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# Avascular Necrosis of the Hip Joint and Femoral Head Related with Long COVID-19 or Post-COVID-19: Case Report Study

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## Abstract

**BACKGROUND:** Post-COVID conditions can include a wide range of ongoing health problems. As a consequence of long COVID-19 or post-COVID-19 an increase in osteonecrosis has been detected in different series of patients.

**CASE PRESENTATION:** We present two patients diagnosed with COVID-19 and pneumonia, one with moderate and the other with severe clinical picture. They were treated with corticosteroid equivalent to prednisolone 993.5 mg (400–1587 mg) which correlates with steroid dose documented in the literature as causative for avascular necrosis (ANV) in patients with COVID-19. After the mean time of 65 days, due to pain in the groin and difficulty in movement, magnetic resonance imaging (MRI) was performed in both patients and AVN was diagnosed. Compared to our results, the literature records a longer time required for the development of AVN in patients without COVID-19, which is 6–36 months. This indicates the potency of the virus itself to cause disturbances in the microcirculation, and thus the development of AVN. The bone damage correlates with the degree of inflammation and the severity of the clinical picture.

**CONCLUSION:** After a course of COVID-19 as part of a long COVID-19, ANV should be considered a possible complication, especially in patients who have clinical manifestations. Early detection of AVN and diagnosis using MRI on clinical suspicion would help early intervention with bisphosphonate therapy in patients with osteonecrosis of the hip. If the disease is detected in the more advanced stage, it is necessary to perform a surgical intervention and even a possible hip replacement.

## Introduction

A novel coronavirus named as SARS-Cov-2 by WHO is the cause of the current pandemic that began in December 2019 in Wuhan City, Hubei Province, China. More than 766,895,075 individuals had been infected with COVID 19 from which 6,935,889 were fatal, according to the data from May 24, 2023 [1].

The pandemic of coronavirus disease 2019 (COVID-19) created huge havoc among global health-care practitioners in terms of the identification of primary disease symptomatology, signs, diagnosis, and management [2]. Its typical clinical manifestations include fever, cough, and shortness of breath, which can progress to pneumonia. This further can deteriorate into a dysregulated immune state characterized by a hyperinflammatory response and a hypercoagulable state, leading to pulmonary and systemic micro- and macro-immunothrombosis, which ultimately may cause multiple organ failure and death [3].

Some people infected with the virus that causes COVID-19 can experience long-term effects from their infection, known as Post-COVID Conditions (PCC) or Long COVID according to the Centers for Disease Control and Prevention. PCC can include a wide range of ongoing health problems; these conditions can last weeks, months, or years [4], [5].

Despite the fact that COVID-19 is classified as a respiratory disease, numerous studies have documented extra-pulmonary manifestations of the disease, making it a widespread public health concern [6], [7]. Emerging evidence suggests that COVID-19 adversely affects different human body systems as a part of long COVID-19, such as the immune system (including but not limited Guillian–Barre syndrome and pediatric inflammatory multisystem syndrome), respiratory system (lung fibrosis and

pulmonary thromboembolism), cardiovascular system (cardiomyopathy and coagulopathy), neurological system (sensory dysfunction and stroke), as well as cutaneous and gastrointestinal manifestation, impaired hepatic and renal function [7]. Mental health in patients with COVID1-19 was also found to be adversely affected [7].

COVID-19 has a 30% prevalence of symptoms related to the musculoskeletal system [6], [8], [9], [10], [11]. Musculoskeletal manifestations of COVID-19 and post-COVID-19 include arthralgia, myalgia, inflammatory arthritis, reactive arthritis, osteoporosis, osteonecrosis of the femoral head and the knee, myositis and myopathies [12], [13], [14], [15], [16], [17]. In SARS-Cov-1, cases of osteonecrosis appeared 3 months–3 years after the infection [9]. After the COVID-19 epidemic, an increase in osteonecrosis has been detected in different series of patients [10], [11], [16], [17]. In the case of COVID-19, the thrombo-inflamatory cascade causes endothelial injury and predisposes microthrombosis [18]. The hypercoagulability state of SARS-CoV-2 infection is also considered a risk factor for osteonecrosis (On) [16], [17], [18].

