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Prevention of Osteoporosis in Heart Transplant Recipients: A Comparison of Calcitriol with Calcitonin and Pamidronate

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Abstract. Bone loss and osteoporotic fractures are common in cardiac transplant recipients. To compare two prophylactic medical regimens after heart transplantation, 26 consecutive heart transplant recipients were randomized to receive either continuous oral calcitriol (0.5 μg/day) combined with nasal salmon calcitonin (200 U/day) for the first 3 months (group A) or intermittent intravenous pamidronate (0.5 mg/kg body weight) every third month (group B). Bone mineral density (BMD) and biochemical indices of bone turnover were measured at baseline and 3, 6, 12, and 18 months after transplantation. The mean pretransplant BMD, measured by dual energy X-ray absorptiometry (DXA) was significantly lower in the patients compared with age-matched healthy controls. During the first year of treatment, rates of bone loss at the lumbar spine and femoral neck were slightly but significantly slower in the patients treated with pamidronate, but there was no longer a significant difference between the two groups after 18 months of heart transplantation. Irrespective of the mode of osteoporosis prevention, osteocalcin levels increased whereas urinary deoxypyridinoline decreased after transplantation, and significant bone loss was observed in both treatment groups. We found no relationship between initial BMD, markers of bone turnover, cumulative glucocorticoid dose, or cyclosporine levels and the rate of bone loss after cardiac transplantation. In summary, we found that the rapid and severe bone loss following heart transplantation could be attenuated by two preventive measures, pamidronate or calcitriol with calcitonin.

Key words: Osteoporosis — Heart transplantation — Calcitriol — Calcitonin — Pamidronate.

Cardiac transplantation is an effective therapy for end-stage heart disease [1]. The immunosuppression that is required for graft acceptance, however, is associated with rapid bone loss and increased prevalence and incidence of fractures [2–5]. These complications compromise the quality of life of these patients and justify attempts to slacken bone loss. Patients with end-stage heart failure awaiting heart transplantation tend to have reduced BMD [6] related to prolonged physical inactivity, cardiac cachexia with poor nutrition, and other factors. In the posttransplant period, immunosuppressive therapy with prednisone and cyclosporine A produces further bone loss, mostly during the first year after the transplantation [7–12]. At the same time, improved physical performance after a period of immobilization enhances exposure of the patients to hazards that may predispose them to fractures. Accordingly, fractures have been reported to occur most often within the first year of transplantation [5].

The present longitudinal study evaluates bone status in heart transplant patients and compares the effects of two preventive treatments; i.e., calcitriol with calcitonin versus pamidronate, on bone loss and on biochemical markers of bone turnover after transplantation.

Patients and Methods

Subjects

We prospectively evaluated 31 patients who underwent cardiac transplantation between May 1994 and November 1995 at the University Hospital of Zürich. Four died within 6 months, one within 12 months after the transplantation. The remaining 26 patients with a survival exceeding 18 months after transplantation (53 ± 8 years of age, range 21–63, 24 men and 2 postmenopausal women) had been randomized by simple alternating allocation of consecutive patients to either treatment group (calcitriol with calcitonin or pamidronate) and are described in this study (Table 1). Group A was treated with continuous oral calcitriol (Rocaltrol, Roche, Basel, Switzerland) at an incremental dose starting at 0.25 μg/day and up to a maximum of 0.5 μg/day, combined with nasal salmon calcitonin 200 U/day (Miacalcic, Sandoz, Basel, Switzerland) for the first 3 months. Group B was treated with intermittent intravenous pamidronate (Aredia, Ciba, Basel, Switzerland) 0.5 mg/kg body weight every third month. All patients received a supplement of 1 g calcium carbonate p.o. (Sandoz, Basel, Switzerland) daily. Treatment for osteoporosis prevention was started within the first 2 weeks after heart transplantation.

After transplantation, all patients received glucocorticoids and cyclosporine A. Rejection was managed by high dose i.v. glucocorticoids, followed by rapid tapering. Cumulative doses of glucocorticoids were calculated and serum trough cyclosporine levels were recorded at the same time interval (Table 2).

