High Prevalence of Low Bone Turnover and Occurrence of Osteomalacia after Kidney Transplantation

MARIE-CLAUDE MONIER-FAUGERE, HANNA MAWAD, QUANLE QI, ROBERT M. FRIEDLER, and HARTMUT H. MALLUCHE

Division of Nephrology, Bone and Mineral Metabolism, Department of Internal Medicine, University of Kentucky, Lexington, Kentucky.

Abstract. Kidney transplantation corrects most of the metabolic abnormalities that cause renal osteodystrophy. However, many transplanted patients develop osteoporosis and other bone lesions that are related, at least in part, to their immunosuppressive regimen. The precise histologic patterns of bone disease after transplantation are not well defined. In a study designed to investigate this issue, 57 adult posttransplant patients agreed to undergo bone biopsies and blood drawings. There were 32 men and 25 women, mean age 45 ± 2 yr, who had received a kidney transplantation 5.6 ± 0.8 yr before biopsy. History of bone pain, fractures, and avascular necrosis was found in 22, 12, and 7 patients, respectively. Serum creatinine was 1.68 ± 0.1 mg/dl, 21% of patients were hypercalcemic, 63.2% had elevated parathyroid hormone (PTH) (>65 pg/ml), and 91.2% had normal calcitriol levels. Cancellous bone volume/tissue volume was below normal compared to age- and gender-matched control subjects in 56.1% of patients. Bone turnover (activation frequency) was low in 45.6%, normal in 28.1%, and elevated in 26.3% of patients. Bone formation rate/bone surface was low in 59.7%, normal in 35%, and elevated in 5.3% of the patients. Erosion surface/bone surface was high in 21.1% of patients. Mineralization was prolonged in 87.5% of patients, including 9 patients with osteomalacia and 12 patients with focal osteomalacia. Cumulative and maintenance doses of prednisone and time elapsed since transplantation correlated negatively with bone volume and bone turnover ($r = -0.32$ to -0.59, $P < 0.05$ to 0.01), whereas cumulative doses of cyclosporine or azathioprine, age, gender, or serum PTH levels did not. Regression analysis identified prednisone as the main factor responsible for low bone volume and bone turnover ($r = 0.54$ and $r = 0.43$, $P < 0.01$). No factors were found to predict delayed mineralization. The present study shows that low bone volume, low bone turnover, and generalized or focal osteomalacia are frequent histologic features in transplanted patients. The effects of age, gender, PTH, and cyclosporine on bone volume and bone turnover are apparently overridden by the prominent effects of glucocorticoids. The prevalence of mineralization defect in the presence of normal serum levels of calcidiol and calcitriol suggests vitamin D resistance and deserves further study.

The bone disease that develops after kidney transplantation has generated much interest because of the severity of its clinical complications, particularly osteoporosis, the increase in the number of transplanted patients, the prolonged survival rate, and the availability of new therapeutic agents such as bisphosphonates that could prevent or treat posttransplant osteoporosis. To develop adequate therapeutic strategies for post-kidney transplant bone disease, however, it is essential to understand the underlying histologic bone abnormalities and their evolution with time. At time of transplantation, patients already suffer from renal osteodystrophy, *i.e.*, they exhibit various levels of bone volume and bone turnover (1–3). Thereafter, the immunosuppressive regimens, particularly glucocorticoids and cyclosporin A (CsA), affect bone and calcium metabolism resulting in bone loss (4–6). The results of the few reports on the bone abnormalities in patients after renal transplantation are somewhat conflicting (7–15). Heterogeneity of bone lesions has been noted in some studies (7,14), whereas others report a high prevalence of: (*1*) high bone turnover associated with persistence of secondary hyperparathyroidism (9,11,12,15,16); (*2*) normal bone formation (14); or (*3*) low bone turnover (10,13). Prolonged mineralization lag time without osteoid accumulation has been found in some studies (10,13,15), whereas frank osteomalacia has been rarely observed (7,8,17). Moreover, in one study iron accumulation at the mineralization front has been observed in the majority of patients (13). The discrepancies among the results of the various studies may be multifactorial. In most studies, inclusion of patients was highly selective, and within most of the studies, patients underwent bone biopsies at a standardized time (from 6 mo to 8 yr) after transplantation. Moreover, in individual studies, the immunosuppressive regimens were standardized among the patients. Also, the first histologic observations were done at a time when bone aluminum accumulation was still a prominent feature in renal osteodystrophy and after kidney transplantation (7,12).

