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Prevention of Glucocorticoid Induced Osteoporosis with Alendronate or Alfacalcidol: Relations of Change in Bone Mineral Density, Bone Markers, and Calcium Homeostasis

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ABSTRACT. *Objective.* To explore the relation of changes in measures of bone turnover and changes in bone mineral density (BMD) of the lumbar spine and total hip over 18 months in a double-blinded, randomized trial, comparing the effect of alfacalcidol (101 patients) versus alendronate (100 patients) on BMD in patients who recently started treatment with glucocorticoids for various rheumatic diseases.
Methods. Associations between changes in serum procollagen type I C-propeptide (P1CP), fasting urine N-terminal telopeptide of type I collagen (NTx), serum calcium, parathyroid hormone (PTH), osteocalcin, and change from baseline in BMD over 18 months were explored with regression and correlation analyses.
Results. In both treatment groups, there was a statistically significant decrease in NTx. In the alfacalcidol group there was also a significant increase in P1CP and osteocalcin, in contrast to the alendronate group, but BMD in the alfacalcidol decreased versus an increase in the alendronate group (p < 0.001). In neither treatment group were changes in biochemical measures correlated with the change in BMD, with the exception of a negative correlation in the alendronate group between changes in total hip BMD and NTx. Use of alendronate resulted in an increased PTH in 27 patients, but the increase in BMD of these patients was not statistically significantly different compared to patients taking alendronate with normal PTH levels.
Conclusion. Changes in BMD were not associated with changes in bone measures, with the exception of NTx in the alendronate group. For the patient taking glucocorticoids in clinical practice, the value of serial assessment of bone markers is low; changes in markers are no substitute for changes in BMD. ClinicalTrials.gov number: NCT00138983. (First Release April 1 2007; J Rheumatol 2007;34:1051–7)

Key Indexing Terms:
BONE MINERAL DENSITY   BONE MARKERS   OSTEOPOROSIS
ALENDRONATE   ALFACALCIDOL   GLUCOCORTICOIDS

For many rheumatic diseases, glucocorticoids (GC) are one of the keystones of therapy. One of the major adverse effects is glucocorticoid-induced osteoporosis (GIOP), especially with GC dosages of ≥ 7.5 mg prednisolone equivalent daily for at least 6 months. Bone loss is already initiated early in GC treatment. In recent decades, several international guidelines for prevention and therapy of GIOP have been developed[1-5]. In general, in these guidelines, apart from calcium and vita-

min D$_3$ supplementation, bisphosphonates are recommended in patients with a high risk of fractures. Alendronate has been proven to be effective in GIOP[6-8].

GIOP is characterized by uncoupling of bone resorption and formation: bone formation is decreased (by inhibition of osteoblast proliferation)[9] with initial increase of bone resorption. Bisphosphonates decrease bone resorption and, by the coupling of bone resorption to bone formation, probably also bone formation, but with a positive net result on bone mineral density (BMD). An important mechanism of inhibition of bone resorption by bisphosphonates is induction of apoptosis of osteoclasts[10].

Theoretically, for the prevention and therapy of GIOP, medication that increases bone formation would be more appropriate than medication that decreases bone resorption. The mode of action of active vitamin D$_3$ metabolites is mainly increased bone formation by direct stimulation of osteoblasts[11], but active vitamin D$_3$ metabolites also inhibit bone resorption[12]. Active vitamin D$_3$ has been shown to have favorable results in the prevention and therapy of GIOP[13]. This was the rationale of a double-blind double-dummy multicenter clinical trial that we performed on the effects and tolerance of alendronate versus those of alfacalcidol in the prevention of GIOP in patients with rheumatic diseases, who recently had been started with GC therapy. The results of the effects of the medication on BMD have been published recently[14]. This study is aimed at exploration of interrelations of changes in measures of bone turnover, calcium homeostasis, and BMD in the 2 groups taking GC (the alendronate and the alfacalcidol group) to determine the mode of action of these therapies for prevention of GIOP and to analyze the predictive value of changes in markers toward changes in BMD.

