Mini review

Glucocorticoids in osteonecrosis of the femoral head: A new understanding of the mechanisms of action

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A R T I C L E   I N F O

A B S T R A C T

Glucocorticoid (GC) usage is the most common non-traumatic cause of osteonecrosis of the femoral head (ON). Despite the strong association of GC with ON, the underlying mechanisms have been unclear. Investigators have proposed both direct and indirect effects of GC on cells. Indirect and direct mechanisms remain intimately related and often result in positive feedback loops to potentiate the disease processes. However, the direct effects, in particular apoptosis, have recently been shown to be increasingly important. Suppression of osteoblast and osteoclast precursor production, increased apoptosis of osteoblasts and osteocytes, prolongation of the lifespan of osteoclasts and apoptosis of endothelial cells (EC) are all direct effects of GC usage. Elevated blood pressure through several pathways may raise the risk of clot formation. High-dose GC also decreases tissue plasminogen activator activity (t-PA) and increases plasma plasminogen activator inhibitor-1 (PAI-1) antigen levels increasing the procoagulant potential of GC. Inhibited angiogenesis, altered bone repair and nitric oxide metabolism can also result. Also, GC treatment modulates other vasoactive mediators such as endothelin-1, noradrenalin and bradykinin. Thus, GCs act as a regulator of local blood flow by modulating vascular responsiveness to vasoactive substances. Vasoconstriction induced in intraosseous femoral head arteries causes femoral head ischemia. GCs also cause ischemia through increased intraosseous pressure, which subsequently decreases the blood flow to the femoral head by apoptosis of ECs as well as elevating the level of adipogenesis and fat hypertrophy in the bone marrow.

It is difficult to predict which patients receiving a specific dose of GC will develop ON, indicating individual differences in steroid sensitivity and the potential of additional mechanisms. The textbook model of ON is a multiple hit theory in which, with a greater number of risk factors, the risk of ON increases. While more effort is needed to better comprehend the role of GC in ON, newer data on GC action upon the endothelial cell and the regional endothelial bed dysfunction theory sheds new light on particular GC mechanisms. Better understanding of GC pathomechanisms can lead to better treatment options.

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1. Background

Harvey Cushing recognized the adverse effects of hypercortisolism on bone as early as 1932. Currently, more than 30 million Americans require glucocorticoid (GC) drugs as part of their treatment regime. Depending on both the duration of therapy and dose, up to 50% of steroid users develop bone loss leading to fractures [1], while up to 40% of steroid users develop some degree of ON, a debilitating skeletal disorder [2]. GCs are known to be the most common non-traumatic cause of ON [3]. In 1987, Felson and Anderson performed a meta-analysis demonstrating that mean daily GC dose was strongly correlated with the disease. In this review, a 4.6-fold increase in the rate of ON was postulated for every 10 mg/day increase in mean daily oral dose of prednisone during the first 6 months of therapy [4]. Most series report agree that a sustained large dose of GC is required to sustain symptomatic ON [2,5]. Rare reports of ON after low dose or no GC exposure are probably related to underlying medical conditions, coagulopathic dyscrasias and genetic susceptibility [6–11]. Unfortunately, most patients with symptomatic ON of the femoral head eventually need surgery, usually total hip arthroplasty (THA), within a few years of onset [12]. Because the average age at presentation is about 33 years of age, these patients often require multiple increasingly difficult surgeries over the course of a lifetime [13]. A more complete understanding of why GC use is associated with ON would be helpful.

New research has revealed that there may be more to the disease process than an effect on bone cells alone. Endothelial cell susceptibility may actually be just as important or more pertinent to the evolution of the pathophysiology of ON in the femoral head [14]. Several mechanisms have been postulated for the role of GC-induced ON (Fig. 1). Some investigators assume a direct effect of the drug on bone cells. Older theories have considered an indirect effect of GC via an influence on the gonads and parathyroid glands. Recently, it has been shown that secondary hyperparathyroidism and hypogonadism appear to have no major role in the pathogenesis of GC-induced ON or in the resultant fractures [1] unlike earlier thinking. Thus, direct effect of GC on bone and other cells responsible for ON is undoubtedly more important than the indirect effect.

