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Bone Mineral Density in Children and Adolescents with Diabetes Mellitus Type 1 of Recent Onset*

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Abstract. There is still controversy over the impact of diabetes control and duration on bone mass and growth parameters in children and adolescents with insulin-dependent diabetes mellitus (IDDM). The aim of this study was to assess bone mineral density (BMD) at axial and appendicular sites, in children with noncomplicated IDDM of recent onset, and its relation to metabolic control and auxological parameters (weight, height, and puberal stage). Fifty-five young Spanish IDDM, otherwise healthy patients (26 males, aged (SD 9.7 ± 4.3 years) and 29 females, aged (SD 11.2 ± 3.8 years) were studied. Duration of diabetes was 1–13.8 years. Two hundred eighty-two age-matched, healthy, Spanish children served as controls. HbA_1 was assayed by high pressure liquid chromatography (HPLC) and BMD was measured using dual X-ray absorptiometry (DXA) densitometry at the spine and forearm. Results showed a Gaussian BMD distribution of patients according to sex and age, without sexual-stage differences. There was no correlation between BMD and glycated hemoglobin (average life disease or last HbA_1 values) or duration of the disease; moreover, no differences in bone mass were found between <3 and ⩾3 years of disease duration. Diabetes impact index (mean HbA_1 × duration of disease in months) showed no significant influence of diabetes control on BMD. We could not demonstrate any impact of diabetes on BMD and growth parameters in children with IDDM of short duration.

Key words: Bone mineral density — Insulin-dependent diabetes mellitus — Auxological parameters.

Different studies support the presence of a reduced bone mineral density (BMD) in patients with juvenile and adult insulin-dependent diabetes mellitus (IDDM) [1–4] in contrast with a normal or even increased BMD in patients with noninsulin-dependent diabetes mellitus [5].

Proposed pathogenetic mechanisms for this reduced BMD are hyperglycemia [6], insulinopenia [7], alterations in mineral metabolism with an increased loss of calcium or phosphate [8], and in vitamin D metabolism [9], bone microangiopathy [10], and the production of advanced glycated end-products of type I collagen [11].

Although some studies have suggested that this osteopenia is more pronounced in poorly controlled diabetes [12] and in longstanding adult IDDM patients [13], an increase in the risk of fractures remains to be proven [4, 14], suggesting that this reduction is likely to be clinically insignificant. Conflicting results about the degree and timing of osteopenia in IDDM could be due to heterogeneous groups of subjects studied, and to different bone measurement procedures. In juvenile IDDM, metabolic disarrangements could chronically exert their influence on a continuously high-rate remodeling bone. Thus, sequential observations become critical for a proper assessment of effects of the disease on bone.

The aim of this study was to assess axial and appendicular bone mass evaluated by dual X-ray absorptiometry (DXA) in children with IDDM of short duration, and to analyze the potential relationships between bone mass and auxologic parameters with duration of the disease and the degree of metabolic control.

Patients and Methods

Subjects

Fifty-five (26 males, 29 females) young Spanish outpatients with IDDM, defined according to WHO criteria, were recruited over a 6-month period. All had been diagnosed in one hospital (HNJ) because of IDDM-related symptoms. Mean age was 9.7 ± 4.3 years (SD) in males and 11.2 ± 3.8 years in females. They had been visited regularly every 3–4 months since their diagnosis. Data were obtained from their clinical records. Patients were treated with two or more daily doses of subcutaneous insulin, and their diet and exercise were supervised at every visit. Exclusion criteria for the study included use of drugs that could interfere with bone metabolism, ketoacidosis occurring in the preceding 6 months, and the presence of chronic diabetic complications or other chronic disease. Neuropathy was evaluated by clinical history and physical examination, nephropathy by three repeated determinations of 24-hour urine microalbuminuria (>30 mg/day) measured by immunoturbidimetry, and retinopathy by fundoscopy examination. A control group of 282 healthy Spanish children (142 males and 140 females, aged 1 through 18 years) was simultaneously studied. For each patient, 12–15 control subjects were selected according to sex and age (patients' age ± 6 months). The study was authorized by our Ethical Committee, and parents gave informed consent.

