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Clinical Investigation

Osteopenia in Juvenile Diabetes

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Summary. The bone mineral status of fifty-one children with diabetes mellitus was studied by single photon absorptiometry. The mean bone mineral content was 13% below values predicted by age, sex, height, and weight. Those children whose diabetes was one year or less in duration were as osteopenic as those whose diabetes was of longer duration. The demineralized children received a higher daily insulin dose than the others. No association was noted between the degree of skeletal demineralization and sex, statural growth, renal function, and serum calcium and phosphorus. No significant changes in bone mineral content were noted longitudinally.

Key words: Bone — Osteoporosis — Diabetes mellitus.

Osteopenia in children with diabetes mellitus, first recognized radiographically in 1927 [1], can be measured more accurately by photon absorptiometry. Previous studies [2–5] using this technique have all been cross-sectional, indicating osteopenia at a single point in time. This study reports photon absorptiometry used longitudinally to follow bone mineralization in children with diabetes.

Patients and Methods

Patients

Our study included 29 boys and 22 girls with insulin-dependent juvenile-onset diabetes mellitus. Mean age at entry was 11.9 ± 3.9 years ($\bar{x}$ ± SD), and duration of diabetes was 4.2 ± 3.7 years. Twenty-three children were prepubertal. Total daily insulin doses were 0.79 ± 0.31 units/kg. One child had mild peripheral neuropathy, and another had nonproliferative retinopathy; the other children had no chronic diabetic complications. No children had bone pain, pathologic fractures, or other symptoms of osteoporosis. The mean height percentile was 40%, and 8 of the 51 children were below the 10th percentile (National Center for Health Statistics). Although hemoglobin AlC measurements are now routinely used in our clinic to follow diabetic control, these were not available when the photon absorptiometry data were collected. Seven of these children had measurements of calcium, phosphorus, alkaline phosphatase, and creatinine, all of which were normal. The means and their standard deviations for these measurements were calcium 9.7 ± 0.2 mg/dl, phosphorus 4.2 ± 0.8 mg/dl, alkaline phosphatase 211 ± 88 units/liter, and creatinine 0.6 ± 0.1 mg/dl. The two children in this group who were in the demineralized range did not differ from the others with respect to these biochemical measurements.

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Photon Absorptiometry

Bone mineral content (BMC), bone width (BW), and BMC/BW for the nondominant radius, ulna, and humerus were measured by photon absorptiometry. Details of this method and precise definition of terms are given elsewhere [6, 7]. *BMC* and *BMC/BW* indicate the percent deviation of BMC and BMC/BW from expected values determined by a multiple regression formula for age-, sex-, height-, and weight-matched control children. For an individual subject −20% for either *BMC* or *BMC/BW* indicated significant osteopenia as these values represented the third percentile for the control population.

Results

Cross-Sectional Study

The initial values for *BMC* and *BMC/BW* are given in Table 1. For the entire study population these values were significantly below zero ($P < 0.0001$), indicating that BMC and BMC/BW were less than predicted. There was no significant difference between boys and girls. The 11 children whose duration of diabetes was less than 1 year also had significantly reduced BMC and BMC/BW.

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Table 1. Initial absorptiometric determinations ($\bar{x} \pm SD$)

	BMC%	*BMC/BW%*
Boys ($N = 29$)	-11.7 ± 9.7	-13.6 ± 8.3
Girls ($N = 22$)	-14.5 ± 12.8	-14.6 ± 10.8
Duration of diabetes < 1 year ($N = 11$)	-12.0 ± 10.0	-13.6 ± 8.4
Complicating disorders (see text) ($N = 8$)	-21.4 ± 9.8	-20.5 ± 9.2
No complicating disorders ($N = 43$)	-11.3 ± 10.7	-12.8 ± 9.4
Total ($N = 51$)	-12.9 ± 11.1	-14.0 ± 9.4

Table 2. Comparison of demineralized and nondemineralized children at time of initial determinations ($\bar{x} \pm SD$)

	Demineralized N = 16	Nondemineralized N = 35
Age (years)	12.7 ± 3.2	11.3 ± 4.0
Duration of diabetes (years)	4.6 ± 3.3	3.8 ± 3.6
Pubertal status (prepubertal:pubertal)	7:9	16:19
Total daily insulin dose[a] (units/kg)	0.92 ± 0.13	0.74 ± 0.07

[a] $P < 0.05$

Sixteen children were initially in the demineralized range. Table 2 compares this demineralized group to the nondemineralized children with respect to age, duration of diabetes, pubertal status, and insulin requirements. Of all variables, only insulin dose was significantly different with the demineralized group receiving more insulin.

Eight children had coexistent diseases which could potentially alter their bone mineral status. These disorders included hypothyroidism (2), hyperthyroidism (2), adrenal insufficiency, seizure disorder (treated with anticonvulsants) (2), and multiple sclerosis (treated with prednisone). These children were significantly more osteopenic than the others ($P < 0.05$). As there were only eight children in this group, their contribution to the mean for all diabetic children was small. Patients without these complicating conditions were still osteopenic with values for *BMC* and *BMC/BW* significantly below zero ($P < 0.001$) (Table 1).

Longitudinal Study

Forty-one children had a total of 106 additional bone mineral measurements made up to 48 months beyond their baseline determinations. Table 3 shows the distribution of follow-up measurements to the nearest 6-month interval as well as the mean changes ΔBMC and $\Delta BMC/BW$ where all subsequent measurements are compared to the individual's own base line. At 18 months there was a small but significant increase in *BMC* which was not documented at any other time interval. Similar small but significant improvements in *BMC/BW* were shown at multiple intervals in follow-up. When initial and final measurements (made 26.2 ± 12.0 months later) for each of the 41 children are compared, ΔBMC was $+0.5 \pm 5.5\%$ and $\Delta BMC/BW$ was $+3.5 \pm 5.7\%$. This represents an insignificant change in *BMC* and a small but significant ($P < 0.001$) change in *BMC/BW*.

