Middle-Aged Premenopausal Women With Type 1 Diabetes Have Lower Bone Mineral Density and Calcaneal Quantitative Ultrasound Than Nondiabetic Women

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OBJECTIVE — To determine whether middle-aged premenopausal women with type 1 diabetes had more self-reported fractures and lower bone mineral density (BMD) compared with nondiabetic women.

RESEARCH DESIGN AND METHODS — Participants were premenopausal women aged 35–55 years with type 1 diabetes ($n = 67$; 32.2 ± 5.3 years duration) and without diabetes ($n = 237$). Total hip, femoral neck, whole-body, and spine BMD were measured by dual X-ray absorptiometry. Calcaneal broadband ultrasound attenuation (BUA) was assessed with quantitative ultrasound.

RESULTS — Women with type 1 diabetes were more likely to report a fracture after age 20 years compared with nondiabetic women (33.3 vs. 22.6%; age-adjusted odds ratio 1.89 [95% CI 1.02–3.49]). Type 1 diabetes was associated with lower total hip BMD (0.890 vs. 0.961 g/cm^2; $P < 0.001$), femoral neck BMD (0.797 vs. 0.847 g/cm^2; $P = 0.001$), whole-body BMD (1.132 vs. 1.165 g/cm^2; $P < 0.01$), and lower calcaneal BUA (71.6 vs. 84.9 dB/MHz; $P < 0.001$) after multivariate adjustment. BMD was 3–8% lower in type 1 diabetic compared with control women and calcaneal BUA was 15% lower. Spine BMD and biomarkers of bone remodeling were not significantly different between groups. In the type 1 diabetic women, reduced monofilament detection and blindness were both associated with lower BMD.

CONCLUSIONS — Lower BMD in premenopausal women with type 1 diabetes may substantially increase their risk of developing osteoporosis after menopause. Type 1 diabetic women should be targeted for osteoporosis screening and possible fracture prevention as they transition through menopause.

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The impact of the menopause transition on osteoporosis in type 1 diabetes is not well established. The Nord-Trodelag Health Survey (1) and the Iowa Women's Health Survey (2) found a 7- and 12-fold increase in hip fractures, respectively, in older type 1 diabetic women. Type 1 diabetes was associated with ~10% lower bone mineral density (BMD) compared with nondiabetic adults (3–10) in most but not all studies (11–13), though many include only small numbers of cases and lack adjustment for traditional osteoporosis risk factors (e.g., lower body weight and smoking). Few investigations (3,5,13) of type 1 diabetes and BMD focus exclusively on middle-aged and postmenopausal women, those at highest risk for osteoporosis and fractures.

Evidence exists for the role of diabetes complications of peripheral neuropathy (6,12,14,15), retinopathy (14,16–18), and nephropathy (14,17,19) in osteoporosis. Peripheral measures of bone, such as calcaneal quantitative ultrasound (QUS) (20,21), could be more affected by peripheral vascular disease or peripheral neuropathy (15). Worse glycemic control in type 1 diabetes was generally not related to lower BMD (4–12,17,22). Genetic variants in the vitamin D receptor (8) or collagen type 1 α-1 (9) are possibly associated with low BMD in type 1 diabetes. Decreased BMD in middle-aged type 1 diabetic women could be due to increased bone turnover (16,23,24), but recent studies do not find this (10,22,25). Longer type 1 diabetes duration may be related to decreasing BMD (14,16–18,23–25), though this is not certain (4,5,7,10–12,19,22).

We evaluated type 1 diabetic and nondiabetic women at an age close to menopause due to the higher risk for osteoporosis and fractures often observed with this transition. The objectives of the current study were to determine whether middle-aged women with type 1 diabetes had more self-reported fractures as adults and lower BMD than nondiabetic women after adjustment for a wide range of potential confounding and mediating factors.

