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Timing and quantification of bone loss in cardiac transplant recipients

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Abstract To evaluate osteopenic bone disease in heart transplant patients, we prospectively measured bone mineral density (BMD) in 33 consecutive male recipients before hospital discharge and 1 year later, using dual photon absorptiometry. At hospital discharge BMD measurement at the lumbar spine was only 90 % of that expected in healthy age- and sex-matched controls ($P = 0.005$). One year later BMD had further decreased by 8.5 % at the lumbar spine and by 10.4 % at the femoral neck ($P = 0.0001$). Five patients suffered vertebral compression fractures during the 1st postoperative year. Our results indicate that osteopenia of the lumbar spine is already present at the time of hospital discharge after transplantation and that further bone loss occurs at a considerable rate during the 1st postoperative year at the lumbar spine and at the femoral neck.

Key words Heart transplantation, osteoporosis · Osteoporosis, heart transplantation

Introduction

Cardiac transplant recipients are at an increased risk of developing osteopenic bone disease [5, 7, 12, 13, 18]. When severe enough, this complication may cause newly rehabilitated patients to once again become disabled. Several etiologic factors can play a role in this frustrating sequence of events. Prior to heart transplantation, disuse osteodystrophy may already be present due to prolonged periods of physical inactivity [10]; the extensive use of diuretics and a poor nutritional status also have an adverse effect on bone mass [1]. In the postoperative period, immunosuppressive maintenance therapy most often implies chronic intake of corticosteroids and, almost invariably, lifelong treatment with cyclosporin. The former is notorious for the damage it causes to bone metabolism [9, 16, 17, 19], and there is some evidence that the latter may have similar deleterious effects [2, 4, 8, 11, 14, 15, 21].

The present study examines the temporal evolution of post-transplant osteopenic bone disease as monitored by sequential measurements of bone mass. This kind of information is essential when evaluating the need for, and modalities of, possible preventive treatment.

Patients and methods

At the time of this writing, 131 heart transplantations and 4 heart-lung transplantations had been performed in our institution. Currently, about 30 patients undergo transplantation each year; the 1-year and 3-year actuarial patient survival is 89 % and 87 %, respectively.

Table 1 Cyclosporin blood levels and cyclosporin and corticosteroid intake at 3, 6, and 12 months postoperatively

	3 months	6 months	12 months
Cyclosporin blood level (n/ml)	264 ± 70	242 ± 79	218 ± 60
Dose of cyclosporin (mg/kg per day)	5.1 ± 1.9	4.9 ± 1.5	4.7 ± 2.5
Dose of corticosteroids in prednisone equivalents (mg/kg per day)	0.17 ± 0.04	0.12 ± 0.04	0.08 ± 0.03

The patient population for the present study consisted of 33 consecutive male patients who received a first orthotopic heart transplant between April 1989 and December 1990 and who survived for more than 1 year.

Immunosuppression was achieved with a 5-day course of antithymocyte globulin in the immediate postoperative period and with triple maintenance therapy with corticosteroids, azathioprine, and cyclosporin A. Rejection was treated with intravenous pulses of methylprednisolone (0.5–1.0 g) on 3 consecutive days. No patient in this study needed additional courses of polyclonal or monoclonal antibodies for recalcitrant rejection. Cyclosporin levels were measured in whole blood using a specific radioimmunoassay (CYCLO-Trac SP whole blood, INCSTAR, Stillwater, Minn., USA).

Bone mineral density (BMD) measurements at the lumbar spine (L_2–L_4) and the femoral neck were performed before hospital discharge (i.e., 3.7 ± 1.6 weeks postoperatively) and 1 year later. Using dual-energy X-ray absorptiometry and dedicated software (Hologic QDR-1000/w, Hologic, Waltham, Mass., USA), area densities were obtained and expressed in grams of hydroxyapatite, divided by the area of interest in square centimeters [20].

By comparing a patient group with a healthy age- and sex-matched reference group, a measured value for BMD can be converted into a percentage of expected BMD or it can be expressed as a Z score, which indicates the number of standard deviations a given value deviates from the mean of the reference group. A measured value for BMD can also be compared to the peak bone mass in the reference group and expressed as a percentage of peak bone mass, or as a T-score, which indicates the number of standard deviations a given value deviates from the mean peak bone mass of the reference group [3]. Whereas the Z score places a patient in relation to an age- and sex-matched control population, the T score gives an indication of the risk of developing pathologic fractures; this risk rises exponentially with decreasing T-score values. A T score of –2 is considered a "fracture threshold" by some [20]. In the present study, X-rays of the dorsolumbar spine or the femoral neck were performed only upon clinical indication.

