RESEARCH ARTICLE

Screening for Femoral Head Osteonecrosis Following COVID-19: Is It Worth It?

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Abstract

Objectives: Based on WHO data, as of June 2022, there were 532.2 million confirmed COVID-19 cases globally. In the initial phase of the COVID -19 pandemic, patients experiencing critical illness marked by severe respiratory distress were commonly subjected to corticosteroid treatment. Regrettably, the administration of exogenous corticosteroids stands as the prevailing cause of ONFH. In the current narrative review, we aim to evaluate if active screening should be utilized to diagnose post-COVID-19 ONFH in its early stages.

Methods: The databases for PubMed, CINAHL, and Science Direct were systematically queried in March 2022. The search terms were as follows: "COVID-19", "severe acute respiratory syndrome", "coronavirus", "systemic steroid", "corticosteroid", "femoral head osteonecrosis", "avascular necrosis", or "steroid therapy." The included studies for review were all required to be peer-reviewed studies in the English language with Reported complications linked to steroid therapy in COVID-19 patients or potential connections to the development of ONFH in individuals recovering from the novel coronavirus have been documented.

Results: Systemic corticosteroids were frequently employed in managing critically ill COVID-19 patients. The CDC reports up to June 2022 showed more than 4.8 million COVID-19 hospitalizations in the US, with approximately over one million patients receiving steroids. In a study of ONFH after infection with COVID-19, all patients had bilateral involvement. The average duration from the initiation of corticosteroid treatment to the onset of symptoms was 132.8 days.

Conclusion: In summary, a distinct correlation exists between the administration of steroids to individuals with COVID-19 and the subsequent risk of ONFH. Moreover, an elevated dosage and prolonged duration of steroid therapy in COVID-19 patients are associated with an increased likelihood of developing ONFH. Therefore, active screening for high-risk patients, that may have received systemic corticosteroid treatment during a COVID-19 illness, may be reasonable.

Level of evidence: IV

Keywords: COVID-19, Osteonecrosis of femoral head, Steroid

Introduction

As of June 2022, the World Health Organization[1] data estimated 532.2 million global COVID-19 cases, 6.305 million deaths, and a daily infection report of approximately 574,000 cases despite more than 11.8 billion vaccine doses provided worldwide.[2] In the initial phase of the COVID-19 pandemic, patients experiencing critical illness marked by severe respiratory distress were commonly subjected to corticosteroid treatment, which became part of many early treatment protocols due to the overwhelming volume and urgency of respiratory compromised patients. Corticosteroids have an unquestionable beneficial effect in treating severe acute

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respiratory distress syndrome (ARDS) and inflammatory cytokine storm,[3-8] but this treatment also has significant associated risks. In reaction to the COVID-19 crisis, orthopedic surgeons worldwide suspended elective surgeries during the peak of the pandemic, leading to unforeseen morbidity for patients awaiting surgical procedures and subsequent follow-up appointments.[9] thankfully, widespread vaccination and improved treatment modalities have contributed to a flattened disease curve; however, post-COVID-19 orthopaedic complications may be of concern. The emergence of severe acute respiratory syndrome (SARS) in 2003, a condition also managed with high-dose corticosteroids, resulted in an elevated incidence of ONFH in the months and years subsequent to the illness.[10, 11]

ONFH is a challenging orthopaedic condition with an estimated annual prevalence of 300,000 to 600,000 in the US and reports in Japan of up to 24,000 annually.[12,13] It has been approximated that the global prevalence of individuals impacted by ONFH may reach 20 million.[14] The predominant demographic afflicted by ONFH comprises individuals aged less than 40 years. The untreated course of the ailment manifests in the development of secondary osteoarthritis of the hip, often precipitating within a relatively brief span of two years. This rapid disease progression may necessitate multiple surgeries and ultimately total hip arthroplasty, which makes ONFH an important focus in the field of orthopaedic surgery.[15]

Exogenous corticosteroid use, the most common etiology of ONFH with up to 51% in some regions,[16, 17] was used for COVID-19, based on experiences within similar diseases such as the recent outbreaks of MERS and SARS.[18, 19] Systemic steroids, used as a potent therapy to control cytokine storms in severe cases of COVID-19,[7] significantly decreased mortality and the need for mechanical ventilation.[20, 21] Recent studies have noted evidence of post-COVID ONFH,[22, 23] but the exact prevalence of ONFH in COVID-19 survivors is unknown. In the years following the 2003 SARS outbreak, which infected less than 10,000 people, an increase in ONFH occurrence was seen,[24] which may shed light on the potential increase of ONFH cases seen as a result of treatment from the novel coronavirus pandemic. Therefore, in the current narrative review, we aim to evaluate if active screening should be utilized to diagnose post-COVID-19 ONFH in its early stages.