The present study was undertaken to determine the impact of bone biopsy timing, selection of patients, underlying kidney

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Correspondence to Dr. Hartmut H. Malluche, Division of Nephrology, Bone and Mineral Metabolism, Room MN 564, U.K. Medical Center, 800 Rose Street, Lexington, KY 40536-0298. Phone: 606-323-5049; Fax: 606-257-1052; E-mail: hhmall@pop.uky.edu

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disease, and various immunosuppressive regimens on bone lesions after successful kidney transplantation.

Materials and Methods

Patients

The study was designed as a prospective study. All adult patients with successful kidney transplantation were screened. The exclusion criteria were unstable kidney function and treatment of established osteoporosis with bisphosphonate, calcitonin, or calcitriol. The inclusion criterion was willingness to undergo a bone biopsy. Among the 120 patients screened, 108 qualified and 57 of those agreed to undergo a bone biopsy. These patients signed an informed consent form and were enrolled in the study. There were 32 men and 25 women with a mean age of 42.9 ± 1.72 (range, 23 to 64) and 48.2 ± 2.70 (range, 25 to 70) yr, respectively. All patients were Caucasian. Before transplantation, 51 patients underwent chronic maintenance dialysis for 3.1 ± 0.68 yr (range, 4 mo to 26 yr), 32 were hemodialyzed, and 19 were dialyzed peritoneally. Six patients were never on dialysis before transplantation. The underlying kidney diseases were glomerulonephritis ($n = 12$), reflux nephropathy ($n = 10$), diabetic nephropathy ($n = 6$), hypertensive nephropathy ($n = 6$), polycystic kidney disease ($n = 4$), Alport disease ($n = 4$), analgesic nephropathy ($n = 3$), lupus ($n = 1$), IgA nephropathy ($n = 1$), thrombotic thrombocytopenic purpura ($n = 1$), and unknown etiology ($n = 9$). While patients were on dialysis, phosphate binding was achieved with calcium salts alone ($n = 28$) or in combination with aluminum-containing phosphate binders ($n = 19$). Fifteen patients had been treated with calcitriol at a dose ranging from 0.25 to 0.5 μg/d at time of transplantation, and seven patients had undergone partial parathyroidectomy 1 to 10 yr before transplantation.

The time elapsed after transplantation was 5.4 ± 0.8 yr (range, 6 mo to 27 yr). At time of biopsies, immunosuppression consisted of the following: triple therapy with prednisone, azathioprine, and CsA ($n = 19$), prednisone and azathioprine ($n = 14$), prednisone and CsA ($n = 6$), prednisone and mycophenolate mofetil ($n = 2$), prednisone alone ($n = 4$), CsA alone ($n = 5$), and azathioprine and CsA ($n = 3$). Loop diuretics were given to 30 patients, and thiazide diuretics were prescribed in five patients. Sixteen patients were given phosphate supplementation at time of biopsy. Thirty-five patients were asymptomatic at time of biopsy, whereas 22 patients suffered from various degrees of bone pain, 12 had experienced fractures, and seven had aseptic necrosis.

Protocol

At time of bone biopsy, blood drawings were performed for determination of serum creatinine, calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), calcitriol, calcidiol, and osteocalcin. Cumulative and mean doses per year of prednisone, azathioprine, and CsA were calculated.

