Bone xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Bone status of Indian children and adolescents with type 1 diabetes mellitus

Lavanya S. Parthasarathy [a], Vaman V. Khadilkar [a], Shashi A. Chiplonkar [a], M. Zulf Mughal [b], Anuradha V. Khadilkar [a,*]

[a] Growth and Endocrine Unit, Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, Pune, India
[b] Department of Paediatric Endocrinology, Royal Manchester Children's Hospital, Manchester, UK

ARTICLE INFO

Article history:
Received 20 February 2015
Revised 20 April 2015
Accepted 29 April 2015
Available online xxxx

Keywords:
Bone density
IGF1
Type 1 diabetes
Children

ABSTRACT

Objective: Low bone mineral density has been reported in children and adolescents with type 1 diabetes (T1DM). The aims of this cross-sectional study were to study growth, serum IGF1 concentrations and bone health parameters assessed by Dual Energy X-ray Absorptiometry (DXA).
Methods: Height was measured and converted to Z scores (HAZ). Serum IGF1 concentrations were measured (ELISA) in a subset. Bone mineral content for total body (less head) (TBBMC) and lumbar spine was measured (n = 170, 77 boys, 6–16 years old) and converted to Z scores using local normative data.
Result: Mean age was 11.1 ± 3.8 years, disease duration was 2.2 ± 2.5 years and HbA1C was 10.1 ± 1.8%. Diabetic children were shorter than reference population (HAZ −0.6 ± 1.1); Z scores for height and total body bone area (TBBA) for height were <−2SD in 12% & 6% respectively. Serum IGF1 Z scores were lower amongst group with longer disease duration (−1.58 ± 1.3 vs −2.63 ± 0.7; P = 0.037). Disease duration (β = −0.180, P = 0.000) and metabolic control (HbA1C; β = −0.096, P = 0.042) were negative predictors of HAZ and TBBA for height Z in younger children. Using the Molgaard approach, children with longer disease duration had lower HAZ (−0.31 ± 0.92 vs −1.28 ± 1.11; P = 0.000; "short bones") and TBBA for height Z scores (0.12 ± 1.62 vs −0.53 ± 0.94; P = 0.044; "slender bones"). Older children (tanner stages 4 and 5) had lower BMC and BA as compared to reference population possibly due to delayed growth spurt.
Conclusion: Longer duration of diabetes was associated with shorter and slender but appropriately mineralized bones. Small and slender bones in diabetic children may increase risk of fragility fractures in the future.
This article is part of a Special Issue entitled "Bone and diabetes".

Introduction

A number of studies have shown that the bone mineral density (BMD) as measured by dual energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) is impaired in children with diabetes [1–3]. However, longitudinal studies performed using a pQCT indicate that there is an improvement in bone mineralization over time [4]. The changes in the bone mineral density in diabetes are caused by a number of factors such as hypoinsulinemia, deteriorating renal function, increased production of advanced glycation end products, low peak bone mass and increased production of inflammatory cytokines [5]. The increased urinary calcium excretion linked to hyperglycemia leads to a negative calcium balance [6], alterations in vitamin D metabolism [7], and low insulin like growth factors [8], which lead to impaired growth of bone. Amongst other osteoporotic factors in T1DM is the absence of amylin (a 37 amino acid peptide), that is co-secreted by pancreatic cells [9]. Administration of amylin in a previous study to streptozotocin induced diabetic rats has helped in maintaining bone mass, inhibiting biochemical markers of bone resorption, and elevation of biochemical markers of bone formation [10]. Impaired growth and mineralization in the long run may increase the risk of fractures. There are a number of studies which have reported increased risk of hip fractures in adults with type 1 diabetes [11–14].