Materials and Methods

The databases for PubMed, CINAHL, and Science Direct were systematically queried in March 2022. The search terms were as follows: “COVID-19”, “severe acute respiratory syndrome”, “coronavirus”, “systemic steroid”, “corticosteroid”, “femoral head osteonecrosis”, “avascular necrosis”, or “steroid therapy.” Moreover, the citations documented in each identified article underwent thorough screening and manual exploration to enhance the comprehensiveness of the results. Two authors (HD A and NM) independently conducted the screening, with any disparities resolved through consultation with a third investigator (AP).

The included studies for review were all required to be peer-reviewed studies in the English language with reported complications of steroid therapy in COVID-19 patients or related to the development of ONFH in patients who recovered from the novel coronavirus. Excluded publications consisted of commentaries, editorials, case series/case reports, letters to editors.

The two researchers (HD, NM) who performed the inclusion and exclusion of the literature also independently extracted data from the included studies. The inclusion or exclusion of a publication was made following a consensus of both parties and discrepancies were settled with senior author (AP).

Results

The initial search query identified 173 articles. Ninety-eight articles were duplicates, which left 75 studies to be screened for eligibility. Of these, 46 articles underwent a full-text review, with eight studies meeting all inclusion and exclusion criteria [Figure 1]. Main findings of the included studies are summarized in [Table-1].

Table 1. Study characterisctics and main finding of the included studies

First autjor (Year)	Journal	Level of Evidence	Number of Patients	Main findings
Zhao et al (2017)	Osteoporos Int	III	1137	Higher cumulative doses and longer treatment durations of steroids were more likely to develop osteonecrosis, independent of gender
Lianhua et al (2007)	Front Med China	III	26	CD31, CD61, CD62P, CD63, PAC-1* on platelet membrane and coagulation ndices was not showed hypercoagable state in patient with ONFH following SARS**
Li (2019)	Bone	III	80	Multi-serum biomarker-based model can predict and detect steroid -induced ONFH
Adapala (2016)	Am J Pathology	III		Necrotic bone stimulates macrophageinflammatory responses through TLR4# activation

Table 1. continued

Guo (2014)	The Bone and Joint Journal	III	539	Combination of different types of steroids, higher dose, male gender and young adultage increase the risk of osteonecrosis in SARS
VanVeldhuizen(1993)	Am J Hematology	III	5	There is an association between decreased fibrinolytic potential and the subsequent development of avascular necrosis of the hip
Dhanasekararaja(2022)	Ind J Orthopedics	III	22	Acute and aggressive presentation with rapid destruction of osteonecrosis following COVID-19 is expected
Kabata (2008)	The Journal of Rheumatology, 200	IV	99	Ischemic events that cause osteonecrosis begin soon after the initial corticosteroid treatment

*First procaspase activating compound
**Severe acute respirartor syndrome
#Toll-like receptor 4

