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Bone metabolism is linked to disease duration and metabolic control in type 1 diabetes mellitus

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Abstract

This cross-sectional study analyzed bone mineral density (BMD) in children and adolescents with type 1 diabetes mellitus (DM1) and its relationship with metabolic control, duration of disease and bone markers.

Methods: Forty-four children and adolescents with DM1 (age 8.8 ± 4.4 years, disease duration 6.6 ± 3.9 years) and 22 healthy children were assessed for BMD of the lumbar spine (L1–L4) by dual energy X-ray absorptiometry; osteocalcin (OC) and carboxy-terminal telopeptide (CTX) were measured in the study group.

Results: The BMD was similar in subjects with (−1.15 ± 1.2 S.D.) and without DM1 (−0.85 ± 0.88 S.D., $p = 0.25$). After adjustment for weight, height and pubertal development, the BMD was <−2.0 S.D. in only two diabetic patients (4.5%). Bone area (BA) was inversely correlated with the duration of diabetes ($p = 0.03$) and HbA1c ($p = 0.02$). In girls, who presented a worse HbA1c than boys ($p < 0.01$), BMD was inversely correlated with HbA1c ($p = 0.05$). OC and CTX levels were higher in boys ($p < 0.01$) and both inversely correlated with pubertal development ($p = 0.01$), but not with BMD.

Conclusions: Children and adolescents with DM1 have normal bone mass in the lumbar spine. However, longer diabetes duration and poor metabolic control may have a negative impact on bone mass, requiring further investigation through longitudinal studies.
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Keywords: Bone mineral density; Type 1 diabetes mellitus; Osteopenia; Metabolic control; Bone markers

1. Introduction

Type 1 diabetes mellitus (DM1) has been related to reduced bone mineral density (BMD) in childhood [1–4]. The first report of osteopenia in patients with DM was published in 1948, based on radiographic skeletal evaluation [5]. Whether DM is a risk factor for developing osteoporosis or whether osteoporosis is one of the long-term complications of diabetes remains controversial [6]. Recent advances in the diagnostic tools for bone health assessment in the pediatric population [7] may contribute to better understanding of this important issue.

The aim of the present study was to assess the BMD of the lumbar spine in children and adolescents with DM1 and its correlations with metabolic control, disease duration and bone markers. The influence of sex and age on bone health was also assessed.

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2. Methods

This cross-sectional study included 44 consecutive children and adolescents with DM1 (22 girls), between 10 and 19 years old, who had been followed at the State of Bahia Center for Diabetes and Endocrinology (CEDEBA), and 22 healthy subjects (12 girls), with similar economic and cultural status, recruited from among patients' relatives or neighbors, matched by age and pubertal stage.

Exclusion criteria were as follows: history of alcohol intake, smoking, other chronic diseases, pregnancy or use of medications known to affect bone and mineral metabolism. The CEDEBA Human Research Ethics Committee approved this study.

2.1. Demographic and laboratory data

One of the authors collected the data. A brief questionnaire was used, including data on physical activity, family history of osteopenia, osteoporosis, lumbar spine and/or femoral fractures.

Height velocity (HV) in the last year (S.D.), pubertal development (according to Tanner-Whitehouse) at the time of diabetes diagnosis, daily insulin dose (UI/kg/day), recent serum creatinine and TSH (thyroid-stimulating hormone) measurements, presence of microalbuminuria (>20 mg/day), or diabetic retinopathy were obtained from the patients' charts. Similarly, glycosylated hemoglobin (HbA1c) means were calculated from the values recorded over the previous 2 years (2–4 measurements/year) by the ionic-capture technique, in the same laboratory (reference values 4.4–6.4%).

The total daily calcium intake was calculated through a questionnaire prepared by a nutritionist.

All patients were clinically examined. Height and weight were expressed as S.D. of z scores. Pubertal stage was assessed according to Tanner-Whitehouse.

In the study group, venous blood was withdrawn in the fasting morning to measure osteocalcin (OC) and carboxy-terminal telopeptide (CTX) by chemiluminescent assay. Serum calcium, phosphorus and albumin were also assessed.

