Bisphosphonates for Post-COVID Osteonecrosis of the Femoral Head
Medical Management of a Surgical Condition
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Background: COVID-19 infection can cause long-term effects, cumulatively known as long COVID syndrome. One such sequela is osteonecrosis of the femoral head (also called avascular necrosis of the femoral head, or AVNFH). On the basis of our 20-year experience in using bisphosphonate therapy in the successful management of osteonecrosis, we conducted the present study to evaluate the efficacy of the therapy in the management of post-COVID osteonecrosis of the femoral head. In addition, we aimed to evaluate the cumulative dosage of corticosteroids and the duration between the commencement of corticosteroids and the development of osteonecrosis in COVID-19 survivors.

Methods: This was a retrospective evaluation of 48 patients (88 hips) diagnosed with osteonecrosis of the femoral head at a tertiary care center after COVID-19 infection between September 2020 and May 2021. Patients received intravenous zoledronic acid (5 mg) at the initiation of therapy and oral alendronate (35 mg) twice weekly, and were followed for a minimum of 6 months. Clinical evaluation was conducted using a visual analog scale (VAS) for pain and the Harris hip score (HHS). Radiographic evaluation was performed to assess the progression of the disease and collapse of the femoral head.

Results: At a mean follow-up of 10 months, 84 (95.5%) of the hips showed good clinical outcomes, and only 4 (4.5%) of the hips required surgical intervention. The mean VAS pain score and HHS improved at 6 weeks and steadily improved on subsequent follow-ups. In 16 (18%) of the 88 affected hips, radiographic progression was observed. The mean dose of corticosteroids administered to the patients to manage COVID-19 infection was 841.3 mg of prednisolone equivalents. The mean duration between the commencement of corticosteroid therapy and the development of osteonecrosis was 179 days.

Conclusions: Post-COVID osteonecrosis appears to be more aggressive, with COVID-19 itself contributing to its etiopathogenesis in addition to corticosteroids. However, it can be diagnosed by magnetic resonance imaging (MRI) in symptomatic patients and then effectively treated medically, especially if detected in the early stages.

Level of Evidence: Prognostic Level III. See Instructions for Authors for a complete description of levels of evidence.

COVID-19 survivors may struggle with several long-term effects as a consequence of the infection. NICE (U.K. National Institute for Health and Care Excellence) guidelines define “long COVID syndrome” as the development of symptoms after acute COVID infection and includes both ongoing symptomatic COVID-19 (symptoms developing between 4 and 12 weeks) and post-COVID syndrome (symptoms present for >12 weeks).

Initially, corticosteroids were the only group of drugs demonstrated to be lifesaving in managing moderate and severe COVID-19 infection. Hence, they were used extensively in the first and second COVID waves worldwide. However, one known complication of corticosteroid use is osteonecrosis of the femoral head (also called avascular necrosis of the femoral head, or AVNFH). Our group was the first, to our knowledge, to report on the development of osteonecrosis of the femoral head in COVID-19 survivors. We reported on 3 cases of osteonecrosis of the femoral head after a mean duration of 58 days following COVID-19 diagnosis. We found that those who had COVID-19 infections were susceptible to the development of femoral-head osteonecrosis at a lower threshold dose of corticosteroids, and that the onset of osteonecrosis was earlier, compared with cases documented in the literature. We also found that bisphosphonate combination therapy was beneficial and improved outcomes for these patients. However, that was a preliminary case series of 3 cases with short-term follow-up. Therefore, the actual burden of post-COVID osteonecrosis remains unknown.

Disclosure: The Disclosure of Potential Conflicts of Interest forms are provided with the online version of the article (http://links.lww.com/JBJSOA/A437).
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Osteonecrosis is still unclear. The potential etiological factors and long-term outcome of bisphosphonate therapy in post-COVID osteonecrosis need further evaluation.

