Bone Mineral Density in Patients With Type 1 and Type 2 Diabetes

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OBJECTIVE — To assess the effect of type 1 and type 2 diabetes and insulin treatment on bone mineral density (BMD) in middle-aged and elderly men and women.

RESEARCH DESIGN AND METHODS — We measured BMD and evaluated known determinants of osteoporosis in 56 type 1 and 68 type 2 diabetic patients and 498 nondiabetic community control subjects. All patients, aged 52–72 years, developed diabetes after the age of 30 years (i.e., after achievement of peak bone mass) and were treated with insulin. BMD was measured at the proximal femur with dual-energy X-ray absorptiometry.

RESULTS — Among both sexes, BMD values were significantly lower in type 1 diabetic patients than in type 2 diabetic patients or the control subjects. When adjusted for age and BMI, the differences between type 1 diabetic patients and control subjects remained essentially unchanged in both sexes, whereas the differences between type 1 and type 2 diabetic subjects were significant only in men. After further adjustments for confounding factors, the average BMD values were still lower in type 1 diabetic subjects than in type 2 diabetic subjects although with lesser significance. Past low-energy fractures were more common in type 1 diabetic women than in type 2 diabetic women.

CONCLUSIONS — The lower BMD in type 1 versus type 2 diabetic patients and control subjects probably results from more rapid bone loss after the onset of type 1 diabetes. This cannot be explained by insulin treatment, which was prescribed for both types of patients. Because the causes of low BMD in type 1 diabetes are unknown, these patients should be evaluated for the risk of osteoporosis and related fractures and offered appropriate preventive measures.

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There is still some controversy about the levels of bone mineral density (BMD) and the risk of osteoporosis in type 1 and type 2 diabetes. Most but not all studies have reported low BMD values in type 1 diabetes (1–7). On the other hand, there are studies showing lower (8–10), similar (11,12), or higher BMD values (13–17) in type 2 diabetes than in nondiabetic control subjects. A prerequisite for reliable comparisons of BMD between type 1 and type 2 diabetes is that patients with either type of diabetes are examined in a single study according to the same protocol by using identical methods. Few studies so far have included both type 1 and type 2 diabetic patients. Giacca et al. (18) found no differences in radial BMD between control subjects and patients with type 1 or type 2 diabetes. Buysschaert et al. (19) reported low BMD values in type 1 diabetic patients of both sexes and in male patients with type 2 diabetes but found normal values in female patients with type 2 diabetes. Krakauer et al. (20) found lower baseline BMD values in both types of diabetic patients than in nondiabetic control subjects. In this study, measurements 12 years later showed that bone loss had continued in type 1 but not in type 2 diabetic patients (20). In these three studies, type 2 diabetic patients were treated with diet, oral hypoglycemic agents, and/or insulin.

The causes of the presumably different levels of BMD in type 1 and type 2 diabetic patients are not known. Moreover, it is not known whether the low BMD in type 1 diabetic patients results from reduced peak bone mass or from increased bone loss. To our knowledge, there are no earlier studies on BMD in type 1 diabetic patients who have developed the disease after the age of 30 years (i.e., after the age by which the peak bone mass is generally attained). Moreover, there are no previous studies evaluating the role of insulin treatment on BMD in diabetic patients.

Therefore, we decided to assess the effect of type 1 and type 2 diabetes on femoral BMD in patients with onset of either type of diabetes after 30 years of age, all of whom were treated with insulin. The results from the diabetic patients were compared with those of nondiabetic control subjects of a similar age who were recruited from the same geographical region.

RESEARCH DESIGN AND METHODS

Patients with diabetes

The diabetic patients participated in a large epidemiological survey assessing cardiovascular diseases and their risk factors in diabetes (21). Briefly, the inclusion criteria for the survey were: *1*) 45–64 years of age, *2*) diabetes diagnosed ≥30 years of age, and *3*) residence and place of birth in the Turku University Central Hospital district in southwestern Finland. Altogether, 639 diabetic patients (73% of those invited) participated in the baseline examination in 1982–1984, and 158 of them were being treated with insulin (22). Plasma C-peptide after glucagon stimulation was measured in all of these patients.

In 1990, a questionnaire was sent to all surviving diabetic patients. Patients treated with insulin at baseline and those who had been switched to insulin therapy thereafter were invited to a clinical reexamination, including measurement of BMD. Of the eligible 182 patients, 137 attended the reexamination, and 136 underwent

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Abbreviations: BMD, bone mineral density.