2.2. BMD measurements

In all study participants, BMD of the lumbar spine (L1–L4) was measured by dual energy radiographic absorptiometry (DEXA; Hologic QDR-4500). The assessed parameters included bone area (cm^2) (BA), bone mineral content (g) (BMC) and BMD (g/cm^2 and z-score). In order to minimize the influence of already established height, weight and pubertal development, a predicted mathematical model for BMD correction was applied, thus obtaining an adjusted BMD expressed in S.D. [7].

2.3. Statistical analysis

Continuous variables are presented as means ± S.D. Comparisons between two independent variables were made by the Student's two-tailed t-test or Mann–Whitney test, according to the Gaussian or non-Gaussian distribution of each variable. For three or more groups, one way analysis of variance ANOVA or Kruskal–Wallis was used. Linear correlations were performed by Spearman's or Pearson's test. Statistical significance was derived from a p-value <0.05.

3. Results

The ethnic distribution was similar both in DM1 patients and in their controls, with predominance of the mulatto group (90.9% versus 95.5%, NS).

No difference in age at the time of assessment, or at onset of puberty, height (S.D.), weight (S.D.), and daily calcium intake was found between the two groups (Table 1), even when the data was analyzed according to sex. As expected, puberty began earlier in girls ($p < 0.01$).

The age at diagnosis of DM1 was 8.8 ± 4.4 years (0.3–16.5) and the disease duration was 6.6 ± 3.9 years (1–17). The daily insulin dosage was 1.0 ± 0.3 IU/kg/day (0.38–1.51) administered by at least two daily injections. At diagnosis, 65.9% ($n = 29$) of the patients were pre-pubertal (Tanner I), in 22.7% ($n = 10$) puberty had started, and only five patients (11.4%) had achieved full pubertal development. In the clinical examination at the beginning of the study, 54.5% ($n = 24$) of the patients had completed puberty.

Table 1
Characteristics of the study population

	Patients ($n = 44$)	Comparative group ($n = 22$)	p
Age (years)	15.5 ± 2.4	14.6 ± 2.8	0.18
BMI (kg/m^2)	19.1 ± 2.6	18.3 ± 2.5	0.24
Height (z-score)	−0.63 ± 1.4	−0.11 ± 1.2	0.13
Weight (z-score)	−0.27 ± 1.24	−0.10 ± 0.93	0.58
Onset of puberty (years)	11.5 ± 1.5 ($n = 42$)	11.4 ± 1.2 ($n = 20$)	0.77
Menarche (years)	12.5 ± 1.6 ($n = 18$)	12.1 ± 0.8 ($n = 8$)	0.44
Calcium intake (mg/day)	445.6 ± 285.3	438.1 ± 142.6	0.50

Means ± S.D. t-Test or Mann–Whitney for independent samples.

The mean HV of the DM patients in the previous year was 0.13 ± 1.44 S.D. (−2.88 to 5.0). In 42 patients assessed, microalbuminuria was positive in 16.6% ($n = 7$) and diabetic retinopathy was evidenced in 12.8% (5/39).

3.1. Bone characteristics

The BMD, either expressed in g/cm^2 (0.82 ± 0.13 versus 0.81 ± 0.12, $p = 0.73$) or in z-score (−1.15 ± 1.2 S.D. versus −0.85 ± 0.88 S.D., $p = 0.25$), was similar in the patients and their controls, respectively. Initially, 14/44 children with DM1 (31.8%) and 3/22 (13.6%) healthy children presented "low bone density for chronologic age" ($zs < -2.0$ S.D.). After the adjustment for weight, height and pubertal development, the means were: −0.55 ± 1.20 S.D. and −0.24 ± 1.05 S.D. ($p = 0.25$), respectively, and in only two patients (4.5%, one girl), both in the study group, the z-score remained below −2.0 S.D. There was no variation in bone mass measurements when these patients were excluded from the analysis. No difference in BA, BMC and BMD was evidenced in children with or without diabetes, when the data was analyzed according to sex, but in girls with DM1, the mean BMD after the adjustment for weight, height and pubertal development tended to be lower than in non-diabetic girls (−0.69 ± 1.1 S.D. versus 0.0 ± 0.95 S.D.; $p = 0.06$).

