Musculoskeletal Side Effects Associated with Long-Term Corticosteroid Use

(Review Article)

Abstract

Corticosteroids are widely used medications with increasing prevalence in clinical practice. In autoimmune and rheumatological diseases, the use of corticosteroids in both pulsed and long-term manners is very common. Due to the COVID-19 pandemic, their consumption increased. However, long-term use is associated with several adverse effects on the musculoskeletal system, including osteoporosis, an elevated risk of fracture, avascular necrosis, hypocalcemia, hypovitaminosis D, and impaired bone growth in children. Corticosteroid-induced osteoporosis is the most common form of secondary osteoporosis. Several factors, such as age, time of use, family history of osteoporosis, previous fractures, and calcium intake, contribute to its prevalence. Corticosteroids exert their effects by disrupting the balance between the activity of osteoblasts and osteoclasts. These medications also disturb the calcium metabolism by altering intestinal calcium absorption and renal calcium excretion. To minimize these side effects, corticosteroid therapy should be limited whenever possible. Also, supplementing with calcium and vitamin D, incorporating breaks of at least three months between corticosteroid courses, and considering alternative therapies, especially in pediatric patients, can help mitigate the potential risks.

Keywords: Corticosteroids, Osteoporosis, Musculoskeletal system, Drug side effects.

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Introduction

Glucocorticoid (GC) hormones are known to be primary mediators in the body's response to stress and the regulation of the circadian rhythm. They also affect overall body homeostasis, influence brain function, modulate immune responses, maintain tissue integrity, and impact the musculoskeletal system[(1)]. Glucocorticoid drugs, also known as corticosteroids or steroids, were first introduced in 1901 for controlling sciatica pain and cancer. The effects of glucocorticoid exposure on bone metabolism were first recognized by Cushing in 1932[(2)]. Then, in 1940, after the identification of corticosteroids as substances with potent immunosuppressive properties, their medical use became common in treating chronic inflammatory diseases such as inflammatory bowel diseases, arthritis, anaphylactic shock, and asthma[(1).] In 1953, corticosteroids were used neuroaxially for spine-related diseases[(2).] Since then, corticosteroids have been a common method in the palliative treatment of spine diseases (particularly in patients with radiculopathy and neurogenic claudication caused by herniated discs), musculoskeletal pain disorders, and inflammatory arthropathies[(3)].

Corticosteroids can cause adverse effects on various organs, including the skeletal and muscular systems. These effects include an increased risk of osteoporosis, higher chances of fractures, bone necrosis in different areas of the body, decreased calcium and vitamin D levels, hormonal disturbances, and impaired bone growth in children[(1,2)].

Osteoporosis caused by corticosteroids remains a considerable and common clinical issue. This condition was initially recognized in patients suffering from Cushing's disease or any condition involving elevated endogenous corticosteroid levels. However, since the introduction of therapeutic corticosteroids more than 60 years ago, corticosteroid-induced osteoporosis is now increasingly seen in individuals undergoing corticosteroid therapy[4]. This condition is distinct from postmenopausal or age-related osteoporosis and is thus considered an isolated metabolic bone disease[5,6].

This review provides a comprehensive overview of the bone-related adverse effects related to systemic corticosteroid use. By synthesizing current research and clinical evidence, it aims to clarify the impact of corticosteroids on bone health and to inform strategies for mitigating these complications during treatment.

Epidemiology of Corticosteroid Use

Corticosteroid use remains widespread and continues to rise across different patients. In the United Kingdom, research has shown that around 1% of individuals are long-term users of oral corticosteroids, with the prevalence climbing to nearly 3% among older adults[7,8]. Data from the United States National Health and Nutrition Examination Survey (1999–2008) indicated a comparable rate, with 1.2% of the population on prolonged corticosteroid therapy[9]. Findings from the Global Osteoporosis Study revealed that 4.6% of postmenopausal women were using corticosteroids[10]. Evidence from UK health databases further suggests that long-term use has been steadily increasing over time[11]. Similarly, a Danish population-based investigation found that 3% of residents had filled at least one prescription for systemic corticosteroids, with the prevalence rising to 8–10% in older age groups[12]. Collectively, these data highlight that a substantial fraction of the universal population is regularly exposed to corticosteroids, emphasizing the need for ongoing surveillance of their epidemiological trends.