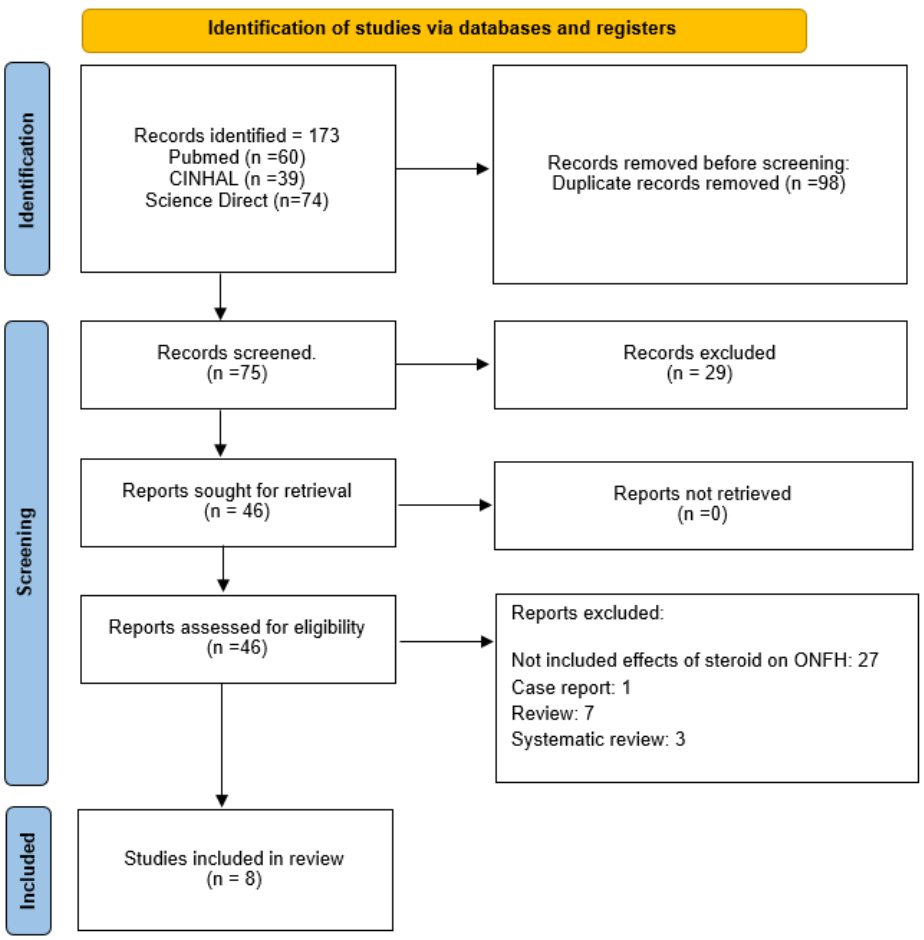

Figure 1. Flowchart of study selection

Steroid Use & ONFH

Factors implicated in the onset of ONFH encompass vascular occlusion or ischemia, alterations in fat metabolism, fat embolism, and intravascular coagulation. Steroids, employed to suppress inflammatory responses, find application in the treatment of various inflammatory

conditions, including systemic lupus erythematosus and rheumatoid arthritis, and are utilized to mitigate natural pro-inflammatory processes subsequent to organ transplantation. The association between the use of systemic steroids and osteonecrosis is a well-established fact.

The administration of high-dose corticosteroids can initiate heightened coagulation, particularly through the impairment of endothelial cells. Numerous investigations have indicated an elevation in the expression of nuclear factor kappa B (NFκB), receptor activator (RANK), RANK ligand (RANK-L), and macrophage colony-stimulating factor (M-CSF), alongside a reduction in osteoprotegerin (OPG) expression in cultured human osteoblasts and human stroma, resulting in osteoblast apoptosis. Beyond apoptotic pathways, studies in mice have demonstrated that systemic corticosteroids can suppress the mechanism responsible for osteoblast production.[1] To compound the issue, osteoclast survival is prolonged by glucocorticoids.[23,25] Significantly, it should be emphasized that RANK, RANK-L, and OPG serve as pivotal regulators in osteoclast production. RANK-L and M-CSF play indispensable roles in the genesis of osteoclasts, while OPG acts to prevent the binding of RANK-L to RANK, thereby inhibiting osteoclasts and the bone resorption facilitated by mature osteoclasts. The suppression of osteoclasts induced by steroids results in a reduction of osteoblast function within the framework of the osteoclast-osteoblast interaction observed in bone remodeling.[26]

Moreover, glucocorticoids exert inhibitory effects on the secretion of sex hormones and the expression of key factors such as bone morphogenetic protein 2 (BMP-2), insulin-like growth factor 1 (IGF-1), and osteocalcin. Additionally, glucocorticoids have adverse impacts on angiogenesis, a crucial process for tissue repair following bone ischemia, as they have been observed to suppress the expression of vascular endothelial growth factor (VEGF) and elevate the expression of antiangiogenic thrombospondin-1 (TSP1).[27-29] Furthermore, the glucocorticoid-induced suppression of matrix metalloproteinases and plasminogen activators detrimentally affects pro-angiogenic processes by impairing basement membrane renewal. Lastly, it has been demonstrated that fibrinolytic activity can be significantly reduced with the use of glucocorticoids.[30] all of these factors contribute to a reduction in angiogenesis, and are compounded during cycles of degeneration as subchondral microfracture sites release cartilage components that further the antiangiogenic environment.

