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Autologous bone marrow mononuclear cell transplantation for osteonecrosis of the femoral head in post-covid-19 syndrome: A case series

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ABSTRACT

Introduction: The emergence of femoral head osteonecrosis in post-COVID-19 patients, possibly related to corticosteroid use, prompted the search for pathophysiological understanding and minimally invasive treatments, such as autologous mesenchymal cell transplantation.
Methodology: Fifteen patients with post-COVID-19 femoral head osteonecrosis between 2021 and 2023 participated. A total of 100 mL of bone marrow was aspirated and processed using the SEPAX® system. The cells were tested for viability using an anti-CD34 antibody and characterized by flow cytometry and clonogenic assays. Postoperative care involved weight-bearing restrictions and clinical monitoring. This is a case series, level of evidence IV.
Results: Thirteen hips of patients affected by mild to moderate COVID-19 were operated on; 40 % of hospitalized patients did not require mechanical ventilation. 66.7 % received corticosteroids. Necrosis mainly occurred in the right hip, with an average necrotic area of 40 %.
Conclusions: COVID-19 infection and corticosteroid use and duration are related to an increased incidence of osteonecrosis. Patients who did not use corticosteroids also developed osteonecrosis. Treatment with autologous bone marrow progenitor cells reduced pain and improved Harris Hip Score.

1. Introduction

Osteonecrosis of the femoral head (ONFH) is a degenerative disease characterized by the progressive death of osteocytes and bone marrow, resulting in the collapse of the femoral head and potential complete degradation of the hip joint. Its pathogenesis may be explained through three hypotheses, including thrombosis or embolism of functional capillaries, decline in the number of osteogenic cells, and apoptosis of osteogenic stem cells [1,2].

This condition may be caused by several factors, mainly trauma, use of corticosteroids, excessive alcohol consumption, chemotherapy and coagulopathies. [3–5]. This scenario seems to have gained a new predisposing factor following the global COVID-19 pandemic from 2019 onwards.

The current number of new cases and deaths is decreasing; the consequences resulting from the infection, however, are the subject of extensive investigation. Post-COVID-19 syndrome or Long Covid was the name attributed to these sequelae and the clinical findings observed over time, after at least 12 weeks, in COVID-19 patients, and osteonecrosis of the femoral head is suggested as a prevalent sequela [6–10].

The number of cases of osteonecrosis of the femoral head in patients infected by the Sars-CoV-2 virus is evident, whether attributed to the use of corticosteroids as an attempt to fight the increased pulmonary inflammatory process or to the pathophysiological pathways that are not yet well understood. Therefore, we must attempt to understand the relationships between these two conditions and verify the effectiveness of the autologous bone marrow mononuclear cell transplantation technique for the treatment of osteonecrosis of the femoral head secondary to coronavirus infection.

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2. Materials and methods

This study was carried out during 2021–2023 with patients who were diagnosed with osteonecrosis of the femoral head whose symptoms started after coronavirus infection, and who did not present other triggering factors of OCFH, known in the literature, prior to this infection. Patients were selected at the Adult Hip Pathology outpatient clinic at the Universidade Federal da Bahia. Diagnosis was made by plain radiographs and magnetic resonance imaging (MRI). The stage of osteonecrosis was classified using the modified Ficat and Arlet staging system.

The procedures for obtaining bone marrow mononuclear cells (BMMC) were performed in the surgical center environment. Bone marrow collection was performed using a Jamshid needle, inserted into the iliac crest, reaching a depth of approximately 5 cm. Approximately 100 mL of bone marrow was aspirated using 10 mL syringes containing anticoagulant. This sample was processed in the automated and closed SEPAX® system. Cells were counted and tested for viability using anti-CD34 antibody. Cell characterization was performed by flow cytometry, and clonogenic assays evaluated the colony-forming capacity of hematopoietic progenitors and mesenchymal cells.

