Does Low Bone Mineral Density Start in Post-Teenage Years in Women With Type 1 Diabetes?

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OBJECTIVE — Type 1 diabetes has been associated with decreased bone mineral density (BMD). However, the natural history and etiopathogenesis of osteoporosis in type 1 diabetes are not clear. The aims of this study were to assess BMD in a cohort of young women with type 1 diabetes compared with nondiabetic control subjects and to evaluate the possible association of BMD with diabetes duration, HbA_{1c}, and biomarkers of bone metabolism.

RESEARCH DESIGN AND METHODS — BMD was measured by dual-energy X-ray absortiometry scan in 39 teenage (age 13–19 years) and 33 post-teenage females (age 20–37 years) with type 1 diabetes and 91 female age-matched control subjects. Serum osteocalcin, IGF-I, IGF binding protein-3 (IGFBP-3), HbA_{1c}, and urine N-telopeptides were measured.

RESULTS — After adjustment for age and BMI, BMD values were significantly lower at the femoral neck and lateral spine in women with type 1 diabetes older than age 20 years compared with control subjects but not in the case subjects younger than age 20 years, nor at the anterioposterior spine, wrist, or whole body. No association was found between BMD and diabetes duration or glycemic control. IGF-I, IGFBP-3, osteocalcin, and N-telopeptides were similar in diabetic subjects and control subjects.

CONCLUSIONS — This study indicates that women with type 1 diabetes exhibit BMD differences early in life with significant differences already present in the post-teenage years. Lower hip BMD in these young women may explain, in part, the higher incidence of hip fracture experienced in postmenopausal women with type 1 diabetes.

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Osteoporosis, a common disease associated with reduced bone mineral density (BMD), affects up to 40% of women at some point during their life and is a major cause of morbidity and mortality, particularly among elderly Caucasian women (1). There is evidence that adults with type 1 diabetes have decreased bone mass compared with control subjects, and a 12-fold increase in hip fracture has been reported in postmenopausal women with type 1 diabetes (2). However, the natural history of osteopenia/osteoporosis in type 1 diabetes is unknown, and the underlying mechanism remains controversial.

Most of the studies published to date have focused on the epidemiology of osteoporosis in middle aged and postmenopausal women with type 1 diabetes, whereas fewer studies have focused on younger patients with type 1 diabetes (2–5). The data concerning the status of BMD at the time of type 1 diabetes diagnosis are inconsistent with some studies showing that new onset type 1 diabetes in adults may already be associated with low BMD (6). Other studies have suggested that metabolic control plays a stronger role in the genesis of osteopenia than age and/or duration (7). Debate also exists regarding the etiopathogenesis of early osteopenia in type 1 diabetes with some studies supporting an imbalance between bone formation and absorption (8).

BMD in young women with type 1 diabetes has not been studied in a well-defined cohort of patients. In fact, information is lacking on the BMD status of young women with type 1 diabetes in the postpubertal and post-teenage years when BMD acquisition is high and for the most part reaches its peak. Our preliminary cross-sectional findings in female teenagers with type 1 diabetes showed that BMD, although still within normal limits, tended to be lower compared with age-matched control subjects (9). The aims of the current study were to assess BMD measures in a larger cohort of teenagers and post-teenage women with and without type 1 diabetes and to evaluate the impact of diabetes duration, metabolic control, and biomarkers of bone metabolism on BMD status.

RESEARCH DESIGN AND METHODS

— Study participants were recruited from a diabetes clinic at a regional tertiary pediatric hospital and from endocrinology practices (cases) in Western New York. Control subjects were recruited from the general population of the same region. Recruitment of case subjects

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Abbreviations: BMD, bone mineral density; CSII, continuous subcutaneous insulin infusion; IGFBP-3, IGF binding protein-3; RIA, radioimmunoassay.

