The progressive fragmentation of bones due to interrupted blood supply is called bone infarction (BI) (1, 2). Chronic use of steroids may produce fat emboli and thrombotic occlusion. It leads to reduction in blood supply to bones resulting in osteocytes necrosis or steroid induced bone infarction (SIBI). It is a painful condition, which resists to patient’s movement. The severity of pain increases with time. Various treatment or preventive options are available if diagnosed earlier; however, late diagnosis complicates the choice of therapeutic approaches. In advanced disease state, only option is surgery of necrotic region (3-9).

Hypercortisolism is the non-traumatic cause of BI. The femoral head is the most common location for SIBI. The incidence of BI is high in young and active individuals. Beside it, other skeletal parts including shoulder, knee, ankle and hand are also affected by SIBI (13). Hypercortisolism results from systemic administration of steroids in large doses for prolonged period i.e., up to 90 days or longer (12-22). For example, methylprednisolone-induced femoral head osteonecrosis, however prediction of its development in a specific patient is not feasible (23). In a study on 6000 patients with femoral head injuries, no signs of osteonecrosis were observed after chronic use of high-dose steroids (24). In another study conducted on patients receiving high-dose steroids, the prevalence of osteonecrosis was not greater than five percent (23). Quite the opposite, the development of osteonecrosis has been reported in patients receiving high-dose steroids for short period (24). Some studies have also reported SIBI of the femoral head after comparatively short periods (one week) of oral steroids (13). First case of SIBI was reported in 1957, and number of reported cases increased to 154 in 1968, due to which SIBI is known as a disease of medical progress (19). However, the cautious use of steroids has now resulted in significant decrease in the incidence of BI among patients, chronically treated with systemic steroids (20). As far as epidemiology of glucocorticoid-induced BI is concerned, SIBI
produces significant morbidity accounting for approximately 10% of all cases of total hip replacement (THR) in the United States (12). The incidence of SIBI with systemic lupus erythematosus and post-renal transplantation as co-morbidities is 3-41% (13) and 4-40% (1), respectively. This prevalence feature depends on the dosage of steroids and their route of administration.

Mode of pathogenesis

The exact pathology of BI is still undiscovered. Based on a hypothesis, BI is developed because of osteocyte necrosis and blood vessel blockage leading to reduced blood flow to bone, which results in BI. Mechanistically, osteocyte necrosis occurs due to apoptosis and fat cell hypertrophy (FCH), while fat emboli causes blood vessel blockage.

Wang et al. administered high-dose cortisone to rabbits and observed the production of FCH and fat embolism, which caused abolition of blood vessels in the subchondral bone of femur. In addition, they also noted the increased number of marrow fat cells in these rabbits (25). After administration of dexamethasone to pluripotent cell line acquired from mice bone marrow, Cui et al. also observed in vitro FCH and hypothesized of FCH-induced expansion of cell volume within a limited volume of the femoral head. It reduces the perfusion of blood leading to BI (26). Conversely, the complement pathway is activated by fat emboli dumped within the subchondral vessels and sinusoids. It causes the dumping of immune complex followed by the initiation of various thrombotic processes including intravascular coagulation and then the development of BI (27). In a study to demonstrate the effect of lipid lowering agent (clofibrate) in the steroid-treated rabbits, the researchers observed the decreased fat cell size and intra-cortical pressure with subsequent improvement of blood flow (28-30).

Another pathologic factor for BI is the apoptosis of osteocytes in the affected bones (31, 32), which is not observed in BI induced by other factors including alcohol usage or trauma (33). Calder et al. and Weinstein et al. observed the apoptotic osteocytes in pathologic specimen of femoral head during THR in patients suffering from SIBI. Owing to gradual accumulation of these apoptotic osteocytes in the bony tissues, osteocyte-lacunar-canalicul system is disrupted and eventually femoral head collapse takes place (31-33).

Steroid-induced bone infarction regions

The literature survey showed various studies conducted on systemic lupus erythematosus (SLE) patients who were chronically treated with steroids (34-36). In these patients, the diagnostic findings revealed SIBI at multiple sites (more than two joint regions). Various case studies elaborated that the SLE patients with BI involving multiple joint regions ranged between 70-90% (34-36). One of these studies conducted on 95 SLE patients with symptomatic BI reported that hip (54.7%) and knee (18.9%) joints were the most frequently affected regions. Another study revealed 12% incidence of BI in SLE patients who received a considerably higher average daily dose of prednisolone (15.62 mg) in comparison to SLE control patients (9.3%) with no BI (5 mg) (8). The most affected site in these patients was the hip joint in 95% patients which was bilateral naturally in 72% of patients. Similar results were reported in another study that showed the incidence rate of SIBI by 82%, 64%, 20%, and 25% in hip, knee, ankle, and shoulder joints, respectively (37).