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

Table 1—*Characteristics of men with and without diabetes*

Characteristic	Type 1 diabetes (n = 29)	P (type 1 vs. type 2)	Type 2 diabetes (n = 34)	Control (n = 240)	P (type 1 vs. control)	P (type 2 vs. control)
Age (years)	60.5 ± 4.3	0.015	63.3 ± 4.5	62.4 ± 5.0	0.056	NS
BMI (kg/m^2)	25.3 ± 2.4	0.046	26.8 ± 3.1	27.1 ± 3.7	<0.001	NS
Use of loop diuretics	6.9	NS	14.7	2.9	NS	0.009
Use of thiazides	6.9	NS	8.8	8.3	NS	NS
Fractures	0	NS	3.0	2.5	NS	NS
Physically active						
At baseline	79.3	NS	82.4	—	—	—
At BMD measurement	79.3	NS	76.5	83.8	NS	NS
Current smokers	10.3	NS	11.8	15.4	NS	NS
Former smokers	51.7	NS	38.2	47.1	NS	NS
Alcohol users	10.3	NS	2.9	4.6	0.182	NS
Calcium intake (mg/day)	1,206 ± 531	NS	1,053 ± 497	983 ± 565	0.045	NS

Data are means ± SD or %.

femoral BMD measurement. We excluded five patients who had undergone lower-limb amputation. In addition, BMD measurement was not performed in one patient. Plasma C-peptide was measured in patients whose baseline plasma C-peptide had exceeded the detection limit of the assay (0.10 nmol/l) and in patients who had been switched from peroral therapy to insulin between the two examinations. We excluded four patients in whom the C-peptide test was erroneously not performed and three patients in whom baseline insulin treatment had been withdrawn.

These exclusions left 124 patients remaining who were treated with insulin at the time of the BMD measurement. Those who had undetectable stimulated C-peptide values at the baseline examination and those who had a C-peptide value <0.20 nmol/l at the follow-up examination were defined as type 1 diabetic patients (n = 56), and the remainder were considered to have type 2 diabetes (n = 68). The stimulated C-peptide level of 0.20 nmol/l was chosen because it has previously been shown to distinguish between type 1 and type 2 diabetes (23).

Nondiabetic control subjects

Nondiabetic control subjects, aged 57–67 years, were randomly drawn from the population registers of the city of Turku and surrounding rural and urban communities in southwestern Finland. Femoral neck and trochanter BMD measurements were obtained from 533 subjects (63% of those contacted in random sampling order). The measurements in the control group were carried out in parallel to those in the diabetic patient series by the same personnel using the same equipment. Seven subjects were excluded because of missing background information, and 28 were excluded due to diabetes. This left 498 subjects (240 men and 258 women) in the nondiabetic control group.

Methods

Participants were defined as alcohol users if they consumed more than three portions of alcohol per day (one portion = a bottle of beer, 12 cl of wine, or 4 cl of strong alcoholic drinks). To be defined as a current smoker required a smoking history of at least 1 year. Similarly, subjects who had smoked for at least 1 year at any time during their lives but had quit were considered former smokers. Those who were engaged in physically demanding hobbies or sports or other heavy exercise during their leisure time were classified as physically active. Women were defined as estrogen users if they had used estrogen for at least 1 year after menopause. Subjects who had used diuretics for at least 1 year were defined as diuretic users. Calcium intake (mg/day) was calculated from the use of dairy products.

BMD (g/cm^2) was measured in the proximal femur (the neck and the trochanteric region) by using dual-energy X-ray absorptiometry (Norland XR-26 Mark II; Norland, Fort Atkinson, WI).

Endogenous insulin secretion capacity was assessed by plasma C-peptide measurement 6 min after intravenous injection of 1 mg of glucagon (24). At baseline, HbA_1 was determined by affinity chromatography (Isolab, Akron, OH; reference range 5.5–8.5%). At the reexamination, HbA_{1c} was determined with fast liquid chromatography (MONO S HR 5/5; Pharmacia, Uppsala, Sweden; reference range 4.2–6.0%).

Statistical methods

The data analyses were performed with SAS statistical software (SAS Institute, Cary, NC). For comparisons of the basic characteristics between the groups, we used Student's t test for numerical variables and the χ^2 test or Fisher's test for categorical variables. Variables with skewed distributions were analyzed after log transformation. BMD results between the groups were compared with the t test (unadjusted) or analysis of covariance when numerical or categorical covariates were present. This was done with the general linear models procedure, which was also used to calculate the adjusted mean BMD values. According to the study protocol, the subjects with type 1 and type 2 diabetes were first compared mutually and thereafter one by one with the control group. An additional overall comparison of all three groups was needed to calculate comparable adjusted mean values for Fig. 1. For all comparisons, the exact P values <0.20 are given. Higher P values are marked as NS.