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Table 1. Cross-sectional data of children with IDDM

	Age (yr)	Weight (Z-score)[a]	Height (Z-score)[a]	BMD (Z-score)[a]	Duration IDDM (yr)	Hb_{A1} (%)[b]	Insulin dose (U/kg)
Total (n = 44)	10.4 ± 4.1	−0.03 ± 1.28	0.20 ± 1.42	−0.12 ± 1.14	3.1 ± 2.6	9.8 ± 1.2	0.65 ± 0.20
Males (n = 26)	9.7 ± 4.3	0.12 ± 1.35	0.02 ± 1.55	−0.34 ± 1.00	2.6 ± 2.4	9.6 ± 1.1	0.61 ± 0.21
Females (n = 29)	11.2 ± 3.8	−0.16 ± 1.23	0.34 ± 1.31	0.07 ± 1.24	3.4 ± 3.0	9.9 ± 1.3	0.69 ± 0.20

Data are shown as mean ± SD. BMD: bone mineral density
[a] Z-scores were calculated from age- and sex-matched control group (n = 282)
[b] Mean Hb_{A1} from the time of diagnosis (normal range 6–9%)

Clinical Measurements

Height was measured on a wall-mounted stadiometer (Holtain Limited, Crymych, Dyfd, UK) to the nearest 0.1 cm. Weight was measured on a balance scale (Seca Model 220, Germany). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Z scores were obtained according to sex and age-matched controls. Sexual development was assessed in patients and in a subset of controls (n = 110), according to Tanner stages [15]. Pubertal stages were grouped for statistical purposes: stage I (infantile), stage II + III (early puberty), and stage IV + V (late puberty). Bone age was assessed from a standard X-ray film of the nondominant hand and wrist, and evaluated by two observers using Greulich & Pyle standards [16], and their mean value was calculated.

Serum Measurements

Fasting blood samples were taken between 8 and 9 a.m. Biochemical routine parameters (serum fasting glucose, calcium, phosphorus, alkaline phosphatase) were measured by autoanalyzer techniques. Metabolic control was assessed by HbA_1 (glycated hemoglobin) measurements (HPLC, Bio-Rad), with a within-assay error of 3.55% and a normal range of 6–9%. To evaluate the effects of the metabolic derangement of the diabetes since the time of diagnosis, a ''diabetic impact index'' (DII) was calculated as mean HbA_1 × duration of disease (%/month). Mean HbA_1 for each patient was obtained from all the recorded values from the onset of the disease. Physical examination, HbA_1, and daily insulin dose were recorded every 3–4 months since the diagnosis of the disease.

Bone Mass Measurements

Bone mineral density (BMD g/cm^2) was measured by DXA (QDR 1000/w, Hologic Inc, Waltham, MA, USA) at the lumbar spine (L2–L4; mainly trabecular), ultradistal radius (UDR; trabecular), and third-distal radius (TDR; cortical) forearm regions. The accuracy of DXA was 0.32% for phantom and 1.3% and 1.2% coefficient of variation (CV) for lumbar and forearm sites, respectively.

Statistics

HbA_1 data from each patient was obtained by calculating the average of 3–4-monthly values since the diabetes diagnosis up to the data of DXA assessment. Auxological and densitometric measurements were normalized for age and sex by converting them to Z scores (subject value-mean)/SD). The significance of the difference between groups was determined by analysis of variance (ANOVA). Linear correlation was used to assess the relationship between BMD sites and of BMD with the metabolic control and auxological variables. A level of $P < 0.05$ was considered statistically significant. Values are expressed as the mean ± standard deviation (SD) unless indicated.

