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Alendronate Prevents Further Bone Loss in Renal Transplant Recipients

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ABSTRACT

The aim of this study was to investigate the effects of alendronate, calcitriol, and calcium in bone loss after kidney transplantation. We enrolled 40 patients (27 men and 13 women, aged 44.2 ± 11.6 years) who had received renal allograft at least 6 months before (time since transplant, 61.2 ± 44.6 months). At baseline, parathyroid hormone (PTH) was elevated in 53% of the patients and the Z scores for bone alkaline phosphatase (b-ALP) and urinary type I collagen cross-linked N-telopeptide (u-NTX) were higher than expected ($p < 0.001$). T scores for the lumbar spine (−2.4 ± 1.0), total femur (−2.0 ± 0.7), and femoral neck (−2.2 ± 0.6) were reduced ($p < 0.001$). After the first observation, patients were advised to adhere to a diet containing 980 mg of calcium daily and their clinical, biochemical, and densitometric parameters were reassessed 1 year later. During this period, bone density decreased at the spine (−2.6 ± 5.7%; $p < 0.01$), total femur (−1.4 ± 4.2%; $p < 0.05$), and femoral neck (−2.0 ± 3.0%; $p < 0.001$). Then, the patients were randomized into two groups: (1) group A—10 mg/day of alendronate, 0.50 μg/day of calcitriol, and 500 mg/day of calcium carbonate; and (2) group B—0.50 μg/day of calcitriol and 500 mg/day of calcium carbonate. A further metabolic and densitometric reevaluation was performed after the 12-month treatment period. At the randomization time, group A and group B patients did not differ as to the main demographic and clinical variables. After treatment, bone turnover markers showed a nonsignificant fall in group B patients, while both b-ALP and u-NTX decreased significantly in alendronate-treated patients. Bone density of the spine (+5.0 ± 4.4%), femoral neck (+4.5 ± 4.9%), and total femur (+3.9 ± 2.8%) increased significantly only in the alendronate-treated patients. However, no trend toward further bone loss was noticed in calcitriol and calcium only treated subjects. No drug-related major adverse effect was recorded in the two groups. We conclude that renal transplanted patients continue to loose bone even in the long-term after the graft. Alendronate normalizes bone turnover and increases bone density. The association of calcitriol to this therapy seems to be advantageous for better controlling the complex abnormalities of skeletal metabolism encountered in these subjects. (J Bone Miner Res 2001;16:2111–2117)

Key words: alendronate, bone density, calcitriol, kidney transplantation, parathyroid hormone

INTRODUCTION

SUCCESSFUL KIDNEY transplant corrects most of the abnormalities than can be observed in the course of renal insufficiency. However, in spite of the normalization of renal function, the alterations in bone metabolism, leading to increased skeletal fragility and fractures, may persist or, in some cases, even worsen.[1] This is caused by mainly the negative effects on bone of immunosuppressive therapy related to corticosteroid use[2,3] and perhaps to cyclosporin

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A (CsA).[4] However, another important risk factor for bone morbidity is represented by the persistence of secondary hyperparathyroidism.[5–7]

Typically, bone loss occurs soon after transplant,[8–10] when the highest doses of immunosuppressive drugs are used. At this time, bone mass generally decreases at a rate of 0.5–1.0%/month within the first 6 months,[8,9] with a tendency toward slower losses thereafter.[11] However, it remains unclear whether or not reduced bone density is a common feature in long-term survivors to renal allograft. Indeed, some authors have shown that the decrease in bone density is no longer evident after the first 12–18 months after transplant,[8,10] whereas others have reported that further bone loss may be experienced by renal transplant recipients even in the long run after the graft.[12,13] In particular, Pichette et al.[12] showed that the majority of their patients tended to loose bone at a rate greater than 2%/year, even 8 years after kidney transplant. Despite the demonstration of increased fracture risk after renal graft,[14,15] few studies have been carried out to evaluate the efficacy of antiosteoporotic drugs in this specific setting. Recently, two studies addressed the question whether bisphosphonates may be effective and safe in the treatment of postrenal transplant bone loss.[16,17] Using oral clodronate in patients transplanted at least 6 months before,[16] Grotz et al. showed that after 12 months of treatment, lumbar bone density was increased by 4.6% without any change in femoral bone mass. Fan et al.[17] treated their patients with intravenous pamidronate at the time of renal transplant and 1 month later and did not find any loss in lumbar and femoral bone density over the 12-month period of follow-up. In both studies, no significant drift in renal function was observed.

