CLINICAL STUDY

Effects of calcium supplementation on bone loss and fractures in congestive heart failure

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Abstract

Background: Cross-sectional studies have shown that more than 50% of patients with congestive heart failure (CHF) have decreased bone mineral density (BMD). There is limited knowledge about the longitudinal changes of BMD and how to treat bone loss in patients with CHF.

Methods: The present study was a prospective, longitudinal trial in which 33 male patients with CHF (ejection fraction (EF): $30 \pm 11\%$) were assigned to 1000 mg calcium supplementation or no supplementation. BMD was measured at the lumbar spine (LS) and the femoral neck (FN) by dual-energy X-ray absorptiometry at baseline and after 12 months.

Results: Osteopenia (LS 33% and FN 36%) and osteoporosis (LS 15% and FN 6%) were frequently seen in these patients; 70% showed impaired renal function, 42% secondary hyperparathyroidism, and 33% hypogonadism. Bone resorption markers were strongly elevated and correlated negatively with the EF. Patients without calcium supplementation revealed a reduction of BMD (LS 1.7% and FN 1.9%) within 12 months. The fracture incidence was 6%. Patients with calcium supplementation also demonstrated a 6% fracture incidence and a decrease in BMD (LS 1.2% and FN 1.6%), which was not significantly different from the untreated group. Loss of BMD at FN was only seen in patients with impaired renal function.

Conclusions: Patients with CHF demonstrate a progressive decrease in BMD when compared with age-matched healthy individuals. Increased bone resorption due to renal insufficiency with consecutive secondary hyperparathyroidism is a main reason for BMD loss in CHF. Calcium supplementation alone cannot sufficiently prevent the decrease in BMD.

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Introduction

New immunosuppressive regimens have resulted in prolonged survival rates after heart transplantation (HTx; 1). However, rapid bone loss is a major side effect of the lifelong immunosuppression, with a prevalence of vertebral fractures ranging from 18 to 50% (2–5). Atraumatic fractures can reduce long-term quality of life postcardiac transplantation (unpublished data).

So far, knowledge of bone mineral metabolism in patients with congestive heart failure (CHF) awaiting heart transplantation is limited. Cross-sectional studies have demonstrated decreased bone mineral density (BMD) in more than 50% of patients with severe CHF (6–8). Kerschman-Schindl *et al.* have also shown that disturbances of bone metabolism in HTx candidates are probably caused by multiple factors, including impaired renal function, regular intake of loop diuretics, limited mobility, and lack of exposure to sunlight (9). Furthermore, low BMD before transplantation increases the fracture incidence after transplantation

(10). In contrast, a single longitudinal study in patients with mild CHF (left ventricular (LV)-ejection fraction (EF) = $60 \pm 13\%$) found accelerated bone loss only in patients with a vitamin D receptor FF genotype (11).

However, the influence of moderate to severe CHF on the annual bone loss and fracture rate is not known. Moreover, it is unclear whether patients with moderate to severe CHF would benefit from an osteoporosis prophylaxis such as daily calcium supplementation, which leads to reduced bone loss and fracture risk in individuals with normal heart function (12). In contrast, calcium supplementation showed no significant clinical benefit in cardiac transplants (13, 14), which was probably due to a co-administration of high doses of glucocorticoids.

Therefore, the aim of this study was to evaluate firstly the longitudinal changes of bone mineral metabolism in male patients with moderate to severe CHF (EF < 40%) over a period of 12 months, as well as the pathogenesis of bone loss. Secondly, in a randomized prospective 12-month study, we examined how a prophylactic

regimen of daily 1000 mg calcium supplementation versus no supplementation affected the rate of new vertebral fractures as well as changes in bone mineral metabolism.

