Prevention of Bone Loss in Renal Transplant Recipients: A Prospective, Randomized Trial of Intravenous Pamidronate

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Abstract. Renal transplant recipients are at risk of developing bone abnormalities that result in bone loss and bone fractures. These are related to underlying renal osteodystrophy, hypophosphatemia, and immunosuppressive treatment regimen. Although bisphosphonates are useful in ameliorating bone mineral loss after transplantation, it is not known whether their use in renal transplant patients leads to excessive suppression of bone turnover and increased incidence of adynamic bone disease. A randomized, prospective, controlled, clinical trial was conducted using the bisphosphonate pamidronate intravenously in patients with new renal transplants. Treatment subjects (PAM) received pamidronate with vitamin D and calcium at baseline and at months 1, 2, 3, and 6. Control (CON) subjects received vitamin D and calcium only. During months 6 to 12, the subjects were observed without pamidronate treatment. Biochemical parameters of bone turnover were obtained monthly and, bone mineral density (BMD) was obtained at baseline and months 6 and 12. Bone biopsies for mineralized bone histology were obtained at baseline and at 6 mo in a subgroup of subjects who underwent scheduled living donor transplantation. PAM preserved bone mass at 6 and 12 mo as measured by bone densitometry and histomorphometry. CON had decreased vertebral BMD at 6 and 12 mo (4.8 $\pm$ 0.08 and 6.1 $\pm$ 0.09%, respectively). Biochemical parameters of bone turnover were similar in both groups at 6 and 12 mo. Bone histology revealed low turnover bone disease in 50% of the patients at baseline. At 6 mo, all of PAM had adynamic bone disease, whereas 50% of CON continued to have or developed decreased bone turnover. Pamidronate preserved vertebral BMD during treatment and 6 mo after cessation of treatment. Pamidronate treatment was associated with development of adynamic bone histology. Whether an improved BMD with adynamic bone histology is useful in maintaining long-term bone health in renal transplant recipients requires further study.

Patients with ESRD are known to have a spectrum of bone disease, ranging from high-turnover bone disease (hyperparathyroid bone disease with or without mineralization defect) to low-turnover bone disease (adynamic bone disease, osteomalacia) (1,2). Osteopenia may also be present and may worsen secondary to immunosuppression (3) or other factors (4). Therefore, the bone disease that develops after renal transplantation differs from the posttransplantation osteoporosis seen after other solid-organ transplantations.

Corticosteroids induce bone loss through depressive effects on osteoblastic activity and enhancing effects on osteoclastic activity (5,6), lowering of gastrointestinal calcium absorption, increased renal calcium excretion, and increased parathyroid hormone (PTH) secretion, all resulting in decreased bone mass (5). Cyclosporine and tacrolimus can affect bone remodeling which can result in increased bone loss (7,8). As a result, 6.8 and 8.8% of bone mineral density (BMD) can be lost by 6 and 18 mo, respectively, after successful renal transplantation (9). Consequently, there is an increased risk for fractures in this population (10).

Bone loss in patients with osteoporosis or those who receive corticosteroid therapy has been treated effectively with bisphosphonates (3,11,12). Bisphosphonates decrease bone turnover mainly by inhibiting osteoclast activity. They have been used with varying success in treatment of bone loss associated with cardiac (13,14) and liver transplantation (15–17). Recent studies have shown favorable effects on BMD in renal transplant recipients (18,19).

It has been shown that renal transplant recipients develop low bone turnover with time (20). A cross-sectional study in renal transplant patients demonstrated a high prevalence of low-turnover or adynamic bone disease with and without mineralization defect (4). Thus, there is concern that bisphosphonates, in depressing bone turnover, may exacerbate adynamic bone disease in renal transplant recipients (21).

The purpose of this study was to determine whether pamidronate, a bisphosphonate, when given prophylactically, is useful in preserving BMD after renal transplantation and

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whether it is associated with oversuppression of bone turnover and thus a higher risk of adynamic bone disease.

Materials and Methods

Study Design

A prospective, randomized, controlled, clinical trial was designed to evaluate the effect of pamidronate on BMD, bone biochemical parameters, and bone histology in adult patients who received a renal transplant. The study was approved by the Institutional Review Board of Montefiore Medical Center. All subjects gave informed consent. They were recruited between August 1, 1999, and November 30, 2000, and followed for 1 yr from entry into the study.