BA, BMC and BMD increased throughout puberty in both groups, with strong significant correlations found between the bone measurements and the five stages (Tanner) of pubertal development (BA: $r = 0.53$, BMC: $r = 0.59$ and BMD: $r = 0.54$; $p = 0.01$). Furthermore, in Tanner V, the BA and BMC measurements in healthy subjects ($n = 5$) were higher than those in DM1 patients ($n = 24$), BA: 59.83 ± 4.67 cm^2 versus 52.23 ± 6.45 cm^2; $p = 0.02$ and BMC: 55.8 ± 6.04 g versus 45.82 ± 8.76 g; $p = 0.02$), in spite of similar weight (0.64 ± 0.58 S.D. versus −0.14 ± 1.27 S.D.; $p = 0.10$) and height (0 ± 1.1 S.D. versus −0.74 ± 1.26 S.D.; $p = 0.20$).

The age at the time of assessment was also positively correlated with the bone measurements in the whole population ($p = 0.01$), weight (S.D.) was correlated with BA ($r = 0.26$; $p = 0.01$) and BMC ($r = 0.28$; $p = 0.01$), and height (S.D.) only with BA ($r = 0.32$; $p = 0.01$). When the data from children with DM1 was analyzed separately, the same positive correlations were found. Moreover, the BA was inversely correlated with the diabetes duration ($r = -0.32$; $p = 0.03$) and HbA1c ($r = -0.34$; $p = 0.02$) (Fig. 1). These correlations remained unchanged after exclusion of the two patients with low BMD.

Girls whose diabetes had been diagnosed over 5 years previously ($n = 13$) presented lower BMD after adjustment (−1.15 ± 0.99 S.D. versus −0.03 ± 0.94 S.D.; $p = 0.02$) in comparison with those with more recent diabetes ($n = 9$). In addition, a negative correlation between BMD and HbA1c was found in girls ($r = -0.42$; $p = 0.05$) (Fig. 2), but not in boys ($p = 0.26$), and this, irrespective of excluding the two patients with low BMD.

No difference in bone measurements was shown in patients with ($n = 7$) or without microalbuminuria ($n = 35$). Those with retinopathy ($n = 5$) presented BMD (−2.30 ± 0.87 S.D. versus −1.07 ± 1.23 S.D.; $p = 0.03$) and height (−2.15 ± 1.07 S.D. versus −0.47 ± 1.30 S.D.; $p < 0.01$) significantly lower than patients without retinopathy ($n = 34$).

Height velocity (S.D.), daily insulin dosage and calcium intake were not correlated with any of the bone mass measurements. BMD after adjustment did not differ between DM1 children with or without regular physical activity.

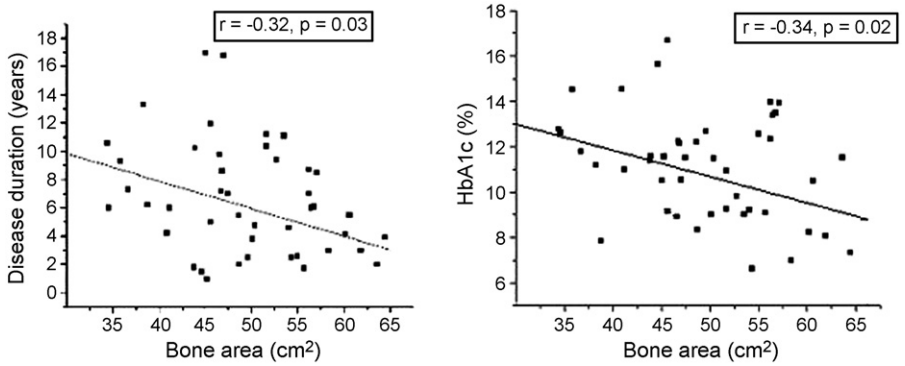

Fig. 1. Correlation between bone area and disease duration and HbA1c in patients with type 1 diabetes mellitus.

