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Bone Resorption in Kidney Transplant Recipients

M.C. Gioviale, G. Damiano, C. Lombardo, C. Maione, G. Buscemi, and A.I. Lo Monte

ABSTRACT

Early diagnosis of persistent hyperparathyroidism (HP) following kidney transplantation may prevent worsening of osteodystrophy and potential damage to the graft. We evaluated the utility of collagen pyridinoline (PYD) and deoxypyridinoline (DPD) urinary cross-links beyond the common HP markers to evaluate 70 selected stable recipients between 1997 and 2006 who were divided into 2 group depending on the immunosuppressive protocol. All patients showed elevated levels of urinary cross-links even though calcemia and phosphoremia values were normal. Their mean creatinine level was slightly increased. Data were assessed as mean values ± SD. All variables underwent a correlation matrix analysis and a stepwise regression, with posttransplant intact parathyroid hormone (iPTH) as the dependent variable and other variables as regressors. A statistically significant correlation was observed between PYD and alkaline phosphatase (ALP; $P = .0026$, $r = .41$); PYD and DPD ($P = .015$, $r = .34$); pre- and posttransplant iPTH ($P = .024$, $r = .31$); and creatinine and ALP ($P = .024$, $r = .31$). Taking the groups separately, there were significant correlations between PYD and ALP ($P = .0076$, $r = .42$); PYD and DPD ($P = .017$, $r = .38$); ALP and posttransplant iPTH ($P = .038$, $r = .33$); osteocalcin (OC) and posttransplant iPTH ($P = .048$, $r = .32$); and pre- and posttransplant iPTH ($P = .019$, $r = .37$) among subjects in the first group, whereas subjects in the second group showed a correlation between posttransplant iPTH and age at transplantation ($P = .032$, $r = .61$). In conclusion, we showed that urinary cross-links may be helpful to reveal bone resorption in kidney recipients when usual bone metabolism parameters do not demonstrate hyperparathyroidism.

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KIDNEY TRANSPLANTATION removes the metabolic stimuli which lead to secondary hyperparathyroidism (HP) in uremic patients. However, excessive production of parathyroid hormone (PTH) often lasts after transplantation leading to a disorder of oversecretion of PTH with hypercalcemia (tertiary HP).[1] Assay of the biochemical markers of osteoclastic activity[2,3] permits an early diagnosis of HP and, therefore, greater control of bone mass loss. Among the various markers which have proven reliable from the point of view of sensitivity and specificity, pyridinolinic urinary collagen "cross-links" (pyridinoline [PYD] and deoxypyridinoline [DPD] seem to play a fundamental role. In fact, PYD and DPD seem to be 2 of the most efficient markers of bone resorption.[4] PYD and DPD are tiny binding molecules (from which the name "cross-links" derives) which provide structural rigidity to type I collagen in bone. They are found mainly in bone and cartilagous collagen and in small quantities in the other connective tissues.[5–7] Compared with other biochemical markers of bone metabolism, their presence is, therefore, extremely useful since they are the only expression of mature bone catabolism, without interference from other intermediary metabolites. Furthermore, urinary cross-link concentrations may be considered the expression of bone resorption, since they are not subject to any metabolic modifications, cannot be reused by the organism, and are not absorbed in the intestine, so that their determination is not affected by diet. In physiologic conditions, their urinary concentrations vary according to sex (higher in women), age (increasing during the first decade and then after the fourth decade of life), and endocrine activity (higher in the postmenopausal stage). Their excretion follows a circadian rhythm with an increase during the night.[8] In light of the above considerations, the aim of this study was to assess the utility of urinary bone collagen cross-links in kidney transplant recipients as markers for early diagnosis of bone resorption in comparison with traditional markers of bone metabolism.[9,10]

MATERIALS AND METHODS

Among a population of 120 subjects who underwent transplantation between 1997 and 2006 at our center, we selected 2 groups of patients with well-functioning kidney transplants (Table 1). One group of 48 patients (A) had undergone immunosuppressive therapy with calcineurin inhibitors cyclosporine (3–5 mg/kg body weight/d with plasma concentration Cmax at 12 months posttransplantation of 400 ± 200 ng/mL) or tacrolimus (0.1–0.3 mg/kg with Cmax at 12 months of 3–8 ng/mL), methylprednisolone (0.1–0.5 mg/kg body weight/d), and mycophenolate mofetil (1–2 g/d). Within this group, 31 subjects were affected by chronic glomerulonephritis; 7, polycystic kidneys; 6, chronic pyelonephritis; and 4, nephrolithiasis.