Subjects

Inclusion criteria encompassed all adult transplant recipients who were hemodynamically stable perioperatively. The recipients were approached either before the renal transplant or within 36 h postoperatively if their BP and electrolytes were stable. A negative serum pregnancy test was required before the surgery. Exclusion criteria included inability to return for regular follow-up or participation in another clinical trial.

Protocol

Subjects were randomized via a computer-generated number system to one of two groups. The treatment group (PAM) received intravenous pamidronate plus oral calcitriol and calcium carbonate. The control group (CON) received oral calcitriol and calcium carbonate alone. PAM patients received 60 mg of pamidronate within 48 h after transplantation followed by 30 mg at months 1, 2, 3, and 6. Subjects in both groups received oral calcitriol and calcium carbonate from months 1 to 12 to maintain serum calcium between 8.5 and 10.5 mg/dl. Pamidronate was chosen because it is the only bisphosphonate whose use is not explicitly contraindicated in renal failure, it has a good safety profile in renal failure, and it can be given intravenously.

A subgroup of subjects who were undergoing scheduled living donor renal transplantation underwent anterior iliac crest biopsies immediately before transplantation and 6 mo thereafter. When possible, the subjects received tetracycline for labeling of bone before the baseline bone biopsy (we were unable to complete tetracycline labeling in some cases because of the inability to predict the exact timing of the transplantations); all subjects who underwent follow-up bone biopsy received tetracycline labeling. The labeling schedule consisted of 2-d oral administration of tetracycline hydrochloride (500 mg twice daily), followed by a free interval of 12 d and subsequent administration of 4 d of demeclocycline (300 mg twice daily). Bone biopsies were performed 4 d thereafter. Bone biopsies (0.5 cm diameter $\times$ 2 to 4 cm length) were taken from the anterior iliac crest using the one-step electric drill technique (Straumann Medical, Waldenburg, Switzerland; MD Tech) as described previously (22).

Subjects received standard immunosuppression with glucocorticoids and cyclosporine or tacrolimus. During the study, episodes of acute rejection and doses of glucocorticoids, cyclosporine, and tacrolimus were recorded.

Biochemical and Hormonal Determinations

Bone biochemical parameters including intact PTH measured by chemiluminescence method (Immulite), serum osteocalcin (OC), bone-specific alkaline phosphatase (BSAP), and urinary N-telopeptide (UNTx) were obtained at baseline and monthly for the next 12 mo. Blood levels of vitamin D were obtained at baseline and at 6 and 12 mo.

Bone Densitometry and Radiographic Studies

BMD of the vertebral spine (L1 to L4) and hip was measured at baseline and at 6 and 12 mo, using the same Hologic 4500 QDC scanner. Vertebral and hip radiographs were obtained at baseline and at 12 mo and evaluated for radiographic evidence of bone fractures.

Mineralized Histology and Bone Histomorphometry

Iliac bone samples were fixed in absolute ethanol, dehydrated, and embedded in methylmethacrylate as described previously (22). Serial sections of 3- and 7-μm thickness were cut with a Microm microtome, model HM360 (Carl Zeiss, Thornwood, NY). Three-micrometer-thick sections were stained with the modified Goldner Trichrome stain (23). Seven-micrometer-thick, unstained sections were prepared for phase contrast and fluorescence light microscopy and staining for detection of aluminum (24,25).

Histomorphometry of the bone was performed at a standardized site in deep cancellous bone. Static and dynamic parameters of bone structure, formation, and resorption were measured with the Osteoplan system II (Carl Zeiss, Thornwood, NY) (26,27). Histologic features were measured at a magnification of $\times$200. All parameters used are in compliance with and were calculated according to the recommendations of the histomorphometry nomenclature committee of the American Society of Bone and Mineral Research (28). All samples were processed and analyzed in a similar manner and were evaluated in a blinded manner, *i.e.*, without knowledge of treatment assignment.

Statistical Analyses

Power calculations were based on previously reported changes in vertebral BMD in renal transplant recipients (9). The power, set at 80% to detect an 8% difference in vertebral BMD in PAM *versus* CON at 12 mo, required a total of 60 participants.

