Young Women With Type 1 Diabetes Have Lower Bone Mineral Density That Persists Over Time

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OBJECTIVE — Individuals with type 1 diabetes have decreased bone mineral density (BMD), yet the natural history and pathogenesis of osteopenia are unclear. We have previously shown that women with type 1 diabetes (aged 13–35 years) have lower BMD than community age-matched nondiabetic control subjects. We here report 2-year follow-up BMD data in this cohort to determine the natural history of BMD in young women with and without diabetes.

RESEARCH DESIGN AND METHODS — BMD was measured by dual-energy X-ray absorptiometry at baseline and 2 years later in 63 women with type 1 diabetes and in 85 age-matched community control subjects. A1C, IGF-1, IGF binding protein-3, serum osteocalcin, and urine N-teleopeptide were measured at follow-up.

RESULTS — After adjusting for age, BMI, and oral contraceptive use, BMD at year 2 continued to be lower in women $\geq$20 years of age with type 1 diabetes compared with control subjects at the total hip, femoral neck, and whole body. Lower BMD values were observed in cases <20 years of age compared with control subjects; however, the differences were not statistically significant. Lower BMD did not correlate with diabetes control, growth factors, or metabolic bone markers.

CONCLUSIONS — This study confirms our previous findings that young women with type 1 diabetes have lower BMD than control subjects and that these differences persist over time, particularly in women $\geq$20 years of age. Persistence of low BMD as well as failure to accrue bone density after age 20 years may contribute to the increased incidence of osteoporotic hip fractures seen in postmenopausal women with type 1 diabetes.

Diabetes Care **31:1729–1735, 2008**

Type 1 diabetes is an autoimmune disorder resulting in loss of pancreatic insulin-producing β-cells that presents in childhood or early adulthood. Along with increased risk of complications including retinopathy, nephropathy, neuropathy, and cardiovascular events, adults with type 1 diabetes have decreased bone mineral density (BMD) compared with control subjects (1,2). In fact, osteoporosis is the most significant metabolic bone disease in individuals with diabetes (3). Patients with diabetes are at risk for osteoporosis and its complications, including hip fracture (4,5).

Recent studies demonstrate that diabetes is associated with alterations in bone health in children and adolescents. Prepubertal and pubertal patients with type 1 diabetes (aged <15 years) have decreased bone mass measured both by duel-energy X-ray absorptiometry (DEXA) scan and quantitative ultrasound (6–8). These observations suggest that adverse effects on bone health may occur early after the diabetes diagnosis. Understanding the natural history of BMD changes in young adults with type 1 diabetes may elucidate how the disease progresses and provide opportunities for prevention of significant bone loss and, presumably, fracture.

We demonstrated previously that premenopausal women (aged 20–35 years) with type 1 diabetes have lower BMD at the femoral neck and lateral spine than nondiabetic control subjects (7). This difference was not associated with diabetes duration, metabolic control, or biochemical markers of bone formation, a finding supported by previous work (9,10). Few studies have followed young women longitudinally to assess whether bone mineral acquisition or turnover play a role in the natural history of low BMD in diabetes. The aim of this study was to address the natural history of bone metabolism in type 1 diabetes by performing a follow-up DEXA 2 years after baseline enrollment to determine whether differences persist over time.

RESEARCH DESIGN AND METHODS

Female study participants were recruited from participants in a cross-sectional study assessing BMD in young women with type 1 diabetes and age-matched community control subjects (7). Cases for the cross-sectional study (baseline) were recruited from a regional tertiary hospital pediatric diabetes center and from endocrinology practices in Western New York. At the time of the initial study, the diabetes center followed over 600 patients aged 2–21 years with type 1 diabetes. Female patients aged 13–21 years in that clinical center were offered the opportunity to participate in the baseline study ($n = 138$). Recruitment of older women involved contacting former center patients (aged >21 years), patients from regional endocrinology practices, and affected relatives of subjects screened by our diabetes center for the Diabetes Prevention Trial. The comparison group included young women recruited from the same region as the case subjects; most were classmates or acquaintances of the case subjects or were volunteers who learned of the study through flyers posted at the university

and hospital. The baseline study enrolled 72 case subjects (diabetes duration >2 years) and 91 control subjects aged 13–37 years who were at least 2 years postmenarchal (7).