The aim of this study was to determine whether or not bone loss may occur in the long term after renal transplant and to evaluate the effects on bone density and metabolism of 1-year treatment with oral alendronate, calcitriol, and calcium.

MATERIALS AND METHODS

Patients

From a larger cohort of patients who had undergone cadaveric kidney transplantation at the University of Padova, we selected patients with a lag time since transplant of at least 6 months. Patients previously treated with bisphosphonates or other antiresorptive drugs were not included. Moreover, patients were not enrolled if they had a history of major upper gastrointestinal (GI) illness such as peptic ulcer, esophagitis, or severe dyspepsia. Forty patients were recruited that had given their informed consent to the study. There were 27 men and 13 women (body mass index [BMI], 24 $\pm$ 4 kg/m^2; time since transplant, 61.2 $\pm$ 44.6 months). Age ranged from 22 to 64 years (mean, 44.2 $\pm$ 11.6 years). The time spent on dialysis before transplant was 34 $\pm$ 23 months. Among the female population, 7 patients were postmenopausal.

The immunosuppressive treatment was as follows:

(1) Methylprednisolone (MP). postoperative (p.o.d.) day 0, 500 mg; p.o.d. 1, 250 mg; p.o.d. 2, 80 mg; p.o.d. 3, 64 mg; p.o.d. 4–6, 40 mg; p.o.d. 7–14, 32 mg; p.o.d. 15–21, 24 mg. From the 22nd p.o.d., MP was reduced by 2 mg every 14 days, until the maintenance dose of 4–8 mg/day was reached.
(2) CsA was administered as soon as possible and in any case within 8 h from transplant. The initial daily dose was 12 mg/kg body weight administered in two doses. Subsequent doses of cyclosporine were adjusted based on the clinical evidence of efficacy and occurrence of adverse effects and to maintain blood levels ranging from 200 to 350 ng/ml.
(3) From the first p.o.d., 100 mg of oral azathioprine was given once a day together with the evening cyclosporine administration.

Acute episodes of rejection were treated with MP, 500 mg intravenously (iv) for 3 days. If no improvement of the clinical signs and symptoms was noted, treatment with a mono-/polyclonal antibody preparation was begun.

At study entry, 29 patients were on a triple immunosuppressive therapy (MP, CsA, and azathioprine), while the remaining 11 were taking MP and CsA, only. The total intake of the immunosuppressive drugs was calculated for each patient. The mean daily intake of MP and CsA was calculated as the total intake divided by the days elapsed since kidney transplantation.

Study design

At baseline, fasting blood and 24-h urine samples were obtained from all patients for the assay of serum creatinine (Cr), calcium, intact parathyroid hormone (PTH), bone alkaline phosphatase (b-ALP), CsA, urinary type I collagen cross-linked N-telopeptide (u-NTX), and Cr. All patients underwent bone densitometry of the lumbar spine and proximal femur. After the first visit, all patients were recommended to introduce a diet containing 980 mg of calcium daily. They were then followed for a year, at the end of which the same biochemical as well as densitometric parameters were reassessed. Immediately afterward, patients were randomized, according to a computer-generated randomization list, into two groups: (1) group A (20 patients, 13 males and 7 females; mean age, 57 $\pm$ 11 years; time since transplant, 71 $\pm$ 38 months)—10 mg/day of oral alendronate 45 minutes before breakfast, 0.50 μg/day of oral calcitriol, and 500 mg/day of calcium carbonate; (2) group B (20 patients, 12 males and 8 females; mean age, 55 $\pm$ 13 years; time since transplant, 76 $\pm$ 53 months)—0.50 μg/day of oral calcitriol and 500 mg/day of calcium carbonate. Patients were treated for the successive 12 months and after this period a further metabolic and densitometric reevaluation was performed.

The study was approved by the local ethical committee.

