Calcium and vitamin D in the prevention and treatment of glucocorticoid-induced osteoporosis

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ABSTRACT

Although there are today a wide range of effective drugs to counteract the deleterious effects of glucocorticoids (GC) on bone, less than 10% of patients on long-term GC therapy receive simultaneously adequate osteoprotective treatment. Before beginning a course of long-term GC therapy, the appropriate strategy of anti-osteoporotic treatment should be determined for the individual patient, based on the initial bone mineral density, underlying disease, requested GC dosage, history of back pain and/or fractures, and age and sex.

Supplementation with 500-1000 mg calcium alone is not sufficient to stop bone loss in these patients. Vitamin D plus calcium may moderately reduce bone loss during GC therapy, especially in the first year, and in vitamin D depleted patients. Furthermore, this combination may be useful as a basic treatment to be combined with specific drugs (e.g., HRT, SERMs, fluoride, calcitonin, or bisphosphonates). The active metabolites calcitriol and alfacalcidol are effective in both the prevention and treatment of glucocorticoid-induced osteoporosis.

Introduction

Today worldwide less than 10% of patients on long-term glucocorticoid (GC) therapy receive simultaneously adequate osteoprotective treatment, although there is today a wide range of effective drugs to counteract the deleterious effects of GC on bone. Every physician who starts long-term GC therapy should determine what strategy of anti-osteoporotic treatment would be appropriate for his individual patient. Important criteria for the composition of the therapeutic concept are initial bone mineral density (BMD), underlying disease, requested GC dosage, history of back pain and/or fractures, and the age and sex of the patients. Within the range of available substances there are mild, moderately effective and very strong drugs (1).

In this review the position of calcium, plain vitamin D and active D metabolites in both the prevention and the treatment of glucocorticoid-induced osteoporosis (GIOP) will be discussed.

Calcium

Calcium promotes the development of skeletal mass in adolescence and is indispensable for reaching an optimal peak bone mass (2). Furthermore it slows down postmenopausal bone loss, and improves bone density in old age (3). There is, however, very little information concerning the efficacy of calcium supplementation in reducing GC-induced bone loss. Since GC patients may differ considerably in their rate of dietary calcium intake, bone turnover, vitamin D supply, and age-dependent intestinal calcium absorption, it is difficult to assess the effects of simple calcium substitution.

There is evidence that calcium alone is able to suppress bone turnover due to moderate secondary hyperparathyroidism in patients on long-term low dose GC treatment. In a small pilot study on 13 asthmatic patients taking an average of 15 mg prednisone per day, treatment with 1000 mg calcium daily significantly reduced urinary hydroxyproline excretion after just two months (4).

From several other prospective studies, where calcium supplementation was used in the control group, BMD data are available. In the well-known study of Sambrook (5), for example, the 29 patients in group 3 who were receiving only 1000 mg calcium showed a mean loss of BMD at the lumbar spine and femoral neck of 4.3% and 2.9%, respectively, after the first year (mean daily prednisone dose during the first year 13.5 mg). In two one-year trials with intermittent etidronate in GIOP (mean prednisone dosage 20 mg/d) the respective control groups were treated 4 times a year cyclically for 14 days with placebo and for 76 days with 500 mg calcium/day (6,7).

In the first study there were small increments of BMD in the etidronate group, but average decreases in the calcium group of 3.2% at the lumbar spine and 1.7% at the femoral neck (6). The results from the second study were very consistent with these findings, the calcium group showing average rates of decrease in the BMD of 2.8% and 2.6% at the respective measuring sites (6).

Despite the positive effects of calcium on bone turnover documented in the small pilot study (4), we conclude that supplementation with 500-1000 mg calcium per day is not effective to avoid progressive bone loss during GC therapy equivalent to > 7.5 mg prednisone per day. This was demonstrated once again by the very recent prevention study with risedronate (8). The 77 patients in the control group who received for one year only 500 mg calcium per day showed an average bone loss of 2.8% at the lumbar spine and 3.1% at the femoral neck and trochanter.

