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Calcitonin, Etidronate, and Calcidiol Treatment in Bone Loss after Cardiac Transplantation

I. Garcia-Delgado,[1] S. Prieto,[2] L. Gil-Fraguas,[1] E. Robles,[1] J. J. Rufilanchas,[2] F. Hawkins[3]

[1]Service of Rehabilitation, University Hospital, 12 de Octubre, Ctra. Andalucia Km 5.4, 28041 Madrid, Spain
[2]Service of Cardiac Surgery, University Hospital, 12 de Octubre, Ctra. Andalucia Km 5.4, 28041 Madrid, Spain
[3]Service of Endocrinology, University Hospital, 12 de Octubre, Ctra. Andalucia Km. 5.4, 28041 Madrid, Spain

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Abstract. Cardiac transplantation is associated with severe bone loss caused by glucocorticoids, immunosuppressive treatment, and other factors. Treatment protocols for the prevention of bone loss is being studied. Forty patients who underwent cardiac transplantation were randomly given calcitonin ($n = 13$; 100 UI/d, nasal route), etidronate ($n = 14$; cyclical treatment 400 mg p.o./d/2 weeks/3 months), or calcidiol ($n = 13$; 32,000 IU/weekly) therapy for at least 18 months. Serum parameters (Ca, P, alkaline phosphatase, osteocalcin, intact PTH), urinary calcium, and vertebral mineral density (VMD; L2–L4, DXA Hologic QDR 1000) were measured immediately before treatment and after 6, 12, and 18 months of therapy after cardiac transplantation. Patients with cardiac transplantation had a VMD significantly lower than age and sex-matched Spanish controls. Prevalence of osteoporosis (Z-score below −2 SD) was 30%. Osteocalcin levels increased at 6, 12, and 18 months of treatment in the three groups. After 18 months of treatment, VMD increased significantly in the calcidiol 4.9%, vs. −1.19% and −0.19% in the calcitonin and etidronate groups, respectively. A lower incidence of fracture was found in patients treated with calcidiol during the study. In summary, we have found in this open randomized study that calcidiol was the most effective drug in the prevention and treatment of bone loss in patients after cardiac transplantation.

Key words: Dual X-ray absorptiometry — Cardiac transplantation — Bone markers — Vitamin D — Bone loss.

Bone disease is an important complication in patients with cardiac transplant, which can modify long-term life quality and morbidity. Several factors are involved in bone loss in cardiac transplantation. Cardiac caquexia and a previous low bone mass in relation to chronic diuretic therapy, recurrent diseases, inactivity, and inadequate calcium intake have been implicated [1]. Immunosuppressive therapy in triple drug protocols (glucocorticoids, azathioprine, and cyclosporine) have increased patients' lives, but their bone turnover effect is complex, with bone disease becoming a hazard for these patients. On the other hand, there is limited experience with antiresorptive drugs in patients after transplants and immunosuppressive treatment [2]. The purpose of this study was to evaluate bone mass after cardiac transplantation and the efficacy of three drugs (calcitonin, bisphosphonates, and calcidiol) in the therapy for bone loss in patients after cardiac transplantation.

Correspondence to: F. Hawkins

Subjects and Methods

We have studied forty patients who underwent cardiac transplantation at our cardiac surgical department between 1991 and 1994, and who voluntarily enrolled in this study. Written informed consent was required from all subjects. The patients were ambulatory, had normal mobilization and diet, and were not taking any other drug known to interfere with calcium metabolism. Men did not exhibit symptoms of hypogonadism, had testes of normal consistency and size (>15 ml) without loss of libido, and therefore a biochemical evaluation of this potential deficit was not performed.

Before cardiac transplantation, thoracic and lumbar spine radiographs, evaluated according to the criteria of Eastell et al. [3], were obtained and were repeated at six month intervals during the study for the diagnosis of vertebral fractures. A new vertebral fracture was reported as an unequivocal fracture of a previously normal vertebra. All patients were treated only after cardiac transplantation with immunosuppression (cyclosporine A, azathioprine, and steroids). Metilprednisolone iv. 500 mg was administered during the operation, followed by 125 mg/8 hours during the following three days.

Oral prednisone was administered subsequently at a dose of 1 mg/kg per day that was lowered to 0.2 mg/kg per day after six weeks. Cyclosporine was scheduled up to 4 mg/kg the first postransplantation day, according to the renal function, to maintain serum levels of this drug between 150 and 250 ng/ml. Oral or iv. azathioprine at a dose of 2 mg/kg was also administered.

