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ETIOLOGY AND PATHOGENESIS OF CORTICOSTEROID-ASSOCIATED OSTEONECROSIS OF THE FEMORAL HEAD: A CURRENT CONCEPT REVIEW

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Abstract

Osteonecrosis of the femoral head (ONFH) is an intractable disease occurring at a relatively young age. The characteristic finding of ONFH – the femoral head collapse with severe hip pain – is observed in many cases, which frequently leads to further joint destruction, requiring surgical treatment. Among the associated factors of ONFH, majority of patients who require high-dose corticosteroid are still challenging due to inevitable therapeutic option regardless of poor prognosis. As a pathological mechanism, ONFH is defined as tissue necrosis in the femoral head region due to occlusion of the nutrient vessels; but the detailed micro-level processes leading to blood flow failure remains unclear. The elucidation of ONFH and the establishment of preventive therapy is desirable for these patients. Here, we discuss the etiology and pathogenesis of corticosteroid-associated ONFH by reviewing current literature.

Key words: *corticosteroid*; *etiology*; *osteonecrosis of the femoral head*; *pathogenesis*

INTRODUCTION

Osteonecrosis of the femoral head (ONFH) is an intractable disease that occurs at a relatively young age. In many cases, it causes a characteristic femoral head collapse with severe hip pain, which leads to further joint destruction and frequently requires surgical treatment.[1] The prevalence of ONFH is reported to be around 5.9−725 (0.0059−0.725%) cases per 100,000 population in Asia, although there may be slight regional variations depending on how these cases are retrieved.[2–5]

The associated factors of ONFH are predominantly high-dose corticosteroid therapy and alcohol abuse.[2] In particular, corticosteroid is an essential treatment option for many diseases, and the fact that the occurrence of ONFH is inevitable for these patients remains critical. Therefore, there is an urgent need to establish preventive treatments for ONFH for patients who need corticosteroid therapy. Various diseases related to corticosteroid-associated ONFH has been reported, including systemic lupus erythematosus (SLE) and nephrotic syndrome.[2,3]

The pathogenesis of ONFH is commonly defined as tissue necrosis of the femoral head region due to occlusion of the nutrient arteries,[6] but the micro-level mechanism leading to the ultimate failure of blood flow has not been elucidated. Lipid metabolism abnormality, thrombosis, blood coagulation, cell death, and oxidative stress has been proposed as possible mechanisms involved in the development of ONFH.[7–12]

Here, we discuss the etiology and pathogenesis of corticosteroid-associated ONFH by bringing together the latest knowledge.

METHODS

For data collection, a literature search was carried out in the database PubMed. As for the etiology and pathogenesis of ONFH, the following search terms were used in combination: “osteonecrosis, avascular necrosis, and necrosis”

and "etiology, epidemiology, pathology, pathogenesis, risk factor, and steroids (corticosteroids, glucocorticoids)". In addition, the reference sections of all the identified publications were manually examined, and other key relevant references necessary to explain the pathogenesis were also included. Publications without an abstract and in languages other than English were basically excluded.

EPIDEMIOLOGY OF ONFH

Investigating the predominant age of onset, gender, and risk factors for ONFH is essential to explore the characteristics of ONFH and the methods of treatment option or prevention. Epidemiological studies of ONFH have been conducted on a large scale basis mainly in Asia, and the prevalence of ONFH has been reported to be approximately 5.9 to 725 cases per 100,000 population (0.0059–0.725%).[2–5] The male to female ratio of ONFH varies considerably between reports.[2–5,13–16] The predominant age of onset tends to be middle age in males and old age in females.[2,3,5,16] Regarding the associated factor of ONFH, corticosteroid has shown a tendency to be more common in females, while alcohol abuse to be more often in males.[3–5,16] Some epidemiological studies have included traumatic ONFH, and this inclusion may affect these results. The data have been summarized in Table 1.

