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The Pathogenesis, Epidemiology and Management of Glucocorticoid-Induced Osteoporosis

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Abstract. Oral glucocorticoids (GCs) are frequently used in the treatment of inflammatory conditions, such as rheumatoid arthritis or asthma. They have adverse skeletal effects, primarily through reductions in bone formation and osteocyte apoptosis. Several findings indicate that changes in the quality of bone may significantly contribute to the increased risk of fracture and that loss of BMD only partially explains the increased risk of fracture in oral GC users. Epidemiological studies have found that the increases in the risk of fracture in oral GC users are dose dependent and occur within three months of starting GC therapy. Daily doses of >2.5 mg prednisone equivalent have been associated with increases in the risk of fractures and randomised studies reported adverse skeletal effects with daily doses as low as 5 mg. After discontinuation of GC treatment, the risk of fracture may reduce towards baseline levels unless patients previously used high cumulative doses of oral GCs. Users of inhaled GCs have also an increased risk of fracture, especially at higher doses. But it is likely that this excess risk is related to the severity of the underlying respiratory disease, rather than to the inhaled GC therapy. It has been recommended that patients who start on oral GC therapy should receive calcium and vitamin D supplementation. Patients with a higher risk of fracture should also receive a bisphosphonate.

Key words: Glucocorticoids — Corticosteroids — Osteoporosis — Fracture — Iatrogenic disease

ral glucocorticoids (GCs) are frequently used in the treatment of inflammatory conditions, such as rheumatoid arthritis or asthma. About 2% of the elderly population use oral GCs in the United Kingdom [1]. Over 70 years ago, Cushing first described the tendency of patients with excess endogenous GCs to develop bone fractures [2]. But whether exogenous GCs also have adverse effects on the bone, especially at lower doses, remained controversial for some time. A 1984 'evidence-based' review concluded that there was no evidence to substantiate a causal role for oral GC therapy in producing clinically important osteoporosis [3]. But new information has clearly discredited the belief that oral GCs have only adverse effects on the bone at high doses and after prolonged use. This article provides an overview of recent information on the pathogenesis, epidemiology and treatment of GC-induced osteoporosis and fracture.

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Pathogenesis

The pathophysiology of GC-induced fracture is multifactorial (Fig. 1). An important mechanism for GC effects on bone is osteoblastic dysfunction [4, 5]. Moderate doses of oral GCs inhibit synthesis of bone collagen by pre-existing osteoblasts and conversion of precursor into functioning osteoblasts [5, 6]. Recently, a study on transgenic mice has found that oral GCs also have direct proapoptotic effects on osteoblasts [7]. In addition to direct effects on osteoblasts, effects of GCs involve intermediate modifications in the synthesis, release, receptor binding of locally produced growth factors [8]. The negative effects of oral GCs on bone formation lead to a reduction in the total amount of bone replaced in each remodelling cycle [4].

Although there are several potential mechanisms for oral GCs to increase bone resorption, the role of bone resorption in the increase of risk of fracture and osteoporosis is still unexplained [4]. An animal study reported that GCs prolonged the survival of osteoclasts, suggesting that the extension of the life span of pre-existing osteoclasts may induce bone loss during early GC therapy [9]. On the other hand, studies of the markers of bone resorption have found inconsistent effects [4]. In a placebo-controlled study, bone resorption markers, specifically urine NTX/Cr and serum NTX, were unchanged throughout a 6-week study period in the low dose GC group compared to placebo. Another bone resorption marker, urine DPD/Cr, decreased signifi-

