Bone Size Normalizes With Age in Children and Adolescents With Type 1 Diabetes

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OBJECTIVE — The aim of this study was to establish whether type 1 diabetes has a long-term effect on bone development in children and adolescents.

RESEARCH DESIGN AND METHODS — Bone characteristics and muscle cross-sectional area (CSA) were analyzed cross-sectionally in 41 (19 female and 22 male) patients and were reevaluated after 5.56 ± 0.4 years using peripheral quantitative computed tomography (pQCT). We hypothesize that bone size and muscle mass normalize with age.

RESULTS — At the first evaluation, mean ± SD age was 9.87 ± 2.3 years and disease duration was 4.31 ± 2.9 years. Height was −0.36 ± 1.9 SD, and BMI was 0.39 ± 0.9 SD. Parameters of bone size were low in the whole patient group (corrected for patient's height). At reevaluation, age was 15.44 ± 2.3 years, and patients had a mean height of −0.12 ± 0.8 SD. BMI SD had increased to 0.57 ± 1.1. Total and cortical CSA had normalized. Those patients with an increase in total CSA had a significant younger age at disease manifestation and a younger age at initial pQCT measurement. Bone size was well adapted to muscle mass expressed as the ratio of bone mineral content per muscle mass, and a close correlation was shown between the increase in bone size and in muscle CSA ($r = 0.46$, $P = 0.03$).

CONCLUSIONS — Patients with manifestation of type 1 diabetes at an early age had transient impaired bone development. Within the follow-up period, the greatest increase in bone size was found in these patients. In adolescence, all patients had a normal bone size and appropriate adaptation of bone on muscle.

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Studies on bone development in children with type 1 diabetes have generated conflicting results (1–5). There are still no conclusive data on the relative importance of several diabetes-specific characteristics, such as age at onset, disease duration, and glycemic control or insulin regimen, on bone health (6).

The majority of earlier studies were cross-sectional using dual-energy X-ray absorptiometry of the spine. In pediatric patients, in particular, this method has limitations because of the two-dimensional measurement and therefore height dependency. Longitudinal data on relatively small numbers of patients over 2–4 years revealed disturbed or normal bone development (7,8). A recently published study over a wide time range from 12 to 84 months showed slightly reduced mineralization of the spine independent of metabolic control or microvascular complications (9). The incidence of bone fractures was not increased in a large adult population with type 1 diabetes (10). Therefore, the clinical importance of possibly lower bone mineralization in type 1 diabetes is not clear.

The objectives of the present longitudinal study were to evaluate bone mineral density (BMD) and bone size and muscle mass in patients with type 1 diabetes at two time points (5.5 years apart) using peripheral quantitative computed tomography (pQCT). Interpretation of BMD and geometry measurements is incomplete without taking into account muscle mass (11). Therefore, we looked at the ratio between bone mineral content (BMC) and muscle mass (12).

RESEARCH DESIGN AND METHODS

— In a cross-sectional study, 88 Caucasian children and adolescents (42 female and 46 male) with type 1 diabetes were included. After a mean time of 5.56 ± 0.4 years, 41 patients (20 female and 21 male) could be reevaluated. Data analysis is restricted to the 41 patients with two pQCT measurements. All participants in the study were observed regularly at the diabetes outpatient clinic of the University Children's Hospital (Munich, Germany) and met the following criteria: *1*) first diagnosis of type 1 diabetes as made before 18 years of age; *2*) no evidence of diabetic retinopathy, neuropathy, or nephropathy; *3*) no intake of medications, hormones, vitamins, or calcium preparation in the preceding 6 months aside from insulin and, if necessary, thyroid hormones; *4*) no chronic disease apart from positive thyroid antibodies with euthyroid status; *5*) no hospitalization or ketoacidosis in the preceding 6 months; and *6*) no restriction on physical activity. All patients were examined every 3 months. At the first measurement, 38 patients were receiving multiple injections (three to four daily) of regular and NPH insulin (intensified conventional therapy [ICT]) and 3 were receiving insulin pump therapy (continuous subcutaneous insulin infusion [CSII[). At the second measurement, 27 patients were receiving ICT and 14 patients were receiving CSII. Diabetes control was monitored by measurements of A1C levels at 3-month intervals. The A1C level was measured by a DCA 2000 analyzer (Bayer AG, Leverkusen, Germany), based on specific inhibition of latex immunoagglutination. Normal values of A1C as established in our laboratory ranges from 4.0 to 6.0%. Moreover, an average A1C was calculated for each patient by taking the mean of four measure-

