Journal of Regenerative Biology and Medicine

Daltro GDC, et al.,2021- J Regn Bio Med
Case Report

Osteonecrosis Development Post Covid-19 Infection

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Abstract

The COVID-19 pandemic, originating in China, has spread across the world, with serious proportions in populations and public health. Systemic lesions in those infected generate cascading changes affecting different organs. Osteonecrosis is a bone pathology, of different etiologies, common throughout the world, which directs the hip to a disabling condition. Furthermore, there is a polygenic and multifactorial interactionin its pathophysiology. The objective of this paper is to present the first series of cases of osteonecrosis of the femoral head after infection by SARS-CoV-2 and to discuss the possible pathological mechanisms. This is a sample with a male majority with a mean age of 43.5 years, bilateral involvement of the hips in 100% of cases, mean time between infection and onset of symptoms was 132.8 days. About 33% had osteonecrosis of the femoral head after a mild infection, 66% were moderate or severe cases that used corticosteroid therapy with a minimum dose of 40mg/day of dexamethasone for an average time of 14.6 days. We believe that the association of hypercoagulability mechanisms inherent to COVID-19, direct cell infection and instituted corticotherapy may be responsible for the high incidence of osteonecrosis inthe post-covid syndrome.

Keywords: COVID-19; Osteonecrosis; SARS-CoV-2.

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Accepted Date: 08-09-2021

Published Date: 09-09-2021

Introduction

The COVID-19 pandemic, originating in China, has spread throughout the world, with serious proportions in populations and public health [1]. Systemic lesions in infected people generate cascading changes compromising different organs and systems, with more than

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millions of people and health system breakdown. In these conditions, the cardiopulmonary, urinary, neuromuscular, osteoarticular and digestive systems are the most affected [2].

Osteonecrosis is a bone pathology, of different etiologies, common throughout the world, which directs the hip to a disabling condition that often affects patients in the second to fifth decade of their lives. When this condition affects multiple joints or skeletal structures, the established disability is greater [3–5].

The incidence of osteonecrosis is increasing worldwide, in China, 75,000 to 150,000 cases are diagnosed annually. After COVID-19, a significant increase in these lesions is expected [4,6].

Osteonecrosis of the femoral head is complex, polygenic, multifactorial with implications for genetic factors and other associated factors such as: corticosteroid use, alcohol abuse, systemic lupus erythematosus, radiation, sickle cell disease, cytotoxic agents, hyperlipidemia, pancreatitis, gout, disease of Gaucher, Legg-Calve-Perthes and unidentified or idiopathic factors [6].

In the post-COVID-19 context, it is likely that the different clinical and imaging manifestations we observed in these patients with osteonecrosis are related to clinical or subclinical conditions compatible with the rapid onset and size of osteonecrosis. The next clinical studies will be important to elucidate these manifestations and the rapid evolution of the lesion. The purpose of this paper is to present the first case series of osteonecrosis of the femoral head following SARS-CoV-2 infection and to discuss the possible pathological mechanisms.

Case presentation

The Orthopedics and Traumatology service at the Complexo Hospitalar Professor Edgard Santos (HUPES) at the Universidade Federal da Bahia has a reference service for osteonecrosis treatment for more than 15 years, in which research and therapy using autologous bone marrow mononuclear cells have been carried out. Thus, cases of aseptic necrosis of patients treated for COVID-19 have been reported at the Orthopedics service of the HUPES. Currently there are twenty-three cases catalogued, three cases operated on, and twenty cases awaiting treatment with autologous mononuclear cell transplantation.

This is a mostly male sample (66%) with a mean age of 43.5 (min 25-max 61) years, bilateral involvement of the hips in 100% of the cases. The average time between SARS-CoV-2 infection and the onset of symptoms of hip pain and functional limitation is 132.8 days (min 64-max 180). Among the patients studied so far, 33% presented osteonecrosis of the femoral head after a mild infection, without the need for hospitalization and corticoid use. The other 66% were moderate or severe cases with hospitalization and who took corticotherapy with a minimum dose of 40mg/day of dexamethasone for a mean time of 14.6 days (min 15-max 21).

Diagnosis

Diagnosis of osteonecrosis of the femoral head in these patients was reached after X-ray

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and MRI examinations of the hips. In general, MRI showed areas of subcortical bone marrow damage in the femoral head compatible with avascular osteonecrosis of varying sizes. The average hip involvement was a 56% area of the femoral head, reaching a maximum area of 80%, considered a severe injury with a risk of collapse of the femoral heads (Figures 1-5). The Harris Hip Score was applied to the patients at the first visit and the average score obtained by the patients was 69.2 (min 42-max 85).

