**International Journal of Research in Pharmacy and Pharmaceutical Sciences**
**ISSN: 2455-698X; Impact Factor: RJIF 5.22**
**Received: 08-12-2018; Accepted: 15-1-2019**
**www.pharmacyjournal.in**
**Volume 4; Issue 1; January 2019; Page No. 53-56**

# Steroid induced fractures and bone loss

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**Abstract**
Bone loss is one of the most serious adverse effects experienced by the patients receiving long term corticosteroid therapy. Bone loss occurs soon after corticosteroid therapy is initiated and results from a complex mechanism involving osteoblastic suppression and increased bone resorption. Long term administration of the steroidal drugs causes a 5 -15 % chance of bone loss. Oral and inhaled steroids and to an extent the topical steroidal preparations also induce severe bone loss. The risk of bone loss and fractures are directly dependent on the dose of the steroidal drugs. The steroidal therapy affects mainly the axial skeleton and femur. Prevention or treatment of the osteoporosis in patients on corticosteroid therapy should be considered as important as the steroid therapy. Risedronate, Bisphosphonates and Alendronate are the current gold standard for the prevention and treatment of Glucocorticoid induced bone loss. Other alternatives of treatment include calcitonin, cholecalciferol, fluorides, hormone replacement therapy and parathormone.

**Keywords:** steroid, osteoporosis, glucocorticoid, fractures, bone loss

## Introduction

Glucocorticoids are quite commonly used in the treatment of many diseases and are one of the most common causes of secondary osteoporosis. Glucocorticoids are used by 0.9% of the total population and approximately 2.5% in the age group of 70–79 years.

Glucocorticoids treatment is associated with many unwanted effects but osteoporosis and fractures are the most serious adverse events. Trabecular bone (primarily in the spine and ribs) is more metabolically active than cortical bone (found in the hip and long bones) and therefore more susceptible to the negative effects of such factors as estrogen withdrawal and GC use. Trabecular bone loss occurs early in treated patients, with the highest rates of bone loss seen in the first 3-6 months of treatment (10-20%) followed by a slower rate of loss (2% per year) over time (2-4). Bone loss at the femoral neck occurs more slowly (2-3% in the first year) but continues over time. Bone loss at both sites is also dose-related, with higher doses of GC causing greater bone loss. Inhaled GC appear to have minimal effects on BMD.

The first reports about steroid effects on bone tissue came in 1932 and were described by Harvey Cushing. Glucocorticosteroids, when administered in greater doses than physiological concentrations, interact indirectly and directly with important groups of bone cells involved in the process of bone turnover (osteoclasts, osteoclasts and osteocytes) stimulating the process of bone resorption and inhibiting bone formation. Glucocorticoids also directly stimulate the secretion of parathormone. As a result of negative calcium balance and inhibited osteoblast activity, bone tissue demineralization foci occur. Bone mass loss observed over the course of steroid therapy begins quickly during the first few months (there can be 10% loss of bone mineral density [BMD] per year), then slows down after the first year of treatment to finally stabilize at the annual rate of 2–5%.

A direct correlation has been found between daily dose of steroids and the risk of fractures, which rises after 3–6 months of therapy and decreasing after treatment cessation. Risk of fracture is increased for all osteoporotic fracture types and in all age groups, including young people. It also depends on BMD, sex and prevalent fractures. In addition, it is well known that up to 50% of patients treated with steroids experience asymptomatic fractures after 3 months of therapy. In a meta-analysis involving 42,000 women and men, it was found that glucocorticoids decreased BMD, which was associated with an increased risk of fractures, particularly of the hip. In addition, fracture risk was higher in younger patients than in postmenopausal women and had no associations with previous fractures.

Fracture risk increases even with small doses of steroids between 2.5 and 7.5 mg. Moreover, the duration of treatment and cumulative doses are also important. The risk of fractures rises even when using steroids in doses of less than 2.5 mg of Prednisolone or daily equivalent. It was demonstrated in another epidemiological study that, in a group of patients treated with systemic Glucocorticosteroids, the risk of vertebral fractures significantly increased (twofold for the hip and the forearm) compared with untreated controls. In patients receiving 10 mg of Prednisolone (or its equivalent) daily for 3 months, the risk of hip fractures increased sevenfold and the risk of lumbar spine fractures increased by 17-fold.

It has been found that the use of steroids for at least 3 months are to be a clinically significant risk factor for bone loss and this value has thus been adopted in 10-year fracture risk

calculators. It is worth mentioning that certain diseases for which steroid therapy is used, significantly increase the risk of osteoporosis themselves, including asthma, inflammatory bowel diseases, post-transplantation status and rheumatoid arthritis.