Pathogenesis

Exposure to corticosteroids, whether endogenous (elevated endogenous glucocorticoids) or exogenous (pharmacologic agents), promotes bone resorption. Endogenous glucocorticoids, regulated through the hypothalamic–pituitary–adrenal axis, play a pivotal role in bone metabolism[1]. Similarly, sex steroids are essential regulators of skeletal homeostasis, as reductions in androgen and estradiol levels are strongly correlated with an enhanced risk of symptomatic fractures of the spine[13].

Corticosteroid exposure results in an imbalance between osteoblast and osteoclast activity. Specifically, corticosteroids enhance resorption of bone by prolonging osteoclast survival, while simultaneously suppressing bone formation through inhibition and apoptosis of osteoblasts and osteocytes. This imbalance leads to net bone loss. In postmenopausal osteoporosis, such corticosteroid-induced acceleration of bone resorption appears to be a central mechanism underlying disease progression[1].

Osteoporosis and Fractures Following Corticosteroid Use

Corticosteroid-induced osteoporosis (CIO) represents one of the leading forms of secondary, drug-related osteoporosis, with approximately 20% of affected individuals reporting prior corticosteroid exposure[14]. Corticosteroid therapy is well known to accelerate bone loss, alter bone structure, and markedly elevate fracture risk[4]. The decline in bone mineral density often begins within the first 3–6 months of treatment and persists for as long as therapy continues. Besides the vertebrae, fractures are frequently observed in trabecular-rich bone such as the ribs and pelvis[15-17], indicating a particular vulnerability of these regions compared to cortical bone. Notably, some reports have documented the occurrence of fractures in corticosteroid users even before measurable reductions in bone mineral density, highlighting that bone quality, in addition to bone mass, is adversely affected by elevated corticosteroid levels[8,17,18].

The most important risk factors for developing CIO include older age (65 years), prolonged exposure to the drug for more than 3 months, a definite history of osteoporosis, positive familial history of osteoporosis, low calcium intake, prior fractures, family history of hip fractures, and rheumatoid arthritis, which themselves increase the likelihood of fractures[2].

Multiple investigations have sought to quantify fracture risk in patients undergoing prolonged corticosteroid therapy. In certain populations receiving prolonged corticosteroid therapy, the probability of acquiring osteoporosis or sustaining spinal fractures exceeds fifty percent[19]. These risks

vary depending on factors such as the underlying condition, as well as the patient age and sex distribution of the study groups. Large-scale, population-based research has further confirmed a strong relationship between corticosteroid exposure and elevated incidence of fractures[20]. Specifically, elevated risks have been documented for hip fractures (relative risk 1.6), vertebral fractures (relative risk 2.6), and non-spinal fractures (relative risk 1.3). Importantly, even at low doses, corticosteroids pose a measurable hazard: daily doses as low as 2.5 mg have been related to vertebral fractures. This relative enhancement in fracture risk is dose-dependent and varies with the duration of corticosteroid use. Additionally, discontinuation of the drug reduces the relative risk of fractures within the first year, with a more prominent reduction observed within the first three months. Therefore, given the relative decrease in fracture risk in the first three months, it seems necessary to apply a 3-month interval between corticosteroid treatments, especially in patients with an elevated risk of osteoporosis[21,22].

Osteonecrosis Following Corticosteroid Use

Osteonecrosis, referred to as avascular necrosis (AVN), is a progressive condition recognized by the death of bone and bone marrow due to compromised blood supply. The primary mechanism involves disruption of circulation to the bone surface, which triggers the loss of fat cells and osteocytes, followed by bone marrow edema and structural deterioration. The femoral head, pelvis, knee, and jaw (particularly in the context of bisphosphonate therapy) are the most frequently affected sites. Among the major contributing factors, corticosteroid therapy and excessive alcohol intake remain the leading causes of osteonecrosis[23].

