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Corticosteroids and rising tide in femoral head avascular necrosis following COVID-19: A critical analysis

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ABSTRACT

Objectives: During the COVID-19 pandemic, increased corticosteroid use to treat severe cases has been linked to a rise in femoral head avascular necrosis (FHAVN) cases post-recovery. This study evaluated FHAVN patients referred to an outpatient clinic after COVID-19, focusing on the severity of FHAVN related to corticosteroid use, and aimed to connect the drug dosage, and disease grade.

Methods: The study was prospectively designed. Patients diagnosed with FHAVN who received corticosteroids for COVID-19 were included. Data collected included demographic information, medical history, corticosteroid dosage, and magnetic resonance imaging results for radiological grading.

Results: A total of 48 patients were evaluated, with a mean age of 46.13 years. A significant majority (81.3%) of the respondents had bilateral FHAVN. The patients received a mean prednisolone equivalent dose of 1295.16±857.98 mg over approximately 18 days. This study found a significant positive correlation between the severity of FHAVN and the dosage and total corticosteroid treatment time.

Conclusions: The findings indicate that the severity of FHAVN is correlated with corticosteroid use. Although corticosteroids have shown benefits in severe COVID-19 cases, their prolonged and high-dose administration poses risks, including the development of FHAVN.

Keywords: Avascular necrosis, corticosteroids, COVID-19

Femoral head avascular necrosis (FHAVN) is an aseptic osteonecrosis resulting in osteocyte death due to impaired blood supply to the proximal femur. FHAVN can occur due to ischemia in a traumatic or non-traumatic background. The most common etiological factors are corticosteroid therapy, fractures, hip joint dislocation, and alcohol abuse. It typically affects physically active individuals between 20 and 40 years old. Symptoms of this condition usually include hip pain, limited range of motion, and

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limping [1]. Non-traumatic osteonecrosis of the femoral head is one of the leading causes of disability in young individuals and results in significant healthcare expenditure [2].

Corticosteroids are widely used to treat rheumatic, autoimmune, and allergic diseases. Mechanisms such as impaired microcirculation in the femoral head, imbalance between osteogenic and adipogenic differentiation, fat embolism, coagulation disorders, and intramedullary pressure change have been proposed for the pathophysiology of FHAVN caused by corticosteroids. Among the various mechanisms of steroid-induced FHAVN, the vascular hypothesis is the most compelling and influential. Bone endothelial cells, which include bone microvascular endothelial cells and endothelial progenitor cells, play a crucial role in maintaining vascular homeostasis. Therefore, these bone endothelial cells are key regulators in both the occurrence and progression of steroid-induced FHAVN. Dysfunction of bone endothelial cells can lead to impaired angiogenesis, abnormal apoptosis, thrombosis, and fat embolism, all of which are considered to contribute to the pathogenesis of steroid-induced FHAVN [3].

During the COVID-19 pandemic, corticosteroids were extensively used to slow down the pulmonary inflammatory cascade and prevent cytokine storms in severely ill patients. However, a significant proportion of patients who survived steroid treatment developed avascular necrosis with rapid and aggressive destruction of the femoral heads [4-6]. The long-term consequences of COVID-19, including unfavorable non-pulmonary complications following recovery, have created a physical, psychological, and financial burden on patients, relatives, and healthcare systems [7-9].

This study aimed to assess FHAVN patients referred to our outpatient clinic after the COVID-19 pandemic. The principal objective of this study was to understand the severity of FHAVN caused by corticosteroid use in patients with COVID-19 and to establish a connection between the drug dosage, total corticosteroid treatment time, and disease stage. Our secondary objective was to conduct a comprehensive review of the existing literature and evaluate the scientific and rational basis for the dosage and duration of corticosteroids used to treat severe cases of COVID-19. In addition, we sought to provide recommendations to minimize the risk of FHAVN in similar scenarios in the future.