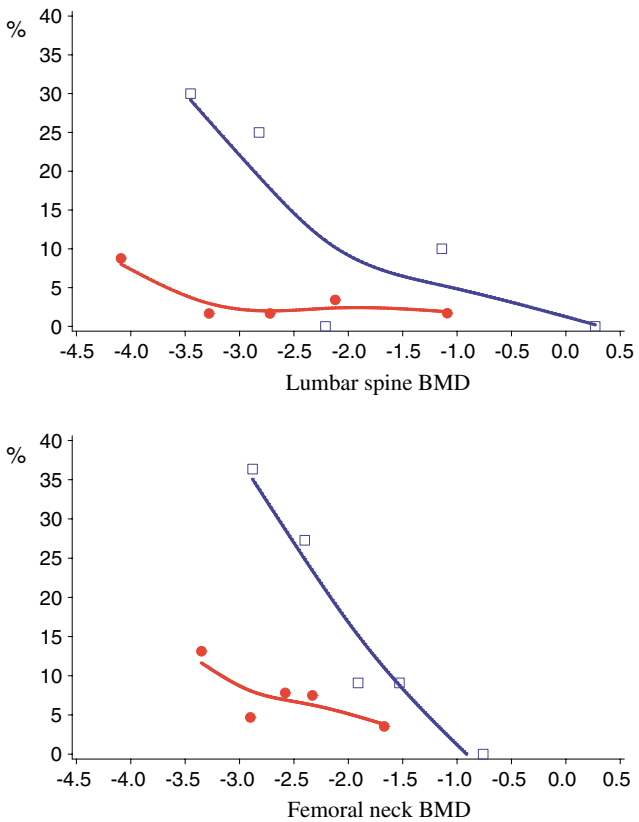


Fig. 1. Incidence of vertebral fracture in oral GC and non-users by baseline lumbar spine and femoral neck BMD (□ = GC users; ● = non-users) (the individual data points correspond to the incidence in subgroups of the GC and non-use populations, as based on quintiles of baseline BMD; the line represents a curve smoothing these individual estimates); Source: van Staa et al. *Arthritis & Rheumatism* 2003;**48**(11): 3224–3229 [35].

cantly compared with placebo. In the same study, multiple indices of bone formation were suppressed following low GC dose compared with placebo [10].

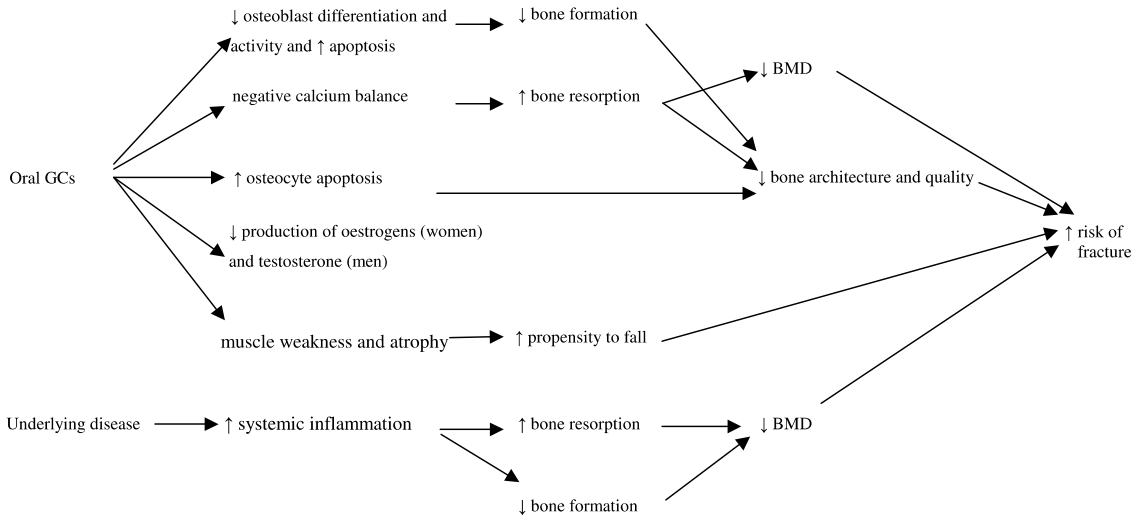
Bone resorption is usually in balance with bone formation. RANKL is involved in this coupling of bone formation and resorption. RANKL is expressed by osteoblasts and it triggers osteoclastogenesis. Osteoprotegerin (OPG), also produced by osteoblasts, prevents osteoclastogenic activity by binding to RANKL and acting as a decoy protein. A study of human cell culture showed that GC dose-dependently reduced OPG and increased RANKL expression [11]. This provides some explanation for an increase in bone resorption in patients treated with oral GCs.