All type 1 diabetic case subjects and nondiabetic control subjects who participated in the baseline study were recruited ~2 years later to assess change in BMD over time. Contact was maintained with study participants between the baseline and follow-up exam via phone and mail. Inclusion criteria for the follow-up study were participation in the baseline study, current negative pregnancy test, and signed informed consent. For individuals younger than 18 years of age, a parent cosigned the informed consent. Exclusion criteria for both the baseline and follow-up study included systemic illness affecting BMD (other than diabetes), other endocrine disorders (except autoimmune thyroiditis), and diagnosis of juvenile osteoporosis or other bone disease. Individuals with autoimmune thyroiditis on levothyroxine therapy were biochemically euthyroid. The study was approved by the institutional review boards of the Women and Children's Hospital of Buffalo and the University at Buffalo. At baseline, study participants completed questionnaires relating to personal and family health, lifestyle habits, dietary intake (food frequency questionnaire), and medication intake including use of calcium supplements. Participants also reported prior fracture history, menstrual history, and demographic information. For participants with type 1 diabetes, information on disease duration, insulin dose schedule (injections versus continuous subcutaneous insulin infusion), and diabetes complications were reported. Weight, height, and blood pressure were measured using standard protocols. BMI was calculated as weight in kilograms divided by the square of height in meters.

DEXA (Hologic QDR-4500A; Hologic, Waltham, MA) was used to measure BMD in the anterior/posterior (L1–4) spine, total hip, femoral neck, total forearm, and whole body. All scans were performed on the same device for both visits. A single technician performed all baseline scans and 65% of the follow-up scans; two additional technicians performed the remainder of the follow-up scans (27% and 7%, respectively). Coefficients of variation (CVs) were determined for measures of all sites for all technicians throughout the study and were all <1% throughout the study. A daily manufacturer quality control phantom was done to ensure no drift. There were no software upgrades during the follow-up interval.

The following biomarkers were measured in nontimed blood samples: serum osteocalcin, IGF-1, IGF binding protein (IGFBP)-3 (by radioimmunoassay), and A1C (by high-performance liquid chromatography with Bio-Rad variant; Bio-Rad, Richmond, CA). Random urinary N-teleopeptide levels were measured by enzyme-linked immunoabsorbent assay. Blood samples were processed using standard protocols. Serum for hormonal assays was frozen at $-80°C$ and stored until sent for analysis in batches to Esoterix Laboratory (Calabasas Hills, CA). A1C (fresh plasma) was assayed in a sequential fashion at the Women and Children's Hospital of Buffalo laboratory (Kaleida Health). Urine samples were stored frozen at $-80°C$. For hormone measurements, intra-assay CV was <3% for N-telopeptide, 6% for IGF-1 and osteocalcin, and 13% for IGFBP-3. Interassay CV was <7% for N-Telopeptide, <9.7% for IGF-1, 13% for osteocalcin, and <17% for IGFBP-3 (Esoterix Laboratories).

Data from study participants were analyzed in stratum based on age at initial enrollment (7). Demographic, lifestyle, metabolic characteristics, and BMD were compared between diabetic case subjects and nondiabetic control subjects, stratified by age. Comparisons were made for baseline differences, differences at follow-up, and percent change between the two time points. Results were presented as both unadjusted comparisons and comparisons of adjusted means (adjusted for age, BMI, and oral contraceptive [OC] use). Unadjusted differences for continuous variables were examined using Student's t test and for categorical variables using the χ^2 test. ANOVA was used for adjusted models. In case subjects only, A1C levels were compared across younger and older age-groups. Data analyses were performed using SAS version 8 (SAS, Cary, NC). Post hoc power analysis of follow-up total hip BMD (adjusted for age, BMI, and OC use) indicated that our dataset of 63 case subjects ($n = 37$, <20 years of age) and 85 control subjects ($n = 36$, <20 years of age) gave our study 80% power to detect a difference between case and control subjects with an α of 0.05 and a target effect size of 0.45 in women <20 years of age and 0.63 in those >20 years of age.

