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Heritability of Spinal Trabecular Volumetric Bone Mineral Density Measured by QCT in the Diabetes Heart Study

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Abstract. The heritability of trabecular volumetric bone mineral density (BMD) determined by quantitative computed tomography (QCT) has not yet been reported. The purpose of this study was to investigate the heritability of BMD as determined by QCT and DXA in 124 women and 120 men (age 39–83 years, BMI 17–75, 84% type 2 diabetics) from 101 families (232 sibling pairs) in the Diabetes Heart Study. Volumetric BMD had a heritability (h^2) estimate of 0.73 (SE = 0.15, $P < 0.0001$) at the lumbar spine and 0.71 (SE = 0.15, $P < 0.0001$) at the thoracic spine. Areal BMD heritability estimates were 0.56 for PA spine, 0.43 for total hip, 0.43 for femoral neck, 0.45 for distal radius, 0.42 for mid-radius, and 0.52 for whole body (all $P < 0.01$). After accounting for familial correlation using generalized estimating equations, volumetric BMD was inversely associated with age ($r = -0.52$, $P < 0.0001$) and duration of diabetes ($r = -0.24$, $P < 0.01$) and positively associated with body weight ($r = 0.25$, $P < 0.01$). In multivariate analysis, adjustment for age, sex, and race lowered the h^2 estimates for volumetric BMD at the lumbar ($h^2 = 0.41$, $P < 0.01$) and thoracic ($h^2 = 0.48$, $P < 0.001$) spine, increased the h^2 estimate for areal BMD at the mid radius ($h^2 = 0.58$, $P < 0.0001$), and had little effect on the h^2 estimate for areal BMD at other sites ($h^2 = 0.41$–0.55, all $P < 0.01$). Additional adjustment for BMI, duration of diabetes, and physical activity had little effect on the h^2 estimates for volumetric BMD or areal BMD except at the hip where they were lowered ($h^2 = 0.31$–0.33, all $P < 0.05$). These data suggest that, like areal BMD, volumetric BMD is highly heritable and may be used in designing linkage studies to locate genes governing bone metabolism.

Key words: Heritability — BMD — DXA — QCT — Diabetes

In clinical practice, osteoporosis is commonly defined based on the presence of low bone mineral density (BMD), the presence (or history) of fragility fracture, or a combination of low BMD and fracture. This approach has been widely accepted mainly because low BMD is such a powerful risk factor for fracture [1–4]. Defining osteoporosis using BMD criteria has, in turn, fueled interest in determining the environmental and genetic factors underlying the variation in BMD.

Despite more than three decades of research into the genetics of osteoporosis, many gaps exist in our understanding of the heritability of phenotypes related to bone mass. Current unknowns include the relative heritabilities of BMD at different skeletal sites, of cortical compared to trabecular bone, and the influence of gender on these heritabilities. Previous heritability studies have used twins [5–10] or parent-offspring pairs [11–20], with other types of family studies being rare [21–24]. The heritability (h^2) estimates range from 0.3 to 0.9 [5–24]. Many previous heritability studies [5–8, 11–13] depended on determination of bone mass by single photon absorptiometry (SPA) or dual photon absorptiometry (DPA) which are now outdated technologies. Although, more recently, dual X-ray absorptiometry (DXA) has been used [9, 10, 14, 15], the measurement of BMD by DXA is not ideal, providing only an *areal* measurement of BMD which is influenced by bone size [25, 26]. While the heritability of a surrogate measure of *volumetric* BMD (mathematical adjustment of *areal* BMD obtained with DXA) has been reported [18–20], to date no studies have examined the heritability of volumetric trabecular BMD determined by quantitative computed tomography (QCT). Despite many known determinants of BMD, including age, sex, race, height, weight, and menopausal status, only a few studies [22–24] have adjusted the heritability estimates for these covariates. Adjustment for lifestyle factors such as diet and exercise has been even less consistent [22–24].