Bone Biopsies, Mineralized Bone Histology, and Bone Histomorphometry

Before bone biopsy, patients received double tetracycline labeling of bone. The labeling schedule consisted of 2-d oral administration of tetracycline hydrochloride (500 mg twice daily) followed by a free interval of 10 d and subsequent oral administration of 4 d of Declomycin® (300 mg twice daily). Bone biopsies were performed 4 d thereafter. Bone samples (0.5 cm diameter × 2 to 4 cm length) were taken from the anterior iliac crest using the one-step electrical drill technique (Straumann Medical, Waldenburg, Switzerland) as described previously (18).

Iliac bone samples were fixed in absolute ethanol, dehydrated, and embedded in methylmethacrylate as described previously (19). Serial sections of 3- and 7-micrometer 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 (20). Seven-micrometer-thick unstained sections were prepared for phase contrast and fluorescence light microscopy and staining for detection of aluminum (21,22) and iron (23).

Histomorphometry of bone was performed at a standardized site below the cortices. Static and dynamic parameters of bone structure, formation, and resorption were measured with the Osteoplan system II (Kontron, Munich, Germany) (24,25). Histologic features were measured at a magnification of 200. Results were compared with histomorphometric parameters of bone of 137 (static) and 53 (dynamic) age- and gender-matched healthy control subjects, respectively. These healthy volunteers had normal renal function and did not exhibit any biochemical disturbances or histologic signs of metabolic bone disease. All bone samples were processed and analyzed in a similar manner. All parameters 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 (26).

Biochemical and Hormonal Determinations

Concentrations of serum calcium, phosphorus, creatinine, and alkaline phosphatase were determined by use of routine laboratory techniques.

Serum PTH levels were determined with the two-sites immunoradiometric assay for intact PTH (Allegro™; Nichols Institute, San Juan Capistrano, CA). The intra- and interassay coefficients of variation are 1.5 and 5.6%, respectively.

Measurements of serum levels of calcidiol and calcitriol were done with the 25-hydroxy and 1,25-hydroxy assay kits (Nichols Institute). The intra- and interassay coefficients of variation of the assays are less than 2.8% and less than 4.0%, respectively.

Determinations of serum osteocalcin concentrations were measured with an immunoradiometric assay (Nichols Institute). The intra- and interassay coefficients of variation are 4.8 and 5.6%, respectively.

Statistical Analyses

Results are expressed as mean ± SEM. All statistical tests were two-sided. An assigned significance level of 0.05 was used. Normality of distribution was assessed by the Lilliefors test, and homogeneity of variance was tested with the Levene test. Adequate transformations of the data were done when results did not meet the characteristics assumed for ANOVA (27). In the present study, the cumulative dose of prednisone was logarithmically transformed. The comparability of groups was tested by *t* test or one-way ANOVA with the Bonferroni *post hoc* test. Significantly correlated results were entered into a stepwise regression to identify independent predictors of bone volume/tissue volume, activation frequency, and mineralization lag time. All computations were performed using the SPSS software package for Windows, version 7.5 (SPSS, Chicago, IL).

Results

Immunosuppression

There was a wide range of doses of immunosuppressive drugs among the patients (Table 1). Doses given at time of transplant and at time of bone biopsy varied greatly, resulting in various cumulative and mean doses of these drugs. All

Table 1. Characteristics of immunosuppressive therapy in 57 patients after renal transplantation[a]

Agent	Dose at Time of Transplant (mg/d)	Dose at Time of Bone Biopsy (mg/d)	Cumulative Dose (g)	Dose/Year of Transplantation (g/yr)
Prednisone	18.4 ± 1.84 (3.52 to 62)	8.8 ± 0.85 (0 to 25)	24.6 ± 4.67 (1.58 to 164)	18.51 ± 3.26 (0.39 to 115)
Azathioprine	100 ± 8 (0 to 225)	58.7 ± 7.55 (0 to 150)	108 ± 28.3 (0 to 810)	16.93 ± 2.93 (0 to 81)
Cyclosporin A	242 ± 29 (0 to 750)	201.7 ± 23.49 (0 to 550)	226.8 ± 50.6 (0 to 1890)	71.82 ± 12.60 (0 to 540)

[a] Ranges are given in parentheses.

patients had taken prednisone at time of transplant. Subsequently, doses were either continued or progressively tapered, and eight patients had stopped to take prednisone for 16.3 ± 3.13 mo (range, 6 mo to 2 yr) at time of bone biopsy. Patients treated with azathioprine or CsA at time of transplant were continued on the drug until bone biopsy. Cumulative dose of mycophenolate mofetil was not calculated because only two patients were treated with this medication and thus would not have any statistical relevance.