The primary objective of the present study was to assess whether bisphosphonate combination therapy effectively improves clinical outcomes, preventing collapse of the femoral head as evidenced on radiographs, the progression of osteonecrosis, and the need for surgery in patients with post-COVID osteonecrosis. The secondary objectives were to evaluate the mean duration between the commencement of corticosteroids and the development of osteonecrosis, and the mean cumulative dosage of corticosteroids administered to the patient to manage COVID-19 infection.

Materials and Methods

In this retrospective study, we evaluated the data of patients with osteonecrosis of the femoral head diagnosed at a tertiary care center between September 2020 and May 2021. Patients who developed osteonecrosis following a confirmed history of COVID-19 infection, and who had a minimum follow-up of 6 months, were included. Patients with Ficat and Arlet stage-IV osteonecrosis and contraindications to bisphosphonate therapy were excluded. The study was reviewed and approved by our institution's ethics committee.

Fifty-one patients (93 hips) who met the above inclusion criteria presented to us during the study period. Two patients (4 hips) with an intolerance to bisphosphonate therapy and 1 patient (1 hip) who was lost to follow-up were excluded. A total of 48 patients (88 hips) were ultimately included.

Assessment

Demographic data, the total dose of corticosteroids administered during and after hospitalization, and the time interval between COVID-19 infection and hip pain were recorded. Clinical assessment was conducted using a visual analog scale (VAS) for pain and the Harris hip score (HHS)•. Radiographic assessment was performed using radiographs of the pelvis with anteroposterior and frog-leg lateral views of both hips. Magnetic resonance imaging (MRI) was performed at the first visit and repeated at 6 months and 1 year. Ficat and Arlet grading was used to stage the disease•.

All patients were seen at 6 weeks, 3 months, 6 months, and every 6 months thereafter. Patients were assessed clinically with the VAS and HHS and radiographically for staging, progression, and collapse at each follow-up. Clinical failure was defined as the need for surgical intervention based on patients' pain and disability. Radiographic progression was considered to have occurred when the osteonecrosis had progressed by 1 to 2 Ficat and Arlet stages. Radiographic collapse was defined as the progression of osteonecrosis from Ficat and Arlet stage I or II to stage III (the collapse stage).

Medical Management

Patients received bisphosphonate therapy according to the following protocol: intravenous zoledronic acid (ZA) injection (5 mg) at the initiation of therapy and oral alendronate (35 mg) twice a week along with calcium (1,000 mg) and vitamin D3 (800 IU) daily•. Analgesics were prescribed according to patient need. Partial weight-bearing with elbow crutches or a walking stick was recommended for the first 3 months, and weight-bearing was increased as tolerated by the patient.

Source of Funding

No external funding was received for this study.

Results

A mean follow-up of 10 months (range, 6 to 13 months), 84 (95.5%) of the 88 hips had good clinical outcomes and did not require any surgical intervention. Clinical failure necessitating total hip arthroplasty occurred in 2 (3%) of the 66 stage-II hips and in 2 (22%) of the 9 stage-III hips. No patient with a stage-I hip required total hip arthroplasty.

Clinical outcomes with respect to the VAS pain score and HHS are presented in Figures 1 and 2, respectively. The mean VAS pain score improved from 7.03 at presentation to 3.13 at 6 weeks. The HHS improved from 59.14 to 71.01 at 6 weeks. Mean VAS and HHS values steadily improved on follow-up. Clinical outcomes improved for all stages of osteonecrosis after the commencement of therapy.

Radiographic progression was observed in 16 (18%) of the 88 affected hips at a mean follow-up of 10 months (Table I). Progression by 2 stages was seen in 1 hip, and progression by 1 stage was observed in 15 hips. Seven (54%) of the 13 stage-I hips, 8 (12%) of the 66 stage-II hips, and 1 (11%) of the 9 stage-III hips demonstrated progression. Nine (10%) of the 88 hips showed radiographic collapse, i.e., progression to stage III. One case of radiographic collapse was observed in a stage-I hip, while the rest of the hips were stage II. Figures 3 and 4 show two case examples with resolution of bone-marrow edema and stabilization of the disease and no radiographic progression after commencement of bisphosphonate therapy.