Differences between PAM and CON groups were analyzed by *t* test. Paired *t* test detected differences in the same subject at two different time points. Independent *t* test compared the same time point in two different populations. ANOVA detected differences in parameters in more than three groups. In normally distributed results, multivariate linear regression analysis was used to determine which independent variables significantly influenced the dependent variable (change in vertebral BMD and percentage change in vertebral BMD at 6 and 12 mo). Independent variables included in the multivariate analyses were those that were significant on univariate analysis. The statistical program SPSS-8 was used to analyze the data. Means are reported as $\pm$ SD.

Results

A total of 112 adults received a renal transplant during the period and were screened: 26 patients declined to participate, and 14 patients were ineligible. Thus, 72 subjects were enrolled into the protocol and were randomized to 36 PAM and 36 CON.

No significant differences were found between the subjects who were randomized and those who were not randomized in terms of age, gender, race, and cause of ESRD and time on dialysis (Table 1). There were no adverse events related to the pamidronate infusion.

Table 1. Transplant recipients: characteristics of subjects *versus* nonparticipants

	Subjects	Nonparticipants
n	72	41
Male/female	41/31	21/20
Age	45.5 ± 13	49 ± 14
Years on dialysis	3.5 ± 3.7	4.5 ± 5
Race		
black	28 (39.4%)	24 (58.5%)
Hispanic	27 (36.6%)	7 (17.1%)
white	15 (21.1%)	10 (24.4%)
Asian	2 (2.8%)	
ESRD		
diabetes	13 (18.3%)	5 (12.2%)
hypertension	28 (38%)	22 (53.7%)
glomerulonephritis	20 (28.2%)	10 (24.4%)
polycystic kidneys	5 (7%)	2 (6.7%)
other	6 (8.5%)	2 (6.7%)

Dropouts and Demographics

Of the 72 randomized subjects, 13 (five in PAM and eight in CON) did not complete the study. Their data were excluded from analysis as they dropped out early in the study and no treatment data were available. Reasons for not completing the study included primary graft failure, loss to follow-up, refusal to continue participation, and one death from myocardial infarction. Thus, 59 subjects were included in the final cohort for analysis, 31 in PAM and 28 in CON.

There was no significant difference in age, race, BMI, and time on dialysis between the two groups. There were more women in the control group (Table 2).

Table 2. Subject demographics

	Pamidronate	Control
n	31	28
Male/female	12/19	19/9[a]
Age	43.8 ± 2.3	44.3 ± 2.3
Years on dialysis	4.5 ± 0.8	2.71 ± 0.6
BMI	24.3 ± 4.9	24.1 ± 4.2
Race		
black	10 (32%)	9 (32.1%)
Hispanic	12 (38.7%)	13 (46.4%)
white	7 (22.6%)	5 (17.9%)
Asian	2 (6.5%)	1 (3.6%)
ESRD		
diabetes	5 (16.1%)	3 (10.7%)
hypertension	11 (35.5%)	17 (60.7%)
glomerulonephritis	13 (41.9%)	3 (10.7%)[b]
polycystic kidneys	2 (6.5%)	2 (7.1%)
other		3 (10.7%)

[a] $P < 0.045$ women *versus* men.
[b] $P < 0.006$ pamidronate *versus* control.

Immunosuppression

During the study period, there were no differences between PAM and CON in immunosuppressive therapy; number of rejection episodes (0.27 ± 0.5 *versus* 0.29 ± 0.5); adverse events (0.87 ± 0.8 *versus* 1.0 ± 0.6); or cumulative doses of glucocorticoid (6.3 ± 1.1 *versus* 5.8 ± 1.7 g), cyclosporine (126.3 ± 46 *versus* 118 ± 31 g), or tacrolimus (4.7 ± 3 *versus* 5.5 ± 3 g).

Biochemical and Hormonal Parameters

There were no significant differences between PAM and CON in baseline chemistries, vitamin D, PTH, BSAP, OC, and UNTx. Serum creatinine decreased significantly ($P < 0.05$) and similarly in both groups. Overall, no significant differences were observed between the two groups in serum calcium, phosphorus, bicarbonate, and magnesium. Likewise, no significant differences were found between the two groups in biochemical parameters of bone turnover and hormone levels at 6 and 12 mo (Table 3). There were no differences in baseline and at 6 and 12 mo in biochemical and hormonal parameters in patients who were treated with tacrolimus *versus* cyclosporine (data not shown).