2. Role in apoptosis

Some action of GC is believed to be mediated by glucocorticoid receptors (GR) [15,16]. *In vitro* studies have shown the presence of GR in human and murine osteoblasts, osteocytes and osteoclasts [17–22]. For the first time, Silvestrini et al. showed that GR were present in cartilage (proliferative and hypertrophic zones) and in osteoblasts, ostocytes and osteoclasts of femurs of young adult rats [23]. Natural and synthetic GC bind to GR, producing major conformational changes that result in nuclear translocation or transrepression of transcription factor. This includes nuclear factor κB, which causes modification of pivotal mediators of innate and adaptive immunity [16]. Due to the ability of GC to modulate immune responses, they have been extensively used as anti-inflammatory agents. The immune response acts commonly through the Fas pathway, one of the best-characterized apoptotic pathways. Binding of FasL to FasR causes receptor oligomerization and recruitment of an adapter protein, FADD, which interacts with caspase-8, and initiates a caspase cascade which leads to apoptosis [24] in immunogenic cells. Dexamethasone (DEXA) and other GCs could also interact through the AP1 proto-oncogenes (c-Jun and c-Fos).

GR and AP1 interactions have been described in GC response elements (GREs), where these two transcriptional factors locate close together [15]. There is a relatively rapid induction of apoptosis in *in vitro* dexamethasone-treated T-lymphocytes that occurs within a few hours of exposure [25].

Despite the apoptosis effect of GC on T-lymphocytes, DEXA can promote proliferation and protect cells from apoptosis and/or necrosis in particular conditions. This effect has been seen in corneal epithelial cells, keratocytes, epithelial cells of the mammary gland, hepatocytes, and thymocytes. The GR gene response may positively or negatively regulate this paradoxical biphasic effect through different responses in different types of cells or through different dosages. For instance, DEXA would increase cell proliferation at low concentrations (below 10 μM) in some brain tumor cells and induce cellular apoptosis and/or necrosis at high concentrations (above 100 μM in brain tumor cells or 0.0001–0.001 M in corneal endothelial cells) [15,26]. Although not clearly defined, these dual effects of GC may also be the result of cross-talk between nuclear comodulators, or interactions of transcription factors [15].

3. Effects on bone

The osteoblasts and osteocytes of the femoral cortex mostly undergo apoptosis after a lengthy period of GC medication [27]. From *in vivo* and clinical studies, abundant apoptotic osteocytes and cells lining the cancellous bone were found juxtaposed to the subtotal fracture crescent in the femurs of the patients with GC excess [28]. A similar study by Calder and his colleagues has shown widespread apoptosis of osteoblasts and osteocytes in steroid- and alcohol-induced osteonecrosis patients [29].

O'Brien and his colleagues have shown that mice harbouring osteoblast/osteocyte-specific-11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) transgene were protected from GC-induced apoptosis of osteocytes and osteoblasts. 11β-HSD2, a high-affinity NAD-dependent enzyme, converts biologically active GC to its inactive metabolite and subsequently the inactivated GC would fail to activate the GR [30]. Despite the prevention from GC-induced decreased bone formation, the osteoblast/osteocyte-specific-11β-HSD2 transgene mice did not prevent the early rapid bone loss, as osteoclasts are not protected from GC [1]. Further studies have shown that the early loss of bone with GC excess is caused by a direct effect of GC on osteoclasts to extend their life span [31]. Osteoclast survival and differentiation are regulated by factors produced by stromal and osteoblastic cells. The critical factor is the receptor activator of NF-κB (RANK) ligand, a member of the tumor necrosis factor (TNF) ligand family. RANK ligand and macrophage-colony-stimulating factor are both crucial and sufficient for osteoclast differentiation in the absence of marrow stromal cells; RANK ligand also prolongs the survival of differentiated osteoclasts [1]. The quantities of TNF-α, RANK ligand and osteoprotegerin are raised in GC-treated osteoblasts and consequently, the differentiation of osteoclasts is blocked [27]. Therefore, it is not completely clear how the process of apoptosis of bone cells alone would result in ON.