Using radioscopy, the femoral head was accessed through the lateral aspect of the thigh and a 4.0 fenestrated trephine tube was used to access the area of necrosis (Fig. 1), through which a 40 mL solution containing BMMC was inserted.

After the procedure, partial weight-bearing was allowed for the first 45 days of the postoperative period and muscle-strengthening exercises were not performed for the first 30 days after surgery. Quarterly follow-up visits took place until the 12th month after the procedure. The Harris Hip Score (HHS) was applied on the day of the procedure and at the last follow-up visit.

This study was approved (CAE: 42651121.9.0000.0049) by the Research Ethics Committee of the Professor Edgard Santos University Hospital - UFBA, and the patients signed the Free and Informed Consent Form in accordance with Resolution 466/12.

3. Results

A population of 15 patients with osteonecrosis of the femoral head affected after COVID-19 were enrolled in this study, and a total of 18 hips were evaluated. Four patients were not operated on as they had personally withdrawn from the proposed procedure, one patient declared after surgery that he was using antiretrovirals, and one patient was not located to conduct final evaluation and obtain data for statistical analysis.

Ten (66.7 %) males and five (33.3 %) females took part in the surgical phase of this study, with a mean age of 46.3 years old (±10.3 years old), totaling 13 (43.3 %) operated hips. Race/skin color was self-reported according to the Brazilian census classification: White, Black, and Brown Eleven patients selfidentified their race as brown (73.3 %), two as white (13.3 %), and two as black (13.3 %).

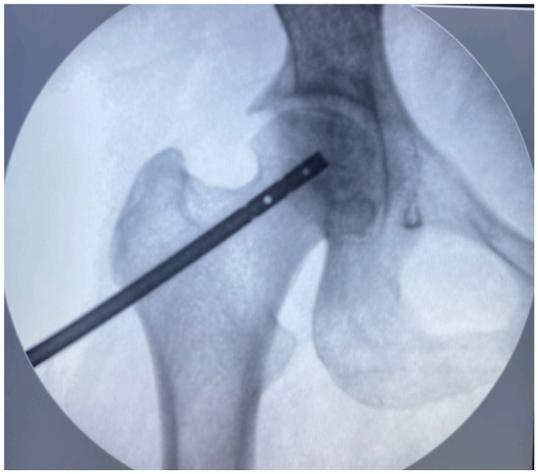

Fig. 1. Radioscopy-guided trephine positioning.

Regarding the characteristics related to infection and illness due to COVID-19, all individuals presented mild to moderate forms of the infection and six (40 %) patients who were hospitalized did not require mechanical ventilation. The mean length of hospital stay was 13.2 days (±4.5 days). Ten individuals (66.7 %) used corticosteroids to treat COVID-19 with an average daily dose of 35 mg of prednisolone and five (33.3 %) patients did not use corticosteroids to treat the infection. This drug was used for at least seven days and up to 60 days. The average use of the corticosteroid was 19 days, resulting in an average accumulated dose of 665 mg of prednisolone. The mean time between the end of coronavirus infection and the onset of hip symptoms was on average 183.3 days (±178.4). The most important demographic and clinical data can be seen in Table 1.

Regarding the specificities related to the necrosis of the femoral head, ten (66.7 %) patients were affected bilaterally, with right-sided involvement predominating in thirteen (86.7 %) patients. As to the classification of osteonecrosis, twelve hips (66.7 %) were classified as grade IIA and Ficat and Arlet, three hips (16.3 %) as grade IIB, and three (16.3 %) hips as III. The necrotic area ratio of the femoral head, analyzed in ten patients who advanced to the surgical phase of this study, was on average 40 % (±12 %).