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The aims of the current study were to determine heritability of volumetric BMD in a family study of type 2 diabetes (DM2), to compare heritability estimates across skeletal sites and across technologies (DXA and QCT), and to investigate how the heritability is modified by covariates. Better understanding of the heritability of volumetric BMD is essential for modern molecular genetic approaches such as linkage studies to be used successfully to locate genes governing bone metabolism.

Materials and Methods

Subjects for this study were from a random sample of the Diabetes Heart Study (DHS). 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 subclinical 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. 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. Waist and hip circumferences were measured in duplicate, to the nearest 0.1 cm, using a steel measuring tape. Laboratory assays included fasting glucose, hemoglobin A1C, lipids, and blood chemistries. Dietary intake (calories per day) was assessed using Block's food frequency [27] and physical activity (calories per day) using Paffenbarger's physical activity [28] questionnaires administered by trained interviewers.

DXA scans of posterior-anterior (PA) spine, proximal femur, forearm, and whole body were obtained using a fan-beam scanner (Delphi A^{TM}, Hologic, Waltham, MA). BMD was determined for all available regions of interest. 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.

CT scans of the chest and abdomen were obtained on a 4-slice multi-detector CT system (GE Medical Systems, Milwaukee, WI) using a protocol validated for volumetric measurement of trabecular BMD in the thoracic and lumbar spine [29]. Volumetric data were acquired in the axial plane with 2.5 mm collimation. Volumetric BMD was measured in the thoracic spine (T8-T11) and lumbar spine (T12-L3) using QCT-5000 software (Image Analysis, Columbia, KY). CVs were $<1\%$ for thoracic and lumbar BMD.

Statistical Analyses

Associations between continuous covariates and BMD at various skeletal sites were determined using Spearman's correlation. The continuous covariates included age, body weight, height, duration of diabetes, fasting glucose, hemoglobin A1C, dietary intake, and physical activity. Due to the correlated data structure, the significance of associations was not valid based on the correlation coefficient test. It was revaluated using the generalized estimating equation (GEE) procedure [30], which accounts for familial correlation via a sandwich estimator of the variance under exchangeable correlation. Although associations between the categorical covariates (e.g., race, diabetes, menopause, and smoking) and BMD cannot be determined by 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.

To determine the contribution of genetic factors to BMD, we analyzed BMD data in family members using the Sequential Oligogenic Linkage Analysis Routines (SOLAR) software package (Southwest Foundation for Medical Research) [31]. SOLAR performs a variance components analysis of family data where the total phenotypic (i.e., BMD) variation is partitioned into genetic and non-genetic sources of variation. To minimize the bias associated with shared environmental factors, the estimates of heritability (h^2) were based on all available family data and were controlled for covariates related to BMD. The measurements of BMD were transformed to approximate the distributional assumptions of the analysis if necessary.

A series of models were developed that incorporated an increasing number of covariates to determine the extent of genetic factors contributing to the variation in BMD independent of the measured risk factors. In univariate analysis, each of the following covariates was examined independently: age, sex, race, height, weight, BMI, menopausal status, diabetes status, duration of diabetes, serum glucose, hemoglobin A1C, smoking, alcohol use, dietary intake, and physical activity. Multivariate analyses examined the combined effect of age, sex, and race (Model 1); age, sex, race, and BMI (Model 2); age, sex, race, BMI, and duration of diabetes (Model 3); age, sex, race, BMI, and physical activity (Model 4); as well as age, sex, race, BMI, duration of diabetes, and physical activity (Model 5). The significance of the heritability estimates was obtained by likelihood ratio tests, where the likelihood of the model in which heritability was estimated was compared with the likelihood of the model in which the heritability was constrained to zero. Twice the difference in the natural logarithmic likelihoods yielded a test statistic that was asymptotically distributed as 1/2:1/2 mixture of a chi-squared variable with 1 degree of freedom and a point mass at zero [32].

Results

Study Sample

Data for this study were obtained in a random sample of 244 participants from 101 families. Pedigree size ranged from 1 to 8, with 8 of 1 member, 65 of 2 members, 15 of 3 members, 9 of 4 members, 1 of 5 members, 2 of 6 members, and 1 of 8 members. There were 200 Caucasian and 32 African American sibling pairs. Among them, 121 sibling pairs were affected with DM2, 26 were not affected with DM2, and 85 were discordant for DM2.