Cumulative doses of prednisone and azathioprine were correlated with the time elapsed since transplantation ($r = 0.72$ and 0.69, $P < 0.001$, respectively), whereas cumulative doses of CsA were not ($r = 0.06$).

Patients with bone pain were transplanted for a longer period of time (7.9 ± 1.7 *versus* 3.2 ± 0.6 yr, $P < 0.01$) and received more prednisone at time of biopsy (10.8 ± 1.1 *versus* 6.8 ± 0.99 mg/d, $P < 0.01$). Fractures were more common in women than men (32 *versus* 12.5%, $P < 0.05$); however, there were no significant differences in immunosuppressive regimen between patients with or without fracture. Patients with aseptic necrosis were transplanted for a longer period of time than patients without osteonecrosis (8.7 ± 2.1 *versus* 4.9 ± 0.8 yr, $P < 0.01$).

Serum Biochemical and Hormonal Parameters

Data obtained at time of biopsy are shown in Table 2. Approximately one-third of the patients had normal renal function, whereas the other two-thirds exhibited moderate renal failure. The majority of patients had normal serum calcium, phosphorus, and alkaline phosphatase levels. However, a non-negligible number of patients were hypercalcemic, hyperphosphatemic, or hyperphosphatasemic; only a few patients had low values for these serum indices. Serum PTH and osteocalcin levels were elevated in approximately two-thirds of the patients. Most patients had normal circulating values of the vitamin D metabolites calcitriol and calcidiol; only a few patients exhibited values below normal.

Serum creatinine levels were positively related to serum phosphorus ($r = 0.35$, $P < 0.05$) and osteocalcin levels ($r = 0.53$, $P < 0.01$) and negatively correlated with serum calcitriol levels ($r = -0.42$, $P < 0.01$) and, to a lesser degree, with serum calcium levels ($r = -0.28$, $P < 0.05$). Serum phosphorus levels were also correlated with alkaline phosphatase ($r = 0.41$, $P < 0.01$) and osteocalcin ($r = 0.65$, $P < 0.01$) and negatively correlated with calcitriol ($r = -0.32$, $P < 0.05$). Serum calcium and calcitriol levels were correlated ($r = 0.39$, $P < 0.05$). Interestingly, serum PTH levels were related only to serum osteocalcin concentrations ($r = 0.62$ $P < 0.01$). Moreover, serum calcium and phosphorus levels were inversely correlated with the cumulative dose of prednisone ($r = -0.36$ and $r = 0.33$, respectively; $P < 0.05$). Serum calcium levels

Table 2. Serum biochemical and hormonal indices in 57 patients after renal transplantation and at time of bone biopsy

Parameter	Mean ± SEM	Range	Normal Values	% of Patients with Values:		
				Low	Normal	High
Creatinine (mg/dl)	1.68 ± 0.11	0.70 to 4.30	0.5 to 1.3	0	36.8	63.2
Calcium (mg/dl)	9.9 ± 0.1	7.8 to 11.9	8.4 to 10.4	1.8	77.2	21.0
Phosphorus (mg/dl)	3.6 ± 0.2	2.0 to 7.7	2.4 to 4.5	5.2	79.0	15.8
Alkaline phosphatase (U/L)	95.2 ± 7.4	24.6 to 350	40 to 110	18.0	73.6	24.6
Parathyroid hormone (pg/ml)	169 ± 27.4	18 to 731	15 to 65	0	36.8	63.2
Osteocalcin (ng/ml)	25.7 ± 4.3	2.5 to 100	5.8 to 14.0[a] 3.1 to 14.0[b]	14.0	24.6	61.4
Calcitriol (ng/ml)	34.7 ± 2.5	10.0 to 75.6	9 to 52	8.8	91.2	0
Calcidiol (pg/ml)	28.6 ± 3.1	9 to 58	15 to 60	12.3	87.7	0

[a] Normal range for men.
[b] Normal range for women.

were also negatively related to the cumulative dose of azathioprine ($r = -0.33$, $P < 0.05$).