Corticosteroids are life-saving in the management of COVID-19, however, it is a predisposing factor for the development of avascular necrosis (AVN) [19], [20], [21], [22]. Based on this premise, in view of the large-scale use of life-saving corticosteroids, there could be the appearance of a number of AVN cases as a consequence [19], [20]. Non-traumatic osteonecrosis has been associated with corticosteroid usage, alcoholism, infections, storage disorders, marrow infiltrating diseases, coagulation defects, and some autoimmune diseases [21]. Risk factors for the development of AVN are radiation therapy, and possibly even cigarette smoking. The pathogenesis of non-traumatic osteonecrosis appears to involve vascular compromise, bone and cell death, or defective bone repair as the primary event [21]. Early diagnosis of AVN is important to halt disease progression and prevent subsequent collapse of the femoral head and the need for surgery [16], [21], [23]. More specifically, there is no report of the incidence of femoral head osteonecrosis (FHOn) or other necrosis lesions of the skeleton [10], [11], [12], [16], [17], [22], [23].

Here, we report two cases of symptomatic FHOn after being treated for COVID-19 in a COVID center.

## Case 1 (S.M)

A 50-year-old male patient (head of the economic crime department in the police with a partially sedentary job), a long-time smoker, was diagnosed with COVID-19 on June 24, 2020. The patient's main complaints were fever, malaise, and cough. The nasopharyngeal swab was taken 3 days after the symptoms and was also positive. Because of COVID-19 and pneumonia, the patient was hospitalized from June 27, 2020, to July 17, 2020, in a COVID center with moderate illness. SpO2 levels were 94–97% in room air. From comorbidities, the patient had well-regulated hypertension. Antibiotic therapy, ceftriaxone 2 g/day, and dexamethasone in doses of 6 mg/day during 10 days (total of 60 mg equivalent to 400 mg of prednisolone) was administrated.

Hemostatic findings at first indicated extended activated partial thromboplastin time (aPTT) of 39 s. The rest of the times were within normal limits and normal values of D-dimers. Anticoagulant treatment with Enoxaparin 40 mg sc was prescribed. The next control suggested the return of the aPTT to normal values. After the control check the values of a PTT were shortened, to 23.9 s which indicated hypercoagulability with normal platelet and D-dimer values. According to hemostasis and in consultation with a transfusion medicine specialist, enoxaparine 2 × 40 mg subcutaneously, was given. The parameters that determine the degree of inflammation were: elevated C-reactive protein (CRP) of 80 mg/L, moderately elevated lactate dehydrogenase (LDH) values of 449 U/L, and elevated creatinine kinase (CK) values of 320 U/L. The basic range of laboratory analyses, apart from elevated values of CK 207 U/L, as well as a liver lesion before the end of the hospitalization, with values of alanine aminotransferase 304 U/L and aspartate aminotransferase 76 U/L, the rest were within normal limits, upon discharge from the hospital.

About a month and a half (45 days) after hospitalization or 62 days after COVID-19 was diagnosed, the patient developed strong pain in the left groin and the lumbar region with difficulty in movement. The patient had no history of hip pain before this. During the first examination at the orthopedist, limited abduction was noted in the right hip, in the left hip all movements are limited and accompanied by pain in