The immunosuppressive therapy among the other group (B; n = 22) included calcineurin inhibitors cyclosporine (3–5 mg/kg body weight/d) or tacrolimus (0.1–0.3 mg/kg) and mycophenolate mofetil (2 g/d), but not cortisone, since 14 of these patients were affected by severe arterial hypertension; 3, iatrogenic diabetes mellitus; 3, glaucoma, and 2, cataract. These subjects were, therefore, included in the study to exclude any possible effects of cortisone on bone remodeling. Within this group, 15 patients were affected by chronic glomerulonephritis; 4, chronic pyelonephritis; 2, papillary necrosis; and 1, Alport's syndrome.

The inclusion criteria required immunologic quiescence for at least 12 months, no administration of drugs which might interfere with bone metabolism, no surgical parathyroidectomy, PTH levels before transplantation between 65 and 400 pg/mL as an indication of functional activation of the parathyroid glands persistent at the moment of transplantation, no cytomegalovirus (CMV) infection, and no use of monoclonal antibody during induction of immunosuppressive therapy.[11,12] Exclusion criteria were: patients who underwent monoclonal antibody induction, those switched in therapy for side effects, those with graft-versus-host disease (GVHD) within 12 months after transplantation, and those with CMV infection. This study included clinical data from 20 healthy control subjects, namely 10 men and 10 women of overall average age of 40.9 ± 11.08 years.

Blood samples were taken in the morning at 1 year posttransplantation; cross-link determinations were performed on fresh urine, also sampled in the morning. Serum levels of creatinine, calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) were measured using a multichannel analyzer of the Central Laboratory of our university. PYD and DPD were determined via

Table 1. Patient Characteristics and Serum Values

Parameter	Patients Receiving Steroids (Group A)	*P*	Patients Not Receiving Steroids (Group B)	Control Group
Male/female	32/16	—	11/11	10/10
Average age of patients (y)	48.9 ± 11.08	NS	45.8 ± 8.50	40.9 ± 11.5
Age at transplantation (months)	46.8 ± 34.01	NS	47.0 ± 30.3	—
Serum creatinine (μmol/L)	144.1 ± 60.2	NS	181.5 ± 64.5	85.2 ± 11.5
Serum calcium (mmol/L)	2.5 ± .15	NS	2.39 ± .19	2.44 ± .20
Serum phosphorus (mmol/L)	1.03 ± .20	NS	1.11 ± .19	1.34 ± .21
ALP (U/L)	72.9 ± 26.2	NS	69.5 ± 17.0	53.1 ± 8.4
OC (ng/mL)	14.3 ± 3.0	NS	15.5 ± 2.8	3.8 ± .9
PYD (nmol/mmol creatinine)	99.3 ± 40.8	<.05	75.3 ± 20.5	29.4 ± 5.4
DPD (nmol/mmol creatinine)	10.8 ± 4.7	NS	11.9 ± 4.7	5.1 ± .8
Pretransplant iPTH (pg/mL)	224.8 ± 44.2	NS	233.8 ± 34.1	35.1 ± 9.6
Posttransplant iPTH (pg/mL)	80.1 ± 15.1	NS	89.0 ± 20.9	—

ALP, alkaline phosphatase; OC, osteocalcin; PYD, pyridinoline; DPD, deoxypyridinoline; iPTH, intact parathyroid hormone; NS, not significant.

Table 2. Correlation Analysis of Group A + B Patients (N = 70)

	Age	Age at Transplantation	Creatinine	ALP	OC	Pretransplant iPTH	Posttransplant iPTH	PYD	DPD
Age	1.0 (.0)	.11 (.44)	−.13 (.36)	.14 (.32)	.06 (.67)	.13 (.35)	.10 (.47)	−.004 (.97)	−.039 (.78)
Age at transplantation	.11 (.44)	1.0 (.0)	.05 (.70)	−.17 (.21)	−.10 (.47)	−.035 (.80)	−.022 (.89)	.019 (.89)	.061 (.67)
Creatinine	−.13 (.36)	.054 (.70)	1.0 (.0)	−.31 (.024)	−.16 (.24)	−.006 (.96)	−.095 (.51)	−.016 (.90)	.16 (.25)
ALP	.14 (.32)	−.17 (.21)	−.31 (.024)	1.0 (.0)	.19 (.18)	−.083 (.56)	.21 (.13)	.41 (.0026)	.13 (.36)
OC	.061 (.67)	−.10 (.47)	−.16 (.24)	.19 (.18)	1.0 (.0)	.23 (.10)	.24 (.08)	.20 (.14)	−.04 (.78)
Pretransplant iPTH	.13 (.35)	−.035 (.80)	−.006 (.96)	−.083 (.56)	.23 (.10)	1.0 (.0)	.31 (.024)	−.16 (.26)	−.047 (.74)
Posttransplant iPTH	.10 (.47)	−.0022 (.87)	−.095 (.51)	.21 (.13)	.24 (.08)	.31 (.024)	1.0 (.0)	.11 (.41)	.14 (.31)
PYD	.004 (.97)	.019 (.89)	−.016 (.90)	.41 (.0026)	.20 (.14)	−.16 (.26)	.11 (.41)	1.0 (.0)	.34 (.015)
DPD	.039 (.078)	.061 (.67)	.16 (.25)	.13 (.36)	−.04 (.78)	−.047 (.74)	.14 (.31)	.34 (.015)	1.0 (.0)