Osteocyte apoptosis may be an important mechanism in the GC-induced loss of bone mineral density (BMD) and microarchitectural detoriation predisposing to fractures [12]. Osteocytes are the most abundant cells in bone, with about 10 times more osteocytes than osteoblasts. Research has suggested that osteocyte apoptosis is prevalent in patients using oral GCs. Femoral heads obtained from patients who underwent prosthetic hip replacement because of osteonecrosis due to chronic GC therapy exhibited abundant apoptotic osteocytes adjacent to the subchondral fracture crescent [13]. Osteocyte apoptosis was also observed in patients with GC-induced osteoporosis [14]. It is believed that osteocytes sense the need for remodelling and communicate it to lining cells, which trigger osteoclast precursors to the specific location [12]. A study of an organ culture found that osteocyte apoptosis turned off the inhibition of osteoclasts triggering local bone resorption [15]. An animal study reported that osteocyte survival contributed to bone strength independently of BMD and that the prevention of GC-induced osteocyte apopotosis preserved the strength of the bone [7]. It has been postulated that the loss of osteocytes may disrupt the osteocyte-canicular network resulting in a failure to detect micro-fractures or changes in the fluid flow within the network. This could reduce the strength of bone, independently of changes in bone remodeling or architecture [7].

Oral GCs also have a negative effect on the sex hormone status in men and women. They inhibit follicle-stimulating-hormone-induced estrogen production in women and decrease testosterone production in men. This negative effect of oral GCs on the gonadal function may increase bone resorption [6]. Increases in parathyroid hormone may also affect bone resorption in oral GC users. GCs decrease intestinal calcium absorption and increase renal calcium excretion and the secondary hyperparathyroidism may increase osteoclastic activity [6]. However, it has been reported that secondary hyperparathyroidism does not accompany chronic oral GC therapy in women on low to moderate doses of oral glucocorticoids. The lack of an elevation in intact parathyroid hormone levels in the presence of oral GC therapy may represent an increased sensitivity of bone to parathyroid hormone, or an alteration in the relationship between calcium and parathyroid hormone, or both [16]. It has been found that the reduction in calcium absorption due to oral GC therapy was reversed by vitamin D supplementation. This suggests that the calcium malabsorption in GC-treated patients is due to a dose-related abnormality of vitamin D metabolism and not to a direct effect of GC on depressing transmucosal intestinal absorption of calcium [17].

Muscle weakness and atrophy is also one of the potential consequences of oral GC therapy. Chronic GC-induced myopathy is generally manifested by weakness particularly of the pelvic gurdle musculature, with lesser involvement of the shoulder girdle and distal musculature. It generally occurs within weeks to months of oral GC therapy. Acute GC-induced myopathy occurs within days of high-dose oral GC therapy and is characterised by marked atrophy of all muscles and rhabdomyolysis [18]. A study that interviewed patients found that 60% of patients treated with oral GCs reported difficulty of getting out of a chair compared to 20% of

Table 1. Pathophysiology of GC-induced fractures



controls [19]. A small study reported that inspiratory respiratory muscle weakness developed after several weeks of oral GC treatment, which was reversible after stopping oral GCs [20]. A 2-week course of 30 mg GC daily was not associated with muscle weakness [21]. But it is unlikely that GC-induced myopathy fully explains the increased risk of fracture in oral GC users. The pattern of increases over time of vertebral and non-vertebral is similar and the risk of forearm is not increased in oral GC users [12, 22].