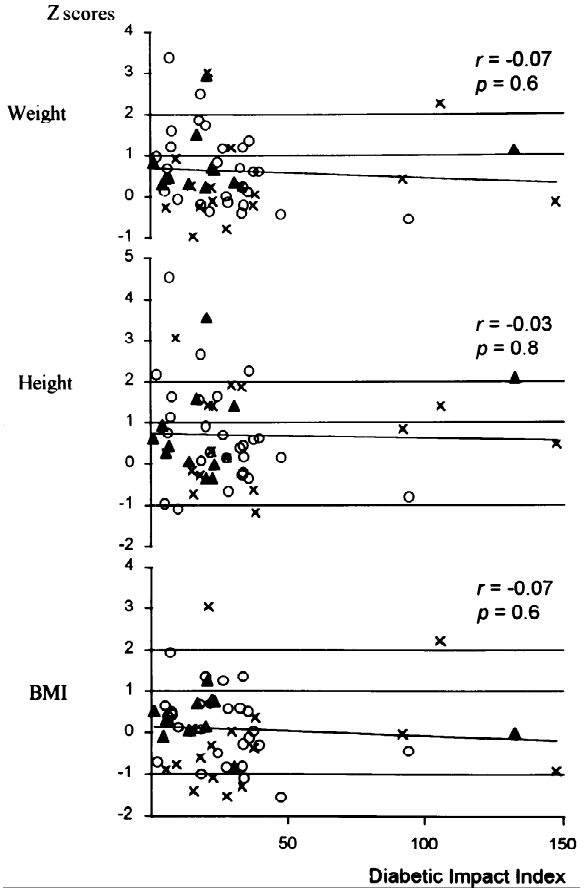

Fig. 1. Linear correlation of Z-scores of weight, height, and BMI, with the diabetic impact index (DII). Tanner stages grouped as stage I (○), stages II + III (▲), stages IV + V (X).

Results

Mean serum values of calcium, phosphorus, and alkaline phosphatase levels at the date of DXA measurement were within the normal range in children with IDDM.

Auxologic and clinical data

Cross-sectional data of patients are shown in Table 1. Diabetic patients showed Z scores for weight, height, and BMI not significantly different from controls. Most patients showed moderate to acceptable metabolic control (HbA_1

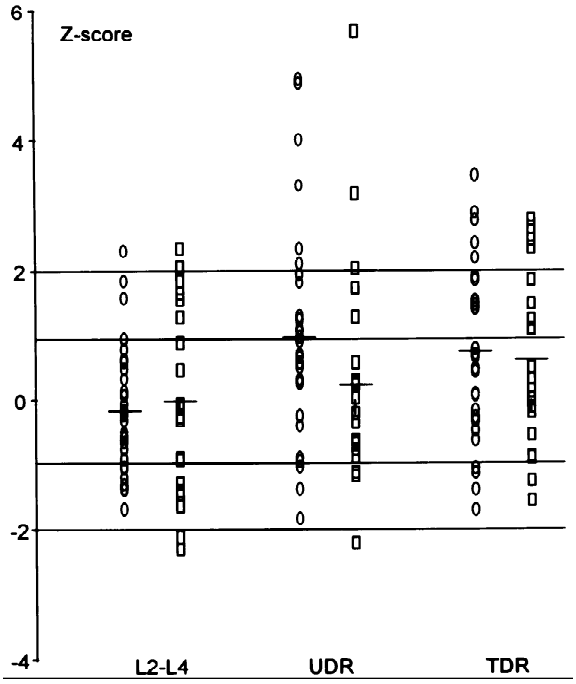

Fig. 2. BMD expressed as Z-scores of the lumbar (L2–L4), ultradistal radius (UDR), and third-distal radius (TDR) in children with IDDM according to duration of the disease. As expressed circles represent patient with <3 years and squares patients with >3 years of duration of diabetes. Lines mark the averages in each group.

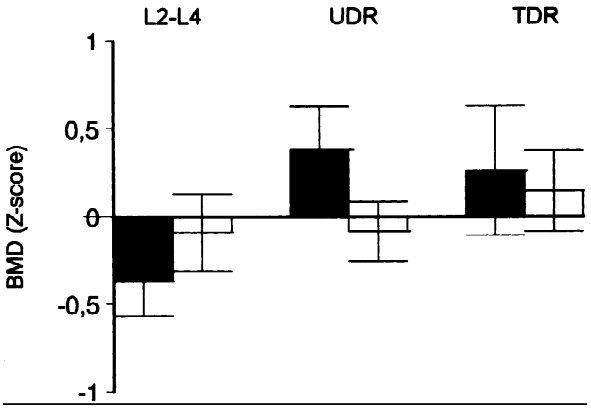

Fig. 3. Bones loss at studied sites (L2–L4, lumbar spine; UDR, ultradistal radius and TDR, third distal radius) in patients with IDDM. No significant differences were found respect normal controls.