Steroid Dose & ONFH Onset

While limited research has focused on precise steroid dosages and their association with ONFH, a Japanese study investigating patients undergoing steroid treatment for systemic lupus erythematosus (SLE) and kidney transplantation has contributed to elucidating the connection between steroid dosage and ONFH. Intuitively, higher daily steroid doses had increasingly stronger effects on ONFH occurrence. Kidney transplant patients who received more than 40 mg per day of prednisolone were 5.0 times more likely to develop ONFH than those patients who received less than 14.92 mg per day.[20] Patients with SLE who were administered prednisolone at doses exceeding 16.6 mg per day exhibited a 3.4-fold higher likelihood of developing ONFH compared to those receiving less than 12.3 mg per day.[31]

Beyond dosage considerations, the onset of ONFH subsequent to steroid administration has been evaluated through sequential MRI in a cohort of renal transplantation patients utilizing postoperative steroids for immunosuppression. Kubo et al. noted that the majority of ONFH lesions were initially discerned on MRI within 16 weeks after the initiation of steroid treatment, with a few cases remaining unimaged until 12 months postoperatively. In contrast, traumatic ONFH demonstrated the emergence of T1-weighted MRI signals as early as 4 weeks after blood circulation disruption due to fractures. Consequently, ischemic attacks in the femoral head may trigger the onset of ONFH within 2-12 weeks after the commencement of steroid therapy. Femoral head collapse, leading to hip pain, was observed in ONFH patients from 6 months to 2 years after the initiation of steroid therapy.[32,7] Similarly, timeframes of hip symptomology since the initiation of steroid therapy have ranged from 1-4 years in patients with SLE. Since some disease processes and conditions may require continuation of steroid therapy even after the discovery of ONFH, studies show that existing lesions are unlikely to change; therefore, there is no need to reduce or stop steroid administration after the occurrence of ONFH.[32]

Patient-related Risk Factors

ONFH is diagnosed most commonly in patients aged 41 to 60 and is seen more commonly in men than women. Interestingly, it also affects men at a younger age compared to age of diagnosis in women. While obesity, a recognized risk factor for numerous diseases, is prevalent among many ONFH patients, no definitive correlation has been made between the conditions. Manual laborers have a higher likelihood of ONFH development compared to other occupations, which is likely due to high levels of stress through the hip joint. Additionally, manual laborers have delayed diagnoses compared to other occupations, which have been postulated due to education level, socioeconomic status, access to healthcare, or culture, among other factors. Other factors beyond steroid use can increase the risk of ONFH, and patients with concomitant connective tissue diseases, history of organ transplantation, and excessive alcohol intake have been shown to have an increased risk of ONFH.[17, 31,33]

Steroid Use in COVID-19 Patients

The current guidance from the COVID-19 Treatment Guidelines Panel advises against the utilization of dexamethasone or other corticosteroids in the treatment of COVID-19. Nonetheless, individuals diagnosed with COVID-19 who are already on corticosteroids for an underlying condition should adhere to their healthcare provider's directives. For hospitalized patients encountering respiratory distress, the recommended dose of dexamethasone is 6 mg intravenously or orally administered once daily for a duration of up to 10 days or until hospital discharge.[34]

In the case of vitally stable patients with COVID-19 experiencing respiratory symptoms, hospital admission is not always necessitated, which was certainly true at the height of the pandemic when hospitals were at maximum

capacity and resources were scarce. For such patients, the Panel further advocates the administration of dexamethasone at 6 mg orally once daily for the duration of supplemental oxygen use, with a maximum course of 10 consecutive days. The Panel also notes that careful monitoring for adverse events should be reviewed with those treated on an outpatient basis.[35]

Despite recent changes in guidelines, systemic corticosteroids like dexamethasone have commonly been employed in managing critically ill COVID-19 patients, aiming to mitigate the cytokine storm, reduce the need for mechanical ventilation, and shorten hospital stays. Reports indicate that corticosteroids were administered to one third of mechanically ventilated ICU patients and 40% of those diagnosed with severe COVID-19. However, the optimal dosage and duration of systemic corticosteroids for COVID-19 remain subjects of ongoing evolution. In 2021, among hospitalized patients, over 80% received low-dose steroids, while less than 20 % received high-dose steroids.[22, 36] with extrapolation of the COVID-19 Centers of Disease Control and Prevention (CDC) data up to June 2022, approximately one million patients with prior steroid treatment can be estimated, given that there have been over 4.8 million COVID-19 hospitalizations in US.[37]

Frequency of ONFH with Steroid Use

The use of glucocorticoids is the most common cause of secondary osteonecrosis and the primary cause of non-traumatic osteonecrosis. ONFH is seen in 9 to 40% of patients who have undergone long-term steroid treatments. Unfortunately, many cases of steroid-induced ONFH have been due to an increasing number of patients who have been treated with improper dosages or durations of steroids for conditions such as lower back pain, gouty arthritis, otitis media, upper respiratory tract infections, and fever typically do not necessitate prolonged steroid use. However, the utilization of steroids for addressing non-urgent or emergent conditions is generally on the rise.[17,33]