The study was approved by the Ethics Committee of the Research and Development Centre of the Social Insurance Institution. All subjects gave informed consent.

RESULTS — Characteristics of the study populations are given in Tables 1 and 2. Patients with type 2 diabetes were an average of 2.8 years older than patients with type 1 diabetes. Compared with control

Table 2—*Characteristics of women with and without diabetes*

Characteristic	Type 1 diabetes (n = 27)	P (type 1 vs. type 2)	Type 2 diabetes (n = 34)	Control (n = 258)	P (type 1 vs. control)	P (type 2 vs. control)
Age (years)	61.7 ± 6.3	0.064	64.4 ± 4.8	61.9 ± 5.0	NS	0.007
BMI (kg/m²)	25.2 ± 3.7	<0.001	30.7 ± 4.6	27.6 ± 5.2	0.004	0.001
Use of estrogens	7.4	NS	17.7	34.5	0.004	0.049
Use of loop diuretics	11.1	0.134	26.5	5.0	0.184	<0.001
Use of thiazides	3.7	NS	14.7	8.9	NS	NS
Age of menarche (years)	14.1 ± 1.4	NS	14.2 ± 1.6	14.0 ± 1.6	NS	NS
Age of menopause (years)	48.7 ± 4.3	NS	49.4 ± 4.2	48.6 ± 4.9	NS	NS
Fractures	18.5	0.014	0	10.9	NS	0.056
Physically active						
At baseline	77.8	NS	64.7	—	—	—
At BMD measurement	77.8	0.008	44.1	81.0	NS	<0.001
Current smokers	11.1	NS	5.9	7.4	NS	NS
Former smokers	11.1	NS	5.9	9.7	NS	NS
Alcohol users	0		0	0		
Calcium intake (mg/day)	1,083 ± 436	0.082	904 ± 352	834 ± 402	0.003	NS

Data are means ± SD or %.

women, BMI was higher in women with type 2 diabetes and lower in women with type 1 diabetes. Men with type 1 diabetes had lower BMI than men with type 2 diabetes and control men. The use of loop diuretics was more frequent among men and women with type 2 diabetes than among control subjects. Compared with control subjects, type 2 and especially type 1 diabetic women used estrogen less frequently. None of the 34 women with type 2 diabetes but 5 of the 27 women with type 1 diabetes had had fractures in their wrists or forearms. Calcium intake was significantly higher in patients with type 1 diabetes than in control subjects.

Type 1 diabetic women had a longer duration of diabetes than type 2 diabetic women (17.6 vs. 14.9 years, respectively, P = 0.012). Among both men and women, the duration of insulin therapy was longer in type 1 than in type 2 diabetic patients (among men 15.6 vs. 9.1 years, respectively, P = 0.001; among women 15.2 vs. 4.5 years, respectively, $P < 0.001$). The insulin dose was greater in men with type 1 diabetes than in men with type 2 diabetes (0.64 vs. 0.51 U · kg^{-1} · day^{-1}, respectively, P = 0.045). At baseline, the mean value of HbA_1 was 9.81% in both type 1 and type 2 diabetic men. At reexamination, their mean HbA_{1c} values were 8.72 and 8.96%, respectively (NS). The mean baseline HbA_1 value was 10.12% in type 1 diabetic women and 10.80% in type 2 diabetic women (P = 0.092). At reexamination, their mean HbA_{1c} values were 9.27 and 9.63%, respectively (NS).

Type 1 diabetic men had significantly lower BMD values at both the femoral neck and the trochanteric region than did type 2 diabetic and control men (Table 3, Fig. 1). BMD values did not differ significantly between the two latter groups. The lower BMD values in men with type 1 diabetes compared with those found in type 2 diabetic and control subjects remained essentially unchanged after adjustment for age and BMI. The differences between the two types of diabetic men remained essentially unaltered after further adjustment for the duration of diabetes but were slightly reduced after additional adjustment for the duration of insulin therapy and insulin dose.

