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**Original Article**

# Ethnic Differences in Osteoporosis After Cardiac Transplantation

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## Abstract

Cardiac transplantation is associated with a high risk of fracture. African Americans (AAs) are believed to have a lower risk of osteoporosis than Caucasians, but it is not clear whether they are also protected from osteoporosis resulting from the use of glucocorticoids and/or organ transplantation. We examined possible ethnic differences in 33 cardiac transplant recipients (16 AAs) in a cross-sectional analysis. In addition to bone mineral density and vertebral fracture assessment, we also compared biochemical variables, trabecular bone score, total body dual-energy X-ray absorptiometry, and disability. Overall fracture rates were low in both groups, with only 6 total subjects with fractures on vertebral fracture assessment or history of fracture. While *T*-scores were similar between groups, *Z*-scores were lower in AA with the difference reaching statistical significance when controlling for important covariates. The trabecular bone score was also lower in AAs than in Caucasians even when adjusting for age and tissue thickness ($1.198 \pm 0.140$ vs $1.312 \pm 0.140$, $p = 0.03$).

While AAs are generally thought to be protected from osteoporosis, our study instead suggests that AAs may be at higher risk of bone deterioration after cardiac transplantation and may need to be managed more aggressively than suggested by current guidelines.

**Key Words:** African Americans; cardiac transplantation; ethnic differences; secondary osteoporosis.

## Background

Osteoporosis and fractures are common after cardiac transplantation. Previous studies have demonstrated vertebral fracture rates of 18%–35% in the first 3 yr after solid organ transplantation *(1)*. Most studies have focused on the initial period following transplantation, but, due to improvements in transplant programs and immunosuppressive medications, many cardiac transplant recipients are living longer. However, the risk of osteoporosis and fractures beyond the early post-transplantation period is not clear.

The pathogenesis of post-transplant osteoporosis is related to the effects of both glucocorticoids (GCs) and calcineurin inhibitors, such as cyclosporin or tacrolimus. These effects may not be the same in different ethnicities. African Americans (AAs) have lower bone turnover than Caucasians (CAs) *(2,3)*, and, although lower bone turnover may be protective against postmenopausal osteoporosis, it may make patients more vulnerable to the effects of GCs, which increase osteocyte apoptosis and decrease osteoblasts *(4)*. We previously reported that in 77 patients with a history of GC use, the probability of vertebral fracture was higher in AA than in CA women after adjusting for age, bone mineral density (BMD), or cumulative GC dose *(5)*. Other studies have shown that AAs have slower clearance of methylprednisolone and are at higher risk of GC-induced diabetes than CA *(6,7)*—positing the idea that AAs are at higher risk of the adverse effects of GCs overall.

Although BMD declines after transplantation, many patients fracture at higher BMD levels than in postmenopausal osteoporosis. This finding could be related to deterioration in bone quality or structure not assessed by BMD. Trabecular bone score (TBS), a textural analysis of the lumbar spine dual-energy X-ray absorptiometry image, provides an indirect measure of trabecular microarchitecture *(8)* and may be valuable in assessing fracture risk after transplantation. In addition, extraskeletal factors, such as frailty,

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disability, and decreased physical activity, may also contribute to fractures. Therefore, assessment of disability and physical activity may also be useful in global fracture risk assessment. Ethnic differences in these non-BMD factors may nonetheless contribute to differences in fracture rates and also deserve further investigation.

To study possible ethnic differences in the above parameters, we recruited AA and CA patients who had undergone cardiac transplantation and examined not only clinical risk factors, biochemical variables, and BMD, but also TBS, disability, physical activity, and body composition.