There were no major differences in serum parameters between patients with bone pain, fractures, or aseptic necrosis and asymptomatic patients.

Histomorphometric Analysis of Bone

Results of the bone histomorphometric parameters are shown in Table 3. Bone volume/tissue volume was below the normal range obtained in age- and gender-matched healthy control subjects in more than half of the patients. Bone turnover (activation frequency) was low in almost half of the patients, and only 15 patients exhibited high bone turnover. Accordingly, osteoblast number, erosion surface, and osteoclast number were elevated in only 12 to 16 patients, and the majority of patients had normal or low values for these parameters. Peritrabecular fibrosis, which indicates active secondary hyperparathyroidism, was found in nine patients, whereas woven osteoid, which reflects either past or present PTH overactivity on bone, was observed in 24 patients with various levels of bone turnover.

Mineralization lag time and osteoid off time, *i.e.*, the duration of interrupted mineralization, were prolonged in the majority of patients (Table 3). This was mainly due to a low rate of formation of new osteoid and a parallel decrease in mineralization. However, nine patients exhibited signs of generalized osteomalacia with osteoid accumulation, wide osteoid seams, and increase in mineralization lag time. Moreover, focal signs of osteomalacia with spotty accumulation of osteoid, increased osteoid seam width (>20 μm), and mineralization defect (prolonged osteoid maturation time) were observed in 12 additional patients. No iron accumulation at the mineralizing front was found in any of the patients. Mild stainable aluminum deposition was seen in nine patients, with a mean aluminum surface of 16.7 ± 3.23% (5 to 30%). These patients had been transplanted for 3.4 ± 0.7 yr (range, 6 mo to 7 yr).

Patients with bone pain had lower bone volume/tissue volume than the other patients (15.7 ± 1.03 *versus* 20.7 ± 1.06%, $P < 0.01$). The same finding was observed in patients who had experienced fractures (16.2 ± 1.5 *versus* 19.5 ± 0.94%, $P < 0.05$). Patients with aseptic necrosis did not differ from the other subjects. Bone turnover and mineralization status were not different between symptomatic patients and the others.

Factors Influencing Bone Volume, Bone Turnover, and Mineralization

Bone Volume. Bone volume/tissue volume was inversely correlated with cumulative doses of prednisone, azathioprine, and time elapsed after transplantation (logarithmically transformed, $r = -0.59$, -0.63, and -0.40, respectively; $P < 0.01$). There were also negative correlations between bone volume and mean doses of prednisone per year and azathioprine per year ($r = -0.49$, $P < 0.01$ and $r = -0.33$, $P < 0.05$, respectively), calculations that control for the effect of time after transplantation on bone volume. Positive relationships were also observed between bone volume and serum calcium levels ($r = 0.38$, $P < 0.01$) and the parameter of bone turnover activation frequency ($r = 0.33$, $P < 0.05$). It is noteworthy that none of the clinical characteristics such as age, gender, underlying kidney diseases, or treatment modalities before or after transplantation showed any relationship with bone volume.

Table 3. Histomorphometric parameters of bone in 57 patients after renal transplantation[a]

