Relationship between various measures of bone mineral density and the prevalence of vertebral fractures in cardiac transplant recipients


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Summary

Background: The incidence rates of osteoporosis and fractures are increased after cardiac transplantation.

Methods: We performed a cross-sectional analysis of cardiac transplant recipients in a late post-transplantation period (4.4 \[2.5\] years after cardiac transplantation, n = 27). We measured bone mineral density (BMD) by DXA at the hip and lumbar spine and by quantitative ultrasound (QUS) at the calcaneus. Vertebral fracture (vfx) prevalence was analysed by anterior-posterior and lateral radiographs of the thoracic and lumbar spine.

Results: Overall, vfx were present in 13 of 27 patients (48.2\%, n = 51 vfx). Vfx were observed in 1 out of 5 patients with normal DXA results, 7 out of 14 osteopenic and 5 out of 8 osteoporotic cardiac transplant recipients. BMD at the femoral neck and more prominently at Ward’s triangle were significantly lower in vfx patients compared to patients without vfx, with adjusted mean values (95\% CI) of 0.804 [0.750–0.859] vs 0.915 [0.860–0.969] g/cm² and 0.573 [0.501–0.646] vs 0.766 [0.697–0.836] g/cm², respectively.

Conclusions: These findings suggest an association between DXA measurements of the hip with vertebral fractures in a late post-transplantation period and thus extend knowledge from previous reports on cardiac transplant recipients studied earlier after CTX. In particular, our data pinpoint a potentially interesting role for BMD at Ward’s triangle.

Key words: post-transplantation bone disease; osteodensitometry; quantitative heel ultrasound; bone turnover marker; osteoporosis

Introduction

Osteoporosis is a frequent complication after cardiac transplantation (CTX) [1]. The patients’ quality of life may be reduced substantially by osteoporotic fracture and pain. Vfx are most frequent whereas only few fractures involve the ribs [2–4]. The pathogenesis of post-transplantation bone disease is multifactorial. Glucocorticosteroids [5] and cyclosporine A (CyA) [6], which are both associated with loss of bone mineral density (BMD), are used in most cardiac transplant recipients [7, 8]. Moreover, renal impairment and 25-OH-Vitamin D₃ deficiency is a significant problem in many of these patients [9].

The prediction of an increase in osteoporotic fracture incidence with decreasing T scores is clearly demonstrated in men [10], postmenopausal women [11] and perimenopausal women [12]. There is an ongoing debate concerning an altered BMD threshold for osteoporotic fractures in glu-
cocorticosteroid-induced osteoporosis [13] and a direct fracture inducing effect independent of BMD has been postulated [14]. In this context the issue arises as to whether there is also a relationship between low BMD and increased prevalence of fractures in post-transplantation bone disease. In fact, there are limitations to the reliable prediction of fracture risk in post-transplantation bone disease [15].

Recently, QUS parameters (i.e. broad band ultrasonic attenuation [BUA], speed of sound [SOS] and quantitative ultrasound index [QUI/stiffness]) have been shown to be useful as predictors of hip fractures in postmenopausal women [16, 17]. It is suspected that QUS parameters reflect bone strength in a different manner than DXA [18]. Although there is a positive correlation between QUS and DXA [19], discordance in patient classification using T scores of different bone densitometry devices and measurement sites may make the clinical application in an individual patient difficult [20, 21]. However, the question as to whether QUS better identifies individual cardiac transplant recipients with vertebral fractures than DXA has not yet been addressed.

The aim of our study was to describe the prevalence of vfx in cardiac transplant recipients in a late post-transplantation period. Furthermore, we analysed the BMD status of these patients using DXA and QUS and tested the hypothesis that patients with prevalent vfx have lower BMD and QUS values compared to those without prevalent vfx. In addition, we investigated markers of bone turnover in cardiac transplant recipients with and without vfx.

