Glucocorticoid-induced osteoporosis

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Key words: bone, glucocorticoids, osteoporosis

ABSTRACT
Glucocorticoid-induced osteoporosis is one of the most important side-effects of glucocorticoid use, leading to an increased fracture risk. In this review, recent advances in the understanding of the mechanisms of glucocorticoid-induced osteoporosis are summarised. Methods to identify persons at risk for fractures are discussed, as well as the new ACR recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis (2010). Different treatment options are summarised considering the pathogenesis of glucocorticoid-induced osteoporosis. Improved insights into pathogenesis might result in development of new treatment possibilities.

Introduction

Glucocorticoids are frequently used in many diseases because of their strong anti-inflammatory and immunosuppressive effects. However, corticosteroids have many metabolic side-effects. Glucocorticoid-induced osteoporosis is one of the most devastating side-effects, since bone loss during long-term glucocorticoid-treatment may cause severe clinical manifestations, *e.g.* vertebral and non-vertebral fractures.

Epidemiology

Glucocorticoids frequently are prescribed in patients with various chronic diseases, such as rheumatoid arthritis, polymyalgia rheumatica, inflammatory bowel disease and chronic obstructive pulmonary disease. It is estimated that 3% of the elderly >50 years has ever used glucocorticoids (1, 2). Treatment with glucocorticoids results in bone loss, and increased risk of vertebral and non-vertebral fractures (3). Glucocorticoid-induced bone loss predominantly affects the trabecular bone and begins within months after initiation of therapy (3, 4). Earlier studies showed a biphasic pattern with a rapid initial phase of 3–5% bone loss in the first year of glucocorticoid-treatment, followed by a slower phase during continued use of 0.5–1% annually (5, 6).

As a consequence of bone loss, use of glucocorticoids increases fracture risk in a dose-dependent manner (7, 8). The risk for vertebral fractures is elevated particularly, 2–5 times, depending on the daily prednisone dosage, and this increase is seen as soon as 3 months after initiation of treatment (9, 10). After cessation of glucocorticoid-treatment fracture risk gradually returns to baseline and therefore appears to be partly reversible (11). Fracture risk is increased for both women and men and is age-dependent. Furthermore, other determinants of bone loss, such as smoking, immobility and the activity of the underlying disease also may contribute to increased fracture risk (12).

Although glucocorticoids reduce bone mineral density (BMD), fracture risk can not be completely explained by changes in BMD, but also is influenced by a reduced bone quality (13). Prior studies have documented a decrease in the so called "bone density threshold for vertebral fractures" (14, 15): more vertebral fractures were documented in postmenopausal women using glucocorticoids *versus* non-users, with the identical T-score.

Effects of glucocorticoids on bone and fracture risk

Earlier data on the pathogenesis of glucocorticoid-induced osteoporosis were mainly based on histomorphometric data derived from patients treated with high-dose glucocorticoids. In these studies, reduced bone formation was observed, characterised by a low mineral apposition rate and a reduced number of osteoblasts, while bone resorption was unchanged or even elevated (16, 17).

Recent studies have provided more insight in the molecular mechanisms involved in glucocorticoid-induced osteoporosis, summarised in Figure 1. These
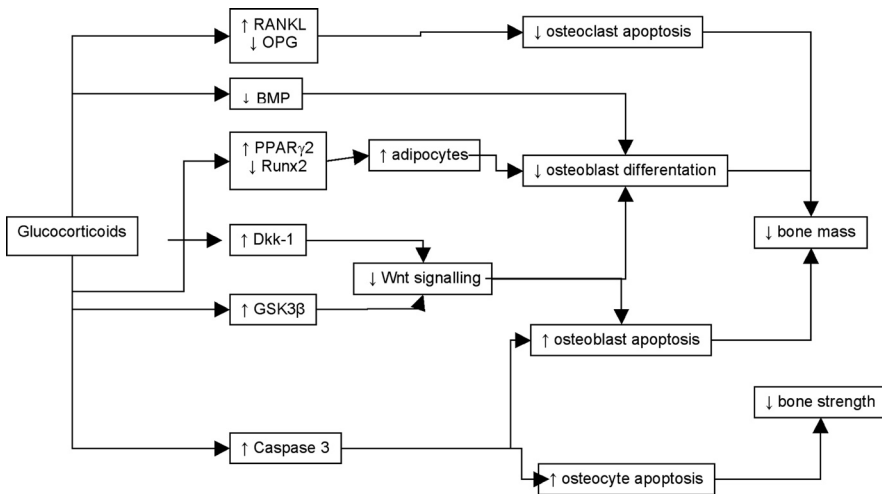
Fig. 1. Pathophysiology of glucocorticoid-induced effects on bone cells. BMP: bone morphogenetic protein; Dkk-1: dickkopf-1; GSK3β: glycogen synthase kinase 3β; OPG: osteoprotegerin; PPARγ2: PPARgamma2; RANKL: receptor activator for nuclear factor kappa B ligand; Runx2: runt-related protein 2.

