Review

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2018, Vol. 46(6) 2141–2148

DOI: 10.1177/0300060517700299
journals.sagepub.com/home/imr
SAGE

# Role of coagulopathy in glucocorticoid-induced osteonecrosis of the femoral head

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**Abstract**

The two major theories of glucocorticoid (GC)-induced osteonecrosis of the femoral head (ONFH) are apoptosis and ischaemia. The traditional theory implicates ischaemia as the main aetiological factor because the final common pathway of ONFH is interruption of blood supply to the bone. The most common causes of interruption of blood supply include fat embolism and coagulation disorders. GCs can directly or indirectly lead to coagulation disorders, producing a hypercoagulable state, followed by poor blood flow, ischaemia, and eventually ONFH. This review summarizes the existing knowledge on coagulation disorders in the context of GC-induced ONFH, including hypofibrinolysis and thrombophilia, endothelial cell dysfunction and damage, endothelial cell apoptosis, lipid metabolism, platelet activation, and the effect of anticoagulant treatment.

**Keywords**

Glucocorticoid, osteonecrosis, femoral head, ischaemia, coagulopathy

Date received: 22 January 2017; accepted: 27 February 2017

## Introduction

Increased glucocorticoid (GC) levels are the most common nontraumatic cause of osteonecrosis of the femoral head (ONFH).[1,2] GC-induced ONFH in young adults usually requires hip replacement[3,4] However, several studies have shown poor prosthetic durability in patients with ONFH.[5–7] A previous study showed that the mean daily GC dose was strongly associated with osteonecrosis (ON).[8] Most cross-study analyses demonstrate that a sustained large dose of GC can induce symptomatic ON.[9,10]

There is no widely held consensus on the pathogenesis of GC-induced ON. Several mechanisms of GC-induced ON have been proposed (Figure 1). A novel mechanism of

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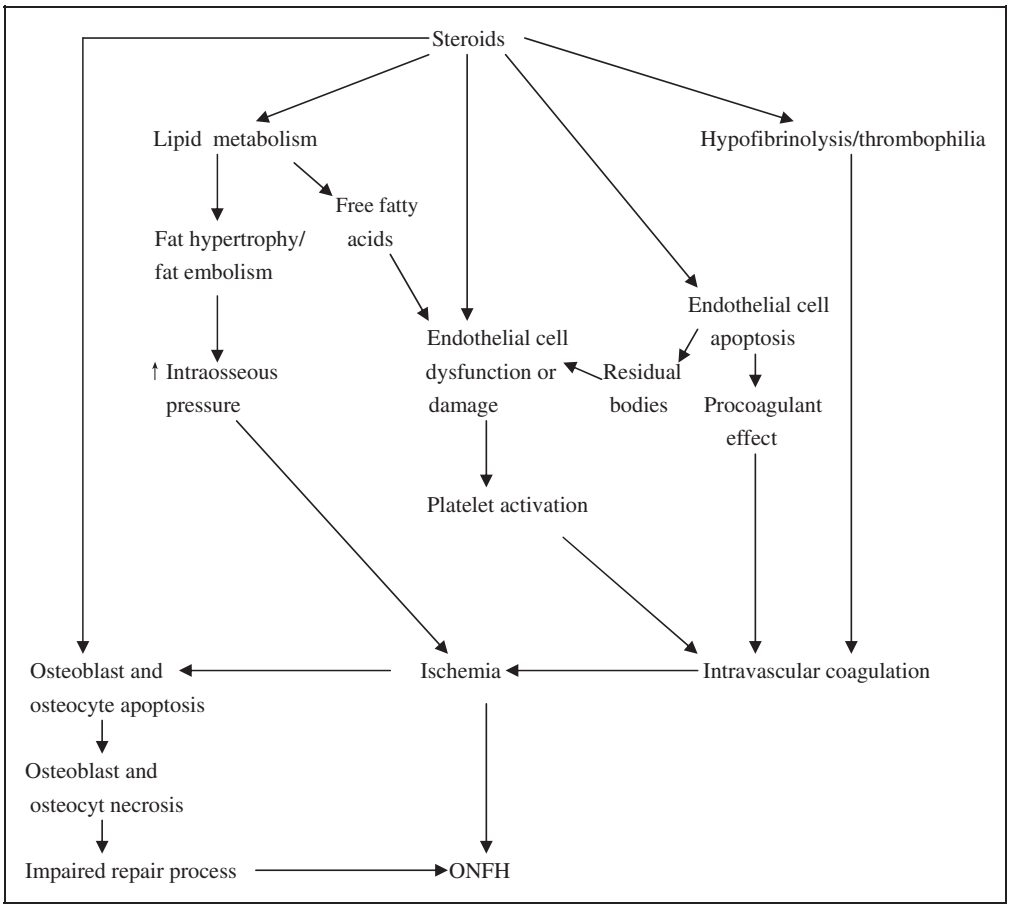