METHODS

The study was initiated after approval from the Kayseri City Hospital Clinical Research Ethics Committee (Decision no: 738 and date: 08.11.2022). The sample size was determined to be 45, with a power of 80% (beta) and a type I error rate of 0.05 (alpha). This calculation was performed using the G*Power software (version 3.1.9.7, 2020) developed by the University of Düsseldorf, Germany, for Windows 10 with references from similar studies in the literature. Patients referred to our outpatient hyperbaric medicine clinic between November 2022 and November 2023 who were clinically and radiologically diagnosed with FHAVN and received corticosteroid treatment due to COVID-19 were prospectively included in the study. COVID-19 diagnosis was made objectively by scanning past patient information through the hospital automation system and seeing PCR test positivity. Also, the patient's corticosteroid treatment was determined objectively by scanning the patient's past hospitalization information through the hospital automation system (time to start corticosteroid treatment, corticosteroid dose, and duration of corticosteroid treatment). Before their involvement in the study, all patients were provided with a comprehensive document delineating the study objectives and procedures. Patients were invited to raise any queries about the document's contents, and their signatures were obtained to indicate their willingness to participate in the study.

The following data were included in the study: age, gender, height, weight, body mass index, smoking habit, history of COVID-19 infection, and use of corticosteroids. The time interval between the onset of FHAVN symptoms and the diagnosis of COVID-19 was documented. The duration and dosage of corticosteroid therapy received by patients with COVID-19 infection treated with corticosteroids were also recorded. The doses of dexamethasone and methylprednisolone administered to patients were converted to prednisolone equivalent doses according to the formulas we present below for comparison with other

steroids. In this calculation, prednisolone and prednisone are typically considered equivalent, and 5 mg of each equals. Other conversions include: 4 mg of methylprednisolone, 0.75 mg of dexamethasone, and 20 mg of hydrocortisone, all equivalent to 5 mg of prednisolone [10].

To ensure standardization, radiological FHAVN diagnosis was made by a single radiologist experienced in this field and immediately after magnetic resonance imaging of the patients according to the Ficat grading system [11]. In patients with bilateral FHAVN, the side with the higher grade was considered the patient's grade.

Patients who did not undergo MRI, whose corticosteroid doses could not be quantified, who received corticosteroid treatment for both COVID-19 and other reasons, and who had a confirmed diagnosis of COVID-19 infection but did not receive corticosteroids as a result of that infection were excluded from the study.

Statistical Analysis

The data collected from the study were analyzed using the SPSS 24.00 software. Descriptive statistics were calculated, such as mean, median, percentage, and number of observations. The Kolmogorov-Smirnov test assessed whether the data followed a normal distribution. For normally distributed measurements, an independent groups t-test was applied for data sets comprising two groups. One-way ANOVA and Kruskal Wallis tests were used to compare more than two groups. Post hoc analysis of significance between Ficat grade groups was performed with one-way ANOVA and post hoc Tukey's test according to the homogeneity test result. After the Kruskal Wallis test, Bonferroni correction and Mann Whitney U test were used. A p-value of less than 0.05 at a 95% confidence interval was considered significant for statistical significance. In post hoc analysis, significance was accepted as significant at values below 0.017 for Ficat grade subgroups with Bonferroni correction, and adjusted P values were used in other post hoc evaluations. The Chi-square (X2) test was used to compare categorical variables. Pearson's and Spearmen's correlation analysis examined the relationship between patient data and grades. The statistical tests used in creating the tables are stated as footnotes under all tables.

RESULTS

A total of 48 patients were included in the study. Of the patients, the mean age was 46.13±13.33 years and FHAVN was found bilaterally in 81.3% (Table 1). Patients were treated with prednisolone at a dose equivalent to 1295.16±857.98 mg for 17.85±11.88 days.

The correlation between patient data and Ficat grade was analyzed, and a significant positive correlation was found between prednisolone dose and Ficat grade (r=0.379, P=0.008), and a significant positive correlation was found between total corticosteroid treatment time and Ficat grade (r=0.306, P=0.035). The Ficat grade increased with increasing prednisolone dose and total corticosteroid treatment time (Tables 2 and 3, Fig. 1).