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

was done by both personal communication and advertisements. Control subjects were recruited by advertisements and friend referrals. The inclusion criteria were as follows: females age 13–37 years, interval elapsed from menarche ≥2 years and age at menarche between 10 and 16 years, signed informed consent, and negative pregnancy test. For subjects with diabetes, additional inclusion criteria were as follows: medical history/records consistent with type 1 diabetes and insulin therapy delivered with at least two daily injections or continuous subcutaneous insulin infusion (CSII). In subjects younger than age 18 years, both the study participant and one parent signed the informed consent. Exclusion criteria were as follows: evidence of a systemic illness (other than diabetes) that would affect BMD, other endocrine disorders except autoimmune thyroiditis, and diagnosis of juvenile osteoporosis or other bone diseases. The study was approved by the Institutional Review Boards of the Women and Children's Hospital of Buffalo and the University at Buffalo.

Determination of current weight, height, and blood pressure were performed using standardized protocols. Study participants were asked to complete questionnaires pertinent to personal health, family health, lifestyle habits, and dietary intake. Questions assessed history of fracture, cigarette smoking, menstrual history, caffeine intake, physical activity, demographic information, current medication intake, and calcium supplement use. For participants with type 1 diabetes, information on disease duration, insulin administration, and complications were collected.

Dual-energy X-ray absorptiometry (Hologic QDR-4500A; Hologic, Waltham, MA) was used to measure BMD in the anterior posterior and lateral spine (lumber 1–lumber 4), femoral neck, wrist, and total body. The following biomarkers were measured in blood samples obtained between days 20 and 24 of the participants' menstrual cycle: serum osteocalcin by radioimmunoassay (RIA), IGF-I by RIA, IGF binding protein-3 (IGFBP-3) by RIA, estradiol by chemiluminescence (Bayer Diagnostics Kit with ACS 180 equipment; Bayer Diagnostics, Norwood, MA), and HbA_{1c} by high-performance liquid chromatography with Bio-Rad variant (Bio-Rad, Richmond, CA). Random urine samples were collected for N-telopeptide and analyzed by enzyme-linked immunoabsorbent assay. All hormonal studies were performed at Esoterix Laboratory (Calabasas Hills, CA). HbA_{1c} was measured at the Women and Children's Hospital of Buffalo Laboratory.

Table 1—*Demographic and clinical characteristics of the study, population*

	Age <20 years		Age >20 years	
	Control subjects (n = 37)	Type 1 diabetes (n = 39)	Control subjects (n = 54)	Type 1 diabetes (n = 33)
Age (years)	16.5 ± 1.5	16.4 ± 1.8	26.5 ± 4.4	27.6 ± 4.3
Weight (kg)	61.9 ± 11.1	65.4 ± 9.2	63.1 ± 9.6	69.9 ± 8.8*
BMI (kg/m^2)	22.8 ± 3.8	24.2 ± 3.2	22.8 ± 3.4	25.2 ± 3.0†
Non-Hispanic Caucasian	33 (89.2)	39 (100)	52 (96.3)	31 (93.9)
Other race	4 (10.8)	0 (0)	2 (3.7)	2 (6.1)
Age at menarche (years)	12.4 ± 1.1	12.2 ± 1.4	12.8 ± 1.2	13.3 ± 1.6
Years from menarche	4.3 ± 1.8	4.4 ± 2.0	12.8 ± 4.2	13.6 ± 4.2
Contraceptive usage	4 (10.8)	5 (12.8)	38 (70.4)	24 (72.7)
Years on contraceptive	0.066 ± 0.28	0.099 ± 0.38	2.45 ± 2.84	3.35 ± 3.85
Smoking status	1 (2.7)	8 (20.5)*	6 (11.3)	5 (16.1)

Data are means ± SD and n (%). *$P < 0.05$; †$P < 0.01$, P values are control versus case subjects in the same age-group (Student's t test for continuous variables and χ^2 for categorical data).

The study participants were divided into two groups based on a cutoff age of 20 years with the rationale of separating those who may still be attaining their peak BMD from those who have largely reached peak bone mass. Moreover, differences exist in the hormonal parameters examined between teenage and post-teenage subjects.

Demographic, lifestyle, metabolic characteristics, and BMD were compared between diabetic subjects and control subjects. Differences for continuous variables were examined using univariate two sample t tests, whereas for categorical variables differences were assessed using the χ^2 test. The assumption concerning multivariate normality of BMD measurements at different sites was verified using graphical diagnostics. T^2-Hotelling test and multiple analysis of variance were used to compare mean BMD vectors between patients with diabetes and control subjects (unadjusted and adjusted for age and BMI) for each age group separately. In the case where the BMD mean vectors were found to be statistically different (women ≥20 years of age), pair wise comparisons were made using analysis of covariance adjusted for age and BMI. To control for multiple comparisons, a Bonferroni adjustment was used to declare statistical significance at 0.05 levels. Data analyses were performed using SAS version 8 (SAS, Cary, NC).