MATERIALS AND METHODS

Patients. Patients with a rheumatic disease, in whom GC were started (not longer than 12 weeks previously) in a dosage of 7.5 mg prednisolone equivalent daily or higher and expected to last for 6 months or longer, were included in a randomized, double-blind, double-dummy clinical trial of 18 months' duration. Patients were allocated to treatment with either alendronate 10 mg and alfacalcidol-placebo daily or alfacalcidol 1 μg and alendronate-placebo daily. In case of insufficient dietary calcium intake (based on a questionnaire), patients received calcium 500 mg daily and, if vitamin D deficiency existed (serum level < 30 nmol/l), supplementation with plain vitamin D$_3$ 400 IU daily. No other drugs known to influence bone metabolism were used. The study is described in detail elsewhere[14]. This study is registered as ClinicalTrials.gov number NCT00138983.

Methods. For changes in BMD, we used changes from baseline at 18 months of BMD of the lumbar spine (LS) and of the total hip, measured in g/cm^2. Baseline represented the day of randomization for alendronate or alfacalcidol; the first urine and blood samples for markers were taken at baseline, before taking the first dose of alendronate or alfacalcidol. The LS was chosen as primary BMD variable because of the high content of trabecular bone, which has a higher bone turnover than in the hip and thus potentially is most sensitive to change. Another argument to choose the LS as primary BMD variable was that the hips could be involved in the disease process in the rheumatic patients included.

In the context of our study, repeated measurements were performed of the following bone markers: serum procollagen type I C-propeptide (P1CP) as marker of bone formation, serum osteocalcin as marker of bone turnover, and fasting urine free deoxypyridinoline (dPyr) and fasting N-terminal telopeptide of type I collagen (NTx) as markers of bone resorption. In addition, repeated measurement of serum calcium corrected for serum albumin, serum parathyroid hormone (PTH), and serum osteoprotegerin (OPG) was performed. Of these measurements, performed at different intervals in time, delta area under the curve values (dAUC), corrected for time, were calculated, "delta" with respect to baseline. These dAUC values thus are comparable with a global mean value for change from baseline and, because of the correction for time, can be interpreted more easily[15]. Serum for measurement of calcium and albumin was collected at baseline and at Months 1, 2, 3, 6, 9, 12, 15, and 18. Calcium was corrected for albumin according to the following method: calcium + [(40 – albumin) × 0.02]. In addition, PTH (baseline and Months 1, 2, 3, and 18; chemiluminescent immunoassay), P1CP (baseline and Months 6, 12, 18; radioimmunoassay) and NTx (baseline and Months 3, 6, 9, 12, 15, and 18; enzyme linked immunosorbent assay, ELISA), osteocalcin and dPyr (both chemiluminescent immunoassay, both at baseline and Months 6, 12, 18) and OPG (ELISA, at baseline and Months 3, 6, 12, 18) were collected. All samples were stored at –70°C at a central laboratory facility until batch analyses.

Statistical analyses. The power calculation of the clinical trial has been described[14]. Changes in BMD of the LS and dAUC values of measures of bone metabolism were tested for statistically significant difference between the 2 treatment groups of patients with 2 sample t tests or Mann-Whitney U tests, as appropriate. Changes from baseline were tested for statistical significance with paired t tests or Wilcoxon rank tests, as appropriate. For correlation analyses, using BMD values in both LS and total hip, Spearman correlation coefficients were applied, and for statistical testing of binary variables between groups, the Fisher exact test. Univariate regression analyses were applied to explore whether changes in BMD of the LS (dependent variable) were predicted by changes in measures of bone metabolism (dAUC values as independent variables) in either of the 2 treatment groups. Identical analyses were performed with changes in bone marker during the first study months as independent variables (changes in serum calcium, NTx, OPG, and PTH after 3 mo and of P1CP, dPyr, and osteocalcin after 6 mo). P values < 0.05 were considered statistically significant; all tests were 2-sided.

RESULTS

Patient characteristics at baseline for the 2 treatment groups are shown in Table 1. Details on completers, dropouts, doses of predniso(lo)ne, adverse effects, and effects on bone have been described[14].

During our study, mean (standard deviation) daily dosage in prednisolone equivalent in the alendronate and the alfacalcidol group was 12 (9) and 11 (7) mg/day, respectively, a statistically nonsignificant difference; cumulative dosage was 5.9 (3.7) and 5.7 (3.4) g, respectively (p > 0.05).

In the alendronate group, there was an increase of 2.3 (4.6)% (p < 0.001) in BMD of the LS from baseline after 18 months (17 BMD missing), and in the alfacalcidol group a decrease of 1.9 (5.7)% (p = 0.001), 17 BMD missing; the difference in change between the 2 groups was 4.2 (5.2)% (p < 0.001)[14].

