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

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Abstract

Purpose—To determine the association between areal and volumetric bone mineral density (BMD) with all-cause mortality in patients with type 2 diabetes (T2D).

Methods—Associations between BMD and all-cause mortality were examined in 576 women and 517 men with T2D in the Diabetes Heart Study. Volumetric BMD (vBMD) in the thoracic and lumbar spine was measured with Quantitative Computed Tomography (QCT). 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 (DXA). 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.

Results—At baseline, mean age was 61.2 years for women and 62.7 years for men. At mean 11.0±3.7 year 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 (HR per SD = 0.79; p = 0.0057) and distal radius (HR per SD = 0.76; p = 0.0056) after

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adjusting for all covariates, including lean mass. In men, vBMD measurements but not aBMD were inversely associated with mortality and only in the unadjusted model.

Conclusions—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.

Keywords

Bone mineral density; dual x-ray absorptiometry; quantitative computed tomography; mortality; 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 Absorptiometry (DXA)-measured areal BMD (aBMD). A recent report detected inverse relationships between Computed Tomography (CT) measures of bone density and mortality in 3673 lung cancer screening trial participants (22). However, that study did not use a calibration phantom and reported bone density in Hounsfield Units (HU), 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 and/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 non-diabetes affected family members (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, 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. Due to 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

Dual X-ray absorptiometry (DXA) scans of posterioranterior (PA) spine, proximal femur, forearm, and whole body were obtained using a fan-beam scanner (Delphi A, software version 12.3, Hologic, Waltham, MA, USA). BMD was determined for all available regions of interest. Whole body lean mass (LM) and fat mass (FM) 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 (CV) were 0.9% for total body BMD, 1.2% for PA 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 FM 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 multi-detector 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, USA) with an external calibration phantom. CVs were <1% for thoracic and lumbar vBMD.

The amount of coronary calcium was scored using a modified Agatston method with the traditional 130-Henry U threshold and a minimal lesion definition of 0.52mm^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 standard deviations. Only T2D affected participants were included in the analysis. In order to compare their relative importance, BMD variables were standardized prior to 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.

Due to the inclusion of related individuals in the DHS, Cox proportional hazards models with sandwich-based variance estimation were used to examine the relationships between BMD and all-cause mortality. Five models were sequentially employed to examine the association of BMD with all-cause mortality: 1) unadjusted; 2) adjusted for age, race, smoking, alcohol use, 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. The hazard ratio (HR) per standard deviation (SD) and its confidence interval are presented. The analysis was further stratified by sex. For analysis in men, estrogen use was not included in adjustments.

Analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). Because eight BMD measures were considered, statistical significance was set at $p < 0.00625$ ($=0.05/8$) after Bonferroni correction for multiple comparisons.

Results

The DHS cohort of 608 women and 546 men was followed for 11.0 ± 3.7 years. Table 1 presents baseline demographic characteristics. Average duration of diabetes was 10.5 ± 7.2 years. Women had significantly higher BMI, a higher proportion of African Americans, and lower proportions of smokers, alcohol users, and those with prior cardiovascular disease.

Table 2 presents baseline aBMD and vBMD at all measured skeletal sites. vBMD was significantly higher in women than men, but aBMD was significantly lower in women than men.

Relationships between QCT volumetric BMD measurements and all-cause mortality are shown in Table 3. In men and women, lumbar vBMD and thoracic vBMD were inversely associated with mortality only in the unadjusted models.

Relationships between DXA areal BMD measurements and all-cause mortality are shown in Table 4. In women, total hip aBMD (HR per SD=0.73; $p=0.0014$), femoral neck aBMD (HR per SD=0.72; $p=0.002$), mid-radius aBMD (HR per SD=0.70; $p<0.0001$), and distal radius (HR per SD=0.69; $p<0.0001$) were associated with mortality in the unadjusted model. The association with both radial aBMD sites remained significant following adjustment for age, race, smoking, alcohol use, estrogen use, cardiovascular disease, hypertension, coronary

artery calcification, BMI, and lean mass, again only in women. In men, the association between aBMD and mortality did not achieve statistical significance.

Discussion

The novel finding in this longitudinal study in patients with T2D is that lower baseline lumbar and thoracic vBMD measurements were associated with higher mortality over a 15 year period in men and women. However, the association of aBMD with mortality was only seen in women and not men. In women, the association at the radius persisted in all models, even after adjustment for coronary artery calcification (CAC), which is independently associated with mortality (31).