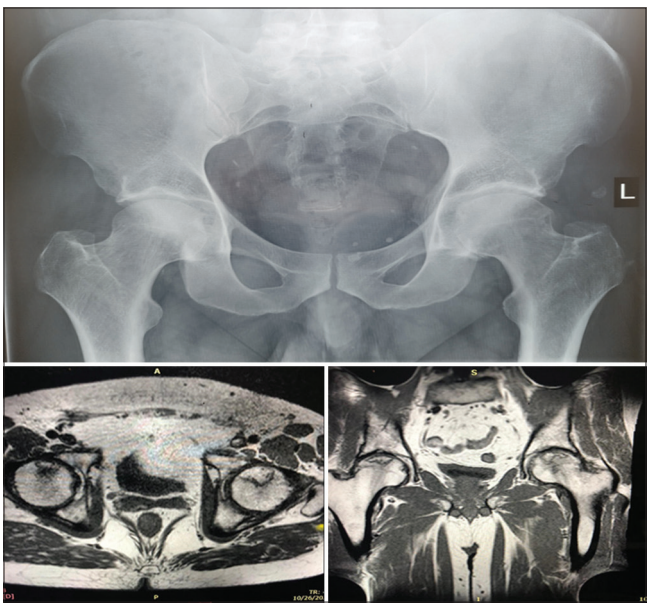


*Figure 1: Anteroposterior radiograph and MRI of the 50-year-old male patient confirming bilateral avascular necrosis of the femoral head (Ficat–Arlet stage I/II)*

all directions. Lasegue sign was positive bilaterally. Magnetic resonance imaging (MRI) of the hip was done (62 days since COVID-19 diagnosis) and showed bilateral hip AVN (Ficat–Arlet stage I-II on both hips) (Figure 1). On MRI, no osteochondral collapse was detected on the heads of both femurs without the presence of surrounding edema, with accompanying synovitis bilaterally.

On the advice of an orthopedist, the patient started therapy with alendronate 70 mg once a week, calcium carbonate 1 g daily, tablet cilostazol 100 mg 2 × 1, and tablet diosmin 1000 mg daily. The patient also underwent therapy in a hyperbaric chamber for 30 days. After a follow-up of 3 months (90 days), there was a reduction in pain from 8 to 3 according to the Visual Analog Scale (VAS) which measures pain intensity. The VAS consists of a 10 cm line, with two endpoints representing 0 ("no pain") and 10 ("pain as bad as it could possibly be").

After 1-year follow-up, the patient has unchanged MRI characteristics with AVN Ficat–Arlet I-II.

## Case 2 (A.A)

A 37-year-old male patient was diagnosed with COVID-19 on January 05, 2021, with a positive nasopharyngeal swab for SARS-Cov-2. The patient is not a smoker, by a professional manager of a private company for trade in plastics (active work with spending a lot of time sitting in a vehicle). The patient was without previous comorbidities. Initially, he was treated in a hospital department for 4 days with ceftriaxone and azithromycin as well as ivermectin. Due to the development of a severe clinical picture with difficulty breathing, dyspnea, and dropping saturation (SpO2 levels in room air < 90%), he was hospitalized in our COVID center from January 11, 2021, to January 25, 2021. He was febrile, with massive bilateral pneumonia, rich lung auscultatory pneumonic findings, with verified hypoxia, hyposaturation, and hypotension on admission. Placed on high-flow mask oxygen therapy. He had hemoptysis for 2 days. He was treated with crystalloid solutions, combined intravenous antibiotic therapy (meropenem, linezolid), and corticosteroids (methylprednisolone 2 mg/kg for 10 days) with a gradual reduction of doses. He received a total of 1270 mg of methylprednisolone iv, equivalent to 1587 mg of oral prednisolone. Coagulation findings indicated thrombocytopenia with a platelet of 100 × $10^9$ L, an easily extended prothrombin time (PT) of 15 s, and D-dimer values of 2073 ng/mL. Therapy with enoxaparin 2 × 80 mg subcutaneously was carried out. The patient had elevated values of CRP 209 mg/L, LDH 620 U/L, and CK 355 U/L.

The patient was with bradycardia and had 38–42 beats per minute. A cardiologist was consulted, an echocardiography was performed without pathological changes, and a computerized tomography of the lungs was performed according to a protocol for pulmonary thromboembolism, which was ruled out. Massive pneumonia with multiple confluent areas of ground glass opacities was verified. He was discharged in an improved general condition with improved laboratory analyses and mild transaminitis.