Serum and bone measurements were made immediately before the cardiac transplantation and at 6, 12, and 18 months of cardiac transplantation and of treatment. Fasting serum samples were assays for routine biochemical parameters using an automated technique (DAX 72). In addition, intact parathyroid hormone (iPTH, RIA, Nichols Laboratory) and osteocalcin (RIA Henning Laboratory) serum levels were measured.

Bone Mass Measurements

Vertebral bone (L2–L4) mineral density (VMD) was measured by dual X-ray energy absorptiometry (DXA) using a Hologic QDR 1000/w densitometer. Only vertebras shown radiographically to be intact were included in the bone density analysis. The coefficient of variation for this technique was 0.3% in vitro and 1.3% in vivo. Results of VMD were expressed as grams of hydroxyapatite divided by the projected area in square centimeters. The patient's

Table 1. Clinical data of patients with cardiac transplantation studied

	Calcitonin (n = 13)	Na Etidronate (n = 14)	Calcidiol (n = 13)
Age (years)	55.9 ± 1.63	52.7 ± 1.82	51.5 ± 2.87
Sex (men/women)	13/0	14/0	11/2
BMI (Kg/m2)	25.38 ± 0.53	25.58 ± 0.70	24.25 ± 0.70
Duration heart disease (months)	37.55 ± 5.44	40.12 ± 4.39	38.52 ± 5.17
VMD (g/cm2)	0.854 ± 0.069	0.871 ± 0.091	0.905 ± 0.043
Z score	−1.65 ± 0.41[a]	−1.47 ± 0.27[c]	−0.99 ± 0.39[c]
Z score at 6 months	−1.86 ± 0.50[a]	−1.65 ± 0.42[a]	−0.89 ± 0.61 ns
Z score at 12 months	−1.79 ± 0.48[a]	−1.57 ± 0.62[b]	−0.72 ± 0.57 ns
Z score at 18 months	−1.74 ± 0.53[a]	−1.50 ± 0.69[c]	−0.55 ± 0.43 ns

(X ± SE); BMI = body mass index; VMD = vertebral mineral density before treatment
[a] $P < 0.001$; [b] $P < 0.01$; [c] $P < 0.05$

Z-score was calculated as: (p–m)/SD (p = measured patient value; m = mean value for sex- and age-matched controls; SD = standard deviation of the mean value for sex- and age-matched controls). Age- and sex-matched Spanish healthy control groups for the bone studies included 1331 women and 1221 men [4]. Variation of VMD was calculated as follows: % variation = $VMD_2 - VMD_1/VMD1 \times 100$, where VMD_2 and VMD_1 are measurements of the period studied and baseline, respectively. Clinical data for these patients are shown in Table 1. There were no significant differences in age and body weight between studied groups.

Therapy for Bone Loss

Immediately after the cardiac transplantation, patients (38 males and 2 premenopausal women) were randomly distributed in three different treated groups during 18 months. Group I ($n = 13$, mean age 55.9 ± 6.5 SD years) received salmon calcitonin, 100 U/daily by nasal spray; group II ($n = 14$, mean age 52.7 ± 7.2 years) received oral bisphosphonates (sodium etidronate) in intermittent cyclic programs of 400 mg daily during 14 days and repeating this treatment after two and half months; group III ($n = 13$, mean age 51.5 ± 10.7 years) received oral 25 hydroxycholecalciferol (calcifediol) 32,000 UI/weekly. All groups received 1 g daily of elemental calcium p.o. in tablets of calcium gluconate–lactate (2.94 g) and calcium carbonate (0.3 g). Baseline mean VMD in group I (calcitonin) was 0.854 ± 0.177 SD, g/cm^2, in group II (sodium etidronate) 0.871 ± 0.091, and in group III (calcidiol), 0.905 ± 0.115 g/cm^2 without significant intergroup differences (Table 1).

Statistical Analysis

The analysis was performed using unpaired student's *t* test for intergroup comparison and lineal regression analysis was used to assess the association between numeric variables. An analysis of variance for changes in VMD was performed, with time after cardiac transplantation as the independent variable. A *P* value of less than 0.05 was considered significant.

Results

The studied serum biochemical parameters (calcium, phosphorus, alkaline phosphatase, creatinine), osteocalcin, and 24 hours of urinary calcium were within the normal range in all patients before treatment in the three groups studied (Tables 2a, b, and c).