Bone Mineral Density

Fifty-five subjects had baseline bone densitometry. Vertebral and hip BMD were not different between PAM and CON at baseline.

Forty of the 55 subjects had bone densitometry at baseline and 6 mo, 50 subjects had bone densitometry at baseline and 12 mo, and 35 subjects had densitometries at baseline and at 6 and 12 mo. There was no difference in baseline measurements between the group that had two densitometries and the group that had all three studies.

Vertebral BMD

Vertebral BMD was higher at 6 mo in PAM than in CON (1.0345 ± 0.22 *versus* 0.8803 ± 0.12 g calcium/cm^2; $P < 0.017$). The percentage decrease in vertebral BMD from baseline was significantly less in PAM as compared with CON (−0.63 ± 0.03 *versus* 4.6 ± 0.08%; $P < 0.05$; Figure 1).

The change (absolute or percentage change) in vertebral BMD at 12 mo was significantly less in PAM (who had not received pamidronate in months 6 to 12) than in CON (0.0105 ± 0.006 *versus* 0.0599 ± 0.009 g/cm^2 [$P < 0.033$] and −0.39 ± 0.05 *versus* −5.81 ± 0.09% [$P < 0.01$]; Figure 1).

Men in PAM showed a lesser decrease in vertebral BMD at 6 mo than men in CON (1.011 ± 0.12 *versus* 0.8975 ± 0.11 g/cm^2; $P < 0.036$). Women in PAM tended to have preserved BMD as opposed to the women in CON (1.054 ± 0.28 *versus* 0.8583 ± 0.15 g/cm^2; $P < 0.064$). Neither tacrolimus nor cyclosporine had a further effect on vertebral BMD in either PAM or CON.

Univariate analysis of covariates that were significantly associated with vertebral BMD at 6 mo included pamidronate use, creatinine at 6 mo, vitamin D 25, and BSAP. Those significant with the absolute change and percentage change at 12 mo included pamidronate use and race.

Table 3. Bone biochemical and hormonal parameters[a]

	Pamidronate Months			Control Months		
	0	6	12	0	6	12
Creatinine[b]	8.5 ± 2.2	1.7 ± 0.5	1.7 ± 0.7	8.9 ± 3.2	1.7 ± 0.6	1.6 ± 0.5
Calcium[c]	7.9 ± 1.3	9.9 ± 0.7	10 ± 0.7	8.2 ± 1.2	10 ± 0.8	10.1 ± 0.6
Phosphorus[d]	5.4 ± 1.8	3.0 ± 0.9	3.0 ± 0.7	5.3 ± 1.8	3.2 ± 0.6	3.1 ± 0.6
Bicarbonate[e]	21 ± 4.5	25 ± 3.7	24 ± 3.9	20 ± 5.2	25 ± 4.2	24 ± 3.8
Magnesium[f]	1.51 ± 0.3	1.45 ± 0.3	1.5 ± 0.2	1.47 ± 0.4	1.48 ± 0.2	1.56 ± 0.3
OC[g]	43 ± 49	18 ± 21	37 ± 45	49 ± 80	31 ± 42	45 ± 79
BSAP[h]	49 ± 53	38 ± 39	40 ± 27	41 ± 22	48 ± 40	54 ± 46
UNTx[i]	134 ± 123	37 ± 75	33 ± 40	150 ± 154	73 ± 100	33 ± 49
PTH[j]	395 ± 429	98 ± 143	102 ± 111	280 ± 258	138 ± 275	119 ± 167
Vitamin D 25[k]	15 ± 9	16 ± 8	18 ± 10	20 ± 14	14 ± 7	18 ± 13
Vitamin D 1,25[l]	24 ± 20	24 ± 11	28 ± 17	25 ± 16	23 ± 12	28 ± 15

[a] OC, osteocalcin; BSAP, bone-specific alkaline phosphatase; UNTx, urinary N-telopeptide; PTH, parathyroid hormone.
[b] nl 0.6 to 1.5 mg/dl.
[c] nl 8.5 to 10.5 mg/dl.
[d] nl 2.5 to 4.5 mg/dl.
[e] nl 24 to 30 meq/l.
[f] nl 1.5 to 2.5 mg/dl.
[g] nl 8 to 36 ng/ml.
[h] nl 13 to 85 U/L.
[i] nl 0 to 35 nM bone collagen equivalents/nM Cr.
[j] nl 5 to 65 pg/dl.
[k] nl 9 to 46 ng/ml.
[l] nl 16 to 55 pg/ml.