Analytical Methods

Each patient was evaluated by bone densitometry and biochemical indices of mineral metabolism before and 3, 6, 12, and 18 months after heart transplantation. DXA of the lumbar spine (L2–L4) and proximal femur (femoral neck and Ward's triangle) was performed

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Table 1. Baseline patient characteristics. No significant difference between group A and group B was observed

	Group A	Group B
Number	12	14
Age (years)	54.5 ± 1	51.1 ± 3
Sex (F/M)	1/11	1/13
Weight (kg)	71.7 ± 2.3	73.4 ± 2.6
Height (cm)	175 ± 2	175 ± 2
Indication for transplantation		
Ischemic heart disease	6	8
Dilated cardiomyopathy	6	5
Other	0	1

Table 2. Immunosuppressive regimen. No significant difference between groups A and B was observed

	Group A	Group B
Cyclosporine blood level (ng/ml)		
3 Months	207 ± 6	197 ± 6
6 Months	206 ± 5	194 ± 4
12 Months	203 ± 5	194 ± 4
Cumulative prednisone intake (g)		
3 Months	10.1 ± 1.0	9.5 ± 1.3
6 Months	12.8 ± 1.1	12.4 ± 1.6
12 Months	14.8 ± 1.2	13.8 ± 1.7

with quantitative digital radiography (QDR 2000, Hologic, Inc., Waltham, Mass.). The *in vitro* reproducibility using an anthropomorphic spine phantom was 0.3–0.5%. The *in vivo* coefficient of variance (cv) was 1.0 for the lumbar spine and 1.0 for the proximal femur. The BMD measurements, expressed as an area density in grams per square centimeter, were compared to sex- and age-matched patients or young-normal control subjects with a computer database (Hologic, Inc.). This database is used to calculate the T-score.

We also collected historic information on atraumatic fractures to determine the clinical impact of heart transplantation-related osteoporosis. Spinal X-ray studies were not routinely obtained at the beginning and end of the study.

Serum for determinations of calcium, albumin, phosphate, creatinine, parathyroid hormone (PTH), osteocalcin, total testosterone, 25-hydroxyvitamin-D_3 ($25OHD_3$) was obtained in the morning under fasting conditions; 2 hour fasting urinary calcium, deoxypyridinoline, and creatinine excretion were also determined.

Intact PTH and osteocalcin levels in serum were measured using two-site immunoradiometric assays (IRMA, Nichols Institute, San Juan Capistrano, CA). Serum $25OHD_3$ was determined by radioimmunoassay (RIA) (Incstar Corporation, Minnesota, USA).

Serum calcium, phosphate, albumin, and creatinine were analyzed according to standard laboratory methods. Serum calcium was corrected for individual variations in serum albumin using the formula:

corrected serum calcium (mmol/liter) = measured serum calcium (mmol/liter) + 0.02 × [40 − measured albumin (g/liter)].

Urinary deoxypyridinoline was measured using a competitive enzyme immunoassay (Pyrilinks-D kit, Metra Biosystems, Inc., Mountain View, CA) and values were expressed relative to creatinine excretion (dpyr/creatinine) and given as nmol/mmol. Urinary calcium and creatinine were analyzed according to standard laboratory methods and the ratio calcium/creatinine was calculated and given as mmol/mmol.

Table 3. Pretransplant bone mineral density values and rates of bone loss between 0 and 18 months after transplantation.

	Group A	Group B
Femoral neck		
Baseline BMD (g/cm^2)	0.77 ± 0.03	0.81 ± 0.03
T-score (SD)	−1.92 ± 0.25	−1.39 ± 0.27
Bone loss (%)		
0–18 Months	6.1 ± 1.9	3.0 ± 1.6
Lumbar spine		
Baseline BMD (g/cm^2)	0.97 ± 0.04	1.01 ± 0.03
T-score (SD)	−1.51 ± 0.32	−0.80 ± 0.30
Bone loss (%)		
0–18 Months	6.5 ± 1.9	3.8 ± 1.9

P = NS between group A and group B

Statistics

Results are expressed as mean ± SD or ± SEM as indicated. The results were analyzed using the SPSS for windows 6.0 and the Wilcoxon's rank sum test. For comparisons between groups of patients, analysis of variance (ANOVA) for repeated measurements and Friedman's nonparametric test were used. A P value <0.05 was considered statistically significant.