Most studies in patients with T2D have previously used DXA to measure aBMD (32–46). In 2012, a meta-analysis reported higher aBMD in patients with T2D (47). In a previous DHS report (29), women with T2D had a significantly higher spine and hip aBMD, which was no longer significant after adjusting for BMI. Paradoxically, the increase in aBMD in patients with T2D does not result in lower fracture rates. A meta-analysis of 16 studies reported a 2.6-fold increase hip fracture risk in men with T2D (48). In a landmark study of 770 women and 1199 men with T2D from three prospective observational studies (the Study of Osteoporotic Fractures, the Osteoporotic Fractures in Men, and the Health, Aging, and Body Composition), Schwartz et al. showed that individuals with T2D have higher risk of hip and non-spine fractures compared to age- and BMD-matched controls (49).

The methodology of BMD measurement requires careful consideration. Most BMD measurements in studies of T2D are obtained using DXA, where spine measurements are frequently overestimated by degenerative changes, diffuse idiopathic skeletal hyperostosis (DISH), and vascular calcifications. Because patients with T2D have an increased incidence of DISH and frequently extensive vascular calcifications, DXA measurements at the spine are less accurate in this group. Sex is another important confounder in studies of T2D. Increased aBMD in T2D is more common in men, who have larger bones resulting in higher aBMD on DXA. Increased aBMD in T2D may also be attributed to higher BMI, as we previously reported (29).

DHS is one of the few studies in participants with T2D that includes vBMD (27). In a previous DHS report (29), we did not see a significant effect of T2D on vBMD, after accounting for BMI. In the current analysis, the association of spinal vBMD with mortality was more consistent compared to that of aBMD, with the exception of aBMD at the radius sites.

Various mechanisms have been proposed for the increased fracture risk in T2D (50). Initially, increased fracture risk was attributed mainly to non-BMD factors such as increased risk of falls, which is consistent with the fact that patients with T2D have higher incidence of orthostatic hypotension, visual impairment, peripheral neuropathy, foot amputations, lower muscle strength, and poor balance. More recent evidence suggests that reduced bone quality may also contribute to increased fracture risk (51).

Patients with T2D have been shown to have decreased bone turnover, increased inflammation, increased marrow adiposity, dysregulation of adipokines, and hypogonadism (50). Recent studies report an inverse relationship in bone marrow adipose tissue (BMAT) and BMD in T2D (52), not surprising considering that there is a reciprocal relationship between adipocytes and osteoblasts which both arise from the same lineage of mesenchymal stem cells (53).

In this report, among all skeletal sites measured with DXA, the radius was most predictive of mortality. Because the radius is not subject to load bearing, BMD at that site may be more susceptible to metabolic and circulating factors and less influenced by body weight. The metabolic effect is supported by high-resolution CT studies that report increased cortical porosity in the distal radius in T2D subjects (54–57). However, recent historical cohort study of 411 men and women with T2D reported an association between spine and femoral neck aBMD and mortality but no association of mid-radius aBMD and mortality (58).

Clinical Relevance

Although BMD screening using DXA has become ubiquitous, its value in patients with T2D has been questioned. The widely used clinical assessment tool for osteoporosis, FRAX, is based on hip aBMD and underestimates the fracture risk in patients with T2D (49). If bone fragility in T2D is primarily a matter of bone quality and/or structure rather than BMD, such caution in the use of BMD screening is justified.

Despite these limitations, our study shows that axial aBMD are useful prognostic biomarkers in T2D. At the radius, lower BMD was associated with increased mortality, independent of coronary calcification, BMI, fat mass, and lean mass. Better understanding of relationships between BMD and outcomes may improve targeting osteoporosis therapy in T2D.

Currently, no guidelines exist to guide the initiation of pharmacologic therapy for osteoporosis in patients with T2D. Although antiresorptive drugs reduce fracture risk in patients with T2D (59), there is no consensus on who and when to treat. Specifically, it is unclear whether therapy should be initiated at higher BMD levels in T2D patient compared with non-affected individuals. This study suggests that DXA measurement at the radius may be useful for stratifying prognosis and determining intervention thresholds in patients with T2D.

Strengths and Limitations

This report has limitations. Fracture data was not collected in DHS. Although much of osteoporosis-associated mortality relates to post-fracture complications, other studies have shown that BMD remains a powerful predictor of mortality independent of fracture, and after fracture. Although we excluded participants on bisphosphonates and steroids, we did not account for the prevalent use of statins and anti-diabetes drugs in the cohort, since the use of these agents varied substantially during the course of the study. Prior studies in individuals with T2D have shown that more severe disease, evidenced by insulin use and HbA1c, is associated with higher fracture risk. We could not evaluate change in BMD as a predictor of mortality because follow-up BMD measures were not obtained. Although there

are few longitudinal studies, evidence supports that patients with T2D lose bone more rapidly than controls (60).