ETIOLOGY OF CORTICOSTEROID-ASSOCIATED ONFH

The associated factors of ONFH are predominantly high-dose corticosteroid therapy, alcohol abuse, and heavy smoking[2] in addition to certain idiopathic cases without any triggers. This is particularly a tricky situation since corticosteroid is a first-line agent for patients including the autoimmune disease SLE, nephrotic syndrome, and after renal transplantation.[2,3] As a risk factor for the development of ONFH, a previous multicenter case-control study (73 ONFH cases and 250 matched controls) showed 20.3 of multivariate odds ratio of oral corticosteroid use in comparison with non-use (95% confidence interval 6.73 to 61.5).[17] A previous regression analysis described a significant relationship between corticosteroid usage and the incidence of ONFH, reporting that the incidence was 6.7% with corticosteroid treatment of more than 2 g of prednisone-equivalent.[18] In addition, each 10 mg per day dose increase of corticosteroid was associated with a 3.6% increase in ONFH occurrence rate, and more than 20 mg per day of corticosteroid usage demonstrated significantly higher

Table 1. Epidemiologic Studies of ONFH

Authors	Country	Year	Prevalence of ONFH (per 100,000 population)	Male to female ratio	Peak age (year)	Associated factor (female / male)
Ando et al.[2] Fukushima et al.[4,13-15]	Japan	2021	5.9–18.2 (0.0059–0.0182%)	1.2–2.1	Female: 60–69 Male: 30–59	Corticosteroid: 76.8% / 37.7% Alcohol: 7.7% / 51.3% Idiopathic 16.0% / 14.4%
Cui et al.[16]	China	2016	–	2.3	Female: 50–59 Male: 40–49	Corticosteroid: 32.9% / 20.5% Alcohol: 5.9% / 40.4% Idiopathic 38.3% / 25.8% Trauma: 22.9% / 13.3%
Zhao et al.[3]		2015	725 (0.725%)	0.7	Female: 65–74 Male: 35–44	Corticosteroid: 55.8% / 26.4% Alcohol: 8.0% / 32.9% Smoking: 4.4% / 21.0% Idiopathic 31.9% / 19.8%
Kang et al.[5]	Korea	2009	28.9 (0.0289%)	3.5	40–59 (mixed-gender)	Corticosteroid: 14.6% Alcohol: 32.4% Trauma: 1.6%

ONFH = Osteonecrosis of the femoral head.

risk of ONFH (odds ratio=9.1; 95% confidence interval, 4.6 to 19.8).[18] In a disease-specific study, corticosteroid use of 16.6 mg and more in SLE was associated with a significantly higher risk of developing ONFH with an odds ratio of 3.7.[19] Also, in a study of renal transplant recipients, the total amount of corticosteroid during the initial two months of treatment was significantly associated with the onset of ONFH in a dose-dependent manner.[20] The femoral head collapse is generally observed as a clinical feature of ONFH, and it frequently requires surgical treatment due to further joint destruction (Figure 1).[1]

PATHOGENESIS OF CORTICOSTEROID-ASSOCIATED ONFH

Lipid metabolism abnormality, thrombosis, blood coagulation, cell death, and oxidative stress have been proposed as possible mechanisms involved in the development of ONFH.[7–12] To date, several studies with prophylactic drugs have shown to inhibit these factors using the established corticosteroid-induced osteonecrosis model in rabbits.[21] It has been reported that drugs such as lipid-lowering agents,[22–25] anticoagulants,[25,26] and vasodilator[27] effectively suppress the development of corticosteroid-induced osteonecrosis in this model. However, the desired results have not yet been achieved in human ONFH. The establishment of a prophylactic treatment for corticosteroid-associated ONFH is a long-standing challenge, especially as some patients cannot avoid long-term or high doses of corticosteroid usage.

Lipid metabolism abnormality

There is a presence of bone marrow adipose tissue in the femoral head. Osteonecrosis is suspected to be involved in corticosteroid-induced abnormalities of lipid metabolism such as increased intramedullary pressure and micro fat embolism due to bone marrow adipocyte hypertrophy. Using a corticosteroid-induced rabbit osteonecrosis model, Miyanashi et al.[28] reported an increase in adipocyte diameter, a decrease in blood flow, and an increase in intramedullary pressure in the osteonecrosis group. Zhou et al.[29] evaluated the pathological process in a corticosteroid-induced osteonecrosis rabbit model. They observed the effect of intramedullary fatty infiltration on vascular changes in the femoral head, and reported fatty tamponade in the medullary cavity of the femoral head and narrow intramedullary vascular sinuses compressed by excessive amount of fat cells.[29] Corticosteroid promotes the differentiation of mesenchymal stem cells into mature adipocytes by activating transcription factors such as CCAAT/enhancer binding protein α (C/EBPα) and peroxisome proliferator-activated receptor γ (PPARγ).[30] Thus, corticosteroid-induced bone marrow adipocyte abnormalities can contribute to the development of ischemic osteonecrosis by reducing or blocking blood flow to the femoral head.