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Abbreviations: BMC, bone mineral content; BMD, bone mineral density; CSA, cross-sectional area; CSII, continuous subcutaneous insulin infusion; ICT, intensified conventional therapy; pQCT, peripheral quantitative computed tomography.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Auxological and diabetes-specific data at the first and second measurements in patients with type 1 diabetes*

	First measurement	Second measurement
n (female/male)	41 (20/21)	41 (20/21)
Age (years)	9.87 ± 2.3	15.44 ± 2.3
Age at onset of disease (years)	5.54 ± 3.2	
Disease duration (years)	4.31 ± 2.9	9.81 ± 2.8
Height SD	−0.36 ± 1.0*	−0.12 ± 1.0
Weight SD	0.11 ± 1.1	0.46 ± 1.0
BMI SD	0.39 ± 0.9*	0.57 ± 1.0*†
Tanner stage group (*n*)		
1	27	3
2	13	9
3	1	29
Latest A1C (%)	7.13 ± 0.9	8.14 ± 1.2†
Average A1C (%)	7.11 ± 0.8	7.74 ± 1.1†
Insulin dose (IU · kg^{-1} · day^{-1})	0.78 ± 0.2	0.91 ± 0.2†

Data are means ± SD. *Significant difference ($P < 0.05$) for mean values between patients and reference population. †Significant difference ($P < 0.05$) for mean values and between the two measurement time points.

ments during the previous 12 months before pQCT measurement.

Anthropometric data were compared with the cross-sectional German growth data of Kromeyer et al. (13). The pQCT results were compared with those in a German reference population using identical methodology. The results for this reference population were described before (14–16).

Height was measured in a standing position to the next 1 mm using a digital telescopic wall-mounted stadiometer (Ulmer Stadiometer; Professor E. Heinze, Ulm, Germany). Weight was determined to the nearest 0.1 kg using an electronic scale (Seca 753 E; Vogel and Hanke, Hamburg, Germany) with the children clothed in underwear. BMI was compared with the German normative data by Kromeyer et al. (13). Forearm length was measured at the nondominant forearm as the distance between the ulnar styloid process and the olecranon using a caliper. The stage of sexual development was determined in all study participants using the grading system by Tanner for breast development in girls and genital status in boys (17). Three Tanner stage groups were formed: prepubertal (Tanner stage 1), early pubertal (Tanner stages 2 and 3), and adolescent (Tanner stages 4 and 5).

pQCT

Two sites of the nondominant radius were analyzed by pQCT: the distal metaphysis and the proximal diaphysis as described previously (14–16). In all patients, a pQCT scanner (XCT 2000; Stratec, Pforzheim, Germany) was used, which is equipped with a low-energy (38 keV) X-ray tube. The effective radiation dose is about 0.1 μSv from the radiation source of 45 kV at 150 μA. For the measurement, the scanner was positioned on the distal forearm, and a scout view was obtained to position the scanner at the site on the radius at which distance to the radial articular surface corresponded to 4 and 65% of the forearm length. At both sites, a 2-mm-thick single tomographic slice was sampled at a voxel size of 0.4 mm. Image processing and calculation of numerical values were done using the manufacturer's software package (version 5.40; Stratec). At the distal radius (metaphyseal site) total and trabecular BMD and at the proximal radius (diaphyseal site) total and cortical BMD, total cross-sectional area (CSA), cortical CSA, medullary CSA, muscle CSA, BMC, and strength strain index, a measure of bone stability, were calculated using the manufacturer's software.

Only measurements of good quality without movement artifacts were taken for analysis. To establish the variability of the measurements, the forearms of six adult volunteers were measured three times with repositioning of the forearm. Reproducibility was 1.08% for trabecular BMD and 1.42% for total BMD at the metaphysis and 1.30% for CSA, 1.36% for total BMD, and 1.11% for cortical BMD at the diaphysis. The accuracy of the previous version of the scanner (XCT-960; not used by us) was determined using the European forearm phantom, and average accuracy values between 1.9 and 1.4% for CSA and BMD values were reported (18). Calibration of the machine was performed with phantoms provided by the manufacturer every other day (single slice) or once a month (multiple slices), respectively.

Statistical analysis

Results in type 1 diabetic patients were converted into sex-, age-, and height-specific SD scores. To evaluate whether a parameter was significantly different from the results of an age-matched healthy population, the difference of the mean SD score to 0 was assessed by a Student's two-tailed *t* test for unpaired observations or a Mann-Whitney nonparametric *U* test as appropriate. A significant difference was assumed when the 95% CI of the mean SD score did not include 0. Pearson's product-moment correlation was used to determine *r* values for possible influencing factors on BMD and geometry parameters. We used general univariate linear regression analysis (ANCOVA) to evaluate the covariant effects with significant levels of the two-sided *P* values <0.05. We checked the normality of residuals and homoscedasticity. All statistical analyses were performed using the SPSS software package (version 14.0 for Windows; SPSS, Chicago, IL).