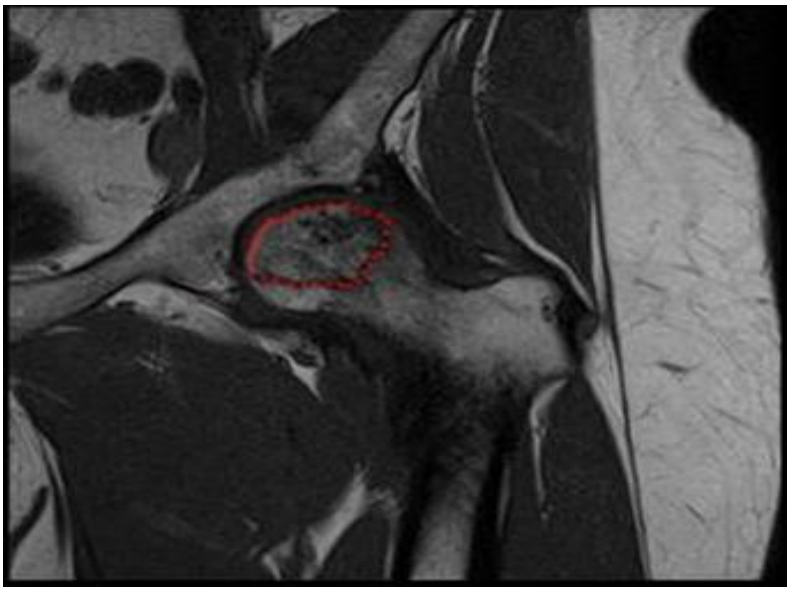

Figure 1: MRIONFH of the left hip 80% involvement.

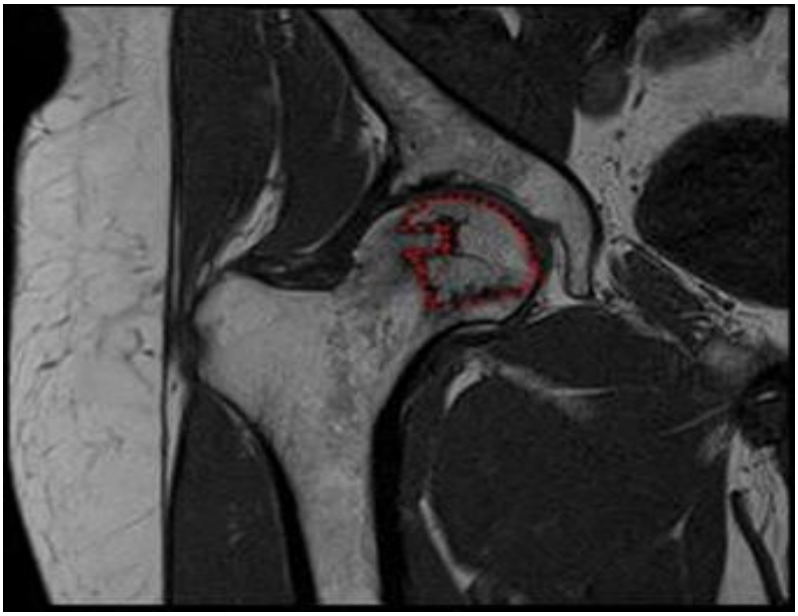

Figure 2: MRI-ONFH of the right hip 60% involvement.

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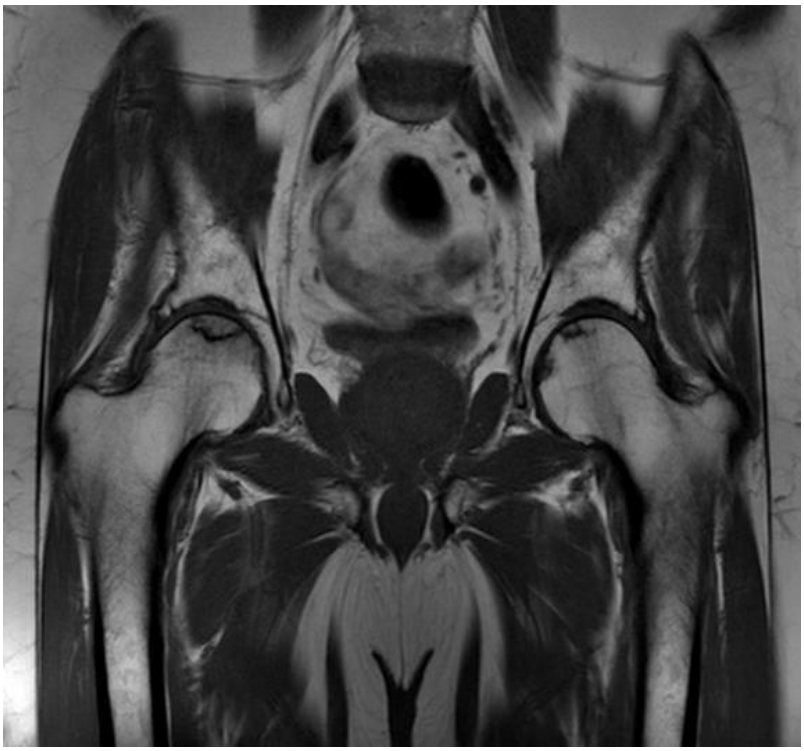

Figure 3: MRI of the pelvis, bilateral ONFH.