Results

Clinical Observations (Table 1)

At the time of the initial evaluation, all patients were in New York Heart Association class III or IV for a time period of 6–7 (range 2–18) months. At the time of evaluation for transplantation, left ventricular ejection fraction was 24% (range 12%–37%).

No side effects were observed during the treatment with both calcitriol and calcitonin or pamidronate, and all patients completed the treatment. Body weight increased in group A patients from 71.7 ± 2.3 to 74 ± 2.7 kg 18 months after transplantation, and in group B patients from 73.4 ± 2.6 to 76 ± 2.7 kg.

One patient of group A suffered a vertebral fracture 4 months after heart transplantation. Standing height decreased by more than 1 cm in five patients of group A and in one patient of group B within 18 months after transplantation.

Bone Densitometry

Before transplantation (Table 3). Mean pretransplant BMD, expressed as g/cm^2, was significantly lower in the patients compared with age-matched healthy controls, and it did not differ significantly between both treatment groups. Analysis of individual T-scores revealed that it was below −2.5 SD in four patients (two patients in group A and 2 in group B) at the femoral neck and in three patients (two and one) at the lumbar spine, respectively.

After transplantation. BMD values and changes during the 18 months after heart transplantation are presented in Table 3 and Figure 1. In group A patients, the mean rate of bone loss was 6.3 ± 2.3% at the femoral neck and 7.4 ± 1.9% at the lumbar spine during the first year ($P < 0.01$). In the second year of treatment, BMD stabilized, as shown in Fig-

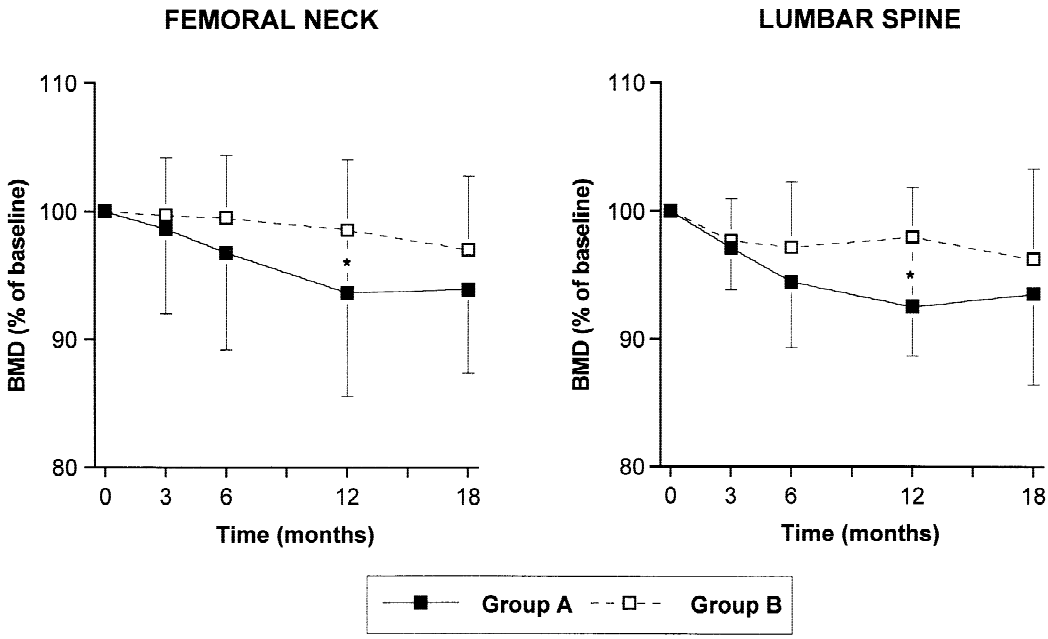

Fig. 1. Evolution of bone mineral density (BMD) of femoral neck and lumbar spine after cardiac transplantation. Mean values ± SD are shown. * = $P < 0.05$ between group A and group B.

ure 1. Rates of bone loss during the first year of treatment in group B patients were significantly slower compared with group A: 1.4 ± 1.4% at the femoral neck and 1.9 ± 1.0% ($P = 0.02$) at the lumbar spine. In the next 6 months of treatment, we detected a further bone loss of 1.5 ± 0.6% at the femoral neck and 1.9 ± 1.9% at the lumbar spine. Thus, after a total of 18 months, the difference between the two groups was lost. The T-score was below −2.5 SD in five patients of group A and three of group B at the femoral neck, and in three patients (A) and two patients (B) at the lumbar spine, respectively. There was no relationship between initial BMD and subsequent bone loss, and no relationship between prednisone intake or cyclosporine blood levels and BMD.

