Journal of Clinical Densitometry: Assessment & Management of Musculoskeletal Health, vol. ■, no. ■, 1–8, 2017

1094-6950/■:1–8/$36.00
https://doi.org/10.1016/j.jocd.2017.11.003

Bone Mineral Density of the Radius Predicts All-Cause Mortality in Patients With Type 2 Diabetes: Diabetes Heart Study

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Abstract

This study aimed to determine the association between areal and volumetric bone mineral density (BMD) with all-cause mortality in patients with type 2 diabetes (T2D). Associations between BMD and all-cause mortality were examined in 576 women and 517 men with T2D in the Diabetes Heart Study. Volumetric BMD in the thoracic and lumbar spine was measured with quantitative computed tomography. Areal BMD (aBMD) in the lumbar spine, total hip, femoral neck, ultradistal radius, mid radius, and whole body was measured using dual X-ray absorptiometry. Association of BMD with all-cause mortality was determined using sequential models, stratified by sex: (1) unadjusted; (2) adjusted for age, race, smoking, alcohol, estrogen use; (3) model 2 plus history of cardiovascular disease, hypertension, and coronary artery calcification; (4) model 3 plus lean mass; and (5) model 3 plus fat mass. At baseline, mean age was 61.2 years for women and 62.7 years for men. At mean 11.0 ± 3.7 years' follow-up, 221 (36.4%) women and 238 (43.6%) men were deceased. In women, BMD at all skeletal sites (except spine aBMD and whole body aBMD) was inversely associated with all-cause mortality in the unadjusted model. These associations remained significant in the mid radius (hazard ratio per standard deviation = 0.79; $p = 0.0057$) and distal radius (hazard ratio per standard deviation = 0.76; $p = 0.0056$) after adjusting for all covariates, including lean mass. In men, volumetric BMD measurements but not aBMD were inversely associated with mortality and only in the unadjusted model. In this longitudinal study, lower baseline aBMD in the radius was associated with increased all-cause mortality in women with T2D, but not men, independent of other risk factors for death.

Key Words: Bone mineral density; dual X-ray absorptiometry; mortality; quantitative computed tomography; type 2 diabetes.

Introduction

Low bone mineral density (BMD) has been shown to predict all-cause mortality in many populations *(1–20)*. In a meta-analysis of 10 studies containing 46,182 participants and 3991 deaths, Qu et al *(21)* reported a 1.17-fold increase in mortality per standard deviation (SD) decrease in BMD. Most of these studies used dual X-ray

Received 07/21/17; Revised 11/9/17; Accepted 11/16/17.
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absorptiometry (DXA)-measured areal BMD (aBMD). A recent report detected inverse relationships between computed tomography (CT) measures of bone density and mortality in 3673 participants in a lung cancer screening trial *(22)*. However, that study did not use a calibration phantom and reported bone density in Hounsfield units, rather than mg/cm^3. Prior studies have not used traditional, phantom-based QCT to determine the association of mortality with volumetric BMD (vBMD).

Osteoporosis and type 2 diabetes mellitus (T2D) are common in older adults. Both conditions have high morbidity and mortality, are increasing in incidence in most developed countries, and commonly coexist. The risk of mortality after hip fracture is increased in patients with T2D *(23–25)*. The proportion of mortality risk in patients with T2D attributable to osteopenia or osteoporosis is difficult to determine. Evidence that patients with T2D fracture at a higher aBMD than non-diabetics suggests that the relative contribution of BMD to mortality may be different in patients with T2D. Although some studies have included participants with T2D, no prior longitudinal study of T2D has evaluated the association of mortality and BMD.

The Diabetes Heart Study (DHS) is one of the largest studies of T2D that includes QCT-derived vBMD measurements in the thoracic and lumbar spine, as well as DXA-derived aBMD measurements in the lumbar spine, proximal femur, and radius *(26–28)*. Now in its 16th year, DHS provides an opportunity to evaluate aBMD and vBMD at various skeletal sites as potential predictors of all-cause mortality in women and men. Our hypothesis was that low BMD measurements would be associated with decreased survival in patients with T2D.

Materials and Methods

DHS is a family-based study including sibling pairs concordant for T2D as well as family members without diabetes *(26–28)*. All T2D-affected participants had diabetes diagnosed after the age of 35 years, in the absence of history of ketoacidosis, and >3 years in duration. Subjects with known serum creatinine concentrations >2 mg/dL were not recruited.

Study examinations included interviews for medical history and health behaviors, anthropometric measures, and BMD measurements by DXA and QCT. Body weight was recorded in lightly clothed, shoeless participants to the nearest 0.1 kg, and height to the nearest 0.5 cm using a stadiometer. Medication use was recorded; relevant for these analyses included hormone replacement therapies, calcium and vitamin D supplements, bisphosphonates, and steroids. The study was approved by the Institutional Review Board at the Wake Forest School of Medicine, and all participants provided written informed consent. Because of their small numbers and large confounding effect on BMD, participants on bisphosphonates (n = 29) or glucocorticoids (n = 59) were excluded from the present analyses. A total of 1154 participants from 562 families were included in the analysis.

DXA Measurements

DXA scans of posteroanterior spine, proximal femur, forearm, and whole body were obtained using a fan-beam scanner (Delphi A, software version 12.3, Hologic, Waltham, MA). BMD was determined for all available regions of interest. Whole body lean mass and fat mass were determined. All DXA scans were performed by technologists certified by the International Society for Clinical Densitometry, following standard quality control procedures, including daily phantom scanning. Coefficients of variation were 0.9% for total body BMD, 1.2% for posteroanterior spine (L1–L4) BMD, 0.9% for total hip BMD, 0.4% for forearm (ultradistal radius) BMD, 0.9% for whole-body BMD, 1.2% for whole-body fat mass, and 0.5% for whole-body lean mass.

QCT Measurements

CT scans of the chest and abdomen were obtained on 4-slice or 16-slice multidetector CT systems (LightSpeed QXi, LightSpeed 16Pro, GE Healthcare, Waukesha, WI) as described using a protocol validated for volumetric measurement of trabecular BMD in the thoracic and lumbar spine *(29,30)*. Trabecular volumetric BMD (mg/cm^3) was measured in the thoracic (T8–T11) and lumbar vertebrae (T12–L3) using QCT-5000 software (Image Analysis, Columbia, KY) with an external calibration phantom. Coefficients of variation were <1% for thoracic and lumbar vBMD.

The amount of coronary calcium was scored using a modified Agatston method with the traditiona130-Henry U threshold and a minimal lesion definition of 0.52 mm^2 *(31)*.

Mortality was determined using the National Social Security Death Index maintained by the United States Social Security Administration. For participants confirmed as deceased, length of follow-up was determined from the date of initial study visit to date of death. For living participants, length of follow-up was determined from the date of initial study visit to December 31, 2015.

Statistical Analysis

For demographic and outcome measures, summary statistics were determined for categorical measures as counts and percentages and for continuous measures as means and SDs. Only T2D affected participants were included in the analysis. To compare their relative importance, BMD variables were standardized before analysis of the association of BMD with mortality. For sex-specific analysis, sex-specific SD was used to calculate the standardized variable. Eight predictor variables were considered: lumbar vBMD, thoracic vBMD, lumbar aBMD, total hip aBMD, femoral neck aBMD, distal radius aBMD, mid-radius aBMD, and whole-body aBMD.