Intensive insulin treatment regimens and monitoring of the disease with multiple daily blood sugar testing is prohibitively expensive for many families in India [15,16]. Hence, optimum control of diabetes is often difficult to achieve in these patients. Lettgen et al. and Heilman et al. have reported a relationship between low bone mineral density and higher HBA1C concentrations in diabetic children and adolescents [3,17]. Disease duration is another important factor discussed in previous studies affecting bone status in children with diabetes [17]. As we

* Corresponding author at: Hirabai Cowasji Jehangir Medical Research Institute, Jehangir Hospital, 32 Sassoon Road, Pune 411 001, India. Fax: +91 20 26141340.
E-mail addresses: parthasarathy.lavanya@gmail.com (L.S. Parthasarathy), vamankhadilkar@gmail.com (V.V. Khadilkar), drsjc_1@yahoo.com (S.A. Chiplonkar), zulf.mughal@cmft.nhs.uk (M. Zulf Mughal), anuradhavkhadilkar@gmail.com (A.V. Khadilkar).

http://dx.doi.org/10.1016/j.bone.2015.04.050
8756-3282/

have previously reported, disease duration also negatively affects growth amongst diabetic children. For children diagnosed with diabetes at less than 5 years of age, a greater loss of height is seen during puberty. Chronic disease affecting bone mineralization often affects body and bone size as well. Reduced height for age and reduced bone area for height will result in short and narrow bones as assessed by dual energy X-ray absorptiometry (DXA) using the method of Molgaard et al. [18]. Taken together, poor metabolic control and disease duration may have a detrimental effect on bone growth and mineralization in children and adolescents with diabetes.

The growth hormone (GH)/IGF axis is a major determinant of bone mass acquisition. Circulating IGF-1 is produced by the liver, is structurally similar to insulin and helps to mediate the skeletal growth promoting actions of GH [8]. Reports suggest that poor metabolic control may alter the GH/IGF-1 axis, and lead to alterations in bone size and density in patients with T1DM.

Thus, our aims were to cross-sectionally study growth, serum IGF1 concentrations and bone health parameters as assessed by DXA in 6–16 year old Indian children and adolescents with type 1 diabetes mellitus attending a specialty out-patient tertiary care clinic in Pune, India. We hypothesized that height and DXA measured bone size and bone mineral density parameters would be impaired in children with type 1 diabetes, when compared with contemporary reference population.

Methods

Parents and children with diabetes aged 6 to 16 years attending the diabetes clinic at a tertiary care hospital in Pune, India were approached to take part in this cross sectional study. Out of 192 patients approached, 170 agreed to take part in the study. The study was approved by the institutional ethics Committee. Parents provided written informed consent and children gave assent for the study. For illiterate parents the information was read out to them either in Marathi or Hindi. If they agreed to take part in the study, then their signature or thumbprint was witnessed by an independent witness, usually one of the senior staff unrelated to the study, from the hospital. This study was conducted between Nov 2011 and March 2014.

Patients on any other medication but insulin for blood glucose control, with known comorbidities such as celiac disease, untreated hypothyroidism and eating disorders or with any other chronic disorder were excluded from the study. In total 3 children were excluded; 2 with celiac disease and one with polyendocrinopathy.

Tanner staging for sexual maturity was performed by a pediatric endocrinologist [19,20]. Data on duration of diabetes, current medications, family and personal medical history, history of fractures, age at onset of diabetes, duration of diabetes and insulin regimen were collected using standardized questionnaires. History of fractures including age at fracture, site, and cause was cross checked from patient records. Medical history provided by parents was verified from hospital medical records.

Anthropometry

Standing height was measured to the nearest millimeter using a portable stadiometer (Leicester Height Meter, Child Growth Foundation, UK), and weight was measured using an electronic scale to the nearest 100 g. Body mass index (BMI) was calculated by the formula weight/height in meter square. The height, weight and BMI were converted to Z scores [21].