Material and methods

Study design

We enrolled all cardiac transplant recipients at our institution in a cross-sectional study between November 1999 and March 2000. The patients were in a late post-transplantation period (4.4 [±2.5] years after CTX, n = 27; 21 males, 6 females), which allowed us to investigate a cohort that had already experienced a considerable number of vfx. The diagnoses leading to cardiac transplantation were ischaemic heart disease (n = 13) followed by idiopathic dilated cardiomyopathy (n = 10), systemic lupus erythematosus with severe cardiac involvement (n = 1; this patient also received kidney transplant due to autoimmune renal disease), late heart failure following mitral valve reparation (n = 1), heart failure due to severe congenital renal disease), late heart failure following mitral valve reparation (n = 1), heart failure due to severe congenital atrial septal defect ostium secundum type (n = 1) and dilated cardiomyopathy due to suspected myocarditis (n = 1).

To analyse the characteristics associated with the presence of vfx in cardiac transplant recipients we subdivided the patients into a group with vfx (≥vfx) and a group without vfx (≤vfx).

Therapy

In the first year after CTX all patients received a triple therapy, which consisted of prednisolone, CyA and azathioprine. Thereafter, based on a clinical decision, we switched 12 of our patients with optimal and stable myocardial biopsy results (≤ 1B International Society for Heart Transplantation [ISHT] Standardized Grading System) [22] to mycophenolate mofetil and CyA, discontinued azathioprine and tapered off prednisolone. Overall our patients received a cumulative prednisolone dose of 11.97 (5.79) g (mean [SD]; minimum 3.90, maximum 20.42) from CTX until patient evaluation.

There were no acute severe late rejections (≥ 1B ISHT) in either group and endomyocardial biopsies demonstrated absence of clinically relevant chronic rejection requiring high-dose methylprednisolone. Bone protective therapy was not routine until this investigation was started. No patient received such therapy previously. After collecting the data for the present study we instituted adequate therapy with calcium, vitamin D 3 (or the activated 1.25 formulation if renal function was impaired) and bisphosphonates if a prevalent vfx was detected and/or DXA T score at the lumbar spine or femoral neck was lower than –1.5. Postmenopausal women (n = 5) did not receive sex hormone replacement therapy and hypogonadism was ruled out biochemically in male patients and one premenopausal woman (the latter also reported regular menstrual bleeding).

BMD measurements and radiographic assessment

We analysed bone mineral density using dual-energy X-ray absorptiometry (DXA Lunar Prodigy, Lunar Corp., Madison, WI 53717 USA). Anterior-posterior lumbar spine measurements represented the average of four vertebrae (L1 to L4). Readings from fractured vertebrae were excluded from the DXA results. BMD was expressed as grams per square centimetre (g/cm²) and as standardized T score value. T scores 2.5 or more standard deviations (SD) below the mean were classified as osteoporosis and T scores between –1.0 and –2.5 SD as osteopenia according to WHO criteria [23].

Furthermore, we performed QUS at the calcaneus (Sahara, Hologic Inc., Waltham, MA 02451, USA) to assess fracture risk. BUA and SOS measurements were carried out. Additionally, QUI/Stiffness, estimated bone mineral density (est. BMD) and T scores were calculated by the ultrasound device.

Anterior-posterior and lateral radiographs of the chest, the thoracic and the lumbar spine were performed so that we could assess the presence of fractures. We classified fractures by combining a semi-quantitative with a quantitative morphometric approach as described previously [24, 25]. For the latter a vertebral fracture was defined as a 20% or greater reduction of at least 4 mm in any vertebral height in any vertebra from T4-L4.

Biochemical analysis

As bone resorption markers, serum β-CrossLaps (Elecsys®, 2010 Systems, Roche Diagnostics GmbH, D-68298 Mannheim, Germany) and urinary N-telopeptide NTx (Osteomark®, NTx, Ostex International Inc., Seattle, WA 98134 USA) were determined. To assess bone formation activity we measured bone specific alkaline phosphatase (Access®, Ostase®, Beckmann Coulter, INC., Fullerton, CA 92834-3100 USA). Serum creatinine, alkaline phosphatase, calcium and phosphate were analysedpen with the Hitachi 717 System (distributed by Boehringer Mannheim, D-68159 Mannheim, Germany). Calcitriol (DiaSorin, Stillwater, Minnesota 55082-0285, USA), 25-OH-Vitamin D3 (Immunodiagnostic System
Limited, Tyne and Wear, NE35 9PD, United Kingdom) and intact parathyroid hormone (iPTH; Nichols Institute Diagnostics, San Juan Capistrano, CA 92675, USA) were determined using routine techniques.