Apart from the direct effect of GC, it has been shown that GC excess could affect the birth rate of bone cells. Weinstein et al. administered prednisolone to 7-month-old mice for 27 days and found decreased bone density, serum osteocalcin, and cancellous bone area along with trabecular narrowing. These changes were accompanied by diminished bone formation and turnover and impaired osteoblastogenesis and osteoclastogenesis [32].
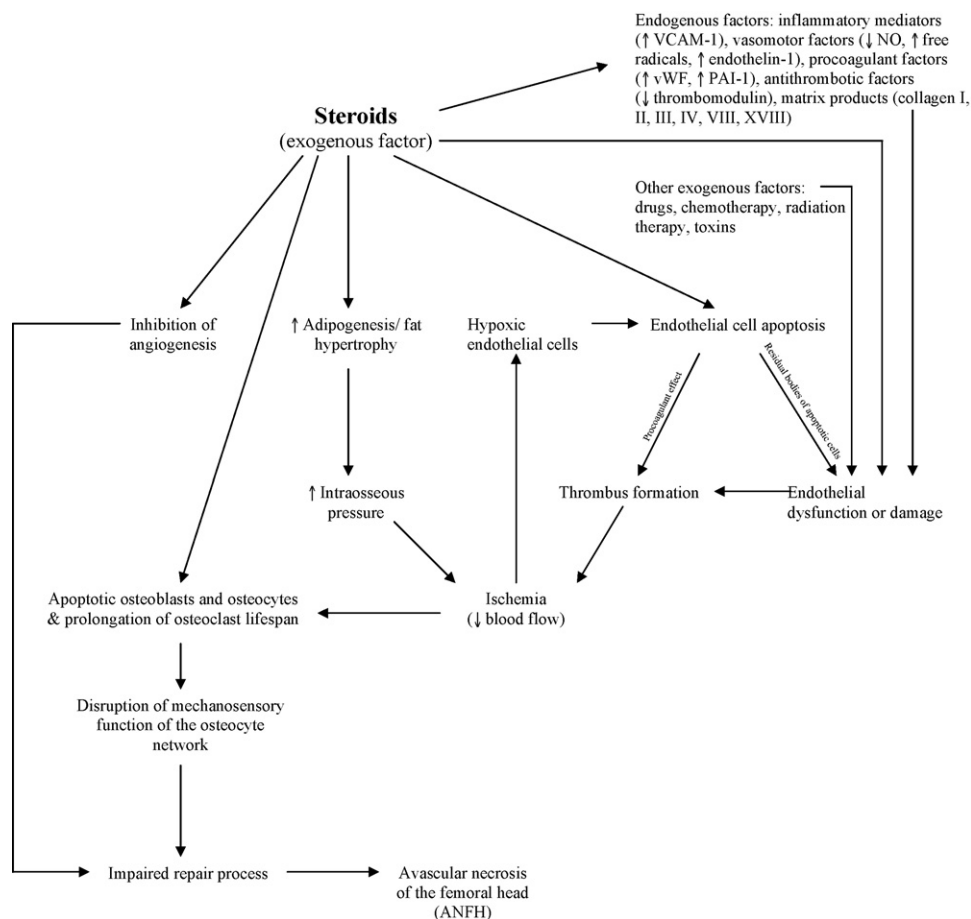
Fig. 1. Plausible mechanisms for steroid-induced ANFH development.

Therefore, it is assumed that the pathogenesis of GC-induced bone disease may at least partially be caused by suppression of osteoblast and osteoclast precursor production in the bone marrow, increased apoptosis of osteoblasts and osteocytes, and prolongation of the lifespan of osteoclasts [1].