RESULTS — The characteristics of the study participants are presented in Table 1. The study includes 72 females with type 1 diabetes and 91 control subjects, age 13–37 years. Non-Hispanic Caucasian participants were predominant in the study population (95%, n = 155). Only 6.5% of the control subjects and 2.7% of the patients with diabetes were of other races. BMI was higher in the diabetic groups compared with the age-matched control subjects with this difference being statistically significant among those older than age 20 years. In those younger than 20 years, the frequency of cigarette smoking was significantly lower in control subjects compared with the subjects with diabetes. Age at menarche, interval from menarche, and oral contraceptive use were similar in subjects with diabetes and control subjects in both teenage and post-teenage groups. Post-teenage patients with diabetes had significantly lower insulin requirements. They were more likely to have kidney, eye, and neurological complications and to be hypertensive than those younger than age 20 years, although these differences were not statistically significant (Table 2).

Significant BMD differences were found among those >20 years (P = 0.0045, T^2 Hotelling), and these differences persisted after adjustment for age and BMI (P = 0.0008, multiple ANOVA). No significant differences were found in the younger group. Table 3 presents BMD

Table 2—*Diabetes-related characteristics*

	Age <20 years (n = 39)	Age >20 years (n = 33)
Diabetes duration (years)	7.1 ± 3.9	14.5 ± 5.7**
Insulin injections	33 (84.6)	16 (48)
CSII	6 (15.4)	17 (51.5)**
Insulin requirement ($U \cdot kg^{-1} \cdot day^{-1}$)	0.95	0.74*
Kidney problems	4 (10.3)	9 (27.3)
Eye problems	1 (2.6)	4 (12/1)
Neurological problems	1 (2.6)	3 (9.1)
Hypertension medication/s	3 (7.7)	8 (24.2)
Levothyroxine replacement	6 (15.4)	4 (12.1)

Data are *n* (%). *$P < 0.05$; **$P < 0.01$, Student's *t* test for continuous variables and χ^2 for categorical data.

data adjusted for age and BMI for each site according to age-group. In the ANCOVA model, adjusted for age and BMI, BMD values at the femoral neck ($P = 0.001$) and lateral spine ($P = 0.009$) were significantly lower among subjects with type 1 diabetes compared with healthy nondiabetic control subjects. A Bonferroni adjustment ($\alpha = 0.05/5 = 0.01$) was used to declare statistical significance to compensate for multiple comparisons. Whereas the number of smokers was higher among the patients with diabetes aged <20 years compared with control subjects, the introduction of smoking status in the regression model did not alter the results.

The case subjects were in variable degrees of metabolic control. Similar to what is reported in the literature, teenagers had overall poorer metabolic control (HbA_{1c} 8.4 ± 1.7%) compared with the post-teenage group (7.8 ± 1.7%; Table 4). No association was found between HbA_{1c} and any of the BMD measures. The insulin dose, collected only for case subjects receiving insulin injections, was 0.82 $U \cdot kg^{-1} \cdot day^{-1}$ and did not correlate with BMD measurements. Moreover, no association was found between BMD measures and diabetes duration, age at menarche, or interval time elapsed from menarche.

IGF-I, IGFBP-3, osteocalcin, and N-telopeptides were not significantly different between case and control subjects (Table 4). As expected, the values of bone formation and absorption biomarkers were higher in the study participants younger than age 20 years compared with older subjects, a finding in keeping with the fact that BMD continues to increase into the late teens. However, no statistical differences were observed in the bone biomarkers between case and control subjects within comparable age-groups. Within age strata, IGF-I and IGFBP-3 levels were not statistically different in patients with type 1 diabetes compared with control subjects. Estradiol levels were within ranges expected in the late follicular phase and were not different between subjects with diabetes and control subjects.