immunoenzymatic microplate methods (Metra PYD and DPD kits, Quidel Corporation), using a competitive enzyme and monoclonal antibody, anti-PYD and anti-DPD, respectively, which were coated into wells.[13] This technique produced 2 curves involving 10 standards and 2 controls, both high and low.

The results were always related to urinary creatinine values expressed in nmol/L. The normal range for PYD is 12.8 to 37 nmol/mmol creatinine and for DPD, 2.3 to 7.4 nmol/mmol creatinine.

We also measured the blood levels of PTH pre- and posttransplantation and osteocalcin (OC) pre- and posttransplantation by an electrochemiluminescence method (Elecsys 2010, Roche Diagnostic). All data were evaluated as mean values ± SD, and all variables submitted to a correlation matrix analysis and thereafter to a stepwise regression, where the posttransplant intact PTH (iPTH) is the dependent variable and the other variables are the regressors. The stepwise procedure consisted of inserting only those variables which were significant at a level of significance $\alpha = 0.15$ and discarding all the others. To obtain a better assessment of the different behavior of the posttransplant iPTH dependent variable in the 2 groups of patients, we added the "dummy" variable as a regressor. This variable incorporates the cortisone effect of the first group compared with the second group, namely, cases where this drug was not included in the immunosuppressive therapy.

We considered the Snedecor F test as the test for statistical significance for the parameters of the independent variables; this can easily be confirmed by the Student t test, since $\sqrt{F_{(1,\,\nu)}} = t_{(\nu)}$.

RESULTS

Table 1 shows that the mean values of serum creatinine in each group were just above the normal range, which is 60 to 97 μmol/L, while the serum levels for the following metrics were normal: Ca (normal range = 2.12–2.60 mmol/L); P (0.81–1.55 mmol/L); OC (1.5–13.6 ng/mL); and ALP (normal range for adult = 70–110 U/L). The posttransplant iPTH serum levels (normal range = 10–65 pg/mL) showed an increase in each group: in group A, 80.1 ± 15.1 pg/mL; and in Group B, 89 ± 20.9 pg/mL. The pretransplant iPTH was, of course, particularly high in both groups: 224.8 ± 44.2 pg/mL in group A (receiving steroids) and 233.8 ± 34.1 pg/mL in group B (not receiving steroids).

The urinary cross-link levels were also fairly high, both in group A (PYD = 99.3 ± 40.8 nmol/mmol creatinine; DPD = 10.8 ± 4.7 nmol/mmol creatinine) and in group B (PYD = 75.3 ± 20.5 nmol/mmol creatinine; DPD = 11.9 ± 4.7 nmol/mmol creatinine) compared with the values obtained in the control group (PYD = 29.4 ± 5.4 nmol/mmol creatinine; DPD = 5.1 ± 0.85 nmol/mmol creatinine). The comparison of the mean values obtained in both groups was significant only for PYD ($P < .05$).