The locally-applied (topical, inhaled) steroids do not seem to increase fracture risk, except when administered in regular doses ≥7.5 mg/day of Prednisolone (1875 μg of Budesonide or Beclomethasone). It has, however, been demonstrated that BMD is lower in both situations: chronic application of inhaled steroids with intermediate doses of oral steroids and also when they are taken continuously in a combined form of therapy. According to the dose of steroids, patients with asthma can be divided into three groups: low, medium and high risk of osteoporosis. The low-risk group includes patients taking Beclomethasone in doses ≤800 μg/day in adults or ≤400 μg/day in children. The medium risk group includes patients receiving inhaled steroids in doses >800 μg/day in adults or >400 μg/day of Beclomethasone in children. Patients at high risk of developing osteoporosis take systemic steroids at least four times a year.

**Discussion**

Glucocorticoids come under an important therapeutic agents that have been used for their potent anti-inflammatory and immunosuppressive properties for over 50 years. According to many studies performed, 0.9% of the general adult population is taking oral steroids at any given time and this proportion increases with age to 2.5% by age 70—79 years. Glucocorticoid-induced osteoporosis is considered to one of the most serious consequence of glucocorticoid therapy leading to fractures in 30—50% of patients. Glucocorticoid treatment is associated with many unwanted effects but osteoporosis and fractures are considered to the most serious adverse events among the uneanted effects affecting 30—50% of patients Despite the prevalence of glucocorticoid therapy and glucocorticoid-induced osteoporosis, many patients on chronic steroid therapy do not receive bone mineral density assessment or the recommended preventative therapy for osteoporosis.

Trabecular bone (primarily in the spine and ribs) is more metabolically active than cortical bone (found in the hip and long bones) and therefore more susceptible to the negative effects of such factors as estrogen withdrawal and Glucocorticoid use. Trabecular bone loss occurs early glucocorticoid treated patients, with the highest rates of bone loss seen in the first 3-6 months of treatment (10-20%) followed by a slower rate of loss (2% per year) over time. Bone loss at both sites is also dose-related, with higher doses of glucocorticoid use causing greater bone loss. Inhaled glucocorticoid appear to have minimal effects on BMD. Bone mass can increase or "recover" after corticosteroid treatment is withdrawn.

Glucocorticoid induced side effects affects all age such as ranging from children often treated for respiratory infections, adolescents treated for inflammation glucocorticoid treatment effects (children) on body weight, growth velocity, bone density, and muscle mass, and sexual maturation in children are all factors which contribute to the acquisition of peak bone mass and future fracture risk.

GC treatment can decrease the childhood growth rate, which is an important predictor of adult fracture rates

A recent study of a large managed care population in the United States, Saag and colleagues found low rates of preventative interventions in individuals on long-term glucocorticoid therapy. Postmenopausal women were expected likely to receive recommended interventions, but only approximately 50% were treated with anti-osteoporotic medication. 10—19% of postmenopausal women underwent bone mass measurements. This number dropped to < 6% in women under 50 years of age and in men. The study also found that rheumatologists were three to four times more likely to initiate the above interventions than internists or family practitioners.

Glucocorticosteroid-induced osteoporosis (GIOP is one of the most frequent types of osteoporosis. GIOP occurs as a result of depressed bone formation due to lower activity and higher death rate of osteoblasts. In addition, calcium/phosphate metabolism get disturbed on gut, kidney, parathyroid glands and gonads through the use of glucocorticoids. Therefore, therapeutic agents which aim at maintaining and restoring of balanced bone cell activity by reducing apoptosis rate of osteoblasts (e.g., cyclical parathyroid hormone) or by increasing apoptosis rate of osteoclasts (e.g., bisphosphonates).Steroids have a significant effect on bone formation, turnover and integrity. The primary action of steroids is on osteoblasts leading to decreasing replication and impairing differentiation and maturation, leading to decreased bone formation. Steroid induced bone loss also involves an element of increased bone resorption. In the early phase of the steroid treatment, decreased bone formation coupled with increased resorption leads to rapid loss of bone integrity and significant fracture risk. Later in the course of treatment, however, resorption reduces leading to a state of chronic decreased bone turnover. During the early phase of steroid therapy, high-dose drugs increase osteoclast generation and osteoblast signaling is affected, causing a reduced osteoprote-gerin (OPG) release and increased receptor activator of NF-KB ligand (RANKL), resulting in osteoclastogenesis. Other actions of glucocorticoids that negatively affect bone including decreased calcium absorption by the gastrointestinal tract and renal calcium loss. Steroid myopathy results in muscle weakness leading to increased risk of falls and fractures. It is proven that corticosteroids deplete preferentially the bones in the axial skeleton. The fact that, the bone loss in trabecular bone occurs more rapidly and significantly than loss in cortical bone, results in a conclusion that there is a greater chance of fractures in bones with higher proportion of trabecular bone, such as the vertebrae and the ribs.

Recent studies have suggested that there is an initial phase of rapid bone loss, followed by slower and continued bone loss. Corticosteroids can influence both bone formation and bone resorption. When given initially, the corticosteroids increase the secretion of parathyroid hormone (PTH), as a result of reduced intestinal absorption, and increased renal loss, of calcium. The corticosteroids also potentiate the activity of PTH on osteoblasts. An increase in PTH levels has been observed shortly after administration of corticosteroids, but the effect of corticosteroid on long term administration is less clear and also the mechanism of inhibition of intestinal calcium absorption by corticosteroids is unknown. Initially, it was suggested that corticosteroids may inhibit cholecalciferol (vitamin D) metabolism, mainly the conversion of cholecalciferol to calcifediol (25-hydroxycholecalciferol).