The underlying disease for which oral GCs are prescribed may also contribute to the increased risk of fracture. Systemic inflammation plays an important role in bone metabolism through pro-inflammatory cytokines and contributes to systemic (or local) bone loss and increases the risk of fracture [23]. Epidemiological studies have reported increases in the risk of fracture in patients with inflammatory bowel disease and rheumatoid arthritis independent of oral GC therapy [24, 25]. But is unlikely that the increase in fracture risk in oral GC users is fully explained by the effects of underlying disease. Oral GC therapy reduces systemic inflammation. Despite this, oral GC users have generally higher risks of fracture than untreated patients with similar underlying disease [26]. Furthermore, two studies that randomized patients to either low dose oral GC therapy or placebo found substantive adverse effects on bone [10, 27].

The relative importance of each of these different mechanisms to the development of fractures is currently not known. There also appears to be a significant individual heterogeneity in the response to oral GC therapy that may be related to genetic polymorphisms in the GC receptor. Van Rossum et al. found that a polymorphism in the GC receptor gene was associated reduced GC sensitivity, as reflected by differences in body composition and insulin and cholesterol levels [28]. The challenge for future research is to combine detailed information from laboratories to clinical fracture outcomes collected for large populations of GC users in order to better understand the relative importance of the various pathophysiological mechanisms.

Epidemiology

Effect of Oral GCs on the Risk of Fractures

The knowledge of the fracture risk associated with oral GC use has greatly increased in the last decade. Table 2 shows the overall results of several large internationally drawn population-based studies [22, 29–33]. The largest study concerned a study of the General Practice Research Database (GPRD) that included over 200,000 GC users and age- and sex-matched controls [22, 29]. Kanis et al. recently studied 40,000 men and women from seven prospective cohorts (about 5% were using oral GCs) [30]. Interestingly, the results of the various studies were consistent. The risk of hip and vertebral fractures was increased substantially in oral GC users, while that of forearm fracture was similar to that of controls. The vertebrae and femoral neck comprise primarily of trabecular bone, while the forearm has relatively more cortical bone. Oral GCs have been found to have larger effects on trabecular than cortical bone [34].

The most detailed information on the association between GC dose and fracture risk comes from the GPRD study. Daily doses of >2.5 mg prednisone equivalent were associated with increases in the risk of hip and vertebral fractures [26]. A large Danish case-control study reported a strong association between risk of hip fracture and total dose of oral glucocorticoids dispensed in the one year before. Patients who used 1500 mg or more in the one year before had a four-fold in-

Table 2. Relative rate (and 95% confidence interval) of fracture in GC users in large epidemiological investigations[a]

	GPRD [22]	Kanis meta-analysis of seven large cohorts [30]	Meta-analysis of smaller studies [34]	US study [31]	Scottish study[b] [32]
Any fracture	1.33 (1.29–1.38)	1.57 (1.37–1.80)	1.91 (1.68–2.15)	1.68 (1.52–1.87)	1.90 (1.68–2.16)
Hip	1.61 (1.47–1.76)	2.25 (1.60–3.15)	2.01 (1.74–2.29)	1.87 (1.19–2.94)	1.87 (1.45–2.42)
Vertebral	2.60 (2.31–2.92)	NA	2.86 (2.56–3.16)	2.92 (2.00–4.27)	4.16 (2.47–7.02)
Forearm	1.09 (1.01–1.17)	NA	1.13 (0.66–1.59)	1.03 (0.76–1.38)	1.64 (0.98–2.75)

[a] Results from a large Danish case-control study were not included in this table, as no overall relative rates were provided [33]
[b] Only fractures that resulted in hospital admission were included [32]

creased risk of hip fracture [33]. Two double-blind randomised clinical studies also found effects of low dose prednisone. One study found statistically significantly decreased markers of bone formation in patients using 5 mg prednisone per day for six weeks compared to randomly selected controls. These changes were reversed during the 2-week recovery phase [10]. The other randomised clinical study found that low GC doses (on average 7.5 mg daily) cause marked vertebral trabecular bone loss in the initial months of therapy in patients with active rheumatoid arthritis. After discontinuation of GC treatment, this bone loss was (partially) reversible [27].