Theories Regarding the Cause of Osteonecrosis

The mechanisms through which glucocorticoids contribute to the development of AVN are not yet completely understood, though several hypotheses have been proposed. Suggested pathways include glucocorticoid-induced hyperlipidemia leading to fat embolism, impairment of local blood flow, and alterations in bone marrow edema that collectively compromise vascular supply to bone tissue. Evidence from animal studies has supported aspects of these mechanisms[24,25]. Furthermore, research indicates that glucocorticoids and alcohol share similar detrimental effects on osteoblast function and osteogenesis, which may exacerbate osteonecrosis and hinder the repair of damage associated with hyperlipidemia[26-28].

Predisposing Factors in the Progression of Corticosteroid-Induced Osteonecrosis

A strong link between AVN and lipid abnormalities has been documented in multiple studies. As early as 1978, Jacobs reported that patients with femoral head necrosis frequently presented with hypercholesterolemia (17 cases) or hypertriglyceridemia (7 cases)[29,30]. Alcohol intake has since been identified as a major risk factor, with fracture risk increasing proportionally to weekly consumption. Compared with non-drinkers, the relative risk (RR) was 3.3 in those consuming less than 400 mL per week, 9.8 for individuals consuming 400–1000 mL, and 17.9 for those exceeding 1000 mL ($P > 0.001$). Patients with liver dysfunction had an RR of 4.6 ($P > 0.001$), which rose to 11 when combined with alcohol intake above 400 mL weekly ($P > 0.001$). Smoking has also emerged as an independent risk factor, with smokers exhibiting a threefold greater likelihood of developing osteonecrosis compared to non-smokers, regardless of alcohol use[31].

A retrospective review of patients with AVN found that 84% exhibited hypercholesterolemia, with an average cholesterol level of 254 mg/dL ($P > 0.0031$)[32]. The use of protease inhibitors in highly active antiretroviral therapy (HAART) has also been associated with elevated cholesterol and triglyceride levels, further linking these agents to an increased risk of AVN[33].

Therefore, factors such as hyperlipidemia, alcohol consumption, smoking, and liver dysfunction can be considered predisposing factors for the development of AVN in patients receiving glucocorticoid treatment.

Required Dose for the Development of Osteonecrosis

The threshold dose and treatment duration of corticosteroids necessary to trigger osteonecrosis remain unclear. However, recent evidence suggests that very high corticosteroid exposure can precipitate AVN, with reports documenting cases after cumulative doses of approximately 5100 mg of methylprednisolone administered over only 2–3 weeks[34].

Research in patients with systemic lupus erythematosus (SLE) has explored the relationship between glucocorticoid therapy, prothrombotic

factors, and the risk of AVN. Findings indicate that two of the strongest predictors of AVN in this population are the daily dose of oral glucocorticoids and the development of Cushingoid features in response to steroid treatment. In one study, individuals who developed AVN were found to have received significantly higher mean doses of prednisone (60 mg/day) compared with those without AVN (37 mg/day)[35].

In a retrospective analysis of patients with SLE, total cumulative prednisone exposure did not differ significantly between those who developed AVN and controls. However, notable differences were observed in the peak cumulative doses during the first month and the first four months of therapy[36]. Interestingly, this early-dose effect on AVN risk was not replicated in a separate study investigating patients with Crohn's disease[37].

Growth disturbance in Children

Physical growth in children is a reflection of their overall health, and proper physical and skeletal development requires the functioning of several key factors. When these factors operate appropriately, normal physical growth occurs. Corticosteroids, through various mechanisms and by affecting multiple systems in the body, can disrupt the physical and skeletal growth of both children and adults[38].