Table 2 shows the changes in the alendronate and alfacalcidol group of lumbar BMD in g/cm^2 and of dAUC values of measures of bone metabolism. In the alendronate group compared with the alfacalcidol group, there are statistically significant differences in changes from baseline with respect to BMD of the LS (increase vs decrease, respectively), P1CP (decrease vs increase), osteocalcin (decrease vs increase), PTH (increase vs decrease), and calcium corrected for albu-

Table 1. Patient characteristics at baseline*

	Alendronate, N = 99**	Alfacalcidol, N = 101
Age, yrs:mean (SD), range	60 (14), 20–87	62 (15), 18–84
Sex and menopausal status		
Females, no. premenopausal/postmenopausal	7/52	10/55
Male, no.	40	36
Caucasian, no	93	87
Height, cm	169 (10)	169 (9)
Weight, kg	74 (13)	73 (12)
Start dosage prednisone equivalents, mg/day	23 (20)	22 (18)
BMD lumbar spine (L2-L4), g/cm^2	1.06 (0.21)	1.09 (0.21)
Patients with vertebral deformity at baseline, no.	6	14
Diagnosis, no.		
Rheumatoid arthritis	33	41
Polymyalgia rheumatica	36	36
Other***	30	24
OPG, pmol/l (normal ≥ 0.5)	4.6 (2.6)	5.0 (2.9)
P1CP, pmol/l (normal, men 870–2340, women 680–2049)	1143 (495)	1166 (575)
Osteocalcin, ng/ml (normal 3.1–13.7)	3.6 (2.4)	3.3 (2.5)
dPyr, nmol/l (normal, men 33–81, women 25–59)	64 (46)	74 (51)
NTx, nmol/l (normal 33–715)	414 (366)	504 (446)
PTH, pmol/l (normal 2–7)	3.5 (2.0)	3.8 (2.2)
Corrected calcium, mmol/l (normal 2.2–2.7)	2.36 (0.11)	2.35 (0.11)

* All means (SD), unless indicated otherwise. OPG: serum osteoprotegerin, P1CP: serum procollagen type 1 C-propeptide, osteocalcin: serum osteocalcin, dPyr: fasting urine free deoxypyridinoline, NTx: fasting urine N-terminal crosslinking telopeptide of type 1 collagen, PTH: serum parathyroid hormone, corrected calcium: serum calcium, corrected for serum albumin. ** One patient in the alendronate group withdrew before initiation of randomized therapy. *** Categories with less than 5 patients totally were grouped into the category "other".

Table 2. Changes in lumbar spine bone mineral density (BMD) and in measures of bone metabolism in the 2 groups*.

Change in	Alendronate Group	p, Change from Baseline	Alfacalcidol Group	p, Change from Baseline	p, Difference Between the 2 Groups
BMD, g/cm^2	0.02 (0.05)	0.000002	–0.02 (0.07)	0.001	0.000001
	0.03 (–0.002 to 0.05)		–0.02 (–0.05 to 0.02)		
OPG, pmol/l	0.02 (1.5)	0.08	0.3 (1.2)	0.02	0.15
	0.1 (–0.2 to 0.6)		0.3 (–0.2 to 1.0)		
P1CP, pmol/l	–157 (488)	0.02`	164 (565)	0.007	0.0002
	–79 (–457 to 130)		188 (–185 to 423)		
Osteocalcin, ng/ml	–0.5 (1.7)	0.1	1.3 (2.3)	0.0003	0.00007
	–0.1 (–1.6 to 0.7)		1.0 (–0.4 to 2.1)		
dPyr, nmol/l	–0.1 (35)	0.9	–11 (42)	0.08	0.2
	–2 (–16 to 20)		–3 (–32 to 15)		
NTx, nmol/l	–172 (325)	0.000001	–143 (399)	0.0007	0.3
	–120 (–202 to –28)		–65 (–320 to 68)		
PTH, pmol/l	1.1 (1.8)	0.000001	–0.7 (1.6)	0.0006	0.000001
	0.9 (0.2 to 2.2)		–0.5 (–1.4 to 0.3)		
Corrected calcium, mmol/l	–0.04 (0.1)	0.001	0.03 (0.1)	0.03	0.00005
	–0.03 (–0.1 to 0.02)		0.02 (–0.04 to 0.09)		

