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Review

The treatment of glucocorticoid-induced osteoporosis

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Abstract

Glucocorticoid use results in an increase risk for fractures. Over the past 10 years, we have a greater understanding of the epidemiology, pathophysiology, prevention and treatment of glucocorticoid induced osteoporosis. This article reviews these recent findings and selective practice guidelines.

Keywords: Glucocorticoids; Osteoporosis; Treatment

1. Introduction

The use of glucocorticoids in the treatment of disease is ubiquitous in medicine today. In the fields of rheumatology, respirology, neurology, hematology, dermatology, gastroenterology and transplant medicine, glucocorticoids have vastly improved the treatment of numerous diseases that were once associated with significant morbidity and mortality. Often these drugs are prescribed on a long-term basis at supraphysiologic doses, and are associated with a number of side effects. The most common and serious of which, however, is bone loss leading to osteoporosis [1]. Glucocorticoid-induced osteoporosis (GIOP) is a widely recognized complication of these drugs, associated with increased risk of fractures to patients. It is estimated that between 30 and 50% of patients on long-term glucocorticoids will experience fractures [2], and that this risk to patients increases rapidly from the onset of therapy [3,4]. Today, loss of bone density and fractures due to GIOP may be prevented through the use of bone sparing agents. Due to the prevalence of glucocorticoid usage and the high costs incurred both personally and to society following a fracture, it is imperative that there be a greater awareness of the issues surrounding GIOP and of therapies that may be offered to patients both for prevention and treatment.

2. Epidemiology

In a large, retrospective cohort study evaluating the relationship between oral glucocorticoid use and fracture risk in the UK, it was estimated that approximately 0.9% of the total adult population was using oral glucocorticoids at any one time [5]. On extrapolation of this percentage to the UK population as a whole it was suggested that around 409,000 people were using glucocorticoids, and while the majority were taking doses of 2.5–7.5 mg of prednisolone daily, an estimated 93,000 people were taking doses greater than 7.5 mg, and had done so for greater than 6 months [5]. A significant dose response was observed for vertebral and hip fractures, such that fracture risk in glucocorticoid users was determined to be about 20% for daily doses of 5 mg or lower of prednisolone, however, rose to an approximate 60% increased risk compared to control group for those on a daily dose of 20 mg or more [3–5]. This risk was similar for men and women, but varied with age. Fracture rates in women rose exponentially with advancing age in both control group and glucocorticoid users, however in both men and women the incidence rates tended to be greater among those on higher doses of oral glucocorticoids [5]. Interestingly, patients aged 70–79 years were using oral glucocorticoids most frequently, and tended to use them for longer periods of time than younger patients. Likewise, patients on higher doses of oral glucocorticoids were more likely to continue treatment for longer periods of time. Based on this study, however, the concomitant use of bone-active treatments during glucocorticoid treatment was found to be very low, ranging from 4.0 to 5.5% [5].

Bone loss occurs rapidly within the first 6–12 months of starting glucocorticoid therapy [6] Fig. 1, and is the

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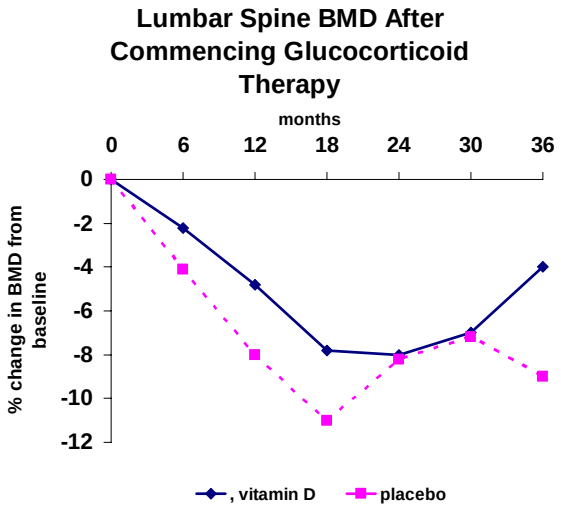

Fig. 1. Bone loss occurs on commencement of glucocorticoid therapy, even with supplementation with vitamin D. A slight insignificant increase in BMD occurs after 18 months with reduction in prednisone dose to less than 7.5 mg per day [6].

greatest in trabecular bone rather than cortical bone [7,8]. In a recent meta-analysis by Van Staa et al., in which 66 papers on bone density and 23 papers on fractures were examined, strong correlations were made between cumulative dose of glucocorticoids and loss of bone mineral density (BMD), and between daily dose and risk of fracture [4]. The risk of fracture was found to increase rapidly upon initiating oral glucocorticoid therapy (within 3–6 months), and this risk was independent of underlying disease, age and gender [4]. Both lumbar spine and hip BMD measurements of glucocorticoid users were consistently lower than expected in age and sex matched controls, and this correlated with the risk of fractures.

While it remains controversial whether lower doses of oral glucocorticoids, inhaled or intermittent doses of glucocorticoids may be free of effects on bones, studies have demonstrated increased fracture risks on doses even as low as 2.5 mg prednisolone daily [9]. In one study examining vertebral fracture rates in those on systemic glucocorticoid therapy, inhaled therapy or controls, a deleterious effect was greatest to those on systemic therapy, however inhaled therapy proved to have a greater risk compared to the control group [9]. Likewise, intermittent oral pulse therapy in men has been shown to increase vertebral fracture risk to the same degree as inhaled glucocorticoids [10]. Both groups demonstrated a greater risk than control subjects but were not as likely to fracture as those on continuous therapy [10]. Thus, most would agree that both inhaled and intermittent glucocorticoids are safer than continuous oral use with respect to vertebral fracture risk, however even these therapeutic options are not benign.