About 50 days after hospitalization or 68 days after COVID-19 was diagnosed, the patient developed pain in the area of the right groin, that is why he was referred to an orthopedist. The patient had no history of hip pain before this. The pain persisted during rest and at night. During the examination, the movements in the right hip are performed within physiological limits. Noted pain in the region of the trochanteric muscle mass with a feeling of tightness. An MRI of both hips was performed, and in the anterosuperior projection of the right hip, an AVN was seen with surrounding edema of the skeletal structure of the head and neck grade III according to the Ficat–Arlet classification, as well as synovitis (Figure 2).

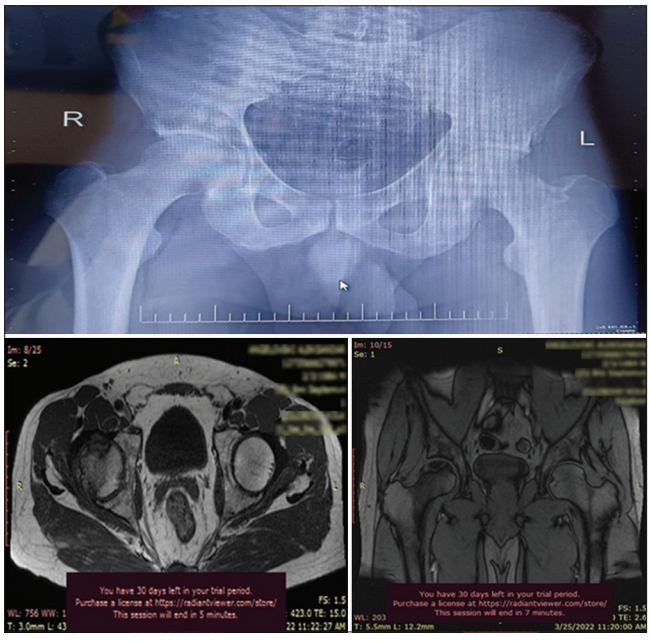


*Figure 2: Anteroposterior radiograph* **and** *MRI of the 37-year-old male patient confirming avascular necrosis of the right femoral head (Ficat–Arlet stage III)*

The patient was initially treated with non-steroidal anti-inflammatory drugs and glucosamine but with minimal pain reduction. According to the VAS scale, pain reduction was from 9 to 8.

After a year, the orthopedist indicated decompression of the head of the femur on the right side. The operation and post-operative course were going well.

## Discussion

ANV most commonly affects the femoral head, but not exclusively. Besides post-traumatic ANV of the femoral head, other sites should also be screened, especially the other hip, the knees, and the shoulders [24].

In our paper, we presented two cases of AVN occurring as a result of post-COVID or long-term COVID-19 infection. Among the first, Agarwala reports three cases in which patients developed AVN of the femoral head after being treated for COVID-19 infection in 2021 [16]. One year later, the same author and his collaborators, published a report on two cases of ANV of the knee as part of a long COVID-19 syndrome [25]. In both studies, patients were treated with corticosteroids in addition to other therapy. Angulo–Ardoy and Ureña–Aguilera from Spain refer a case of a 78-year-old patient with post-COVID necrosis of the knee, after treatment with a total dose of prednisolone 169 mg [26]. Malinowski *et al*. were the first to report two cases of transient spontaneous osteonecrosis of the knee with no corticosteroid administration at all [17]. In February 2022, it was also published article who presented an interesting, rare case of a patient who experienced ANV of the maxilla associated with COVID-19 infection [27]. Two other multicenter studies indicate other musculoskeletal manifestations of COVID-19 [12], [13].

Osteonecrosis has been thoroughly studied since SARS-CoV-1 appeared and is likely to occur after COVID-19. The main risk factor in studies on SARS was the overuse of corticosteroids [9], [28], [29]. Corticosteroids have long been regarded as a predisposing factor for the development of AVN [9], [19], [20].