Methods

Subjects

The study included 40 consecutively enrolled male patients with CHF (New York Heart Association functional classes I–III) and LVEF <40%. All patients were referred to the Department of Cardiology at the Ludwig Maximilians University, Munich for assessment of their heart failure status and/or evaluation of their potential candidacy for heart transplantation. The etiology of CHF (dilated or ischemic cardiomyopathy (CMP)) was confirmed by cardiac catheterization before inclusion in the study. All patients had to be in a stable condition for at least 3 months, with a medication individually optimized according to CHF guidelines (15). Patients were randomized to either 1000 mg elemental calcium supplementation per day or no osteoporosis prevention therapy. Exclusion criteria included disorders known to affect bone and mineral metabolism (e.g., thyrotoxicosis, primary hyperparathyroidism, serum creatinine of more than 2.5 mg/dl, Crohn's disease, and cirrhosis of the liver). Furthermore, patients taking bone-wasting medications other than those necessary for the treatment of CHF were also excluded. Complete data sets after one year were obtained in 33 patients. Seven of the patients had no complete data sets due to death in three, heart transplantation in three, and noncompliance in one. The study was conducted according to the principles of the Declaration of Helsinki and written informed consent for participation was obtained from all subjects.

BMD measurement

BMD of the lumbar spine (LS) and the femoral neck (FN) was measured by dual-energy X-ray absorptiometry using a Lunar Expert-XL bone densitometer (Lunar Inc., Madison, WI, USA) at baseline and after 12 months. The LS measurements represented the average of four vertebrae (L1–L4). BMD was expressed in g/cm² and as standardized *T*- and *Z*-score values. *T*-scores more than 2.5 s.d. below the mean (≤ -2.5) were classified as osteoporosis and *T*-scores between -1.0 and -2.5 s.d. represented osteopenia, in agreement with the WHO criteria, which have been validated for postmenopausal women (16). The *Z*-score is a measurement for the percentage deviation of BMD when compared with an age- and gender-matched healthy control group. Rates of bone loss were expressed as the percentage change in g/cm². BMD measurements were performed and analyzed throughout the whole study by the same

investigator, who was blinded to the osteoporosis therapy. The coefficients of variation

$$CV\% = 100 \left(\frac{S.D.}{\sqrt{2}} \right) \text{mean}$$

at our institution for measurements of BMD were 0.86% (LS) and 0.79% (FN) based on repeated measurements. The least significant change percentage ($1.96 \times CV\%$) is therefore 1.68% at the LS and 1.54% at the FN. Anterior–posterior and lateral radiographs of chest, thoracic and LS were performed to assess the presence of atraumatic fractures. Fractures were classified according to the definitions of the osteoporotic fracture group (17) and included wedge, biconcave and compression deformities. An incident fracture was defined in a blinded manner to treatment as a 20% decrease in any vertebral height when compared with the baseline.

Biochemical analyses

Biochemical analyses were performed on serum/urine samples obtained in the morning after fasting, and on 24-h urine collections at baseline and after 1 year. Serum calcium, protein, albumin, magnesium, phosphate, creatinine, blood urea nitrogen, and alkaline phosphatase were measured using an automated analyzer (Hitachi 917, Boehringer). Testosterone, estradiol, prolactin, gonadotropins, intact parathyroid hormone (iPTH), 25-hydroxy vitamin D, thyroid-stimulating hormone, free triiodothyronine and free thyroxine were measured by immunoradiometric assays. Creatinine clearance from 24-h urine collections was corrected for body surface.

Bone-specific alkaline phosphatase (BAP; Hitachi 917) was measured as a marker of bone formation. Bone resorption markers included measurement of urinary pyridinoline (PYD) and deoxypyridinoline (DPD) by high performance liquid chromatography.