RESULTS

Auxological and clinical data

Auxological and diabetes-specific data are given in Table 1. At the first evaluation, diabetic patients showed reduced SD scores for mean height, which had normalized at the second measurement. Significantly higher mean SD scores for BMI were present at both time points, with a markedly higher number of female patients with a BMI SD >2 at the second evaluation (five female vs. one male). Most patients had moderate to acceptable metabolic control with a range for average A1C of 5.8–9.2% and median 7.2% at the first pQCT and 6.2–11.0% and 7.6%, respectively, at the second pQCT measurement. A comparison of our patients' A1C levels within the diabetes data acquisition system for prospective surveillance (DPV) database, a German diabetes acquisition system for prospective surveillance, showed that they were well within expected levels for patients of this age with type 1 diabetes (19). There was only a slight difference between the latest and averaged A1C levels (Table 1). A1C values

Table 2—*Longitudinal development of bone geometry, BMD, and muscle CAS in patients with type 1 diabetes*

SD values	First measurement	Second measurement
n	41	41
Metaphyseal		
TD	0.28 ± 1.2	−0.01 ± 1.1
TrabD	0.45 ± 1.1*	−0.14 ± 1.1†
Diaphyseal		
TCSA	−0.48 ± 0.9*	0.05 ± 1.0†
CCSA	−0.32 ± 1.0*	0.1 ± 1.0†
MCSA	−0.31 ± 0.8*	0.09 ± 1.0†
CTH	−0.11 ± 0.8	0.02 ± 0.8
relCCSA	−0.06 ± 0.8	0.01 ± 0.8
TD	−0.09 ± 0.8	−0.06 ± 0.8†
CtD	−0.37 ± 1.0*	0.16 ± 0.9†
SSI	−0.26 ± 1.1	0.05 ± 1.0†
MslCSA	−0.24 ± 1.0	−0.05 ± 1.2†
BMC-to-MslCSA ratio	−0.31 ± 0.9	0.19 ± 0.9

Data are means ± SD. *Significant difference ($P < 0.05$) for mean values between patients and reference population. †Significant difference ($P < 0.05$) for mean values and between the two measurement time points. CCSA, cortical CSA; CtD, cortical BMD; MCSA, medullary CSA; MslCSA, muscle CSA; SSI, bone strength strain index; TD, total BMD; TrabD, trabecular BMD; TCSA, total bone CSA.

and daily insulin dose per kilogram of body weight were similar in boys and girls. The older the patients and the longer the duration of diabetes, the higher was the daily insulin dose per kilogram of body weight ($r = 0.61$, $P < 0.001$) and the present and averaged A1C ($r = 0.36$ and 0.38, $P = 0.02$, respectively) at the first measurement. The form of insulin administration (ICT or CSII) had no influence on A1C or insulin dose. There were three patients with positive thyroid antibodies who were euthyroid without hormone replacement. All were well within the range for height, weight, BMI, and A1C of all type 1 diabetic patients. No patient had celiac disease.

Bone densitometric results

At the first measurement, mean SD value of trabecular BMD was even higher in type 1 diabetic patients than in healthy control subjects, irrespective of age, sex, and Tanner stage (Table 2). Data analysis was performed using the new logarithmic approach as suggested by Rauch and Schönau (20). At the diaphysis, patients with type 1 diabetes had significantly reduced mean SD values for total, cortical, and medullary CSA as well as cortical BMD at the first measurement. After 5.5 years, these parameters had normalized. Bone strength strain index and muscle CSA were not significantly different from those for the reference population at the first and second measurements. Bone size was well adapted to muscle mass expressed as the ratio of BMC per muscle CSA (Fig. 1).

Muscle CSA SD values correlated significantly with total bone CSA ($r = 0.64$ and $r = 0.69$, $P < 0.01$) and cortical CSA ($r = 0.75$ and $r = 0.71$, $P < 0.01$) at the first and second measurements, respectively. In separating the patients according to sex or Tanner stage (prepubertal, early pubertal, or adolescent), there was no significant difference in BMD, bone size parameters, or muscle CSA. However, at the first measurement, the majority of patients were prepubertal, and at the second measurement, the majority were adolescents. Group numbers were too small to detect any difference for each Tanner stage. No difference between the sexes was found after correction for Tanner stages.