Our study also has several important strengths. The DHS obtained DXA and QCT measurements at all relevant skeletal sites and had a long follow-up interval. In studies of patients with T2D, calcified plaque is highly predictive of all-cause mortality (61, 62), perhaps beyond effects of BMD. Many studies have shown age-independent inverse relationships between BMD and calcified plaque (63–66). Importantly, we found that aBMD at the radius was predictive of subsequent mortality in women even after adjusting for CAC.

Although patients with T2D fracture at higher BMD than those without T2D, patients with diabetes benefit from BMD measurement. BMD remains a valuable predictor of fracture risk and other outcomes in patients with T2D. The association between distal radius aBMD and mortality was independent of other risk factors for death, suggesting that this region should be included in the routine DXA evaluation of patients with T2D.

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Table 1

Baseline demographic characteristics of Diabetes Heart Study cohort

Variable	Men (n=546)	Women (n=608)	P-value
Age, years	62.7±8.9	61.2±9.3	0.2297
Diabetes duration, years	10.9±7.5	10.1±6.9	0.1540
BMI, kg/m ²	31.1±5.5	33.9±7.3	<0.0001
African American	63 (11.5%)	129 (21.2%)	0.0003
Hypertension, %	469 (85.9%)	543 (89.3%)	0.0964
Current smokers, %	99 (18.2%)	96 (16.0%)	<0.0001 *
Former smokers	324 (59.5%)	166 (27.6%)	
Alcohol use, %	172 (31.5%)	98 (16.1%)	<0.0001
Estrogen use, %	0 (0%)	124 (20.9%)	-
Insulin use, %	144 (26.4%)	198 (32.6%)	0.0266
Prior CVD, %	274 (50.7%)	188 (31.3%)	<0.0001
Deceased, %	238 (43.6%)	221 (36.4%)	0.0202

* overall test for smoking effect

Table 2

Baseline bone mineral density

Variable	Men (n)	Women (n)	P-value
Lumbar vBMD, mg/cm ³	126.5±36.9 (411)	137.0±46.9 (432)	<0.0001
Thoracic vBMD, mg/cm ³	138.6±39.7 (517)	154.3±49.7 (579)	<0.0001
Lumbar (L1–L4) aBMD, g/cm ²	1.09±0.17 (381)	1.04±0.18 (399)	<0.0001
Total hip aBMD, g/cm ²	1.02±0.16 (378)	0.97±0.17 (401)	<0.0001
Femoral neck aBMD, g/cm ²	0.82±0.14 (379)	0.79±0.14 (405)	0.0017
Distal radius aBMD, g/cm ²	0.49±0.07 (383)	0.41±0.07 (405)	<0.0001
Mid radius aBMD, g/cm ²	0.77±0.07 (382)	0.66±0.08 (401)	<0.0001
Whole body aBMD, g/cm ²	1.14±0.11 (382)	1.06±0.12 (404)	<0.0001

Mean ± SD (n) is presented.

Table 3

Association between QCT volumetric BMD and all-cause mortality

	Men		Women	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Lumbar vBMD				
Model 1: Unadjusted	0.70 (0.59, 0.84)	0.0001	0.65 (0.54, 0.78)	<0.0001
Model 2: Adjusted for age, race, smoking, alcohol use, estrogen use (women only)	0.90 (0.75, 1.07)	0.2380	0.87 (0.69, 1.10)	0.2450
Model 3: Model 2 plus HTN, prior CVD, CAC	0.96 (0.81, 1.14)	0.6397	0.89 (0.70, 1.13)	0.3360
Model 4: Model 3 plus whole body lean mass	0.91 (0.75, 1.12)	0.3915	1.00 (0.77, 1.30)	0.9917
Model 5: Model 3 plus whole body fat mass	0.91 (0.75, 1.10)	0.3342	1.02 (0.78, 1.32)	0.9090
Thoracic vBMD				
Model 1: Unadjusted	0.74 (0.64, 0.86)	<0.0001	0.65 (0.55, 0.76)	<0.0001
Model 2: Adjusted for age, race, smoking, alcohol use, estrogen use (women only)	0.92 (0.79, 1.06)	0.2464	0.87 (0.72, 1.04)	0.1242
Model 3: Model 2 plus HTN, prior CVD, CAC	0.94 (0.81, 1.10)	0.4532	0.87 (0.72, 1.05)	0.1547
Model 4: Model 3 plus whole body lean mass	0.91 (0.74, 1.11)	0.3441	0.95 (0.75, 1.20)	0.6644
Model 5: Model 3 plus whole body fat mass	0.90 (0.75, 1.09)	0.2738	0.98 (0.77, 1.23)	0.8379

HR per sex-specific SD is presented.