* Mean [standard deviation (SD)] and median (lower quartile to upper quartile), respectively; change in BMD: change from baseline at 18 months; changes in measures of bone metabolism; mean (SD) delta area under the curve values, corrected for time. OPG: serum osteoprotegerin, P1CP: serum procollagen type 1 C-propeptide, osteocalcin: serum osteocalcin, dPyr: fasting urine free deoxypyridinoline, NTx: fasting urine N-terminal crosslinking telopeptide of type 1 collagen, PTH: serum parathyroid hormone, corrected calcium: serum calcium, corrected for serum albumin. Positive values indicate increase from baseline and negative values a decrease.

min (decrease vs increase). At baseline, 4% of patients had a serum level of PTH > 7 pmol/l (upper limit of normal range 7 pmol/l) in the alendronate group versus 9% in the alfacalcidol group; at 1 month the 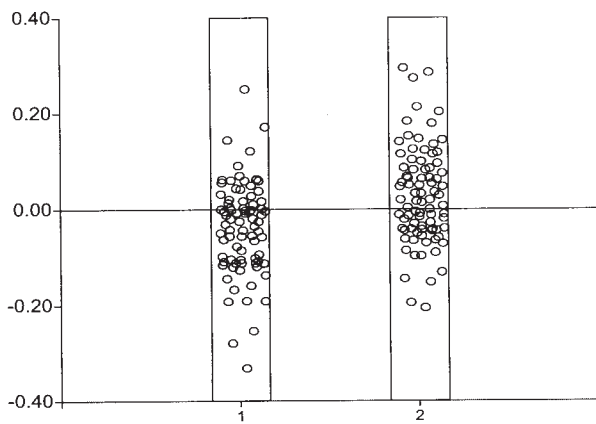percentages were 6% versus 0%, at 2 months 4% versus 0%, at 3 months 8% versus 2%, and at 18 months 25% versus 6%, respectively. These differences were only statistically significant at 18 months (p = 0.001). During the whole study, 26 of the 99 patients taking alendronate had,

at least once, a serum level of PTH > 7 pmol/l versus 12 of the 101 patients taking alfacalcidol (p < 0.01). To facilitate interpretation, the statistically different changes between the 2 groups in measures of bone metabolism are plotted, on the individual patient's level (Figure 1) and as mean changes in time (Figure 2).
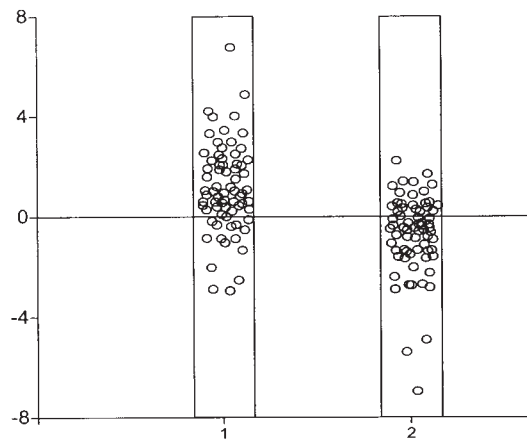
In Table 3, correlations of changes in BMD of LS and total hip and in the dAUC of measures of bone metabolism for the alendronate and alfacalcidol group are presented. There are within both groups positive correlations between the 2 markers of bone formation osteocalcin and P1CP; the same is found for the 2 markers of bone resorption dPyr and NTx. Between PTH and calcium corrected for albumin, correlations are negative within both groups. Between changes in BMD and changes in measures of bone metabolism, there are no statistically significant correlations, with the exception of a negative correlation in the alendronate group between changes in

total hip BMD and NTx. In accord with the missing correlations, regression analyses showed that changes in measures of bone metabolism (dAUC values for the whole study period and changes during the first months of the study) could not significantly predict changes in BMD of the LS in either the alendronate or the alfacalcidol group (data not shown). In addition, in the alendronate group we compared the change in BMD of the LS in the subgroup of patients with a PTH ≤ 7 pmol/l at all points in time (n = 59, 14 missing BMD) versus those with a PTH level > 7 pmol/l at any point in time (n = 23, 3 missing BMD). In the former subgroup the BMD increased, with 2.4 (4.5)% versus 2.1 (4.9)% in the latter subgroup (p = 0.9). In accord with this finding, there was no correlation between changes in BMD and changes in PTH. Serum levels of OPG did not differ between the 2 groups at baseline (Table 1), nor did they change statistically significantly following intervention (Table 2).