Table 1 shows the characteristics of the study sample. There were 120 men and 124 women, ranging in age from 39 to 83 years. Forty-four participants (18%) were African American. Most of the women (91%) were postmenopausal. Two hundred and six participants (84%) had DM2 and 134 participants (55%) were obese (BMI >30). The average dietary intake was 1628 kilocalories per day and the average physical activity level was 690 kilocalories per week. Although the range of physical activity was broad (0-10272 kcal/week), a large

Table 1. Characteristics of the study sample

	Men $n = 120$	Women $n = 124$	Total $n = 144$	
	Mean ± SD or % (n)	Mean ± SD or % (n)	Mean ± SD or % (n)	Range
Characteristic				
Age (yrs)	61.6 ± 8.8	62.3 ± 9.4	62.0 ± 9.2	39–83
Race (African Americans)	19.2 (23)	16.9 (21)	18.0 (44)	
BMI (kg/m^2)	30.9 ± 6.2	32.5 ± 7.7	31.7 ± 7.1	17–75
Duration of diabetes (years)	11.3 ± 8.4	10.9 ± 8.9	11.1 ± 8.6	1–59
Fasting glucose (mmol/l)	143.47 ± 67.02	134.56 ± 56.83	138.94 ± 62.09	32–395
Hemoglobin A1C (%)	7.09 ± 2.76	6.93 ± 2.96	7.01 ± 2.86	1.2–21.8
Dietary intake (kcal/day)	1813 ± 841	1454 ± 636	1628 ± 762	359–6303
Physical activity (kcal/week)	913 ± 1660	475 ± 692	690 ± 1280	0–10272
Smoking				
Current	24 (29)	28 (35)	26 (63)	
Past	57 (68)	22 (27)	39 (95)	
Never	19 (23)	50 (62)	35 (86)	

Notes: Sample size was 244 and varied by no more than one except for duration of diabetes ($n = 206$), dietary intake ($n = 217$), and physical activity ($n = 224$)

Table 2. BMD of the study sample

	Men ($n = 120$)	Women ($n = 124$)	Total ($n = 244$)	
	Mean ± SD	Mean ± SD	Mean ± SD	Range
Volumetric BMD (mg/cm^3) by QCT				
Lumbar spine	129.15 ± 37.02	134.82 ± 49.24	132.07 ± 43.74	32.70–293.45
Thoracic spine	137.33 ± 39.48	149.92 ± 51.36	143.73 ± 46.24	36.82–343.40
Areal BMD (g/cm^2) by DXA				
PA Lumbar spine	1.09 ± 0.16	1.02 ± 0.20	1.06 ± 0.19	0.53–1.80
Total hip	1.04 ± 0.18	0.94 ± 0.17	0.99 ± 0.18	0.49–1.85
Femoral neck	0.86 ± 0.20	0.78 ± 0.14	0.82 ± 0.18	0.44–2.28
Ultra distal (UD) radius	0.49 ± 0.07	0.41 ± 0.07	0.45 ± 0.08	0.22–0.68
Mid (1/3) radius	0.78 ± 0.08	0.65 ± 0.08	0.72 ± 0.10	0.44–1.01
Whole body	1.15 ± 0.12	1.06 ± 0.13	1.11 ± 0.13	0.81–1.65

Notes: UD = Ultradistal radius, epiphyseal region of interest containing mostly trabecular bone, Mid 1/3 Radius = diaphyseal region of interest containing mostly cortical bone

proportion (17%) of participants had activity levels of 0 kcal/week. Most of the characteristics in Table 1 were comparable in men and women with the exception of smoking, dietary intake, and physical exercise which were higher in men (All $P < 0.05$).

Many participants were being treated with insulin (33%), oral hypoglycemic agents (59%), statins (40%), or thiazide diuretics (36%). Twenty-six percent of women were receiving estrogen therapy. The use of glucocorticoids was not common (7%). Fewer than 2% of participants were receiving other antiresorptive therapy (i.e., bisphosphonates, calcitonin, or raloxifene) and fewer than 5% were receiving calcium or vitamin D supplementation.