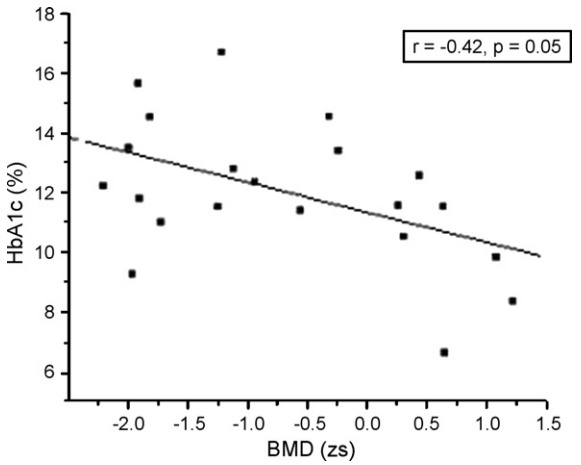

Fig. 2. Correlation between BMD and HbA1c in girls with type 1 diabetes mellitus.

3.2. Laboratory data

In DM1 patients the mean HbA1c was 11.1 ± 2.4% (6.6–16.7), being higher in girls than in boys (12.0 ± 2.3% versus 10.2 ± 2.0%; $p < 0.01$). The mean creatinine (0.75 ± 0.16 mg/dl), serum calcium (9.72 ± 0.44 mg/dl), phosphate (4.46 ± 0.68 mg/dl) and TSH (1.45 ± 0.70 uUI/ml) were within the normal range in all DM1 patients. The bone turnover markers presented significantly higher values among boys (OC: 41.43 ± 19.79 ng/ml and CTX: 0.49 ± 0.20 ng/ml) in comparison with girls (25.71 ± 18.94 ng/ml and 0.28 ± 0.16 ng/ml, respectively; $p < 0.01$).

Osteocalcin and CTX were positively correlated between them ($r = 0.84$ and $p < 0.01$) and with the height velocity ($r = 0.58$ and 0.42, respectively; $p = 0.01$) but inversely with pubertal development ($r = -0.63$ and -0.64, respectively; $p = 0.01$) (Fig. 3). No correlation was found between the bone markers and BMD after adjustment, the duration of diabetes or HbA1c.

4. Discussion

In the present study, the bone mass in young patients with type 1 diabetes mellitus was assessed by BMD and predicted volumetric BMD. As suggested by Warner et al. [7], the predicted model used BA, weight, height and pubertal development in order to obtain an adjusted BMC, calculated after logarithmic transformation of the variables and expressed as a z-score. Lumbar spine dual energy radiographic absorptiometry was preferred because of the lower radiation doses used in children, lower cost and faster method [8].

The results demonstrated that these patients had normal bone mass in the lumbar spine, similar to that of healthy children of the same ethnic, socio-economic and cultural standard. Only two patients in the study group (4.5%) presented bone mass below −2.0 S.D.

Data on bone mineral density in type 1 diabetes is still scarce and controversial. While the present findings are in agreement with previous studies [9–11], others have found significantly lower BMD values in DM1 patients than in their controls [2,12,13]. The positive correlations between the bone mass measurements and variables, such as age, height and weight have been already described. Effectively, Ponder et al. [9] demonstrated important correlations between BMD and these variables in children with DM1, but the reduced BMD in the lumbar spine seemed to be related to low weight. Whereas another study [2], using univariate linear regression models, found lower lumbar BMD in older patients, suggesting that DM in the young may compromise peak bone mass gain.

In the present study, 66% of the patients had been diagnosed as DM1 before puberty and, at the time of the assessment, 54% had already achieved full pubertal development. Thus, in most of them, maximum peak bone mass was acquired during the course of the disease. It has been shown that DM1 patients in the last

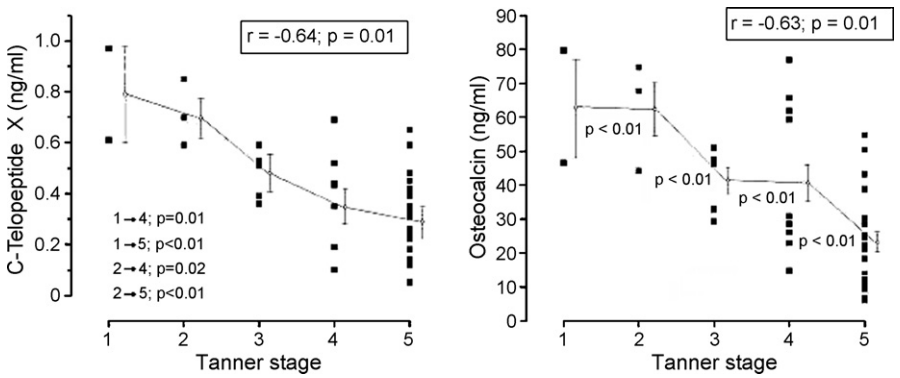

Fig. 3. Evolution of osteocalcin and CTX according to pubertal development in patients with type 1diabetes mellitus.