In addition to the glucocorticoid therapy, the underlying condition being treated often also contributes to bone density loss and increased fracture risk. In patients with long-standing rheumatoid arthritis who had not been treated with glucocorticoids, a significant reduction in BMD at both the lumbar spine and femoral neck was noted [11]. Besides general health status, age, sex, body mass index, previous personal or family history of fractures, diet, physical activity, smoking, alcohol consumption and menopausal status all contribute to a persons risk of osteoporosis and fractures, and must all be considered when assessing the risk of osteoporosis in an individual about to embark on glucocorticoid therapy.

3. Pathophysiology

Bone loss resulting from glucocorticoid therapy is believed to occur through a number of mechanisms. They decrease intestinal calcium absorption and increase renal calcium elimination through a mechanism that remains unclear [2,12]. This purportedly leads to secondary hyperparathyroidism, however measurements of parathyroid hormone (PTH) have lead to conflicting results with at least one reporting reduced levels [13]. Others have reported that glucocorticoids enhance the action of PTH on the skeleton [14]. In addition, glucocorticoids modify the proliferative and metabolic activity of bone cells by inhibiting bone *morphogenetic protein-2* (*BMP-2*) gene expression [15] and thus osteoblastogenesis and by reducing the lifespan of osteoblasts by increasing osteoblast apoptosis [16,17]. BMP's effect RANK ligand gene expression through enhanced Cbfa1 transcription and thus any reduction in BMP would have the effect of reducing osteoclastogenesis [16]. As a result, the exact mechanism by which osteoclasts lead to the increase in bone loss seen early in the development of glucocorticoid induced bone loss is less well understood, however may logically be due to increased osteoclast life span [18]. Likewise, there is no strong correlation between glucocorticoid induced osteoporosis and changes in vitamin D metabolism. Glucocorticoids do, however, alter gonadal function by suppressing the hypothalamic-pituitary-adrenal axis at various levels and inhibiting pituitary gonadotrophin secretion [19]. This leads to a reduction in the production of estrogen and testosterone [20,21]. Sex steroids have been shown to inhibit osteoblastic release of local stimulating factors of osteoclastogenesis. Thus, a decrease in circulating concentrations of these hormones might increase osteoclast precursor formation, resulting in an increased number of osteoclasts and hence greater bone resorption [17,22].

4. Management

In general, it is recommended that any patient currently prescribed or about to initiate glucocorticoid therapy be assessed for risk factors for osteoporosis, and advised on lifestyle modification tactics to reduce the risks. This would include limiting cigarette smoking and alcohol consumption,

reducing caffeine intake, participating in weight-bearing activities and taking precautions to reduce the risk of falls. Particularly in the elderly, in whom the risk of osteoporosis and falls are greatest, medications that cause a sedative effect or worsen orthostatic hypotension should be avoided if possible, and an assessment of transfer skills, gait, and sensory deficits should be conducted to improve functional status. Efforts to stabilize bone mass and ultimately prevent fractures should then be made in light of a patients risk for fracturing. Risk factors include previous vertebral fracture, post-menopausal status, age >65 years, premature menopause at <45 years or male hypogonadism, low BMD, or other causes of osteoporosis such as inflammatory disease, hyperparathyroidism or thyrotoxicosis [23]. With the addition of glucocorticoids and the resultant loss of bone that accompanies treatment initiation, risk for fractures is extremely high, and it could be argued that treatment should be instituted irrespective of bone density.

5. Bisphosphonates

Treatment studies are those which assess the efficacy of a medication to stabilize bone mass, and if possible increase bone mass and reduce the risk of fractures in a person already on chronic glucocorticoid therapy and in whom bone loss has already occurred. Prevention studies examine the efficacy of a drug to prevent bone loss in a patient about to initiate treatment with glucocorticoids. In the case of bisphosphonates, both prevention and treatment studies have demonstrated a beneficial effect in the preservation and improvement of bone mass over time. Bisphosphonates are inhibitors of bone resorption, and have been shown, in vitro, to reverse the increase in osteocyte and osteoblast apoptosis caused by glucocorticoids [24]. Substantial data from randomized control trials exists supporting the use of bisphosphonates in glucocorticoid-induced osteoporosis. In a recent meta-regression analysis comparing the efficacy of drug therapies used for the management of glucocorticoid-induced osteoporosis it was determined that bisphosphonates were the most effective class of drugs to preserve vertebral BMD, with an effect size of 1.03 (95% CI, 0.85–1.17) compared to vitamin D (effect size 0.46, CI 95%, 0.27–0.62), or calcitonin (0.51, CI 95%, 0.33–0.67) therapy [25]. When combined with vitamin D, the effect size of bisphosphonates further increased to 1.31 (1.07–1.50) (Table 1).

Of the prevention studies, risedronate, alendronate, etidronate, clodronate and palmidronate have all been assessed and shown to have beneficial effects on prevention of bone loss, and in some cases improvement of fracture risks [26–29]. In one randomized controlled trial of 224 patients taking at least 7.5 mg prednisolone or equivalent daily and either placebo or 5 mg risedronate, a significant difference in BMD was observed in lumbar spine (3.8±0.8%), femoral neck (4.1 ± 1.0%), and femoral trochanter (4.6 ± 0.8%) after 12 months duration [30]. All patients also received calcium and vitamin D. While the study was not powered to show fracture reduction, the group receiving risedronate did show a trend toward vertebral fracture reduction [30].

In the case of alendronate, Gonnelli et al [31] demonstrated in 43 previously untreated sarcoid patients initiating glucocorticoid therapy, an increase of 0.8% BMD of the ultra-distal radius following 1 year treatment with 5 mg per day alendronate compared to a loss in BMD of 4.5% with placebo. This was a statistically significant difference.