RESEARCH DESIGN AND METHODS

— All participants were part of a volunteer subgroup from the ProHealth Study, a prospective study to determine whether menopause occurs at a significantly younger average age among type 1 diabetic compared with nondiabetic women. Women from a type 1 diabetes registry were diagnosed at age <17

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Abbreviations: BMD, bone mineral density; BUA, broadband ultrasound attenuation; CVD, cardiovascular disease; MNSI, Michigan Neuropathy Screening Instrument; NTx, N-telopeptides of type I collagen; QUS, quantitative ultrasound; VIF, variance inflation factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

years from 1951 to 1983 at either Children's Hospital, as previously described (26), or in Allegheny County. Approximately half (48.6%) of the eligible type 1 diabetic women participated. Control women, without diabetes (type 1 or 2) and without a parent or sibling with type 1 diabetes, were from voter registration lists and University of Pittsburgh employees. Control women were group matched to case subjects for ethnicity, age, and socioeconomic status. Eligible type 1 diabetic and nondiabetic women aged 35–55 years had a menstrual period within the last 3 months before the baseline visit and were not pregnant, breastfeeding, or planning a pregnancy. BMD was evaluated when the women were premenopausal. Participants provided informed consent before their participation, as approved by the institutional review board at the University of Pittsburgh. We excluded participants without BMD data ($n = 15$) or with a kidney transplant ($n = 6$). No participant reported celiac's disease or a history of dialysis without a transplant. Complete data were available for 67 women with type 1 diabetes and 237 nondiabetic women.

BMD, QUS, and body composition at baseline

Height was measured using a stadiometer. Weight was measured with a calibrated balance beam scale. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Waist and hip circumferences were measured twice and averaged before calculating waist-to-hip ratio. Total hip, femoral neck, whole-body, and spine BMD (g/cm^2) were assessed by dual-energy X-ray absorptiometry (Hologic QDR 4500W; Hologic, Bedford, MA). Total bone mineral-free lean mass and total fat mass were derived from the whole-body scan. The coefficient of variation for the scans was 0.35%. Calcaneal QUS (Hologic Sahara; Hologic, Bedford, MA) assessed broadband ultrasound attenuation (BUA). QUS was performed in duplicate ($r = 0.94$) and averaged. Daily quality control was done by scanning bone and whole-body Hologic phantoms to assess calibration and drift.

Other covariates

Clinical fracture history, current and past smoking and alcohol consumption history, exercise and total activity, menstrual cycle length, any hormone use (contraceptives, estrogens, progestins/progesterone, etc.), education, income category, self-reported health and limitations, and any history of physician diagnosis of diabetes-related complications (neuropathy, cerebrovascular disease or stroke, cardiovascular disease [CVD] [myocardial infarction, angina, coronary angiogram, angioplasty, or bypass], and eye disease [retinopathy, glaucoma, or blindness]) were determined by a questionnaire. Blood pressure was measured twice using a random zero machine to calculate mean systolic and diastolic pressures. Participants brought all medications to the clinic for the staff to inventory. Peripheral nerve function assessments included the clinical Michigan Neuropathy Screening Instrument (MNSI) scored from 0 to 8 (27), 10-g monofilament testing (reduced detection defined as inability to feel 8 of 10 touches at either great toe), and vibration score in units from 0 to 20 representing a 200-μ amplitude range as previously described (28,29) (Vibratron II; Physitemp Instruments, Clifton, NJ).

Laboratory measures

Osteocalcin and N-telopeptides of type I collagen (NTx) were measured at the University of Pittsburgh Endocrine Immunoassay Core Laboratory in all available type 1 diabetic cases ($n = 59$) and a subset of control subjects ($n = 99$). Serum osteocalcin, a biomarker of bone turnover, was measured with the NovoCalcin kit by Metra Biosystems (Mountain View, CA), a competitive immunoassay. Intra- and interassay variability for osteocalcin was 4.8 and 4.8%, respectively. NTx, biomarkers of bone resorption, were measured using the Osteomark kit by Ostex (Seattle, WA), a competitive-inhibition enzyme-linked immunosorbent assay. Assay values were corrected for urinary dilution by urinary creatinine analysis and expressed in nanomoles bone collagen equivalent per liter per millimole creatinine per liter. Intra- and interassay variability for urinary NTx was 3 and 5%, respectively.