Tables 2 to 4 report the correlation matrices relative to all interest variables; values in parentheses express the

Table 3. Correlation Analysis of Group A: Patients Receiving Steroids in Therapy (n = 48)

	Age	Age at Transplantation	Creatinine	ALP	OC	Pretransplant iPTH	Posttransplant iPTH	PYD	DPD
Age	1.0 (.0)	.080 (.63)	−.19 (.24)	.17 (.28)	.092 (.58)	.19 (.23)	.003 (.98)	.040 (.80)	−.036 (.82)
Age at transplantation	.080 (.63)	1.0 (.0)	.23 (.88)	−.20 (.21)	−.22 (.17)	−.079 (.63)	−.25 (.11)	.030 (.85)	.091 (.58)
Creatinine	−.19 (.24)	.023 (.88)	1.0 (.0)	−.28 (.08)	−.26 (.10)	−.09 (.57)	−.28 (.8)	.13 (.41)	.15 (.33)
ALP	.17 (.28)	−.20 (.21)	−.28 (.08)	1.0 (.0)	.24 (.14)	−.14 (.38)	.33 (.038)	.42 (.0076)	.15 (.35)
OC	.092 (.58)	−.22 (.17)	−.26 (.10)	.24 (.14)	1.0 (.0)	.31 (.05)	.32 (.048)	.23 (.14)	−.04 (.78)
Pretransplant iPTH	.19 (.23)	−.07 (.63)	−.09 (.57)	−.14 (.38)	.31 (.05)	1.0 (.0)	.37 (.019)	−.17 (.29)	−.09 (.58)
Posttransplant iPTH	.003 (.98)	−.25 (.11)	−.28 (.08)	.33 (.038)	.32 (.048)	.37 (.019)	1.0 (.0)	.19 (.23)	.10 (.51)
PYD	.04 (.80)	−.030 (.85)	.13 (.41)	.42 (.0076)	.23 (.14)	−.17 (.29)	.19 (.23)	1.0 (.0)	.38 (.017)
DPD	−.036 (.82)	.091 (.58)	.15 (.33)	.15 (.39)	−.04 (.56)	−.091 (.58)	.10 (.51)	.38 (.017)	1.0 (0.0)

Table 4. Correlation Analysis of Group B: Patients Not Receiving Steroids in Therapy (n = 22)

	Age	Age at Transplantation	Creatinine	ALP	OC	Pretransplant iPTH	Posttransplant iPTH	PYD	DPD
Age	1.0 (.0)	.25 (.41)	.10 (.75)	.10 (.75)	−.11 (.71)	−.20 (.52)	.45 (.14)	−.41 (.18)	−.051 (.827)
Age at transplantation	.25 (.41)	1.0 (.0)	.17 (.59)	−.04 (.88)	.52 (.07)	.17 (.58)	.61 (.032)	.40 (.19)	−.05 (.86)
Creatinine	.10 (.75)	.17 (.59)	1.0 (.0)	−.48 (.11)	.01 (.96)	.22 (.48)	.10 (.74)	−.42 (.16)	.095 (.76)
ALP	−.10 (.75)	−.04 (.88)	−.48 (.11)	1.0 (.0)	−.06 (.85)	.36 (.24)	−.095 (.76)	.32 (.30)	.074 (.81)
OC	−.11 (.71)	.52 (.07)	.014 (.96)	−.06 (.85)	1.0 (.0)	−.30 (.34)	−.061 (.84)	.46 (.13)	.13 (.68)
Pretransplant iPTH	−.20 (.52)	.17 (.58)	.22 (.48)	.36 (.24)	−.30 (.34)	1.0 (.0)	.12 (.70)	.14 (.66)	.090 (.77)
Posttransplant iPTH	.45 (.14)	.61 (.032)	.10 (.74)	−.09 (.76)	−.06 (.84)	.12 (.70)	1.0 (.0)	.24 (.43)	.17 (.58)
PYD	−.41 (.18)	.40 (.19)	−.42 (.16)	.32 (.30)	.46 (.13)	.14 (.66)	.24 (.43)	1.0 (.0)	.47 (.11)
DPD	−.05 (.87)	−.05 (.86)	.09 (.76)	.07 (.81)	.13 (.68)	.09 (.77)	.17 (.58)	.47 (.11)	1.0 (.0)

significance of the correlation coefficients. The correlation matrices of the variables involved in the 2 groups of study patients (70 subjects) in Table 2 showed the most significant coefficient of correlation to be obtained from comparison of PYD and ALP ($P = .0026$, $r = .41$); PYD and DPD ($P = .015$, $r = .34$); and pre- and posttransplant iPTH data ($P = .024$, $r = .31$).

Table 3 shows for group A (48 subjects) a correlation between PYD and ALP ($P = .0076$, $r = .42$); PYD and DPD ($P = .017$, $r = .38$); and pre- and posttransplant iPTH ($P = .019$, $r = .37$). Unlike the data regarding the entire population, patients of this group showed a correlation between posttransplant iPTH and ALP ($P = .038$, $r = .33$), and between posttransplant iPTH and OC ($P = .048$, $r = .32$).