Cyclical etidronate therapy has been shown in several studies to be effective in the prevention of GIOP at the lumbar spine, however ineffective in improving femoral neck or radius BMD [26,32–34]. Over a 1 year period lumbar spine BMD increased by 0.3–1.4% in etidronate groups as compared to losses of 2.79–5% in placebo groups [26,32–34]. Even 12 months after the drug was discontinued there continued to beneficial effects on BMD in the treatment group, while placebo group continued to lose bone [35]. In addition, an 85% reduction in new vertebral fractures in post-menopausal women in the etidronate group was found compared to placebo [26]. In part, this was due to differences in baseline BMD [26].

Intermittent intravenous pamidronate has also been shown to increase lumbar spine BMD by 3.6% and hip BMD by 2.2% over a 1 year study period compared to a decrease of 5.3% at both sites in study group on only calcium therapy [36].

Treatment studies have likewise demonstrated improvements in lumbar spine BMD from baseline status in patients treated with bisphosphonates compared to placebo control groups for etidronate, alendronate, risedronate and pamidronate [28,29,37–39].

In the case of alendronate, Saag et al. [28], reviewed 477 men and women receiving glucocorticoid therapy and calcium plus vitamin D, and either placebo, 5 mg per day oral alendronate or 10 mg per day oral alendronate for 48 weeks. In the placebo group there was a decrease in lumbar spine BMD of approximately 0.4%, however an increase of 2.9 and 2.1% for the 10 mg per day and 5 mg per day alendronate groups, respectively. There was a non-statistically significant reduction in vertebral fractures in the alendronate group (2.3%), than the placebo group (3.7%), and in a follow up study it was reported that there were significantly fewer patients with new vertebral fractures in the alendronate group [27]. Benefit was seen in men, pre-menopausal women and post-menopausal women, and a gain in bone mass occurred irrespective of the duration of previous glucocorticoid use. An increase in lumbar spine and femoral neck BMD of 2.9% and 1.8%, respectively, was also observed following 5 mg per day risedronate (with calcium and vitamin D) after a 12 month period [29]. A reduction of 70% in the incidence of vertebral fractures was also noted in the risedronate group compared to placebo [29], with reductions to vertebral fractures observed in both men and women.

Table 1
Randomized controlled trials of bisphosphonate therapies in the prevention and treatment of glucocorticoid-induced bone loss[a]

Study authors	Study type	Duration	Patients, *N* (M/F)	GS duration[b]	Treatment for GIOP	Site	BMD change[c] (%)		
							Treat	Pla	Diff
Adachi [26]	Prevention	1 year	141 (54/87)	<100 days	Etidronate	LS	0.6	−3.2	3.8†
						FN	0.2	−1.7	1.9
Roux [32]	Prevention	1 year	117 (42/75)	<90 days	Etidronate	LS	0.3	−2.8*	3.1†
						FN	−1.3*	−2.6*	1.3
Wolfhagen [68]	Prevention	1year	12 (3/9)	<30 days	Etidronate	LS	0.4	−3.0*	3.4†
						FN	−0.1	−1.5	1.4
Jenkins [69]	Prevention	1 year	28	Started GS at baseline	Etidronate	LS	1.8	−3.7	5.5†
Skingle [33]	Prevention	2 years	55 (11/44)	Started GS at baseline	Etidronate	LS	4.8*	−0.7	5.5†
Boutsen [36]	Prevention	1 year	27 (5/22)	Started GS at baseline	Pamidronate	LS	3.9	−6.0	9.9
						FN	3.0	−4.1	7.1
Gonnelli [31]	Prevention	1 year	30 (10/20)	Started GS at baseline	Alendronate	DR	0.8	−4.5*	5.3†
Cohen[d] [30]	Prevention	1 year	228 (77/151)	<90 days	Risedronate	LS	0.6	−2.8*	3.4†
						FN	0.8	−3.1*	3.9†
Nordberg [70]	Prevention	1 year	27 (6/21)	Started GS at baseline	Clodronate	WB	1.0	2.0	−1.0
Frediani [40]	Prevention	4 years	163 (0/163)	<100 days	Clodronate	LS	0.94	−7.84	8.78†
						FN	0.88	−6.54	7.31†
Saag[e] [28]	Treatment	48 weeks	477 (141/336)	<4; 4–12; >12 months	Alendronate	LS	2.9*	−0.4	3.3†
						FN	1.0*	−1.2*	2.2†
Pitt [37]	Treatment	2 years	49 (19/30)	6 months to 35 years	Etidronate	LS	5.1*	1.0	4.1†
						FN	2.5	3.6*	−1.1
Geusens [38]	Treatment	2 years	37 (0/37)	>3 months	Etidronate	LS	4.9*	−2.4	7.3†
						FN	3.6*	−2.4	6.0
Worth [71]	Treatment	6 months	33 (12/21)	>9 months	Etidronate	LS	5.0*	−4.3*	9.3†
Reid [29]	Treatment	1 year	290 (109/191)	>6 months	Risedronate	LS	2.9*	0.4	2.6†
						FN	1.8*	−0.3	2.1†
Reid[f] [39]	Treatment	1 year	35 (19/16)	5.0/6.5 years	Pamidronate	LS QCT	19.6*	−8.8	28.4†

BMD measured by QCT.

[a] *N*: total number of patients enrolled; M/F: number of men enrolled/number of women enrolled; GS: glucocorticoid; BMD: bone mineral density; diff: percent difference between groups following therapy in BMD; DR: distal radius; FN: femoral neck; LS: lumbar spine; WB: whole body; QCT: quantitative computer tomography.

[b] Mean glucocorticoid duration prior to baseline assessment.

[c] Mean percent change from baseline to the end of therapy in BMD.

[d] Cohen et al., comparisons are made for the placebo and the risedronate 5 mg per day groups.

[e] Saag et al., comparisons are made for placebo and the alendronate 10 mg per day groups collapsed across GS duration.

[f] Reid et al., comparisons are made for the placebo and the risedronate 5 mg per day groups.