Table 4

Association between DXA areal BMD and all-cause mortality

	Men		Women	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Lumbar (L1–L4) aBMD				
Model 1: Unadjusted	1.07 (0.91, 1.25)	0.3997	0.86 (0.72, 1.04)	0.1243
Model 2: Adjusted for age, race, smoking, alcohol use, estrogen use (women only)	1.07 (0.92, 1.24)	0.3753	1.01 (0.84, 1.20)	0.9559
Model 3: Model 2 plus HTN, prior CVD, CAC	1.00 (0.88, 1.15)	0.9535	1.02 (0.84, 1.23)	0.8781
Model 4: Model 3 plus whole body lean mass	1.01 (0.87, 1.18)	0.8534	1.00 (0.82, 1.21)	0.9718
Model 5: Model 3 plus whole body fat mass	0.99 (0.86, 1.14)	0.8924	1.01 (0.84, 1.23)	0.8825
Total Hip aBMD				
Model 1: Unadjusted	0.90 (0.77, 1.06)	0.2223	0.73 (0.60, 0.89)	0.0014
Model 2: Adjusted for age, race, smoking, alcohol use, estrogen use (women only)	1.02 (0.87, 1.21)	0.7737	0.95 (0.78, 1.16)	0.6195
Model 3: Model 2 plus HTN, prior CVD, CAC	1.00 (0.85, 1.17)	0.9625	0.99 (0.81, 1.22)	0.9471
Model 4: Model 3 plus whole body lean mass	1.01 (0.84, 1.22)	0.9194	0.93 (0.75, 1.16)	0.5311
Model 5: Model 3 plus whole body fat mass	0.95 (0.80, 1.12)	0.5508	0.99 (0.79, 1.23)	0.8953
Femoral Neck aBMD				
Model 1: Unadjusted	0.93 (0.80, 1.10)	0.3991	0.72 (0.59, 0.89)	0.0020
Model 2: Adjusted for age, race, smoking, alcohol use, estrogen use (women only)	1.05 (0.89, 1.23)	0.5759	0.91 (0.72, 1.14)	0.4011
Model 3: Model 2 plus HTN, prior CVD, CAC	1.03 (0.88, 1.21)	0.6899	0.96 (0.76, 1.22)	0.7301
Model 4: Model 3 plus whole body lean mass	1.05 (0.88, 1.25)	0.5704	0.91 (0.71, 1.16)	0.4352
Model 5: Model 3 plus whole body fat mass	1.00 (0.85, 1.18)	0.9882	0.95 (0.74, 1.21)	0.6751
Distal radius aBMD				
Model 1: Unadjusted	0.87 (0.75, 1.02)	0.0879	0.69 (0.59, 0.81)	<0.0001
Model 2: Adjusted for age, race, smoking, alcohol use, estrogen use (women only)	0.94 (0.81, 1.09)	0.4043	0.81 (0.68, 0.97)	0.0191
Model 3: Model 2 plus HTN, prior CVD, CAC	0.97 (0.84, 1.12)	0.6618	0.80 (0.65, 0.97)	0.0219
Model 4: Model 3 plus whole body lean mass	0.98 (0.83, 1.14)	0.7701	0.76 (0.63, 0.92)	0.0056
Model 5: Model 3 plus whole body fat mass	0.96 (0.83, 1.11)	0.5468	0.78 (0.64, 0.95)	0.0134
Mid radius aBMD				
Model 1: Unadjusted	0.87 (0.74, 1.01)	0.0592	0.70 (0.59, 0.82)	<0.0001
Model 2: Adjusted for age, race, smoking, alcohol use, estrogen use (women only)	0.96 (0.82, 1.11)	0.5587	0.81 (0.68, 0.96)	0.0162
Model 3: Model 2 plus HTN, prior CVD, CAC	0.99 (0.86, 1.15)	0.9451	0.81 (0.68, 0.96)	0.0164
Model 4: Model 3 plus whole body lean mass	1.00 (0.86, 1.17)	0.9655	0.79 (0.67, 0.93)	0.0057
Model 5: Model 3 plus whole body fat mass	0.98 (0.85, 1.14)	0.8139	0.81 (0.68, 0.96)	0.0135
Whole Body aBMD				
Model 1: Unadjusted	0.91 (0.77, 1.09)	0.3076	0.79 (0.65, 0.96)	0.0160

	Men		Women	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Model 2: Adjusted for age, race, smoking, alcohol use, estrogen use (women only)	0.99 (0.84, 1.17)	0.9311	0.97 (0.80, 1.18)	0.7851
Model 3: Model 2 plus HTN, prior CVD, CAC	0.94 (0.81, 1.09)	0.4158	1.01 (0.82, 1.23)	0.9611
Model 4: Model 3 plus whole body lean mass	0.94 (0.79, 1.12)	0.5156	0.98 (0.79, 1.20)	0.8195
Model 5: Model 3 plus whole body fat mass	0.92 (0.79, 1.08)	0.3138	1.00 (0.82, 1.23)	0.9779

HR per sex-specific SD is presented.