In post-COVID series, osteonecrosis of the femoral head has manifested with a shorter latency between the index event and symptoms. In Agarwala's classic report, the average was 58 days after infection; other post-COVID cohorts describe similar windows of 30–56 days. In contrast, in corticosteroid-associated ONFH in other conditions, symptom onset typically occurs between 1 and 16 months after initiation of therapy, with a mean of 5.3 months. In our cases, when patients used corticosteroids for the treatment of COVID-19, we observed a mean progression to diagnosis of 8.3 months, compared to cases where no corticosteroids were used, with a faster progression, with a mean of 4.9 months. Although, when observed individually, our case, which progressed more rapidly to bilateral necrosis (15 days), is likely associated with the cumulative dose of corticosteroids used.

A previously healthy 33-year-old woman developed mild COVID-19 and was treated as an outpatient without corticosteroids. Ninety days after diagnosis, she developed significant left hip pain associated with progressive claudication and a HHS of 42.9. Magnetic resonance imaging demonstrated an anterosuperior subchondral lesion, stage IIA (Ficat), without collapse. The lesion was managed surgically, with partial pain improvement and lesion stabilization after final follow-up, and a postoperative HHS of 64.1.

A previously healthy 52-year-old man developed COVID-19 and required hospitalization for 22 days. He received methylprednisolone at a daily dose of 80 mg. Two months after hospital discharge, he underwent bilateral hip transplants. Magnetic resonance imaging revealed bilateral stage IIA osteonecrosis, still without subchondral collapse. Femoral decompression with cellular grafting was performed on both hips. At final follow-up, he maintained good function with a postoperative HHS of 87.6.

A 47-year-old man with no comorbidities or other risk factors presented with mild COVID-19 and was treated as an outpatient with low-dose prednisone (10 mg) for 7 days. He developed bilateral hip pain approximately 7 months after infection. Initial MRI showed bilateral stage IIA osteonecrosis. Despite surgical treatment, the left hip progressed to collapse within 3 months, and total hip replacement was indicated. This was the only hip treated subsequently due to worsening pain and function.

The functional assessment used the HHS to examine the twelve hips that advanced to the final follow-up stage of this study and presented a preoperative mean of 65.4 (±13) and a postoperative mean of 75.9 (±12) (Chart 1) with an average variation between pre-and-

Table 1
Demographic data of individuals included in the study.

Pacient	Gender	Age	Race/skin color	Hospitalization (days)	Daily dose (mg)	Duration of use(days)	Symptoms (days)
Case 1	M	52	Brown	22	80	21	100
Case 2	M	64	Brown	8	80	8	90
Case 3	M	49	Brown	15	20	21	90
Case 4	F	46	Brown	0	20	60	15
Case 5	M	56	Brown	0	20	15	90
Case 6	M	47	Brown	0	10	7	210
Case 7	M	48	White	10	40	10	365
Case 8	M	55	Black	0	0	0	120
Case 9	F	33	Brown	0	0	0	90
Case 10	F	58	Brown	0	0	0	200
Case 11	F	32	White	0	40	15	60
Case 12	F	30	Brown	0	0	0	100
Case 13	M	32	Brown	12	20	18	480
Case 14	M	59	Black	0	0	0	360
Case 15	M	34	Brown	15	20	20	380