Risk factors

There are conflctions among different studies on the association between BI development and steroid usage factors, i.e., dose, route of administration and duration of use. Some studies report the emergence of BI after prolonged, high-dose steroids usage (15, 38, 39), while few investigators claim that high-dose steroids usage for short period may also produce BI (39-41). For example, BI was observed in significantly higher number of SLE patients who received methylprednisolone pulse treatment (19%) as compared to control group of SLE patients who did not receive methylprednisolone pulse treatment (6%) (40). In another study, BI was not noted in 17 SLE patients who received steroid pulse treatment (42). Moreover, some investigators have reported the development of BI after steroids usage through various routes including oral, intravenous, intra-articular and intra-muscular (43, 44).

In some meta-analysis studies, positive relationship between BI development in SLE patients after renal transplantation and daily dose of steroids was determined (15, 45-52). A retrospective study revealed the emergence of BI in 190 SLE patients who used > 40 mg of prednisolone per day for one month (40). Another similar study reported the development of BI in SLE patients who used 30 mg of prednisolone per day for one month (45). Moreover, positive correlation also exists between BI development in SLE patients and cumulative dose of steroids (10, 50, 53). The incidence of BI was higher in SLE patients who received the cumu-
lative dose of prednisolone at 1 and 4 months compared to the control group (10). In renal transplant cases, the incidence of femoral head BI was also higher when larger total steroid dose was used during first 2 months of therapy (50, 53).

**Initiation**

Table 1 describes the onset time of BI after commencing of steroid treatment. It is evident from the tabulated data that development of BI commences as early as 3.1 months of steroid usage (54-57). It can be concluded that patients and their physicians should remain cautious for the risk of BI development during the treatment course, mainly during first 12 months of commencement of steroid treatment.

**Progression and regression**

Literature study elaborates various studies about the progression of SIBI after its initiation. Spontaneous regression has been observed in SIBI cases of femoral head, hip and knee (56-59). The serial MRI scan revealed spontaneous incomplete regression in 41.1% of patients who suffered from stage I SIBI of knee showing no subsequent symptoms such as bone tissue failure (59). In another study on knee BI, serial MRI scan showed natural improvement of necrotic region in 45% of patients for 12 months after start of steroid followed by no more improvement in the subsequent years (58). Another follow up study revealed spontaneous size regression in 28% renal transplant patients with hip BI. The spontaneous regression depends upon the stage of BI, for example, the probability of regression of early stage BI is higher than that of later stage. In addition, regression of BI depends upon the time duration between treatment initiation of steroid and diagnosis of BI, i.e., the probability of regression of early diagnosed BI is higher than that of later diagnosed after start of steroid therapy. Moreover, the regression of BI is not influenced by the size and site of necrosis (59).

**Pharmaceutical option for treatment**

Pharmaceutical strategy for treatment of SIBI involves the use of various pharmacologically active compounds including bisphosphonates, hyperbaric oxygen (HBO), coenzyme Q<sub>10</sub>, erythropoietin, antihyperlipidemics, anticoagulants, antioxidants and tissue repair protein (66-87).

**Bisphosphonates**

Though bisphosphonates are unable to stop progressiveness of joint destruction; however, these compounds are useful for improving clinical and pain status of patients with steroid-induced bone infarction (SIBI) (60). Pharmacologically, bisphosphonates promote osteoclasts apoptosis and reduces resorption of the osteoclasts. Moreover, the apoptosis of osteoblasts and osteocytes is also inhibited by bisphosphonates. On the other hand, clinical findings and animal studies have revealed that usage of bisphosphonate leads to development of osteonecrosis of the jaw (61, 62). Due to such unwanted effects, further investigations involving larger number of patients should be done for loss-benefit analysis to check therapeutic efficacy of bisphosphonates in SIBI patients (63). Patient’s movement in SI-BN has been made pain-free by using alendronate, which is observed to be capable of inhibiting bone marrow edema (64-66). However, alendronate is not found therapeutically effective in another study conducted in SIBI for 25 weeks. This study showed 7% and 76% therapeutic effectiveness of alendronate and placebo treatment, respectively (67, 68).

**Hyperbaric oxygen**

Patient’s mobility in SIBI has also been improved by using hyperbaric oxygen (69). The mode of analgesic action of hyperbaric oxygen involves the improvement in oxygen supply to the hypoxic tissues resulting in suppression of edema leading to vasoconstriction (70).