It is also postulated that GC-induced osteocyte apoptosis disrupts the mechanosensory function of the osteocyte network, which is believed to constitute the mechanosensor and apparatus controlling repair processes in bone [33]. This may start the inexorable sequence of events leading to femoral head collapse [1]. In addition, the end result of fracture collapse may be facilitated by the co-existing osteoporosis mediated by GC-induced osteoblast apoptosis [33].

Bone morphogenic protein-2 (BMP2) gene expression also decreases after GC treatment. Individuals who were more susceptible to a GC-induced decrease in BMP2 and osteocalcin gene expression were more likely to have ON [34].

4. Effects on endothelial cells

GC has abundant effects on endothelial cells that line the sinusoids and inner layer of blood vessels in the femoral head. Experimental evidence of GC-induced hypertension indicates that raised arterial blood pressure is related to an elevated peripheral resistance [35]. GC action resulting in vasoactive mediators is discussed below. Another hypothesis that has been advanced as a mechanism for the enhanced peripheral resistance is a decrease in the number of functional microvessels or capillary rarefaction [36]. GC can directly injure endothelial cells [14] and enhance hypercoagulability [37]. In a study by Jacobs et al.,

damaged or abnormal reticular vessels was suggested to be the underlying mechanism of ON [38]. Damage of endothelial cells may result in abnormal blood coagulation and thrombi formation with ON occurring distal to the site of arterial occlusion [14].

6-Ketone prostaglandin $F_{1\alpha}$ (6-keto-PGF$_{1\alpha}$), a metabolite of prostaglandin I_2 (PGI$_2$), is considered as a marker of endothelial cell injury [39]. PGI$_2$, mainly produced by vascular endothelial cells, strongly dilates blood vessels and inhibits platelet aggregation. In a study by He et al., the level of 6-keto-PGF$_{1\alpha}$ decreased significantly compared to controls in an ON rabbit model induced by endotoxin and GC. This suggests another endothelial cell impairment in ON [40], which may be GC-mediated.

It has been postulated that apoptotic endothelial cell death serves as a mechanism for the capillary rarefaction in glucocorticoid-mediated hypertension [41]. Therefore, it is plausible that GC-induced hypertension in the femoral head disturbs the blood flow in the femoral head vessels and aborts the repair process [14]. Furthermore, enhanced blood pressure in the blood vessels of the femoral head could increase thrombin, which converts fibrinogen to fibrin, forming fibrin clots. Studies on the enzymes involved in the coagulation cascade have shown that thrombin is elevated in the established phase of hypertension as a consequence of raised blood pressure [42].

5. Avascular necrosis and the coagulation pathway

It has been shown in both *in vivo* and *ex vivo* studies, that lower doses of several types of GC will initially inhibit arterial thrombosis through inhibition of platelet aggregation. At higher doses,

these effects are counteracted by a significant inhibition of the fibrinolytic activity [43–47]. The latter was shown to occur as a result of decreased tissue plasminogen activator activity (t-PA) and increased plasma plasminogen activator inhibitor-1 (PAI-1) antigen levels [43,44]. Decreased fibrinolytic activity, which may be a consequence of increased PAI-1, has been described in patients with ON [48]. In a study performed by Yamamoto et al., DEXA upregulated PAI-1 gene expression in human umbilical vein endothelial cells (HUVEC) stimulated by TNF-α conditioning. They postulated that such inflammatory conditions (DEXA exposure and TNF-α conditioning) could promote blood procoagulant effect by acting on vascular endothelial cells [49]. Furthermore, Drescher et al. showed in an ON animal model, that plasma fibrinogen was significantly increased at the early stage of ON following a megadose steroid treatment [50] suggesting a pro-inflammatory condition in steroid-induced ON.