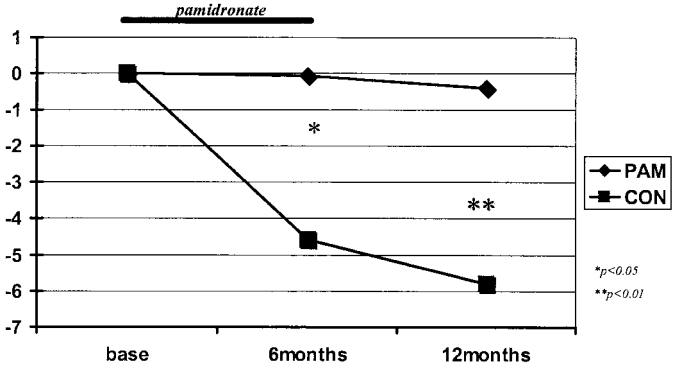

Figure 1. Percentage change in vertebral bone mineral density. *$P <$ 0.05; **$P <$ 0.01.

As the bone mineral densities were normally distributed at baseline and at 6 and 12 mo, multivariate linear regression analyses that included variables that were significant on univariate analysis were performed. Pamidronate use was significantly related to vertebral BMD at 6 mo ($P < 0.015$) as was BSAP ($P <$ 0.029). Pamidronate use and race were significantly related to the percentage change of vertebral BMD at 6 and 12 mo (Table 4).

Table 4. Multivariate analysis of predictors of vertebral bone mineral density[a]

	B	Confidence Index	*P* Value
$BMD_{6\ mo}$			
pamidronate	0.149	0.030, 0.268	0.016
vitamin D 25OH	−0.0086	−0.017, 0.000	0.043
$BSAP_6$	−0.0016	−0.003, 0.000	0.030
% change $BMD_{6\ mo}$			
pamidronate	0.040	0.005, 0.125	0.042
% change $BMD_{12\ mo}$			
pamidronate	0.051	0.013, 0.088	0.009
race	0.033	0.011, 0.054	0.003

[a] BMD, bone mineral density. Covariates used in the multivariate analysis were those significant on univariate analysis, which included pamidronate use, serum creatinine at 6 mo, BSAP at 6 mo, vitamin D 25 at 6 mo, and race.

Hip BMD

Hip BMD, as measured by bone densitometry, did not change appreciably at 6 and 12 mo in either PAM (0.9131 ± 0.21 and 0.8933 ± 0.20) or CON (0.8289 ± 0.13 and 0.8216 ± 0.12). There was no significant difference between the two groups at any time during the treatment year (Figure 2). Tacrolimus or cyclosporine did not affect hip BMD.

Fractures

Vertebral fractures diagnosed by x-ray were present at baseline in four participants. There were three new vertebral fractures at 12 mo (one PAM, two CON). There were no hip fractures during the year of study.

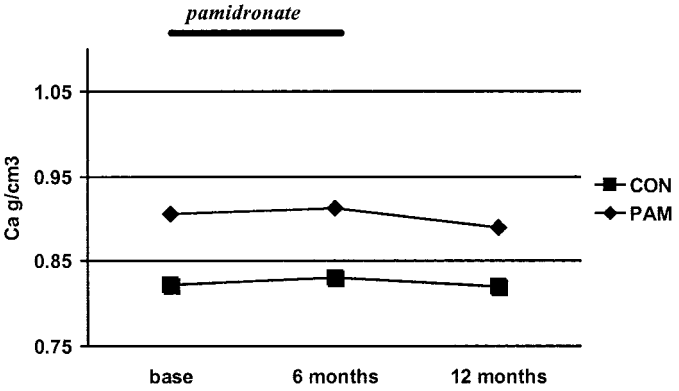

Figure 2. Hip bone mineral density (PNS).

Bone Biopsy

Demographics. Twenty-six subjects underwent living donor renal transplants; 21 had baseline bone biopsies (eight PAM, 13 CON); 14 had follow-up biopsies at 6 mo of protocol (six PAM, eight CON). The bone biopsy population was similar to the total nonbiopsy population in terms of gender, race, BMI, ESRD distribution, and biochemical parameters. The baseline biopsy subjects had had less time on dialysis (1.7 ± 2.2 *versus* 4.8 ± 3.9 yr). Similarly, the subjects who had follow-up bone biopsies were not different from the nonbiopsy population except for less time on dialysis (1.8 ± 2 *versus* 4.3 ± 4 yr, Table 5). They received standard immunosuppression with corticosteroids and cyclosporine or tacrolimus.