Statistics were computed using the SAS program. For comparisons between groups of patients, Student's *t*-test, paired or unpaired, was used as appropriate. A P value less than 0.05 was considered to be statistically significant. Results are expressed as means ± SD.

Results

Patient characteristics

At the time of transplantation, the 33 men in this study had a mean age of 54 ± 8 years (range 32–66 years). The reason for transplantation was an ischemic cardiomyopathy in 20 patients (61 %), a dilated cardiomyopathy in 12 (36 %), and valvular heart disease in 1 (3 %). Thirteen (39 %) had been in the hospital awaiting their transplantation. Recipients were discharged 30 ± 14 days postoperatively. Nineteen required one or more additional hospitalizations for an average total duration of 21 ± 22 days. One year after transplantation, the vast majority of patients had a normal level of physical activity: 29 (88 %) were in New York Heart Association class I, 3 suffered mild functional impairment (N.Y.H.A. class II), and 1 was in class III due to respiratory insufficiency. Serum creatinine was 1.36 ± 0.36 mg/dl (range 0.78–2.37 mg/dl) before transplantation and 1.42 ± 0.37 mg/dl (range 0.86–2.60 mg/dl) 1 year after surgery.

Immunosuppression

Table 1 summarizes the cyclosporin blood levels and the daily dose of cyclosporin and corticosteroids at 3, 6, and 12 months postoperatively. The cumulative corticosteroid load over the 1st postoperative year amounted to the equivalent of 6.13 ± 2.66 g of predisone (range 2.56–14.45 g) Twelve patients (36 %) had one or more episodes of rejection that were treated with high-dose intravenous methylprednisolone pulses. Accordingly, the total steroid load over the 1st year in this group was higher than in the 21 patients who were never treated for rejection: 9.18 ± 1.95 g versus 4.27 ± 1.09 g of prednisone ($P < 0.0001$).

Bone mineral density measurements

The results are summarized in Fig. 1 and Table 2. At the time of hospital discharge after heart transplantation, the bone mineral reserve at the level of the spine was already reduced by 9.7 % as compared to an age- and sex-matched control group, resulting in a Z score of –0.93 ± 1.44. At the same time, 9 patients (28 %) had a T score of < –2 in the spine and 13 patients (40 %) were below this theoretical "fracture threshold" at the level of the femoral neck.

One year later no patient had increased his impaired bone mass and the number of recipients with a T score of < –2 had increased to 15 (47 %) and 18 (56 %) at the spine and the femoral neck, respectively. By this time, the bone mineral density had further decreased to a

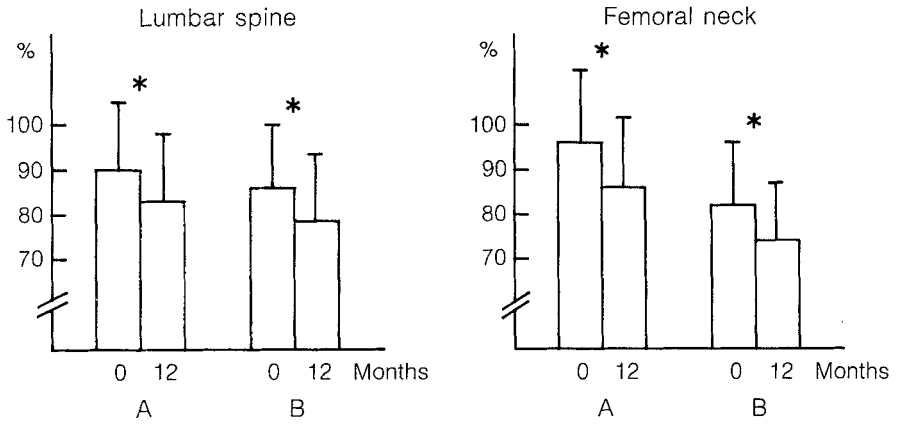

Fig. 1 Mean bone mineral density in 33 male heart transplant recipients at hospital discharge *(0)* and 1 year later *(12)*. Values are expressed as a percentage of the expected value in an age- and sex-matched control group *(A)* or as a percentage of the expected peak bone density in this control group *(B)*.
* $P = 0.0001$ between measurements at hospital discharge and 1 year later