Influencing factors

To look for potential confounders, diaphyseal total bone and muscle CSA were used as dependent variables and the latest A1C/average A1C, insulin dose, and diabetes duration were used as the independent variables. Age, sex, pubertal stage, and BMI were used as covariates. There was no significant influence of the independent variables on diaphyseal total and muscle CSA at either time point. There was no significant influence of insulin regimen (ICT or CSII) on bone and muscle CSA parameters.

The younger the patients were at disease manifestation and at the first evaluation, the more the increase in total CSA was detectable ($r = -0.45$ and $r = -0.54$, $P < 0.01$, respectively). Additionally, the change in total CSA was significantly correlated with the change in muscle CSA ($r = 0.46$, $P = 0.03$). A linear regression model revealed age at manifestation ($\beta = -0.32$, $P = 0.028$) and change in muscle CSA ($\beta = 0.41$, $P = 0.05$) as the major influencing factors for bone size development, accounting for 31% of variability ($P = 0.005$). Muscle development was significantly influenced by the change in BMI SD ($\beta = 0.32$, $P = 0.025$), the change in total CSA ($\beta = 0.4$, $P = 0.006$), and the change in average A1C ($\beta = 0.26$, $P = 0.07$), accounting for 39% of variability ($P = 0.01$).

CONCLUSIONS — BMD and BMC have been measured cross-sectionally in children and adolescents with type 1 diabetes using different methodologies. Most reports indicated decreased bone mass in relation to a healthy reference population. Although loss of bone mass has not been classified as a typical complication of type 1 diabetes, a relation to metabolic control has been proposed (21). Longitudinal studies on bone development in type 1 diabetes are sparse. In this investigation, patients were studied after a fixed time interval of 5–6 years from the first measurement. Therefore, a possible impact of disease manifestation on bone development should be excluded. Longitudinal data on skeletal growth and mineral acquisition are necessary to distinguish between temporal or long-term effects of diabetes on bone development. Previously, we identified early manifestation of type 1 diabetes as a risk factor for smaller bone size and hypothesized that there could be a normalization of bone size parameters with age (22). We further proposed that after clinical manifestation of type 1 diabetes, an initial derangement of bone development may take place, possibly followed by a catch-up in bone development over a long period of time. In this study, we could show that patients with an early onset of disease had the most pronounced increase in bone size over time. There was also a greater increase in muscle CSA, with both accounting for ~31% of variability of change in total CSA SD values. Gunczler et al. (23) described decreased BMD of the lumbar spine in children a few months after the onset of clinical type 1 diabetes. In a follow-up study on patients with mean ± SD disease