RESULTS —Table 1 includes baseline and follow-up characteristics of women who participated in this follow-up study. For comparative purposes, study subjects were grouped by age at baseline (<20 years/≥20 years). The follow-up group included 63 women with type 1 diabetes (58.7% <20 years of age) and 85 control subjects without diabetes (42.4% <20 years of age) at ages 15–39 years at enrollment. The average follow-up time was 2.14 years. Of the participants in the baseline study with diabetes, 87.5% (63 of 72) participated in this follow-up study, and 93.4% (85 of 91) of control subjects participated in both examinations. More subjects from the baseline cohort ≥20 years of age were lost to follow-up (13.8 vs. 3.94%, cohort <20 years of age), with the highest attrition being from individuals with diabetes ≥20 years of age (21.2%). The primary reason for loss to follow-up was geographic relocation. Participants in this follow-up study were predominantly non-Hispanic Caucasian (95%) and were similar in age at menarche and years since menarche. Participants ≥20 years of age with diabetes used OC therapy longer than control subjects ($P \leq 0.05$). Although few participants were smokers, more women with diabetes reported current smoking; there were no smokers among the control subjects <20 years of age.

At follow-up, women with diabetes, particularly the older women, continued to have higher BMI than control subjects. Weight change (in percent) was not significantly different over the follow-up period. As reported previously, more patients in the older cohort were using continuous subcutaneous insulin infusion ($P < 0.01$, data not shown). While a trend toward lower daily insulin requirement was present in the older cohort (0.86 ± 0.42 vs. 0.75 ± 0.22 units $\cdot$ kg^{-1} $\cdot$ day^{-1}), that difference was not statistically significant. Subjects ≥20 years of age were more likely to have diabetes-related complications, although no statistical differences were found. More younger subjects were on levothyroxine therapy.

Table 2 presents BMD values at baseline and follow-up for each body site measured. Unadjusted means and means adjusted for age, BMI, and OC use are shown stratified by age-group and diabetes diagnosis. In those <20 years of age, both case and control subjects had an increase in BMD over the 2-year interval. The percent increase in BMD from base-

Table 1—Demographic and clinical characteristics of the study population

	Age <20 years			Age ≥20 years		
	Control	Type 1 diabetic	*P**	Control	Type 1 diabetic	*P**
n	36	37		49	26	
Baseline characteristics						
Age (years)	15.9 ± 1.5	16.2 ± 1.8	0.478	25.7 ± 4.4	27.3 ± 4.1	0.124
Non-Hispanic white	32 (88.9)	37 (100)		47 (95.9)	25 (96.2)	
Other race	4 (11.1)	0 (0)	0.037	2 (4.1)	1 (3.9)	0.961
Age at menarche (years)	12.4 ± 1.03	12.3 ± 1.40	0.653	12.9 ± 1.17	13.2 ± 1.40	0.220
Years from menarche	4.0 ± 1.6	4.3 ± 2.0	0.452	13.2 ± 4.5	14.6 ± 4.2	0.204
OC use	4 (11.1)	5 (13.5)	0.755	33 (67.4)	20 (76.9)	0.386
Years on OC	0.078 ± 0.28	0.092 ± 0.37	0.859	2.24 ± 2.76	3.94 ± 4.06	0.050
Smoking status	0 (0)	7 (18.9)	0.006	3 (6.1)	4 (16.0)	0.170
Follow-up						
Follow-up years	2.10 ± 0.27	2.19 ± 0.30	0.226	2.16 ± 0.27	2.12 ± 0.19	0.546
Weight (kg)						
Baseline	61.5 ± 11.0	65.2 ± 8.5	0.105	62.7 ± 9.5	69.0 ± 8.5	0.006
Follow-up	63.7 ± 11.4	66.9 ± 9.3	0.187	63.9 ± 11.3	70.2 ± 10.3	0.020
Change	2.21 ± 4.52	1.69 ± 4.41	0.616	1.21 ± 4.96	1.21 ± 5.0	0.998
BMI (kg/m^2)						
Baseline	22.6 ± 3.5	24.2 ± 2.9	0.036	22.5 ± 3.0	25.0 ± 2.8	0.001
Follow-up	23.1 ± 3.6	24.4 ± 2.7	0.093	22.9 ± 3.7	25.4 ± 3.5	0.007
Change	0.53 ± 1.7	0.19 ± 1.6	0.374	0.38 ± 1.9	0.42 ± 1.8	0.927