Clinical parameters

Transthoracic echocardiograms were obtained by using a commercially available sector scanner (Sonos 5500, Philips GmbH, Böblingen, Germany) with a 2.5 MHz transducer. Fractional shortening (FS) was calculated as the percentage of systolic fall in left ventricular dimension when compared with end-diastolic diameter. Left ventricular ejection fraction (LVEF) was measured angiographically (Philips Medical Systems, Delft, Holland). Furthermore, all patients underwent an incremental cardiopulmonary exercise test (CPX) on an ergometric bicycle. Respiratory gas analysis was measured using a metabolic cart (Oxycon-alpha, Jaeger, Würzburg, Germany). Peak VO_2 ($\text{VO}_{2\text{ max}}$) was defined as the highest VO_2 observed during the exercise test.

Statistical analyses

All data were expressed as mean $\pm$ s.d. and 95% confidence intervals were calculated. Test statistics were computed using the Wilcoxon test (paired data) and the Mann–Whitney *U*-test (unpaired data). Normal distribution was tested using the Kolmogorov–Smirnov test. For correlation analyses, bivariate Pearson's correlation coefficients were calculated. For all tests, a two-tailed *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using the software package SPSS 13 for Windows NT.

Results

In the study, 33 patients with CHF (NYHA class I/II/III = 21%/70%/9%; mean duration of CHF 3.7 ± 2.6 years) due to dilated cardiomyopathy (dil CMP; $n=22$) or ischemic CMP (isch CMP; $n=11$) were included. The baseline demographic and clinical characteristics of the patients are shown in Table 1.

BMD measurements and radiographic assessment

At baseline, five out of the 33 patients (15%) had six prevalent vertebral fractures documented on the radiographs. Within 12 months, one patient (6%) in the calcium group and one in the control group sustained a new fracture. When compared with the normal population, at baseline, BMD was reduced at the LS (BMD 1.14 ± 0.19 g/cm², *T*-score -0.69 ± 1.62 s.d., *Z*-score -0.83 ± 1.35 s.d.) and the FN (BMD 0.96 ± 0.14 g/cm², *T*-score -0.72 ± 0.97 s.d., *Z*-score -0.15 ± 1.1 s.d.). There was no significant difference between both groups (Table 2). Corresponding to the WHO criteria, 33% of the patients had an osteopenia at the LS and 36% at the FN. Osteoporosis was seen in 15% of the patients at LS and in 3% at FN. BMD decreased significantly in both the control and the treatment group during the 12-month study

Table 1 Baseline demographic and clinical characteristics of the patients.

	No therapy	1000 mg Ca ²⁺ /day
<i>N</i>	16	17
Age (years)	52 $\pm$ 10	51 $\pm$ 9
Dil CMP/isch CMP	10/6	12/5
BMI	27.3 $\pm$ 4.5	28.6 $\pm$ 5.0
NYHA I/II/III (<i>n</i>)	2/12/2	5/11/1
LVEF (%)	28 $\pm$ 10	32 $\pm$ 12
VO _{2 max} (ml/min/kg)	15.9 $\pm$ 6.0	18.1 $\pm$ 3.2
Medication (<i>n</i>)		
Loop diuretics	11 (69%)	12 (71%)
Thiazides	5 (31%)	8 (47%)
Warfarin	11 (69%)	10 (59%)

BMI, body mass index; LVEF, left ventricular ejection fraction; dil CMP, dilated cardiomyopathy; isch CMP, ischemic cardiomyopathy; VO_{2 max}, peak oxygen consumption during spiroergometry.

Table 2 Bone mineral density (BMD) status at baseline.

		No therapy	1000 mg Ca ²⁺ /day	
BMD (g/cm ²)	LS	1.16 $\pm$ 0.23	1.12 $\pm$ 0.15	n.s.
	FN	1.01 $\pm$ 0.12	0.95 $\pm$ 0.13	n.s.
<i>T</i> -score (s.d.)	LS	-0.48 $\pm$ 1.97	-0.88 $\pm$ 1.25	n.s.
	FN	-0.47 $\pm$ 0.90	-0.93 $\pm$ 1.00	n.s.
<i>Z</i> -score (s.d.)	LS	-0.75 $\pm$ 1.44	-0.89 $\pm$ 1.30	n.s.
	FN	0.15 $\pm$ 1.12	-0.26 $\pm$ 0.94	n.s.
Osteopenia (<i>n</i>)	LS	6 (37.5%)	5 (29.4%)	n.s.
	FN	4 (25.0%)	7 (47.1%)	n.s.
Osteoporosis (<i>n</i>)	LS	2 (12.5%)	3 (17.6%)	n.s.
	FN	1 (6.3%)	1 (5.9%)	n.s.