Table 3—*Unadjusted and adjusted mean BMD (g/cm²) in the proximal femur of men with and without diabetes*

	Type 1 diabetes (n = 29)	P (type 1 vs. type 2)	Type 2 diabetes (n = 34)	Control (n = 240)	P (type 1 vs. control)	P (type 2 vs. control)
Unadjusted						
Femoral neck	0.816 ± 0.129	0.066	0.881 ± 0.143	0.872 ± 0.131	0.031	NS
Trochanter	0.778 ± 0.135	0.019	0.860 ± 0.134	0.838 ± 0.130	0.020	NS
Adjusted for age and BMI*						
Femoral neck	0.805	0.024	0.891	0.871	0.036	NS
Trochanter	0.777	0.028	0.860	0.836	0.053	NS
Adjusted for age, BMI, and other factors*						
Femoral neck	0.803	0.040†	0.891		0.030‡	NS§
Trochanter	0.784	0.099†	0.855		0.051‡	0.196§

Data are means ± SD. *In each comparison, adjustment was made including only subjects in the two groups to be compared. Other adjustment factors: †duration of diabetes, duration of insulin therapy, insulin dose; ‡calcium intake; and §use of loop diuretics.

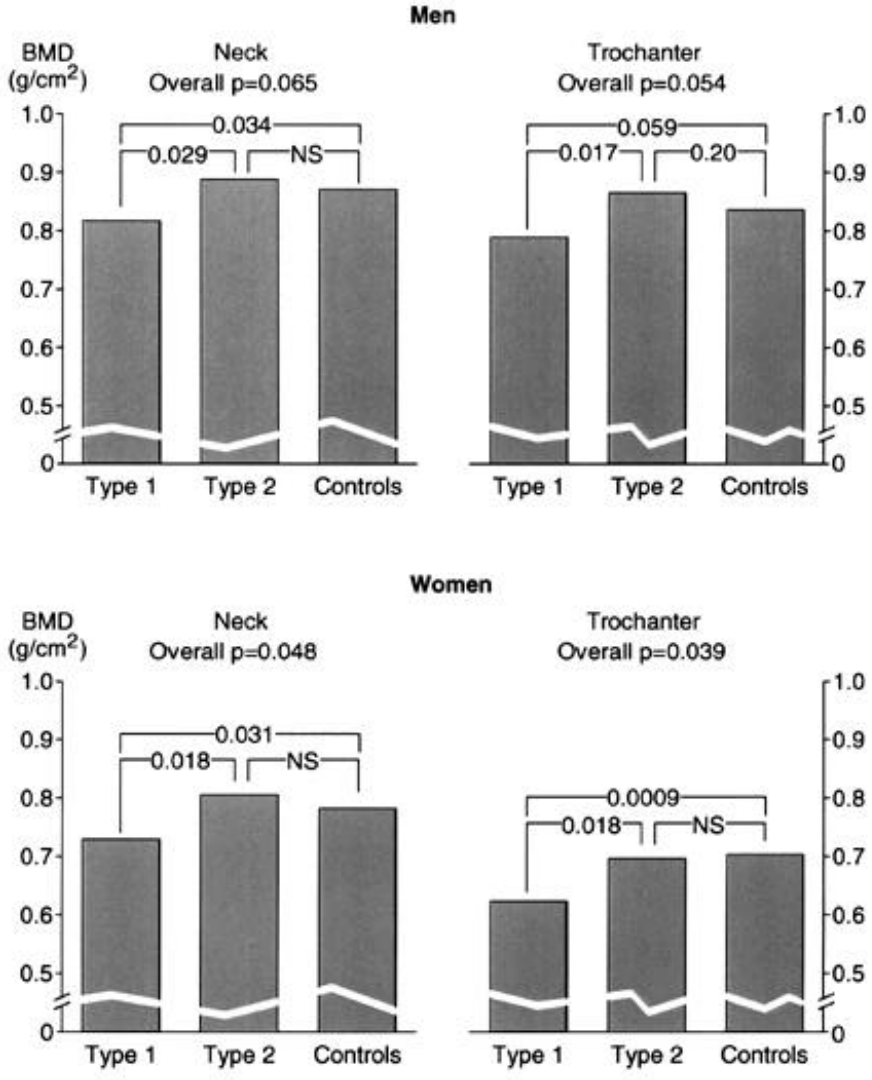

Figure 1—*Mean age- and BMI-adjusted BMD at the proximal femur of subjects with type 1 diabetes (29 men, 27 women), type 2 diabetes (34 men, 34 women), and without diabetes (240 men, 258 women).*

The differences between type 1 diabetic and control men remained after adjustment for age, BMI, and calcium intake.