Corticosteroids affect the gastrointestinal system, impairing calcium absorption, and act on the kidneys to increase excretion, thereby disrupting calcium reabsorption and leading to increased parathyroid hormone levels. They also influence bones, disrupting their function by reducing the amount of osteoblasts and increasing the number of osteoclasts. Additionally, corticosteroids induce apoptosis and atrophy in muscle cells, decrease sex hormones, and consequently reduce skeletal load. Furthermore, corticosteroids interfere with the growth hormone-insulin-like growth factor 1 (GH-IGF-1) axis, have a direct effect on the growth plate, reduce the proliferation of chondrocytes and hypertrophy, and increase chondrocyte apoptosis. These effects reduce the production of the matrix and its mineralization, impair osteogenesis, and ultimately lead to disturbances in the longitudinal growth of bones[39].

Growth Hormone and IGF-1 Axis

Linear growth of bone in the growth plate and the subsequent process of chondrogenesis and conversion of cartilage to bone (enchondral ossification) occur with the support of growth hormone (GH) and insulin-like growth factor 1 (IGF-1), both of which are essential stimulators of linear bone growth[40].

Corticosteroids affect this axis at various levels. Short-term use of corticosteroids stimulates the production of GH and IGF-1, while long-term use eventually leads to a decrease in the function and production of growth hormone[41].

Corticosteroids reduce ghrelin receptors in the arcuate nucleus of the brain, leading to reduced GH-releasing hormone (GHRH) in the hypothalamus. Additionally, corticosteroids reduce the reaction of somatotrope cells in the pituitary to GHRH and increase the production and activity of somatostatin in the hypothalamus, a hormone that inhibits growth hormone production. In this way, corticosteroids affect growth hormone levels at multiple points, from the arcuate nucleus to the pituitary, and reduce the sensitivity of target cells to IGF-1, thereby disrupting growth in children[42].

Direct Effect on Growth Plate

Corticosteroids can disrupt bone growth in children by directly affecting the growth plate in various ways. Corticosteroids reduce the expression of GH receptors and directly decrease IGF-1 production, leading to reduced cell differentiation and increased apoptosis. In the proliferative zone, corticosteroids prevent chondrocyte proliferation by reducing IGF-1 production. In fact, corticosteroids disrupt the expression of growth hormone receptors, the production of IGF-1, and the hormone's binding to its receptor[43].

Corticosteroids also interfere with collagen matrix production and mineralization, as well as increase cell death (apoptosis) and disrupt vascularization[44].

Direct Effect on Bone and Muscle

Corticosteroids exert profound effects on bone by directly interfering with multiple cellular and structural components. They impair longitudinal bone growth by suppressing growth plate activity and attenuate osteoblast function, resulting in reduced bone formation. Concurrently, they stimulate osteoclast proliferation and activity, thereby enhancing bone resorption[45].

Moreover, corticosteroids diminish IGF-1 production, which subsequently compromises bone matrix and collagen synthesis, as well as mineralization. Indirect mechanisms, including disturbances in calcium homeostasis, further contribute to a decline in trabecular bone volume (accompanied by an

apparent increase in cortical bone volume) and a reduction in bone mineral content. Additionally, corticosteroids disrupt IGF-1 signaling, thereby exacerbating muscle cell apoptosis[46].

Vitamin D Deficiency and Calcium Metabolism

Vitamin D deficiency, specifically 25-hydroxyvitamin D (25(OH)D), is commonly observed in populations, and several studies have recognized its role in musculoskeletal diseases, increased fracture risk, cardiovascular diseases, kidney diseases, autoimmune diseases, and infections[47].

Recent studies have demonstrated that corticosteroid use can result in a decrease in vitamin D and its metabolites[44]. In a study conducted by Skversky et al between 2001 and 2006, 0.9% of the American adult and pediatric population reported recent corticosteroid use within the past 30 days, with a significant percentage having 25-hydroxyvitamin D levels less than 10 ng/ml, which was noteworthy compared to those not using steroids[47].

Studies by Toloza et al.[48], which included 124 patients with SLE under corticosteroid therapy, and by Searing et al.[49], involving 100 asthma patients treated with corticosteroids, found a significant correlation between corticosteroid therapy and reduced levels of 25-hydroxyvitamin D.