BMD and Fracture Risk Associated with Oral GC Therapy

The GPRD study also reported that the risk of fracture was related primarily to daily rather than cumulative dose [29]. This strong relationship of fracture risk to daily dose is different to that observed for bone mineral density (BMD). A comprehensive review of literature reported a strong inverse relation between cumulative GC dose and BMD [34]. But there is evidence to suggest that the increase in fracture risk in oral GC users is mostly independent of BMD. The meta-analysis of Kanis et al. reported that adjustment for BMD did not change substantially the relative rate for fracture in oral GC users [30]. An analysis of the placebo groups of randomized clinical trials found that GC users had considerably higher risks of vertebral fracture at the same levels of BMD than controls (Fig. 1). Among the oral GC users, daily dose was a strong predictor of fracture risk. In fact, the fracture risk was similar between patients who recently had started GC treatment and patients who had been on GC treatment for at least 6 months [35]. These findings all suggest that GC therapy influences fracture risk by a mechanism independent of BMD.

The possibility that oral GC therapy increased the risk of fracture by a mechanism independent of BMD was suggested following a finding that the BMD of patients with a prevalent fracture and treated with oral GGs was higher than that of patients with postmenopausal osteoporosis [36]. This finding was not confirmed in another study that found that the distribution of BMD of prevalent fracture cases was similar between users of non-users of oral GCs [37]. But it can be argued that an analysis of the BMD of prevalent fracture cases may not be useful in determining the BMD threshold for fracture risk in GC users. The reason is that analyses of prevalent cases do not measure BMD at the time of the fracture occurrence. As the BMD decreases over time, the BMD of long-standing prevalent fracture cases will be different from incident cases.

Offset of Excess Fracture Risk in Oral GC Users

There is evidence to suggest that the effects of oral GC therapy on the risk of fracture are substantially reversible in most patients. The large GPRD study found that the excess risk of fracture in oral GC users mostly disappeared within one year of stopping therapy and this was most pronounced for vertebral fractures. The risk of hip fracture also reduced towards baseline levels after stopping oral GC therapy [22]. The Danish case-control study reported that the risk of hip fracture was comparable between controls and patients who had stopped oral GC therapy more than one year before [33]. A study in patients who had been cured from Cushing's syndrome reported normal BMD, in contrast to patients with active Cushing's syndrome who reported reduced BMD [38]. A histomorphometric analysis found that the major microarchitectural alteration in GC was progressive trabecular thinning without perforations [39]. But perforations and loss of bone architecture did occur in some patients treated with GC. Patients with high cumulative GC doses (>10 g) showed dramatic alterations in the trabecular network, characterized by thinner and less connected trabeculae than patients treated with low cumulative doses of GCs or patients with postmenopausal osteoporosis [40]. This observation suggests a possible threshold at which bone recovery after withdrawal of GC is impossible due to a disruption of the trabecular network [4]. Epidemiological studies of oral GC users in daily practice may not detect increases in the risk of fracture in a subgroup of users due to the small number of patients with these high cumulative GC doses.

Effect of Inhaled GCs

Inhaled GCs are widely used in the asthma and chronic obstructive pulmonary disease. A recent Cochrane re-