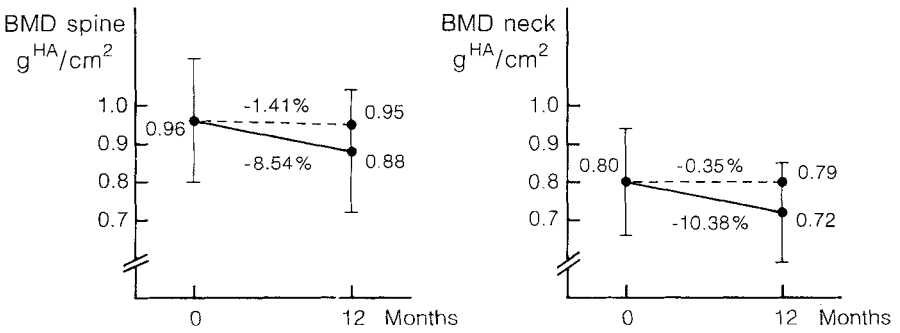

Fig. 2 Decrease in bone mineral density during the 1st year after heart transplantation (——) versus "normal" decrease in a healthy population (—) with a comparable bone mineral density at baseline (P. Geusens, personal communication). (g*HA* gram of hydroxyapatite)

Table 2 Bone mineral density (BMD) in 33 male heart transplant recipients (g*HA* gram of hydroxyapatite)

	At hospital discharge	1 year postoperatively	*P*
BMD spine (gHA/cm^2)	0.96 ± 0.16	0.88 ± 0.16	0.0001
Z score spine	−0.93 ± 1.44 (0.005)[a]	−1.66 ± 1.49 (0.0001)[a]	0.0001
T score spine	−1.43 ± 1.45	−2.17 ± 1.48	0.0001
BMD femoral neck (gHA/cm^2)	0.80 ± 0.14	0.72 ± 0.13	0.0001
Z score femoral neck	−0.29 ± 1.27 (NS)[a]	−0.99 ± 1.15 (0.005)[a]	0.0001
T score neck	−1.62 ± 1.27	−2.4 ± 1.19	0.0001

[a] Significance level versus an age- and sex-matched reference population

mean Z score of −1.66 ± 1.49 at the level of the spine and −0.99 ± 1.15 at the level of the femoral neck, both of which differed significantly from an age- and sex-matched control group. This decrease in bone mass of 8.5 % and 10.4 %, respectively, is considerable when compared to the expected yearly decrease of 1.41 % at the spine and 0.35 % at the femoral neck in a healthy control population [22, and own data, to be published] (Fig. 2). During the 1st year after transplantation, five patients (16 %) developed a clinically evident and radiologically confirmed vertebral collapse. In Table 3 their values of baseline BMD and decrease in bone mass are compared to those of the patients without pathologic fractures. There was a trend towards a lower bone density at baseline in the patients who would eventually develop a fracture. Avascular bone necrosis was not observed.

Patients who received extra corticosteroids because of rejection tended to lose more bone than those who took maintenance corticosteroids only, but the difference did not reach statistical significance (Table 4).

Discussion

Heart transplant recipients develop osteopenia for various reasons. Before transplantation many are exposed to numerous risk factors such as inactivity, cardiac ca-

Table 3 Baseline bone mineral density (BMD) and decrease in bone mass in patients who suffered a vertebral collapse versus those who did not (g*HA* gram of hydroxyapatite)

	No vertebral collapse	Vertebral collapse	*P*
Number	28	5	
Age (years)	53.7 ± 8	58.6 ± 4	NS
BMD spine (gHA/cm^2)	0.98 ± 0.16	0.83 ± 0.12	0.056
BMD neck (gHA/cm^2)	0.82 ± 0.14	0.70 ± 0.04	NS
Δ spine (%)	−8.7 ± 5.0	−7.5 ± 8.8	NS
Δ neck (%)	−9.9 ± 7.8	−13.0 ± 5.8	NS