After 18 months of treatment, a decrease ($P < 0.01$) in the calcitonin-treated group and a significant ($P < 0.01$) increase in the other two groups (bisphosphonates and calcidiol) in serum alkaline phosphatase was found. Serum osteocalcin significantly increased at 6, 12, and 18 months in patients without significant intergroup differences. Serum PTH levels were within the normal range in patients throughout the 18 months of the study.

The mean cumulative dosage of prednisone in patients with calcitonin (11,310 ± 1050 SE mg), etidronate (11,908 ± 1336 mg), and calcidiol (11,473 ± 978 mg) was not significantly different among groups.

Basal VMD, expressed as Z-scores (Table 1), was −1.65 ± 0.41 SE in the calcitonin group, −1.47 ± 0.27 in the etidronate group, and −0.99 ± 0.39 in the calcidiol group, which were significantly lower as compared with normal ones ($P < 0.001$, $P < 0.001$, and $P < 0.01$, respectively). Z-score below 2 SD of age- and sex-matched controls, was found before treatment in 12 patients (30%) with cardiac transplantation. There were no significant intergroup VMD differences. According to WHO criteria, 40% of the patients had osteoporosis (*T* below 2.5, SD below the peak of our normal population; 7 patients in the calcitonin group, 3 in the etidronate, and 6 in the calcidiol) and 57.5% had osteopenia (*T* between −1 and −2.5 SD; 6 patients in the calcitonin group, 11 in the etidronate, and 6 in the calcidiol).

After six months of therapy (Fig. 1), a variation of −4.20% and −3.95% in calcitonin- and sodium etidronate-treated patients was found, respectively. In patients with calcidiol treatment a significant ($P < 0.001$) increase of 0.96%, in relation to the other groups, was found.

After 12 and 18 months of treatment, VMD was only significantly increased in patients who were treated with calcidiol. A tendency toward less bone loss was observed after twelve months in the calcitonin and sodium etidronate groups, but only significantly at the end of the study. After 18 months, the amount of bone variation was −1.19% in calcitonin-treated patients vs. −0.19% in etidronate-treated patients and +4.92% in those with calcidiol. Other biochemical data for the treated population at the end of the study are summarized in Table 2a, b, and c. No differences were observed between the studied groups. VMD did not correlate with cumulative total doses of immunosuppressive drugs received, and routine biochemical parameters. No significant linear relationships between VMD and serum osteocalcin levels were found in our study. In addition, VMD was related ($r = 0.26$, $P < 0.05$) to the patient's age in our study, probably because of the severe bone loss and the number of patients included. Rejection frequency or severity was not related to bone mass in the total for each group. Seven patients had vertebral crush fractures during the

Table 2a. Serum biochemical values in patients with calcitonin treatment

	Baseline	6 Months	12 Months	18 Months	Normal range
Calcium (mg/dl)	9.4 ± 0.15	9.57 ± 0.19	9.33 ± 0.15	9.52 ± 0.11	8.4–10.2
Alkaline phosphatase (UI/L)	129 ± 5.16	103.22 ± 6.15[a]	102.55 ± 4.12[a]	106.66 ± 6.91[b]	30–115
Osteocalcin (ng/dl)	5.22 ± 0.85	12.97 ± 1.88[a]	14.24 ± 1.71[a]	14.86 ± 1.52[a]	4.5–6.5
PTH (pg/ml)	41.88 ± 6.21	44.87 ± 5.11	43.77 ± 5.94	49.51 ± 4.79	3–50
Creatinin (g/dl)	1.26 ± 0.09	1.56 ± 0.09[b]	1.72 ± 0.08[a]	1.74 ± 0.09[a]	0.8–1.3
Steroids dosage (mg)		9626.6 ± 1094.04	11085.2 ± 1061.82	11310.7 ± 1049.18	
Cyclosporine dosage (g)		8.13 ± 1.9	15.65 ± 1.82	21.6 ± 3.2	

Table 2b. Serum biochemical values in patients with sodium etidronate treatment

	Baseline	6 Months	12 Months	18 Months
Calcium (mg/dl)	9.15 ± 0.25	9.40 ± 0.23	9.11 ± 0.10	9.13 ± 0.18
Alkaline phosphatase (Ul/L)	71.5 ± 5.30	117 ± 4.35[a]	126 ± 5.45[a]	134.11 ± 4.27[a]
Osteocalcin (ng/dl)	6.38 ± 1.35	11.37 ± 1.30[a]	26.57 ± 6.40[b]	17.6 ± 7.5[a]
PTH (pg/dl)	58.56 ± 8.13	60.42 ± 5.66	51.93 ± 5.03	50.91 ± 9.42
Creatinine (g/dl)	1.14 ± 0.08	1.33 ± 0.10	1.52 ± 0.12[b]	1.71 ± 0.14[a]
Steroids dosage (mg)		10288 ± 1395.89	11474 ± 1260.97	11908 ± 1336.49
Cyclosporine dosage (g)		8.27 ± 1.6	15.88 ± 2.06	21.78 ± 2.8