Steroids can be used in patients with COVID-19, who show progressive deterioration of oxygen saturation, increased activation of the pro-inflammatory response, and rapid worsening of features on chest imagining [30], [31]. Various trials have recorded the beneficial outcome of corticosteroids in decreasing the mortality and morbidity of COVID-19 [32]. In the context of a severe COVID-19 case, where the infection has not been cleared by the initial immune response and has entered the pulmonary phase, the proposed benefit of the introduction of corticosteroids is thought to be due to the downregulation of immune-mediated lung injury and cytokine storm [18]. Methylprednisolone was the first steroid indicated initially [19], [20]. Recently dexamethasone has also been found to be effective for decreasing mortality in severe and critically ill cases [30], [31]. Systemic steroids can affect multiple organ systems and lead to various side effects, and those are generally related to the average dose and duration of treatment [33], [34]. These include immunosuppression with a predisposition to opportunistic infections, osteoporosis, osteonecrosis, fractures, hyperglycemia, promoted insulin resistance, Cushing syndrome or cushingoid features, psychiatric disturbances, hypertension, adrenal suppression, glaucoma, and cataracts [33], [34], [35]. Corticosteroids can directly injure endothelial cells and thus initiate the coagulation cascade [36]. They can induce osteoblast apoptosis and suppress osteoblast-osteoblast production during bone remodeling [10], [37].

However, these issues are dependent on the average dose of corticosteroids and the cumulative duration of treatment. McKee and all, in their study, report 15 male patients with AVN of the femoral head that occurred as a result of a short course of corticosteroid therapy [22]. The mean steroid dose in equivalent milligrams of prednisone was 850 mg (range 290–3300 mg), and the mean duration of drug therapy was 20.5 days (range 7–39 days) [22]. From the administration of steroids to the development of hip symptoms was 16.6 (range 6–33) months [22]. In our trial, the mean value of corticosteroid equivalent to prednisolone was 993.5 mg (400–1587 mg). These values correlate with the previously mentioned values in the paper by McKee [22]. In the study of Agarwala et al., the mean steroid value was 758 mg (400–1250 mg) [16], which also correlates with the values in our study. The mean time from finishing the therapy with steroids to the development of symptoms of AVN in our cases was 45 days in the first case and 50 days in the other case, or a mean value of 47.5 days. In contrast to the time required for AVN to occur in other cases when corticotreatment is used (pneumonia, brain abscess, optic neuritis, asthma, Bell's palsy, and others) is much longer and amounts to 6–36 months [21], [22], [36], [38].

This shorter time for the occurrence of osteonecrosis, except for the influence of corticosteroid therapy, indicates the potency of the SARS-CoV-2 virus itself for osteonecrosis [10], [16], [17]. The study by Malinowski *et al*. indicates that the impact of recent SARS-Cov-2 infection may contribute as a causative factor for osteonecrosis with no corticosteroid administration at all [17]. Osteonecrosis is death on the bone caused by poor blood supply. Complications of COVID-19 include coagulopathy and the virus SARS-Cov-2 has been linked with abnormalities in more coagulation parameters [39], [40], [41]. This is likely driven by a combination of a dysfunctional, hyperinflammatory state, and direct and indirect endothelial injury, ultimately leading to micro-immunothrombosis both in the lungs and systemic tissues [41]. Significant evidence of endotheliopathy and a secondary thrombotic microangiopathy or thrombotic microangiopathy-like phenomenon has emerged. This multisystem microvascular injury in COVID-19 leads to impaired tissue perfusion and ultimately causes ischemic necrosis of the bone. It can be hypothesized that there is an increased risk of spontaneous osteonecrosis of the bone related to COVID-19 [17]. Especially in more severe and critically ill patients COVID-19 associated coagulopathy,

laboratory findings, include a mild prolongation of the PT, increased D-dimers, thrombocytopenia, and disseminated intravascular coagulation [39], [40].