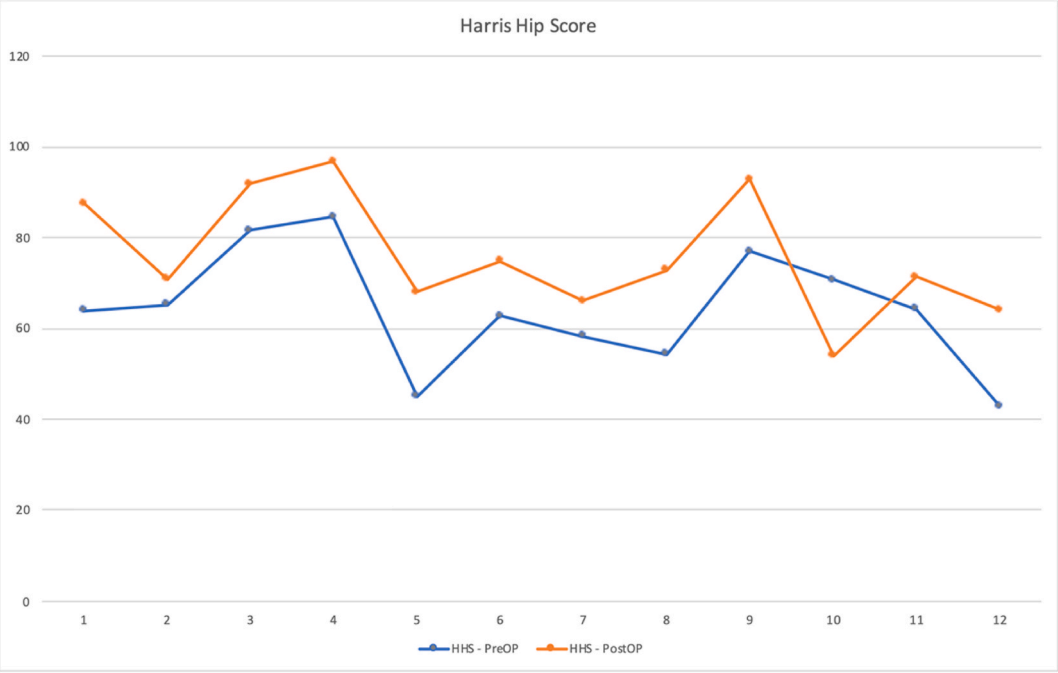

Chart 1. Pre-and-postoperative HHS distribution.

postoperative measurements of 12.1 positive points. One of the operated hips (8.3 %) developed worsening HHS, leading the patient to undergo total hip arthroplasty 6 months after the initial procedure.

Chart 2 describes the interfaces between the variables studied. Consequent relationships between the length of time of corticosteroid use and the ratio of the necrosis of the femoral head were found, as well as other factors, such as the corticosteroid dose and patients' age, and the scores before and after HHS.

Qualitatively, when asked about the current condition of the hip, ten (76.9 %) reported they felt better, one (7.6 %) reported no change, one (7.6 %) did not respond, and one (7.6 %) reported they felt worse.

4. Discussion

ONFH can be caused by several conditions that result in compromised microvascular circulation in the femoral head. Factors such as mechanical interruption of blood flow or extracellular compression, as a result of lipid accumulation in the bone marrow, associated with the prolonged use of corticosteroids, are important. More recently, we observed patients with complaints related to osteonecrosis after developing COVID-19, without association with other known etiological factors.

The COVID-19 pandemic imposed extreme measures on global health systems and several therapeutic protocols were instituted and at the height of the pandemic, 70 % of patients were administered some dose of corticosteroids [11]. However, the use of corticosteroids has presented detrimental effects, including prolonged time for viral clearance, increased likelihood of infection, psychosis, adrenal dysfunction, and the emergence of avascular bone necrosis [6,12].

In this study, the majority of individuals affected by osteonecrosis were male (66.7 %) with an average age of 46.3 years old. A multicenter evaluation carried out in Japan in 2018 by Uesugi et al. with 274 patients with osteonecrosis of the femoral head included a total of 166 male patients (60.6 %) with a mean age of 46 years old, data similar to the French Hernigou et al. (2002) who encountered 65 % affected men, as well as Daltro et al. (2010) with 52.8 % of male patients and a mean age of 27.3 years old [1,13,14].

Similarly to other times in history, when there was an increase in the incidence of ONFH secondary to the use of corticosteroids for the treatment of severe acute respiratory syndrome, researchers Gou et al.

