Glucocorticoid-induced Osteoporosis

Since their introduction almost seven decades ago, glucocorticoids continue to be one of the most commonly prescribed classes of drugs in various autoimmune and inflammatory conditions and in states of hypocortisolism.[1] However, their use has been limited by the occurrence of various adverse effects such as osteoporosis, myopathy, glucose intolerance, dyslipidemia, hypothalamic–pituitary–adrenal axis suppression, cataracts, and increased risk of infections. Glucocorticoid-induced osteoporosis (GIO) with increased fracture risk is a well-recognized entity contributing to significant morbidity. This is compounded by nutritional calcium and Vitamin D deficiencies which are widely prevalent in India.[2]

The bone loss secondary to initiation of glucocorticoids is early and rapid, and the bone mineral loss correlates well with cumulative dose and duration. Fracture risk is increased even with a daily dose of prednisolone that is <5 mg.[3] Parenteral, oral, and even long-term inhaled glucocorticoids are associated with a significant bone loss. The rate of bone loss is noted to be more than 10% in the first year of therapy and thereafter tends to stabilize at 2%–3% every year.[4] It predominantly involves trabecular bone, thus increasing the risk of vertebral fractures. Later, cortical bone is also involved (e.g., femoral neck).[5] About 20% of those treated with glucocorticoids will have a fragility fracture within the first year of treatment.[6] Postmenopausal women and elderly men are at a higher risk for developing glucocorticoid-induced bone loss and fractures.[7]

Glucocorticoid therapy affects all three bone cell lines – osteoblasts, osteoclasts, and osteocytes.[3] The predominant action is by suppression of osteoblastic activity, resulting in inhibition of bone formation. The expression of dickkopf-related protein and sclerostin and the inhibitors of WNT signaling pathway are upregulated, thereby leading to decreased bone formation by osteoblasts.[8] In addition, glucocorticoids stimulate osteoclastogenesis through a receptor activator of nuclear factor kappa B ligand (RANKL)-dependent mechanism. Glucocorticoid-induced suppression of gonadal hormones and its effects on the neuromuscular system (e.g., myopathy) resulting in an increased tendency to falls further contribute to fracture risk.

Even though glucocorticoid therapy has been associated with osteoporosis and fractures, more than half of those on treatment are not assessed or treated for the same.[9] A number of guidelines have underlined the importance of initiating anti-osteoporotic medications in patients receiving glucocorticoid treatment on a long-term basis or until they are stopped. Although many societies have recommended bone mineral density (BMD) assessment by dual-energy X-ray absorptiometry scanning, the association between low BMD and increased fracture risk is not linear. This implicates additional factors such as genetic susceptibility and heightened sensitivity of steroid receptors to therapeutic levels of administered glucocorticoids. The use of fracture risk assessment tool (FRAX, India) has also been advocated to decide on the initiation of prophylactic treatment for GIO. Radiographic imaging of the spine and vertebral fracture assessment are the other useful tools to be considered before initiating glucocorticoids or while on treatment. A recently developed tool trabecular bone score may enable us to determine the microarchitectural deterioration of the bone, thus complementing BMD measurement and FRAX assessment.[10] There is a paucity of evidence to show that bone turnover markers predict fracture risk except the marked suppression of osteocalcin seen in glucocorticoid-induced bone loss. Biochemical assessment of calcium, 25 hydroxy Vitamin D, and liver and renal functions is recommended before initiation of treatment.

The management strategies of osteoporosis are multipronged. General measures include weight-bearing exercises, smoking cessation, avoidance of excess alcohol consumption, and ensuring adequate calcium and Vitamin D intake (both dietary intake and supplements).[3] The recommended calcium intake in glucocorticoid users is about 1000–1500 mg/day.[11] Calcium carbonate is the most commonly used preparation, and it is to be ingested with food to facilitate an acidic environment that enhances its absorption. Calcium citrate is preferred in people on proton pump inhibitors and in those with achlorhydria. Cholecalciferol in the doses of 1000–2000 units/day is recommended in the Indian context.[12] Calcium and Vitamin D together have shown to decrease the rate of bone loss in patients using glucocorticoids although a reduction in fracture risk has not been demonstrated.[13]

In postmenopausal women and men over 50 years of age who are at a higher risk for steroid-induced bone loss, anti-osteoporotic agents should be initiated early. However, the evidence for treating premenopausal women and younger men is weak with regard to risk reduction of new vertebral fractures.[3] Hence, treatment needs to be individualized based on the patient's clinical condition. Although various studies have analyzed the effect of anti-osteoporotic agents either in the prevention or in the treatment of glucocorticoid-induced bone loss, these were limited to a duration of 12–36 months.[8] The risk of fractures has been shown to decline after stopping steroids, and hence, it is opined that bone protective agents may be withdrawn thereafter.

Antiresorptive agents such as bisphosphonates (e.g., alendronate, risedronate, and zoledronic acid) are commonly used in the prevention and treatment of GIO. Alendronate (70 mg weekly) and risedronate (35 mg weekly) have shown to increase BMD at spine and reduce the incidence of new vertebral fractures. Studies have demonstrated that alendronate helps in preserving BMD at the femoral neck when administered to patients with glucocorticoid-induced bone loss.[14] A 70% risk reduction in the incidence of new vertebral fractures in the risedronate treatment group was noted on pooled analysis of two key studies.[15] Yearly administration of zoledronic acid (5 mg) is documented to be more efficacious than risedronate in increasing the BMD at lumbar spine and hip although the frequency of new vertebral fractures was low and comparable in both groups.[16] Zoledronate may cause an acute phase reaction consisting of fever, arthralgia, and myalgia in about one-tenth of patients.[3]

Teriparatide, a recombinant human parathyroid hormone preparation 1–34, is an anabolic agent which increases the number and survival of osteoblast precursors and promotes their differentiation into mature osteoblasts, leading to increased bone formation. In GIO, these effects might help in counteracting the adverse actions of steroids on the osteoblasts. Teriparatide, when compared with alendronate in the treatment of GIO, was found to cause greater increment in BMD at lumbar spine and femoral neck. The incidence of vertebral fractures rates was lower in the teriparatide-treated group at the end of three years.[17] On comparing with risedronate over an 18-month period in 77 men with steroid-induced osteoporosis, there was more improvement in the spinal BMD and bone formation markers in the teriparatide group at the end of the study.[18]

Patients with GIO and associated hypogonadism may be considered for treatment with sex steroids to reduce the bone resorption associated with deficiency of these hormones.

There are limited studies available with agents such as raloxifene (a selective estrogen receptor modulator) and denosumab (a monoclonal antibody targeting RANKL). Cathepsin K inhibitors (e.g., odanacatib) and monoclonal antibodies to sclerostin (e.g., romozozumab) may be explored as newer options in the treatment of GIO.[19]

In conclusion, glucocorticoids are widely used in the treatment of a variety of clinical conditions and have established deleterious effects on the bone which may result in fractures. Their use should be limited to a minimum dose for the shortest possible duration of time. The timely initiation of preventive treatment will help in ameliorating bone loss secondary to glucocorticoid use. Meanwhile, it is expected that studies using newer molecules targeting key cellular pathways will offer novel agents for the future.

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