6–11% in two-thirds) with 36 in the acceptable range (HbA_1 6–9%). Among diabetics, HbA_1 values and daily insulin dose per body weight did not significantly differ according to sex. No significant correlation was found between DII and weight, height, and BMI, expressed as Z scores (Fig. 1), with no differences observed when studying patients according to Tanner stages, when compared with controls.

Bone Densitometric Results

BMD values expressed as g/cm^2 and also as Z scores showed excellent correlation among sites studied: L2–L4 versus UDR, $r = 0.78$ and $r = 0.38$; L2–L4 versus TDR, $r = 0.82$ and $r = 0.34$, and UDR versus TDR, $r = 0.77$ and $r = 0.32$, , all $P < 0.05$. BMD expressed as Z scores as normally distributed at L2–L4 ($Z = -0.12 \pm 1.14$), UDR ($Z = 0.13 \pm 1.11$), and TDR ($Z = 0.19 \pm 1.54$) sites (Figs. 2, 3), showing no significant differences in relation to controls. No significant differences were found between BMD (Z scores) in patients with higher mean HbA1 (>9%) (-0.13 ± 0.25 SE, $N = 19$) compared with those in the normal range (-0.11 ± 0.19 SE, $n = 36$).

Patients with acceptable HbA_1 (range 6–9%) had lumbar BMD that was not significantly different from those in the upper range. Neither disease duration nor the mean three last HbA_1 values correlated significantly with BMD in any region studied. No significant differences were found in BMD Z scores when patients were divided according to duration of the disease (<3 versus ⩾3 years) at L2–L4 ($Z = -0.17 \pm 0.95$ versus -0.04 ± 1.43), UDR ($Z = 0.95 \pm 1.69$ versus 0.21 ± 1.81) and TDR ($Z = 0.74 \pm 1.35$ versus 0.60 ± 1.32) among the six groups.

There was no significant relationship between BMD expressed as Z-scores and DII (Fig. 4); only the UDR site showed a weak, negative ($r = -0.27$; $P = 0.05$) linear correlation with DII. No differences were observed in BMD Z scores when the patients were grouped according to Tanner stages subgroups (Table 2).

Discussion

Prevalence, degree, and time of initiation of IDDM-related osteopenia remain controversial [17]. The heterogeneity of patients, the inadequacy of selected controls, and the different bone measurement techniques could partially explain some of these discrepancies. Recently, low radiation techniques have been developed to produce the DXA, which greatly improved in precision and accuracy [18]. On the other hand, studies on the effects of diabetic metabolic control on bone and auxological parameters need to prospectively consider the influence of metabolic status at the time of diagnosis of IDDM, given the bone loss reported at the time of the diagnosis by some authors [1, 3].

Decreased cortical BMD, with or without trabecular bone loss, has been reported with different approaches, the majority based on radiographic or single photon absorptiometry [19, 20]. Measurement of both cortical (femoral neck) and trabecular (lumbar spine) BMD with DXA has been found normal in premenopausal women with type 1 diabetes, aged 23–32 years [21]. Normal trabecular BMD has also been recently described by Olmos et al. [22] in 94 patients with IDDM and older age (18–62 years) with DXA, although related to the degree of metabolic control. In contrast, Lettgen et al. [23], using quantitative computed tomography, has found low trabecular and normal cortical and total body BMD in 21 IDDM patients. We have tried to overcome some of these problems by measuring trabecular and cortical BMD, using DXA, in children with recent onset and noncomplicated IDDM, and in 282 age- and sex-pubertal stage-matched Spanish controls.