Biochemical Markers of Mineral Metabolism

Table 4 and Figure 2 show the time course of the biochemical parameters in the two groups. Serum creatinine increased slightly (but not significantly) from 112 ± 8 to 120 ± 11 μmol/liter (group A) and from 114 ± 5 to 122 ± 6 μmol/liter (group B). Serum osteocalcin levels remained unchanged after 3 months, but rose significantly ($P < 0.02$) to 160% (group A) and 180% (group B) of baseline after 6 months and persisted high until 18 months after transplantation in both treatment groups. The total alkaline phosphatase activity in serum decreased significantly ($P < 0.02$) in both groups after 3 months and then remained at this level during the observation time. Mean serum levels of PTH remained high during the 18 months. The mean urinary deoxypyridinoline/creatinine ratio decreased within 3 months (n.s.) and significantly ($P < 0.02$) after 12 months in both groups, and remained at the same level until 18 months after transplantation. The urinary calcium excretion increased to maximal levels at 3 months after transplantation and then returned to baseline in group A and significantly decreased further ($P < 0.05$) in group B. Mean serum levels of total testosterone, calcium, and phosphate remained unchanged during the 18 months.

We found no relationship between markers of bone turnover or immunosuppressive treatment and the rate of bone loss after cardiac transplantation.

Discussion

The management of posttransplantation osteoporosis is difficult and important because of the preexisting bone disease and the absolute necessity for immunosuppressive drugs, which contribute substantially to accelerate bone loss. As patients live longer after the life-saving procedure of heart transplantation, osteoporosis and its resulting fractures may lead to suffering and debilitation.

The deleterious effects of glucocorticoids on bone mineral metabolism are well recognized [13, 14]. Among the spectrum of glucocorticoid actions that can negatively influence bone, the decrease in osteoblast function and bone formation appears to be most relevant, resulting in bone loss, usually most marked within the first 6 months of glucocorticoid treatment [14]. In addition, cyclosporine A might play a role as well [15, 16]. Although its effects on human bone metabolism are not clearly defined, cyclosporine A increases bone turnover; several reports show that osteocalcin levels are increased in patients treated with cyclosporine A [9, 10, 15, 16].

Since posttransplant osteoporosis is a potentially preventable disorder, it appears logical to look for prophylactic measures to diminish the rapid bone loss in transplant recipients. As for most published longitudinal trials on transplantation osteoporosis, there is no randomized placebo control group in our study. The choice of the two prophylactic regimens tested was based on previous studies, suggesting that calcitriol and calcitonin as well as pamidronate could prevent corticosteroid-induced bone loss [17–20].

In agreement with previous studies (7–12), we found a

Table 4. Values of mineral metabolism before and after cardiac transplantation

		Group A	Group B
Calcium (mmol/liter)	Baseline (months)	2.27 ± 0.03	2.28 ± 0.04
(2.1–2.6)	3	2.28 ± 0.04	2.31 ± 0.02
	6	2.35 ± 0.04	2.30 ± 0.02
	12	2.38 ± 0.04	2.30 ± 0.02
	18	2.35 ± 0.04	2.34 ± 0.02
Phosphate (mmol/liter)	Baseline (months)	1.03 ± 0.06	1.02 ± 0.08
(0.6–1.3)	3	1.02 ± 0.06	1.09 ± 0.06
	6	0.97 ± 0.05	1.01 ± 0.06
	12	1.00 ± 0.09	1.02 ± 0.05
	18	0.91 ± 0.06	0.96 ± 0.05
Creatinine (μmol/liter)	Baseline (months)	112 ± 8	114 ± 5
(<105)	3	114 ± 10	106 ± 8
	6	124 ± 13	109 ± 6
	12	132 ± 15	114 ± 5
	18	119 ± 11	121 ± 6
Parathyroid hormone (ng/liter)	Baseline (months)	86.5 ± 13.7	106.1 ± 25.9
(10–65)	3	55.7 ± 9.7	74.0 ± 13.9
	6	79.6 ± 28.5	71.0 ± 6.6
	12	88.6 ± 22.5	105.8 ± 25.0
	18	63.6 ± 9.0	90.8 ± 14.5
Total testosterone (nmol/liter)	Baseline (months)	15.0 ± 1.8	11.2 ± 2.5
(9.4–37.0)	3	10.9 ± 0.9	13.0 ± 1.6
	6	11.1 ± 0.8	11.6 ± 1.1
	12	12.3 ± 1.3	14.7 ± 1.4
	18	10.8 ± 0.8	11.6 ± 1.0