The exact mechanism for this association is not completely understood. Still, it's demonstrated that dexamethasone, a commonly used corticosteroid, increased the expression of the enzyme vitamin D 24-hydroxylase, leading to a reduction of vitamin D metabolites such as 25-hydroxyvitamin D and 1,25-hydroxyvitamin D[50].

It appears that corticosteroids, directly through their receptors and in conjunction with C/EBP and vitamin D receptors, increase the transcription of the enzyme 24-hydroxylase. It also reduce 25(OH)D levels by raising the 24-hydroxylase enzyme activity. Despite the suspicion that underlying diseases, such as those requiring corticosteroid prescriptions, along with malnutrition and reduced sunlight exposure, may be the primary factors contributing to vitamin D deficiency, various studies have adjusted for these factors and identified corticosteroid use as an independent factor in vitamin D reduction[51].

Vitamin D deficiency, when compounded by other effects of corticosteroids, contributes to a reduction in serum ionized calcium levels. In addition, corticosteroid therapy impairs intestinal calcium absorption, enhances renal tubular calcium excretion, and interferes with its reabsorption within the kidneys[52].

Therefore, serum vitamin D levels should be closely monitored in patients initiating corticosteroid therapy, given the increased risk of developing hypocalcemia[53]. Corticosteroids may also be used in the treatment of hypercalcemia due to their effects on reducing serum calcium. By interfering with calcium absorption from the intestines and disrupting renal reabsorption, corticosteroids can decrease serum calcium levels in hypercalcemic conditions. In normal calcium states, although corticosteroids may create a negative calcium balance, clinically evident hypocalcemia rarely occurs. Therefore, it seems that hypocalcemia induced by corticosteroid use may require predisposing conditions, such as vitamin D deficiency and hypoparathyroidism[1].

Shouchak et al. observed a negative correlation between cumulative corticosteroid dose and vitamin D levels in patients suffering SLE under corticosteroid therapy. Specifically, lower vitamin D concentrations were associated with higher corticosteroid doses. Based on this study, patients with cumulative corticosteroid doses over 42.8 grams had an average vitamin D level 31.7% lower than those with a dose under 42.8 grams. Among patients receiving higher doses of corticosteroids, 72.5% had vitamin D deficiency, compared to 52% in the lower-dose group. The results of this study demonstrated a statistically significant inverse association between cumulative corticosteroid dose and serum vitamin D levels in patients with SLE receiving corticosteroid therapy. Furthermore, vitamin D deficiency was found to be highly prevalent in this population and was associated with increased disease activity, elevated inflammatory markers (including Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP), and interleukin-6), greater organ damage severity, higher cumulative corticosteroid exposure, alterations in bone turnover markers (such as reduced osteocalcin), and decreased bone mineral density. In contrast, no significant correlation was observed with patient age or disease duration[54].

Conclusion

Corticosteroid drugs, as one of the most commonly used medications, are associated with numerous side effects. The musculoskeletal system is one of the main target organs for these drugs. The most important adverse effects of corticosteroids on the

musculoskeletal system include osteoporosis and fractures, avascular necrosis, bone growth disturbances in children, hypocalcemia, and vitamin D deficiency. Corticosteroids reduce the number and function of osteoblasts, increase their apoptosis, increase the number of osteoclasts, and decrease their apoptosis, leading to an increase in bone resorption and a reduction in bone formation. They also reduce calcium absorption from the gastrointestinal system, increase renal excretion, and directly affect the growth plate in children. Furthermore, they disrupt the growth hormone and IGF-1 pathway, leading to detrimental effects.

Therefore, given the potential adverse effects of corticosteroid therapy, it is crucial to minimize their use and, whenever possible, substitute them with more appropriate alternatives to prevent complications. In cases where corticosteroid treatment is unavoidable, strategies such as limiting the duration of therapy, maintaining intervals of at least three months between treatment courses, and prescribing the lowest effective dose are recommended. These measures can significantly reduce the risk of osteoporosis and fractures. Moreover, supplementation with calcium and vitamin D is advised to further mitigate these adverse skeletal effects.

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