Table 2 shows BMD values for the study sample. At all measured sites the mean *areal* BMD (DXA) was lower in women than in men (all $P < 0.0001$), while *volumetric* BMD (QCT) was not significantly different (all $P > 0.1$).

Association of BMD with Potential Covariates

After accounting for familial correlation using generalized estimating equations, mean BMD was higher in African Americans compared to Caucasians. Volumetric BMD was not associated with diabetes status, menopausal status, smoking history, or alcohol use. As expected, due to the low number ($n = 11$) of premenopausal women, the study did not have sufficient power to detect the influence of menopausal status on BMD. Mean areal BMD was significantly higher in smokers and in diabetics at some skeletal sites.

Table 3 shows Spearman correlations of various possible covariates with BMD. Age was inversely associated with BMD at all measured sites with the strength of the association greatest for volumetric BMD (measured by QCT). Body weight was positively associated with BMD at all sites while height was significantly associated with

Table 3. Correlation between BMD and its covariates

Characteristic	Volumetric lumbar BMD *r*	Areal lumbar BMD *r*	Areal total Hip BMD *r*	Areal midradius BMD *r*
Age (years)	−0.52****	−0.12*	−0.28****	−0.28****
Weight (kg)	0.25**	0.30***	0.54****	0.34***
Height (m)	-0.02^{NS}	0.19*	0.28****	0.57****
Duration of diabetes (years)	−0.24**	-0.05^{NS}	-0.11^{NS}	-0.04^{NS}
Fasting glucose (mmol/l)	0.07^{NS}	0.0^{NS}	0.2**	0.1^{NS}
Hemoglobin A1C (%)	0.13^{NS}	0.05^{NS}	0.17^{NS}	0.14^{NS}
Dietary intake (Kcal/day)	0.02^{NS}	-0.08^{NS}	0.08^{NS}	0.17*
Physical activity (Kcal/week)	-0.02^{NS}	-0.01^{NS}	-0.05^{NS}	0.09****

Notes: Spearman correlation coefficients; GEE1 *P*-values (adjusted for relatedness): NS = not significant, *P*-value >0.05, * = *P*-value <0.05, ** = *P*-value <0.01, *** = *P*-value <0.001, **** = *P*-value <0.0001

Table 4. Unadjusted heritability estimates for BMD

	Men h^2 (SE)	Women h^2 (SE)	Total h^2 (SE)
Volumetric BMD (mg/cm^3) by QCT			
Lumbar spine	0.99*** (0.24)	0.56* (0.26)	0.73**** (0.15)
Thoracic spine	0.88** (0.25)	0.62** (0.24)	0.71**** (0.15)
Areal BMD (g/cm^2) by DXA			
PA lumbar spine	NA	0.63** (0.24)	0.56*** (0.15)
Total Hip	0.45^{NS} (0.28)	0.66** (0.24)	0.43*** (0.15)
Femoral neck	0.35^{NS} (0.28)	0.85*** (0.23)	0.43** (0.15)
Ultra distal (UD) radius	0.44^{NS} (0.29)	0.68** (0.23)	0.45*** (0.14)
Mid (1/3) Radius	0.88*** (0.22)	0.36^{NS} (0.28)	0.42** (0.15)
Whole body	0.54* (0.28)	0.78*** (0.22)	0.56**** (0.15)

Notes: h^2 = heritability, SE = standard error of h^2, NS = Not significant, *P*-value >0.05, * = *P*-value <0.05, ** = *P*-value <0.01, *** = *P*-value <0.001, **** = *P*-value <0.0001

areal but not with *volumetric* BMD. Conversely, duration of diabetes was inversely associated with volumetric BMD but was not significantly associated with areal BMD. Serum glucose, physical activity, and dietary intake did not show a consistent association with BMD. Hemoglobin A1C levels were not associated with BMD.

