Recent Advances in the Management of Steroid Induced Osteoporosis

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Abstract: Glucocorticoid-induced osteoporosis is the most common cause of drug-induced osteoporosis, leading to fragility fractures, decrease in mobility and quality of life. Patients who receive equivalent dose of prednisolone 5 mg for more than six months are at risk of glucocorticoid-induced osteoporosis, but there is no conclusive evidence for a safe cutoff for either dose or duration of steroid exposure and bone loss. The general view is 'dual action'. Both increased bone resorption and decreased bone formation contribute to the pathogenesis of glucocorticoid-induced osteoporosis. Glucocorticoids increase the expression of receptor activator of nuclear factor kB ligand (RANK-L) and decrease the expression of its soluble receptor osteoprotegerin (OPG) in stromal and osteoblastic cells, leading to increased differentiation of pre-osteoclast to osteoclast. Fracture risk is related not only to bone mineral density, bone structural and mechanical properties, but also other clinical risk factors such as smoking, excessive alcohol, lack of exercises. Treatment threshold in glucocorticoid-induced osteoporosis is much lower than that in postmenopausal osteoporosis since fractures in glucocorticoid-induced osteoporosis occur at a higher bone mineral density than in postmenopausal osteoporosis. Bisphosphonates, being the first line therapy, have been shown to be effective in the prevention of vertebral fractures and they should be given together with adequate vitamin D and calcium supplement. The anabolic therapy parathyroid hormone, which targets on bone formation, has shown to be effective in increasing bone mineral density and reducing fractures and it may act as an alternative therapy.

Keywords: Bisphosphonates, Bone mineral density, Calcium, Fractures, Glucocorticoid-induced osteoporosis, Parathyroid hormone

Introduction

Osteoporosis is a skeletal condition characterized by low bone mass, which is associated with microarchitectural disruption and increased bone fragility that leads to reduced bone strength and an increased risk of fractures. Glucocorticoids are used widely in the treatment of different kind of rheumatic diseases. A recent analysis of the national databank for rheumatic diseases in the USA found prednisolone use in 38% of rheumatoid arthritis (RA) patients. Bone loss with risk of fractures resulting from glucocorticoid therapy is a relatively common issue and it is the most prevalent form of secondary osteoporosis. An estimated 50% of patients taking glucocorticoids for longer than 6 months will develop secondary osteoporosis. Long-term glucocorticoid use worldwide is estimated at between 1% to 3% of adults. Treatment was usually short term, with 22.1% taking oral glucocorticoids for over 6 months and 4.3% for over 5 years. Historically, glucocorticoids at a prednisolone-equivalent dose of less than 7.5-10 mg/day are considered low dose. This is based on a review of a number of studies which show decreased rates of osteoporosis, myopathy, cardiovascular disease, and glaucoma below this dose. Use of the lowest corticosteroid dose is possible because fracture risk is dose dependent. Generally, in most patients, doses below 5 mg/day prednisone equivalent result in minimal bone loss, whereas doses above 10 mg/day will result in significant bone loss. The severity of bone loss also depends on the cumulative
dose. Alternate-day glucocorticoid use may lead to as much bone loss as daily regimens. Inhaled glucocorticoids are also associated with some degree of bone loss. However, there is no conclusive evidence for a safe cutoff for either dose or duration of glucocorticoid exposure and bone loss. This article focuses on the recent advances in the pathogenesis and assessment of glucocorticoid-induced osteoporosis and the updated evidence on various treatment modalities.

**Loss of Bone Mineral Density and the Relationship with Glucocorticoid**

There is a substantial and accelerated decrease in bone mineral density (BMD) with glucocorticoid therapy, most pronounced in the first year, with trabecular bone more affected than cortical bone. Markedly decreased BMD at the lumbar spine, femoral neck and whole body has been reported 2 months after initiating high-dose glucocorticoids (40 mg/day), with the greatest loss occurring predominantly in the trabecular lumbar vertebrae. In a meta-analysis of 66 studies reporting bone density measurements in 2891 glucocorticoid users with an average daily dose of 9.6 mg, lumbar spine and hip BMD were lower than a group of age and sex-matched patients who were non-steroid users (89.4% and 88.8%, respectively). Decreases in BMD in the hip and lumbar spine correlate with cumulative glucocorticoid dose.

A complicated relationship between chronic glucocorticoid therapy and bone density may exist in subgroup of patients having underlying chronic inflammatory diseases. For example, accelerated bone loss occurs early in the course of rheumatoid arthritis in association with persistent inflammation and immobility. Although glucocorticoids intrinsically causes a decline in bone density and increased fracture risk, appropriate use of low-dose glucocorticoid therapy to reduce inflammation might also suppresses rheumatoid arthritis disease activity and thereby attenuate bone loss.