Histomorphometry. Histomorphometry was consistent with adynamic bone disease at baseline in 11 of 21 patients on the basis of static parameters of cellularity, woven osteoid, and fibrosis (Table 6). There was no evidence of aluminum bone disease in any of the biopsies. Histomorphometric findings in the follow-up biopsies of the individual patients are shown in Table 7. At 6 mo, there was no loss of cancellous bone volume or trabecular thickness in PAM, whereas CON showed lower cancellous bone volume and decreased trabecular thickness. There was decreased erosion depth in PAM compared with CON. We found that both groups in general showed decreased bone activity in terms of static and dynamic parameters. There was a decrease in cellular elements in both groups. Five of the six subjects developed adynamic bone disease, and one continued to have adynamic bone disease; all six PAM subjects demonstrated a low activation frequency, significantly lower than CON (0.049 ± 0.031 *versus* 0.381 ± 0.112l; $P < 0.022$, PAM *versus* CON), consistent with adynamic bone disease (Table 7). CON developed decreased bone turnover in four of the eight subjects; two of the eight subjects developed higher turnover from baseline adynamic histology, and two continued to have adynamic bone disease (Figure 3).

Discussion

This prospective, randomized, clinical trial describes the effects of pamidronate, a bisphosphonate, on bone health of renal transplant recipients. The study, which includes both men and women, confirms that pamidronate ameliorates bone loss as reported by Fan *et al*. (18) in men alone. Although there was a downward trend noted in the vertebral BMD after the last dose of pamidronate, PAM continued to have significantly higher BMD than did CON.

Hip BMD did not change appreciably in either PAM or CON during the year of study. Both CON and PAM received vitamin D and calcium, which are commonly prescribed in patients who receive long-term steroid therapy for various underlying conditions (3,5,6). Vitamin D and calcium were not given in the previously reported trials of use of bisphosphonates in renal

Table 5. Characteristics of bone biopsy population as compared with nonbiopsy population

	Biopsy	Nonbiopsy
N baseline/follow-up	21/14	38/45
Gender (M)	11 /8	21 /22
Age (yr)	42.3 ± 13 /44.9 ± 13	45 ± 12 /43.8 ± 12
Dialysis years	1.8 ± 2 /1.8 ± 2	4.6 ± 4[a] /4.3 ± 4[b]
BMI	24.3 ± 6 /23.6 ± 4	24.1 ± 4 /24.3 ± 5
Race (*n* [%])		
black	6 (31.6) /3 (21.4)	12 (31.6) /15 (34.9)
Hispanic	8 (42.1) /7 (50)	17 (44.7) /41.9
white	4 (21.1) /3 (21.4)	7 (18.4) /18.6
other	1 (5.4) /1 (7.1)	2 (5.3) /2 (4.8)
ESRD (*n* [%])		
diabetes	3 (14.3) /3 (21.4)	4 (11.1) /4 (10.5)
hypertension	8 (38.1) /5 (35.7)	19 (52.8) /20 (52.6)
glomerulonephritis	5 (23.8) /3 (21.4)	11 (30.6) /11 (28.9)
polycystic kidney	2 (9.5) /2 (14.3)	2 (5.6) /2 (5.3)
other	3 (14.3) /1 (7.1)	0 /1 (2.6)

[a] $P < 0.006$ baseline biopsy population *versus* baseline nonbiopsy population.
[b] $P < 0.023$ follow-up biopsy population *versus* 6-mo nonbiopsy population.