**Figure 1.** Plausible mechanisms for steroid-induced development of ONFH

GC-induced ON is apoptosis in osteoblasts and osteocytes, thus compromising bone formation and integrity.[11–14] However, the traditional concept of GC-induced ON implicates ischaemia as the main aetiological factor. GCs are thought to interrupt blood supply to the bone and eventually cause ONFH in a variety of ways.[15–18] The most common causes of interruption of the blood supply include fat embolism and coagulation disorders.[19–22] This article summarizes existing knowledge on coagulation disorders in the context of GC-induced ON. We review the literature and highlight controversies, with emphasis on the questions of how GC-induced coagulation disorders, directly or indirectly, relate to ischaemia in GC-induced osteonecrosis.

## Hypofibrinolysis and thrombophilia

Previous studies showed that high doses of dexamethasone administered to rats inhibited fibrinolytic activity by decreasing tissue plasminogen activator (t-PA) activity and increasing plasma plasminogen activator inhibitor-1 (PAI-1) antigen levels.[23–25] PAI-1 plays a role in fibrinolysis by forming complexes with t-PA. The t-PA/PAI-1

complexes do not have the ability to activate plasminogen to plasmin. GCs increase the activity of PAI-1, leading to hypofibrinolysis and a relatively hypercoagulable state.[26] Subsequent research showed decreased fibrinolytic activity, as a consequence of increased PAI-1, and decreased t-PA, by GCs in animals and patients with ON.[18,27–29]. Furthermore, as important factors of hypofibrinolysis, plasma fibrinogen and lipoprotein (a) (Lp(a)) are also abnormalities found in GC-induced or idiopathic ON.[30–34] In an ON animal model, Drescher et al.[30] showed that plasma fibrinogen was significantly elevated in ON following mega-dose GC treatment, which suggested a hypercoagulable condition in GC-induced ON. In a clinical study, Pósán et al.[34] found that Lp(a) levels were elevated in patients with primary and secondary ONFH. Other studies have investigated the association between thrombophilia and development of ON following GC treatment.[17,32,35–37] Guan et al.[35] showed that, at 24 hours after prednisolone injection, abnormal hypercoagulability occurred in a rabbit model. Glueck et al.[32] compared 36 patients with primary and secondary ONFH with healthy volunteers. They found that these patients were more likely to have thrombophilic disorders, heterozygosity or homozygosity for platelet glycoprotein IIIa P1A1/A2 polymorphism, anticardiolipin antibodies, lupus anticoagulant, or both, and deficiency in proteins C and S, or antithrombin III.

However, the association between hypofibrinolysis or thrombophilia with primary or secondary ON is unclear. Seguin et al.[38] showed that there was no association between thrombophilia with ON and considered that GC-induced regional endothelial dysfunction was a more likely reason. Asano et al.[39] found that genotypes of PAI-1 4G/5G and MTHFR C677T or plasma concentrations of PAI-1 Ag and tHcy had no effect on the incidence of ONFH in Japanese subjects, and suspected that this may differ according to race.

## Endothelial cell dysfunction and damage

Endothelial dysfunction may present early in GC-induced ONFH. Yu et al.[40] found that GC significantly affected the transcriptome of vascular endothelial cells of the human femoral head. Chen et al.[41] showed circulating endothelial progenitor cell damage in patients with GC-induced ONFH. In a histopathological study, Nishimura et al.[42] found endothelial cell damage by electron microscopy in steroid-treated rabbits. Li et al.[27] also showed endothelial cell damage with a high coagulant and low fibrinolytic milieu in an experimental study on GC-induced ON. In patients with dysbaric osteonecrosis, Slichter et al.[43] found platelet thrombus formation, which was secondary to endothelial cell damage in the femoral head.