In our study, the first patient with moderately severe disease had hypercoagulability with normal values of D-dimers and platelets. He had less damage, according to the scale of Ficat–Arlet degree I-II, but on the head of both hips [42]. Since the beginning of the hospitalization, he has been on anticoagulant therapy with low molecular weight heparin. In the other patient in our paper, with a severe clinical picture, prolonged PT, low platelets, and elevated D-dimer values were recorded. The findings are the same as in the studies of Di Minno *et al*. and Williams *et al*., which correlate with the severity of the clinical picture and the COVID-19-associated coagulopathy [39], [40]. The damage to the femoral head in this patient is greater according to the scale of Ficat–Arlet grade III. It has been established that even after recovery, heightened systemic inflammatory, and pro-coagulation activity can persist long after the resolution of the index infection which may lead to adverse cardiovascular outcomes in the long-term [7]. In the two treated patients, there is also a difference in the markers of inflammation, especially the values of CRP and LDH. This confirms the theory that the damage correlates with the degree of inflammation and the severity of the clinical picture. CRP and LDH were higher in patients with musculoskeletal symptoms compared to those without musculoskeletal symptoms [13], [32]. One of the potential risk factors for the development of AVN in the first patient is the long-term smoking experience and hypertension. Shetty in 2021 singles out pre-existing factors for the development of AVN, among which is smoking, in addition to alcoholism, cardiovascular or cerebrovascular disease, autoimmune disorders treated with steroids, blood disorders, etc [43].

In the first patient, the therapy with bisphosphonate (alendronate 70 mg once a week) and CaCO3 1 g daily was started. The condition stabilized with pain reduction. The use of bisphosphonates in the treatment of ANV of the femoral head is an encouraging but relatively new option with most published data being derived from small trials with limited follow-up. Agarwala *et al*. in 2009 presented a clinicoradiological analysis of 395 hips with ANV gradus I-II, which were treated with oral alendronate for 3 years, with a mean follow-up of 4 years [23]. The results show an improvement in the clinical function, a reduction in the rate of collapse, and a decrease in the requirement for total hip replacement, compared with the findings of other studies in which no treatment was given [23].

In the second patient, decompression of the head of the right femur was performed. Core decompression improves symptoms and prevents progression and femoral head collapse by reducing subchondral bone marrow pressure and promoting neovascularization with new bone formation. The overall success rate of this procedure is high with pain relief and improved function in the patients [44]. Furthermore, the use of stem cells obtained by bone marrow aspirate concentrate in the treatment of ANV of the femoral head has achieved good functional results and reduced pain in operated patients [45]. If these treatments fail, total joint replacement is advised [44].

## Conclusion

During the COVID-19 pandemic, the health-care system was in chaos with limited functioning indeed. After a course of COVID-19 as part of a long COVID-19, ANV should be considered a possible complication, especially in patients who have clinical manifestations. In particular, it should be taken into account if the patient is treated with corticosteroid therapy, which is used especially in more severe forms of the disease. In this case, the length of the corticosteroid treatment as well as the cumulative dose administered to the patient are also important. More and more cases of ANV of the hip are being described after a documented COVID-19 infection, although other joints, such as other musculoskeletal manifestations, are not excluded. Coagulation disorders as a result of COVID-19 also play a significant role in the occurrence of osteonecrosis. According to the instructions, therefore, timely anticoagulant prophylaxis and therapy should be implemented. The severity of the clinical picture and elevated markers of inflammation are also factors that correlate with the possible occurrence of AVN.

Early detection of AVN and diagnosis using MRI on clinical suspicion would help early intervention with bisphosphonate therapy in patients with osteonecrosis of the hip. If the disease is discovered in the more advanced stage, surgical intervention is inevitable, and sometimes even provides joint replacement surgery. However, to prove these claims, more and of course multicenter trials are needed.

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