HbA_{1c} (A1C) was measured with the Variant Hemoglobin Analyzer (Bio-Rad), utilizing the principle of ion exchange high-performance liquid chromatography. Intra- and interassay variability was 0.1 and 2.0%, respectively. Thyroid-stimulating hormone was measured with the Delfia hTSH assay, a solid-phase, two-site fluoroimmunometric assay based on the direct sandwich technique, by Wallac Oy (Turku, Finland). Intra- and interassay variability was 3.6 and 6.8, respectively.

Statistical analyses

Differences in prevalence and univariate associations between diabetic and nondiabetic participants were tested using Pearson χ^2 test and Fisher's exact test when appropriate. For continuous variables, nonparametric one-way Mann-Whitney tests were performed. Age-adjusted odds ratios (ORs) for fracture were calculated with logistic regression analyses. BMD and BUA means were calculated with ANCOVA, adjusted first for age, then additionally for total lean and fat mass. In diabetic women, ANCOVA adjusted for age and diabetes duration evaluated the relationship of A1C, diagnosed diabetes complications (entered individually and as a total count of complications), and peripheral nerve function assessments to BMD.

Stepwise multiple linear regression modeling was performed with BMD or BUA as dependent variables and diabetes as the independent variable of interest, while adjusting for age, total lean and fat mass, height, waist-to-hip ratio, current smoking and drinking, exercise and total activity, menstrual cycle length, current hormone use, education, self-reported health and limitations, thyroid-stimulating hormone level, A1C, blood pressure, diabetes-related complications (neuropathy, clinical MNSI score, vibration score, and reduced monofilament detection), osteoporosis medication use (bisphosphonates, calcitonin, raloxifene, fluoride), calcium and vitamin D supplement use, thiazide diuretic use, and statin use. Interaction terms for diabetes with other independent risk factors for BMD were also entered in the models. Models met underlying assumptions and were built progressively by entering variables in the following order: age, body composition factors, other risk factors for BMD, and finally diabetes-related complications. Diabetes and age were included in all models regardless of the P value and remaining variables were removed at $P > 0.10$. Multicollinearity for variables was assessed using the variance inflation factor (VIF), the inverse of the proportion of variance not accounted for by other independent variables; no VIF was >10 and the mean VIF for each regression model was ≤2 (30). Percentage difference in BMD or BUA due to diabetes in the final linear regression models was calculated using the formula: [(unstandardized β for diabetes)(unit change in diabetes)/unadjusted BMD or BUA mean for entire sample] × 100. For percentage change in BMD or BUA due to diabetes, 95% CIs were calculated