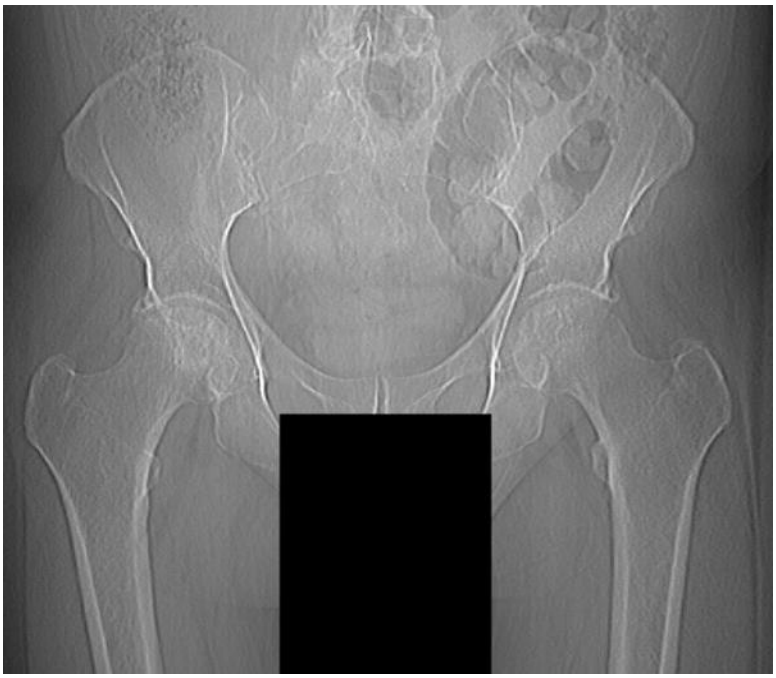

Figure 4: Pelvis X-ray, bilateral ONFH.

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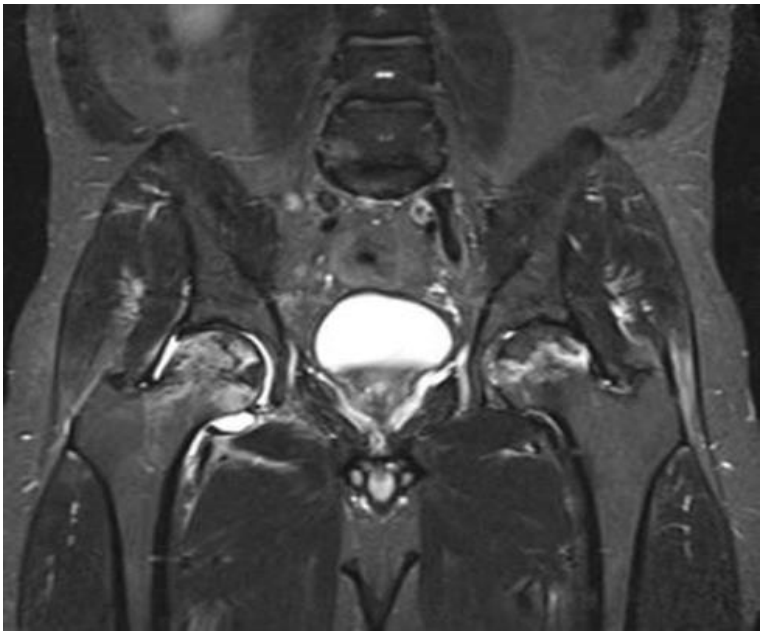

Figure 5: MRI of the pelvis, bilateral ONFH.

Discussion

The pathogenesis of most etiologies of ON is still not well elucidated, and most probably is multifactorial, where an association between one or more factors, such as environmental and genetic, can further increase its occurrence [5]. In the various etiologies, the final causative outcome seems to be, in most cases, the failure of nutrients to reach the affected bone, consequently causing bone tissue death [5–7].

The first animal studies relating the use of glucocorticoids and the occurrence of osteonecrosis date back to the 1950s. The systemic effects of GCTs were, until then, only noticed a few years after their introduction into clinical practice, showing how aggressive these can be in some tissues and the various adverse effects generated, especially when administered in high doses, as well as depending on the route of administration and the duration of treatment. However, glucocorticoid-induced osteonecrosis (ON-GCT) can be triggered in individuals who have used this drug in high doses for a short period of time and/or by individuals who have received doses over a prolonged period of treatment with lower doses, or even after intra-articular injection or application of topical preparations [8]. In our sample, patients who used glucocorticoids during treatment for COVID-19, received high doses 40mg/day which, according to Kallas et al, 2020, increases the risk for developing osteonecrosis [9].