A high positive correlation between prednisolone dose and total corticosteroid treatment time was also identified with the Pearson correlation test, r = 0.678 and P<0.001 (Fig. 2). It is determined that the pred-

Table 1. Demographic characteristics and diagnostic profiles of patients

Variables	Data
Age (years)	46.13±13.33
Height (cm)	170.50±9.29
Weight (kg)	84.77±14.21
Prednisolone dose (mg)	1295.16±857.98
Gender, female	17 (35.4)
Smoking habit, yes	8 (16.7)
Location, bilateral	39 (81.3)
BMI (kg/m²)	
< 24.9	9 (18.8)
25-29.9	20 (41.7)
>30	19 (39.9)
Ficat grade	
Grade 2	21 (43.8)
Grade 3	19 (39.6)
Grade 4	8 (16.7)
Total corticosteroid treatment time (days)	17.85 ± 11.88

Data are shown as mean±standard deviation or median (minimum-maximum) where appropriate. BMI=body mass index

Table 2. Correlation between the severity of the grade and patient data.

Patient data	Grade gegree	
	r	P value
Age	0.177	0.229**
BMI	0.134	0.364**
Height	-0.173	0.240**
Weight	0.033	0.826**
Gender	0.174	0.237*
Smoking habit	0.230	0.116*
Prednisolone dose	0.379	**0.008***
Total corticosteroid treatment time	0.338	**0.019****

BMI_body mass index. r=correlation coefficient.
*Spearmen's rho test, **Pearson correlation test

nisolone dose increases as the total corticosteroid treatment time increases.

The mean time between the start of corticosteroid treatment and FHAVN diagnosis was 10.88±6.29 months. No correlation was found between the time between corticosteroid treatment - FHAVN diagnosis and Ficat grade with an r = 0.080 and P=0.589 (Pearson correlation test).

DISCUSSION

The present study identified a correlation between the severity of FHAVN and increased corticosteroid dose and total corticosteroid treatment time. Corticosteroids are frequently administered to patients with severe COVID-19 during the ongoing pandemic. However, at the onset of the pandemic, several studies raised concerns about the use of corticosteroids in this context [12, 13]. A systematic literature review has indicated that the administration of corticosteroids does not result in a reduction in mortality rates or a decrease in hospitalization durations among patients diagnosed with Severe Acute Respiratory Syndrome (SARS) or Middle East Respiratory Syndrome (MERS) [14]. Studies in this review highlight the importance of corticosteroid dosage and total corticosteroid treatment time. The World Health Organization (WHO) initially issued a recommendation against the routine utilization of corticosteroids for the management of viral pneumonia. This advice was grounded in the understanding that the use of corticosteroids carries with it

Table 3. Relationship between treatment parameters and Ficat grade

Variable	Ficat grade 2	Ficat grade 3	Ficat grade 4	P value
Prednisolone dose (mg)[a]	1013.30 (50.00-2.500.00)	1.352.00 (266.70-4.076.7)0	1.939.46 (793.30-2913.30)	**0.030***
Total corticosteroid treatment time (days)[b]	14.86 ± 7.70	17.16 ± 14.48	27.38 ± 10.38	**0.034****
Time between FHAVN diagnosis and corticosteroid treatment (months)	10.67 ± 7.41	10.42 ± 5.84	12.50 ± 4.11	0.729**

Data are shown as mean±standard deviation or median (minimum-maximum) where appropriate.
*Kruskal Wallis Test, ** One-Way ANOVA test,
[a]Mann Whitney U test, In the subgroup analysis, a difference was identified between Grade 2 and Grade 4 with P=0.010 in favor of group 4.
[b]Tukey's test, In the subgroup analysis a difference was identified between Grade 2 and Grade 4 with P=0.028 in favor of group 4.