One could argue that GC may potentially be responsible for a systemic response resulting in ON. Some cases have shown that clinically significant ON in several joints can result from the use of high dose GC [36,51,52]. However, this is the exception rather than the normal presentation. Recently, the literature has been at odds for an opinion of whether systemic defects in the clotting mechanism actually account for clinically significant ON. Several studies have revealed that the prevalence of thrombophilic and hypofibrinolytic coagulation abnormalities in patients with GC-induced ON is increased compared to controls [9,10,53–55]. A few studies have reported that there were no significant differences in the levels of thrombotic and fibrinolytic factors [56,57]. The general irreproducibility of systemic blood clotting defects amongst patients with ON is concerning. Dozens of different blood thrombophilic factors probably cannot be responsible for a single disease process. Also, still unexplained are the many patients without known systemic defects. A mechanism by which ON of the femoral head is dependant on a local dysregulation of coagulation at the level of the femoral head can explain the disease process [14]. Clotting at the microcirculation level is more likely dependant on the local balance of pro- and hypo-coagulant factors at the endothelial cell surface of the bone regional vascular bed than it is upon the systemic clotting factors.

Slichter et al. showed endothelial cell damage followed by platelet thrombus formation with secondary fibrin deposition in the femoral head in dysbaric ON [58]. Li et al. also showed endothelial cell damage as well as a pro-coagulant and a low fibrinolytic milieu – as potential pathologic mechanisms of GC-induced ON [39]. Intravascular coagulation is itself an intermediary event that has both hereditary and acquired risk factors. There are two forms of plasminogen activator inhibitor (PAI). PAI-2 is a thromboblastic product and PAI-1 is a serine protease inhibitor that is synthesized and released by endothelial cells in blood vessel walls. PAI-1 exerts its regulatory activity on fibrinolysis by forming complexes with tissue plasminogen activator (t-PA). The t-PA/PAI-1 complex does not have the ability to activate plasminogen to plasmin. Increase in PAI-1 activity suppresses the generation of plasmin resulting in hypofibrinolysis and a relative hypercoagulable state [59]. In a clinical and experimental study, the activity of t-PA and PAI-1 decreased and increased respectively in patients with ON [39]. Endothelial injury or dysfunction can activate the thrombotic cascade, followed by ischemia and infarction in the femoral head [14]. Thrombus formation can also be stimulated by other mechanisms such as the microparticles, composed of residual bodies of apoptotic endothelial cells, directly inducing endothelial dysfunction followed by activation of the thrombotic cascade. Apoptosis of endothelial cells stimulates the binding of thrombocytes to the endothelium that further induces platelet activation and thrombus formation [60].

6. Effects on angiogenesis and the repair mechanism

Following necrosis of the femoral head, a repair process begins with the entry of blood vessels into the necrotic region, followed by bone resorption and subsequent bone formation. Several essential factors such as vascular endothelial growth factor (VEGF), act directly on endothelial cells and induce angiogenesis [61]. Dysregulation of these essential factors will have an effect on angiogenesis, and consequently the repair process. Yang et al. used VEGF gene transfection to enhance the repair of ON in a rabbit model of ON [61,62]. It has been shown that DEXA can decrease the synthesis of VEGF protein, as measured by ELISA, by 45% in a multipotential cell line (D1) derived from bone marrow [63]. Myofibroblastic cells induce capillary formation by producing endothelial growth factor and collagen [64,65]. Harada showed that GC inhibited capillary growth significantly by suppressing collagen synthesis by myofibroblastic cells [65]. In addition, other mechanisms may impede angiogenesis. One of them appears to be related to basement membrane turnover, which is determined, in part, by proteolytic activity associated with proliferating vessels [26]. Plasminogen activators are serine proteases that convert plasminogen to plasmin and can cleave extracellular proteins, either directly or indirectly as a result of plasmin production. This alters cell–matrix interactions by liberating mitogens and angiogenic factors that stimulate endothelial migration and proliferation [26]. Decreased fibrinolytic activity, which may be a consequence of increased PAI-1, has been described in patients with ON [10,11,66]. Inhibition of proteolytic steps involved in vessel growth may underlie, in part, the mechanism by which GCs induce ON.