view of seven randomised clinical trials found no effects of inhaled GCs on BMD or fracture [41]. But this study only included a small number of patients, who were mostly young with mild respiratory disease and followed for a short period of time. Thus, these published randomised clinical trials provide little information on the long-term effects of inhaled GCs. A meta-analysis of epidemiological studies reported that users of inhaled GCs had, on average, lower BMD than control patients [42]. Several epidemiological studies have reported increases in the risk of fracture in patients using inhaled GCs [33, 43, 44]. Whether this increased risk of osteoporosis and fracture risk is caused by systemic absorption of inhaled GCs or by the underlying disease is controversial [45, 46]. Two large epidemiological studies that used the same data source both reported dose-related increases in the risk of fracture in patients using inhaled GCs, but they reached opposite conclusion on the aetiology of this risk [43, 44]. The study by Hubbard et al. did not adjust for disease severity, with the exception of oral GC use [44]. Recently, de Vries et al. replicated the results of this study, but found that the initial dose response between inhaled GCs and fracture risk disappeared when adjustment was made for disease severity and use of bronchodilators [47]. A study nested within a population with asthma or chronic pulmonary disease found no increases in risk in patients treated with inhaled GCs [48].

Users of other respiratory medications also have an increased risk of fracture, suggesting a contribution of underlying disease to the excess fracture risk [43]. Two cross-sectional studies found that airflow obstruction was associated with increased odds of low BMD, independent of treatment [49, 50]. There are various plausible mechanisms that may be responsible for an increased risk of osteoporosis and fractures in patients with asthma or chronic obstructive pulmonary disease. Physical activity is known to have a positive influence on BMD and patients with obstructive airway disease may have reduced physical activity. Cigarette smoking could also explain this relation, as it is a major cause of airway disease and may also have negative effects on BMD. The adverse effects of hypoxia and of the ongoing inflammatory processes may also play in the aetiology of osteoporosis in the patients with airway disease.

Management

Non-pharmacological Interventions for GC-induced Osteoporosis

There are only few data on the effects of lifestyle interventions in patients using oral GCs [51]. But it is generally recommended that patients have adequate intake of calcium and vitamin D, exercise, good nutrition and normal body weight. In addition, patients should be advised not to smoke and to avoid alcohol abuse [51, 52]. Although muscle weakness and atrophy is one of the recognised side effects of oral GC therapy, the effects of physical exercise in this have not been systematically evaluated. A small study of 12 patients using oral GC reported that training of the inspiratory respiratory muscles prevented the deterioration of respiratory muscle function [53]. Unfortunately, the compliance to exercise programs may be limited. A study of 135 postmenopausal women reported that only 17.8% still adhered to a home-based exercise program after 18 months [54].

Pharmacological Interventions for GC-induced Osteoporosis

Various pharmacological therapies have been assessed for the prevention and treatment of GC-induced osteoporosis, including bisphosphonates, vitamin D, fluoride and hormone replacement therapy. Beneficial effects on BMD have been found for most therapies [51]. A recent meta-analysis attempted to rank various therapies according to the level of efficacy on BMD [55]. It found that bisphosphonates were the most effective therapy (4.6% difference in percent change in lumbar spine relative to no therapy/calcium). The efficacy of bisphosphonates was enhanced when used in combination with vitamin D (6% difference in BMD). Vitamin D and calcitonin were more effective than no therapy/calcium (about 2% BMD difference). Fluoride also appeared effective (+2.9% BMD difference), although this was based on a small number of studies. The meta-analysis concluded that bisphosphonates are the most effective of the various therapies that have been assessed for the management of GC-induced osteoporosis [55]. But one can dispute whether one can use BMD to determine the efficacy of a therapy and whether larger effects on BMD are indicative of larger effects on fracture risk. In postmenopausal osteoporosis, this purported relationship between greater increases in BMD and greater decreases in fracture risk has been seriously questioned. Fluoride, a bone-forming drug, has been associated with large increases in lumbar spine BMD with no subsequent reduction in the risk of vertebral fractures [56]. Even within one therapy, greater increases in BMD do not correlate to larger decreases in fracture risk and the BMD change only explains a small proportion of the efficacy [57]. Given the complexity in the pathogenesis of GC-induced fractures, efficacy should be determined on the basis of fracture prevention, rather than BMD changes.