include: 1) increased apoptosis of osteoblasts and osteocytes, 2) impaired differentiation of osteoblasts and 3) increased life-span of osteoclasts, as discussed below:

1. Glucocorticoid-induced increased apoptosis of osteoblasts results in reduced bone formation, and the loss of osteocytes is thought to result in a disrupted osteocyte-canicular network and failure to respond to bone damage, leading to reduced bone strength (18). Apoptosis of osteoblasts and osteocytes is induced by activating caspase 3 (19), and, furthermore, apoptosis of osteoblasts is related to activation of glycogen synthase kinase 3β (GSK3β), which plays a role in the Wnt signalling pathway (20). The Wnt signalling pathway is important in bone metabolism and especially osteoblastogenesis. Normally, binding of Wnt to the low density lipoprotein receptor-related protein 5 and 6 (LRP5/6) and its co-receptor frizzled stabilises β-catenin leads to transcription of target genes and subsequent induction of bone formation. Glucocorticoids have been shown to suppress this pathway by increasing the production of Wnt pathway inhibitors, such as dickkopf-1 (Dkk-1) (21, 22).

2. Glucocorticoids are recently shown to interfere with the bone morphogenetic protein (BMP) pathway (23). Furthermore, glucocorticoids stimulate bone marrow stromal cells to differentiate towards adipocytes instead of osteoblasts, through increased expression of the peroxisome proliferator-activated receptor-γ2 (PPARγ2) and repression of the osteogenic transcription factor runt-related protein 2 (Runx2) (24). Recent research suggested that high doses of glucocorticoids cause a shift towards adipogenesis by repression of activator protein-1 (AP-1) (25).

3. Interestingly, the apoptosis of osteoclasts is reduced during glucocorticoid-treatment. The lifespan of osteoclasts is extended due to an up-regulation of RANKL (receptor activator for nuclear factor kappa B ligand) and suppression of osteoprotegerin (OPG) (26). The Wnt signalling pathway might be involved in the glucocorticoid mediated suppression of OPG (27). However, this prolonged life-span of osteoclasts might be associated with reduced function.

Glucocorticoids directly affect osteoclasts, including interference with the formation of ruffled border and disruption of the cytoskeleton, causing a suppressed capacity for bone resorption (28).

Indirect effects by which glucocorticoids impair bone metabolism include inhibition of intestinal calcium resorption and renal tubular calcium reabsorption, which may lead to hypocalcaemia

and hyperparathyroidism. Glucocorticoids influence bone mineralisation by transrepression of osteocalcin and collagen I, two important matrix proteins (29). Furthermore, glucocorticoids might increase fracture risk indirectly by increasing the risk of falls, due to steroid myopathy (3).

Management of glucocorticoid-induced osteoporosis
General measures
First, efforts should be made to prescribe glucocorticoids in the lowest possible doses for the shortest period of time. Physicians should recommend patients to stop smoking, limit alcohol intake, to have a sufficient calcium intake and to perform weight-bearing activities daily. Furthermore, an assessment of fall risk is recommended and a variety of approaches are available (30).