Parameter	Mean ± SEM	Range	Normal Values	% of Patients with Values:		
				Low	Normal	High
Bone volume/tissue volume (%)	18.6 ± 0.84	6.77 to 34.1	16.8 to 22.9	56.1	28.1	15.8
Activation frequency (yr^{-1})	0.62 ± 0.12	0.01 to 4.55	0.29 to 0.72	45.6	28.1	26.3
Osteoblast number/bone length (*n*/100 mm)	218 ± 32.0	2 to 964	10 to 240	10.5	61.4	28.1
Erosion surface/bone surface (%)	3.43 ± 0.53	0.1 to 18.5	0.1 to 5.69	19.3	59.6	21.1
Osteoclast number/bone length (*n*/100 mm)	24.0 ± 3.58	0.10 to 97.1	0.01 to 36.1	28.1	49.1	22.8
Bone formation rate/tissue volume (mm^3/cm^3 per yr)	21.6 ± 5.76	0.12 to 140	11.5 to 110	59.7	35.0	5.3
Fibrosis surface/bone surface (%)	0.37 ± 0.15	0 to 5.76	0	NA	84.2	15.8
Woven osteoid surface/bone surface (%)	1.67 ± 0.54	0 to 22.5	0	NA	57.9	42.1
Osteoid volume/tissue volume (%)	8.1 ± 0.87	0.68 to 32.7	0.57 to 6.0	0	45.6	54.4
Osteoid surface/bone surface (%)	40.1 ± 2.77	5.87 to 84.1	3.45 to 37.9	0	50.9	49.1
Mean osteoid thickness (μm)[b]	8.94 ± 0.34	4.53 to 14.7	4.38 to 11.8	0	84.2	15.8
Maximum osteoid thickness (μm)[c]	18.0 ± 1.03	9.6 to 33.2	<20	NA	63.9	36.1
Mineralization lag time (days)	280 ± 43.4	38.8 to 1,613	13.3 to 58.4	0	12.5	87.5
Osteoid maturation time (days)	24.7 ± 1.80	9.77 to 50.0	7.1 to 24.6	0	73.7	26.3
Off time (%)	279 ± 43.4	37.8 to 1,612	2 to 465	0	1.8	98.2

[a] NA, not applicable.
[b] Osteoid thickness values are corrected for obliquity, *i.e.*, divided by 1.199.
[c] Maximum osteoid seam thickness is measured directly, *i.e.*, uncorrected.

Besides serum calcium, none of the other studied biochemical and hormonal markers correlated with bone volume.

Stepwise regression analysis, including all factors that had significant correlation with bone volume, revealed that the cumulative dose of prednisone was the main factor influencing bone volume/tissue volume (Figure 1). The relationship was summarized as: Bone volume = 27.4 − 7.8 log (cumulative dose of prednisone), $r = 0.54$, $P < 0.05$.

Bone Turnover. Activation frequency was negatively correlated with the cumulative dose of prednisone (Figure 2) and the time elapsed after transplantation (log transformed, $r = -0.45$ and $r = -0.37$, $P < 0.01$). The mean dose of prednisone per year also correlated negatively with activation frequency ($r = -0.32$, $P < 0.05$). It is of note that doses of cyclosporine were not related to bone turnover. Also, none of the serum biochemical and hormonal parameters, including serum PTH levels, correlated with activation frequency.

Regression analysis showed that the cumulative dose of prednisone was also the main factor influencing bone turnover according to the equation: Activation frequency = 1.6 − 0.37 log (cumulative dose of prednisone), $r = 0.43$, $P < 0.01$.

Mineralization Status. There was no correlation between osteoid thickness, mineralization lag time, osteoid maturation time, and osteoid off time and any immunosuppressive doses, phosphate supplementation, or biochemical hormonal parameters, including serum phosphorus, calcidiol, and calcitriol levels. Patients with focal osteomalacia did not exhibit more bone aluminum deposition than patients without osteomalacia (5.4 ± 2.26 *versus* 4.1 ± 2.12%).