Figure 1. Changes within each individual during the 18 months of measures of bone metabolism that were statistically significantly different between alendronate group (1) and alfacalcidol group (2). Dots are delta AUC values, one dot for each patient, corrected for time; for p values see Table 2.
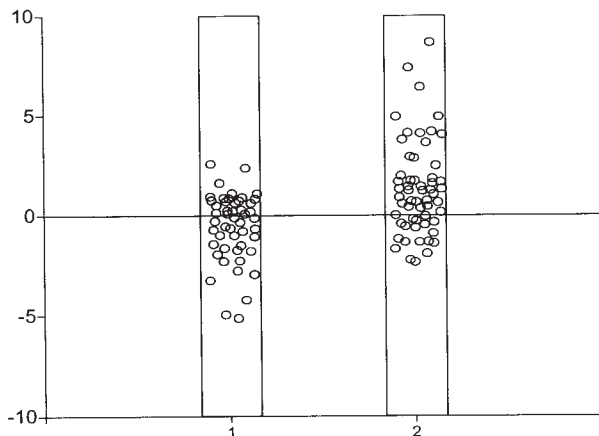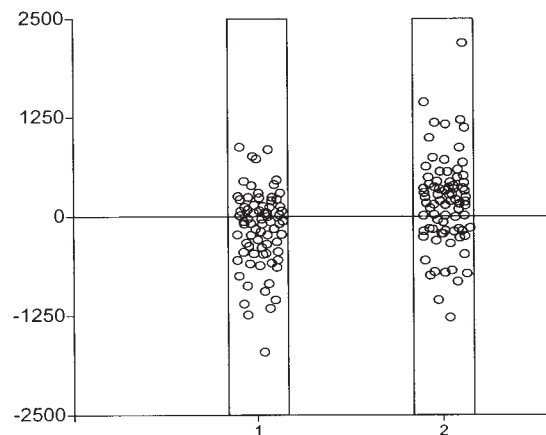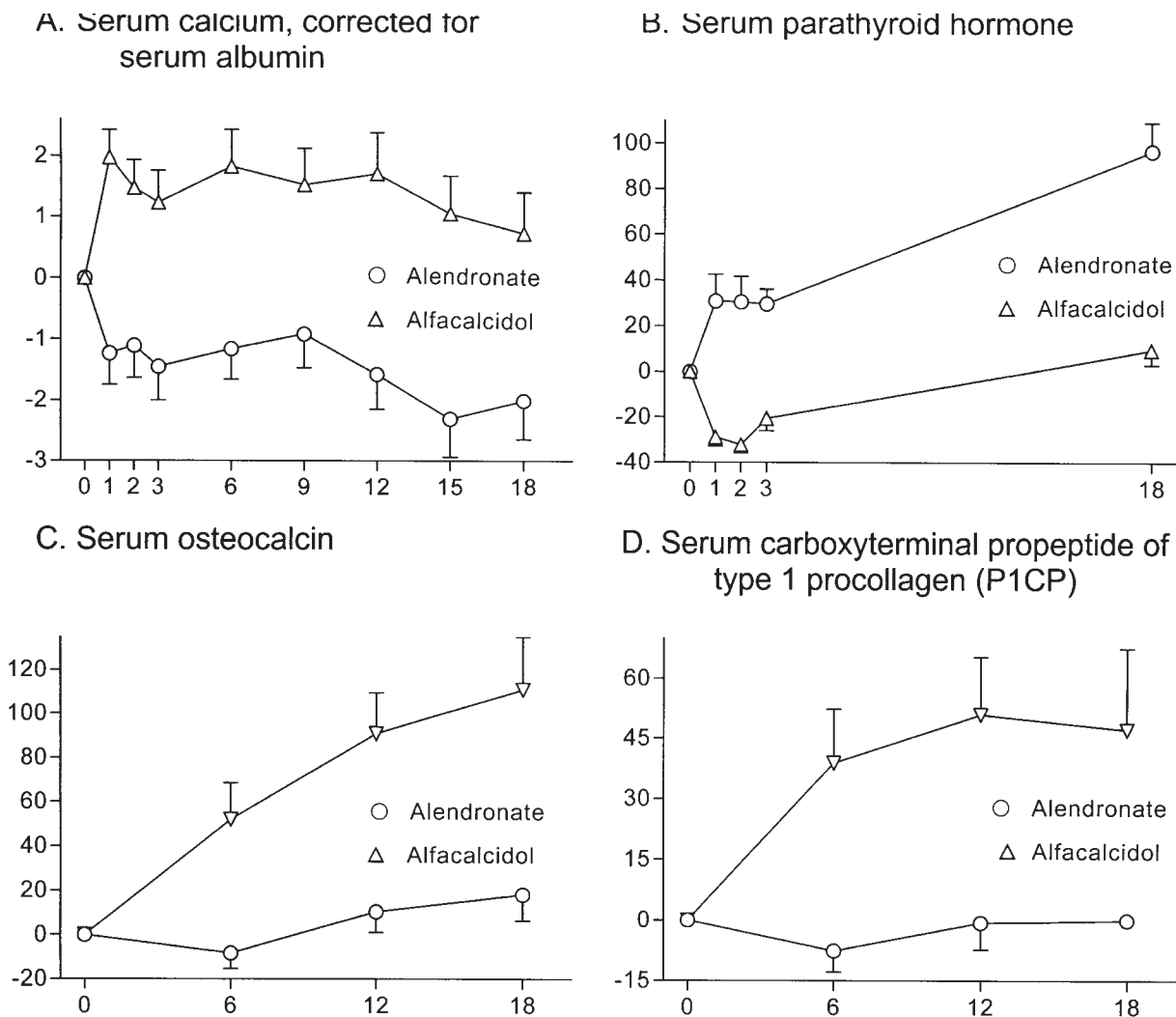
A. Serum calcium, corrected for serum albumin