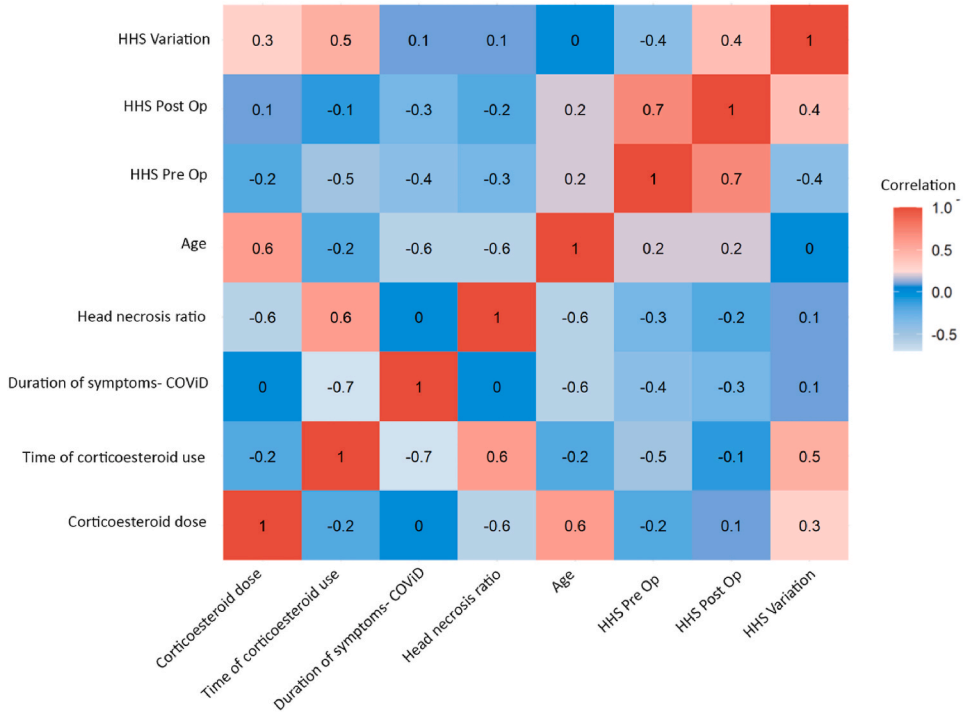

Chart 2. Variables relationships.

(2014) present a retrospective study that also seeks to establish the relationship between these two variables and approximately 25 % of their patients who used corticosteroids to treat SARS developed ONFH. In line with these studies, 66.7 % of our patients were administered corticosteroids.

The average dose of prednisolone used was 35 mg/day, for an average period of 19 consecutive days, equivalent to an accumulated dose of 665 mg of prednisolone. The literature tends to agree on the direct relationship between the dosage of corticosteroid and the risk of developing osteonecrosis. Zhang et al. (2008) as well as LaPorte et al. (2008) describe an increase in the number of multifocal lesions and even diaphyseal lesions in higher doses of corticosteroid. A multicenter study carried out in China, with 1203 patients undergoing corticosteroid therapy, observed after a period of 6–9 months an increase in the relative risk for the development of ONFH of 26 times and osteonecrosis of the knee of 63 times in cases where the accumulated dose reaches the value of 200 mg/kg of prednisolone.

A portion of the patients involved in this research (33.3 %), however, developed osteonecrosis of the femoral head after mild COVID-19, without having used corticosteroids. We believe that this fact can be seen as a new etiological possibility for ONFH.

It is possible that the hypercoagulable state inherent to the pathophysiology of COVID-19 contributes significantly to the occurrence of ONFH in this group of patients. There is a considerable amount of reports demonstrating the pathophysiology of coronavirus infection and the induction of a hypercoagulable state, significantly increasing the risk of thrombosis [15–18].

The combination of a hypercoagulable state, inflammation in the vessel walls and increased adhesion between leukocytes and platelets can impair blood flow in the thinnest vessels, which in turn can lead to the development of osteonecrosis, especially in the femoral head, which is known to have terminal circulation and small caliber.