Table 2c. Serum biochemical values in patients with calcidiol treatment

	Baseline	6 Months	12 Months	18 Months
Calcium (mg/dl)	9.60 ± 0.15	9.59 ± 0.11	9.37 ± 0.17	9.52 ± 0.08
Alkaline phosphatase (Ul/L)	87.5 ± 8.11	113.11 ± 5.6[a]	123 ± 4.34[a]	134 ± 3.14[a]
Osteocalcin (ng/dl)	6.45 ± 1.12	15.14 ± 2.50[b]	19.42 ± 4.05[b]	13.70 ± 1.73[a]
PTH (pg/ml)	41.88 ± 6.21	44.87 ± 5.11	43.77 ± 5.94	49.51 ± 4.79
Creatinine (g/dl)	1.15 ± 0.07	1.57 ± 0.09[b]	1.66 ± 0.09[a]	1.79 ± 0.09[a]
Steroids dosage (mg)		8437.25 ± 1021.03	10848.5 ± 1026.78	11473.5 ± 978.42
Cyclosporine dosage (g)		8.24 ± 1.2	15.72 ± 2.41	22.53 ± 1.98

(X ± SE)
[a] $P < 0.001$ (from baseline)
[b] $P < 0.01$ (from baseline)

study: four belonged to the calcitonin- and three to the etidronate-treated group. None in the calcidiol group had vertebral fractures.

Discussion

Bone disease is a major complication of cardiac transplantation, which is a threat to the future quality of life for these patients [5]. Using DXA, a technique that measures small changes in bone mass with great accuracy [6], we have found a prevalence of 40% for osteoporosis (*T* below 2.5 SD) in our patients with cardiac transplantation, which is similar to the percentage reported by others [7, 8]. We have tried to prevent bone loss in our patients by maintaining adequate dietary calcium intake (1000 mg/daily) and by the use of calcitonin, sodium etidronate, or calcidiol. A control group ingesting calcium supplements alone was not chosen because, excluding severe osteoporosis, oral calcium in patients with adequate diets, as in our study, has been reported to have minimal effects [9]. Patients were receiving chronic steroid therapy, which reduces calcium absorption.

In our study, calcidiol was the most effective in inhibiting bone resorption, the effect of which was observed by bone measurements at six months. It is also possible that the vitamin D effect of increasing calcium intestinal absorption can contribute to this action. Although our patients were not elderly and had normal sunlight exposure and nutritional status, a certain vitamin D deficiency cannot be discounted because we did not measure the serum level of this vitamin.

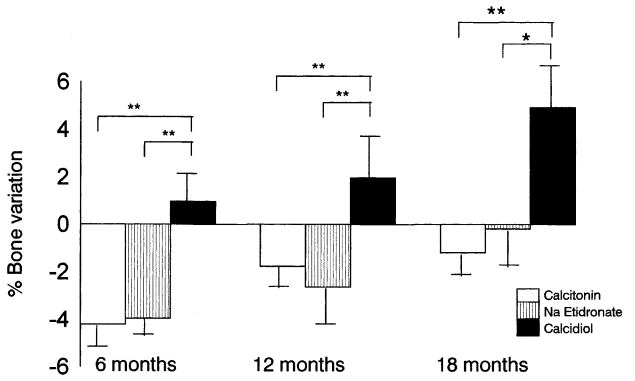

Fig. 1. Observed changes in vertebral mineral density in groups studied during the 18 months of antiresortive therapy. (X ± SE) (*P < 0.05 and **P < 0.001 between groups compared.)

Serum calcidiol levels are only slightly lower in subjects who are more than 70 years old in our medium [10].

Calcitonin and bisphosphonates were also able to prevent bone loss, to a lesser extent, in our study. It is well known that the effect of these antiresorptive drugs is to slow the rates of bone loss [11], but their efficacy in bone disease after cardiac transplantation is still being studied. Salmon calcitonin has been shown to prevent high-turnover osteoporosis in rats treated with cyclosporin A [12] and it has been shown to reduce glucocorticoid-induced bone loss [13] and, therefore, salmon calcitonin has been suggested as a first therapy approach to transplant patients. In our patients, this drug was less effective in preventing bone loss during the 18 months of treatment, although in some patients the analgesic effects in bone pain of vertebral fracture were reported [14]. The effect of calcitonin should probably be reevaluated in these patients, using the 200 UI/d of salmon calcitonin nasal spray that has been recommended for the prevention of early postmenopausal bone loss [15].