* Significant change from baseline ($P < 0.05$).

† Significant difference between groups ($P < 0.05$).

Recently clodronate given imtramuscularly in a dose of 200 mg weekly was shown to increase BMD in the spine by 8.78% and in the hip by 7.92% compared to placebo over 4 years and to reduce the risk of vertebral fractures by 37% [40].

Finally, in a RCT, intermittent intravenous pamidronate was demonstrated to yield a 19.6% increase in lumbar spine BMD, compared to a decrease of 8.8% in the calcium-alone treated group over a 1 year period [39]. In patients that proceeded to a second year of therapy, the gain in bone mineral density was maintained, while there was a progressive loss in the placebo group.

Bisphosphonate treatment consistently has been shown to stabilize, and in some cases improve BMD in glucocorticoid-treated patients, despite heterogeneous populations studied, varying glucocorticoid doses and durations and initial skeletal status. The variability of these studies makes these results far more generalizeable to the patient population seen in practice. Cyclical etidronate, alendronate and risedronate therapies reduce the incidence of vertebral fractures in

patients, generally within the first year of treatment. While effects are most evident in post-menopausal women who are at greatest risk for fractures, men and pre-menopausal women also benefit. In addition to the beneficial effects bisphosphonates offer to individuals, they too have been demonstrated to be of benefit to the healthcare system as a whole through cost effective analysis studies. Both etidronate and alendronate have been shown in rheumatoid arthritis and post-menopausal female populations requiring glucocorticoids to be cost effective in the prevention of vertebral fractures [41,42].

6. Hormone replacement therapy

In post-menopausal women, lower circulating estradiol and free testosterone have been shown to be associated with a greater risk of hip and vertebral fractures [43]. In the case of GIOP, intervention studies have been performed to evaluate the benefits of hormone replacement therapy [44,45]. In one retrospective cohort study, post-menopausal women of average ages 56–68 years suffering from either rheumatoid arthritis or asthma were assessed. Study results demonstrated a significant difference between the treatment and placebo groups, with an increase in lumbar spine BMD for those on hormone replacement therapy, but a decrease in the placebo group [44]. A non-significant difference at the femoral neck between treatment groups was observed [45]. These results differed from a two year study of alendronate in patients on glucocorticoids [27]. Adachi et al. [27], demonstrated a loss of bone mass in the lumbar spine in a small number of women on stable estrogen and placebo therapy, however, those on stable estrogen and alendronate experienced increases in BMD (Table 2).

A great deal of controversy has recently surrounded the issue of hormone replacement therapy and debate exists as to whether or not the benefits outweigh the risks associated with this therapy. Results from the women's health initiative, a multi-centered, randomized controlled primary prevention trial assessing hormone replacement therapy in 16,608 healthy post-menopausal women concluded that the overall health risks exceeded the benefits after an average 5.2 year study [46]. While there was a reduction in clinical vertebral and hip fractures to those on hormone replacement, and a decrease in colorectal and endometrial cancer, there was an increased risk of invasive breast cancer (hazard ratio 1.26, 95% CI, 1.0–1.59), coronary heart disease (1.29, 1.02–1.63), stroke (1.41, 1.07–1.85), and pulmonary embolism (2.13, 1.39–3.25). Likewise, results from the heart and estrogen/progestin replacement study (HERS) and the follow up study (HERS II) demonstrated a greater risk of deep vein thrombosis, pulmonary embolism, and breast cancer in older women with pre-existing coronary heart disease, and a decreased risk of colon and endometrial cancer as well as vertebral fractures [47,48]. Interestingly, in this study, the risk of hip fractures increased in those individuals on hormone replacement, while the risk of vertebral and other fractures decreased. No significant decreases in rates of coronary events were noted in those on hormone replacement as compared to placebo [49].

In summary, while hormone replacement therapy has exhibited a positive effect on lumbar spine BMD in the treatment of glucocorticoid induced osteoporosis, there is significant evidence to suggest increased risk of invasive breast cancer, coronary heart disease, deep vein thrombosis and pulmonary embolism as well as stroke in post-menopausal women. At present we do not have any firm data on the effects of hormone replacement therapy on those commencing glucocorticoids. A beneficial effect is gained for the management of climacteric symptoms that impair the quality of life of a number of women, a reduction in colon and endometrial cancer and a reduction in hip fractures. Due to the controversy that surrounds this therapy and the risks associated, hormone replacement therapy should only be initiated in patients at risk of GIOP when it is deemed that there will be an improvement in quality of life to alleviate

Table 2
Hormone replacement therapy in the treatment of glucocorticoid-induced bone loss[a]

Study author	Study design and duration	Patients enrolled, *N* (M/F)	GS duration[b] (Treat/Pla)	GS Dose[c] (Treat/Pla)	Treatment for GS induced osteoporosis	Site/ instrument	BMD change[d] (%)		
							Treat	Pla	Diff
Hall[e] [45]	RCT; 2 year	42 (0/42)	N/A	7.5/6.2	Transdermal oestradiol 50 m per day Oral norethisterone, 1 mg for 12 days per month, elemental calcium 400 m per day	LS/DXA FN/DXA	3.8* 1.6	−0.9 1.1	4.7† 0.5

[a] *N*: total number of patients enrolled; M/F: number of men enrolled/number of women enrolled; GS: glucocorticoid; Treat: treatment group; Pla: placebo group; BMD: bone mineral density; Diff: percent difference between groups following therapy in BMD; RCT: randomized controlled trial; NA: not available; LS: lumbar spine; FN: femoral neck; DXA: dual energy X-ray absorptiometry.

[b] Mean glucocorticoid duration prior to baseline assessment.

[c] Mean baseline glucocorticoid dose (mg per day).

[d] Mean percent change from baseline to the end of therapy in bone mineral density.