While steroids are extensively employed to hinder the advancement of acute lung injury and ARDS in individuals with SARS and COVID-19, their application in treating pervasive lung conditions has faced criticism due to their immunosuppressive effects. Such immunosuppressive effects include impaired antibody response, delayed viral clearance, and avascular necrosis and osteoporosis in prolonged use[37,38]. Dhanasekararaja et al. showed that ONFH following COVID-19 infection had bilateral involvement in all patients evaluated[39]. The average duration from the initiation of steroid treatment to the onset of ONFH symptoms was 132.8 days. Around one third of assessed patients exhibited mild femoral head osteonecrosis subsequent to a mild infection, with two third of them undergoing corticosteroid therapy, receiving a minimum dose of 40 mg/day dexamethasone for an average duration of 14.6 days.[15, 17, 38-40]

Role of Serum Markers in Early ONFH Diagnosis

Previous studies have shown that there are few biomarkers that can be used for early detection of ONFH, including apolipoprotein A-IV and plasma interleukin 33 concentrations. Other studies also showed that, compared with healthy controls, patients with non-traumatic ONFH particularly in high-risk individuals with a history of steroid exposure during COVID-19 treatment. Although this can be done with serum marker analysis, a more cost-effective and efficient way to screen such patients may be had significantly higher triglyceride concentrations, reduced plasma adiponectin levels and decreased high-density lipoprotein cholesterol (HDL-C) are associated with ONFH. Additionally, plasma interleukin-33 concentrations, along with zinc-a2-glycoprotein and p-glycoprotein (P-gp), may contribute to the diagnostic profile of ONFH).[16]

Recent investigations have identified novel biomarkers for ONFH diagnosis, including CBL, PAK1, BIRC3, CCR5, TLR4, LYN, PTEN and RAF1. Multiple studies have scrutinized the presence of these biomarkers in the context of disease discovery. One study revealed that reduced expression of CBL (CBL proto-oncogene) impeded vascular permeability and VEGF-induced osteoclast activity, potentially offering therapeutic benefits for regenerating femoral head necrosis. Additionally, pathways related to EGF/EGFR are implicated in immune system modulation, bone formation, and microvascularization.[41-43]

BIRC3 (Baculoviral IAP repeat-containing 3) is a potential protein that could aid in the diagnosis of ONFH. As a member of the inhibitors of apoptosis proteins (IAP) family, BIRC3 encodes apoptosis by binding to TNF receptor-associated factors, TRAF1, and TRAF2. It exhibits ligase activity and inhibits cysteine-type endopeptidases, playing a role in focal adhesion and the NF-kappa B signaling pathway.[44,45]

CCR5 (C-C motif chemokine receptor 5) is involved in bone-destroying diseases by regulating osteoclasts.

Moreover, the activation of the Akt signaling pathway, a pathway linked with CCR5, has been shown to stimulate angiogenesis and inhibit bone resorption in ONFH[46, 47]Similarly, impaired immune systems linked to ONFH may result from RAF1 (Raf-1 proto-oncogene) and LYN (LYN proto-oncogene). LYN encodes a tyrosine protein kinase, while RAF1 encodes a MAP kinase (MAP3K). Both LYN and RAF1 are implicated in the regulation of immune response through Fc epsilon RI-mediated signaling pathways. PAK1 (P21 activated kinase 1), encoding an active serine/threonine family member of p21, has demonstrated a positive influence on cartilage anabolism.

In conclusion, research indicates the involvement of TLR4 (toll-like receptor 4) in osteonecrosis, particularly in corticosteroid-induced osteonecrosis of the femur, where it hinders the immune response. TLR4 prompts inflammatory responses in macrophages, leading to increased expression of IL-1β, TNF-α, and IL-6. The aforementioned literature findings strongly suggest that the identified candidate gene markers may be linked to the onset and progression of ONFH.[48, 49]

Conclusion and Recommendations

In summary, a distinct association exists between steroid treatment in individuals with COVID-19 and an elevated risk of ONFH following the infection. Furthermore, an augmented dosage and prolonged duration of steroid therapy in COVID-19 patients are correlated with an increased likelihood of developing ONFH. Unfortunately, no definitive literature supports a widespread screening protocol for patients with a prior history of COVID-19. Nevertheless, a case-by-case screening, guided by the patient's healthcare provider, is undoubtedly justified,

using AP pelvic and frog lateral hip radiographs. Additional investigation is essential to ascertain the precise risks of ONFH in COVID-19 patients who have undergone or are currently undergoing steroid treatments.

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