Table 4 Baseline bone mineral density (BMD) and decrease in bone mass in patients who received additional high-dose corticosteroid treatment for rejection versus those who did not (g*HA* gram of hydroxyapatite)

	No pulse	Pulse	*P*
Number	21	12	
Age (years)	55 ± 8	52.8 ± 8	NS
BMD spine (gHA/cm^2)	0.99 ± 0.16	0.90 ± 0.15	NS
BMD neck (gHA/cm^2)	0.82 ± 0.14	0.77 ± 0.15	NS
Δ spine (%)	−7.46 ± 6.16	−10.3 ± 4.2	NS
Δ neck (%)	−8.3 ± 9.6	−10.7 ± 6.8	NS

chexia with poor nutrition, cigarette smoking, and prolonged loop diuretic therapy. After the transplantation most of these conditions can be reversed, but the aggression against the bone mass continues with the start of immunosuppressive therapy. The deleterious effect of corticosteroids is well known and results in a "low bone turnover" osteopenia, mainly due to a reduced differentiation and function of the osteo blasts [9, 16, 17, 19]. The exact effect of cyclosporin on bone metabolism is less well established. Initially, in vitro studies suggested that cyclosporin reduced cytokine-mediated bone resorption. Later, rat experiments showed a dose-dependent increase in activity of both osteo blasts and, to a much greater extent, osteoclasts resulting in a devastating "high bone turnover" osteopenia [11, 21]. The concomitant use of corticosteroids in most transplant recipients prevents a systematic analysis of the effect of cyclosporin alone. Despite a lowering of the maintenance dose of corticosteroids, the introduction of cyclosporin has not resulted in a decreased incidence of post-transplant bone disease [6].

Quantitative data on osteoporosis after cardiac transplantation are scarce [5, 12, 13, 18]. The only longitudinally studied group of patients is described by Muchmore and colleagues [12, 13]. They examined 76 cardiac transplant recipients using single-energy computerized tomographic scans of the lumbar spine at regular intervals and found an important reduction in vertebral bone density both before and after transplantation when compared with age-matched controls. Only patients younger than 40 jears ($n = 10$) seem to escape this effect. Because of the confounding use of hormone substitution (59 %) and salmon calcitonine (38 %) in patients considered to be at risk of developing vertebral fractures, the natural history of the bone mass post-transplantation cannot be deduced from these data. Rich et al. performed a cross-sectional study in 20 patients referred for evaluation of suspected bone disease [18]. Despite this selection bias, the bone mineral reserve, as measured with dual photon absorptiometry, was significantly reduced only in male recipients at the level of the femoral neck when compared with age- and sex-matched controls. In the spine, the reduction did not reach statistical significance. This lack of evidence of lumbar osteopenia in a rather small group of middle-aged (mean 52 years) patients 26 months after transplantation can probably be partially explained by the fact that extensive vertebral fractures made spinal BMD measurements technically impossible in four patients.

In agreement with the findings of Muchmore et al., the present study confirms that cardiac transplant recipients have "a bad start" in terms of bone mineral content: their BMD is already significantly reduced when they leave the hospital after their transplantation. The larger part of this reduction undoubtedly is present even before transplantation, although the amount of bone loss in the first 2 or 3 postoperative weeks cannot be deduced from our data. Even more disturbing than this confirmation of "a bad start" is the tremendously high rate at which bone loss continues in the 1st year after transplantation. A decrease of almost 10 % in bone mineral content is in sharp contrast with the expected yearly bone loss of 1 %–2 % in normal adults [22]. This reduction in bone mass is most pronounced in the 1st postoperative months and levels off after the 1st year [13, own preliminary data]. Fifteen percent of our patients developed a radiologically confirmed vertebral collapse, while none did in the treated group of Muchmore and colleagues, and 50 % did in the selected group of Rich et al. The rather low incidence of fractures in the former two groups is probably due to the lack of systematic radiological evaluation of the patients.

It seems clear that osteopenic bone disease can become a crippling complication after heart transplantation in a substantial number of patients. There is a need for an effective, preventive strategy to diminish or even stop bone loss in transplant candidates and recipients if the post-transplant quality of life is to be maximally preserved. The essential components of such a strategy and the optimal time for its implementation are, as yet, unclear.

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