Heritability of BMD

Table 4 shows unadjusted heritability estimates for BMD. Volumetric BMD at the spine had heritability estimates ranging from 0.56 to 0.99. Areal BMD had heritability estimates ranging from 0.35 to 0.88. Although it appears that the heritability of volumetric BMD was higher than areal BMD and that men had higher heritability compared to women at some sites (volumetric BMD at the spine and areal BMD at mid-radius), the differences were not significant when considering the standard errors associated with the point estimates.

Heritability estimates remained significant in univariate analyses adjusting for potential covariates (i.e., age, sex, race, height, weight, BMI, menopausal status, diabetes status, duration of diabetes, serum glucose, hemoglobin A1C, dietary intake, alcohol use, smoking, and physical activity). Age adjustment had the greatest influence on *volumetric* BMD, lowering heritability estimates when compared to other covariates. In univariate analyses, other covariates had little impact on heritability of volumetric BMD. In contrast, heritability of *areal* BMD was influenced by sex, height, and weight adjustments. The proportions of phenotypic variance due to sex, height, and weight, respectively, were higher than those due to other covariates (data not shown). Sex adjustment increased heritability estimates. This adjustment reduced the remaining unexplained phenotypic variance, which allowed the genetic contribution to BMD to become more apparent.

Table 5 shows heritability estimates for BMD adjusted for covariates using two multivariate models. Adjustment for age, sex, and race (Model 1) lowered the heritability estimates for volumetric BMD at the spine (h^2 = 0.41–0.48), increased the heritability estimate for areal BMD at the mid-radius (h^2 = 0.58), and had little effect on areal BMD at other sites (h^2 = 0.41–0.55). Additional adjustment for BMI and physical activity (Model 4) had little effect on the heritability estimates. Similarly, heritability estimates remained stable in three other multivariate models (data not shown).

Table 5. Adjusted heritability estimates for BMD

	Unadjusted h^2 (SE)	Model 1 h^2 (SE)	Model 4 h^2 (SE)
Volumetric BMD (mg/cm^3) by QCT			
Lumbar spine	0.73**** (0.15)	0.41** (0.16)	0.39* (0.17)
Thoracic spine	0.71**** (0.15)	0.48*** (0.15)	0.49** (0.16)
Areal BMD (g/cm^2) by DXA			
PA lumbar spine	0.56*** (0.15)	0.57*** (0.16)	0.60** (0.17)
Total hip	0.43*** (0.15)	0.44*** (0.15)	0.42* (0.15)
Femoral neck	0.43** (0.15)	0.41** (0.15)	0.39* (0.15)
Ultra distal (UD) radius	0.45*** (0.14)	0.49*** (0.14)	0.52** (0.15)
Mid (1/3) radius	0.42** (0.15)	0.58**** (0.15)	0.59*** (0.15)
Whole body	0.56**** (0.15)	0.55**** (0.15)	0.55** (0.16)

Notes: Model 1 adjustments: age, sex, and race; Model 4 adjustments: age, sex, race, BMI, and physical activity. * = P-value < 0.05, ** = P-value < 0.01, *** = P-value < 0.001, **** = P-value < 0.0001

Discussion

To our knowledge, this is the first report of heritability of volumetric BMD using QCT. In this family study of type 2 diabetes, after adjusting for age, sex, race, BMI, and physical activity, *volumetric* BMD had heritability (h^2) estimates of 0.39 in the lumbar spine and 0.49 in the thoracic spine. Adjusted for the same covariates, h^2 of *areal* BMD ranged from 0.39 to 0.60.

