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Type 2 diabetes is not independently associated with spinal trabecular volumetric bone mineral density measured by QCT in the Diabetes Heart Study

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Abstract

The purpose of this study was to investigate the association between type 2 diabetes mellitus (DM2) and trabecular volumetric bone mineral density (vBMD) of the thoracic and lumbar spine measured by quantitative computed tomography (QCT) in 483 female (410 with DM2) and 398 male (365 with DM2) adults (age 36–86 years, BMI 16–58, 88% with DM2) in the Diabetes Heart Study. After accounting for familial correlation using generalized estimating equations (GEE), lumbar spine vBMD was positively associated with BMI ($r = 0.24$, $P < 0.0001$) and inversely associated with age ($r = -0.51$, $P < 0.0001$). In women, age-adjusted thoracic spinal vBMD (mg/ml, mean ± SE) was higher in diabetics (147.6 ± 2.3) compared to unaffected individuals (138.6 ± 3.4) ($P = 0.02$), with age-adjusted lumbar spinal vBMD showing a similar but non-significant trend (132.9 ± 2.1 in diabetics vs. 127.2 ± 3.6 in unaffected individuals, $P = 0.15$). In contrast, in men, age-adjusted lumbar and thoracic vBMD were not different between diabetics and unaffected controls (lumbar vBMD = 125.0 ± 1.8 in diabetics and 125.8 ± 5.6 in unaffected individuals, $P = 0.89$; thoracic vBMD = 137.4 ± 2.1 in diabetics vs. 134.2 ± 5.5 in controls, $P = 0.56$). After multivariate analysis adjusting for age, sex, race, BMI, physical activity, dietary intake, smoking, and alcohol use, interaction between diabetes status and trabecular vBMD of the spine was no longer observed. In women only, age-adjusted areal BMD (determined by dual X-ray absorptiometry (DXA)) of the spine and hip were significantly higher in diabetics than non-diabetic (all $P < 0.05$), although the differences disappeared after additional adjustment for BMI. These data suggest that areal BMD measured by DXA and trabecular volumetric BMD measured by QCT are not associated with type 2 diabetes independently from BMI.

Keywords: Cortical; Cancellous; Vertebral; BMD; Diabetes

Introduction

Associations between type 2 diabetes mellitus (DM2) and bone mineral density (BMD) have been difficult to prove, in part because many DM2-affected individuals are overweight or obese, and body weight is strongly associated with BMD. Most of the studies [1–8] examining BMD relationships with type 2 diabetes (DM2) have used *areal* BMD (aBMD) measured by dual X-ray absorptiometry (DXA) rather than *volumetric* BMD (vBMD) measured by quantitative computed tomography (QCT). Areal BMD measurements do not take into account bone thickness (anterior–posterior dimension) and are influenced by body size and bone size [9–13]. Obese individuals have higher aBMD in part because of their larger bones.

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Although many studies [2,4,7,8,14] of subjects with DM2 have reported higher aBMD compared to controls, some studies have shown similar [5] or even lower [1,3,6] aBMD. In a recent Hertfordshire Cohort study [14], the relationship between newly diagnosed diabetes status and aBMD of the proximal femur and the spine was stronger in women than men but was attenuated by adjustment for body mass index (BMI).

Volumetric BMD assessments by QCT are valuable in that the more metabolically active trabecular compartment of bone can be examined independently from the generally less metabolically active cortical compartment. Few studies have assessed potential relationships between trabecular vBMD and DM2. In one recent report, trabecular vBMD of the spine was determined by QCT and hip and whole body aBMD determined by DXA in a subset (n = 1446 of 3075, age 70–79 years) of the Health, Aging, and Body Composition (HABC) study [15]. In this relatively aged cohort of individuals, black women and white men with DM2 had significantly higher trabecular vBMD than those without DM2, but this effect was not observed in white women or black men. A second, smaller study [16] reported no difference in trabecular vBMD (by QCT) in 47 peri- and postmenopausal women with DM2 who had not received insulin within the previous 6 months, relative to 252 age-matched normal controls.

In the current study, we used QCT to determine trabecular vBMD and DXA to determine aBMD in a family study of DM2 which also contained family members unaffected by DM2. Our aims were to determine potential associations of DM2 with trabecular vBMD of the spine and with aBMD of the spine and other sites and to determine if the relationships differed in women compared to men.

Materials and methods

The Diabetes Heart Study (DHS) is a family study of sibling pairs concordant for DM2 as well as unaffected family members designed to locate and identify genes contributing to sub-clinical atherosclerosis. All DM2-affected participants must have had diabetes diagnosed after the age of 35, in the absence of history of ketoacidosis, and of at least 3 years duration. Subjects with renal insufficiency (serum creatinine ≥1.5 mg/dl or blood urea nitrogen ≥35 mg/dl) were excluded. Unaffected siblings, similar in age to siblings with DM2, were also recruited. Subjects were recruited from internal medicine clinics and through community advertising. The study was approved by the Institutional Review Board of the Wake Forest University School of Medicine. All participants gave informed consent.