LS, lumbar spine; FN, femoral neck.

period (Fig. 1). There was no significant difference between the groups, although the control group showed a trend towards higher BMD loss. In addition, *Z*-scores decreased showing a further reduction of the BMD when compared with an age- and gender-matched healthy control group.

Bone formation and resorption markers

Markers of bone resorption, DPD and PYD, were strongly elevated at baseline, while the marker of bone formation, BAP, was in a normal range (Table 3) indicating bone loss mainly caused by elevated bone resorption. At baseline, PYD ($r = -0.44$; $P < 0.05$) and DPD ($r = -0.43$; $P = 0.05$) correlated negatively with the LVEF.

Baseline creatinine correlated with the percentage change of DPD ($r = 0.57$; $P < 0.05$) and PYD ($r = 0.61$; $P < 0.05$), and the baseline creatinine clearance correlated negatively with the percentage change of PYD ($r = -0.53$; $P < 0.05$).

Biochemical analyses

Table 4 shows the baseline biochemical analyses. Correspondingly, Table 5 demonstrates the percentage of patients with hypogonadism, lack of 25-OH-VitD, renal insufficiency and hyperparathyroidism in the two groups. At baseline, there was a significantly higher serum creatinine level in the patients without osteoporosis therapy corresponding to a higher frequency of renal insufficiency (75 vs 65%, n.s.). Figure 2 shows the influence of renal function on BMD loss. Total testosterone level was lower in the patients with calcium supplementation (41% hypogonadal patients versus 25% in the control group), but remained constant during the study period (baseline: 427 ± 187 ; after 12 months: 445 ± 195 ng/dl, $P = 0.54$).

After 12 months, the calcium group showed a significant reduction (-12%) in iPTH. In contrast, the control group revealed a further, although nonsignificant, increase ($+28\%$) in iPTH, which correlated negatively ($r = -0.54$; $P < 0.05$) with the BMD loss at LS. After 12 months of calcium administration, a

Figure 1 Percentage change of bone mineral density (BMD) within 12 months; * $P<0.05$, † $P<0.01$. LS, lumbar spine; FN, femoral neck.

secondary hyperparathyroidism was only seen in one patient (6%), whereas the control group revealed an increase of patients (56%) with hyperparathyroidism. Hypercalcemia as well as hypercalciuria were not seen during the study period. Furthermore, at baseline, there was no difference in BMD after checking for hypogonadism, renal insufficiency, secondary hyperparathyroidism or medical therapy, including loop diuretics, thiazides or warfarin.

Clinical parameters

Clinical parameters including body mass index (baseline $28.0 \pm 4.7 \text{ kg/m}^2$; after 12 months $27.9 \pm 4.7 \text{ kg/m}^2$; $P=0.79$), LVEF (baseline $29.4 \pm 10.7\%$; after 12 months $31.4 \pm 11.1\%$; $P=0.18$), FS (baseline 17.7 ± 4.3 ; after 12 months 17.1 ± 5.9 ; $P=0.64$), peak oxygen consumption (baseline 17.0 ± 4.8 ; after 12 months 17.5 ± 5.0 ; $P=0.91$), and NYHA class distribution stayed stable during the study period. The duration of CMF, EF or peak oxygen consumption did not correlate with BMD.