In contrast to the first group, the correlation matrices in Table 4 showed for group B (22 subjects) a correlation only between posttransplant iPTH and age at transplantation ($P = .032$, $r = .61$). No correlation was observed between the PYD and DPD data and the other parameters.

Table 5 shows data regarding the stepwise regression procedure, where the dependent variable is posttransplant iPTH. Although the first step in this procedure gives a rather low R^2 ($R^2 = .10$), we verified that pretransplant iPTH was, nevertheless, significant (Prob $> F = .024$). The intercept was also highly significant (Prob $> F = .01$). The relation between the pre- and posttransplant iPTH was significant as well, as confirmed by the Snedecor F test, where Prob $> F = .024$. In the second step, the addition of the second variable, ALP, led to an increase in the R^2 value ($R^2 = .16$), while the regression equation of the posttransplant iPTH on the regressors (pretransplant iPTH and ALP) was significant, as confirmed by the F test (Prob $> F = .0169$). Still, the coefficient of the regressor ALP was not significant (Prob $> F = .0775$).

Finally, the addition of the "dummy" variable incorporating the effect of the different therapies (with or without cortisone) increased the R^2 value to .20. It is obvious that there is also an increased significance of the regression, as confirmed by the F test (Prob $> F = .0141$). As can be seen, the coefficients of the variables ALP and "dummy" were not significant. The procedure was interrupted at the third step, since the remaining variables were not significant for an $\alpha = 15\%$.

DISCUSSION

The persistence or relapse of hyperparathyroidism among kidney transplant patients is a well-known pathology. It

Table 5. Stepwise Regression Procedure for the Dependent Variable Posttransplant iPTH

	Degrees of Freedom	Sum of Squares	Mean Square	F	Prob $> F$	Variable	Parameter Estimate	Residual Standard	F	Prob $> F$
Step 1*										
Regression	1	1414.53	1414.53	5.39	.0245	Intercept	53.18	12.74	17.43	.0001
Residual	48	12587.37	262.23			Pretransplant iPTH	.12	.05	5.39	.0245
Total	49	14001.90								
Step 2†										
Regression	2	2230.68	1115.34	4.45	.0169	Intercept	39.14	14.68	7.11	.0105
Residual	47	11771.22	250.45			Pretransplant iPTH	.13	.05	6.35	.0152
Total	49	14001.90				ALP	.16	.09	3.26	.0775
Step 3‡										
Regression	3	2853.21	951.07	3.92	.0141	Intercept	46.58	15.17	9.43	.0036
Residual	46	11148.69	242.36			Pretransplant iPTH	.12	.05	5.81	.0200
Total	49	14001.90				ALP	.17	.09	3.69	.0611
						"Dummy"	−8.30	5.18	2.57	.1159

*Step 1: introduced the variable pretransplant iPTH.
†Step 2: introduced the variable ALP ($R^2 = .15$).
‡Step 3: introduced the variable "dummy" ($R^2 = .20$).

occurs when, after the removal of the parathyroid hyperplasia stimulus, subsequent to a well-functioning kidney transplant, excessive PTH secretion persists and there is no regression of the symptoms of bone dystrophy. The result may be damage to the new kidney and to vascular tissue. Only preventive measures can forestall the development of this pathological condition.[14,15]

The clinical use of collagen cross-links is already common in other pathological conditions involving high levels of bone resorption, such as Paget's disease or postmenopausal osteoporosis. This application led us to assess their diagnostic usefulness in patients following kidney transplantation who showed normal levels of serum Ca, P, and ALP, and moderately high levels of OC and PTH, indicating activation of the bone remodeling process and, therefore, persistent hyperparathyroidism.[16]

Among all subjects we observed urinary values of PYD and DPD were not particularly high, but certainly indicative of persistent bone osteoclastic activity, despite recovery of homeostasis by the presence of the new kidney. A statistical comparison of all studied parameters, both of apposition and those regarding bone resorption, led to a significant correlation. This might cause an aggravation of the osteopenia, with serious clinical repercussions on the quality of life of the transplant recipients.[17]

It must be emphasized that moderately high levels of posttransplant iPTH, when examined singly, may be considered to be an index of residual activation of the parathyroid glands, showing the presence or persistence of hyperparathyroidism, even though the metabolic stimuli leading to gland hyperplasia have been removed. The high urinary cross-link levels, which are caused only by the processes of bone resorption, are further confirmation of this hypothesis. Pretransplant iPTH, as can be seen in the stepwise regression procedure, certainly affects the results of bone parameters, and continues to do so even after transplantation.