Although this is the first study to examine the familial aggregation of volumetric BMD, extensive research has been conducted on heritability of other measures of bone mass (i.e., BMC and areal BMD), with estimates ranging from 0.3 to 0.9 [5–24]. Many of these studies [5–8, 11–13] measured BMC (in g/cm) by single photon absorptiometry (SPA) or BMC and areal BMD (in g/cm^2) by dual photon absorptiometry (DPA) which are now outdated technologies. In studies of twins using SPA and/or DPA, Pocock et al. [5] reported h^2 of 0.92 for the spine, 0.57–0.73 for the proximal femur, and 0.42 for the radius, Dequeker et al. [6] reported h^2 of 0.88 for the spine and 0.75 for the mid-radius, Hustmyer et al. [7] reported h^2 of 0.70 for the spine, proximal femur, and distal radius and 0.40 for the proximal radius, and Smith et al. [8] reported h^2 of 0.49–0.75 at the distal forearm. Heritability estimates in twins may be overestimated because the twin model assumes that environmental covariances are equal for monozygotic and dizygotic twins and that there are no gene interactions. In fact, there is evidence that monozygotic twins have higher environmental correlation and that gene interactions are present [10]. Familial resemblance studies using parent-offspring pairs have also been reported. Using SPA and/or DPA, correlations in bone mass between parents and their children have ranged from 0.22–0.58 [11, 12]. Since parents and offspring typically share many environmental factors, the reported associations in bone mass are a measure of familial resemblance that includes both genetic and environmental components.

With the advent of DXA, the heritability of BMD was reconfirmed in studies of twins and parent offspring pairs. In a study of 97 female twin pairs, Harris et al. [9] reported an h^2 range of 0.71–0.77. In parent off-spring studies, Danielson et al. [14] reported an h^2 range of 0.51 to 0.63 and Gueguen et al. [15] an h^2 range of 0.34 to 0.84. Several large family studies [21–24] have also used DXA to estimate heritability of BMD. In a study of 535 women from 137 pedigrees, Sowers et al. [21–23] reported an h^2 range of 0.45 to 0.67. In the Creighton family study of osteoporosis, 40 pedigrees of 212 men and 351 women had an h^2 range of 0.64 to 0.86 [23, 24]. In addition to heritability of *areal* BMD, two studies have reported heritability of *volumetric* BMD determined with DXA. In a study of 138 mothers and their prepubertal daughters, Ferrari et al. [18, 19] reported an h^2 range of 0.27 to 0.38, which was similar to that of areal BMD. In a study of 50 families, Nordstrom et al. [20] reported h^2 of 0.42 for volumetric BMD and 0.32 for areal BMD at the spine. Our study is the first to show that volumetric BMD measured directly with QCT is also highly heritable. Collectively, these data suggest that bone mass is heritable regardless of the phenotype (i.e., BMC, areal BMD, or volumetric BMD).

In addition to determining the h^2 of volumetric BMD, we compared the h^2 estimates across skeletal sites and across technologies (DXA and QCT). It is plausible that the h^2 of volumetric BMD would be different than that of areal BMD measured at the same skeletal site because volumetric measurements contain more trabecular bone relative to cortical bone. Genetic determinants of cortical and trabecular bone may differ, and trabecular bone is more metabolically active and susceptible to change than cortical bone, particularly in peri- and post-menopausal women. In addition, volumetric and areal measurements may be differentially influenced by environmental covariates. Our data show that unadjusted h^2 of the lumbar spine volumetric BMD was higher than areal BMD at the same skeletal site

(0.73 versus 0.56). After adjustment for age, sex, race, BMI, and physical activity, the heritability of volumetric spine BMD was lower than areal BMD (0.49 versus 0.60). However, comparison of the h^2 at two different sites in the radius results in a contradictory finding. In men, the predominantly *cortical* BMD in the mid-radius was more heritable than predominantly *trabecular* BMD in the distal radius (0.88 versus 0.44) whereas, in women, the cortical portion was *less* heritable than the trabecular portion (0.36 versus 0.68). Although it is tempting to conclude from these results that h^2 of BMD varies according to proportion of trabecular bone, the large standard errors associated with point estimates do not support such conclusions. Furthermore, the h^2 estimates were comparable for other DXA measured sites (i.e., whole body, PA spine, femoral neck, and total hip) despite the fact that they contain various proportions of cortical and trabecular bone. Due to its relatively small sample, our study may lack the power to determine whether genetic contributions to bone mass have any site specificity. Similarly, previous studies have not been consistent in showing differences in heritability of cortical versus trabecular bone or among different DXA measured sites [33].