Normal values in parentheses. For serum total testosterone values, only the 24 men were considered

No significant differences between groups A and B were observed; there was no significant change over time within the groups

reduced BMD at the time of transplantation and a marked loss of BMD during the first postoperative year. Our prospective study documents that patients treated with pamidronate exhibit a slower bone loss compared with those treated with calcitriol in the first, fearful year after transplantation. Overall, some bone loss occurred, but both treatments were well tolerated and no side effects were recognized with the doses used. Using different treatment regimens (calcitriol versus pamidronate), one might have expected distinct effects on calciuria and PTH secretion. However, such an idea is not supported by the experimental data (except for the calciuria values 12 and 18 months after transplantation, Fig. 2), which may be explained by the fact that the markers were monitored before the pamidronate infusion and that the dosage of calcitriol was moderate. The findings are again consistent with the conclusion that relatively low doses were used. Our prospective study shows that the PTH levels, which are often elevated in patients awaiting heart transplantation [21, 22], remain elevated after transplantation irrespective of treatment. Since correlations between laboratory values (e.g., calcium, creatinine, $25OHD_3$) or treatment regimen and PTH levels could not be defined throughout the observation period, potential explanations for the persistently high PTH values cannot be supported by data.

The inhibitory effects of corticosteroids on osteoblasts lead to reduced serum levels of osteocalcin, often considered as a marker of bone formation. Serum osteocalcin levels increased after 6 months of treatment, as found in previous studies [10, 12, 15, 16, 23, 24]. The raised osteocalcin levels were not related to increased serum creatinine levels, which did not significantly increase in our study, even less than in other published trials [7, 12, 23]. Osteocalcin is a specific and popular osteoblast marker, but it remains unclear whether the increase in serum osteocalcin levels after transplantation reflects increased bone formation. Osteocalcin levels do not appear to correlate with bone histomorphometry in cardiac transplant recipients [25]. Total alkaline phosphatase activity, in contrast to osteocalcin, fell after transplantation. In a recently published study, enzyme activity was lowered in patients treated with calcitonin but raised in those treated with etidronate or calcidiol [21]. Urinary excretion of deoxypyridinoline, considered a reliable marker of bone resorption, decreased in response to transplantation and/or immunosuppression, irrespective of treatment. We previously found a highly significant correlation between deoxypyridinoline excretion and fasting calciuria in the pretransplant state [6]; after transplantation, such a positive correlation was lost. Fasting hypercalciuria was marked at the time when bone loss occurred.

Our present data confirm that prevention of bone loss by antiresorptive agents such as bisphosphonates or by vitamin D derivations is feasible during the critical first year after transplantation [12, 23]. As tested in our study (at relatively low doses) both osteoporosis-preventing strategies can be considered safe in these patients. Possibly, such prophylaxis may be more effective but also may have more adverse effects at higher doses. Moreover, we demonstrated that biochemical bone turnover markers cannot predict those patients who are most at risk of bone loss. Remarkably, the