Our results show that in our patients, bone mass in IDDM was not different from healthy controls. Moreover, growth and maturation expressed in Tanner stages were normal, and there were no sex-related differences. No differences were found with controls when bone mass adjusted

Table 2. Comparison of BMD values in patients and a subset of controls (n = 110) according Tanner stages

	Tanner I	Tanner II + III	Tanner IV + V
Males			
Controls	0.603 ± 0.061 (n = 40)	0.734 ± 0.061 (n = 12)	0.906 ± 0.139 (n = 5)
IDDM	0.571 ± 0.083 (n = 16)	0.722 ± 0.094 (n = 5)	0.874 ± 0.083 (n = 5)
Females			
Controls	0.586 ± 0.076 (n = 33)	0.726 ± 0.112 (n = 12)	0.910 ± 0.085 (n = 8)
IDDM	0.608 ± 0.085 (n = 11)	0.704 ± 0.069 (n = 11)	1.001 ± 0.123 (n = 7)
Total			
Controls	0.616 ± 0.083 (n = 73)	0.730 ± 0.088 (n = 24)	0.908 ± 0.103 (n = 13)
IDDM	0.586 ± 0.084 (n = 27)	0.710 ± 0.075 (n = 16)	0.947 ± 0.122 (n = 12)

Data are shown as mean ± SD

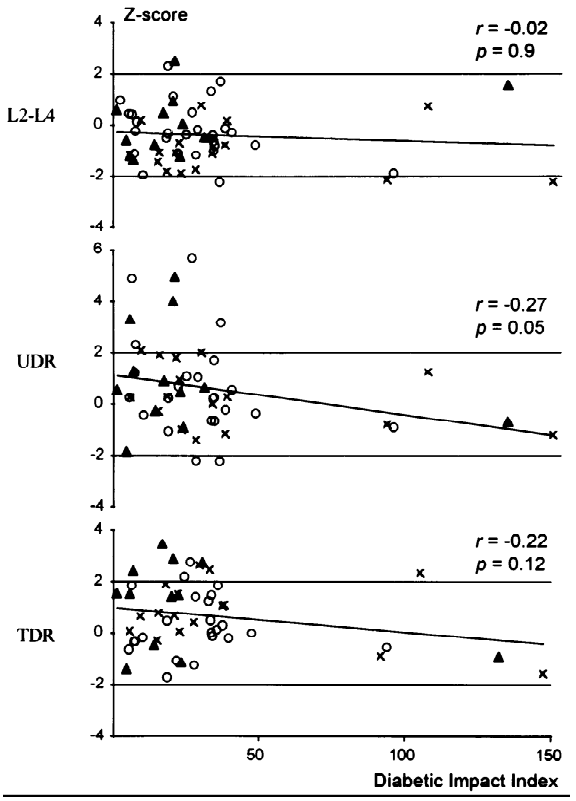

Fig. 4. Linear correlation of lumbar, ultra distal and third distal radius BMD Z-scores radius with diabetic impact index (DII). Tanner stages grouped as stage I (○), stages II + III (▲), stages IV + V (X).

by age and sex was measured at trabecular (L2–L4 and UDR) or cortical (TDR) areas. Therefore, we do not confirm any early osteopenia, neither at the appendicular nor axial skeleton of children with IDDM [1, 2, 24].

A strong correlation between lumbar BMD and height, both expressed as Z scores, was found, as previously shown by Ponders et al. [25]. On the other hand, Christiansen et al. [26] reported weak correlations at the forearm level with auxological parameters. UDR BMD (Z score) correlated with weight, and together, weight and duration of disease account for 25% of the variance at that site. Z scores of TDR showed no correlation with auxological parameters nor duration of disease. The reduction in spinal BMD reported in other studies appears to occur in most subjects in association with deficient metabolic control, long-term evolution, diabetic complications, or low weight [4, 12, 13]; these have been excluded or adjusted by Z score in our study.

Hence, we have been unable to find any relation between BMD and metabolic control of young and noncomplicated IDDM patients, assessed by their average life-disease or last three HBA_1 values. In our view, the relationship of BMD and the last HbA_1 reported [23] is a controversial issue, given the fact that it only represents the patients' glycemic control of the last 3 months.

It is tentative to speculate that a subnormal peak bone mass attained during maximal skeletal growth (from adolescence to 20–30 years of age) could account for the later reduction of BMD in adult IDDM, as has been recently suggested [27]. In our study, duration of the disease—although short—was not related to BMD.

In conclusion, our results show that osteopenia is not present in young and noncomplicated IDDM patients of short duration. The timing and extent to which later diabetes control, diabetes complications, and other risk factors are related to adult IDDM associated osteopenia requires further longitudinal studies.

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