Preliminary data also suggest a role for bisphosphonates in osteoporosis posttransplantation. Etidronate has been described as being capable of preventing bone loss in steroid-treated postmenopausal women [16]. The addition of ergocalciferol to cyclical etidronate has been reported to increase bone density in 15 postmenopausal women treated for variable periods of time and variable doses of prednisone [17].

The reasons for using calcidiol and not calcitriol in our study were its lower cost and that previous studies have shown improvement in metabolic and histologic parameters in glucocorticoid-induced osteopenia treated with this drug [18]. In addition, hypercalcemia and hypercalciuria are more frequent when using calcitriol [19]. Calcitriol, used prophylactically with or without calcitonin, has been shown to prevent lumbar bone loss in a group of 103 patients with rheumatic, immunologic, or respiratory diseases treated with a mean daily dose of 13.5 mg of prednisone [20].

One g of calcium and 1000 IU/daily of calcidiol have been described as effective in preventing bone loss in 27 patients with cardiac transplantation followed for two years [21]. Our result shows that the administration of calcidiol at lower doses of 32,000 IU per week is of clear benefit in reducing bone mass loss in cardiac transplantation patients.

Although sodium fluoride has been reported to produce a significant and linear increase in lumbar bone mass that can reach up to 7.8% per year, we feel that it should continue to be considered as experimental, because a decrease in cortical bone was also found [22].

Patients treated with calcidiol did not present vertebral fracture during the study. There were four new vertebral fractures in the calcitonin and three in the bisphosphonates groups, which appeared during the first year of treatment. Therefore, vertebral fractures were present in 17.5% of the patients, which is a frequency lower than that found in patients with cardiac transplantation without antiresorptive drugs (35%) [23]. No clear relationship between VMD and vertebral fractures in our series was found, probably because of the number of patients included as it requires longer studies with an increased number of patients to confirm these findings.

All serum parameters, excluding alkaline phosphatase and osteocalcin, were normal and were not different among the groups studied. The PTH increase, secondary to steroids and diuretic therapy as described by others [24, 25], was not found in our study. Although the immunosuppressor therapy used to achieve fewer graft rejections has significantly increased life expectancy in these patients, the therapy can also contribute to bone loss and remodeling alterations. No predictive factor for osteoporosis was found in our study (age, number of rejection episodes, biochemical parameters including osteocalcin levels). Our findings of persistently elevated serum osteocalcin levels during the 18 months of treatment, agrees with other reports in cardiac [26, 27], liver [28, 29], and renal [30] transplants. High osteocalcin serum levels found in our study could not be related to creatinine clearance because of the fact that its concentrations rise when it is less than 20 ml/min [31], which was not present in our patients. A regression analysis showed that age and cyclosporin doses were the only variable that had influence in creatinine clearance reduction in our patients. It is known that prednisone acts directly in suppressing osteoblast function and in reducing serum levels of osteocalcin, with doses as low as 7.5 mg daily associated with bone loss and with the most rapid demineralization occurring during the first six months of treatment [32]. In patients with cardiac transplantation associated with other risk factors, this accelerated bone loss period has been reported as being earlier; during the first six months [8, 33]. Bone loss induced by glucocorticoids affects trabecular bone to a greater extent than cortical bone, therefore the spine is the preferred site for measuring this damage [34]. Cyclosporine has been also been shown to induce a rapid trabecular bone loss in rats [35], characterized by high turnover [36]. It is possible that cyclosporine may partially counteract the suppressive effect of glucocorticoids on the osteoblast and increase bone formation, as described in renal transplant recipients treated only with this drug [37]. On the other hand, the action of azathioprine upon bone in patients with transplants also included in this protocol is unknown. Low osteocalcin levels and decreased osteoblast activity in rats, which were given only this drug, have been described without short term bone loss [38].

In conclusion, our study evaluates the efficacy of calcitonin, sodium etidronate, and calcidiol combined with daily supplements of 1 g of elemental calcium in the prevention of bone loss in heart transplant patients on immunosuppressive therapy. In this open randomized study we have observed that 32,000 IU per week of calcidiol was the best drug to control bone loss and increasing spinal bone mass during the 18-month treatment period.

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