Patients with systemic lupus erythematosus (SLE) have a high risk of symptomatic vertebral and nonvertebral fractures (9-16.5%), or prevalent vertebral deformities as a result of fractures. Risk factors for fractures in SLE patients included the duration of use of glucocorticoids, ever use of IV methylprednisolone and male sex. A recent local study on 152 patients with SLE also reported that around 20% of patients had asymptomatic vertebral fractures, in which thoracic vertebrae fractures being the most common. Fractures occurred in 30% of SLE patients with normal BMD, similar to previous studies.

A local study evaluating the effect of calcitriol on bone mineral density in premenopausal Chinese women taking chronic glucocorticoid therapy with a mean cumulative prednisolone dose of 28±16.2 g found that the baseline T score at the lumbar spine of the study group was <-1 in 43.2% and <-2.5 in 3.7% of the patients.

**Fracture Risk**

Higher fracture rates in glucocorticoid users have been reported in numerous studies. A cross-sectional study found a 37% prevalence of asymptomatic vertebral fractures in postmenopausal women on chronic glucocorticoid therapy, increasing with age. This increased risk of fracture has been confirmed in a large metaanalysis of studies which included 2891 glucocorticoid users, with a relative risk (RR) of any fracture of 1.91, hip fracture 2.01, vertebral fracture 2.86 and forearm fracture 1.13. A study of a UK primary care database, comprising 244 235 oral glucocorticoid users and a similar number of controls, found a RR of any fracture of 1.33, hip fracture 1.61, vertebral fracture 2.60 and forearm fracture 1.09.

Fracture risk has been related to dose and duration of glucocorticoid treatment. Those exposed to intermittent high-dose glucocorticoids (daily dose more than 15 mg/day) with little prior exposure had a small increased risk of osteoporotic fracture, but this risk increased substantially with increasing cumulative exposure and in those patients who were receiving at least 30 mg/day and whose cumulative dose was over 5 g, the RR was 3.63 for osteoporotic fracture.

**Pathogenesis of Glucocorticoid-induced Osteoporosis**

The initial bone loss occurring in patients exposed to glucocorticoids might be secondary to increased bone resorption. Glucocorticoids increase the expression of receptor activator of nuclear factor kB ligand (RANK-L) and decrease the expression of its soluble receptor osteoprotegerin (OPG) in stromal and osteoblastic cells, leading to increased differentiation of pre-osteoclast to osteoclast. Glucocorticoids also enhance the expression of macrophage colony-stimulating
factor (M-CSF), which in the presence of RANK-L induces osteoclastogenesis. Moreover, glucocorticoids have been demonstrated to upregulate receptor subunits for osteoclastogenic cytokines of the glycoprotein 130 family. Glucocorticoids might have direct effects on osteoclasts also by suppressing the expression of an autocrine cytokine, such as interferon -beta, that normally exerts inhibitory effects on osteoclastogenesis. All these mechanisms could contribute towards increased in bone resorption.

Corticosteroid also plays a central role in the pathogenesis of osteoporosis by suppression of bone formation. Corticosteroid lead to a reduction in osteoblast number and function by inhibition of replication and differentiation of cells of osteoblastic lineage, and enhanced apoptosis of osteoblasts and osteocytes. Glucocorticoids induce apoptosis of osteoblasts and osteocytes by activating caspase 3, a common downstream effector of several apoptotic signaling pathways.

Prevention and Treatment of Glucocorticoid-induced Osteoporosis

Diagnosis of Steroid Induced Osteoporosis

Bone mineral density (BMD) assessment by Dual Energy X-ray Absorptiometry (DEXA) is the gold standard to diagnose osteoporosis. The World Health Organization (WHO) established a classification of BMD according the standard deviation (SD) difference between a patient's BMD and that of a young-adult reference population (T-score). The Z-score is a comparison of the patient's BMD to an age-matched population. A BMD T-score that is 2.5 SD or more below the young-adult mean BMD is defined as osteoporosis. Premenopausal osteoporosis is defined as premenopausal women who have low bone density (Z score less than -2.0) and/or fragility fractures.

The American College of Rheumatology (ACR) recommends a BMD measurement before starting bisphosphonates in all subjects taking glucocorticoids. It is recommended that the treatment threshold in glucocorticoid-induced osteoporosis is much lower than in postmenopausal osteoporosis since fractures in glucocorticoid-induced osteoporosis occur at higher BMDs than in postmenopausal osteoporosis. The intervention threshold of the ACR recommendation is a T-score of less than or equal to -1, which is much lower than that for postmenopausal women (T-score < of -2.5).