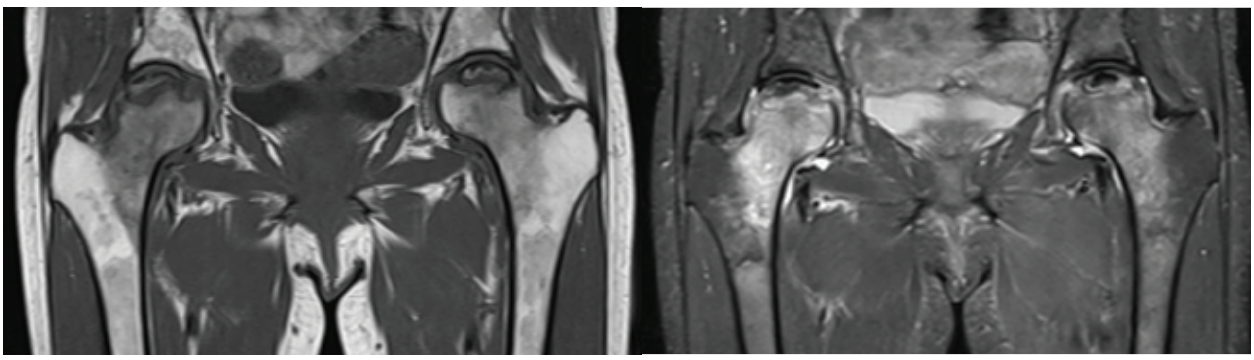

Figure 1. Magnetic resonance imaging findings of a case of 59-year-old woman classified as bilateral idiopathic ONFH with ARCO stage II. Coronal T1-weighted imaging [repetition time/echo time (TR/TE) 500/11 ms] and short-tau inversion recovery (STIR) sequence image (TR/TE 4000/23 ms). ONFH = osteonecrosis of the femoral head, ARCO = Association Research Circulation Osseous, TR = repetition time, TE = echo time.

Thrombosis and Blood coagulation

Thrombosis and blood coagulation disorder are well-known possible causes of ONFH.[9,11,31,32] The use of high doses of corticosteroids may affect the synthesis of nitric oxide (NO), which in turn exacerbates blood coagulation and thrombus formation.[31] Corticosteroids affect blood platelet aggregation and fibrinolytic activity via a reduction in tissue plasminogen activator (t-PA) and an increase in plasma plasminogen activator inhibitor-1 (PAI-1) antigen levels.[31,32] Starklint et al.[33] investigated the histological vascular structure of 14 femoral heads with late stage avascular necrosis of different etiologies, reporting the presence of intravascular fibrin clot aggregations and collapsed small vessels, mainly on the venous side in the reparative zone at the border of the necrotic region. These results suggest that obstruction to the venous outflow due to intravascular thrombosis and perivascular fibrosis is important in the pathogenesis of ONFH. Zalavras et al.[11] measured hematological parameters and assessed biochemical and lipid profiles in 68 patients with non-traumatic ONFH and 36 healthy controls. They reported a higher proportion of abnormal levels of von Willebrand factor (vWF), lipoprotein (a) [Lp(a)], protein C, and S levels in ONFH patients. This series supports the hypothesis that intravascular coagulation due to a thrombotic predisposition can be the main pathogenic mechanism of ONFH. In a study of patients with SLE, ONFH patients had a higher proportion of lupus anticoagulant and a shorter activated partial thromboplastin time (APTT) compared to without ONFH group. These results suggest that abnormalities in hemostasis due to the effects of corticosteroids and young age may play some role in the development of ONFH.[34]