Calcium and vitamin D supplementation have been proven essential in the management of glucocorticoid-induced osteoporosis. The total calcium intake should be at least 1000-1200 mg per day. An adequate vitamin D level, defined as a minimum serum level of >50 nmol/L 25(OH)D$_3$, is advised during the whole year (29, 31). Vitamin D supplementation in doses of at least 800 IU daily is recommended to achieve these therapeutic levels. In some patients higher dosages are needed, probably because many glucocorticoid users do not go outdoors often, and because glucocorticoids might interfere with vitamin D absorption. Calcium and vitamin D supplementation are shown to more or less stabilise BMD in patients on chronic glucocorticoid-treatment (32).

Fracture risk
The pathophysiology of osteoporotic fractures during glucocorticoid-treatment is multifactorial, including bone- and fall-related factors, and is also strongly related to baseline risk (34). Identifying patients with increased fracture risk solely by BMD measurements has several shortcomings, such as its age-dependency and inaccuracy in measuring bone quality. Therefore, the assessment of fracture risk using models calculating the absolute fracture risk for the individual patient has

been recommended, although a lack of consensus exists regarding the level at which treatment should be initiated. Several algorithms are available to support treatment decisions, usually based on the daily prednisone dosage and on the T-score of BMD measurements. First, the General Practice Research Database (GPRD), also known as FIGS (Fracture In GIOP Score) has been developed (8). This model calculates the 5- and 10-year risk for an osteoporotic fracture of the hip, vertebrae and wrist. The use of this approach is somewhat complicated, but this scoring method has the advantage that the underlying disease, the glucocorticoid dosage and the fall-risk are taken into account.

Another approach is the Fracture Risk Assessment (FRAX tool) as proposed by the World Health Organization (WHO) (34). This tool does not include the number of falls and the presence or absence of prevalent vertebral deformities. Furthermore, glucocorticoid usage, but not dosage, is recorded in the FRAX. Besides being useful in treatment decisions, the assessment of fracture risk might also help improving patient treatment adherence, since it presents the degree of risk reduction if treatment with anti-osteoporotic drugs is initiated.

Medication
Bisphosphonates have been shown to be effective in preventing glucocorticoid-induced bone loss in several randomised controlled trials (RCTs) (6, 35-39) (Table I). Alendronate improved lumbar spine BMD in patients on long-term glucocorticoids after one year, while BMD decreased in patients receiving placebo (38). This difference is sustained over 2 years (5), although the greatest increase in BMD occurred within the first year.

Two trials addressed the efficacy of risedronate in preventing glucocorticoid-induced osteoporosis. One study demonstrated that risedronate prevented bone loss in patients starting with glucocorticoids (35). Another study showed that risedronate increased BMD in patients who were taking long-term glucocorticoid-treatment (36). Amin showed, in a meta-analysis, a small, but significant

difference in percentage BMD change in patients using bisphosphonates of +4.6% *versus* patients using placebo/calcium (39). Furthermore a reduction of vertebral fractures has been observed in RCTs of both alendronate and risedronate in glucocorticoid-treated patients (6, 37) (Table I), although no reduction in non-vertebral fractures was observed in both studies.

Recently, zoledronic acid, given yearly by intravenous infusion, was shown to prevent glucocorticoid-induced osteoporosis (5). Zoledronic acid was found to be more effective than risedronate in both the treatment and prevention subgroup after 12 months of treatment. No statistically significant difference in fracture rate was observed, which might be due to the fact that zoledronic acid was compared with an anti-osteoporotic drug and not with placebo. The larger increase in BMD in the zoledronic acid group is difficult to interpret, since it is unknown whether this is associated with a larger increase in bone strength and/or a larger reduction in fracture rate. Zoledronic acid is administered as a short-term infusion, which might include a small risk of renal failure.

The effects of ibandronate have been studied recently in a placebo-controlled RCT in men after cardiac transplantation, all of whom received high-dose glucocorticoids directly after transplantation. After one year, spine BMD remained unchanged in men treated with ibandronate compared with a decline in spine BMD of 25% in placebo-treated patients. Furthermore, a significant reduction in the rate of morphometric vertebral fractures was demonstrated (40). The reduction in BMD with ibandronate appears large, however, comparison with other bisphosphonates is hampered by the difference in study population and cumulative glucocorticoid dose. Monthly intramuscular neridronate improved BMD in the lumbar spine and femoral neck compared with placebo in RA patients during glucocorticoid-treatment (41).