Most randomised clinical studies that evaluated different pharmacological therapies in patients treated with oral GCs only included small number of patients and only measured the effects on BMD rather than fracture. Fracture outcomes were only measured in a few studies, and only included as secondary endpoint. Figure 2 shows the efficacy of bisphosphonates on the risk of

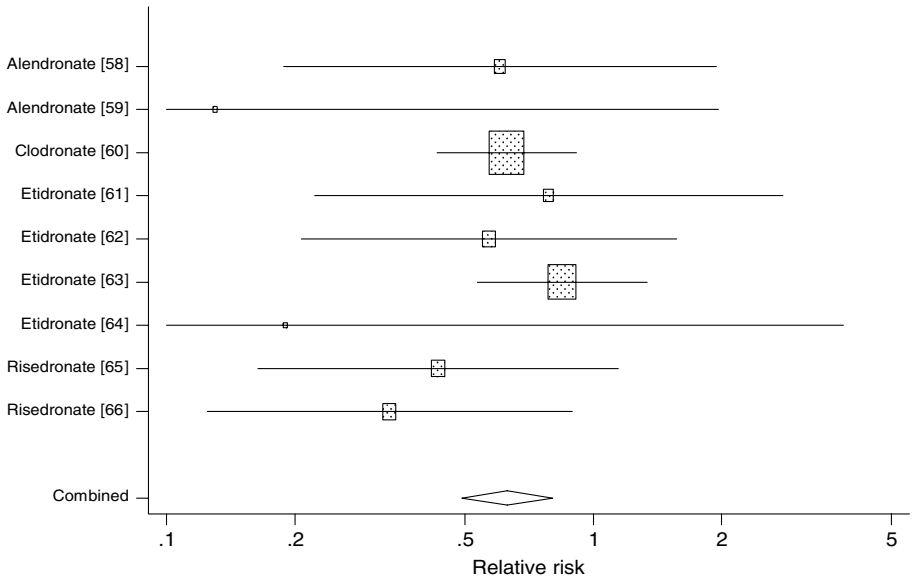


Fig. 2. Efficacy of bisphosphonates on the risk of morphometric vertebral fractures in randomised clinical trials that included more than 50 patients in each treatment arm.

morphometric vertebral fractures in randomised clinical trials that included more than 50 patients in each treatment arm [58–66]. The overall reduction in risk of morphometric vertebral fractures was 37% (relative rate [RR] 0.63, 95% confidence interval [CI] 0.49–0.80). The mechanisms by which bisphosphonates counteract the effects of oral GCs on the bone are still under discussion. Bisphosphonates reduce bone resorption, but GC therapy may affect bone primarily through reductions in bone formation and increases in osteocyte apopotosis and not increases in bone resorption. It has been found that bisphosphonates and other antiresorptive therapies (such as calcitonin and estrogen) inhibit osteoblast and osteocyte apoptosis induced by GC [14, 67–69]. The prolongation of the lifespan of osteoblasts and osteocytes may contribute more than the antiresorptive properties to bone effects of bisphosphonates [14]. There are no data on the efficacy of bisphosphonates in oral GC users on the risk of hip and other nonvertebral fractures. But the effects of bisphosphonates on hip and vertebral fractures in postmenopausal osteoporosis have been well studied and the assumption is generally made that anti-fracture efficacy is similar in GC users, although this has not been rigorously tested [51]. Given the differences in pathophysiology between postmenopausal and GC-induced osteoporosis, evidence for nonvertebral and hip fracture efficacy of bisphosphonates in oral GC users would be very useful.

Calcium and vitamin D supplementation has been found to prevent loss of BMD in oral GC users, as reported in a Cochrane meta-analysis. This meta-analysis compared patients using calcium and vitamin D to patients using calcium alone or placebo. The studies were underpowered to detect a statistically significant reduction in fracture risk, but a trend towards a lower risk of fracture was seen in the patients treated with calcium and vitamin D. It was suggested that because of low toxicity and costs all patients who start on oral GC therapy should receive prophylactic therapy with calcium and vitamin D [70].