In addition to GC, constituents of cartilage as well as interferons have been shown to be potential inhibitors of angiogenesis. Following subchondral fracture, the cartilage components are directly exposed to the ongoing repair process through the fracture cleft. Cartilage constituents may thus play a role in the development and/or continuance of the disease process in ON and explain the localization of ON to subchondral bone tissue [48]. ON has also been reported secondary to interferon treatment in multiple sclerosis, Crohn's disease, leukemias, and hemangiomas [54] when used alone or in association with GCs.

7. Action on vasoactive substances

Vascular endothelial cells regulate vascular tone through the release of relaxing and contracting factors that modulate the contractile activity of vascular smooth muscle cells. GC excess causes overproduction of reactive oxygen species (ROS) such as superoxide, hydrogen peroxide and hydroxyl radicals, and thereby perturbs nitric oxide (NO) availability in the vascular endothelium. These events can lead to vascular complications in patients with GC excess. Nitric oxide (NO), an endothelial cell-derived relaxing factor, is an important vasoactive mediator for the reaction of endothelium-dependant vascular relaxation. A decrease in its availability due to perturbation of synthesis and/or release of NO by vascular endothelial cells causes an increase in vascular resistance [67].

GC excess enhances superoxide-induced inactivation of eNO (endothelial nitric oxide) and suppresses eNO production through decreasing the expression of endothelial nitric oxide synthase (eNOS). The synthesis of eNO could be influenced by GC through three potential mechanisms: direct injury effect of GC on endothelial cells, repressing eNOS activity and increasing blood lipid levels [39]. eNO has several anticoagulant actions, including dilatation of blood vessels, prevention of platelet aggregation and inhibition of monocyte adherence to the endothelium [68]. GC-induced decrease in NO bioavailability elicits vascular endothelial dys-

function, leading to insufficiency of peripheral circulation, thus a potential mechanism for glucocorticoid-induced ON [69].

The response of isolated intraosseous femoral head arteries (lateral epiphyseal arteries which provide the major blood supply to the femoral head) to endothelin-1 was enhanced after long-term corticosteroid treatment (3 months of methylprednisolone) in an immature pig. The response to other physiological vasoactive substances such as noradrenalin, substance P nitric oxide and bradykinin was unchanged [70]. Endothelins are potent vasoconstrictors that are synthesized and released by vascular endothelial cells and that bind to vascular smooth muscle in bone. In another study by Drescher et al. [71] vasoconstriction by noradrenalin was not altered by methylprednisolone. However, bradykinin elicited a concentration-dependent vasodilatation, which was lower in the GC-treated vessels than in the non-treated vessels. In contrast, endothelin-1-induced vasoconstriction was stronger in the GC-treated vessels. Endothelin causes vasoconstriction by increasing intracellular calcium levels in vascular smooth muscle. Endothelin-1 has the strongest vasoconstrictive potential among endothelins. Hence, methylprednisolone was shown to enhance constriction of femoral head lateral epiphyseal arteries, decreasing femoral head blood flow [72].

Prostacyclin is another potent vasodilator produced by vascular smooth muscle cells and endothelial cells, and its production is decreased by GC treatment [72]. From studies on proteases involved in blood pressure homeostasis, DEXA was shown to increase angiotensin-converting enzyme aminopeptidase, while suppressing the kallikrein-kinin system. These effects resulted in enhancement of angiotensin II and angiotensin III levels which also contribute to elevation of blood pressure. The suppression of the kallikrein-kinin system (by DEXA itself and by elevation of angiotensin-converting enzyme) also has additive effect by inhibiting vasodilation [73].

Thus, GCs appear to act as regulators of local blood flow by modulating the vascular responsiveness to vasoactive substances. This phenomenon potentiates the hypertension induced by endothelial cell apoptosis as discussed above. GC-induced vasoconstriction in the intraosseous femoral head arteries reduces blood flow and causes inadequate blood supply to the femoral head.