The mean dose of corticosteroids administered to the patients to manage COVID-19 infection (during the hospital admission and after discharge) was 841.3 mg (range, 100 to 3,520 mg) of prednisolone equivalents. The mean duration between the commencement of corticosteroid therapy and the development of osteonecrosis was 179 days (range, 59 to 459 days).

Discussion

The public discourse on COVID-19 has primarily centered around those with a severe or fatal illness. However, even after recovery from COVID-19 infection, people may experience symptoms defined as long COVID syndrome. From an online survey of 3,762 people diagnosed with COVID-19 infection, Davis et al. concluded that, in the majority (close to 90%), the final recovery from COVID exceeded 35 months•. The long-term effects of COVID-19 infection may be due to the virus's direct effect on the body, symptoms that may develop because of lifestyle modification or prolonged hospitalization, medications, or a combination of the above. Bone aches, joint pains, muscle aches, and spasms are a few of the most common musculoskeletal-related complications•. Our study focuses on one of the long COVID-related musculoskeletal complications, namely, osteonecrosis.
Our group previously reported on 3 cases of osteonecrosis of the femoral head following COVID-19 infection. We concluded that the development of osteonecrosis in the case series could be due to the use of corticosteroids for COVID-19 management. We also reported that, in comparison to cases in the literature, osteonecrosis in COVID-19 occurred with a smaller dose of corticosteroid usage (mean, 758 mg [range, 400 to 1,250 mg]) and had an earlier presentation. Dhanasekararaja et al. reported on a series of 22 patients who recovered from COVID and who developed osteonecrosis of the femoral head after the use of corticosteroids in COVID management.

The risk of corticosteroids with respect to the development of osteonecrosis depends on the daily dose, cumulative dose, maximum dose, and route of administration as well as underlying disease states. The mean dose of corticosteroids administered prior to the development of osteonecrosis of the femoral head was typically >2 g of prednisolone equivalents.

In the present study, the average dose of corticosteroids taken by patients was 841.3 mg (range, 100 to 3,520 mg). This dose is substantially less than the mean dose of corticosteroids associated with the development of osteonecrosis in the general population. The duration between the initiation of corticosteroid intake and the development of osteonecrosis was >1 year as reported in the literature. In the present study, we found that the mean duration between the initiation of corticosteroid therapy and the development of osteonecrosis was 179 days (range, 59 to 459 days).

As the duration and the dose of corticosteroids in the present study are much less than those documented in the literature, other possible factors may play a role in the pathogenesis of osteonecrosis following COVID-19 infection. The probable etiopathogenic mechanisms leading to the development of osteonecrosis may be (1) a hypercoagulable state and thrombotic complications, which have been documented and are seen in...
almost 79% of patients with COVID-19 infection\textsuperscript{15}; (2) direct endothelial injury\textsuperscript{15}; (3) microvascular microthrombi triggering active tissue factor expression on macrophages and endothelial cells\textsuperscript{15}; (4) complement pathway activation causing a hypercoagulable state in COVID-19 infection\textsuperscript{16}; and (5) mast cell activation syndrome\textsuperscript{7,17}.

Of these proposed mechanisms, a hypercoagulable state in itself has been documented to be a risk factor for the development of osteonecrosis\textsuperscript{18}. From their case series of 10 patients, Sulewski et al. concluded that COVID-19 infection alone might represent a risk factor for the development of osteonecrosis of the femoral head\textsuperscript{19}. Symptomatic osteonecrosis of the knees has also been reported in patients who have recovered from COVID-19\textsuperscript{20}.