Calcium plus vitamin D

Based on the early pilot studies of Hahn *et al*. using calcium together with plain vitamin D or 25-hydroxy-vitamin D in GIOP (9, 10) it was generally believed that this combination is effective in the prevention and treatment of GC-induced bone loss. In these studies BMD measurement at the radius by single-photon absorptiometry had shown very impressive increments compared to untreated controls. The dose of cholecalciferol had been rather high, the authors administering 50,000 I.U. three times per week in the first study (9) and 40-100 µg 25-hydroxy-vitamin D in the other (10). In both studies each patient received an additional supplement of 500 mg calcium per day (9, 10).

These very positive effects of calcium/vitamin D (Ca/D) supplementation were never confirmed by later studies using a range of different dosages, however (11-14). The latter resulted only in very small increases in BMD or no significant differences between Ca/D treatment and controls. Furthermore, in different therapeutic trials using 500 mg calciun and 400 I.U vitamin as placebo, once again no significant changes in BMD could be demonstrated (15-17).

The most relevant preventive study in this context is a 3-year double-blind, placebo-controlled trial on 62 patients who had started GC within one month prior to the study onset (18). The 31 patients in the active treatment group received 50,000 I.U. vitamin D per week plus 1000 mg calcium per day, while the other 31 patients were on double placebo. The average changes in lumbar spine BMD for the two treatment groups during the trial are shown in Table I.

The authors concluded that Ca/D-therapy may be beneficial in the early prevention of GC-induced bone loss, but that no long-term effect could be expected from Ca/D supplementation in patients undergoing extended therapy with GC (18). It can be suggested that the moderate effect of Ca/D during the first year of intervention may be due to a subgroup of vitamin D deficient patients.

Using a meta-analytic approach to evaluate eleven studies, it was concluded that Ca/D is superior to no therapy at all or to calcium alone in the management of GIOP (19). The problem with this meta-analysis, however, is the fact that among the 11 studies included, 6 had been carried out with plain vitamin D and 5 with active metabolites, i.e. a mix of vitamin D metabolites with potentially different effects on calcium metabolism and bone turnover.

Taking into consideration all of this data, there is no convincing evidence today that plain vitamin D (even at rather high doses, e.g. 50,000 U/week = 7143 U/day) combined with 500 to 1000 mg of elemental calcium, is consistently able to prevent bone loss in early GC treatment or to restore significantly BMD in patients with established GIOP (20). Furthermore, there is no evidence that the liver metabolite 25-hydroxy-vitamin D has any advantage as compared to native vitamin D.

Table I. Mean changes in lumbar spine BMD in patients on GC therapy given either 50,000 U vitamin D/week plus 1000 mg calcium/day (group A) or double placebo (group B) (18).

	Average change in lumbar spine BMD		
	Group A	Group B	p
Month 12	-2.6%	-4.1%	n.s.
Month 24	-3.7%	-3.8%	n.s.
Month 36	-2.2%	-1.5%	n.s.

Active vitamin D metabolites

25-hydroxyvitamin D (calcidiol) is hydroxylated in the kidney at position 1 to 1,25-dihydroxy-vitamin D (calcitriol), the most active metabolite, which can be considered as a hormone of the kidney. Alfacalcidol is a prodrug of calcitriol and is transformed into the latter by hydroxylation at position 25 during the first passage of the liver. Correspondingly alfacalcidol cannot immediately bind to the intestinal receptors after oral intake. Therefore it has a slower onset of action than calcitriol and a lower risk of hypercalcemia. The recommended average daily doses for osteoporosis patients are 0.5 µg for calcitriol and 1.0 µg for alfacalcidol.