Data are means ± SD and *n* (%). *P values by Student's *t* test for continuous and χ^2 test for categorical variables.

line to follow-up was not statistically different between younger subjects and control subjects. For all participants in the population ≥20 years of age, the BMD from baseline to follow-up remained stable.

Significant differences in BMD were identified at the total hip, femoral neck, and whole body in the case subjects ≥20 years of age compared with the control subjects. As in the previous report, no differences in BMD were seen between groups in the younger cohort. In the adjusted model (for age, BMI, and OC use), BMD values at the total hip (baseline, *P* = 0.003; follow-up, *P* = 0.007) and femoral neck (baseline and follow-up, *P* < 0.001) were significantly lower in older women with diabetes compared with control subjects. After adjustment, the whole-body BMD was no longer significantly different between case and control subjects; however, both age-groups showed a trend toward lower whole-body BMD in the case subjects. Further adjustment for dietary intake of calcium and vitamin D as well as physical activity did not alter the BMD results (data not shown). When the analysis was restricted to nonsmokers, the adjusted means changed very little. For the older cohort, however, the *P* values were attenuated for the total hip (*P* = 0.017) and whole body (*P* = 0.215). In non-

smokers >20 years of age, the percent change difference at the total hip became more pronounced between case and control subjects and reached statistical significance (*P* = 0.008).

Overall, IGF-1 levels were lower for all groups compared with baseline (Table 3). This is consistent with a physiologic decrease in IGF-1 in postteenage years (Esoterix normative data 11). At the 2-year follow-up, however, the IGF-1 level was significantly lower in the younger diabetic subjects than in the control subjects, although still within the normal range. IGF-1 levels were not statistically different between diabetic participants and control subjects in the older cohort. Within the older age-group, IGFBP-3 levels were lower in participants with diabetes than in control subjects (*P* < 0.05). IGFBP-3 levels were comparable for control and diabetic subjects in the cohort <20 years of age.

Serum osteocalcin levels were lower at follow-up for all groups, even with increased bone mineral accrual in the group <20 years of age (Table 3). There was no difference in osteocalcin or N-teleopeptide levels between case and control subjects <20 years of age (Table 3). After adjusting for age and BMI, case subjects had significantly lower osteocalcin levels than control subjects in the population

≥20 years of age (*P* < 0.04; Table 3). In addition, the percent change in osteocalcin level from baseline to follow-up was significantly different in diabetic women ≥20 years of age compared with control subjects after adjustment (*P* < 0.03). Markers of bone formation did not correlate with BMD in our subjects.