Biochemical assays

Serum calcium and Cr were analyzed by Automatic Analyzer (Technicon Instruments Corp., Tarrytown, NY,

TABLE 1. CLINICAL, BIOCHEMICAL, AND DENSITOMETRIC PARAMETERS IN KIDNEY-TRANSPLANTED PATIENTS AT BASELINE AND AFTER THE FIRST YEAR OF FOLLOW-UP

	Baseline (n = 40)	*After the first year (n = 40)*	p†
Mean daily MP intake (mg)	7.0 ± 3.8	6.8 ± 1.8	NS
Mean daily Cs A intake (mg)	190 ± 9	190 ± 6	NS
Serum calcium (mmol/L)	2.30 ± 0.20	2.32 ± 0.20	NS
Serum Cr (μmol/L)	144 ± 50	145 ± 39	NS
PTH (pg/ml)	78.1 ± 49.9	80.4 ± 33.0	NS
b-ALP (U/L)	36.6 ± 18.7	33.7 ± 13.0	NS
u-NTX (nM; BCE/mmol Cr)	80.3 ± 41.2	80.7 ± 35.4	NS
Z score b-ALP (SD)	0.9 ± 1.2*	0.7 ± 0.9*	NS
Z score u-NTX (SD)	2.4 ± 2.7*	2.4 ± 2.3*	NS
U-lx[a] (SD)	1.5 ± 3.1	1.7 ± 1.6	NS
Lumbar spine BMD (g/cm^2)	0.85 ± 0.11	0.83 ± 0.12	<0.01
Total femur BMD (g/cm^2)	0.73 ± 0.10	0.72 ± 0.10	<0.05
Femoral neck BMD (g/cm^2)	0.63 ± 0.10	0.62 ± 0.10	<0.001

[a] Uncoupling Index.
* $p < 0.001$ versus expected values for sex and menopausal status–matched controls; † p versus baseline.

USA). CsA concentration on whole blood was determined by radioimmunoassay (RIA) method (Incstar Corp., Diasorin, Saluggia, Vercelli, Italy). b-ALP in catalytic activity was determined by lectin from wheat germ precipitation (isoenzyme of ALP; Boehringer Mannheim, Milano, Italy). After the total ALP activity had been determined (according to International Federation of Clincial Chemistry; Roche Diagnostics, Milano, Italy), b-ALP was precipitated using lectin from wheat germ as precipitant and the remaining ALP activity in the supernatant was measured (normal range, 5–56 U/liter). This method has intra- and interassay CVs <4% and <10%, respectively. This procedure has a good correlation with an immunoradiometric assay, measuring b-ALP mass concentration.[18] Intact PTH was evaluated by a commercial immunoradiometric assay (normal range, 10–60 pg/ml; Biorad Laboratories, Milano, Italy), with intra- and interassay CVs of 6% and 8%, respectively. Urine samples were evaluated for Cr (as mentioned previously) and u-NTX. NTX was measured by a competitive-inhibition ELISA (Osteomark; Ostex International, Inc., Seattle, WA, USA). Assay values were corrected for urinary Cr and expressed in nanomoles of bone collagen equivalents (BCE) per liter (nM) per millimole of Cr (mM). The intra- and interassay CVs for this method were 7.6% and 14%, respectively (normal range, 12–101 nM of BCE per mM of Cr).

Because of the heterogeneity of the population included in the study, the results from bone turnover marker measurements were expressed both as absolute values and as number of SDs with respect to the predicted levels for sex and menopausal status–matched normal controls (Z score). For this reason, fasting blood and 24-h urine sample for the evaluation of b-ALP and NTX were obtained from 87 normal subjects (60 men, mean age, 45.2 ± 6.6 years; 15 premenopausal women, mean age, 37.6 ± 8.4 years, and 12 postmenopausal women, mean age, 55.2 ± 9.3 years). An uncoupling index (U-Ix) was then calculated as the Z score of the bone resorption marker minus the Z score of the bone formation marker (Z score NTX − Z score b-ALP).

Bone densitometry

Dual-energy X-ray absorptiometry (DXA) evaluation of the lumbar spine (L2–L4) was performed by Hologic QDR 4500 (Hologic Corp., Waltham, MA, USA). DXA scans of the proximal femur were obtained also. The results were expressed as bone mineral density (BMD; g/cm^2) and T score (number of SDs of difference between the patient's BMD value and the BMD level of normal young adults). According to the World Health Organization (WHO) recommendations, osteoporosis was defined as a T score value < −2.5 SD. The "in vivo" CV, calculated as described in detail elsewhere,[19] was 1.06% for the spine, 1.16% for the total femur, and 1.63% for the femoral neck.