Parathyroid hormone (PTH) may also play a role in the management of patients treated with oral GCs. A randomized study of 51 postmenopausal women who were taking oral GC therapy and hormone replacement therapy found that daily PTH injection dramatically increased BMD [71]. The women using PTH had increased levels of serum RANKL and modestly suppressed OPG, suggesting the stimulation by PTH of osteoblast maturation and function [72]. Although these new data on PTH are encouraging, evidence of a significant fracture risk reduction would be important, as BMD change may not always predict the level of fracture efficacy.

Selection of Patients for Preventative Therapy

The guidelines of the American College of Rheumatology recommend that primary prevention should be instituted in all patients who start GC therapy with a daily dose of ≥5 mg and with an expected treatment duration of ≥3 months [52]. The UK guidelines restrict primary prevention to elderly patients (age ≥ 65 years) or younger patients with low BMD (T-score ≤ −1.5) [51]. These differences probably reflect varying expert opinions on the cost-effectiveness of primary prevention in patients starting oral GC therapy. A recent analysis evaluated the cost-effectiveness of bisphosphonates in patients starting oral GCs. It found that the cost-effectiveness varied substantially across GC dose, indication, baseline fracture risk, life expectancy and on the outcome measure (cost per fracture avoided or Quality-Adjusted Life Years [QALY] gained). Interestingly, el-

derly GC users with shorter life expectancy showed high costs per QALY gained, but low costs per fracture prevented [73]. In these patients, bisphosphonates may prevent fractures, but it is implied in the QALY approach to cost-effectiveness that sicker patients and patients with short life expectancy have less "capacity to benefit" from reductions in risk. This underlying ethical assumption of QALY has been strongly criticized [74], but now seems widely accepted. But alternative approaches to cost-effectiveness may need to be developed in order to overcome these ethical concerns of using QALYs to prioritise health care.

Routine BMD measurement is not recommended in all patients starting GC therapy [51, 52]. But if required, the T-score used to determine the threshold for intervention is higher than that used in postmenopausal osteoporosis. The intervention threshold of the Royal College of Physicians is a T-score of −1.5 and that of the American College of Rheumatology is −1 (in postmenopausal osteoporosis, a T-score of −2.5 is used). This use of a higher intervention threshold in oral GC users reflects the observation that fracture rates are considerably higher in oral GC users than in non-users [35]. But different definitions of 'normal' may of course be confusing to practitioners. It has been recommended that intervention thresholds should not be at a fixed T-score but vary according to absolute long-term fracture probabilities [75]. This could also be applied to patients using oral GCs [26].

Conclusions

Users of oral GCs have an increased risk of fracture and osteoporosis. The pathogenesis of this is multifactorial. Reductions in bone formation and osteocyte apoptosis appear to be important mechanisms. Several findings indicate that changes in the quality of bone may significantly contribute to the increased risk of fracture and that loss of BMD only partially explains this increased risk. But there is clear need for further research to better understand the relative contribution of the different mechanisms to the increased risk of fracture and to elucidate the factors that determine the individual susceptibility to the adverse effects of GCs.

Epidemiological studies have found that the increases in the risk of fracture in oral GC users are dose dependent and occur within three months of starting GC therapy. Daily doses of >2.5 mg prednisone equivalent have been associated with increases in the risk of fractures [26] and a randomised study reported adverse effects on markers of bone formation in patients using 5 mg prednisone per day for six weeks [10]. After discontinuation of GC treatment, the risk of fracture may reduce towards baseline levels, unless patients have previously used high cumulative doses of oral GCs.

Various pharmacological therapies have been evaluated in patients using oral GCs. It has been recommended that patients who start on oral GC therapy should receive calcium and vitamin D supplementation. Patients with a higher risk of fracture should also receive a bisphosphonate. Intervention thresholds for these therapies should not be based on a fixed T-score of BMD but on absolute long-term fracture probabilities.

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