Metabolic control, as measured by A1C, was poorer in the younger diabetic cohort, as we reported previously (7). Overall metabolic control was stable within a given age stratum between the baseline and follow-up studies. No correlation was found between A1C and any of the BMD measurements (data not presented). When evaluating for associations between metabolic control and BMD measurements that were statistically lower in case than in control subjects at follow-up (Table 2), the Pearson correlation coefficient (*R* value) for A1C and BMD was between 0.121 (total hip) and 0.334 (femoral neck) (*P* > 0.095, data not shown). As in our previous study, there was no association found between BMD and diabetes duration, baseline A1C, or years since menarche.

CONCLUSIONS — While longitudinal studies have examined the effect of insulin therapy on BMD in patients with long-standing type 1 diabetes (12), few

Table 2—BMD measurements (g/cm²) by age-group

	Age <20 years			Age ≥20 years		
	Control	Type 1 diabetic	P	Control	Type 1 diabetic	P
n	36	37		49	26	
Unadjusted data						
Total hip*						
Baseline	0.975 ± 0.12	0.950 ± 0.11	0.341	0.973 ± 0.12	0.906 ± 0.10	0.015
Follow-up	0.983 ± 0.12	0.953 ± 0.11	0.265	0.968 ± 0.11	0.910 ± 0.10	0.029
Percent change	0.87 ± 3.67	0.32 ± 3.02	0.486	−0.55 ± 2.58	0.50 ± 2.51	0.092
Femoral neck*						
Baseline	0.884 ± 0.13	0.870 ± 0.10	0.613	0.876 ± 0.12	0.795 ± 0.10	0.003
Follow-up	0.891 ± 0.12	0.872 ± 0.10	0.468	0.867 ± 0.12	0.790 ± 0.09	0.005
Percent change	1.02 ± 3.71	0.31 ± 3.54	0.407	−0.68 ± 3.56	−0.49 ± 3.31	0.823
Wrist*						
Baseline	0.533 ± 0.06	0.534 ± 0.04	0.904	0.565 ± 0.04	0.553 ± 0.04	0.245
Follow-up	0.549 ± 0.05	0.552 ± 0.04	0.775	0.565 ± 0.04	0.551 ± 0.04	0.163
Percent change	3.19 ± 2.85	3.42 ± 2.46	0.716	−0.041 ± 1.46	−0.41 ± 1.31	0.190
A/P spine*						
Baseline	0.991 ± 0.11	0.978 ± 0.09	0.594	1.055 ± 0.11	1.029 ± 0.11	0.335
Follow-up	1.010 ± 0.11	1.00 ± 0.10	0.747	1.059 ± 0.11	1.032 ± 0.12	0.329
Percent change	1.96 ± 3.88	2.40 ± 3.67	0.626	0.36 ± 2.43	0.26 ± 2.88	0.868
Whole body*						
Baseline	1.090 ± 0.08	1.069 ± 0.08	0.274	1.142 ± 0.08	1.097 ± 0.09	0.031
Follow-up	1.106 ± 0.08	1.084 ± 0.08	0.251	1.138 ± 0.08	1.096 ± 0.09	0.041
Percent change	1.51 ± 2.12	1.44 ± 2.18	0.890	−0.33 ± 2.00	−0.04 ± 1.92	0.556
Adjusted data						
Total hip†						
Baseline	0.986 ± 0.13	0.940 ± 0.10	0.067	0.979 ± 0.12	0.898 ± 0.10	0.003
Follow-up	0.993 ± 0.12	0.943 ± 0.10	0.058	0.972 ± 0.12	0.902 ± 0.09	0.007
Percent change	0.80 ± 3.67	0.39 ± 3.02	0.598	−0.55 ± 2.58	0.50 ± 2.51	0.124
Femoral neck†						
Baseline	0.895 ± 0.13	0.859 ± 0.10	0.158	0.883 ± 0.12	0.783 ± 0.10	<0.001
Follow-up	0.901 ± 0.12	0.862 ± 0.10	0.120	0.876 ± 0.12	0.777 ± 0.09	<0.001
Percent change	0.89 ± 3.71	0.44 ± 3.54	0.610	−0.57 ± 3.42	−0.69 ± 3.31	0.887
Wrist†						
Baseline	0.538 ± 0.06	0.529 ± 0.04	0.413	0.566 ± 0.04	0.551 ± 0.04	0.168
Follow-up	0.553 ± 0.05	0.548 ± 0.04	0.630	0.566 ± 0.04	0.550 ± 0.04	0.116
Percent change	2.99 ± 2.85	3.62 ± 2.46	0.257	0.002 ± 1.38	−0.34 ± 1.31	0.353
A/P spine†						
Baseline	1.002 ± 0.11	0.968 ± 0.09	0.117	1.060 ± 0.11	1.020 ± 0.11	0.169
Follow-up	1.020 ± 0.11	0.992 ± 0.10	0.243	1.062 ± 0.11	1.026 ± 0.12	0.215
Percent change	1.88 ± 3.88	2.47 ± 3.67	0.498	0.20 ± 2.41	0.55 ± 2.88	0.601
Whole body†						
Baseline	1.097 ± 0.08	1.063 ± 0.08	0.055	1.142 ± 0.08	1.097 ± 0.09	0.043
Follow-up	1.113 ± 0.08	1.078 ± 0.08	0.061	1.138 ± 0.08	1.097 ± 0.09	0.065
Percent change	1.48 ± 2.12	1.47 ± 2.18	0.986	−0.39 ± 2.01	0.09 ± 1.91	0.344