Rationale to adopt vitamin D-metabolites

Two major pathogenetic mechanisms of GIOP can be counteracted by active D metabolites. The first effect is the reversal of the mechanism of reduced intestinal calcium absorption. In a study on 20 patients with rheumatoid arthritis (RA) who were treated with 5-15 mg prednisone per day, fractional calcium absorption from the gut was measured before and after therapy with alfacalcidol or calcitriol (21). Both active D metabolites induced a significant increase in intestinal calcium absorption and urinary calcium excretion. This intestinal effect of active D metabolites was followed by a reduction of secondary hyperparathyroidism, thereby normalizing bone resorption (22).

Secondly, there is evidence for direct stimulatory effects of 1alpha-hydroxylated D metabolites on osteoblasts (23, 24), and specific high affinity receptors for 1,25-hydroxy-vitamin D were found in human osteoblast-like cells. In accordance with the suggested anabolic effect of active D metabolites, opposing effects on serum osteocalcin levels have been shown for prednisone and calcitriol (25). The hypothesized rationale to use D metabolites in GIOP can be summarized in three points:

1. Active vitamin D metabolites are primarily anti-resorptive agents which decrease the augmented bone turnover and consequent bone loss in GC patients.
2. The catabolic effect of GC on new bone formation may be overcome at least in part by a stimulatory effect on osteoblasts.
3. Anti-inflammatory and immunomodulating properties demonstrated for both alfacalcidol and calcitriol may have additional beneficial effects in GC patients (26).

Calcitriol

The first trial with calcitriol from 1984 was a double-blind randomized study on 23 patients with rheumatic disease, comparing a regimen of 0.4 µg calcitriol plus 500 mg calcium to calcium alone. During the 18 months of observation no significant difference in the diaphyseal or metaphyseal radius BMD was registered between the two groups (27). Possible explanations may be the rather low dose of calcitriol used and the primarily cortical measuring sites at the radius adopted.

The largest study conducted so far with calcitriol in GIOP was performed on 92 patients with RA (5).The mean daily dose of calcitriol in this preventive study was 0.6 µg/day and was given together with 1000 mg calcium. Measurements of BMD at the lumbar spine after 1 year showed a significant bone sparing effect compared to calcium alone. The combination of calcitriol with calcitonin in a separate treatment arm gave no significant additional effect (5).

In an open, uncontrolled two-year trial on 90 liver transplant patients treated with GC and other immunosuppressant drugs, therapy with 0.5 µg calcitriol plus 500 mg calcium was able to moderately increase lumbar and femoral BMD (28). A preventive effect on bone loss was also shown in 58 patients after cardiac or lung transplantation with doses of 0.50 to 0.75 µg of calcitriol (29).

Alfacalcidol

While calcitriol in most countries has only been approved for the prevention and treatment of renal osteopathy, alfacalcidol is available for osteoporosis in a large number of countries. Accordingly, more studies on GIOP have been performed with this metabolite.

Since 1980 alfacalcidol has been used in a number of small clinical studies on different patient groups being treated with GC (30-35). All of these trials, involving kidney transplant patients, asthmatics, SLE patients, and cardiac transplant cases, showed positive effects on BMD. No clear distinction, however, was made between the prevention of GC-induced bone loss and therapy for established GIOP. In a prospective controlled study from Hungary 0.25-1.0 µg of alfacalcidol was compared with calcium in 41 patients with different underlying diseases requiring GC therapy (36). Measurement of lumbar spine BMD after 12 months showed a loss of 4.4% in the calcium group and a loss of only 0.5% in the alfacalcidol group.