Statistical analysis

The results are expressed as means ± SD. Two-sample Student's *t*-test was used to determine statistical differences between means. Paired Student's *t*-test (two-tailed) was used to compare intragroup changes. Multifactor analysis of variance (ANOVA) was used when appropriate. Linear regression analysis was used to evaluate the relationship between the considered variables. Values of $p < 0.05$ were considered statistically significant.

RESULTS

At study entry, total MP and CsA intakes were 11.4 ± 8.6 g and 366 ± 340 g, respectively. Serum Cr values were slightly elevated (Table 1). Mean levels of PTH were above the normal range (Table 1). In particular, 53% of the patients showed high PTH level. Mean levels of both serum b-ALP and u-NTX were within the normal range (Table 1). However, when these parameters were corrected for the expected values for sex and menopausal status–matched normal controls, the relative Z scores were significantly increased (Table 1).

TABLE 2. CLINICAL AND BIOCHEMICAL PARAMETERS IN GROUPS A (ALENDRONATE PLUS CALCITRIOL AND CALCIUM) AND B (CALCITRIOL AND CALCIUM) AT THE RANDOMIZATION TIME AND AFTER THE 12-MONTH TREATMENT PERIOD

	Before treatment		*After treatment*	
	Group A (n = 20)	*Group B (n = 18)*	*Group A (n = 20)*	*Group B (n = 18)*
Mean daily MP intake (mg)	6.7 ± 2.2	7.0 ± 1.2	6.5 ± 1.6	6.1 ± 1.3
Mean daily CsA intake (mg)	180 ± 6	210 ± 7	200 ± 10	200 ± 10
Serum calcium (mmol/L)	2.28 ± 0.18	2.35 ± 0.23	2.34 ± 0.15	2.37 ± 0.16
Serum Cr (μmol/L)	141 ± 45	151 ± 41	148 ± 51	157 ± 39
PTH (pg/mL)	81.2 ± 37.2	79.2 ± 27.0	103 ± 61‡	62 ± 65
b-ALP (U/L)	34.3 ± 15.9	32.9 ± 11.0	26.1 ± 10.7*	31.7 ± 10.1
u-NTX (nM; BCE/mmol Cr)	82.9 ± 44.3	78.5 ± 24.7	47.4 ± 24.4†,‡	66.6 ± 31.7

* $p < 0.05$; † $p < 0.01$ versus pretreatment values; ‡ $p < 0.05$ versus group B.

T score values for lumbar spine (−2.4 ± 1.0), total femur (−2.0 ± 0.7), and femoral neck (−2.2 ± 0.6) were lower than expected ($p < 0.001$). Particularly, spinal osteoporosis (WHO criteria) was detected in 43% of the patient population, while only 12% of the subjects were normal at this site. Femoral osteoporosis was found in 20% of the patients, with only 5% of them showing normal values. PTH was positively correlated with u-NTX ($r = 0.44$; $p < 0.01$) and the U-Ix ($r = 0.42$; $p < 0.01$).

After the first year of follow-up (only on normal calcium diet), most of the biochemical parameters considered were substantially unchanged (Table 1). The Z scores for b-ALP and u-NTX remained elevated ($p < 0.001$), as were PTH levels. At this time, PTH levels were correlated with both b-ALP ($r = 0.39$; $p < 0.02$) and u-NTX ($r = 0.37$; $p < 0.05$). Bone density decreased significantly at the lumbar spine (−2.6 ± 5.7%; $p < 0.01$), total femur (−1.4 ± 4.2%; $p < 0.05$), and femoral neck (−2.0 ± 3.0%; $p < 0.001$). The percent decrease in spinal bone density during the first 12 months of follow-up was higher as compared with the median value (−2.5%) in 19/40 (39%) patients (Δ%, −7.4 ± 3.2). The rate of spinal bone loss was similar between patients with longer (>18 months) or shorter (≤18 months) duration of the transplant (−2.3 ± 5.8 vs. −2.3 ± 4.7%)