Evaluation of the Changes in Bone Mineralization and Architecture

Apart from bone density, fracture risk is also related to bone strength, including structural and material properties of bone. Deterioration of cancellous structure can have a major impact on fracture risk independent of BMD. As in other forms of secondary osteoporosis, in glucocorticoid-induced osteoporosis vertebral fractures may be asymptomatic. Consequently, a radiological approach with morphometric analysis is useful for the identification of vertebral deformities.

Therapeutic Guidelines

Guidelines published by the American College of Rheumatology (ACR) advocates the following measures for the prevention and treatment of glucocorticoid-induced osteoporosis: general health awareness, administration of sufficient calcium and vitamin D, reduction of the dose of corticosteroids to a minimum and, when indicated, therapeutic intervention with bisphosphonates. The ultimate goal is to prevent fractures. Appropriate preventive measures include intake of calcium (1500 mg daily) and vitamin D (800 IU daily). Depending on the individual patient BMD and risk factors, the use of calcium and vitamin D could be considered to be sufficient, particularly if the level of glucocorticoid exposure is lower than 7.5 mg of prednisone equivalent daily and for less than three months.

Guidelines from the UK suggest that treatment in glucocorticoid-induced osteoporosis is indicated in (i) patients who are at high risk of osteoporosis, such as those taking prednisone equivalent doses higher than 7.5 mg daily, those with a personal history of fractures or those with lifestyle risk factors for osteoporosis; (ii) patients with a low risk of osteoporosis but with T-scores lower than -1.5 SD as assessed by vertebral dual energy X-ray absorptiometry; and (iii) patients with a low risk of osteoporosis and a T-score higher than -1.5 SD but with a decline in vertebral BMD of at least 4.0% after one year of glucocorticoid treatment.

Various pharmacological agents have been assessed for prevention and treatment of glucocorticoid-induced osteoporosis. Vitamin D and calcium are recommended by both ACR and Royal College of Physicians guidelines, although the latter restrict the administration to patients with...
vitamin D insufficiency and/or with inadequate calcium intake.\textsuperscript{47,51,52} Vitamin D and its analogues prevent bone loss during glucocorticoid therapy.\textsuperscript{53,54} Alfacalcidol, a vitamin D analogue, is said to have dual effects on bone by increasing bone formation and reducing bone resorption. Alfacalcidol suppresses the synthesis and release of parathyroid hormone and increases the intestinal absorption of calcium and its reabsorption in the distal renal tubule. In a 2-year randomized trial, subjects with rheumatoid arthritis receiving prednisolone therapy (mean dose 5.6 mg day) BMD fell at a rate of 2.0\% and 0.9\% per year in the lumbar spine and trochanter, respectively. In contrast, patients randomized to calcium (1000 mg/day) and vitamin D (500 IU/day) gained BMD at an annual rate of 0.72\% at the spine and 0.85\% in the trochanter.\textsuperscript{55}

Bisphosphonates are considered to be the gold standard for the prevention and treatment of glucocorticoid induced osteoporosis.\textsuperscript{52} Both ACR and Royal College of Physicians guidelines point out the efficacy of these drugs.\textsuperscript{47,51} Available data are for risedronate and alendronate, although newer bisphosphonates ibandronate have been recently tested with encouraging results.\textsuperscript{56} The benefits of bisphosphonates in glucocorticoid induced osteoporosis have been ascribed primarily to their antiresorptive effect.\textsuperscript{57} Bisphosphonates are more effective than vitamin D in the prevention of fractures in glucocorticoid-induced osteoporosis, but should be given with supplemental calcium and vitamin D.\textsuperscript{55}

Study comparing Alendronate 10 mg daily with Alfacalcidol 1 mcg daily in glucocorticoid-induced osteoporosis showed that at 18 months, the bone mineral density of the lumbar spine increased by 2.1\% in alendronate group, and decreased by 1.9\% in alfacalcidol group.\textsuperscript{58} An overall reduction in risk of radiological vertebral deformities of 37\% (relative rate 0.63, 95\% confidence interval 0.49-0.80) was reported.

Risedronate is shown to be as effective as alendronate. A local 6-month randomized double-blind placebo controlled trial comparing Risedronate 5 mg daily with placebo showed a significant gain in spinal BMD in the risedronate group (+0.7±0.3\%; \textit{p}=0.03) but a drop in the placebo group (-0.7±0.4\%; \textit{p}=0.12). No new fractures developed in risedronate or placebo group.\textsuperscript{59}

Parenteral administration of more potent bisphosphonates has the advantages of less esophageal side effects. Ibandronate 2 mg administered intravenously every 3 months over 3 years reduced the frequency of new vertebral fractures compared with 1 mg/day alfacalcidol (8.6\% versus 22.8\%, respectively) in an open-label, parallel group study of 115 patients with established glucocorticoid-induced osteoporosis.\textsuperscript{60} There was also a significantly greater increase in mean BMD at the lumbar spine (13.3\% versus 2.6\%) and femoral neck (5.2\% versus 1.9\%) with intravenous ibandronate versus daily oral alfacalcidol.