A large prospective placebo-controlled study whose stated aim was to prevent high dose GC-induced bone loss was published recently (37). A total of 145 patients with initial doses of GC > 30 mg/day and not more than 15 days of GC within the previous 24 months were randomized to receive either 1 µg alfacalcidol or placebo for 12 months. Both groups were given a supplement of 405 mg elemental calcium/day. The total study population comprised 25 different primary conditions, the mean age was 57 years, and the male to female ratio was 39/61%. The mean equivalent dose of prednisolone at baseline was 46.6 and 46.3 mg/day, respectively, for the two treatment groups. Among the 107 patients who completed the study only 71 (38 on alfacalcidol and 33 on placebo) had paired lumbar spine BMD data both at baseline and at 3, 6 and 12 months. After one year the percentage changes in BMD were +0.4% in the alfacalcidol group and -5.7% in the placebo group, i.e. despite the very high initial doses of prednisone, treatment with 1 µg alfacalcidol plus calcium was able to prevent bone loss after 1 year. The authors conclude that alfacalcidol provides a reasonable, safe and effective option for the prevention of corticosteroid-induced bone loss from the lumbar spine (37). Long-term use of alfacalcidol was not associated with any significant adverse event (e.g., hypercalcuria).

Comparison of native and active vitamin D

There have been often controversial discussions regarding whether expensive vitamin D metabolites are really more effective than the less expensive alternative cholecalciferol in patients with normal kidney function.

Treatment with native vitamin D is indicated in patients with vitamin D deficiency. In particular, elderly populations show beneficial effects (38,39). Supplementation with plain vitamin D is not a pharmacological therapy but a dietary substitute. Due to the feedback-regulation of the final activation step of 25-OH-vitamin D in the kidney into the active hormone 1,25-$(OH)_2$, oral supplements of native vitamin D will never lead to an increase of calcitriol above the upper normal level. That means that in vitamin D replete patients therapeutic effects can only be achieved by active vitamin D metabolites.

The effect of 0.5 µg alfacalcidol or 500-1000 I.U. vitamin D2 on intestinal calcium absorption and bone turnover was studied in 49 postmenopausal osteoporotic women (mean age 69 years). Fractional 45Ca absorption increased after 3 months of treatment with alfacalcidol ($p < 0.05$), but was unchanged in the group receiving plain vitamin D. Correspondingly a significant decrease in PTH was only seen in the alfacalcidol group (40).

We have performed a direct comparative, two-arm trial with alfacalcidol versus plain vitamin D in patients with established GIOP (41). Patients on long-term corticoid therapy were given either 1 µg alfacalcidol plus 500 mg calcium per day (group A, n = 63) or 1000 IU vitamin D3 plus 500 mg calcium (group B, n = 61). The two groups were not different in terms of age range, sex ratio, percentages of underlying diseases, average initial bone density values or the rates of vertebral and non-vertebral fractures (Table II).

During the 3-year study we found a significant increase in the lumbar spine density in group A (+2.24%) and a decrease in group B (-0.82%) ($p < 0.001$; Fig. 1). A positive effect in favor of alfacalcidol could also be verified at the femoral neck, the results being +1.04% versus +0.70% ($p< 0.05$). There were only two occur-

Table II. Initial characteristics of the patients studied in a prospective trial conducted by the authors to compare the efficacy of alfacalcidol versus plain vitamin D (BMD results shown in Fig. 1).

	Alfacalcidol	Vitamin D_3
Demographic characteristics		
Patients (no.)	63	61
Female/male	41/22	38/23
Mean age (yrs.)	59.4	59.7
Age range (yrs.)	37 - 76	39 - 76
Mean weight (kg)	64.0	65.4
Mean height (cm)	163.8	165.1
Diagnoses		
Chronic obstructive lung disease (COLD)	29	27
Rheumatoid arthritis	20	18
Polymyalgia rheumatica	14	16
Mean duration of GC therapy (yrs.)	5.1	4.4
Mean daily dose of GC therapy (mg)	9.2	9.2
Bone mineral density (BMD) at onset		
L_2-L_2 (T-score)	-3.24	-3.25
Femur-N (T-score)	-2.79	-2.86
Patients with/without prevalent vertebral fractures	35/28	32/29
Vertebral fractures at onset		
No. pts. / total no. of pts. with fractures	91/35	78/32
Mean/patient	2.6	2.4
Non-vertebral fractures		
No. pts. / total no. of pts. with fractures	30/18	29/19
Mean/patient	1.7	1.5

rences of moderate, transient hypercalcuria which did not necessitate any dose reduction. At the end of the study, 14 new vertebral fractures had occurred in 12 patients from group A and 26 new vertebral fractures had occurred in 22 patients from group B ($p = 0.0765$). In accordance with the observed lower fracture rate, the alfacalcidol group showed a significantly higher decrease in back pain as compared to the vitamin D group ($p < 0.001$).