[e] Hall et al., comparisons are made for a subgroup of patients who were receiving glucocorticoids.

* Significant change from baseline ($P < 0.05$).

† Significant difference between groups ($P < 0.05$).

Table 3
Calcitonin therapy in the prevention and treatment of glucocorticoid-induced bone loss[a]

Study authors	Study type	Study design and duration	Patients enrolled, *N* (M/F)	GS duration[b]	GS dose[c] (Treat/Pla)	Treatment for GS induced osteoporosis	Site/instrument	BMD change[d] (%)		
								Treat	Pla	Diff
Adachi [72]	Prevention	Minimized RCT; 1 year	31(13/18)	All patients <1 months	NA	Intranasal calcitonin 200 IU per day	LS/DXA	−1.3	−5.0	3.7†
							FN/DXA	−3.6	−2.4	−1.2
Healey [53]	Prevention	RCT; 2 year	48(12/36)	All patients <3 months	NA	SC calcitonin 100 IU 3× per week Vitamin D 400 IU per day calcium 1500 m per day	LS/DXA	−0.1	−0.2	0.1
							FN/DXA	−3.6	−6.8	3.2
Sambrook [52]	Prevention	RCT; 1 year	63(13/50)	All patients <4 weeks	NA	Intranasal calcitonin 400 IU per day Calcitriol 0.5–1.0 μg per day calcium 1000 mg per day	LS/DPA	−0.2	−1.3	1.1
							FN/DPA	−2.8	−2.8	0.0
Kotaniemi [73]	Treatment	RCT; 1 year	63(0/63)	All patients = 2.5 years	8.5/8.6	Intranasal calcitonin 100 IU per day Calcium 500 mg per day	LS/DXA	0.5	−0.6	1.1
							FN/DXA	0.3	−2.7	3.0
Luengo [74]	Treatment	RCT; 2 years	44(6/38)	All patients >1 year	NA	Intranasal calcitonin 200 IU per day, calcium 1000 mg per day	LS/DPA	2.8	−7.8*	10.6†
Luengo [51]	Treatment	RCT; 1 year	40(16/24)	9.6/11.3 years	10.5/10.9	SC calcitonin 100 IU 3× per week, calcium 1000 mg per day	LS/DPA	4.0*	−2.5*	6.5†
Ringe [54]	Treatment	6 months	36(7/29)	67.3/75.4 months	22.6/17.2	SC calcitonin 100 IU alternate days	DR/SPA	2.7	−3.5	6.2†

Sambrook et al.: comparisons are made for the calcitonin plus calcitriol plus calcium group vs. the calcitriol plus calcium group; Kotaniemi et al.: absolute changes in LS and FN BMD were converted to percent changes. In the study, a significant absolute difference between groups was found in FN BMD.

[a] *N*: total number of patients enrolled; M/F: number of men enrolled/number of women enrolled; GS: glucocorticoid; Treat: treatment group; Pla: placebo group; BMD: bone mineral density; RCT: randomized controlled trial; Diff: percent difference between groups following therapy in BMD; NA: not available; LS: lumbar spine; DR: distal radius; FN: femoral neck; DPA: dual photon absorptiometry; SPA: single photon absorptiometry; DXA: dual energy X-ray absorptiometry.

[b] Mean glucocorticoid duration prior to baseline assessment.

[c] Mean baseline glucocorticoid dose (mg per day).

[d] Mean percent change from baseline to the end of therapy in bone mineral density.

* Significant change from baseline ($P < 0.05$).

† Significant difference between groups ($P < 0.05$).

a woman's symptoms. A careful assessment of a woman's current health status as well as her long-term health risks must performed, and risks must be weighed against benefits.

7. Calcitonin

Calcitonin acts to reduce bone resorption through specific receptors on osteoclasts. Randomized controlled studies have been conducted to assess the efficacy of calcitonin in glucocorticoid induced osteoporosis, and the results have been conflicting. (Table 3) Both Rizzato et al. [50] and Luengo et al. [51] demonstrated a prevention of bone loss in patients injected with salmon calcitonin over a 15 and 12 month period, respectively. A significant difference in the BMD of the treatment versus the placebo group was noted at both the distal radius and femoral neck. In the case of the vertebral bone mass, an increase in spinal bone density of 4% in those receiving calcitonin compared to a decrease of 2.5% in the control group was noted [37] (Table 3).

However, in a study by Sambrook et al. [52], the addition of nasal calcitonin did not confer any additional protective effect. Likewise, Healey et al. [53], found that calcitonin offered no greater benefit than calcium and vitamin D in protection of bone loss over a 2 year period of time in a group of patients initiating glucocorticoids for polymyalgia rheumatica or giant cell arteritis. A meta-regression analysis has demonstrated the efficacy of calcitonin in maintaining BMD to be of greater benefit compared to no therapy or calcium alone (effect size 0.51; 95% CI, 0.33–0.67), but less effective than bisphosphonates.

Calcitonin treatment may offer the additional benefit of relieving the pain associated with vertebral fractures. This was demonstrated by Ringe et al. [54], who found that in those treated with calcitonin, pain was significantly less compared to placebo group, and this differential persisted for the duration of the study. Thus, while bisphosphonates have been shown to have a greater effect on the maintenance of BMD following glucocorticoid initiation than calcitonin, positive changes in spinal BMD have been demonstrated, and pain control serves as an added benefit. Larger studies are necessary to prove a fracture risk reduction also exists with calcitonin therapy.