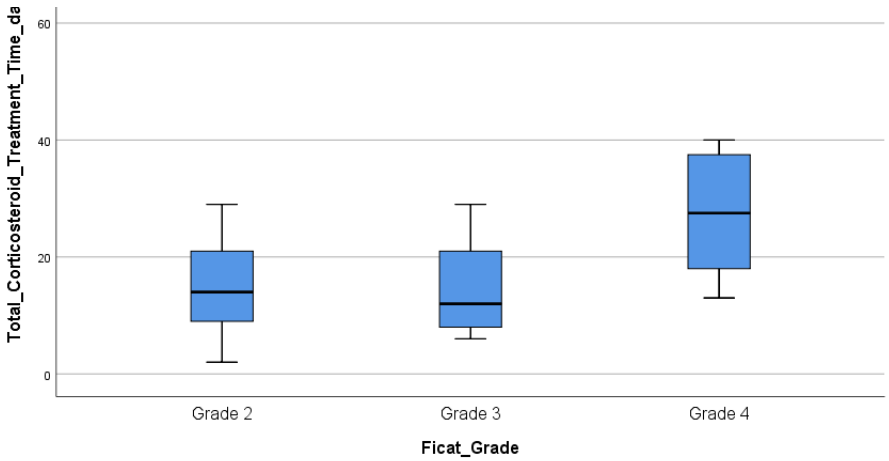

Fig. 1. Histogram showing the relationship between total corticosteroid treatment time (day) and Ficat grade.

a series of potential risks, including the possibility of delayed viral clearance and an elevated mortality risk [15]. Furthermore, the presence of viral RNA was observed to be persistent in patients receiving corticosteroids, indicating a potential delay in recovery.

The publication of the results of the RECOVERY study has precipitated a major shift in the approach to the treatment and study of patients with COVID-19 [16]. Following this development, the WHO recommended administering systemic corticosteroids to patients with severe or critical COVID-19, rather than not administering them [17].

Despite concerns about the use of corticosteroids, some studies suggest that low-dose corticosteroids may lower mortality in patients with severe COVID-19, particularly among those on mechanical ventilation [18]. Moreover, the early administration of corticosteroids in severe cases has been associated with better clinical outcomes [19]. However, administration of high-dose corticosteroids has been associated with an elevated risk of bacteremia [20].

It was highlighted that long-term, high-dose corticosteroid use during the pandemic contributed to the development of FHAVN, underscoring the importance of caution when administering corticosteroids to patients with confirmed or suspected COVID-19 infec-

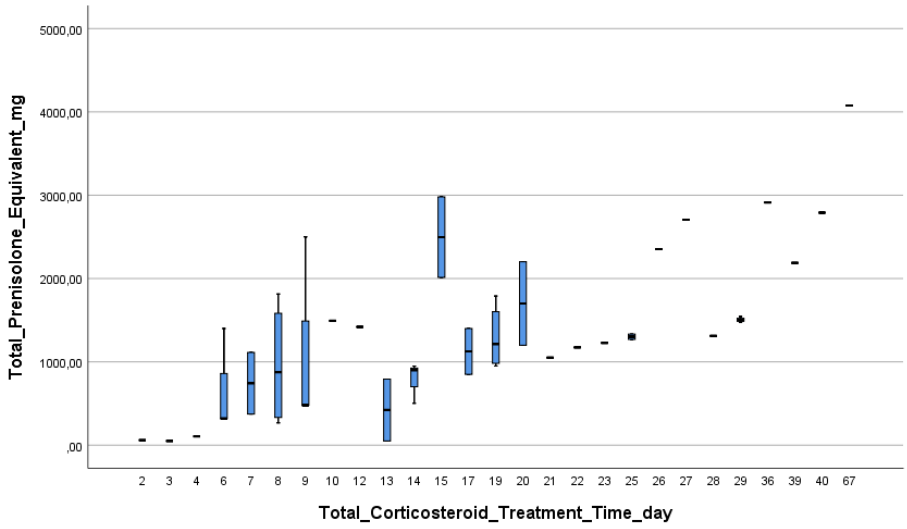

Fig. 2. Histogram of total prednisolone equivalents versus total corticosteroid treatment time (day).