Cell death

Cell death is classified into two categories: programed apoptosis or necroptosis and non-programed necrosis due to severe damage by external forces. As cell death, not only necrosis but also apoptosis or necroptosis has been reportedly linked with corticosteroid-associated osteonecrosis. In fact, apoptosis of osteocytes has been observed in extracted femoral head from patients with corticosteroid-associated ONFH. Previous in-vitro studies reported that corticosteroid administration induced apoptosis of osteocytes and osteoblasts.[35] Furthermore, a previous study reported that high concentrations of corticosteroids induced apoptosis of vascular endothelial cells, resulting in vascular occlusion and local ischemia related to osteonecrosis through endothelial dysfunction.[36] In addition to this, the presence of apoptosis and necroptosis after corticosteroid administration has been confirmed in a rabbit osteonecrosis model.[7,37] The above findings suggest that high doses of corticosteroids may play an important role in the development of osteonecrosis not only through direct cell death, but also through secondary vascular abnormalities.

Oxidative stress

Overdose or long-term administration of corticosteroids has adverse effects on multiple organs through elevated oxidative stress.[38] Previous in-vitro studies have reported that long-term incubation with exogenous corticosteroid increased intracellular reactive oxygen species (ROS) production in osteoblasts,[39] and that high-dose corticosteroid treatment increased hydrogen peroxide (H_2O_2) production and decreased NO availability in vascular endothelial cells.[40] In addition, previous studies have reported the development of osteonecrosis by monotherapy with oxidative stress-inducing agents in a rat model.[8] Also, increased oxidative stress has been found immediately after corticosteroid administration in an established rabbit corticosteroid-induced osteonecrosis model.[41–43] Several studies have revealed abnormal oxidative stress and/or antioxidant markers in corticosteroid-associated ONFH patients.[44,45] Interestingly, oxidative stress has been reported to increase adipogenesis through mesenchymal stem cell dysfunction,[46] cause cell death by damaging nuclear and mitochondrial DNA,[47,48] and lead to vascular endothelial cell dysfunction by reducing NO bioavailability,[49] which eventually contributes to a variety of vascular events, including blood coagulation, platelet aggregation, thrombosis.[45,50] In short, these mechanisms brought about by oxidative stress overlap with many of the events associated with osteonecrosis.[45]

Table 2. Pathogenesis of Corticosteroid-Associated ONFH

Factor	Possible mechanism based on previous reports	Reference No.
Lipid metabolism abnormality	Promotion of differentiation of MSCs into mature adipocytes (PPARγ ↑ or C/EBPα ↑) Compression of intramedullary blood vessels and fat embolism by excessive amounts of adipocytes	28–30
Thrombosis / Blood Coagulation	Blood coagulation and thrombus formation by NO synthesis impairment t-PA ↓, PAI-1 antigen ↑ Abnormal levels of vWF, Lp(a), protein C/S Lupus anticoagulant and APTT ↓ (in SLE)	9,11,31–34
Cell death (Necrosis, Apoptosis, and Necroptosis)	Cell death of osteoblasts, osteocytes, and vascular endothelial cells (direct effect) Secondary vascular occlusion or local ischemia by vascular endothelial dysfunction (indirect effect)	7,35–37
Oxidative stress	Increase in adipogenesis through MSC dysfunction Vascular endothelial cell dysfunction by reducing NO bioavailability→Thrombosis, Blood coagulation Overproduction of ROS→Nuclear and mitochondrial DNA damage→Cell death	8,38–50

MSCs = mesenchymal stem cells, PPARγ = peroxisome proliferator-activated receptor γ, C/EBPα = CCAAT/enhancer binding protein α, NO = nitric oxide, t-PA = tissue plasminogen activator, PAI-1 = plasma plasminogen activator inhibitor-1, vWF = von Willebrand factor, Lp(a) = lipoprotein (a), SLE = systemic lupus erythematosus, APTT = activated partial thromboplastin time, ROS = reactive oxygen species.

CONCLUSION

In this review, the current knowledge about the etiology and patho-mechanism of ONFH was summarized. We also discussed important factors related to the pathogenesis of ONFH such as lipid metabolism abnormality, thrombosis, blood coagulation, cell death, and oxidative stress (Table 2). Corticosteroid administration is closely linked to these factors and acts on cells and tissues in a complex manner, leading to eventual tissue necrosis and occlusion of nutrient vessels in the femoral head region. We believe that further investigation of these factors lead to elucidation of the pathogenesis of ONFH and the establishment of a preventive therapy.

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