CONCLUSIONS — These data demonstrate that BMD appears to be lower in women with type 1 diabetes age 20–37 years compared with age-matched control subjects: specifically, BMD was found to be significantly lower at the femoral neck and lateral spine. It should be noted that control subjects were volunteers and not a population-based sample; however, control subjects were similar to the U.S. population with respect to key variables, including BMI and height (10). Additionally, mean BMD at the femoral neck in control subjects was similar to published data in women with comparable age (11,12). No significant differences in BMD were seen between case and control subjects in the subjects <20 years of age. Our data are consistent with the hypothesis that BMD differences in type 1 diabetes may begin early in life, perhaps by the early post-teenage years.

Similar to other published studies, we were unable to demonstrate an association between BMD measures and metabolic control or diabetes duration (range 2–30 years). The differences in BMD values between case and control subjects persisted even after adjustment for age and BMI, which are two factors found to be associated independently with BMD in our study. Other potential confounding variables were assessed and determined to have no demonstrable impact on the association between BMD and type 1 diabetes, including smoking, race, age at menarche, and contraceptive use. Serum estradiol level was not associated with glycemic control status or with BMD. BMD differences found in young women over age 20 years could presumably be associated with type 1 diabetes through many mechanisms, potentially including the effect of treatment regimen (insulin), diabetes sequelae, or some other mechanism. Osteopenia has been reported to be present at the onset of type 1 diabetes, suggesting the existence of pathogenic mechanisms that operate before the overt manifestation of type 1 diabetes (13). It is well established that islet cell destruction and insulinopenia begin several years be-

Table 3—*Bone mineral density measurements (g/cm^2)*

	Age <20 years			Age >20 years		
	Control subjects (n = 37)	Type 1 diabetes (n = 39)	P	Control subjects (n = 54)	Type 1 diabetes (n = 33)	P
Femoral neck	0.886 ± 0.13	0.859 ± 0.10	0.300	0.881 ± 0.11	0.804 ± 0.11	0.001
Wrist	0.533 ± 0.06	0.530 ± 0.05	0.780	0.570 ± 0.04	0.555 ± 0.04	0.107
AP spine	0.997 ± 0.11	0.970 ± 0.09	0.213	1.056 ± 0.11	1.028 ± 0.10	0.236
Lateral spine	0.818 ± 0.10	0.820 ± 0.08	0.908	0.874 ± 0.08	0.825 ± 0.08	0.009
Whole body	1.090 ± 0.09	1.063 ± 0.08	0.144	1.141 ± 0.08	1.105 ± 0.09	0.064

Data are (mean ± SD). Adjusted for age and BMI. *P* values are by ANCOVA statistical significance of $P < 0.01$ (Bonferroni adjustment). AP, anterio-posterior.

Table 4—*Glycemic control and hormonal values*

	Age <20 years		Age >20 years	
	Control subjects	Type 1 diabetes	Control subjects	Type 1 diabetes
HbA_{1c} (%)	5.2 ± 0.4 (24)	8.4 ± 1.7 (39)*	5.2 ± 0.3 (51)	7.8 ± 1.6 (32)*
IGF-I (ng/ml)	304 ± 68.5 (37)	284 ± 81.6 (39)	224 ± 85.6 (54)	200 ± 61.7 (32)
IGFBP-3 (ng/ml)	3.2 ± 0.52 (24)	3.1 ± 0.64 (25)	2.9 ± 0.75 (54)	2.8 ± 0.70 (32)
Osteocalcin (ng/ml)	18.6 ± 8.3 (37)	19.3 ± 8.5 (39)	10.5 ± 5.7 (51)	9.2 ± 4.9 (31)
N-Telopeptides/creatinine ratio (nm BCE/mm creatinine)	76.0 ± 35.8 (37)	79.4 ± 48.2 (37)	32.3 ± 12.5 (54)	32.9 ± 16.7 (32)
Estradiol (ng/dl)	7.7 ± 4.7 (24)	12.8 ± 13.2 (23)	7.7 ± 7.5 (52)	8.2 ± 8.7 (32)

Data are means ± SD (*n*). *$P < 0.05$ controls vs. cases in the same age group (Student's *t* test). BCE, bone collagen equivalent.

fore the onset and clinical recognition of disease. It is possible, therefore, that some of the autoimmune and auto inflammatory response, ongoing before and after diabetes onset, may be playing a role in bone loss (14).