Statistical analysis

Data are expressed as mean (standard deviation) if not otherwise stated. Differences between patients without vfx and patients with vfx were tested for significance with the Mann-Whitney U test. Furthermore, we adjusted for the covariates age, gender, body mass index, time since CTX, creatinine clearance and cumulative glucocorticosteroid dose by analysis of covariance (ANCOVA). The main results are described by adjusted means together with the respective 95% confidence intervals. For correlation analysis, bivariate Spearman-Rho correlation coefficients were calculated. A two-tailed p value of less than 0.05 was considered statistically significant for all tests. All statistical analyses were performed with the software package SPSS 11.0 for Windows.

Results

Table 1 describes the clinical characteristics of our patients. There was no significant difference between patients with and without vertebral fractures regarding age, body mass index (BMI), gender and medication at the time of data acquisition (table 1 and 2).

Table 3 summarizes the biochemical parameters of renal function and calcium/phosphate metabolism. There were no significant differences between the two groups. Modest reduction of creatinine clearance was seen only in a few patients in both groups. Parathyroid hormone (iPTH) levels were borderline or moderately elevated in only a few patients in both groups with no significant difference between groups. 6 out of 14 patients of group –vfx showed elevated iPTH levels (highest iPTH value: 120 ng/L; reference range 10–65 ng/L), whereas 2 out of 13 patients of group +vfx exhibited iPTH levels above the reference range (highest iPTH value: 96 ng/L). As is known from the general population [26] 25-OH-Vitamin D deficiency was also common in our cardiac transplant recipients. Six patients in group –vfx and three patients in group +vfx had 25-OH-Vitamin D levels lower than 37.5 nmol/L. Mean levels of 25-OH-Vitamin D and Calcitriol (1,25-OH-Vitamin D) were not significantly different in either group (table 3).

Overall, osteopenia (lumbar and/or femoral neck DXA T score < –1 SD) was frequent (51.9%) in our cardiac transplant recipients and 29.6% had osteoporosis as defined by a lumbar and/or femoral neck DXA T score ≤ –2.5 SD. Only 18.5% of our patients had BMD within the reference range of healthy young adults.

Vfx were present in 13 of 27 patients (48.2%, n = 51 vfx) and many patients had multiple fractures (table 1). None of the CTX patients were aware of a vfx, however, 9 patients reported some increase in back pain since CTX. Vfx were observed in 1 out of 5 cardiac transplant recipients (20%) with normal DXA results, 7 out of 14 (50%)
osteopenic and 5 out of 8 (63%) osteoporotic patients. No fractures of the hip, the ribs or the radius were observed.

BMD of femoral neck exhibited a strong positive correlation with BMD of Ward’s triangle (rs = 0.872). It correlated less strongly but also statistically significantly with all QUS parameters measured in our investigation (SOS rs = 0.520; BUA rs = 0.593; QUI/Stiffness rs = 0.555).

The QUS parameters, DXA at lumbar spine (table 4) and bone turnover markers (table 5) were not significantly different between patients with and without vfx. However, BMD and corresponding T scores of Ward’s triangle and femoral neck were significantly lower in patients with vfx than in patients without vfx (table 4). Analysis of co-variance confirmed a significant association between vfx and BMD both at Ward’s triangle and at the femoral neck after adjustment for age, gender, body mass index, time since CTX, creatinine clearance, and cumulative glucocorticosteroid dose. Adjusted mean values of BMD (95% CI) for patients with and without vfx were 0.573 (0.501–0.646) vs 0.766 (0.697–0.836) g/cm² at Ward’s triangle and 0.804 (0.750–0.859) vs 0.915 (0.860–0.969) g/cm² at the femoral neck, respectively.