In addition, type 1 diabetic women had significantly lower BMD values than did type 2 diabetic and control women (Table 4, Fig. 1). These latter groups had very similar values. After adjustment for age and BMI, the differences in BMD remained essentially unchanged between women with type 1 diabetes and control women, whereas the statistical significance was lost between women with type 1 and those with type 2 diabetes. The difference between type 1 diabetic and control women in BMD at the trochanteric region remained significant after adjustment for age, BMI, use of estrogen, and calcium intake. For BMD at the femoral neck, however, the difference was not quite significant after adjustment for these factors.

CONCLUSIONS — Our results confirm the findings of previous studies that reported lower BMD in type 1 diabetic patients than in control subjects (1–7). A new finding in our study was that low BMD in type 1 diabetic patients probably results from increased bone loss after peak bone mass has been attained. This conclusion is based on the fact that all of our patients developed diabetes after 30 years of age, and there is no reason to believe that they had not attained a normal peak bone mass before the onset of diabetes. However, we cannot completely exclude the theoretical possibility that patients with type 1 diabetes may have a lower peak bone mass due to a common genotype that makes them susceptible to both low BMD and type 1 diabetes. Our study does not rule

Table 4—*Unadjusted and adjusted mean BMD (g/cm²) in the proximal femur of women with and without diabetes*

	Type 1 diabetes (n = 27)	P (type 1 vs. type 2)	Type 2 diabetes (n = 34)	Control (n = 258)	P (type 1 vs. control)	P (type 2 vs. control)
Unadjusted						
Femoral neck	0.711 ± 0.123	0.008	0.813 ± 0.157	0.783 ± 0.129	0.007	NS
Trochanter	0.603 ± 0.103	0.004	0.709 ± 0.168	0.703 ± 0.126	<0.001	NS
Adjusted for age and BMI*						
Femoral neck	0.729	0.114	0.799	0.782	0.026	NS
Trochanter	0.624	0.111	0.692	0.703	<0.001	NS
Adjusted for age, BMI, and other factors*						
Femoral neck	0.709	NS†	0.803		0.068‡	0.074§
Trochanter	0.601	0.141†	0.709		0.002‡	NS§

Data are means ± SD. *In each comparison, adjustment was made including only subjects in the two groups to be compared. Other adjustment factors: †duration of diabetes, duration of insulin therapy, physical activity, calcium intake; ‡use of estrogens, calcium intake; §use of estrogens, use of loop diuretics, and physical activity.

out the possibility that type 1 diabetes may lead to reduced peak bone mass in patients developing diabetes at a younger age. The differences in BMD values between type 1 diabetic and control subjects were not explained by possible confounding factors such as age, BMI, calcium intake, or use of estrogen. Regarding a host of other possible confounders, the two groups were similar. The lower BMD in type 1 diabetes cannot, therefore, be explained by the known determinants of osteoporosis but is presumably a direct effect of type 1 diabetes or its treatment on bone metabolism.

Unadjusted as well as age- and BMI-adjusted BMD values were similar in type 2 diabetic patients and control subjects. No significant differences were found between the two groups even when further adjustments were made for other possible confounders. Our study confirms the results of previous studies that reported similar BMD values in type 2 diabetic and control subjects (11,12) but contradicts earlier observations of higher BMD in type 2 diabetes (13–17). These discrepancies may be explained by methodological differences and diverse patient selection criteria. For example, in the Rotterdam study (15), which showed higher than normal BMD in type 2 diabetic subjects, many of the patients had relatively mild previously undiagnosed diabetes, whereas in our patients, type 2 diabetes was of long duration and required insulin therapy.

One of the advantages of our study was that we compared BMD values in type 1 and type 2 diabetic patients of a similar age, all of whom were treated with insulin. We found a lower age- and BMI-adjusted BMD in type 1 than in type 2 diabetic men. After further adjustments, the difference was still significant at the femoral neck. In addition, among women, BMD values were lower in type 1 than in type 2 diabetic patients, although the statistical significance was lost after adjustment for possible confounding factors.

Thus, BMD is lower in type 1 than in type 2 diabetic men, and this difference is not explained by differences in BMI or insulin treatment. Insulin treatment itself is not likely to induce bone loss because, in that event, type 2 diabetic patients would have had lower BMD values than control subjects.

Although our study was not designed to compare fracture rates, it is of interest that the proportion of women with previous low-energy fractures was significantly higher for type 1 than for type 2 diabetic patients.

In conclusion, this study shows that type 1 diabetic patients have significantly lower BMD values than type 2 diabetic patients or healthy control subjects. Because the specific causes of low BMD in type 1 diabetes are unknown, these patients should be evaluated for known determinants of osteoporosis and offered all appropriate measures to prevent and treat osteoporosis with the ultimate goal of preventing fractures.

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