There is lack of agreement regarding the relationship between diabetes microvascular complications and osteopenia. In a prospective study, Pastor et al. (15) have shown that the percentage of patients with osteopenia or osteoporosis was significantly higher in a group of older patients with retinopathy. The interpretation of the data is difficult because it is unclear whether the data have been adjusted for age, BMI, and diabetes duration. A histomorphometric evaluation of 118 patients with diabetes revealed significant osteopenia, decreased erythropoiesis with a concomitant increase in fatty tissue, and reduced sinusoidal capillaries. Microangiopathy was found in 82% of biopsy specimens in subjects with diabetes (16). However, other data similar to ours have not demonstrated an association between known diabetes complications (retinopathy, hypertension, microalbuminuria) and BMD, thus suggesting that bone loss in type 1 diabetes may not be viewed as part of the constellation of the classic diabetes complications but rather two distinct outcomes related to diabetes progression.

Differences in menstrual history may be present in type 1 diabetic subjects compared with control subjects and may have an impact on BMD. Ours is the first study where BMD data were examined in the context of age at menarche in a population of young women with type 1 diabetes. In our study, age at menarche is not significantly different in patients with diabetes compared with control subjects, and age at menarche is compatible with the reported normative data for the U.S. population (12.6 years) (17). This is a relevant finding in view of the data reporting that age of menopause is significantly younger in women with type 1 diabetes (mean age 45 years) compared with U.S. women overall (18). Evidence of a shorter period of time with reproductive levels of endogenous estrogens as a result of younger age at menopause in women with type 1 diabetes may not be the only mechanism by which postmenopausal women with type 1 diabetes are at higher risk of fracture. More likely it is a combination of factors related to bone acquisition and bone loss.

Both insulin and IGF-I are potent growth factors playing a key role in bone metabolism. In animal studies, insulin infusion normalized the number of osteoblasts, serum osteocalcin, and IGF-I concentrations without, however, normalizing bone mineralization. This finding suggests that additional factors other than insulinopenia contribute to osteopenia in type 1 diabetes (19). In a small study ($n = 35$) carried out in the Netherlands, IGF-I values were significantly lower in individuals with osteopenia at the femoral neck but not in the overall group with type 1 diabetes compared with control subjects (20). This study also found a correlation between IGF-I and BMD at the femoral neck or spine. In our study, IGF-I values were not lower in patients with diabetes compared with control subjects. This may be due to the fact that serum concentrations do not necessarily reflect autocrine production. Yet recent data in an animal model demonstrate that a threshold of circulating IGF-I is necessary for normal bone growth, confirming that IGF-I and IGFP-3 play a prominent role in the pathophysiology of osteoporosis (21). Based on the above data and on the possibility of low IGF-I levels in type 1 diabetes, the possible relationship between IGF-I, IGFBPs, and BMD in type 1 diabetes needs to be further explored.

No association was found between HbA_{1c} or diabetes duration and BMD in analyses restricted to the subset of women with type 1 diabetes. This may suggest that diabetes control does not play a major role in the genesis of bone loss in type 1 diabetes. However, this finding is limited by the fact that the HbA_{1c} at the time of dual-energy X-ray absorptiometry scan is only reflective of short-term glycemic control. Moreover, our study population includes young women with relatively recent diabetes onset and fewer diabetes complications compared with other studies.

The early bone loss at the femoral neck site is clinically significant, suggesting that BMD may decrease relatively early in the course of the disease. Thus, type 1 diabetes may impact peak bone acquisition at an early age, leading to the higher risk of low bone density and subsequent hip fracture in postmenopausal women. However, the results of this study should be viewed cautiously given that this is a relatively small cross-sectional study. Larger longitudinal studies assessing the association of type 1 diabetes and bone density, with appropriate control of potential confounding factors, are needed to further understand the link between the metabolic disturbance and BMD in type 1diabetes. It is critical to determine the relationship between type 1 diabetes and bone density in young women. This information will allow us to better understand the mechanisms by which bone loss occurs in these women and ultimately to implement strategies for prevention of bone loss and fracture.

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