stages of puberty have lower lumbar bone mass measurements, when compared with healthy individuals [1]. In the present study, the BA and BMC measurements in healthy subjects in Tanner V were higher than those in DM1 patients, in spite of similar weight and height. Because of the reduced number of patients, this difference must be further confirmed. It is well established that at the end of puberty, estradiol determines epiphyseal growth plate fusion [19] and decrease in biologic bone metabolism markers. Nevertheless, in healthy children bone mass continues to increase through the influence of sexual steroids and IGF-1 [18].

Whether [2,14,15] or not [1,4,12,13] bone mass is associated with the duration of diabetes continues to be an important issue. In this study, the inverse correlation between bone area and diabetes duration ($r = -0.32$, $p = 0.03$) and the lower BMD after adjustment, in girls that have had the disease for longer than 5 years, are elements that strengthen the need for systematic inquiry into bone metabolism in young patients with long-duration diabetes. Moreover, the inverse correlation with HbA1c ($r = -0.34$, $p = 0.02$), suggests that metabolic control plays an important role in bone mass, as recently proposed by Heap et al. [4], who assessed BMD by computed tomography. Other studies, however, present conflicting findings [1,12–14]. Vargas et al. [3] assessed 23 diabetic children and adolescents and found no correlation between HbA1c (only one dosage) and BMD. Through multiple linear regression models, however, there was evidence of a clear association between bone measurements and the mean HbA1c since the onset of the illness [2]. Indeed, isolated dosages of HbA1c reflect only metabolic control for the preceding 3 months, while significant changes in the BMD require longer periods. In the present study, girls presented poor metabolic control and lower bone mass, which was correlated with longer diabetes duration. Recently, sex-related difference in bone mineral characteristics was identified in children with DM1. Girls had significantly lower lumbar spine values than control girls ($p = 0.002$), whereas no such difference was observed in boys [20].

The bone mass measurements showed no association with the daily insulin dosage, as previously described [1] or with the presence of microalbuminuria which, in adults with disease duration of 12 years, was associated with a lower bone mass [15]. In the present study, the mean diabetes duration (6.6 years) is probably insufficient to induce a deleterious effect on the bone. With respect to diabetic retinopathy, the lower bone mass must be related to the shorter stature in this subgroup of patients.

Although daily calcium intake in the present study was not associated with bone mass, the mean adjusted BMD (*z*s) was negative in all the subjects. Longitudinal studies are required for following-up bone mass acquisition in these children to assess the impact of low daily calcium intake.

No consensus has been reached as regards normality values for bone markers in healthy children. Bone marker levels increase during the first 3–4 years of life due to increased bone turnover and remain steady until the beginning of puberty, after which they appear to increase parallel to pubertal and height velocity. After 21 years of age, the bone markers return to pre-pubertal levels [16,17].

In healthy adolescents, height velocity positively correlates with bone markers and these with the BMC [18]. In the present study, in DM1 patients, there was positive correlation between bone markers and HV, but not between these markers and BMD after adjustment. In children with DM1, osteocalcin levels were reported to be lower than those in controls at the same pubertal stage [21], however, as in this study, these markers presented no correlation with bone mass [12,14].

Decreased bone metabolism has been described in DM1 patients [21]. Differences in bone formation and absorption biomarkers were evidenced in boys and girls in the present study. Our results suggest that poor metabolic control can reduce the bone turnover and may determine damage to bone health in DM1.

In synthesis, although the normal bone mass of the lumbar spine in children with DM1 is similar to that of healthy children, longer diabetes duration and poor metabolic control may impact on peak bone acquisition at an early age. The small sample size in the present study is a limiting factor, and further confirmation through longitudinal studies may clarify the pattern of changes in BMD in children with DM1. However, since osteopenia prevention is supported by nutritional, physical, and endocrine factors, it must be started early by encouraging intensive metabolic control in diabetic children.

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