Very recently, a placebo-controlled trial showed that raloxifene increased spine and hip BMD significantly (42). The observation that anti-resorptive drugs like bisphosphonates are useful in glu-

cocorticoid-treated patients might theoretically be unexpected, since the effect of glucocorticoids is dominated by its inhibiting effect on bone formation. Theoretically, anabolic agents should be the first choice in glucocorticoid-treated patients, based on the pathogenetic mechanisms in glucocorticoid-induced osteoporosis (13). This has been discussed in a recent editorial, in which it was stated that in the early phase of glucocorticoid-treatment bone formation is depressed and bone resorption increased, while in the chronic phase, the coupling between bone formation and resorption leads to low bone turnover, which provides an argument to prescribe anabolic agents (43). Indeed, clinical studies show that the anabolic agent PTH 1-34 (teriparatide) is more effective in prevention of glucocorticoid-induced osteoporosis than bisphosphonates. Recombinant human PTH 1-34 was compared with the active comparator alendronate in 428 women and men with osteoporosis, who received glucocorticoids (>5mg per day) for at least three months (44). After 18 months, lumbar spine BMD was significantly more increased in patients receiving teriparatide than in alendronate-treated patients. Remarkably, a difference in the percentage of patients with new vertebral fractures was also observed (Table I). In line with other studies, no difference was found in non-vertebral fracture rate. This finding was confirmed in the follow-up study during another 18 months of treatment (45). Teriparatide did not only reduce fracture rate, but was also shown to reduce back pain and improve quality of life in the European Forsteo Observation Study (EFOS) (46).

Intervention with PTH 1-34 restored trabecular bone volume, increased bone formation and increased bone strength in an animal model (47, 48). PTH treatment counteracts the negative effects of glucocorticoids on osteoblast and osteocyte apoptosis. These effects were demonstrated to be obtained by increasing the expression of Wnt signalling agonists (47, 48). No data are available on the effects of strontium ranelate and PTH 1-84 with respect to the prevention of glucocorticoid-induced osteoporosis.

Table I. Treatment effects on bone mineral density and incident vertebral fractures in glucocorticoid-induced osteoporosis.

Intervention	Comparative	Number of patients	Design	Duration	% change BMD Spine		% change BMD Fem neck		Vertebral fractures Placebo	Study drug
					Placebo	Med	Placebo	Med		
Risedronate (35)	Placebo	224	Prevention	1 year	-2.8	+0.6*	-3.1	+0.8*	9/52 (17.3%)	3/53 (5.7%)
Risedronate (36)	Placebo	290	Treatment	1 year	0.4	+2.9*	-0.3	+1.8 a	9/60 (15%)	3/60 (5%)
Risedronate¥ (37)	Placebo	518	Both	1 year	-1.0	+1.9*	-1.5	+1.3*	18/111 (16.2%)	6/111a (5.4%)
Alendronate (38)	Placebo	477	Treatment	1 year	-0.4	+2.9*	-1.2	+1.0*	8/135 (5.9%)	8/268 (2.9%)
Alendronate (6)	Placebo	477	Treatment	2 years	-0.8	+3.9*	-2.9	+0.6a	4/59 (6.8%)	1/143 (0.7%)b
Alendronate (37)	Placebo	173	Treatment	1 year	-0.6	+2.5*	+0.1	+0.4		
Zoledronic acid (5)	Risedronate	545 / 288	Treatment / Prevention	1 year	+2.7 / +2.0	+4.1# / +2.6#	+1.5 / +1.3	+0.4* / -0.03*	5/833 (0.6%)	3/833 (0.4%)
Ibandronate (40)	Placebo	58	Prevention	1 year	-25	0*	-23	0*	(53%)	(13%)b
Neridronate (41)	Placebo	68	Treatment	1 year	-2.97	+3.34*	-2.40	+1.78a		
Strontium Ranelate	No data									
Teriparatide(44)	Alendronate	428	Treatment	18 months	+3.4	+7.2*			10/165 (6%)	1/171 (0.6%)ᵉ
Teriparatide(45)	Alendronate	428	Treatment	36 months	+5.3	+11.0*	+3.4	+6.3*	13/169 (7.7%)	3/173 (1.7%)#
PTH(1-84)	No data									
Raloxifene (42)	Placebo	114	Treatment	1 year	-0.9	+1.3a	-0.8	+1.0	2/57 (4%)	0/57 (0%)