8. Fluoride

The fluoride ion acts to potentiate osteoblast mitosis. Intervention studies have demonstrated the addition of fluoride therapy in the treatment of glucocorticoid-induced osteoporosis leads to a sustained increase in spinal BMD when used long term [55–58]. In one randomized controlled trial looking at 35 patients with respiratory disease, the addition of 100 mg sodium monofluorophosphate twice daily with calcium increased lumbar spine BMD by 11%, compared to a 1.2% increase in the calcium-alone group after two years [57]. There was no difference in the rate of new vertebral fractures between the two groups, however. The addition of sodium fluoride to cyclical etidronate for individuals with established osteoporosis on glucocorticoids demonstrated an increase in lumbar spine BMD of 9.3% versus an increase of only 0.3% with etidronate alone [56]. Again, there was no difference in the fracture rate, and a loss of BMD at the hip for both groups was observed. In a treatment study by Lems et al. [55], 44 patients with predominantly rheumatological diseases were assessed, of whom 14 had just initiated glucocorticoid treatment. There was a 2.2% increase in lumbar spine BMD after 2 years in the sodium fluoride (25 mg twice daily) and calcium group compared with a 3% loss in the calcium group alone after 2 years. Again, femoral neck BMD decreased from baseline in both treatment and placebo groups.

In summary, fluoride appears to increase BMD at the spine, however, it offers no protection to the hip from the effects of glucocorticoids and has not been shown to prevent fractures in glucocorticoid-induced osteoporosis. In fact, at high concentrations fluoride interferes with the normal mineralization of bone, and indeed may increase the risk of non-vertebral fractures at these doses. Thus, there may be an added benefit in using fluoride as adjunctive therapy with an antiresorptive agent for those individuals with severe bone loss, however, it should not be used as a first line agent in GIOP.

9. Anabolic therapy

Three randomized controlled trials have used anabolic therapy in the treatment of GIOP [59–61]. (Table 4) One study each examined human parathyroid hormone, testosterone, and nandrolone decanoate. While the testosterone study examined men, the other two enrolled post-menopausal women. Results of the studies indicated that BMD of the lumbar spine [59,60] and forearm [61] increased in the treatment groups, whereas it decreased in the placebo groups following therapy. No effect was noted on the femoral neck, trochanter, total hip or distal radius BMD with human parathyroid hormone [59], and testosterone was found to have no effect on whole body BMD following therapy [60]. Thus, anabolic therapy may have some benefit in the treatment of GIOP, however the prevention of glucocorticoid-induced osteoporosis with these agents needs to still be determined (Table 4).

10. Calcium, vitamin D and its analogues

A recent meta-regression analysis demonstrated that vitamin D and its analogues offered a modest benefit in preserving bone density in individuals receiving glucocorticoid treatment, compared to no therapy or calcium therapy alone [62]. Of the prevention studies, Adachi et al. [6] failed to

Table 4
Anabolic hormone therapies in the treatment of glucocorticoid-induced bone loss[a]

Study authors	Study design and duration	Patients enrolled, *N* (M/F)	GS duration[b] (Treat/Pla)	GS dose[c] (Treat/Pla)	Treatment for GS induced osteoporosis	Site/ instrument	BMD change[d] (%)		
							Treat	Pla	Diff
Lane [59]	RCT; 1 year	51 (0/51)	12.4/14.9	8.9/9.4	PTH (1–34) 25 μg per day, Premarin 0.625 mg per day	LS/DXA	11.1*	1.3	9.8†
					Vitamin D 800IU per day, calcium 1500 mg per day	FN/DXA	2.9	1.2	1.7
Reid [60]	RCT crossover; 1 year	15 (15/0)	All patients = 8 years	9.2/11.6	IM testosterone esters 250 mg per month	LS/DXA	5.0*	−0.1	5.1†
					Calcium 1000 mg per day	WB/DXA	0.7	−0.4	1.1
Adami [61]	RCT with an additional retrospective control; 1.5 years	35 (0/35)	24/18[e]	10/10[e]	IM nandrolone	DR/DPA	5.1*	−11.3*	16.4†

[a] *N*: total number of patients enrolled; M/F: number of men enrolled/number of women enrolled; GS: glucocorticoid; Treat: treatment group; Pla: placebo group; BMD: bone mineral density; RCT: randomized controlled trial; Diff: percent difference between groups following therapy in BMD; LS: lumbar spine; FN: femoral neck; DR: distal radius; WB: whole body; DXA: dual energy X-ray absorptiometry; DPA: dual photon absorptiometry.
[b] Mean glucocorticoid duration prior to baseline assessment.
[c] Mean baseline glucocorticoid dose (mg per day).
[d] Mean percent change from baseline to the end of therapy in bone mineral density.
[e] median values are expressed.
* Significant change from baseline ($P < 0.05$).
† Significant difference between groups ($P < 0.05$).

find any benefit on lumbar spine BMD over a 3 year study period between individuals initiating glucocorticoid therapy of >10 mg per day, and treated with 1000 mg per day of calcium and either placebo or 50,000 IU per week of vitamin D. While the lumbar spine BMD decreased from baseline in both treatment groups, it did so to a lesser extent in the active treatment group as compared with the placebo group. Sambrook et al. [52], did however demonstrate calcitriol (1,2,5-dihydroxyvitamin D) to have a beneficial effect on lumbar spine BMD. In this randomized controlled trial, patients on calcium therapy alone demonstrated a loss of 4.3% per year in bone density, while the calcitriol group experienced a 1.3% loss in BMD. The addition of calcitonin to calcium and calcitriol prevented the annual loss in BMD to 0.2%. Likewise, beneficial effects were also noted with alfacalcidol (1α-hydroxyvitamin D), as demonstrated by Sambrook et al. [52], whereby patients beginning high dose glucocorticoid treatment suffered a loss of 5.67% in bone density compared to those on 1 μg per day alfacalcidol. No benefit was noted to femoral neck BMD or at the distal radius with the use of calcitriol [52] (Table 5).