The participant examinations were conducted in the General Clinical Research Center of Wake Forest University. The examination included interviews for medical history and health behaviors, anthropometric measures, fasting blood draws, spot urine collection, resting blood pressure, and 12 lead EKG. All patients had fasting plasma glucose and HbA1c determined. For clinical diagnosis of diabetes, ADA criteria were used (e.g., fasting plasma glucose >126 mg/dl). Unaffected status was defined as not previously diagnosed with DM2 and fasting glucose <100 mg/dl at examination time. 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. Dietary intake (calories per day) and physical activity (calories per day) were assessed using Block food frequency [17] and Paffenbarger physical activity [18] questionnaires administered by trained interviewers.

In order to assess vascular calcium content and volumetric bone density, scans of the chest and abdomen were obtained with computed tomography (CT) using a standardized protocol calibrated to an external phantom (Image Analysis, Columbia, KY), details of which have been previously described by our group [19,20]. Chest CT examinations with ECG gating were performed between 1999 and 2005 with the protocol altered to take advantage of the improved temporal resolution possible with each CT system while maintaining comparable image quality as measured on the biweekly QCT phantom scans. Examinations were performed on either a single slice subsecond helical CT, a four-channel multidetector CT, or a 16-channel multidetector CT (CTi, LightSpeed QXi, LightSpeed 16Pro with the SmartScore Cardiac package (General Electric Healthcare, Waukesha, WI)). Chest CT technical parameters were: 3 mm slice thickness, retrospective cardiac gating, 120 kVp, 240 mA (~100 mA s utilizing the partial scan reconstruction algorithm) and scan pitch adjusted to heart rate as previously described for the single slice system. For the multidetector CT systems, a 2.5 mm slice thickness in 4 or 8 slice mode, prospective cardiac gating at 50% of the RR interval, 120 kVp, gantry rotation time of 0.5 and 0.4 s such that 105 mA s technique was obtained. For participants who weighed 220 lbs. (100 kg) or more, the mA s was increased by 25%. CT scans of the abdomen were obtained in the helical mode using a 3 mm slice collimation, 120 kVp, 250 mA, 0.8 s gantry speed, and a pitch of 0.875 (8.75 mm/rotation). We have validated this protocol for measurement of trabecular vBMD in the thoracic and lumbar spine [19]. Trabecular vBMD was measured in the thoracic spine (T8–T11) and lumbar spine (T12–L3) using QCT-5000 volumetric software (Image Analysis, Columbia, KY). Coefficients of variation determined in house were <1% for thoracic and lumbar BMD.

DXA scans of posterior–anterior (PA) spine, proximal femur, forearm, and whole body were obtained using a fan-beam scanner (Delphi A™, Hologic, Waltham, MA). BMD was determined for all available regions of interest. In-house coefficients of variation (CV) were 1.2% for PA spine (L1–L4) BMD, 0.9% for total hip BMD, 0.4% for ultradistal radius BMD, and 0.9% for whole body BMD.

Statistical analyses

The sample means, standard deviations, minima, and maxima were computed for the continuous characteristics (e.g., age, body weight, height, BMI, duration of diabetes, fasting glucose, hemoglobin A1C, dietary intake, and physical activity) and the measures of BMD. For the discrete demographic characteristics (e.g., race, diabetes, menopause, and smoking), the proportions were calculated.

To compare means of BMD between diabetes and non-diabetes groups, we used the generalized estimating equation (GEE) procedure [21], which accounts for familial correlation via a sandwich estimator of the variance under exchangeable correlation. A family of power transformations for each of the five BMD measures conditional on the covariates was explored. To minimize the heterogeneity of variance, BMD measures were transformed to best approximate the normality assumptions if necessary. Thus, the results represent analyses on the square root of vBMD for thoracic and lumbar vertebrae and aBMD for total hip and the natural logarithm of aBMD for lumbar spine. Midradius aBMD was not transformed. The GEE P value for diabetes status in each model was reported in Table 2. The back-transformed least squares means and standard errors were calculated using a one-term Taylor expansion [22].

Associations between continuous covariates and BMD at various skeletal sites were determined using Spearman's correlation. Due to the correlated data structure, the significance of associations was not valid based on the correlation coefficient test. It was re-evaluated using the GEE model. Although associations between the categorical covariates and BMD cannot be determined using the correlation coefficients, the GEE procedure can still be used to evaluate the significance of associations. All statistical analyses were considered significant when $P < 0.05$. SAS software (Cary, NC) was used for the statistical analyses.

A series of models were developed that incorporated an increasing number of covariates to determine the extent the diabetes status contributed to the variation in BMD. Multivariate analyses examined combined effect of age, sex, race, and diabetes status (Model 1); age, sex, race, BMI, and diabetes status (Model 2); age, sex, race, smoking, dietary intake, alcohol intake, physical activity, and diabetes status (Model 3); age, sex, race, smoking, dietary intake, alcohol intake, physical activity, diabetes status, and BMI (Model 4). A similar series of models were developed to determine the extent the duration of diabetes