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**Table 1. Time of onset of BI after initiation of high-dose steroid treatment.**

<table>
<thead>
<tr>
<th>No.</th>
<th>Total number of patients</th>
<th>Number of patients with BI detected after initiation of treatment</th>
<th>Time of onset of BI after initiation of steroid</th>
<th>BI type</th>
<th>Evidence</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>21</td>
<td>12 months</td>
<td>Femoral head</td>
<td>MRI</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>32</td>
<td>3.1 months</td>
<td>Hips and knees</td>
<td>MRI</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>48</td>
<td>3.6 months</td>
<td>Femoral head</td>
<td>MRI</td>
<td>57</td>
</tr>
</tbody>
</table>
Coenzyme Q₁₀

Coenzyme Q₁₀ is a lipophilic vitamin-like potent antioxidant. Kömürçu et al. studied the prophylactic effect of coenzyme Q₁₀ in 20 Sprague-Dawley rats with methylprednisolone acetate induced-BI. After 30 days, the hematological examinations revealed the restored normal levels of blood glutathione and malondialdehyde in rats treated with coenzyme Q₁₀ in comparison to control group (not treated with coenzyme Q₁₀). Conclusively, coenzyme Q₁₀ was found to have preventive role in the development of SIBI, possibly due to its antioxidant property (71).

Erythropoietin

Keeping in mind anti-apoptotic and tissue protective role of erythropoietin, Chen et al. tested this compound for managing methylprednisolone acetate induced-BI in rats. Beside reduced expression of caspase-3, the findings of this study reported the improvement in histological state of femoral head in erythropoietin treated rats (test group) as compared to that of control group rats (rats with SIBI but not treated with erythropoietin). Moreover, the preventive role of erythropoietin against SIBI was also observed in test group. The authors also mentioned inhibition of apoptosis of osteocytes and osteoblasts and enhanced expression of vascular endothelial growth factor as the mechanism of anti-SIBI (anti-steroid-induced bone infarction) activity of erythropoietin (72, 73).

Antihyperlipidemics and anticoagulants

The development of SIBI may also be prevented through statin treatment (74, 75). For example, significant reduction in bone fat volume and serum lipid levels, in comparison to the control group, has been reported in rabbits with SIBI after treating with lovastatin (76). According to another study, the usage of cholesterol- and lanolin-rich diets may decrease the incidence of SIBI in comparison to control group of rabbits (77). Since SIBI progression depends on combination of hyperlipidemia and abnormal coagulation, antihyperlipidemics and anticoagulants were simultaneously administered to model rabbits with SIBI to test their therapeutic effectiveness. It resulted in significantly lower incidence of SIBI as compared to that of individual treatments (78, 79). Jiang et al. reported that pravastatin may be used for prevention of SIBI in rats. Mechanistically, pravastatin inhibits PPARγ expression and activate Wnt signaling pathway (80). Thus, antihyperlipidemic and anticoagulant drugs may be suggested to treat SIBI.

Antioxidant treatment

The usage of steroids leads to the induction of oxidative stress, which results in the development of SIBI. It can, therefore, be managed by using the antioxidants (81, 82). In this context, significant reduction in the incidence of SIBI and oxidative stress by using vitamin E in model animals has been observed (83, 84). The possible mode of action...
might be the oxidative stress reducing action of Vitamin E on blood and blood vessels, which leads to the anticoagulant effect.

**Iloprost**

Iloprost is a synthetic analogue of prostacyclin PG\(\text{I}_2\). It acts as vasodilator and has been proposed to be a suitable therapeutic agent at the early stages of SIBI (85, 86). The mode of action of iloprost involves vascular dilation restoring the blood flow to necrotic region.

**Tissue repair protein**

Ding et al. transplanted HIF (hypoxia inducible factor)-\(\text{I}\alpha\) transgenic bone marrow cells and noted the improvement in bone regeneration in necrotic regions of SIBI. They attributed tissue repair function of this protein to enhanced expression of mRNA of osteogenic genes and osteogenic differentiation (87).

**CONCLUSION**

Though above stated studies propose some pharmaceutical agents as possible remedy for SIBI, but all of these strategies have serious limitations. Thus, it can be concluded that no efficient pharmaceutical remedy is yet discovered or introduced. The possible fact might be that the exact pathology of SIBI is still undiscovered. Many factors are found to be responsible for SIBI development; therefore, there are multiple biomarkers of this disease. Conclusively, protein-protein interactions should be conducted with the help of computational chemistry and new therapeutic agents should be introduced.

**REFERENCES**


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