Four treatment studies have been done assessing calcium and vitamin D or its analogues [63–66]. Of the three studies examining vitamin D, a meta-analysis concluded that calcium and vitamin D was more effective than no treatment or calcium alone in the treatment of GIOP at the lumbar spine [67]. In the fourth treatment study, Buckley et al. [63], studied the effects of calcitriol (500 IU daily) with calcium (1000 mg daily) on patients with rheumatoid arthritis receiving low-dose prednisone. An increase in lumbar spine BMD by 0.72% per year was noted in the calcitriol group compared to a loss of 2% per year in the placebo group. A difference in trochanter BMD was also noted in this study between treatment groups, in favor of vitamin D therapy.

The most frequent side effect reported with vitamin D therapy was hypercalciuria. Due to relative frequency of this side effect, urinary calcium levels and serum calcium levels should be monitored before instituting therapy and regularly thereafter, and doses should be adjusted if necessary.

In summary, evidence has indicated that calcium and vitamin D or its analogues offer some benefit in the prevention of GIOP, however the outcomes of the studies have been variable, and it is clear that these agents cannot completely prevent GIOP. Nevertheless, it does seem reasonable to review an individual's calcium intake, and suggest supplementation when dietary intake is unsatisfactory (i.e. less than four to six servings per day), and in whom there are no contraindications. It is also important to remember that many of those taking chronic glucocorticoids are frail elderly individuals who are house bound, and seldom outdoors. In this population, an assessment of vitamin D status and supplementation is appropriate for glucocorticoid-treated patients at risk. As vitamin D therapy has been shown to maintain spine BMD in patients taking chronic glucocorticoids, these agents are an important adjunctive therapy to additional bone-sparing medications.

11. Summary of therapeutic options

It appears clear that bisphosphonates offer the greatest protection for the prevention and treatment of glucocorticoid-induced osteoporosis. In addition to maintaining bone density and preventing further losses in individuals who have

Table 5
Calcium and Vitamin D and its analogues in the prevention and treatment of corticosteroid-induced bone loss[a]

Study authors	Study type	Study design and duration	Patients enrolled, *N* (M/F)	GS duration[b] (Treat/Pla)	GS dose[c] (Treat/Pla)	Treatment for GS induced osteoporosis	Site/instrument	BMD change[d] (%)		
								Treat	Pla	Diff
Sambrook [52]	Prevention	RCT; three drugs Calcitonin calcitriol Calcium 1 year	63(14/49)	All patients <4 weeks	N/A	Calcitonin 400 IU per day	LS/DPA	−1.3	−4.3	3.0†
						Calcitriol 0.5–1.0 μg per day	FN/DPA	−2.8	−2.9	0.1
						Calcium 1000 mg	DR/DPA	0.8	−3.0	3.8
Adachi [6]	Prevention	Minimized RCT; 3 years	62(20/42)	All patients <4 weeks	21.2/16.6	Vitamin D 50000 IU per week, calcium 1000 mg per day	LS/DPA, DXA	−4.2	−9.0	4.8
Buckley [63]	Treatment	RCT; 2 years	66(19/47) GS patients	N/A	5.9/5.0	Vitamin D 500 IU per day	LS/DXA	0.7	−2.0	2.7†
						Calcium 1000 mg per day	TR/DXA	0.9	−0.9	1.8†
Bernstein [64]	Treatment	RCT; 1 year	17(14/3)	5.4/2.5	NA	Vitamin 250 IU per day	LS/DXA	3.4	0.6	2.8
						Calcium 1000 mg per day	TH/DXA	3.1	−1.6	4.7
							WT/DXA	2.4	0.6	1.8
Bijlsma [65]	Treatment	RCT; 2 years	21(5/16)	38.0/44.2 months	N/A	Vitamin D 4000 IU every 2 days	LS/DPA	1.7	3.7	−2.0
						Calcium 500 mg per day	FN/DPA	2.3	−0.5	2.8
Dykman [66]	Treatment	RCT; 1.5 years	23(4/19)	4.8/7.3 years	12.2/11.3	Calcitriol 0.25 μg per day, calcium 500 mg per day	PR/SPA	1.0	2.0	−1.0
						Vitamin D 400 IU per day	DR/SPA	8.0	5.0	3.0

Sambrook et al.: comparisons are made for the calcitriol plus calcium group vs the calcium alone group; Buckley et al.: percentage BMD change are express as rates of change per year; Significant change from baseline ($P < 0.05$).

[a] *N*: total number of patients enrolled; M/F: number of men enrolled/number of women enrolled; GS: corticosteroid; Treat: treatment group; Pla: placebo group; BMD: bone mineral density; RCT: randomized controlled trial; Diff: percent difference between groups following therapy in BMD; NA: not available; LS: lumbar spine; TR: trochanter; FN: femoral neck; PR: proximal radius; DR: distal radius; TH: total hip; WT: Ward's triangle; DXA: dual energy x-ray absorptiometry; DPA: dual photon absorptiometry; SPA: single photon absorptiometry.

[b] Mean corticosteroid duration prior to baseline assessment.

[c] Mean baseline corticosteroid dose (mg per day).

[d] Mean percent change from baseline to the end of therapy in bone mineral density.

† Significant difference between groups ($P < 0.05$).