## Methods

### *Study Population*

The University of Chicago's cardiac transplant clinic maintains a cardiac transplant registry. All ambulatory patients over the age of 20 who had cardiac transplantation at the University of Chicago at least 6 mo prior to the study were invited to participate in the study. Both men and women were eligible. Exclusion criteria included use of GC prior to cardiac transplantation, end-stage renal disease, being off prednisone, and being nonambulatory. Study personnel contacted all 147 living patients in the registry. Of the 147 patients, 34 did not qualify as they were not being treated with prednisone. Of the remaining 113 patients, 44 agreed to participate, 33 completed the study, and 11 were not enrolled due to the following: not completing the requirement of the study (5 patients), not meeting the inclusion criteria (3 patients), development of a new malignancy (2 patients), and death prior to completing the study (1 patient). Compared to the 44 subjects who consented to the study, the 61 subjects who declined participation were significantly less likely to be AA (24.6% vs 45%, $p = 0.03$). The time since transplantation was not significantly different in those who declined ($4.4 \pm 3.4$ yr vs $4.1 \pm 3.9$ yr, $p = 0.66$). The University of Chicago's Institutional Review Board approved the study, and all patients signed a written informed consent.

### *Procedures*

All subjects completed a questionnaire regarding medical history, personal and family history of fractures, medication use (such as bisphosphonates [BSPs], diuretics, and immunosuppressants), young adult height, alcohol use, smoking, and activity level. The subjects were also questioned about histories of diseases of the liver, thyroid, or kidneys; digestive disease; an eating disorder; rheumatoid arthritis; or diabetes mellitus. Information was supplemented by using the patient's electronic medical record. The patients' total GC use since the time of transplantation was determined through a chart review. One patient's total GC use was not calculable due to poor follow-up. In addition, all patients completed the Stanford 7-day Physical Activity Recall *(9)* and a calcium intake questionnaire.

Height and weight were measured using standard clinic equipment. BMD was measured at the lumbar spine, proximal femur, and calcaneus. For the lumbar spine, we used L1–L4 with exclusion of artifact-laden vertebrae as recommended by the International Society for Clinical Densitometry *(10)*. For the proximal femur, we used the femoral neck (FN) and total hip (TH). *T*-scores in all ethnicities were calculated using the white (CA) database. *Z*-scores were calculated using an age-, gender-, weight-, and ethnicity-matched normative database. Central BMD, body composition, and vertebral fracture assessment (VFA) were obtained using Prodigy (GE Medical Systems, Madison, WI, USA). Body fat and lean percentage were calculated by dividing total fat and lean mass, respectively, by total tissue mass.

TBS measurements were performed in the Bone Disease Unit at the University of Lausanne, Lausanne, Switzerland (TBS iNsight® Software version 2.1; Med-Imaps, Pessac, France), using anonymized spine dual-energy X-ray absorptiometry files from the University of Chicago to ensure blinding of the Swiss investigators to all clinical parameters and outcomes. The software uses the anteroposterior spine raw image(s) from the densitometer, including the BMD region of interest and edge detection, so that the TBS calculation is performed over exactly the same region of interest as the BMD measurement. In the current analysis, we used a research version of the commercialized TBS iNsight software (Med-Imaps) that allows for batched analyses from a workstation. Tissue thickness is a variable generated by the TBS program, which captures the thickness of soft tissue in the window where TBS is measured.

Patients had fasting blood sample and 24-h urine collected for biochemical measurements as shown in Table 2. All biochemical analyses were performed in the clinical laboratory of the University of Chicago.

### *Statistical Analyses*

All analyses were performed using STATA 13 (StataCorp, College Station, TX, USA). Differences between the AA and CA patients were assessed using *t*-test for continuous variables and chi-squared or Fisher's exact test, where appropriate, for categorical variables. We used linear regression analysis to examine the relationship between BMD *Z*-scores or TBS and ethnicity while controlling for covariates such as family history, smoking history, self-reported physical activity (metabolic equivalent [MET] per day), and cumulative prednisone exposure. We also used linear regression to examine relationships between disability index, body composition, physical activity, and cumulative prednisone exposure.

## Results

### *Patient Characteristics*

There were 17 CA and 16 AA participants. The etiologies of the patients' CHF were idiopathic in 15, ischemic in 12, pregnancy-related in 2, valvular disease in 2, viral