T score. We think that the reason for this is that the duration of ICU use of the patients is not very long.

The development of osteoporosis in the femoral neck is important for hip fracture. Hip fracture in patients with osteoporosis is an important cause of morbidity and mortality. In a study conducted in Germany, the rate of hip fracture was found to be 6% in general practitioners and 13% in orthopedists in 2016-2019. These rates increased by 8.3% during the pandemic period (20). In another study, a significant decrease was found in the trabecular area and bone volume in the femur bone of mice infected with Covid-19 infection (15). These two studies suggest that Covid-19 infection may increase the risk of hip osteoporosis and hip fracture. In our study, a significant relationship was found between ICU stay in Covid-19 infection and the development of femoral neck osteoporosis. However, a decrease in bone mineral density was also observed in patients followed in the intensive care unit for a reason other than Covid-19 infection (21). Does Covid-19 increase hip osteoporosis? More work is needed to come to a definite conclusion on this issue.

In several studies conducted during the Covid-19 period, it was found that patients with low bone mineral density had a higher mortality rate than patients with high bone mineral density (22, 23). To the best of our knowledge, osteoporosis is observed in advanced age. With age, immunity decreases, so resistance to infections decreases (24). This situation causes elderly patients to have more severe Covid-19 infection (25). Therefore, clinicians and researchers should pay attention to the connections and interactions between the patient's age, CS use, Covid-19 infection severity, level of immobilization, and the patient's immunity when examining the development of osteoporosis in COVID-19 infection.

If we look at the strengths of our work; It is the first study to quantitatively evaluate patients with Covid-19 in terms of osteoporosis severity with bone mineral density. In our study, besides the Covid-19 history of the patients, the evaluation of parameters that may contribute to osteoporosis such as the use of CS, length of stay in the service and ICU, and treatments for osteoporosis also contributed to the literature.

The limitations of our study are; Our study was done retrospectively. The reason for this was that it was very difficult to conduct a prospective study due to the risk of transmission during the pandemic period. Our other limitations are the lack of a control group that has not experienced Covid-19 infection and the low number of patients.

Conclusions

In our study, it was found that as the length of stay in the intensive care unit of patients with Covid-19 increased, there was a decrease in the femoral neck T score. No correlation was found between the use and amount of CS, the treatment used for osteoporosis, and the number of days in the service and the development of osteoporosis. For patients with prolonged intensive care stay, taking additional measures against osteopo-

rosis (dietary change, early mobilization, calcium-vitamin D supplements, etc.) may be beneficial. In order to understand whether osteoporosis developing in the hip is due to the effect of Covid-19, the length of stay in the ICU or the synergistic effect, studies involving more patients and a control group are needed.

Conflicts of interest
All other authors have no conflicts of interest.
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