Clinical and biochemical data of the two treatment groups at the randomization time and after the 12-month therapy period are reported in Table 2. Two patients in group B did not complete the study period (one for lack of interest and the other because he moved to another Italian region). Before treatment, the two groups did not differ for mean daily intake of immunosuppressive drugs, serum Cr, PTH, and bone turnover markers (Table 2). T score values for bone density were similar between the two groups (lumbar spine, −2.3 ± 1.0 vs. −2.5 ± 1.1; total femur, −2.1 ± 0.6 vs. −2.4 ± 0.8; femoral neck, −2.6 ± 0.7 vs. −2.8 ± 0.8 in group A vs. group B, respectively). The rate of spinal bone loss over the year before starting the therapy had been similar between the two groups (group A, −2.8 ± 5.9%; group B, −2.4 ± 5.7%).

At the end of the study period, the mean daily intake of immunosuppressive drugs was still comparable between alendronate-treated patients and group B subjects (Table 2).

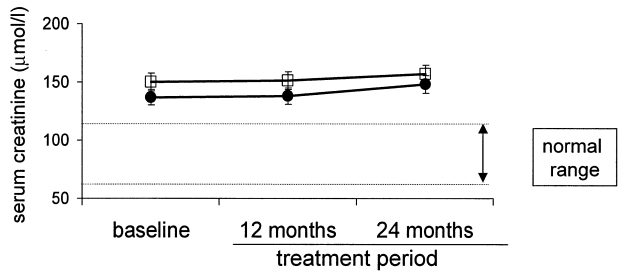

FIG. 1. Serum Cr in renal allograft recipients before and after treatment. -●-, alendronate + calcitriol + calcium (group A); -□-, calcitriol + calcium (group B).

A slight and nonsignificant increase was observed in serum Cr in both groups of patients (Fig. 1). PTH levels increased in the alendronate group and slightly decreased in calcitriol and calcium-only treated patients (Table 2).

Figure 2 shows the trend in bone turnover markers throughout the 24-month study period according to the treatment group. b-ALP and u-NTX did not change significantly during the first year of follow-up in group A and group B patients. After starting the treatment, bone turnover markers showed a slight and nonsignificant fall in group B patients, while both b-ALP and u-NTX decreased significantly and tended to completely normalize in alendronate-treated patients. Accordingly, the U-Ix showed a very marked decrease in this patient group.

As reported in Fig. 3, a significant increase in bone density of the spine (+5.0 ± 4.4%), femoral neck (+4.5 ± 4.9%), and total femur (+3.9 ± 2.8%) was observed only in the alendronate-treated patients. However, no trend toward further bone loss was noticed in calcitriol and calcium-only treated subjects. The changes in bone density remained similar in both groups after adjustment for the cumulative intake of corticosteroids (lumbar spine, +5.0% vs. +0.7% and $p < 0.05$; femoral neck, +4.5% vs. +0.7% and $p < 0.05$; total hip, +3.9% vs. −0.3% and $p < 0.02$ in alendronate vs. calcitriol and calcium-only treated patients, respectively).

No major adverse effects were recorded in the two groups after starting the treatment. Two patients in group A and 1

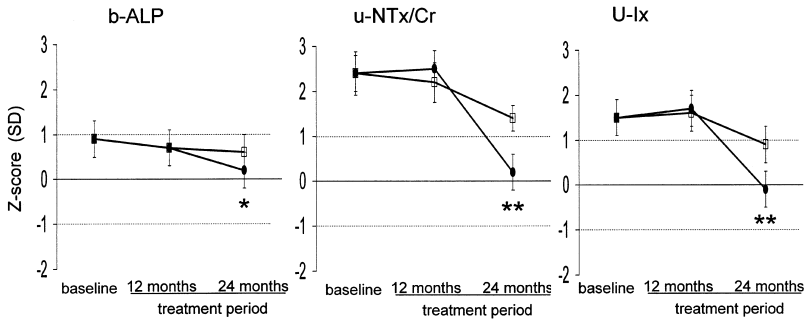

FIG. 2. Bone turnover markers in renal allograft recipients before and after treatment. *$p <$ 0.02 versus 12 months; **$p < 0.01$ versus 12 months. -●-, alendronate + calcitriol + calcium (group A); -□-, calcitriol + calcium (group B).