Data are means ± SD. *P values by Student's *t* test. †P values by ANCOVA, adjusted for age, BMI, and OC use. A/P, anterior/posterior.

have reported on the natural history of metabolic bone disease in younger women. Here we present BMD data for a well-characterized cohort of young women with type 1 diabetes at baseline and 2 years later. The baseline study demonstrated that the older cohort had significantly lower BMD at the femoral neck and lateral spine than age-matched control subjects (7). The data presented here demonstrate that case subjects in the older cohort had persistently lower BMD than age-matched healthy control subjects. In this cohort, BMD at the total hip and femoral neck remained lower than in control subjects after adjusting for age, BMI, and OC use, even with no significant decrease in BMD from baseline to follow-up (Table 2). Similar to our initial study, there was no difference in BMD between women with diabetes aged <20 years and control subjects at any of the sites measured. However, there was a trend toward lower BMD at the total hip and whole body in women with diabetes. This difference occurred in the face of BMD increases (percent change) at both the total hip and whole body in this population, suggesting that bone mineral accrual is altered in a subtle manner during late adolescence in women with type 1 diabetes.

Individuals with type 2 diabetes have

Table 3—*Hormonal values and glycemic control by age-group in type 1 diabetic young women and nondiabetic control subjects*

	Age <20 years			Age ≥20 years		
	Control	Type 1 diabetic	P	Control	Type 1 diabetic	P
n	36	37		49	26	
Unadjusted data						
IGF-1 (ng/ml)*						
Baseline	308 ± 67.4	280 ± 81.8	0.121	222 ± 89.6	209 ± 64.6	0.512
Follow-up	288 ± 78.1	213 ± 83.4	<0.001	166 ± 48.7	147 ± 41.1	0.097
Percent change	−3.5 ± 30.2	−20.9 ± 27.2	0.013	−20.4 ± 21.2	−25.7 ± 25.7	0.345
IGFBP-3 (mg/ml)*						
Baseline	3.2 ± 0.51	3.0 ± 0.60	0.234	2.9 ± 0.78	2.8 ± 0.72	0.527
Follow-up	3.3 ± 0.91	3.1 ± 0.73	0.232	2.9 ± 0.75	2.6 ± 0.65	0.043
Percent change	−3.7 ± 13.3	3.4 ± 20.9	0.182	4.0 ± 29.8	−6.1 ± 21.1	0.129
Osteocalcin (ng/ml)*						
Baseline	18.9 ± 8.3	19.3 ± 8.8	0.829	10.4 ± 5.8	9.7 ± 5.2	0.615
Follow-up	12.6 ± 6.7	10.3 ± 4.6	0.097	7.7 ± 2.9	6.7 ± 3.3	0.155
Percent change	−22.9 ± 52.9	−34.4 ± 44.1	0.317	−4.3 ± 56.2	−22.8 ± 35.3	0.138