Discussion

Approximately two-thirds of patients with moderate to severe CHF demonstrated a low BMD at the FN and/or LS in this longitudinal study. Osteopenia was seen in 58%

and osteoporosis in 15% of CHF patients. A normal BMD was found in approximately one-third of these patients. These results correspond with cross-sectional studies (6–8), which reported decreased BMD in more than 50% of patients with severe CHF. So far, longitudinal data on bone loss were lacking in this patient group. In the present study, BMD decreased without osteoporosis prophylaxis significantly at the LS (–1.7%) and the FN (–1.9%) within 12 months. A similar reduction in Z-scores shows the age independency of the BMD decrease. The fracture incidence was 6% within 12 months. The decrease in BMD was independent of changes in heart function, body weight, exercise, nutritional behavior and testosterone status, which all remained constant during the study period. Furthermore, BMD did not correlate with the duration and severity of CHF, which was probably the result of multifactorial causes of bone loss and the low number of patients with severe CHF.

These results resemble a cross-sectional study by Christ *et al.* who found the correlation between LVEF and BMD at the FN to be weak (6). Nevertheless, the bone resorption markers PYD and DPD were strongly elevated in patients with moderate to severe CHF and correlated negatively with the LVEF. Despite increased bone resorption, the bone formation marker, BAP, remained within a normal range. These results indicate that accelerated bone loss in CHF patients is caused by increased bone resorption without adequate compensation from bone formation.

Table 3 Bone formation and resorption markers.

Parameter (normals)	No therapy		1000 mg Ca ²⁺ /day		
	Baseline	Percentage change within 12 months	Baseline	Percentage change within 12 months	
BAP (10–80 U/liter)	32.8±26.6	+50.6	25.9±13.1	+57.2	n.s.
PYD (18–24 nmol/mmol Cr)	89.0±18.8	+23.9	107.6±40.9	+4.6	n.s.
DPD (4.5–6 nmol/mmol Cr)	25.1±5.3	+13.9	29.6±10.5	+8.7	n.s.

BAP, bone-specific alkaline phosphatase; PYD, pyridinoline; DPD, deoxypyridinoline.

Table 4 Biochemical analyses at baseline.

Parameter (normals)	No therapy	1000 mg Ca ²⁺ /day	*P<0.05
Calcium (2.1–2.6 mmol/l)	2.3±0.1	2.3±0.1	n.s.
Phosphate (2.5–4.8 mg/dl)	2.9±0.4	2.7±0.7	n.s.
Magnesium (0.65–1.2 mmol/l)	0.8±0.1	0.8±0.2	n.s.
Creatinine (0.5–1.2 mg/dl)	1.4±0.3	1.1±0.2	*
25-OH-VitD (50–300 nmol/l)	114±104	102±45	n.s.
iPTH (10–55 pg/ml)	69±33	50±27	n.s.
Alkaline phosphatase (40–190 u/l)	100±50	94±69	n.s.
Estradiol (15–45 pg/ml)	21±16	16±9	n.s.
Testosterone (350–900 ng/dl)	480±196	379±162	*

iPTH, intact parathyroid hormone.

Impaired renal function might be the major contributor to the increased bone resorption. The data in this study reveal accelerated bone loss only in patients with renal insufficiency, although the degree was mild to moderate. This is in accordance with data by Kerschman-Schindl *et al.* who found an increased bone resorption that was frequently associated with mild renal insufficiency (9). Reichel *et al.* reported that already incipient renal failure triggers a secondary hyperparathyroidism due to disturbed renal calcitriol biosynthesis followed by a vitamin D deficiency (18). In our study, 53% of the patients without osteoporosis prophylaxis showed a secondary hyperparathyroidism at baseline. Within 12 months, the prevalence of secondary hyperparathyroidism increased further and correlated negatively with the BMD loss at LS. Furthermore, loop diuretics (69% of patients) may also have promoted secondary hyperparathyroidism (19).