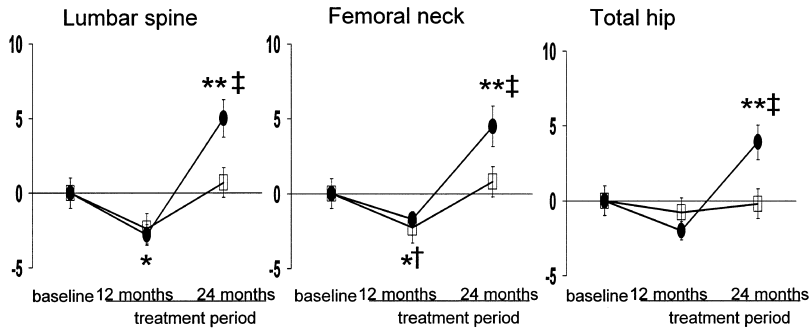

FIG. 3. BMD in renal allograft recipients before and after treatment. *$p < 0.05$ group A versus baseline; **$p < 0.001$ group A versus 12 months; †$p < 0.001$ group B versus baseline; ‡$p < 0.05$ group A versus group B. -●-, alendronate + calcitriol + calcium (group A); -□-, calcitriol + calcium (group B).

patient in group B complained of nausea. Acid regurgitation was reported in 1 patient in group A, and abdominal pain was present in 1 patient and 3 patients in groups A and B, respectively.

DISCUSSION

Bone loss and fragility fractures have been reported as frequent complications in the early stages after renal transplant.[14,15]

Nevertheless, few studies have focused on the long-term outcome in bone health of these patients. Contrasting results have emerged from cross-sectional studies about the persistence of significant bone loss years after transplant.[5,10] In a 1-year longitudinal study, Grotz et al.[11] found that further bone loss was experienced only by patients with the shortest time lag since transplant. On the contrary, Pichette et al.[12] found that most of their patients were still loosing bone at a rate >2%/year even 8 years or more from transplant. Even excluding subjects who were within 6 months after the graft, we also observed that our long-term survivors to kidney transplant continued to loose a significant amount of bone. These results are not surprising, because a number of risk factors for low bone density are still present even in the long term after renal transplantation. Even at low doses, glucocorticoids are believed to decrease bone density and increase fracture risk.[2,3] Accordingly, we previously found that prednisone treatment is one of the most important predictors of low bone density even in long-term liver transplant recipients.[20] CsA may affect skeletal metabolism, possibly through an induction of high turnover osteopenia, at least in animal models.[4] Persisting hyperparathyroidism reported in up to 50% of kidney transplant recipients[6,7] can contribute to posttransplant bone disease.[5,7] On the basis of these facts, it is reasonable to expect that bone remodeling could not be normal, even many years after renal transplant. Indeed, we observed that the age and sex-adjusted levels of urinary N-telopeptide exceeded that for b-ALP, suggesting an imbalance in bone turnover, with bone resorption prevailing on bone formation. These findings are in keeping with several bone histomorphometric studies on long-term renal transplant survivors, and show the presence of high bone turnover coexisting with altered bone formation processes.[21,22] Consequently, it is not surprising that kidney-transplanted patients continue to loose bone even in the long term after the graft. These considerations may have important implications because they can explain why, besides the dramatic increase in fracture incidence observed soon after transplant, fracture rate remains stable and does not tend to decline over time since kidney graft. Indeed, clinical fracture rate has been reported to be 0.039/year and 0.032/year in patients with an average posttransplantation period of 2 years and 8½ years, respectively[14,15] In view of this, the treatment of long-term survivors to kidney graft should be considered as a valid therapeutic opportunity.