Table 6. Histomorphometric parameters in pamidronate and control groups

	Baseline	6 Months
Pamidronate ($n = 6$)		
bone volume/tissue volume (%)	27.2 ± 11.3	26.8 ± 11.8
mineralized bone volume (%)	26.0 ± 11.4	25.8 ± 11.0
trabecular thickness (plate; μm)	120.4 ± 22.6	125.6 ± 51.1
osteoid thickness (μm)	7.5 ± 2.2	8.0 ± 4.3
osteoblast number/bone length/100 mm	167.6 ± 154	26.4 ± 44
osteoclast number/bone length/100 mm	71.4 ± 72	24.7 ± 8.4
erosion depth (μm)	16.1 ± 9.9	12.9 ± 9.6
activation frequency		0.049 ± .031
Control ($n = 8$)		
bone volume/tissue volume (%)	28.6 ± 4.5	25.7 ± 10.1
mineralized bone volume (%)	27.2 ± 4.2	24.4 ± 9.7
trabecular thickness (plate, μm)	142.7 ± 37.3	115.6 ± 24.1[a]
osteoid thickness (μm)	8.5 ± 1.4	7.8 ± 1.7
osteoblast number/bone length/100 mm	57.3 ± 80.8	39.9 ± 56.8
osteoclast number/bone length/100 mm	32.0 ± 27	8.7 ± 12.4
erosion depth (μm)	22.7 ± 11.9	15.8 ± 5
activation frequency		0.381 ± .112[b]

[a] $P < 0.032$ control change in baseline *versus* 6 mo.
[b] $P < 0.022$, pamidronate *versus* control at 6 mo.

transplant recipients (18,19), possibly accounting for the decrease in hip BMD in their control groups during their study period. In addition, as the hip consists mainly of cortical bone, which has lower remodeling rates than the mainly cancellous bone found in the vertebrae, it may require a longer time of observation before any treatment differences can be detected.

Vertebral BMD results at 6 mo were corroborated by trends observed in changes in iliac crest bone volume and trabecular thickness at follow-up bone biopsies. The bone activity present at baseline was interpreted without the benefit of tetracycline to quantify the bone turnover so that baseline diagnoses were made on static parameters only. Nonetheless, we were able to distinguish among the various classifications of renal osteodystrophy on the basis of the presence and the quality of the cellular and architectural elements. This technique has been useful to classify renal osteodystrophy (22,29,30). The cellular parameters of bone formation and resorption (osteoclasts and osteoblasts number/bone length) revealed an impressive decline after 6 mo of pamidronate treatment. In CON, mean values of these parameters also fell but were less pronounced. These observations are in keeping with known effects of bisphosphonates on bone turnover (31) and the turnover-reducing effects of steroids (3,5). The histologic findings raise the concern of adynamic bone as a possible complication of the positive effects of pamidronate. Further studies are needed to determine whether this may reduce overall bone strength and thus increase the risk of fractures.

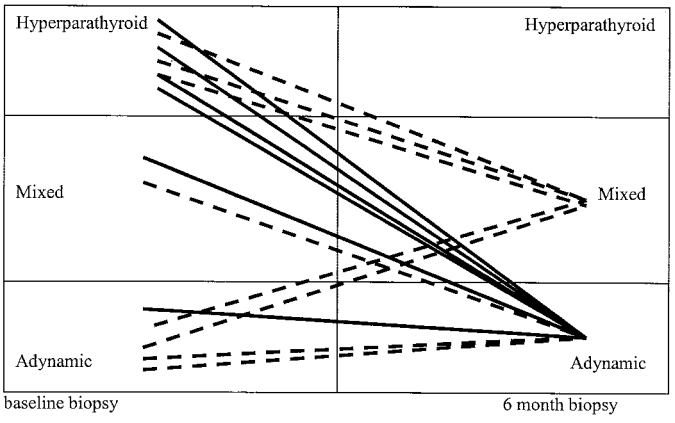

Figure 3. Bone histomorphometry. Distribution of histomorphometry based on static and dynamic parameters. —, pamidronate; - - -, control.

Standard biochemical parameters of bone metabolism such as UNTx, BSAP, and OC, although useful in monitoring bone health in the nonrenal transplant patient (32), did not predict bone activity or mineralization in the renal transplant recipient in our study. Because serum phosphorus levels were not different between PAM and CON, the observed findings do not seem to be a result of low phosphate levels.

PTH may affect vertebral BMD. In the nonrenal patient, PTH may have an anabolic effect on vertebral BMD and may increase measured density. Exogenous PTH may be useful in improving bone health in osteoporotic patients (33,34). In our study, PTH was similarly corrected in both PAM and CON, thus rendering an added influence of PTH on BMD unlikely.

The total amounts of immunosuppressive agents were similar in both groups, thus eliminating a specific effect of these drugs on BMD. Likewise, the total dose of corticosteroids was similar in both groups.