Calcium and vitamin D should be a systematic adjunctive measure to any drug treatment for GIOP. GCs induce a dose-

dependent inhibition of calcium (and possibly phosphate) absorption in the gut and a compensatory increase in parathormone secretion, an increase in renal calcium elimination, a reduction of the sex hormone levels through inhibition of gonadotropin secretion and they directly interfere with estrogen, testosterone and adrenal androgen production. Long-term administration of steroids induces a rapid loss of bone mass of between 5 and 15%.Not all patients treated with GCs are suffering effects of bone loss. Mainly differences are genetically determined and could be related to varying steroid receptor and individual pharmacokinetic differences. Fracture risk increases in a dose-dependent manner in patients treated with oral GCs. The adverse skeletal effects of GCs increased with increasing daily doses. In addition, fracture risk was increase rapidly within the first 3–6 months after initiation of therapy with GCs and to remain increased during the duration of treatment. Risedronate, Bisphosphonates and Alendronate are the current gold standard for the prevention and treatment of GIOP, based on their documented increase in BMD at all clinically targeted sites and their effect to reduce fractures. Calcitonin is an alternative for patients whom Bisphosphonates cannot be given and/or who are suffering from acute pain after an osteoporotic fracture. Parathormone is attractive and promising treatment alternative, data about fracture risk reduction are still lacking for patients with GIOP. An initial assessment should be done in patients before initiating the steroid therapy whom we suspect to have conditions such as hypogonadism. The initial assessment measures include measurement of spinal bone density, urinary calcium level, and serum testosterone level and plasma calcifediol. Patients should take as much physical activity, maintain an sufficient daily intake of calcium (1000 mg/day) and cholecalciferol (400 to 800 U/day), cessation of smoking and avoid excessive alcohol intake. It is important to detect and treat hypogonadism in men, if present, and to replace gonadal hormones in postmenopausal women or amenorrhoeic premenopausal women, and to detect and correct cholecalciferol deficiency. A thiazide diuretic should be considered if hypercalciuria is present (urinary calcium excretion in excess of 4 mg/kg/day).Inhaled steroids also cause significant bone loss. In up to 50% of kidney transplantation patients, steroids produce alterations in bone architecture that leading to a declined bone mineral density and progressive vertebral height loss. Risk factors for steroid-induced bone loss are diminished bone mass, negative calcium balance, chronic renal failure, vitamin D deficienc, metabolic acidosis, suppressed osteoblast function hyperparathyroidism and malnutrition.ICS therapy have a positive effect on bone density through reduction of chronic inflammation and avoidance of need for acute short courses of oral corticosteroids during exacerbations. In addition, ICS may allow better control of asthma in patients such that they become more active, thereby slowing or preventing steroid-induced osteoporosis through the beneficial effects of physical activity on BMD. Auranofin is considered as the choice of drug in patients with corticosteroid dependent asthma. patient should maintain adequate daily intake of calcium (1000 mg /day) and cholecalciferol (400-800units per day). In case of alcoholics, they should avoid excessive alcohol intake. Many drugs such as thiazide diuretics, cholecalciferol (vitamin D), Bisphosphonates, Calcitonin, Fluoride, Estrogens, Progesterone and anabolic steroids have been used to prevent osteoporosis in patients with long term steroid therapy.

## Conclusion

From the analysis of the above studies we have came to a conclusion that the intake of steroids both oral and inhaled and to an extent the topical steroids have induced severe bone loss in most patients. It has been found that corticosteroid induced osteoporosis is the common form of secondary osteoporosis and the primary reason in young people. Bone loss and an increased rate of fractures occur often early after the initiation of corticosteroid therapy and depends on the dose as well. Prevention or treatment of the osteoporosis in patients on corticosteroid therapy should be considered as important as the steroid therapy. Long-term administration of steroids induces a rapid loss of bone mass of between 5 and 15%.Not all patients treated with GCs are suffering effects of bone loss. The locally-applied (topical, inhaled) steroids do not seem to increase fracture risk, except when administered in regular doses ≥7.5 mg/day of Prednisolone (1875 µg of Budesonide or Beclomethasone). These bone losses are not usually considered to be reversible as it is a consequence of ageing process too. However an improvement in bone mineral density have been reported in certain cases after surgical treatment for e.g. in Cushing's syndrome. Calcium and vitamin D should be a systematic adjunctive measure to any drug treatment for glucocorticoid induced osteoporosis. When treating patients with topical corticosteroids, lowest effective dose should be used.

## Acknowledgement

We thank God Almighty and our parents for their blessings. We also extend our sincere gratitude towards our principal Dr. Elessy Abraham and our teachers especially Dr.Abel Abraham Thomas for guiding us in our studies on this topic.

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