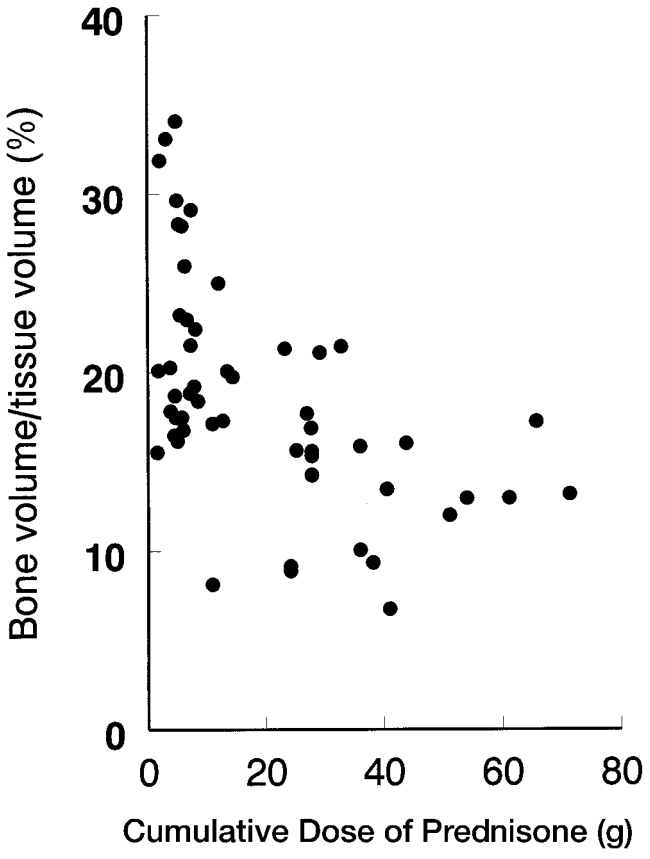

Figure 1. Relationship between cumulative dose of prednisone and bone volume/tissue volume in 53 post-kidney-transplanted patients. $r = 0.54$, $P < 0.05$.

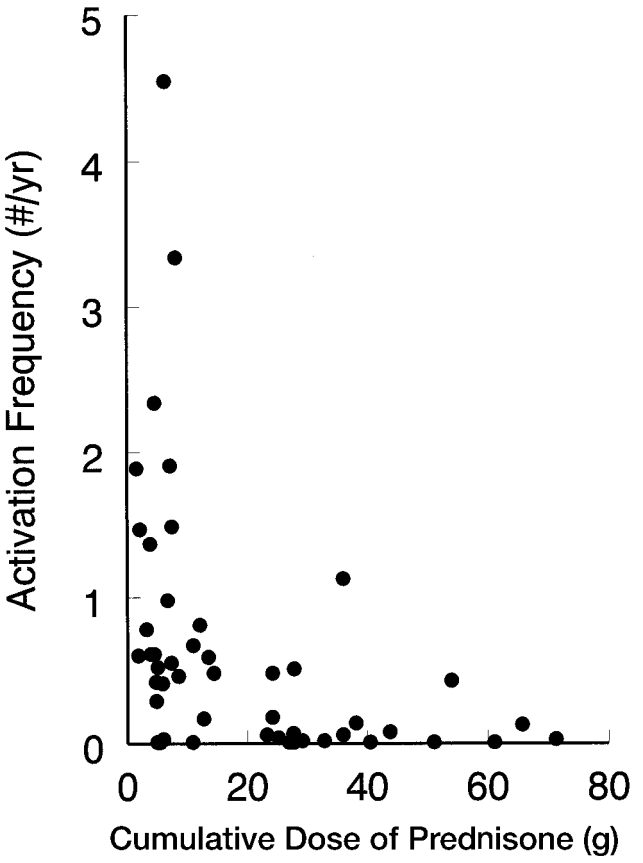

Figure 2. Relationship between cumulative dose of prednisone and activation frequency in 53 post-kidney-transplanted patients. $r = 0.43$, $P < 0.05$.

Discussion

The present study shows that after kidney transplantation, patients exhibit various histologic abnormalities of bone despite restoration of kidney function. These results are in agreement with previous studies (7,9,12–15). However, one of the major findings of the present study is that both bone volume and bone turnover decrease in parallel with time after transplantation. This could explain, at least in part, the discrepancies in bone volume and bone turnover reported in previous studies, which differed in timing of bone sampling after transplantation. However, the study of Julian *et al.* (10) reported that as early as 6 mo after renal grafting, patients exhibited low bone mass and low bone turnover. It is noteworthy that at time of transplantation, among the 20 patients studied, 11 underwent kidney transplantation before they required dialysis therapy and the other nine patients were on dialysis therapy less than 5 yr. Thus, bone lesions at time of transplantation in these patients were not severe and, indeed, consisted of mild secondary hyperparathyroidism. It is therefore conceivable that the high doses of glucocorticoids required soon after transplan-

tation together with only moderately increased bone turnover at baseline explain the high prevalence of low bone turnover 6 mo after transplantation.