8. Glucocorticoid and fat metabolism

It has been proposed that GCs produce serious intramedullary fatty infiltration [74]. The effect of this fatty tamponade in the medullary cavity is the result of lipocytes on the surface of vascular sinusoids resulting in less efficient function of vascular sinusoids and diminished vascular area in the femoral head [75]. The diminished blood flow at the femoral head level can lead to secondary necrosis [74].

In an in vitro study by Li et al., DEXA-induced adipogenesis in a pluripotent marrow cell lineage (D1) cloned from BALB/c mice, was accompanied with lipid vesicle accumulation within the cells, up-regulation of the expression of adipogenic genes (AP2 and PPAR [gamma]), and down-regulation of osteogenic gene expression, type I collagen, Runx2/Cbfa1, and osteocalcin [63,76]. The effect of steroids on adipogenesis by D1-BAG, a pluripotent cell cloned from mouse bone marrow and transfected with traceable genes encoding beta-galactosidase and neomycin resistance, was investigated in in vitro, ex vivo and in vivo in mice. Treatment of D1-BAG cultured cells with DEXA produced an accumulation of lipid vesicles and stimulated expression of fat cell-specific 422(aP2) mRNA. Data from the mice (in vivo) study showed adipogenesis from steroid treatment in 5–9% of transplanted cells. These results indicate that steroid-induced differentiation of potentially osteogenic marrow cells into adipocytes may contribute to the development of ON [77]. It has been shown that the number of adipocytes in culture increased with longer marrow stromal cells' exposure to DEXA and the concentration of DEXA [78]. As above, data from in vivo studies demonstrated that adipocytes in bone marrow increased after steroid exposure. Fat degeneration and necrosis, considered early signs of ON, were also observed [12]. Li et al. have also shown that DEXA can directly induce differentiation of marrow stromal cells into a large number of adipocytes and inhibit their osteogenic differentiation [78]. Kitajima et al. showed that mature fat cells exposed to high-dose GC were bigger than control cells both derived from bone marrow [79]. In their study, Jones et al. suggested that liquid fat, thromboplastin and other vasoactive substances released from injured marrow adipocytes in ON affect the vascular walls (endothelial cells) and produce a hypercoagulable state through the endothelial cells [80].

Therefore, these studies suggest that GC might cause ischemic ON through elevation of intraosseous pressure, and subsequently decreased blood flow to the femoral head via adipogenesis and fat hypertrophy in the bone marrow.

9. Interaction with regional endothelial beds

As mentioned above GC excess causes overproduction of reactive oxygen species and thereby perturbs NO availability in the vascular endothelium. The endothelial cell monolayer constitutes the inner lining of the vascular wall and plays an essential role in the homeostasis of the blood. Due to its unique localization, the endothelium is continuously exposed to inflammatory cells and circulating factors which can induce endothelial activation and/or injury [81]. The concept of a focal nature of a systemic haematological defect resulting in local hypercoagulable state is relevant to femoral head ON [54]. Clotting abnormalities often manifest in isolated endothelial beds. Deficiencies of antithrombin III, protein C and protein S result in deep venous thrombosis of the extremities. Thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome result in microthrombotic lesions that are detectable in all organs except the liver and lungs. Antiphospholipid-antibody syndrome results in clotting of only particular venous and arterial areas including the retina and the placenta. The heterogeneity of the endothelial cell structure amongst these many different organs has been postulated to be a probable cause for the varied clotting responses in the separate endothelial beds [82]. Regional endothelial beds (REBs) have a different local expression of systemic defects. This regional endothelium dysfunction may be a mechanism for ON [14].

Endothelium dysfunction or activation, primarily by endothelium itself or secondary to a stimulator, could activate the thrombosis cascade, followed by ischemia and infarction. Medications such as GCs reinforce the vascular processes leading to thrombotic occlusion. They directly injure endothelial cells and amplify hypercoagulability [37].