Table 1—*Descriptive characteristics by diabetes status*

	Type 1 diabetes	No diabetes
n	67	237
Age (years)	43.1 ± 4.3*	45.2 ± 4.2
Fractured after age 20 years (%)	33.3	22.6
Current smoker (%)	10.6	9.8
Current drinker (%)	46.3*	67.8
Any hormone use (%)	16.4	21.9
Contraceptive hormones	10.6	15.5
Oral estrogen/estrogen + progestin	1.5	1.7
Oral progestin/progesterone	1.5	2.1
Osteoporosis medication (%)	4.5†	0
Calcium supplement (%)	40.6	44.6
Vitamin D supplement (%)	14.3†	6.4
Statin medication (%)	25.4*	2.1
Poor or fair self-reported health (%)	13.5†	5.9
Moderate activities limited due to health (%)	25.4†	13.6
Climbing stairs limited due to health (%)	29.9	20.8
Height (cm)	163.2 ± 7.5	164.2 ± 6.9
Weight (kg)	69.1 ± 14.1†	74.5 ± 19.6
BMI (kg/m^2)	26.0 ± 5.4	27.6 ± 6.8
Waist-to-hip ratio	0.80 ± 0.07	0.79 ± 0.06
Bone-free lean mass (kg)	43.1 ± 6.2	44.1 ± 6.9
Total fat mass (kg)	23.3 ± 9.0†	26.6 ± 11.2
A1C (%)	7.9 ± 1.2*	5.1 ± 0.4
Thyroid-stimulating hormone (mU/l)	2.7 ± 2.8	2.0 ± 1.3
Osteocalcin (mg/ml)‡	8.4 ± 3.2	8.6 ± 6.6
NTx (nmol/l BCE/mmol/l creatinine)‡	30.1 ± 18.4	32.7 ± 14.4
Exercise (median hours/week)	1.9	2.2
Family income <$40,000 (%)	28.5	22.4
College graduate (%)	51.5	59.3
Diabetes-related complications		
Cardiovascular disease (%)	4.8†	0.5
Cerebrovascular disease (%)	0	0.5
Systolic blood pressure (mmHg)	109.7 ± 12.9	110.2 ± 10.6
Diastolic blood pressure (mmHg)	65.8 ± 7.1†	68.7 ± 7.9
Neuropathy (%)	29.7*	0.9
Vibratron score (vibration units)	3.9 ± 2.6*	1.8 ± 1.0
Clinical MNSI score	1.4 ± 1.2*	0.8 ± 0.9
Reduced monofilament detection (%)	17.9*	1.7
Retinopathy (%)	56.1*	0
Glaucoma (%)	4.5	0.9
Blindness (%)	10.6*	0.4

Data are means ± SD, unless otherwise indicated. *$P < 0.001$, †$P < 0.05$ for diabetic versus nondiabetic women. ‡For all available case subjects ($n = 59$) and a subset of control subjects ($n = 99$). BCE, bone collagen equivalent.

using the formula: {[(unstandardized β for diabetes)(unit change in diabetes) ± (SE of β for diabetes)(1.96)]/unadjusted BMD or BUA mean for entire sample} × 100. Data were analyzed using SPSS (SPSS, Chicago, IL) statistical software package.

RESULTS — Descriptive data and the prevalence of diabetes-related complications are shown in Table 1. Women with type 1 diabetes were younger than nondiabetic women (43.1 vs. 45.2 years; $P < 0.001$). A third of women with type 1 diabetes reported a fracture after age 20 years compared with under a quarter of nondiabetic women (33.3 vs. 22.6%; age-adjusted OR 1.89 [95% CI 1.02–3.49]; $P = 0.04$). Type 1 diabetic women were less likely to drink and more likely to take bone-active osteoporosis medications, statins, and vitamin D supplements. Although more diabetic women reported poor or fair health and limitations with moderate activities, both diabetic and nondiabetic women exercised for a similar number of hours per week. Weight was lower in type 1 diabetic compared with nondiabetic women, possibly due to their lower total fat mass since lean mass was statistically similar. No statistical differences between diabetic and nondiabetic women were found in other traditional risk factors for BMD such as smoking, estrogen use, calcium supplement use, or bone remodeling biomarkers.

Women with type 1 diabetes had significantly lower BMD for the total hip, femoral neck, and whole-body and lower calcaneal BUA compared with nondiabetic women (Table 2). These differences corresponded to approximately half of 1-SD–lower BMD and 1-SD–lower BUA. Adjusting for age, lean mass, and fat mass reduced but did not eliminate these differences in BMD and BUA between participants with and without diabetes.