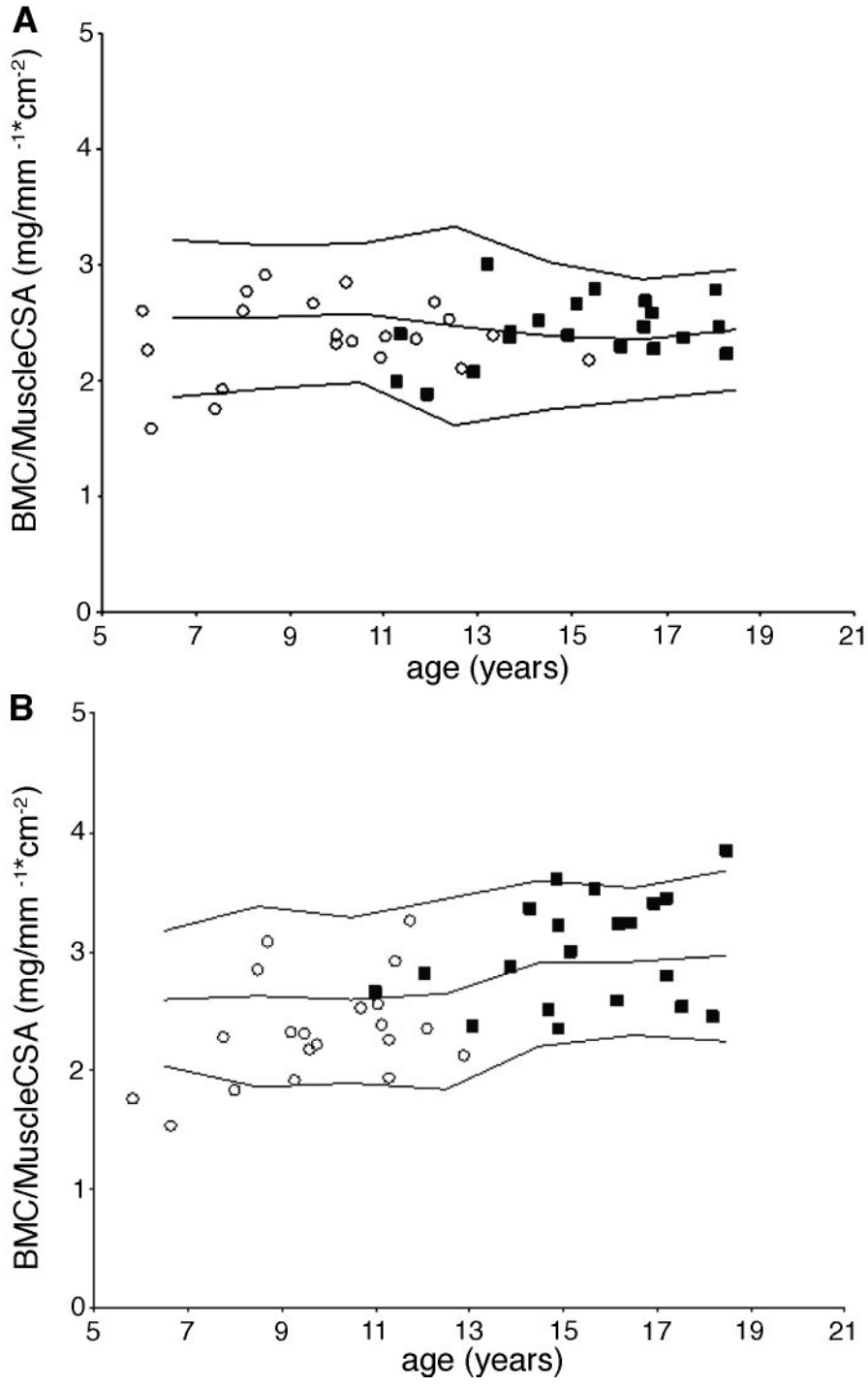

Figure 1—*BMC per muscle cross-sectional area (BMC/MuscleCSA) related to age in female* (A) *and male* (B) *patients with type 1 diabetes. The graph shows patients' data at first* (○) *and second* (■) *measurement.*

duration of 4.3 ± 2.9 years, they reported on a stabilization of BMD parameters expressed as *z* scores after 1 year (7). However, Moyer-Mileur et al. (8) stated that in adolescents with disease duration of 4.2 ± 3.1 years, gain of tibial cortical mineral bone was attenuated. A lower ratio of BMC to lean body mass was inversely related to A1C levels. After a period of >5 years after disease manifestation, McNair et al. (24) noted a stabilization of BMD values. They suggested a defect in bone mass accretion early in the course of type 1 diabetes, which then ameliorates with time. This is in accordance with data from adult patients with significant bone loss at the time of diagnosis of type 1 diabetes and a possibly rapid decrease within the 1st year, followed by attainment of normal values (25,26).

In analogy to our results, the effect of metabolic control on BMD and bone mass development has been excluded by several authors (6,27). The A1C values in our patient population were quite satisfactory and comparable to those in a German type 1 diabetic patient population of the same age (19). Therefore, we cannot exclude the possibility that children with poorly controlled diabetes over a prolonged period of time might have more significant bone deficits than our patients. Further disease-specific parameters such as insulin dose, insulin treatment regimen, or duration of disease had no significant influence on BMD and bone size.

A significant increase in bone size took place in the majority of patients. This catch-up in bone cross-sectional size was most pronounced in those patients with manifestation of type 1 diabetes at a young age. It is possible that patients with the diagnosis of type 1 diabetes early in life may be more susceptible to metabolic derangement after clinical manifestation of the disease. Muscle CSA correlated significantly with total and cortical CSA levels, supporting the mechanostat theory in patients with type 1 diabetes and putting emphasis on the importance of the muscle-bone unit (11). Overall, development of muscle and bone was well adapted as indicated by a normal ratio of BMC per muscle CSA. This finding is in contrast to the study by Moyer-Mileur et al. (8) who reported an ~8% reduction of BMC for muscle CSA in type 1 diabetic adolescents. This discrepancy may result from the fact that their patients were younger and less advanced in puberty than ours.

A limitation of our study is the relatively small number of patients. A strength of our study is the long observation period and the comparison of mostly prepubertal children at the first measurement with postpubertal adolescents at the second measurement.

In summary, early onset of type 1 diabetes may be a risk factor for transient altered bone CSA. Bone size normalizes over time and is well adapted to muscle size. Diabetes-specific parameters seem to be less important for bone development. A longitudinal study beginning at diabetes manifestation could provide further insight into bone development in children and adolescents with type 1 diabetes.

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