10. Risk factors and underlying disease

GC may potentiate the effects of endogenous hypercortisolism (Cushing's disease), a pre-existing condition known to increase the risk of ON [83], although ON is more likely to develop following exogenous GC administration [84]. Specific binding for [3H]DEXA with high affinity and low capacity has been demonstrated in the isolated osteoblasts, mostly binding in the nuclear fraction, with a dissociation constant (Kd) of approximately 3.3 nM [22]. The Kd of [3H]triamcinolone acetonide, another exogenous GC, was equal with 4.0 ± 1.43 nM, reflected high-affinity binding [85]. In contrast, the Kd for GR of endogenous GC, cortisol/corticosterone has been reported to be 10–20 nM [86]. Thus, the relative binding affini-

ties of steroid for receptor were found to be greater in exogenous than endogenous GC. The use of high doses of hydrocortisone or methylprednisolone for an extended duration was shown to be a significant risk factor for ON in patients suffering from severe acute respiratory syndrome [87]. ON has been reported with moderate to high doses of short duration steroid usage in infertility treatment [88,89]. Amongst many other disease processes, ON has also been reported during the treatment of hay fever with corticosteroid use over a period of 10 years [90–92]. Some diseases have been reportedly associated with ON, regardless of GC treatment [54].

Amongst patients receiving a specific GC dose, only an unpredictable subset will develop ON, suggesting the presence of individual differences in steroid sensitivity and the potential presence of additional specific risk factors. A genetic risk factor for intravascular coagulation may not, by itself, provide an answer. Although the prevalence of coagulation abnormalities in patients with GC-induced ON is increased in some studies compared to controls [9,10,53–55], a considerable proportion of ON patients does not demonstrate an increased prevalence for thrombophilic disorders [56,57]. Furthermore, not all patients with both GC usage and thrombophilic factors develop ON [33]. Likewise, although alcoholism is associated with ON as an etiological factor, not all heavy alcohol users develop the disease. Therefore, it is difficult to say whether ON that occurs in patients with an underlying or predisposing factor, is actually due to the underlying disease or risk factor rather than GC treatment or alcohol. Many of the patients with predisposing factors or underlying diseases, such as systemic lupus erythematosus or acute leukemia, also have been administered GC as part of their treatment regimen. Similarly, while most therapeutic regimens in oncology include steroids as part of the protocol or as an adjunctive measure in the control of nausea and/or prophylaxis against hypersensitivity reactions, cases of ON developing after chemotherapy (with or without steroids) or radiation therapy have been well described in the oncology literature [93–95]. As well, several investigators have reported ON developing in patients before GCs or replacement treatment regimen take place [6,96–98]. Hence, the current pathophysiological model of ON puts forward a multiple hit theory in which, with increasing number of risk factors, the risk of ON increases [99]. Amongst the many risk factors, GCs have the leading role in ON.

11. Conclusion

The pathogenesis of ON is multifactorial. One strategy to prevent the development of ON is to reduce the potential risk factors. For example, one such strategy is the use of an anticoagulant or a lipid-lowering agent to prevent the development of ON as shown in some animal models [68,79,100]. Experimental studies showed that combined use of an anticoagulant and a lipid-lowering agent was found helpful in preventing steroid-induced ON in rabbit models [101]. While more effort is needed to better comprehend the role of GC in ON, trial therapies involving antithrombotic drugs that interfere with the function of endothelial cells, medical interventions promoting angiogenesis, administration of lipid-lowering agents and anti-apoptotic drugs may all be useful in the treatment of patients with ON. The textbook model of ON is a multiple hit theory in which, with a greater number of risk factors, the risk of ON increases. Nevertheless, GCs being considered having a leading role in ON, newer data on GC action on endothelial cells and the regional endothelial bed dysfunction theory will hopefully shed new light on GC mechanism of action in ON. Several pathways of GC are now better understood. Future medical and surgical management of ON may be better served by treatment modalities exploring these new important pathways.

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