Multivariate linear regression analyses for all participants

Type 1 diabetes was a statistically independent correlate of lower BMD at the hip, femoral neck, and whole-body and lower calcaneal BUA, with multivariate adjustment for potential confounding or mediating factors (Table 3). Type 1 diabetes was associated with 7.5% (95% CI −4.4 to −10.6) lower total hip BMD, 6.1% (−2.8 to −22.2) lower femoral neck BMD, 2.9% (−0.82 to −4.9) lower whole-body BMD, and a 15.8% lower calcaneal BUA (−9.4 to −22.2). Type 1 diabetes was not related to spine BMD in multivariate models (not shown). Higher lean mass was consistently related to higher BMD, though not at the peripheral calcaneal site. While higher total fat mass was related to higher BUA at the calcaneal site and lower whole-body BMD, there was not a consistent relationship with fat mass. Lower systolic blood pressure and higher diastolic blood pressure were associated with higher whole-body BMD. Any current hormone use was associated with higher femoral neck BMD. Interactions between diabetes and independent risk factors for BMD in Table 3 were not significant.

Diabetes-related complications were not associated with BMD or BUA and did not explain the effect of type 1 diabetes. Exclusion of women using oral corticosteroids ($n = 2$ case subjects, 1 control subject) did not change the relationship of type 1 diabetes and BMD or BUA. For all available cases ($n = 59$) and the subset of control subjects ($n = 99$) with osteocalcin and NTx measures, addition of these bone

biomarkers to the models did not alter the association between type 1 diabetes and BMD. Independent of type 1 diabetes status, higher osteocalcin levels were associated with lower total hip and femoral neck BMD and higher NTx levels were associated with lower BUA.

Participants with type 1 diabetes

The mean age at diagnosis in women with type 1 diabetes was 10.9 ± 3.7 years (range 8 months to 17 years), and their mean duration of diabetes was 32.2 ± 5.3 years. Neither diabetes duration nor quartiles of duration (1st, 23.0 to <28.0 years; 2nd, 28.0 to <31.75 years; 3rd, 31.75 to <35.5 years; and 4th, 35.5–46.0 years) were significantly associated with either BMD or BUA, adjusting for age. There was a suggestion of a relationship of lower mean femoral neck BMD with progressive quartiles of diabetes duration (0.839, 0.797, 0.800, and 0.745 g/cm^2 from shortest to longest duration quartile, respectively; $P = 0.07$), though this did not reach statistical significance. Neither A1C levels nor quartiles of A1C were associated with BMD or BUA, adjusting for age and duration. Presence of physician-diagnosed complications of CVD, neuropathy, retinopathy, and glaucoma or the total number of complications were not related to BMD or BUA, adjusting for age and diabetes duration. Blindness was associated with lower femoral neck (0.804 ± 0.107 vs. 0.712 ± 0.114 g/cm^2; $P = 0.05$) and whole-body BMD (1.131 ± 0.084 vs. 1.062 ± 0.085 g/cm^2; $P = 0.05$). Reduced 10-g monofilament detection was related to lower femoral neck BMD (0.801 ± 0.111 vs. 0.666 ± 0.111 g/cm^2; $P = 0.05$), adjusted for age and diabetes duration. The MNSI clinical score and reduced vibratory sensation were not related to BMD or BUA.

CONCLUSIONS — Type 1 diabetes in middle-aged women was associated with a 3–8% lower BMD at the total hip, femoral neck, and whole body and a 15% lower calcaneal BUA, after adjustment for the lower fat mass and other potential confounders or mediators. Previous studies of type 1 diabetes did not focus on women close to the menopausal transition, during which bone loss due to aging often occurs, although similar reductions in BMD were observed (3–10). A 1-SD decrease in BMD is associated with a two- to threefold hip fracture increase, particularly for women immediately after menopause (31,32). The differences in BMD that we observed for type 1 diabetic women compared with control women at multiple sites approached 1 SD and suggest that this lower BMD in type 1 diabetic women could account for a substantial increase in the risk of fracture. One SD in BUA, as we observed in type 1 diabetic women, may relate to an approximately twofold increase in hip fracture risk (32). Indeed, these premenopausal diabetic women had an approximately twofold higher age-adjusted OR for fracture.

The large decrease in calcaneal BUA in type 1 diabetic women compared with control women suggests that peripheral bone sites may be even more compromised than other sites. Cortical bone sites at the hip and femoral neck were more negatively impacted by type 1 diabetes, compared with the trabecular bone site at the spine. We found no difference in markers of bone turnover with type 1 diabetes, similar to other recent studies (10,22,25).