In conclusion, although all our data were obtained from a rather limited number of subjects, they seem to indicate that urinary cross-links of bone collagen are useful markers of bone resorption. These markers should certainly not be considered to be indices of bone metabolism alone, but with the main parameters of hyperparathyroidism, such as ALP, OC, and iPTH, to provide a valid contribution to study of bone behavior among kidney transplant patients. The significant correlation between our PYD and DPD results, which was observed in the entire population of subjects, as well as in patients that used steroids, makes it possible to dissect activation of bone metabolism due to bone mass reconstruction versus persistent osteoclastic activation caused by hyperparathyroidism. The rather small number of patients (n = 22) whose immunosuppressive therapy did not include cortisone (group B) did not permit us to draw significant conclusions regarding the effect of cortisone on the urinary elimination of cross-links. Nevertheless, the significantly lower levels of PYD ($P < .05$) in this group compared with those of group A suggested that steroids may have some effect on the elimination of urinary PYD. Furthermore, comparison with the control subjects showed considerably higher values of both types of urinary cross-links in each transplant group. This study demonstrated the utility of such parameters for the diagnosis of hyperparathyroidism in patients with well-functioning kidney transplants.[18]

REFERENCES

1. Gioviale MC, Gambino G, Maione C, et al: Intraoperative parathyroid hormone monitoring during parathyroidectomy for hyperparathyroidism in waiting list and kidney transplant patients. Transplant Proc 38:1003, 2006

2. Seibel MJ, Gartenberg F, Silverberg SJ, et al: Urinary hydroxypyridinium cross-links in primary hyperparathyroidism. J Clin Endocrinol Metab 74:481, 1992

3. Rojas E, Carlini RG, Clesca P, et al: The pathogenesis of osteodystrophy after renal transplantation as detected by early alterations in bone remodelling. Kidney Int 63:1915, 2003

4. Delmas PD: Clinical use of biochemical markers of bone remodelling in osteoporosis. Bone 13(suppl 1):S17, 1992

5. Roth M, Uebelhart D: Search for new urinary biochemical markers of collagen degradation in man. Clin Chim Acta 3271–2: 81, 2003

6. Fujimoto D, Suzuki M, Ughiyama A: Analisys of pyridinoline, a cross linking compound of collagen fibers, in human urine. J Biochem 94:1133, 1983

7. Gunja-Smith Z, BouceK R: Collagen cross linking compounds in human urine. J Biochem 197:759, 1981

8. Eastell R, Calvo MS, Burritt MF, et al: Abnormalities in circadian patterns of bone resorption and renal calcium conservation in type I osteoporosis. J Clin Endocrinol Metab 74:487, 1992

9. Hoshino H, Kushida K, Takahashi M, et al: Short-term effect of parathyroidectomy on biochemical markers in primary and secondary hyperparathyroidism. Miner Electrolyte Metab 23:93, 1997

10. Carlini RG, Rojas E, Weisinger JR, et al: Bone disease in patients with long-term renal transplantation and normal renal function. Am J Kidney Dis 36:160, 2000

11. Montalban C, De Francisco AL, Marinoso ML, et al: Bone disease in long-term adult kidney transplanted patients with normal renal function. Kidney Int Suppl 85:S129, 2003

12. Koller H, Mayer G: Immunosuppressive therapy and bone metabolism after kidney transplantation. Acta Med Austriaca 28:81, 2001

13. Gomez B Jr, Ardakani S, Evans BJ, et al: Monoclonal antibody assay for free urinary pyridinium cross-links. Clin Chem 42:1168, 1996

14. Tanimoto K, Ohno S, Imada M, et al: Utility of urinary pyridinoline and deoxypyridinoline ratio for diagnosis of osteoarthritis at temporomandibular joint. J Oral Pathol Med 33:218, 2004

15. Simsek B, Karacaer O, Karaca I: Urine products of bone breakdown as markers of bone resorption and clinical usefulness of urinary hydroxyproline: an overview. Chin Med J (Engl) 117:291, 2004

16. Shankar S, Hosking DJ: Biochemical assessment of Paget's disease of bone. J Bone Miner Res 21(suppl 2):22, 2006

17. Sprague SM, Josephson MA: Bone disease after kidney transplantation. Semin Nephrol 24:82, 2004

18. Zisman AL, Sprague SM: Bone disease after kidney transplantation. Adv Chron Kidney Dis 13:35, 2006