¥ combination of 2 studies, *$p \leq 0.001$, a $p \leq 0.01$, # $p \leq 0.0001$, b $p = 0.02$, ᵉ $p = 0.004$, # $p = 0.007$.
BMD: bone mineral density; Fem neck: femoral neck; GIOP: glucocorticoid induced osteoporosis; Med: medication studied; PTH: parathyroid hormone.

So far, no clear guidelines exist to identify which glucocorticoid-treated patients should be treated with teriparatide, particularly because of its relatively high cost price. One suggestion could be to treat a) only in those glucocorticoid-users with high age (>70 years?), with a low BMD (T-score <-2.5?), and at least 1 vertebral deformity at baseline or b) in those with a very high 10 year absolute fracture risk. In several countries reimbursement is only possible when a subsequent fracture occurs in a high risk patient, treated at least one year with a bisphosphonate, e.g. in the Netherlands, where it is available only in postmenopausal women with 2 vertebral fractures, suffering from a third fracture. Since the fracture threshold for glucocorticoid users is different (15), another cut-off threshold could be reasonable; e.g. that in glucocorticoid users above 50 years of age, it will be possible to prescribe teriparatide in a patient with at least 1 prevalent vertebral deformity, suffering from a second vertebral deformity during glucocorticoid-treatment. It is important to recognise that these are examples of possible guidelines, and that we propose that a consensus document is needed for the rheumatology community.

Recent studies on the molecular pathways underlying bone metabolism have identified potential novel therapeutic targets for the management of osteoporosis (49). New drugs, interfering with the Wnt signalling or RANKL/OPG pathways, might prove to be more effective than current treatment options in reducing glucocorticoid-induced osteoporosis in the future. Importantly, new anti-osteoporotic drugs for glucocorticoid-induced osteoporosis (such as denosumab, cathepsin K inhibitors and monoclonal antibody against sclerostin) should be tested against an active comparator, for ethical reasons.

Very recently, the American College of Rheumatology (ACR) recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis were updated, including renewed recommendations for counseling and monitoring and updated pharmacotherapeutical interventions (50). These recommendations provide a guideline for the management of glucocorticoid-induced osteoporosis for postmenopausal women and men >50 years and premenopausal women and men <50 years initiating or receiving glucocorticoids. Although a possible advance, the risk categories were identified using the FRAX tool, which does not include the daily prednisolone dose, the presence of prevalent vertebral fractures, and fall risk. Furthermore, the risk categories were arbitrarily defined by an expert panel.

Conclusions

Glucocorticoid-induced osteoporosis is one of the most important causes of secondary osteoporosis and associated with an evident clinical impact due to increased fracture risk. Increased insight in molecular mechanisms has suggested an important role for the RANKL/OPG pathway and Wnt signalling route in the pathophysiology of glucocorticoid-induced osteoporosis. To identify patients with increased fracture risk more accurately, new tools to assess absolute fracture risk are available. The first step in the management of glucocorticoid-induced osteoporosis is to minimalise the dose and duration of glucocorticoid-treatment when possible. Glucocorticoid-induced osteoporosis can be partly prevented by oral bisphosphonates. However, PTH 1-34 therapy seems to be superior to oral bisphosphonates, but is more expensive. Recent advances in the pathophysiology of glucocorticoid-induced

osteoporosis have lead to the development of new treatments, which will be available in the (very near) future to reduce glucocorticoid-induced osteoporosis and improve the quality of life of these patients.

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