Glucocorticoids are widely used as therapeutic agents to treat a wide variety of disease causes, but some have a high prevalence of cases, such as systemic lupus erythematosus (SLE), kidney transplantation or leukemia, and currently for COVID-19 [5,9]. Osteonecrosis has been frequently reported in patients with severe SARS, with rates ranging from 5% to 58% and in patients receiving long-term therapy, glucocorticoids induce osteonecrosis in 9 to 40% [2,10,11]. As in this series, most cases described in the literature involve the femoral head and knee,

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humeral head, talus, calcaneus, and other sites are affected at lower frequencies [12].

The use of glucocorticoids seems to favor this lack of vascular supply in the femoral head, through a series of mechanisms such as alterations in the apoptosis and autophagy processes, through damage to endothelial cells and alterations in the coagulation pathways through oxidative lesion and alterations in the viability of osteoblasts, favoring osteonecrosis [5,11,13–15]. Associated with these mechanisms, due to its vascular anatomy, the hip has a susceptibility to osteonecrosis, facilitating the reduction of supply in case of formation of an embolus or thrombus [14].

The action of GCT is perceptible in all bone tissue cells and is capable of inducing apoptosis and/or suppressing osteoblast production in the bone marrow, maintaining osteoclast life span for a longer time, and inducing osteocyte apoptosis, which results in a mechanosensory dysfunction of the osteocyte network, leading to impaired bone repair processes, favoring the occurrence of osteonecrosis [16].

In addition to the inducing effect of GCTs for osteonecrosis, it should be noted that the SARS- CoV-2 infectious process induces a systemic inflammation that can impact the musculoskeletal system. Several types of musculoskeletal cells express receptors for angiotensin-converting protein 2 (ACE2), which allow direct viral infection [10,17]. The SARS-CoV-2 spike protein combines with its functional receptor ACE2 and is then activated to release peptides for membrane fusion. Thus, ACE2 expression is a key input for SARS-CoV-2 invasion and enhances the proper conditions for virus replication [18]. Being also found in the bone cells, osteoblasts, and osteoclasts, that regulate bone homeostasis it is possible that it is also related to the occurrence of ON to direct viral infection in bone tissue. In addition to this mechanism, an in vitro study showed that a specific SARS-CoV protein, 3a/X1, directly promotes osteoclast genesis by accelerating osteoclast maturation and differentiation of monocyte/macrophage precursors, increasing expression of the receptor activator of NF-kB ligand (RANKL) and inflammatory cytokines, such as TNF-α, which indirectly promote osteoclast genesis [5,10].

In addition to these mechanisms, it is important to consider the hypercoagulability state observed during the evolution of COVID-19. Infected patients commonly develop thrombocytopenia and may have elevated D dimer while these rates are even higher in patients with moderate and severe disease. Emerging data support that patients infected with this novel coronavirus are at risk of developing disseminated intravascular coagulation Increased levels of D-dimer, fibrin degradation products, and prolonged prothrombin time have been associated with poor prognosis in affected patients. D-dimer levels increased, while CRP levels did not change significantly from pre-diagnosis to diagnosis. These data suggest that patients with higher levels of inflammation have an increased risk of osteonecrosis [5,6,12,13].

Conclusion

COVID-19 can lead to osteonecrosis of the femoral head and several mechanisms, both treatment-related and disease-related, may participate in the pathophysiology. We believe that the association of the hypercoagulability mechanisms inherent in COVID-19, direct cellular infection, and the

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instituted corticotherapy may account for the high incidence of osteonecrosis in post-covid syndrome. Thus, it is critical that joint pain in this group of patients be valued, and osteonecrosis of the femoral head be considered in the post-COVID syndrome spectrum.

Declaration of authors' contribution –

Each author contributed individually and significantly to the development of this article. GD (0000-0002-4802-7953)*: surgeries, statistical analysis and intellectual concept ofthe article and preparation of the entire research project; BAFMF (0000-0002-9381-0605)*: writing the article, reviewing, performing the surgeries and analyzing the data; DAVR (0000-0001-7595-9011)*: article writing, surgeries, data analysis; TBF (0000-0002-6122-3609)*: article writing, surgeries, data analysis, article review; PBD (0000-0003-1545-7786)*: laboratory analysis and article review; RM (0000-0002-4727-4805)laboratory analysis and article review VL (0000-0001-8021-7012)*: statistical analysis and review of the article;, *ORCID (Open Researcher and Contributor ID); FV (0000-0002-2235-5983) statistical analysis and review of the article.

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