B. Serum parathyroid hormone

C. Serum osteocalcin

D. Serum carboxyterminal propeptide of type 1 procollagen (P1CP)

Figure 2. Percentage change in time during the 18 months of measures of bone metabolism that were statistically significantly different between the alendronate and alfacalcidol groups; delta AUC values; for p values see Table 2; circle = alendronate group, triangle = alfacalcidol group.

DISCUSSION

As expected, in the alendronate treated group of patients taking GC there were decreases in the markers of bone formation P1CP and osteocalcin and a decrease in the markers of bone resorption, and increase in lumbar BMD. These changes in bone markers in the alendronate group indicate decreased bone resorption and, by the coupling of bone resorption and bone formation, also decreased bone formation, with a net positive result on BMD.

In contrast, in the alfacalcidol treated group of patients taking GC we found increases of P1CP and osteocalcin, indicating stimulation of bone formation and decreases of dPyr and NTx, indicating inhibition of bone resorption. This suggests that bone formation and resorption are uncoupled during treatment with alfacalcidol. In addition to stimulating effect on bone formation, active vitamin D_3 enhances intestinal calcium absorption, which may lead to a tendency of hypercalcemia,

which results in lower circulating levels of PTH and subsequently decrease of markers of bone resorption. As treatment with alfacalcidol was followed by signs of inhibition of bone resorption and in addition, in contrast to treatment with alendronate, also signs of stimulation of bone formation, one would expect a superior effect of alfacalcidol on BMD compared to alendronate. However, we and others observed the opposite outcome[6,14], although results of other studies on alfacalcidol were promising[13]. The effects of alfacalcidol and alendronate on fractures will be studied during prolonged followup of the STOP trial[14].

In both groups, although markers of bone metabolism changed on the group level, as can be expected from the mode of action of the 2 bone loss-preventing therapies, changes in BMD could not be predicted by nor were they associated with changes in biochemical measures, with the exception of a negative correlation in the alendronate group between changes in

Table 3. Correlation coefficients of changes after 18 months in bone mineral density (BMD) of lumbar spine (left value) and total hip (right value) with changes in measures of bone metabolism for the alendronate group (upper values) and the alfacalcidol group (lower values)*.