Very few data are available on the use of bisphosphonates in post-kidney transplantation bone disease. Intravenous pamidronate has been capable of fully preventing bone loss when administered immediately after transplant.[17] Oral clodronate has been found to be effective in increasing spinal density but not femoral bone density in long-term renal allograft recipients.[16] Alendronate is a potent bisphosphonate capable of increasing bone density and low-

ering the incidence of skeletal fractures in several clinical settings.[23–25] However, to our knowledge, this is the first time that this drug has been used after renal transplantation. In this study, alendronate induced a fall in urinary N-telopeptide by approximately 50%, confirming its effectiveness in reducing osteoclastic-mediated bone resorption and correcting the imbalance in bone remodeling under a wide variety of circumstances.[24–26] Likewise, in this study alendronate induced a remarkable increase in bone density both at the spine and proximal femur, similar to that reported on this drug in other conditions for treatment periods of the same length.[23,27]

Nevertheless, our results cannot be compared with those from other studies. Indeed, even if alendronate is able to prevent bone loss and, to some extent, vertebral fractures in glucocorticoid-induced osteoporosis,[25] post-kidney transplantation bone disease cannot be considered "simply" a corticosteroid-induced osteoporosis. However, the benefit provided by alendronate treatment against the bone-damaging properties of corticosteroids may well be applied even to renal allograft recipients.

Persistent hyperparathyroidism is a very common feature after successful renal transplant.[6] This condition is believed to be important in producing or maintaining bone loss after renal transplant. Indeed, bone turnover has been found to be high in renal transplant recipients with elevated PTH values.[5,7] In this study, we found that PTH values correlated with bone turnover markers before but not after alendronate treatment. The effect of oral alendronate in hyperparathyroid patients has not been studied extensively. Recently, Bertoldo et al.[27] reported that alendronate significantly increased both spinal and femoral bone mass and decreased bone turnover markers in patients with primary hyperparathyroidism. The proportion of all these changes was quite close to the proportion we found in our patients. Another bisphosphonate pamidronate reverted bone loss in rats with gene-induced severe hyperparathyroidism.[28] Thus, it is likely that much of the positive action on bone of alendronate was exerted by preventing the negative effects on the skeleton of persistently high PTH concentrations.

We observed an only small but significant increase in PTH levels observed after alendronate, which did not seem to be detrimental to bone. Indeed, in our patients, both spinal and femoral bone densities increased significantly more than in controls. This was not the case with Grotz's study[16] in which PTH increased by approximately 100% after 1 year of oral clodronate and femoral bone density decreased slightly although not significantly. Besides the intrinsic lesser efficacy of oral clodronate on femoral density,[19] it seems likely that the absence of any effect on femoral bone mass in that study can be attributed partly to the drug-mediated increase in PTH levels. Indeed, PTH exerts its catabolic action mainly at skeletal sites that are rich in cortical bone.

The reason for the only moderate increase in PTH after alendronate, which is far more potent than clodronate, may reside in the concomitant use of calcitriol and calcium. According to this hypothesis, PTH levels tended to decrease, although not significantly, in patients taking calcitriol and calcium only. Thus, our study suggests that calcitriol and calcium by themselves may be somewhat advantageous in this specific clinical setting. Indeed, in subjects treated with calcitriol and calcium only, bone density did not show any further decrease after starting the treatment. This observation is in line with a recent report on long-term survivors to renal allograft, in which the treatment with calcitriol and calcium lowered PTH levels and preserved bone density.[29] The usefulness of calcitriol treatment has been proposed recently also after cardiac and lung transplantation.[30] Given these data, we suggest that the addition of calcitriol and calcium to alendronate treatment may provide further benefits in controlling the wide spectrum of alterations of bone metabolism seen after renal transplant.

Although the demonstration of antifracture efficacy is the most important endpoint in patients with bone fragility, this study was not designed to answer this important issue. Consequently, no conclusion may be drawn from our data on this point. However, recent studies have established that the antifracture effect of alendronate is, at least in part, related to the changes in bone density.[31,32] It remains to be elucidated whether this could be true even in this particular setting.

Both alendronate and calcitriol were safe and well tolerated in our patients. Serum Cr did not vary over the study period. None of the subjects complained of relevant side effects. In particular, very few symptoms related to possible GI disturbances were recorded in both groups. These considerations are reassuring in view of the complexity of this clinical condition and of the number of drugs that these patients have to be treated with.

In conclusion, this study shows that renal-transplanted patients may continue to loose bone even many years after the graft. Alendronate normalizes bone turnover and increases bone density in renal allograft recipients. The association of calcitriol to this therapy seems to be advantageous for better control over the complex abnormalities of skeletal metabolism encountered in these subjects.

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