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>−vfx (n = 14)</th>
<th>+vfx (n = 13)</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.41 (0.12)</td>
<td>2.44 (0.07)</td>
<td>2.02–2.60</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>1.16 (0.15)</td>
<td>1.23 (0.19)</td>
<td>0.87–1.45</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>132.6 (26.5)</td>
<td>130.0 (24.8)</td>
<td>70.7–106.1</td>
</tr>
<tr>
<td>Creatinine Clearance (ml/s)</td>
<td>1.30 (0.53)</td>
<td>1.35 (0.60)</td>
<td>1.25–2.08</td>
</tr>
<tr>
<td>iPTH* (ng/L)</td>
<td>62.2 (24.9)</td>
<td>52.2 (20.1)</td>
<td>10–65</td>
</tr>
<tr>
<td>Calcitriol (pmol/L)</td>
<td>80.0 (20.0)</td>
<td>75.2 (22.9)</td>
<td>38–134</td>
</tr>
<tr>
<td>25-OH-Vitamin D₃ (nmol/L)</td>
<td>45.0 (34.2)</td>
<td>55.2 (37.7)</td>
<td>20–100</td>
</tr>
</tbody>
</table>

* Intact parathyroid hormone (iPTH); data are shown as means; standard deviations are given in parentheses; vfx = vertebral fractures; −vfx: patients without vertebral fractures; +vfx: patients with vertebral fractures.

### Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>−vfx (n = 14)</th>
<th>+vfx (n = 13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine (BMD, g/cm²)</td>
<td>1.082 (0.196)</td>
<td>1.012 (0.149)</td>
<td>0.307</td>
</tr>
<tr>
<td>Lumbar spine (T score)</td>
<td>−1.157 (1.743)</td>
<td>−1.179 (1.124)</td>
<td>0.317</td>
</tr>
<tr>
<td>Ward’s triangle, right (BMD, g/cm²)</td>
<td>0.754 (0.119)</td>
<td>0.587 (0.102)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ward’s triangle, right (T score)</td>
<td>−1.464 (0.926)</td>
<td>−2.792 (0.791)</td>
<td>0.001</td>
</tr>
<tr>
<td>Femoral neck, right (BMD, g/cm²)</td>
<td>0.903 (0.091)</td>
<td>0.816 (0.093)</td>
<td>0.023</td>
</tr>
<tr>
<td>Femoral neck, right (T score)</td>
<td>−1.092 (0.779)</td>
<td>−1.823 (0.722)</td>
<td>0.021</td>
</tr>
<tr>
<td>Quantitative Ultrasound (est. BMD)</td>
<td>0.481 (0.188)</td>
<td>0.443 (0.101)</td>
<td>0.524</td>
</tr>
<tr>
<td>Quantitative Ultrasound (T score)</td>
<td>−0.9 (1.7)</td>
<td>−1.2 (0.9)</td>
<td>0.518</td>
</tr>
<tr>
<td>Quantitative Ultrasound (SOS)</td>
<td>1540.7 (47.5)</td>
<td>1529.4 (21.5)</td>
<td>0.445</td>
</tr>
<tr>
<td>Quantitative Ultrasound (BUA)</td>
<td>71.7 (24.7)</td>
<td>63.6 (18.8)</td>
<td>0.356</td>
</tr>
<tr>
<td>Quantitative Ultrasound (QUI/Stiffness)</td>
<td>88.2 (29.8)</td>
<td>82.1 (15.9)</td>
<td>0.524</td>
</tr>
</tbody>
</table>

Data are shown as means; standard deviations are given in parentheses; vfx = vertebral fractures; −vfx: patients without vertebral fractures; +vfx: patients with vertebral fractures. We tested for statistical difference by applying the Mann-Whitney U test.

### Table 5

<table>
<thead>
<tr>
<th>Parameter</th>
<th>−vfx (n = 14)</th>
<th>+vfx (n = 13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum β-CrossLaps (pg/ml)*</td>
<td>588.4 (302.0)</td>
<td>557.1 (271.9)</td>
<td>0.780</td>
</tr>
<tr>
<td>Urinary NTx (µmol/mmol creatinine)</td>
<td>40.5 (15.7)</td>
<td>42.1 (18.6)</td>
<td>0.828</td>
</tr>
<tr>
<td>BSAP (µg/L)#</td>
<td>12.5 (4.7)</td>
<td>13.9 (5.0)</td>
<td>0.538</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>126.9 (63.8)</td>
<td>117.2 (24.0)</td>
<td>0.605</td>
</tr>
</tbody>
</table>