	Corrected Calcium	PTH	NTx	dPyr	Osteocalcin	P1CP	OPG
BMD	--/--	--/--	--/--0.33	--/--	--/--	--/--	--/--
	--/--	--/--	--/--	--/--	--/--	--/--	--/--
OPG	--/--	--/--	--/--	--/--	--/--	--/--	
	--/--	--/--	--/--	--/--	--/--	--/--	
P1CP	--/--	--/--	--/--	--/--	0.26/0.26		
	--/--	--/--	--/--	--/--	0.32/0.32		
Osteocalcin	--/--	--/--	--/--	--/--			
	--/--	--/--	--/--	0.37/0.37			
dPyr	--/--	--/--	0.64/0.64				
	--/--	--/--	0.62/0.62				
NTx	--/--	--/--					
	--/--	--/--					
PTH	−0.25/−0.25						
	−0.36/−0.36						

* Corrected calcium: serum calcium, correected for serum albumin, PTH: serum parathyroid hormone, NTx: fasting urine N-terminal crosslinking telopeptide of type 1 collagen, dPyr: fasting urine free deoxypyridinoline, osteocalin: serum osteocalcin, P1CP: serum procollagen type 1 C-propeptide, OPG: serum osteoprotegerin. Change in BMD: 18 month value minus baseline value; changes in measures of bone metabolism: delta area under the curve values; Spearman correlation coefficients, only coefficients with absolute values ≥ 0.25 are given; |r| ≥ 0.25: p < 0.05, |r| > 0.30: p < 0.01, |r| > 0.60: p < 0.000001.

total hip BMD and the bone resorption marker NTx. This association mirrors the increased BMD by decreased bone resorption in this group. In postmenopausal women with osteoporosis treated with bisphosphonates, an increase in OPG serum levels along with reduction of bone resorption markers predicted gain of BMD[16], in contrast to findings in our study. So for the individual patient in daily clinical practice who is treated with GC, the value of serial assessment of measures of bone metabolism seems low. Also, in the absence of fracture data, BMD seems to be the best surrogate endpoint for a study in GIOP[17].

Limitations in our study that restrict direct interpretation of associations between changes in measures of bone metabolism and changes in BMD are that all patients used GC and had a rheumatic disease, both factors that also influence bone markers. Further, the baseline values of measures of bone metabolism often were taken when patients were already taking GC (with a maximum duration of 12 weeks before the start of the study). It is possible that measures of bone metabolism can detect short-term changes (i.e., within weeks) in bone turnover better than longterm changes. Third, there was heterogeneity of the group with respect to the rheumatological diagnoses and patients[14].

In the alendronate group, there was a decrease in serum calcium with concomitant increase in PTH. We do not attribute these changes to GC use. First, similar changes did not occur in the alfacalcidol group, although perhaps alfacalcidol prevented this[18]. Second, the role of secondary hyperparathyroidism in the cause of GIOP is in doubt[19]; and third, in another study, an increase in PTH was also found, albeit only in nocturnal values[20]. Bisphosphonate treatment causes an immediate reduction in bone resorption leading to a reduction in serum calcium that leads to an increase of PTH. The increase in the PTH following bisphosphonate therapy is a response to the change in serum calcium. The hypocalcemic response to bisphosphonates is occasionally severe, especially in patients with hypoparathyroidism[21]. The signs of slight stimulation of PTH by alendronate in our study occurred in spite of supplementation with calcium and, if indicated, with vitamin D_3.

For pragmatic reasons we gave a standard calcium supplement of 500 mg daily to patients with a daily dietary calcium intake < 1000 mg. This dose was generally accepted as adequate in The Netherlands at the time the study was designed, but could have been too low in some patients. Similarly, the standard dose of 400 IU of cholecalciferol for participants of the study with baseline serum 25-OHD levels < 30 nmol/l could have been too low in some. In patients taking alendronate, increased PTH was not associated with differences in change in BMD compared with patients without increased PTH, indicative of a normal calcium homeostasis in these patients taking standard-dose calcium and vitamin D_3 supplementation. However, tailoring the dose of these supplements to the intake of the individual patient probably is to be preferred.

In our study, changes in markers of bone metabolism were more favorable in patients taking GC treated with alfacalcidol than in those treated with alendronate. Nevertheless, BMD increased in the alendronate group and decreased in the alfacalcidol group. Changes in BMD were in general not predicted by changes in measures of bone metabolism. Alendronate treatment results in slight secondary hyperparathyroidism that without calcium and vitamin D_3 supplementation could have been more pronounced, which suggests that adequate calcium and vitamin D_3 supplementation is indicated when alendronate is used or bisphosphonates are used.

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