We conclude that at the doses used in this trial, alfacalcidol is superior to vitamin D in the treatment of established GIOP in both men and women.

The role of calcium, vitamin D and D metabolites in the management of GIOP

From the existing literature and our own clinical experience the following conclusions can be drawn:

1. Supplementation with 500-1000 mg calcium is not sufficient to stop bone loss in patients on long-term GC therapy.
2. Vitamin D plus calcium may moderately reduce bone loss during GC-therapy (especially in the first year and in vitamin D-depleted patients).
3. The active metabolites calcitriol (e.g.

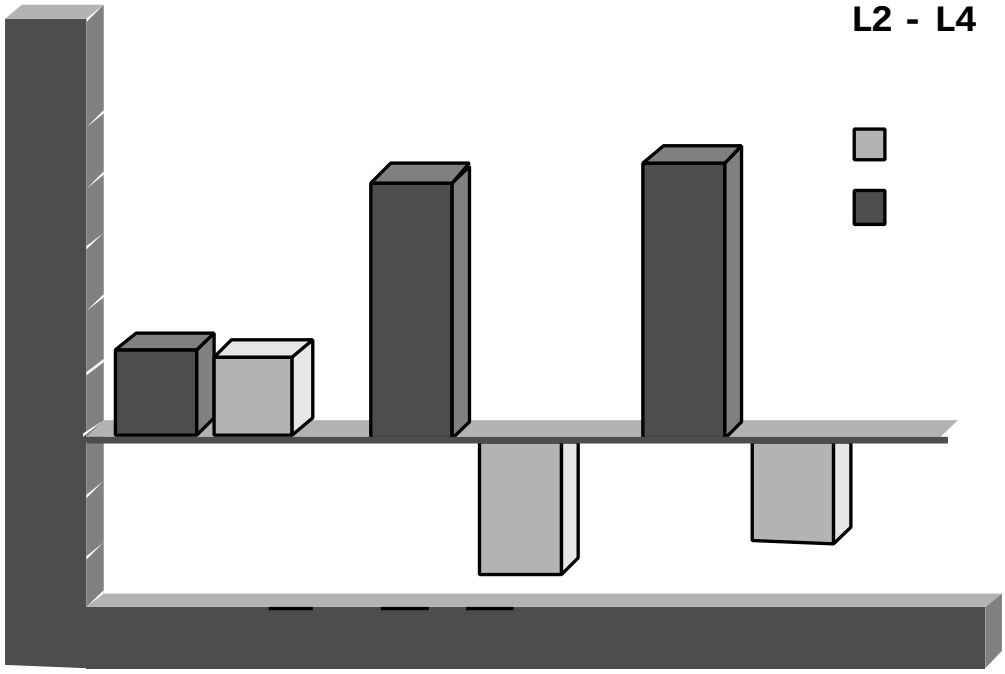

Fig. 1. Mean changes in bone mineral density at the lumbar spine (expressed as a percentage of the initial values) during a 3-year period of treatment with an active vitamin D metabolite + calcium or plain vitamin D + calcium in 124 patients on long-term glucocorticoid therapy.

0.5 µg/d) and alfacalcidol (e.g. 1.0 µg/d) are both effective in the prevention and treatment of GIOP. At these dosages no significant adverse events will be observed.

4. In established GIOP, vitamin D plus calcium may be useful as a basic treatment to be combined with specific drugs (e.g., HRT, SERMs, fluoride, calcitonin, bisphosphonates).

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