Table 6
Canadian, American and UK guidelines

Guidelines	Canadian, 2002 [75]	ACR, 2001 [76]	UK, 1998 [62]
Prevention	>3 months of prednisone 7.5 mg/day	Planned treatment duration of 3 months with prednisone equivalent of 5 mg per day	6 months of glucocorticoid 7.5 mg per day
Lifestyle			
Smoking cessation	Yes	Yes	Yes
Alcohol reduction	Yes	Yes	Yes
Exercise	Yes (weight bearing)	Yes (weight bearing)	Yes
Initiate calcium	Yes (19–50 years [till menopause for women] −1000 mg per day; >50 years [postmenopausal for women] −1500 mg per day)	Yes	If deficient in diet or high-risk (house-bound or elderly)
Initiate Vitamin D	Yes (19–50 years −400 IU per day; >50 years −800 IU per day)	Yes (800 IU per day)	If deficient in diet or high-risk (house-bound or elderly)
Risk factor evaluation	Yes	Yes	Yes
Consider bisphosphonate	Yes	Yes	Yes
Consider gonadal sex hormones if deficient or otherwise indicated	Consider risks and benefits	Yes	Yes
Treatment	>3 months prednisone 7.5 mg per day	>3 months prednisone equivalent of 5 mg per day	6 months prednisone equivalent of 5 mg per day
Lifestyle			
Smoking cessation	Yes	Yes	Yes
Alcohol reduction	Yes	Yes	Yes
Exercise	Yes (weight bearing)	Yes (weight bearing)	Yes
Initiate calcium	Yes (19–50 years [till menopause for women] −1000 mg per day; >50 years [postmenopausal for women] −1500 mg per day)	Yes	If deficient in diet or high-risk (house-bound or elderly)
Initiate Vitamin D	Yes (19–50 years −400 IU/day; >50 years −800 IU per day)	Yes (800 IU per day)	If deficient in diet or high-risk (house-bound or elderly)
Consider gonadal sex hormones if deficient or otherwise indicated.	Consider risks and benefits	Yes	Yes
Risk factor evaluation (fracture, age, BMD)	Yes	Yes	Yes
Prescribe bisphosphonate	Increased fracture risk	BMD *T*-score <−1, then prescribe bisphosphonate (use with caution in premenopausal women)	Increased fracture risk or BMD *T*-score <−1.5
Consider calcitonin as second-line agent if contraindications to or does not tolerate bisphosphonate	Yes	Yes	Yes
If BMD is normal, follow up and repeat BMD measurement either annually or biannually.	Yes	Yes	Yes (up to 3–5 years if BMD maintained for 2 years)

already sustained complications of glucocorticoids, these medications have also been demonstrated to reduce the risk of fractures. Data is by far more compelling for the bisphosphonates than any other agent. While hormone replacement therapy was extensively used in the past for the treatment of primary osteoporosis, data now suggests the risks of thromboembolic events, invasive breast cancer, strokes and coronary heart disease to outweigh the beneficial effects of fracture reduction in post-menopausal women. These medications should therefore be considered in women only after a careful evaluation of current health status and future health risks, and for those women in whom the medications may offer an improvement in quality of life to alleviate post-menopausal symptoms. Calcitonin may be considered in those individuals who cannot tolerate bisphosphonate therapy, or in those with pain secondary to vertebral fractures. For patients who have been treated but continue to lose bone, fluoride, anabolic therapy, and vitamin D or its analogues should be considered as adjunctive therapy.

12. Clinical approach

As always, a patient's individual risk factors should be carefully reviewed when initiating glucocorticoid therapy. Since the evidence indicates that bone loss is most rapid at the onset of glucocorticoid therapy, within the first 3–6 months, preventative measures should be initiated concurrently with the glucocorticoids. Risk factors that should be considered include bone mineral density at the lumbar spine and femoral neck at the onset of glucocorticoid therapy, family history, hormonal status, fracture history, age, and other medications that may interfere with normal bone metabolism. Lifestyle factors must also be assessed, including diet, alcohol, smoking habits and physical activity level. In considering all of these factors, a clinician will have a better understanding of the individual's unique susceptibility to bone loss and fracture upon glucocorticoid usage. The presence of secondary causes of osteopenia or osteoporosis should likewise be assessed and treated if possible (i.e. hypercalciuria, hyperparathyroidism, multiple myeloma). As a general principle, routine blood work including a complete blood count, serum measures of creatinine, alkaline phosphates, calcium and phosphorus should be conducted to aid in the diagnosis of secondary causes of osteopenia or osteoporosis, and in those over the age of 65 years, measures of serum protein electrophoresis, lipids and a urinary calcium to creatinine ratio may also be justified.

In general, if the course of glucocorticoid treatment is anticipated to be short (<3 months), individuals may continue on calcium and vitamin D supplementation. Calcium intake should be approximately 1500 mg per day, as a total of both dietary and supplemental sources, and vitamin D should be prescribed at a dose of 400–500 IU per day in individuals less than 65 years of age, and 800–1000 IU per day in older patients. Activated forms of vitamin D (calcitriol or alfacalcidol) have been shown to be more effective than vitamin D, however greater monitoring for hypercalciuria or hypercalcemia is required with these agents. If therapy is anticipated to go beyond the 3 month time frame then more effective bone-sparing treatment beyond calcium and vitamin D is required. For courses of glucocorticoid therapy greater than 3 months, a bisphosphonate should be prescribed. In the case of hypogonadal men, testosterone replacement should be considered. For post-menopausal women hormone replacement therapy should only be considered in those with menopausal symptoms that are affecting their quality of life, or in whom after explicit discussion of risk/benefit profile expresses a desire to initiate this therapy. Pre-menopausal women who do not plan to conceive may be prescribed a bisphosphonate. However, for those with future plans for childbirth, other agents such as calcitonin, calcium and vitamin D should be consider first. As bisphosphonates have extremely long half lives and the risks to the developing fetus even years from the time of termination of the bisphosphonate is yet unknown, these medications should be avoided in individuals who wish to conceive.

After 1 year of therapy, a follow-up bone density assessment should be performed, and if bone loss at a rate greater than 3% per year at any site measured has occurred then the intervention should be changed or an additional therapy added. If bone loss is less than 3% per year then treatment should be continued for the duration of the glucocorticoid therapy, and 3 years afterward in those with low bone mass. Bone mineral density should be reassessed every 2 years until glucocorticoid therapy is terminated. At this time, patients should then be assessed and managed in a manner similar to those not using glucocorticoids. A summary of guidelines for the treatment of glucocorticoid-induced osteoporosis is summarized in Table 6.

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