N-telopeptides/creatinine (nmol/l BCE/mmol/l creatinine)*						
Baseline	76.9 ± 35.9	80.3 ± 49.4	0.737	32.2 ± 12.7	34.0 ± 18.1	0.614
Follow-up	58.1 ± 28.3	47.9 ± 23.7	0.099	34.1 ± 17.5	32.0 ± 13.8	0.604
Percent change	−20.7 ± 28.9	−26.3 ± 40.3	0.503	24.0 ± 91.3	7.0 ± 47.1	0.378
Adjusted data						
IGF-1 (ng/ml)†						
Baseline	310 ± 67.4	279 ± 81.8	0.090	217 ± 89.6	218 ± 64.6	0.942
Follow-up	284 ± 78.1	216 ± 83.4	0.001	161 ± 48.7	155 ± 41.1	0.558
Percent change	−5.1 ± 30.2	−19.3 ± 27.2	0.043	−20.2 ± 21.2	−26.0 ± 25.7	0.347
IGFBP-3 (mg/ml)†						
Baseline	3.2 ± 0.51	3.0 ± 0.60	0.258	2.8 ± 0.78	3.0 ± 0.72	0.525
Follow-up	3.3 ± 0.91	3.1 ± 0.73	0.434	2.9 ± 0.75	2.6 ± 0.65	0.127
Percent change	−4.3 ± 13.3	4.0 ± 20.9	0.119	5.3 ± 29.8	−8.4 ± 21.1	0.051
Osteocalcin (ng/ml)†						
Baseline	18.0 ± 8.3	20.3 ± 8.8	0.187	10.1 ± 5.8	10.2 ± 5.2	0.952
Follow-up	12.2 ± 6.7	10.6 ± 4.6	0.221	8.0 ± 2.9	6.3 ± 3.3	0.038
Percent change	−20.9 ± 52.9	−36.4 ± 44.1	0.188	0.24 ± 56.2	−30.9 ± 35.3	0.023
N-telopeptides/creatinine (nmol/l BCE/mmol/l creatinine)†						
Baseline	74.4 ± 35.9	82.9 ± 49.4	0.331	32.0 ± 12.7	34.5 ± 18.1	0.523
Follow-up	57.4 ± 28.3	48.6 ± 23.7	0.130	34.5 ± 17.5	31.1 ± 13.8	0.436
Percent change	−18.4 ± 28.9	−28.7 ± 40.3	0.214	26.8 ± 91.3	1.7 ± 47.1	0.238
A1C (%)‡						
Baseline		8.2 ± 1.2			7.4 ± 0.9	0.008
Follow-up		8.5 ± 1.5			7.6 ± 0.9	0.007
Percent change		4.3 ± 16.0			3.5 ± 12.3	0.833

Data are means ± SD. Lab values were calculated in the cohort aged <20 years for IGF-1, telopeptides/creatinine, and A1C (case subjects, n = 36); IGFBP-3 (control subjects, n = 23; case subjects, n = 22); and osteocalcin (case subjects, n = 36); and in the cohort aged ≥20 years for osteocalcin (control subjects, n = 46; case subjects, n = 25). *P values by Student's t test. †P values by ANCOVA, adjusted for age and BMI. ‡P values by Student's t test in case subjects between age-groups. BCE, bone collagen equivalent.

higher than average BMD compared with control subjects (13), in part due to the mechanical load of obesity. In our study, women with type 1 diabetes had higher BMI than control subjects. However, BMD continued to be lower in older women with type 1 diabetes, even after adjusting for BMI; thus, overweight status does not confer protection against poor bone mineralization in these young women.