In previous studies of type 1 diabetes and BMD in women, traditional risk factors for low BMD were either not considered or not included in multivariate analyses. Adjustment for well-established confounders (e.g., total lean and fat mass) did reduce our absolute difference in BMD and BUA between type 1 diabetic and nondiabetic women and were independently related to lower BMD. This underscores the importance of adjusting analyses for risk factors such as body composition when evaluating type 1 diabetes and bone.

Microvascular complications could be a marker for tissue ischemia that is directly affecting bone. Furthermore, bone tissue is innervated and there is evidence that neurotransmitters directly affect bone remodeling (33). Our data on lower femoral neck BMD in the type 1 diabetic women with reduced monofilament detection confirms previous reports of peripheral neuropathy and lower BMD in type 1 diabetes (6,12,14,15).

We did not find a relationship between diabetes complications and BMD or BUA in multivariate models including both diabetic and nondiabetic women, though small sample sizes may have compromised our power to detect an association. Our results do not support previous studies that found a relationship of lower BMD with increased disease duration (14,16–18,23–25), but these did not adjust for the well-recognized effect of older age on lower BMD as we have. We did not find an inverse relationship of CVD with

Table 2—*Adjusted BMD and calcaneal BUA means (±SD) for type 1 diabetic and nondiabetic participants*

Adjustment for covariates	Total hip BMD (g/cm^2)		Femoral neck BMD (g/cm^2)		Whole-body BMD (g/cm^2)		Spine BMD (g/cm^2)		BUA (dB/MHz)	
	Type 1 diabetes	No diabetes	Type 1 diabetes	No diabetes	Type 1 diabetes	No diabetes	Type 1 diabetes	No diabetes	Type 1 diabetes	No diabetes
None	0.882 ± 0.114*	0.964 ± 0.107	0.795 ± 0.114*	0.852 ± 0.122	1.123 ± 0.089*	1.170 ± 0.092	1.050 ± 0.122	1.062 ± 0.122	70.6 ± 18.0*	85.3 ± 18.4
Age	0.877 ± 0.114*	0.965 ± 0.106	0.782 ± 0.114*	0.856 ± 0.107	1.120 ± 0.089*	1.170 ± 0.091	1.048 ± 0.122	1.061 ± 0.121	70.3 ± 19.3*	85.3 ± 18.3
Age + total lean and fat mass	0.886 ± 0.106*	0.962 ± 0.106	0.793 ± 0.097*	0.853 ± 0.091	1.123 ± 0.089*	1.169 ± 0.076	1.054 ± 0.114	1.060 ± 0.106	71.5 ± 17.9*	85.2 ± 18.2
Final model‡	0.890 ± 0.102*	0.961 ± 0.105	0.797 ± 0.046*	0.847 ± 0.188	1.132 ± 0.079†	1.165 ± 0.073	1.045 ± 0.128	1.060 ± 0.117	71.6 ± 18.4*	84.9 ± 17.7

*$P < 0.001$; †$P < 0.01$ for diabetic vs. nondiabetic participants. ‡Covariates listed in Table 3.

Table 3—*Final multiple linear regression models for total hip, whole-body, and femoral neck BMD and calcaneal BUA in diabetic and nondiabetic women