Biochemical measurements

Control of blood sugar was evaluated by measuring glycosylated hemoglobin (HbA1C). A fasting blood sample (5 ml) was collected between 7 and 9 am by a trained pediatric nurse. HbA1C was measured by HPLC (BIO-RAD, Germany). Serum IGF1 concentrations were measured in a subset of children (n = 54) by Enzyme Linked Immunosorbent Assay (Thermo Scientific Multiskan EX reader). The serum IGF1 concentrations were then converted to Z scores using available Asian reference data [22].

DXA measurements

The GE-Lunar DPX Pro (GE Healthcare, Wisconsin, USA) Pencil Beam DXA scanner (software version encore 2005, 9.30.044) was used to measure bone mineral content (BMC [g]), bone area (BA [cm^2]) for total body (less head) and lumbar spine in 170 children with T1DM. While measuring the lumbar spine, the child was supine, and the physiological lumbar lordosis was flattened by elevation of the knees. For body composition variables, technique precision was 12.5 g for TBBMC (0.98% cv), 13.8 cm^2 for TBBA (1.13% cv) and 166.8 g for lean body mass (0.74% cv). For LSBMC, technique precision was 0.50 g (2.04% cv) while for LSBA it was 0.80 cm^2 (2.74% cv). Z scores for TBBMC for bone area (TBBA), TBBA for height, lean body mass (LBM) for height, TBBMC for LBM and lumbar spine bone mineral apparent density (LSBMAD) were computed using ethnic specific reference data [23].

Statistical analysis

All statistical analyses were carried out using the SPSS for Windows software program, version 12 (SPSS, Chicago, IL, USA). All outcome variables were tested for normality before performing statistical analyses. Differences in means were tested using Student's t test. One way ANOVA with post hoc Tukey's test was used to compare the means between groups according to disease duration. Linear regression was used to identify factors affecting HAZ and TBBA for height Z scores. A p value of <0.05 was considered significant.

In order to interrogate the effect of diabetes on bone size (whether it was caused by both short and or slender bones) and mineralization we used the method of Molgaard et al. [18]. In order to look at the effect of diabetes on LBM and whether this affected the bone mineralization we used the method of Crabtree et al. [24].

Results

Mean age of the study group was 11.1 ± 3.8 years. There were no significant differences in the anthropometric parameters or Z scores calculated for height, weight and BMI between the genders except for height (Table 1). However, diabetic children were shorter and lighter as compared to the reference population (HAZ −0.6 ± 1.1, WAZ −0.6 ± 1.0). The mean HbA1C was 10.1 ± 1.8% indicating suboptimal metabolic control. Bone and body composition parameters are illustrated in Table 2; both boys and girls had mean values within the reference range. Boys had significantly higher TBBMC for TBBA Z scores as compared to girls (0.2 ± 1.1 vs −0.2 ± 1.0, $p < 0.05$). Twelve percent children had their HAZ scores less than −2 and 22% had scores less than −1. For TBBA for height Z scores 6% children had scores less than −2 and 18% children had scores less than −1. Using linear regression, predictors for both these parameters were assessed. Disease

Table 1
Anthropometric characteristics in boys and girls.

Parameters	Boys (77)	Girls (93)	P value
Age (year)	11.4 ± 3.6	10.8 ± 3.9	0.314
Height (cm)[a]	140.4 ± 20.0	133.8 ± 18.0	0.026
Weight (kg)	34.9 ± 14.5	31.7 ± 13.1	0.130
BMI (kg/m^2)	16.7 ± 3.1	16.5 ± 3.6	0.740
Height Z score	−0.6 ± 1.2	−0.6 ± 1.0	0.963
Weight Z score	−0.6 ± 1.0	−0.5 ± 1.0	0.538
BMI Z score	−0.4 ± 0.9	−0.3 ± 0.9	0.477
HbA1C (%)	10.3 ± 2.5	10.1 ± 1.8	0.717

[a] Mean significantly different between genders, $P < 0.05$.

Please cite this article as: Parthasarathy LS, et al, Bone status of Indian children and adolescents with type 1 diabetes mellitus, Bone (2015), http://dx.doi.org/10.1016/j.bone.2015.04.050