Table 7. Histomorphometry in subjects who had follow-up biopsies

Patient	BV/TV %	BV/TV2 %	TbTh μm	TbTh2 μm	OsTh μm	OsTh2 μm	OB/100 mmbone	OB/1002 mmbone	OC/100 mmbone	OC/1002 mmbone	EDE μm	EDE2 μm	MLT2 days	AcFy2
Pamidronate														
1P	10.45	19.02	142.29	213.80	5.33	8.70	00	00	00	00	8.12	NA	4.87	0.01
2P	45.22	48.02	154.36	147.48	8.70	11.59	00	00	00	26.47	33.54	28.91	NA	0.01
3P	24.73	23.69	100.84	100.57	10.60	6.32	376.62	2.94	56.49	2.94	12.64	10.67	1848	0.20
4P	26.00	25.54	102.54	94.72	7.57	16.43	255.08	113.04	149.4	47.96	10.90	6.41	92.2	0.20
5P	24.70	30.16	116.60	127.95	8.65	5.65	196.20	11.76	167.42	47.03	13.49	13.62	NA	0.01
6P	31.85	14.09	105.82	68.79	6.05	5.80	135.83	30.45	55.25	23.68	9.93	4.93	306	0.06
Controls														
1C	33.81	26.49	118.57	102.76	10.04	9.99	00	144.04	63.18	27.95	15.80	7.63	41.08	0.61
2C	32.17	23.63	124.60	97.26	7.48	6.94	4.77	35.48	4.77	5.07	NA	NA	NA	0.01
3C	24.10	26.19	227.72	160.29	6.55	9.78	00	4.09	10.18	00	13.35	15.02	258.4	0.70
4C	26.19	22.15	153.91	121.49	7.12	7.42	112.15	00	3.62	00	13.27	18.75	99.7	0.07
5C	19.30	23.90	124.17	132.19	9.8	5.98	194.04	3.41	67.32	00	32.87	17.83	67.94	0.64
6C	29.66	49.37	112.80	126.60	8.70	8.29	147.54	113.72	58.55	28.43	14.70	13.61	87.1	0.23
7C	28.79	20.94	129.23	91.55	10.02	8.43	00	18.84	19.34	8.07	44.12	23.52	NA	NA
8C	31.49	15.01	150.46	92.26	8.17	5.33	00	00	29.42	00	24.63	14.23	NA	0.01

This study suggests that pamidronate can preserve vertebral BMD in renal transplant recipients when it is given prophylactically, at the time of renal transplantation. BMD continued to be maintained even after pamidronate was stopped, as compared with CON receiving vitamin D and calcium alone. It is likely to have a similar effect on hip BMD.

Loss of BMD is associated with increased fracture risk (35,36). Although the number of fractures at 12 mo was too small in our study to analyze, it would be expected that the better preserved vertebral BMD at 1 yr in PAM would be associated with decreased fracture risk. A recent study using the bisphosphonate ibandronate prophylactically in renal transplant recipients did not decrease the rate of vertebral fractures, although BMD increased (37). Of concern is the tendency toward very low bone turnover evidenced by bone histology at 6 mo in our study. We and others have reported that low PTH and presumably low bone turnover are associated with increased fractures in dialysis patients (38,39). Whether low bone turnover with increased bone density in these subjects treated with bisphosphonates carries the same risks associated with adynamic bone disease in dialysis patients is unclear (21).

That pamidronate is effective in preserving BMD is shown by the present study. Although the bone histology seems to have been affected by pamidronate, our study was not powered to detect differences on the effect that the bisphosphonate might have on bone turnover. Before our study, no data existed to demonstrate such an effect, so it was not possible to power the study to show a difference. In addition, because we did not have quantifiable measures of bone turnover because of lack of tetracycline double labeling on the baseline bone biopsies, we are not able to report a measured difference in bone turnover at the follow-up biopsy. Therefore, conclusions regarding the effect of bisphosphonates on renal transplant osteodystrophy cannot be reached on the basis of the histologic observations seen in our study but may serve as a basis of future investigation.

In summary, the present study demonstrates that bisphosphonate therapy in the adult with a new renal transplant is associated with preserved BMD and low bone turnover. Whether this therapy is useful in attenuating long-term bone loss of renal transplantation and decreasing bone fractures in this population of renal patients will require further study.

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