The pathogenesis of GC-induced endothelial cell dysfunction and damage is multiple, and oxidative stress may play an important role.[44–47] After initial damage of endothelial cells triggered by GCs or other factors, a hypercoagulable state is produced. This is followed by vascular problems (thrombosis, poor blood flow, and ischaemia), and this in turn results in endothelial cell damage, which may be cyclic.[48–51]

## Endothelial cell apoptosis

GCs can induce endothelial cell apoptosis by a different signalling pathway.[52–55] Endothelial cell apoptosis consequently promotes thrombus formation and ON by two major mechanisms. First, apoptotic bodies can indirectly lead to coagulopathic changes by endothelial dysfunction. Second, apoptotic endothelial cells can stimulate adhesion of platelets to endothelial cells and activate platelets, eventually leading to thrombus formation.[50]

However, GCs can induce endothelial cell apoptosis and lead to a hypercoagulable state. Cessation or a reduction in blood flow along capillaries could also play an aetiological role in endothelial cell apoptosis.[59–61]

## Lipid metabolism

There is abundant evidence that excessive GCs can induce hyperlipidaemia, fat hypertrophy, fat deposition within the femoral head intramedullary tissue, and fat embolism. These factors may cause ischaemia by elevating intraosseous pressure and decreasing blood flow, eventually leading to ONFH.[62–70]

However, beyond the above-mentioned changes, dyslipidaemia can also lead to a hypercoagulable state and aggravate ischaemia.[20-22,50,71] Jones et al.[22] found intraosseous fibrin thromboses after induction of experimental fat emboli and speculated that fat emboli could trigger intravascular coagulation. Additionally, some vasoactive substances that are released from injured marrow adipocytes can affect endothelial cells that line blood vessels and produce a hypercoagulable state.[50]

## Platelet activation

High doses of GCs induce platelet aggregation.[72,73] There is evidence that platelet activation is involved in GC-induced ON. Masuhara et al.[74] found that platelet activation may play an important role in experimental ON in rabbits. In patients with ONFH, Pósán showed that platelet activation (measured by beta triglyceride) was significantly higher compared with that in healthy controls.[34] Similarly, in some animal studies on GC-induced femoral head necrosis, blood platelet levels were decreased in the early stage.[35,75] This finding indicates the occurrence of consumption coagulopathy caused by activation not only of endothelial cells, but also of platelets. Additionally, platelet thrombus formation has been detected in arterioles adjacent to the necrotic area by histopathological observation.[43,71,75]

In summary, platelet activation is involved in progression of GC-induced ON and the effect may be secondary to endothelial cell damage by GC.

## Anticoagulant treatment

Hypofibrinolysis (decreased ability to lyse clots) and thrombophilia (increased likelihood of forming thrombi) appear to play important roles in ON. If coagulation abnormalities cause ON, then anticoagulation therapy might ameliorate it. Wada et al.[76] found that warfarin decreased the incidence of ON in spontaneously hypertensive rats. Glueck et al.[77] studied patients whose ON was caused by heritable thrombophilia or hypofibrinolysis. They showed that 12 weeks of therapy with enoxaparin before femoral head collapse may slow progression or stabilize ON, as determined by X-ray and MRI, while providing pain relief. Motomura et al.[78] demonstrated that the combined use of warfarin and probucol helps prevent steroid-induced ON in rabbits. Kang et al.[79] also found that combination treatment with enoxaparin and lovastatin reduced the incidence of GC-induced ON in the rabbit.

In summary, coagulation abnormalities may play an important role in GC-induced ON. Additionally, anticoagulation therapy can significantly decrease the incidence of ON in GC-treated rabbits.

## Conclusion

This article provides an overview of the role of coagulopathy in GC-induced ON. GCs can directly lead to hypofibrinolysis and thrombophilia or indirectly lead to endothelial cell dysfunction and damage. Endothelial cell apoptosis, lipid metabolism, and platelet activation lead to a hypercoagulable state, followed by poor blood

flow, ischaemia, and eventually ONFH. Experimental studies have shown that use of an anticoagulant alone or combined with a lipid-lowering agent is beneficial in preventing GC-induced ON. Better understanding of the pathogenesis of GC-induced ON can generate better treatment options.

## Declaration of conflicting interest

The Authors declare that there are no conflicts of interest.

## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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