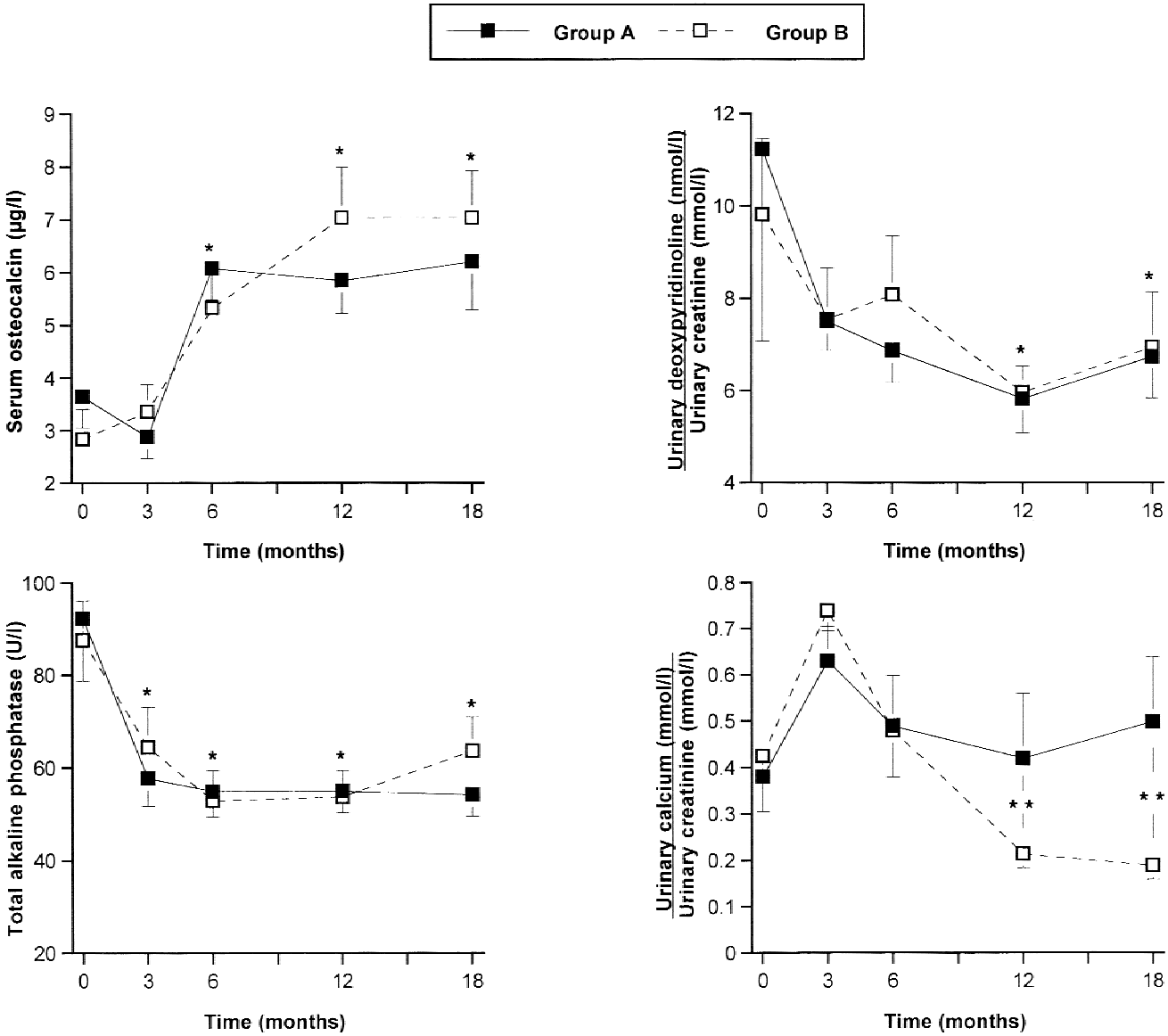

Fig. 2. Biochemical markers of bone turnover after cardiac transplantation. Mean values ± SEM are given. * = $P < 0.05$ versus baseline value within group; ** $P < 0.05$ between groups A and B.

biochemical uncoupling of bone formation and resorption was much more pronounced before than after transplantation, and bone loss progressed over a period when urinary deoxypyridinoline, but not calcium excretion, was no longer elevated and when serum osteocalcin levels but not alkaline phosphatase activity were high.

In conclusion, this study suggests that rapid and severe bone loss following heart transplantation could be attenuated by two preventive measures, pamidronate or calcitriol and calcitonin.

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