In addition, a frequent gonadal dysfunction may also indirectly result in the enhanced bone resorption and bone loss. Hypogonadism was found in 33% of the male CHF population in this study despite relatively good physical conditions, which exceeds the normal range of age-associated hypogonadism (20). This data resembles the results of Kontoleon *et al.* who found strongly reduced testosterone levels in patients with moderate to severe heart failure (LVEF 25%) when compared with healthy individuals (21). Estradiol levels remained within the normal range comparable with previous data on HTx candidates (17). The lack of androgens might have resulted in a reduced inhibition control of interleukin-6 (IL-6) transcription, which is followed by an elevated production of the cytokine IL-6. IL-6

Table 5 Baseline frequency (patient number) of hypogonadism, lack of 25-OH-VitD, renal insufficiency, and hyperparathyroidism in the control versus treatment group.

	No therapy	1000 mg Ca ²⁺ /day	
Hypogonadism	4 (25%)	7 (41%)	n.s.
Renal insufficiency	11 (75%)	10 (63%)	n.s.
Lack of 25-OH-VitD	1 (6%)	3 (18%)	n.s.
Hyperparathyroidism	8 (53%)	6 (35%)	n.s.

Figure 2 Percentage change of bone mineral density at femoral neck depends on renal function; *P<0.05, †P<0.01.

stimulates the production of osteoclasts followed by an increase in bone resorption (22). Furthermore, decrease in sex hormones can enhance the sensitivity of skeletal cells to iPTH (23). Therefore, sex hormone replacement therapy might be beneficial for hypogonadal patients with low EF. Moreover, testosterone might improve cardiac output, mood, functional capacity and insulin sensitivity in CHF (24). However, the preferred i.m. injection of testosterone is often contraindicated due to anticoagulation in patients with CHF.

In the study presented in this paper, 64% of patients were treated with warfarin due to a low LVEF. The vitamin K antagonist warfarin reduces the vitamin K-dependent carboxylation of osteocalcin, a noncollagenous protein of the bone matrix, and therefore can cause a decrease in bone formation. This might explain the lack of increased bone formation markers in spite of increased bone resorption. During warfarin therapy, Philip *et al.* found a BMD reduction of 10% in the LS and 9% in the radius (25).

So far, there are no prevention studies of osteoporosis in patients with CHF. In healthy postmenopausal women, a daily supplementation of 1 g elemental calcium could reduce bone loss and reduce fracture risk (12). In our study, patients on treatment with 1 g elemental calcium per day demonstrated a decrease in BMD in the LS and the FN within 12 months. Although the BMD loss seemed to be slightly lower during calcium supplementation, there was no statistically significant difference in BMD loss between the patients with calcium supplementation and the patients without osteoporosis prophylaxis. Fracture incidence of 6% was also similar to the untreated group. In contrast, calcium supplementation significantly reduced the frequency of secondary hyperparathyroidism within 12 months. A reduced iPTH should result in a decrease in bone resorption. However, bone resorption markers remained markedly elevated during calcium supplementation, although there was a greater increase in bone resorption markers in the control group.

In conclusion, patients with CHF demonstrate a progressive decrease in BMD due to increased bone resorption. Renal insufficiency followed by secondary hyperparathyroidism appears to be the main reason for the enhanced bone resorption. In addition, other risk factors for osteoporosis such as hypogonadism, decreased physical activity, smoking, vitamin D deficiency and therapy with anticoagulants and/or loop diuretics may play a role. A routine screening for osteoporosis, including BMD measurement and determination of renal function, iPTH and sex hormone status, should be recommended in patients with moderate to severe CHF. Calcium supplementation alone can reduce the frequency of secondary hyperparathyroidism, but it is not sufficient to prevent the decrease in BMD within 12 months. Therefore, antiresorptive therapy such as vitamin D metabolites and/or bisphosphonates might be indicated in patients with CHF and low BMD, especially in patients awaiting heart transplantation, which is associated with post-transplantation osteoporosis (2–5). Lastly, sex hormone replacement therapy in hypogonadal patients might have an additional positive effect on bone mineral density.

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