Although the younger cohort had poorer diabetes control than the older cohort, we were again unable to demonstrate an association between BMD measures and metabolic control, as measured by A1C. Others have reported similar findings with respect to BMD in children and adolescents with diabetes (14). A1C measures short-term diabetes control; perhaps cumulative life-time glycemic control is a better indicator of os-

teoporotic risk. This hypothesis is supported by studies demonstrating that decreased lumbar spine and femoral neck BMD in adults with type 1 diabetes is associated with retinopathy, nephropathy, and peripheral neuropathy, all of which are long-term complications of poor metabolic control (15–17). In addition, our data did not find a correlation between diabetes duration and BMD, further supporting a possible relation to lifetime dia-

betes control. The adverse effects of chronic hyperglycemia related to osteoblast function, osteoclast activity, and formation of advanced glycosylated end products that may impact bone quality as well as bone quantity (18) are difficult to measure in a systematic fashion.

The role of insulin as a direct anabolic agent in bone metabolism is unclear (19). Animal models of spontaneous and pharmacologically induced diabetes demonstrate that as insulinopenia develops, there is a suppression of osteoblast markers (20). It has been postulated that in addition to insulinopenia, relative IGF-1 deficiency, whether systemic or local, contributes to low BMD in diabetes. IGF-1 levels are lower in individuals with type 1 diabetes, and poor glycemic control negatively impacts IGF-1 production by the liver. In adults with type 1 diabetes, IGF-1 levels were lower in individuals with osteopenia at the femoral neck (1). Additionally, in a study of 127 children (aged 6–20 years) with diabetes, low bone mineral content correlated with low IGF-1 levels (9). In our study, IGF-1 levels of case subjects were significantly lower than those of control subjects only for the younger cohort. However, IGF-1 levels of subjects with diabetes were lower in the group ≥20 years of age compared with the group <20 years of age, and IGFBP-3 levels in the older cohort were significantly lower compared with control subjects. Given that no biochemical markers of bone metabolism correlated with BMD at the hip or femoral neck in our study, it could be hypothesized that a cumulative history of insulinopenia and low IGF-1 levels are better correlates for low bone density. These proposed mechanisms require further exploration.

Our data demonstrate significant differences in BMD at the femoral neck and total hip that are likely to be clinically significant and may explain why women with type 1 diabetes have an increased risk of hip fractures later in life (4,5). Our data also indicate that alterations in bone mineral accrual occur within years of achievement of peak bone mass and that there is not a later period of "catch-up" bone mineralization. The most clinically relevant factor is whether a decrease in BMD correlates with fracture risk, which cannot be determined in this study. Besides BMD, multiple factors impact fracture risk including, but not limited to, age, nutrition status, smoking history, degree of frailty, and fracture history (21).

The well-characterized population,

the large percentage of women who participated in the follow-up study, and the standard procedures used in this longitudinal study all represent significant strengths. Yet, we acknowledge certain limitations. The study population is small, limiting its ability to detect true differences that may still exist. Study control subjects were community based and may not represent the general population of women. Finally, the results presented should be interpreted keeping in mind that multiple comparisons were made. We are aware of the lack of unanimity of opinion regarding the statistical approach when adjusting the statistical testing for many comparisons (22). Because many of our hypotheses are nested, and not independent, we feel that using a Bonferroni approach is overly conservative. However, we have interpreted our results with caution and believe they are stronger when considered as a whole rather than as independent statistical tests.

Our findings demonstrate lower BMD in young women with type 1 diabetes compared with control subjects. The differences are seen at early ages and may impact future fracture risk. Although bone density testing is not routinely performed in young women, these data suggest that screening may be important in young women with type 1 diabetes. In addition, these women should be counseled regarding lifestyle interventions that may improve bone health, including adequate intake of calcium and vitamin D, and exercise.

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