In this context, hypercoagulability associated with COVID-19 may have implications in the pathogenesis of osteonecrosis of the femoral head, as observed in the data presented by this study. It is still not possible to precisely state that COVID-19 is currently one of the main causes of osteonecrosis of the femoral head. However, considering that a number of patients who did not receive corticosteroid treatment may be susceptible to developing COVID-19-associated osteonecrosis due to the hypercoagulable state induced by the infection.

The time span between coronavirus infection and the onset of symptoms related to osteonecrosis does not present a pattern. In our sample, the time span was 183.3 days (±178.4). In the group of ten patients described in the series of cases that occurred in Switzerland, the time between active coronavirus infection and the onset of symptoms in the musculoskeletal system was 7–22 days [19]. Specifically, femoral head injuries have surfaced later, according to the data from the review published by a team from Egypt with 104 patients with osteonecrosis of the femoral head after COVID-19, which found an average time of 142.1 days (±107.6) [8].

The data from this work regarding the characteristics of the evolution of osteonecrosis in the femoral head is supported by other findings in literature. It is common for ONFH to occur bilaterally, according to the Japanese cohort published by Uesugi et al. (2018) 69.3 %. Daltro et al. (2018) found bilateral injuries in 86.9 % of cases [20] and we obtained a prevalence of 66.7 % of patients affected in both limbs. Another fundamental piece of information for assessing the severity of osteonecrosis is the area ratio of the affected femoral head. Our data indicate extensive lesions reaching 40 % (±12 %) of the femoral head, mostly occupying the weight-bearing area of the hip, a fact that worsens the prognosis. Larger lesions tend to evolve more quickly, and we found 66.7 % of hips in stage IIA of the Ficat and Arlet classification, 16.3 % hips in stage IIB and the remaining 16.3 % in stage III. Unlike our case series, Kandari et al. (2022) present 6.5 % of cases in the first Ficat and Arlet stage, 50 % in stage II, 31 % in stage III and 12.5 % in stage IV. The hips examined in the case series presented by the team from the University of Tunisia have 30.7 % of injuries in stage I, 30.7 % in stage II and 38.6 % in stage III(33).

The initial assessment of the patients enrolled in this study returned an HHS of 65.4 (±13) points. After surgery to implant mesenchymal cells in the hip, these patients were periodically reassessed and, at the end of 12 months, the average HHS value was 75.9 (±12) points, a positive variation of 12 points, with one hip (8.3 %) presented a decrease in the HHS score, requiring total hip arthroplasty. We did not

find another study in the literature with a similar methodology for statistical comparison purposes.

5. Conclusion

Our findings suggest that post-COVID-19 syndrome may represent a contributing factor in the development of osteonecrosis of the femoral head. The dose and duration of corticosteroid use may be associated with the onset of osteonecrosis. Contrary to previously established data, patients who were infected with the coronavirus but did not use corticosteroids during treatment also developed osteonecrosis, possibly due to microcirculatory or hematological alterations. Treatment for osteonecrosis of the hip in these patients, based on the use of mesenchymal cells, has shown promising results, although a larger number of cases treated with similar protocols is needed to confirm these findings.

Author contribution statement

Each author contributed individually and significantly to the development of this article. Franco BAFM: Substantial contribution to the design, acquisition, analysis and interpretation of data for the work; Writing the work. Garrido SS: Substantial contribution to the conception, critical review of its intellectual content, Final approval of the version of the manuscript to be published. Faleiro TB: analysis and interpretation of data for the work, Final approval of the version of the manuscript to be published. Rosário DAV: Substantial contribution to the conception, critical review of its intellectual content. Daltro PB: analysis and interpretation of data for the work, critical review of its intellectual content. Pereira BNR: acquisition of data for the work, substantial contribution to the design of the work. Daltro GC: Substantial contribution to the conception of the work, critical review of its intellectual content; final approval of the version of the manuscript to be published.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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