Another aim of our study was to investigate how the h^2 estimates are modified by covariates. The first step in this process was to determine what covariates are associated with volumetric BMD. After accounting for familial correlation using generalized estimating equations, volumetric BMD was inversely associated with age and duration of diabetes and positively associated with body weight. Although increasing age was inversely associated with BMD at all measured sites, the strength of the association was greatest for volumetric BMD ($r = -0.42$ to -0.55). These findings are not unexpected since QCT measures primarily trabecular bone and is thus more sensitive to the effects of aging than DXA which measures both trabecular bone and less metabolically active cortical bone. Although several prior studies [34–36] have shown a positive association between body weight and volumetric BMD determined from mathematical manipulation of DXA results, this is one of the first studies to show an association with directly measured volumetric BMD (QCT). This study lacks sufficient power to test whether the relationship between weight and volumetric BMD (by QCT) is significantly different from that between weight and areal BMD (by DXA). Certainly it is plausible that the relationship would be different given the fact that areal BMD is partly determined by body size. In this study, height, dietary intake, and physical activity were not significantly associated with volumetric BMD but were associated with areal BMD at some skeletal sites.

The h^2 estimates for volumetric BMD were modified mainly by age and gender. Adjusting by age lowered the h^2 estimates for volumetric BMD but had little effect on areal BMD. This finding is not unexpected since volumetric BMD is more sensitive to age (because it contains more trabecular bone and because it is less influenced by degenerative changes than areal BMD). In our study, men had higher h^2 estimates than women in the mid-radius (DXA) and spine (QCT). In contrast, men had lower h^2 estimates than women for BMD measured by DXA at the whole body, spine, and hip sites. However, the differences were not significant considering the large standard errors associated with the point estimates. Our results are consistent with the Creighton family study of osteoporosis [23], where after adjusting for covariates, h^2 was higher in men (0.68 and 0.86) compared to women (0.64 and 0.67) but the differences were not considered significant.

In prior studies, BMD in DM2 has been reported as decreased, increased, or the same compared to controls [37–44]. In our study, duration of diabetes was inversely associated with volumetric BMD but not areal BMD. The association between BMD and fasting glucose and hemoglobin A1C were not significant. We did not measure serum insulin or insulin sensitivity. It should be noted, however, that the diabetes patients in this study are long-term diabetics and likely to be very insulin resistant and showing little variance in measures of insulin sensitivity. Adjusting for duration of diabetes slightly increased the h^2 estimate for volumetric BMD but had an inconsistent effect on heritability of areal BMD. Adjusting for serum glucose or hemoglobin, A1C had no effect on heritability estimates.

There was little effect of adjusting our h^2 estimates for other potential covariates (i.e., race, height, weight, BMI, menopausal status, smoking, alcohol use, dietary intake, or physical activity). In a multivariate model that adjusted the h^2 for the combined effect of age, sex, and race (Model 1), and age, sex, race, BMI, and physical activity (Model 4), the h^2 for volumetric BMD was somewhat lowered. Due to large standard errors these results should be interpreted with caution until they can be confirmed in a larger cohort.

In previous studies h^2 estimates were obtained in either normal populations or in populations where some subjects had low BMD or fracture. Heritability of BMD in elderly populations affected by chronic disorders has not been studied. Many such populations are being used in genetic epidemiology research related to other disorders. In particular, DM2 is an increasingly prevalent condition that has a broad range of clinical consequences, and as such is of particular interest to geneticists. Our demonstration of substantial h^2 of BMD in families with DM2 is quite valuable, providing a strong rationale to look into genetic influences on skeletal characteristics, particularly as this study continues with additional subject recruitment and future plans for genome wide scans across the whole subject population.

In summary, this is the first study to show that volumetric BMD measured by QCT is highly heritable. In addition, we explored how the heritability of volumetric BMD compared to areal BMD and how it was modified by covariates. Further studies are needed to confirm our findings and to provide heritability estimates for other osteoporosis-related phenotypes (i.e., body composition, bone loss, bone turnover, bone size and structure, fracture) in order to improve strategies for the prevention and treatment of osteoporosis.

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