	Total hip BMD (g/cm^2) (R^2 = 0.294)		Femoral neck BMD (g/cm^2) (R^2 = 0.339)		Whole-body BMD (g/cm^2) (R^2 = 0.322)		Calcaneal BUA (dB/MHz) (R^2 = 0.189)	
	Standardized β	*P* value	Standardized β	*P* value	Standardized β	*P* value	Standardized β	*P* value
Type 1 diabetes	−0.250	<0.001	−0.189	0.001	−0.149	0.007	−0.279	<0.001
Age (years)	−0.059	0.259	0.173	0.002	−0.035	0.523	−0.010	0.866
Total lean mass (g)	0.432	<0.001	0.480	<0.001	0.614	<0.001	—	—
Total fat mass (g)	—	—	—	—	−0.274	<0.001	0.224	<0.001
Osteoporosis medication use	−0.096	0.060	−0.095	0.066	−0.095	0.067	—	—
Calcium supplement use	—	—	−0.104	0.041	−0.178	0.001	−0.157	0.005
Current hormone use	—	—	0.109	0.034	0.092	0.073	0.097	0.082
Systolic blood pressure (mmHg)	—	—	−0.110	0.082	−0.208	0.001	−0.126	0.063
Diastolic blood pressure (mmHg)	—	—	0.069	0.270	0.177	0.004	0.025	0.713
Height (cm)	—	—	0.124	0.055	—	—	−0.094	0.091
History of adult fracture	—	—	—	—	−0.123	0.019	—	—
Income category	−0.088	0.089	−0.106	0.080	—	—	—	—
Osteocalcin (mg/ml)†	−0.011	<0.001	−0.010	<0.001	—	—	—	—
NTx (nmol/l BCE/mmol/l creatinine)†	—	—	—	—	—	—	−0.218	0.014

*For n = 62, 63, 64, and 64 cases and n = 226, 215, 215, and 218 control subjects, respectively. Categorical variables were coded as "0 = no" and "1 = yes". Variables not reported in Table 3 had $P > 0.10$, did not affect the association between diabetes and BMD, and were therefore excluded from the final models. Current smoking, current drinking, exercise and total activity, menstrual cycle length, waist-to-hip ratio, education, self-reported health and limitations, thyroid-stimulating hormone level, A1C, thiazide use, vitamin D supplement use, statin use, and other diabetes-related complications were not significant at $P < 0.10$ in any model. †Models did not include all participants, as osteocalcin and NTx measures were available for n = 59 case and n = 99 control subjects. BCE, bone collagen equivalent.

BMD as suggested by two small type 1 diabetic cohorts (14,15). Proliferative retinopathy (14,16–18) was related to lower BMD (femoral neck, lumbar spine) in previous reports. We confirm this association between the serious ocular complications of blindness in our data and BMD in the diabetic women.

Our study has a number of strengths. We enrolled type 1 diabetic women from a well-established registry. State-of-the-art measures of BMD were used, including QUS, a peripheral bone measure that may reflect aspects of bone quality not captured by traditional BMD measures (21). We used dual-energy X-ray absorptiometry to directly assess lean and fat mass (instead of surrogate measures such as BMI) and considered many potential confounding or mediating covariates. However, our study also had several limitations. Our cross-sectional data allows only suggestion of causal relationships; longitudinal studies through the menopause transition are needed to determine whether type 1 diabetic women are at a greater risk of bone loss and fractures postmenopausally. Type 1 diabetic men were not included due to the focus on menopause but may also be at risk for lower BMD. Although this represents one of the largest case-control studies of bone health in premenopausal middle-aged women with type 1 diabetes, we still had a relatively small number of case subjects, and they were largely free of severe complications. Therefore analyses of diabetes-related complications and BMD lacked sufficient statistical power to find differences in BMD. We measured sensory nerve function, although other complications were self-reported. Our cohort of type 1 diabetic women has a survival bias; however, these women are the ones who will reach the menopause transition and experience age-related bone changes in conjunction with further diabetes complications.

Advances in treatment have improved metabolic control of patients with type 1 diabetes and have reduced the prevalence of severe complications at young ages. Many individuals with this disease are now living into old age. Type 1 diabetic women with lower BMD before menopause may be at an even greater risk for osteopenia and osteoporosis after the menopausal transition compared with nondiabetic women. Type 1 diabetic women may experience an earlier decrease in BMD due to aging, given their younger age at menopause, as we previously reported (26). Since our data and several recent studies indicate that type 1 diabetic women are at a markedly increased risk for fractures (1,2), osteoporosis screening or fracture prevention efforts may be appropriate for women with type 1 diabetes.

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