* 30–50 years old male healthy probands, (reference range for 50–70 years old male healthy probands: 70–710; premenopausal women: <573; postmenopausal women: <1008); # BSAP – bone specific alkaline phosphatase; data are shown as means; standard deviations are given in parentheses; vfx = vertebral fractures; −vfx: patients without vertebral fractures; +vfx: patients with vertebral fractures. None of the differences between the groups (−vfx vs. +vfx) was statistically significant. However, due to the sample size a nonsignificant p value does not necessarily indicate that there is no clinically relevant difference between the groups.
BMD at the femoral neck and at Ward’s triangle measured by DXA was significantly lower in those cardiac transplant recipients who had already suffered vertebral fractures. However, DXA results in the lumbar spine were not significantly different between patients with and without vfx, although we could observe a trend towards lower BMD in the group who had already sustained vfx. This is surprising because we assumed that the lowest BMD would provide the best discrimination between patients with vfx and those without vfx at the site of the fracture, i.e. lumbar spine [27, 28]. The concept of site-specific risk assessment did not apply in our patients. We excluded fractured vertebrae from the analyses. However an increase in BMD through microfractures resulting in a non-significant vertebral height reduction may be a possible explanation for this finding, as may confounding factors such as moderate atherosclerosis of the abdominal aorta, osteoarthritis of the spine and spinal osteophytosis [29].

Detecting patients at high risk for vfx is an important issue. However there is considerable overlap between BMD levels of patients with and without vertebral fractures as measured by DXA. Our data confirm previous reports [30], which found that vfx could occur even before DXA shows osteoporosis in CTX patients. The pathophysiology of this fact is not well understood. A complex interaction of osteoporosis risk factors appears to be important in this context [30]. High cumulative doses of glucocorticosteroids used in the treatment of CTX patients probably play a key role. Similar observations are reported in patient groups receiving glucocorticosteroids for other diseases [31].

The analyses of quantitative ultrasound parameters showed a very small non-significant trend towards lower BUA and SOS in the group with vfx compared to the group without vfx. QUS studies show a good correlation with femoral neck BMD [16] and fracture prediction in other populations [19]. Generally, QUS values exhibit smaller reductions of estimated BMD in patients with osteoporosis both in a cross-sectional and in a longitudinal analysis. This could explain why we did not find lower QUS parameters in patients with vfx. In our patient cohort of cardiac transplant recipients QUS did not provide additional information on bone quality nor improve characterization of fracture status. This is consistent with results in an otherwise healthy female population with and without vfx [32].

Bone turnover markers were shown to reflect risk of fragility fractures in different patient groups [33]. However, in our setting of CTX patients bone turnover markers did not reliably help characterize patients with vfx.

We treated 12 (44.4%) of the 27 patients with glucocorticosteroid-free immunosuppression. This endorses published data [34] that a considerable number of cardiac transplant recipients can safely be treated without glucocorticosteroids. Although the glucocorticosteroid doses were kept at a minimum, as many as half of the cardiac transplant recipients without bone protective therapy had suffered one or multiple vertebral fractures by the late post-transplantation period. This impelled us to implement osteologic surveillance into the management of cardiac transplant recipients, starting at the listing for transplantation. Preventive measures including drug therapy should be initiated.

The main limitation of our analysis is the cross-sectional study design and the small cohort, a problem inherent in many studies of cardiac transplant recipients. A statistically non-significant difference between the groups does not necessarily indicate that there is no relevant difference at all. Thus, our findings should be confirmed in larger patient groups.

On the other hand our data are strengthened by data acquisition before osteoprotective therapy was instituted. This eliminates the influence of bone protective therapy on the incidence of vfx and makes it possible to study the “natural course” of post-transplantation bone disease until a late post-transplantation period. Furthermore, selection bias was minimized by inclusion of all patients treated at our institution.

Our findings suggest a significant association between DXA measurements of the hip and vertebral fractures in a late post-transplantation period and thus extend knowledge from previous reports on cardiac transplant recipients studied earlier after CTX. In particular, our data point out a potentially interesting role for BMD at Ward’s triangle. The high frequency of osteoporotic fractures in cardiac transplant recipients impels high clinical alertness and preventive measures.

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