Table 3. Changes in *BMC* and *BMC/BW* over time ($\bar{x} \pm SD$)

Time (months)	Number	ΔBMC	$\Delta BMC/BW$
6	17	$-0.3 \pm 6.0\%$ NS	$+0.5 \pm 5.2\%$ NS
12	23	$+1.1 \pm 6.2\%$ NS	$+3.6 \pm 6.0\%$ $P < 0.01$
18	21	$+3.0 \pm 6.1\%$ $P < 0.05$	$+5.9 \pm 6.6\%$ $P < 0.001$
24	16	$+1.6 \pm 8.2\%$ NS	$+4.1 \pm 8.4\%$ NS
30	11	$+1.8 \pm 6.9\%$ NS	$+5.0 \pm 6.7\%$ $P < 0.05$
36	10	$+0.2 \pm 5.0\%$ NS	$+5.9 \pm 3.1\%$ $P < 0.001$
42	7	$-2.9 \pm 5.4\%$ NS	$+2.3 \pm 6.3\%$ NS
48	1	-4.6% — —	$+1.4\%$ — —

Among the 41 children with longitudinal data, 28 were initially in the normal range and 13 were in the demineralized range. During the follow-up period the children initially in the normal range experienced changes of $\Delta BMC = 0.5 \pm 4.5\%$ and $\Delta BMC/BW = +2.3 \pm 4.8\%$ over a period of 27.0 ± 11.9 months, indicating no change in *BMC* and a small change in *BMC/BW* ($P < 0.05$). Of these 28 children, 5 crossed over into the demineralized range at the end of the study. For the 13 who were initially demineralized, ΔBMC was $+2.4 \pm 7.0\%$ and $\Delta BMC/BW$ was $+5.1 \pm 7.2\%$, again showing no significant change in *BMC* and a significant change in *BMC/BW* ($P < 0.05$) over an interval of 24.5 ± 12.8 months. Of these 13 children, 6 crossed over into the normal range. The changes for the group initially in the normal range were not different from those initially in the demineralized range.

Statural growth was compared between those children who were demineralized and those who were always in the normal range. Height velocity was 5.4 ± 1.1 cm/year for those who were demineralized, and 5.9 ± 1.4 cm/year for those in the normal range, indicating no significant difference.

Discussion

In this study we have shown children with diabetes mellitus to be osteopenic with BMC and BMC/BW

12.9% and 14.0% below predicted and no difference between boys and girls. The 8 children with other disorders predisposing to osteopenia showed a greater bone mineral deficit, but this did not explain the osteopenia found for the entire group, since the children without these disorders still had BMC and BMC/BW 11.3% and 12.8% below predicted. Furthermore, 8 children with these disorders are not unexpected in a group of 51 diabetic children. For comparison, Levin et al. [2] found BMC to be 6% and 14% below predicted, depending on site of measurement, in those subjects less than 21 years old. Rosenbloom et al. [3] showed deficits in BMC/BW of 8.3% for white girls and 4.7% for white boys, and McNair et al. [4, 5] found BMC to be 13.9% below predicted for juvenile-onset diabetics, although many of their subjects were adults when studied.

In cross-sectional studies, McNair et al. [4] showed that the deficit in BMC was identifiable 2–3 years after the onset of diabetes and stable after that time. Levin et al. [2] demonstrated that those subjects whose duration of diabetes was less than 5 years had osteopenia at least as severe as those whose diabetes was longer standing. In the present study, the osteopenia observed in the 11 children whose diabetes was less than 1 year was not different from that of the entire diabetic population. In addition to these cross-sectional data, longitudinal measurements on 41 children showed no consistent changes in *BMC* during the follow-up period. The changes in *BMC/BW* during follow-up were small relative to the absolute deficit observed for *BMC/BW*. Furthermore, with no change in *BMC*, it is not clear that the small improvement seen in this derived ratio is of any importance.

Statural growth was assessed in these children because of an association between osteopenia and decreased height velocity shown by us in several other conditions including renal disease, glucocorticoid therapy, and growth hormone deficiency [6, 7]. As a group the diabetics did not exhibit short stature, and height velocity was not different for those in the demineralized range compared to those in the normal range. Thus the osteopenia of juvenile diabetes appears to be associated with normal statural growth.

Comparison of those children in the demineralized range with those in the normal range showed that the demineralized group received a higher insulin dose. This most likely represents greater severity of insulin insufficiency. McNair et al. [5] also observed that the degree of osteopenia correlated positively with both higher insulin dose and absence of endogenous insulin secretory ability as shown by C-peptide measurements.

Work with experimental diabetes in rats has shown decreased skeletal deposition of both calcium and citrate which is ameliorated with insulin therapy [8]. Excessive urinary losses of calcium and phosphorous have been shown in humans with diabetes which correlated with the severity of hyperglycemia and glycosuria [5, 9]. Abnormal vitamin D metabolism may also be involved in diabetic osteopenia. Serum levels of 1,25-dihydroxyvitamin D_3 have been shown to be low in rats with streptozotocin-induced diabetes [10]. Although diabetic rats show histologic evidence of slow bone turnover, neither these rats nor bone biopsies from patients with juvenile-onset diabetes have shown evidence of osteomalacia, arguing against a vitamin D abnormality producing the osteopenia in diabetes [11]. Despite these observations, neither the pathogenesis of diabetic osteopenia nor its relationship to diabetic control is well understood. It remains to be established if excellent control of diabetes could prevent its development.

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