The treatment for osteonecrosis is directed at pain relief, preventing joint collapse and the development of arthritis, and preventing clinical-radiographic progression of the disease. Various treatment modalities ranging from conservative to surgical approaches are utilized.

| TABLE 1 Stage-wise Radiographic Progression, Collapse, and Clinical Failure Rate |
|---------------------------------------------|
| Ficat and Arlet Stage at Commencement of Treatment | No. of Affected Hips at Presentation | No. of Hips Showing Radiographic Progression | No. of Hips Showing Radiographic Collapse | No. of Hips that Underwent Surgery |
|---------------------------------------------|
| I 13 | 7 (54%) | 1 (8%) | 0 |
| II 66 | 8 (12%) | 8 (12%) | 2 (3%) |
| III 9 | 1 (11%) | — | 2 (22%) |
| Total 88 | 16 (18.2%) | 9 (10.2%) | 4 (4.5%) |

Fig. 3
A 40-year-old male patient with post-COVID osteonecrosis of the left hip. Fig. 3-A Anteroposterior radiograph at presentation showing Ficat and Arlet stage-II osteonecrosis (black arrow). Fig. 3-B T2-weighted MRI at presentation showing the sector of osteonecrosis and bone-marrow edema (yellow arrowheads). Fig. 3-C Anteroposterior radiograph at 1 year of follow-up showing stabilization of the osteonecrosis at Ficat and Arlet stage II (black arrow). Fig. 3-D T2-weighted MRI at 1 year of follow-up showing almost complete resolution of the bone-marrow edema (yellow arrowheads).
have been described in the literature. Medical therapies described in the past, such as iloprost, nifedipine, and hyperbaric oxygen, have not been shown to be of benefit. Therefore, surgery remained the mainstay of treatment. Many studies have shown improvement in outcomes following bisphosphonate therapy in the early stages of the disease.

In a 20-year study of the medical management of osteonecrosis, we found that bisphosphonate therapy effectively improves clinical outcome, halting disease progression and precluding the need for surgery. At a mean follow-up of 69 months (range, 37 to 105 months), 88.9% of hips in the combination treatment group did not require surgical intervention. The clinical failure rate was 5% for stage I, 9% for stage II, and 32% for stage III, emphasizing the importance of early diagnosis. A significantly better improvement was observed in the VAS score at 6 weeks (from 7.10 to 3.66) in the combination treatment group compared with the alendronate treatment group. The follow-up duration in the study exceeded that of any other study, allowing us to conclude that bisphosphonates given for 3 years maintain their benefit for up to 18 years in some patients. Our group also previously reported good clinical outcomes with the use of bisphosphonate therapy in the management of post-chemotherapy osteonecrosis of the femoral head in young adolescents with acute lymphoblastic leukemia.

Our findings in the current study suggest that bisphosphonate combination therapy is effective in the early outcome period in post-COVID patients with osteonecrosis. This study of osteonecrosis of the femoral head in survivors of COVID-19 is, to our knowledge, the first and largest such series, and we found that osteonecrosis is possibly an important musculoskeletal component of long COVID syndrome and contributes to substantial morbidity and prolonged recovery from COVID-19. We have also shown that bisphosphonate therapy is highly effective in post-COVID osteonecrosis. A shortcoming of this study is the lack of case and control groups for comparing the pathogenesis of osteonecrosis and the effectiveness of bisphosphonate therapy for osteonecrosis in patients after COVID compared with those who did not have COVID. In spite of this limitation, the study establishes the prevalence of osteonecrosis in patients after
COVID and the effectiveness of bisphosphonate therapy in its management. Therefore, we believe that this study will be crucial in improving awareness of post-COVID osteonecrosis and its early detection and management within the medical community, ultimately benefiting patients.

Conclusions
In symptomatic patients, post-COVID osteonecrosis of the hip can be diagnosed early by MRI and treated successfully by medical means, avoiding surgical intervention. Our findings suggest that post-COVID osteonecrosis may have a more aggressive course and presents earlier compared with other etiologies of osteonecrosis reported in the literature. COVID-19 infection and the use of corticosteroids to treat it could contribute to the aggressive nature and presentation of osteonecrosis. The combination of intravenous ZA and oral alendronate provides early pain relief and halts the clinical and radiographic progression of osteonecrosis. The 4 hips in the present study that required surgical management presented very early after COVID infection but progressed rapidly. While the world focuses on the pernicious aspect of this viral infection, we seek to bring relief to the survivors facing its long-term effects in the hip. On the basis of our findings, we believe that the described medical regimen is the best way to treat this debilitating condition of post-COVID osteonecrosis.

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