The other novel finding of the present study is the rather high number of patients with generalized or focal osteomalacia in the presence of normal circulating levels of calcitriol. This finding could not be related to the usual causes of mineralization defect, such as hypophosphatemia or aluminum deposition. Also, there was no obvious relationship with any immunosuppressive therapy. A greater number of patients might be needed to unravel the determining factor(s) leading to mineralization defect. However, even though glucocorticoids have been shown to decrease osteoblastic activity and collagen synthesis (4,5,28,29), no current evidence indicates that glucocorticoids impair the mineralization process. Because the mineralization defect occurs in the presence of normal circulating vitamin D metabolites, it is conceivable that the apparent resistance of bone cells to vitamin D is due to abnormal response of its receptor (VDR) or postreceptor defect. The direct or indirect mechanisms responsible for such VDR resistance deserve further study.

In the present study and the one reported by Julian *et al.* (10), glucocorticoid therapy emerged as the sole determinant of bone volume and bone turnover, and there was no evidence of an effect of CsA on these parameters. Several animal studies (30–33) and some data in patients after transplantation (9,34) have pointed to a stimulatory effect of cyclosporine on bone turnover. It is conceivable that the overwhelming effects of glucocorticoids on lowering bone turnover may mask the potential stimulatory effect of cyclosporine. Also, the cross-sectional design of the study, which included patients with a wide range of clinical and biochemical characteristics, may have masked the potential effect of cyclosporine. In the present study, glucocorticoids negated the known differences in bone volume between male and female patients and its decrease with age despite restoration of kidney function.

One possible limitation of the present study is that patients who agreed to participate in the study may have been more symptomatic than those who did not complain of bone-related symptoms. However, among the patients who refused to undergo bone biopsies, a non-negligible number of patients were symptomatic or had experienced fractures or aseptic necrosis. It is not unusual that patients who have undergone many medical procedures in the past are more likely to refuse an additional invasive test if not absolutely necessary. Moreover, in the present study, the only striking histologic difference between symptomatic and asymptomatic patients was a lower bone volume. There was no difference in bone turnover or mineralization status between the two groups of patients. Depressed bone turnover and occurrence of focal or generalized osteomalacia represent the two main novel findings of the present study. These findings are likely to be found in the entire population of patients after kidney transplantation.

PTH levels are usually considered good indicators of bone turnover in patients with renal failure despite their limitations (35). In the present study, as in others (10,14), serum PTH levels did not reflect bone turnover, pointing again to the strong interference of glucocorticoids on bone cell recruitment. Moreover, glucocorticoids have been shown to decrease calcium absorption and thus stimulate PTH secretion (36). These facts explain, at least in part, the apparent overestimation of hyperparathyroid bone disease in past studies in which diagnosis was made by assessment of serum PTH and serum calcium levels (16,37–40). Thus, monitoring serum PTH levels in transplanted patients may have limited value for assessment of bone turnover, with the exception of extremely high levels.

In summary, the present study shows that bone volume and bone turnover decrease in parallel with time after transplantation, and this decrease is mainly the result of glucocorticoid therapy. These findings suggest that immunosuppressive regimens that minimize the amount of glucocorticoid therapy have a better chance of preventing bone loss and low bone turnover. Moreover, treatment with antiresorptive agents such as bisphosphonates or calcitonin has a greater chance to be maximally efficient if initiated shortly after transplantation when bone volume is conserved and bone turnover is not yet suppressed. Finally, the non-negligible occurrence of generalized or focal osteomalacia unexplained by hypophosphatemia or other studied parameters deserves further study.

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