tion. Based on experience following the SARS outbreak in 2003, an incidence of FHAVN from 23% to 28.8% was reported in patients receiving corticosteroids [21]. In a systematic review, individuals who developed FHAVN after COVID-19 used corticosteroids for an average of 24.8±11 days, with a mean prednisolone equivalent dose of 1238.5±492.8 mg. In detail the systematic review analyses 14 studies of which only six mention the steroid dose. Of these six, three report a higher, and the other three report a lower than the steroid dose in our study. Similarly, the total corticosteroid treatment time is presented in nine reports. Seven of them report a longer time than our study [22]. In our study, patients used an average prednisolone equivalent dose of 1295.16±857.98 mg for 17.85±11.88 days. The dosage and the total corticosteroid treatment time vary between studies, and our results do not contradict these findings.

Non-COVID-19 and corticosteroid-induced AVN tend to occur in multiple sites, as shown in studies of SLE patients receiving long-term glucocorticoid therapy. The reported proportion of patients with AVN involving more than two joint sites ranges from 70% to 90% in several case series. Furthermore, the hip was the most common site of involvement, with bilateral hip involvement occurring in 72% of patients [23]. The present study reports an 81.3% bilateral FHAVN rate, which may suggest that the development of FHAVN is not solely dependent on corticosteroids, but may also influenced by other factors in the context of COVID-19 infection. The potential mechanisms contributing to the development of FHAVN in COVID-19 infection include the release of cytokines that inhibit bone cell growth, ACE2 deficiency contributing to bone loss, and a hypercoagulable state caused by systemic inflammation, microthrombus formation, and other factors [24, 25].

It is feasible to avoid the recurrence of this catastrophic outcome in similar circumstances in the future, contingent on a more profound understanding of the disease. It is hypothesized that genetic factors play a significant role in the development of avascular necrosis in patients diagnosed with COVID-19. The utilization of biomarkers may help identify high-risk individuals [26]. In some studies, it is claimed that "the administration of nutritional supplements [27]" or "bisphosphonates, anticoagulants, vasodilators, and traditional Chinese medicine may be considered in combination with extracorporeal shock wave therapy (ESWT), hyperbaric oxygen (HBO), and other physical therapies [21]" could help in reducing the risk of developing FHAVN. Further research in these areas will undoubtedly provide valuable insights.

CONCLUSION

Our study demonstrated that the severity of FHAVN is correlated with the dosage of corticosteroid therapy and total corticosteroid treatment time. Studies examining corticosteroid-associated FHAVN in COVID-19 have identified a high rate of prolonged and high-dose corticosteroid use. In light of this evidence, it seems reasonable to conclude that high-dose and long-term corticosteroid administration may be a riskier approach for treating severe COVID-19-like conditions in terms of the potential risk of FHAVN. Although challenging, implementing personalized treatment strategies and comprehensive evaluation may prove an effective means of preventing a similar post-pandemic FHAVN pandemic in the future.

Ethical Statement

This study was approved by the Kayseri City Hospital Clinical Research Ethics Committee (Decision no: 738 and date: 08.11.2022).

Authors' Contribution

Study Conception: LD, MA, MÖ, MŞT, SK; Study Design: LD, MK, MÖ, MŞT; Supervision: LD, MA, TYU, SK; Funding: LD, TYU, MK, SK; Materials: LD, TYU, MK, SK; Data Collection and/or Processing: LD, MA, TYU, SK; Statistical Analysis and/or Data Interpretation: LD, MÖ, MŞT; Literature Review: LD, MK, MŞT; Manuscript Preparation: LD, MA, MÖ; and Critical Review: LD, MA, TYU, MÖ, MŞT, SK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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