Anabolic therapy has become the novel therapy for glucocorticoid induced osteoporosis. Once-daily recombinant human parathyroid hormone (PTH 1-34) (teriparatide) stimulates bone formation, increases bone mass, and reduces the risk of vertebral and nonvertebral fractures.\textsuperscript{61,62} Teriparatide may be a rational treatment for glucocorticoid-induced osteoporosis because it directly stimulates osteoblastogenesis and inhibits osteoblast apoptosis, thereby counteracting two key mechanisms through which glucocorticoid therapy promotes bone loss.\textsuperscript{63} Patients with large deficits in bone mineral density are at high risk for fracture and might preferentially benefit from such anabolic therapy.\textsuperscript{64}

Promotion of bone formation with parathyroid hormone was shown to dramatically increase vertebral bone density in a small trial of 28 postmenopausal women on a stable dose of prednisone who were receiving concurrent estrogen therapy and given daily human PTH 1-34 (hPTH (1-34)) for 12 months and then had 12 months without treatment compared with 23 women receiving estrogen alone.\textsuperscript{65} Lumbar spine BMD increased dramatically in the first year and the mean percentage differences in BMD of the lumbar spine by quantitative computed tomography at 12 and 24 months were 32\% and 43\%, respectively, and by dual energy X-ray absorptiometry were 11.8\% in the first year and 11.9\% at 2 years. There was a smaller difference between the treatment groups in hip BMD of 2\% at 12 months and 4.7\% at 24 months, 12 months after hPTH treatment was discontinued. Biochemical markers of bone turnover increased to more than 150\% during the first 6 months of hPTH therapy, remained elevated throughout the 12-month treatment period, and returned to baseline values within 6 months of discontinuing the PTH treatment.

Latest study which compared teriparatide 20 \(\mu\)g daily with alendronate 10 mg daily in 428 women and men with
osteoarthritis who had received prednisone equivalent, 5 mg daily or more for at least 3 months showed increase in the mean bone mineral density at the lumbar spine more in teriparatide group than in the alendronate group (7.2±0.7% vs. 3.4±0.7%, P<0.001). At 12 months, bone mineral density at the total hip had increased more and new vertebral fractures become less in the teriparatide group.66

**Other Drugs for Glucocorticoid-induced Osteoporosis**

AlthoughRaloxifene, a selective oestrogen receptor modulator, is not the mainstream treatment in glucocorticoid-induced osteoporosis, study showed that it may play a role in prevention. An open controlled trial studying the effects of raloxifene on bone mineral density in postmenopausal women with systemic lupus erythematosus, in which low dose prednisolone, illustrated that after 12 months, femoral neck BMD and lumbar spine BMD was preserved in the raloxifene group.67

Strontium ranelate, which act by increasing bone formation and decreasing bone resorption was proven to be effective in post-menopausal osteoporosis. SOTI trial (Spinal Osteoporosis Therapeutic Intervention Trial) evaluated postmenopausal women with >=1 vertebral fractures receiving strontium 2 g daily showed increase in lumbar spine BMD by 8.1%, reduce in new vertebral fractures at 1 year by 49%, and decrease in overall fracture risk after 3 years by 41%.68 Studies for glucocorticoid-induced osteoporosis are underway.

All patients receiving long-term glucocorticoid treatment should be assessed for hypogonadism since patients receiving prolonged glucocorticoid therapy may develop hypogonadism due to inhibition of secretion of luteinizing hormone and follicle-stimulating hormone from the pituitary gland, as well as direct effects on hormone production by the ovary and testes. When hypogonadism is present, this should be corrected if possible. In a trial of postmenopausal women with RA who were taking prednisone and were randomized to receive either HRT or placebo, those who received HRT had a significant (3-4%) increase in their lumbar spine BMD compared with controls, while there was no significant change in femoral neck BMD in either group.69

**Conclusions**

Glucocorticoid induced osteoporosis is the most common form of drug-induced osteoporosis. The clinical impact of this disease is related to the high prevalence of osteoporotic fractures with associated impairment of quality of life. Osteoporosis with increased risk of fracture is a serious complication of using glucocorticoids, particularly at high doses for prolonged periods. Interventions have been shown to be effective at preventing bone loss and reducing fracture risk. Bisphosphonates remain the gold standard of therapy at present. Parathyroid hormone is the novel therapy that was shown to be even more effective in management of glucocorticoid-induced osteoporosis and studies are awaited for evidence of its long term use.

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