Thieme

The Relationship Between Bone Mineral Density and Type 2 Diabetes in Obese Children and Adolescents at the Time of Initial Diagnosis

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ABSTRACT

Long-term effects of type 2 diabetes mellitus (T2D) on bone health remain unclear. The objective of this study was to assess the possible association of bone mineral density (BMD) at multiple sites with T2D after correcting for several potential confounders such as age, sex, Tanner stage, and BMI known to affect BMD in adolescents with newly developed T2D. In this cross-sectional study, 17 children and adolescents with T2D and 59 age, sex, and BMI-matched controls were included. All subjects underwent dual-energy X-ray absorptiometry to measure regional and whole-body composition with Lunar Prodigy at the time of initial diagnosis. A BMD Z-score was calculated using data from healthy Korean children and adolescents after adjusting for height-for-age. The mean age of all subjects was 12.9 ± 2.4 years (range, 8.3–18.3 years). BMD_{ht} Z-scores for lumbar spine and total body after adjusted for age, sex, BMI SDS, and Tanner stage were not significantly different between patients and controls. However, BMD_{ht} Z-scores for femur neck and bone mineral apparent density (BMAD) Z-scores of lumbar spine were significantly lower in T2D patients than those in healthy controls. HOMA-IR or HbA1c was not associated with BMD_{ht} Z-scores at multiple sites. BMD_{ht} Z-scores at multiple sites except femur neck in adolescents with newly developed T2D were similar to those in obese controls after adjustment for potential confounders.

Introduction

The increasing prevalence of childhood obesity is a worldwide problem [1]. In 2011, among Korean children and adolescents, 11.6 % of boys and 10.9 % of girls were obese as defined by a body mass index (BMI) of 25 kg/m^2 or greater [2]. During the past 5 years, the number of overweight children in Korea has more than doubled and the prevalence of type 2 diabetes mellitus (T2D) has increased dramatically in children and adolescents.

Complications such as retinopathy, nephropathy, and neuropathy are well known to exist in patients with T2D. Recent studies on T2D have been done on other organ systems such as the skeletal system [3]. Although decreased bone mineral density (BMD) is consistently observed in patients with type 1 DM, the relationship between T2D and bone density remains unclear in adults, although there are a few reports on children and adolescents with T2D [4]. Most studies on adults with diabetes have produced conflicting data. Several studies have reported increased BMD in patients with T2D while other studies have shown decreased or unchanged bone mass in patients with T2D compared to normal controls [5–7]. Adolescence is a critical period of peak bone mass. T2D may affect bone density when it develops in adolescents. In addition, most patients with T2D suffer from impaired glucose tolerance, which can lead to increased resistance to insulin [8]. Thus, insulin resistance and T2D might lead to skeletal complications.

The aim of this study was to assess BMD at multiple sites after correcting for several potential confounders such as age, sex, Tanner stage, and body mass index (BMI) known to affect BMD in children and adolescents with newly developed T2D.

Subjects and Methods

Subjects

This was a cross-sectional case-control study. A total of 17 obese children and adolescents with T2D were enrolled in this study. All patients were diagnosed with T2D at a single tertiary hospital between 2008 and 2014. The control group consisted of 59 healthy obese children and adolescents matched for age, sex, and body mass index (BMI) [9]. These control subjects were recruited from Seoul and Gyeonggi-do area where 50 % of the Korean population resides. All participants were of the same ethnicity (Korean). Their parents had normal heights and weights. "Obese" was defined as having a BMI above the 85th percentile for age and sex based on Korean national population standards. T2D was diagnosed according to the criteria of the ADA: 1) classic symptoms such as polyuria, polydipsia, and polyphagia, and random glucose level ≥ 200 mg/dl, 2) fasting glucose level ≥ 126 mg/dl, or 3) 2-h plasma glucose level ≥ 200 mg/dl after an oral glucose tolerance test (OGTT) [10]. All patients were negative for insulin autoantibody (IAA), glutamic acid decarboxylase antibodies (GADA), or islet cell antibody using radioimmunoassay (RSR, Cardiff, Wales, UK) at the time of initial diagnosis. Patients who had previously used medications such as glucocorticoids that might affect glucose and bone mineral metabolism were excluded. Subjects with genetic syndromes such as Prader–Willi syndrome and endocrine disorders were also excluded. No subjects had microvascular complications such as retinopathy, nephropathy, or neuropathy. No subjects had history of fracture.

Height, weight, bone age, and levels of insulin, serum glucose, calcium, phosphorus, alkaline phosphatase, and HbA1c of patients were collected from their clinical charts at the time of evaluation. Height was measured using a Harpenden stadiometer (Holtain, Crosswell, Crymych, UK) and weight was recorded with a digital scale. BMI was calculated as weight in kilograms divided by height in meters squared. Standard deviation scores (SDS) of height, weight, and BMI were calculated according to the 2007 Korean National Growth Charts [11]. Pubertal status was assessed according to the Tanner and Marshall method for genital developmental status in boys and for breast development in girls [12].

Laboratory measurements

Of 17 patients, 11 children and adolescents underwent OGTT before treatment. After fasting for 12-h overnight, standard OGTT was done by ingestion of 1.75 g/kg glucose to a maximum of 75 g. One antecubital intravenous catheter was inserted for blood sampling. Its patency was maintained by slow infusion of normal saline. Blood samples were obtained every 30 min for 120 min to measure plasma glucose and insulin levels. Plasma glucose level was determined using a glucose analyzer by the glucose oxidase method (TBA200-FR, Toshiba, Japan). Plasma insulin was measured by radio immunoassay (Cobra II Gamma counter, Packard, USA). HbA1c was measured with turbidimetric inhibition immunoassay (COBAS Integra 800, Roche, Swiss). To assess insulin resistance, we used homeostasis model assessment of insulin resistance (HOMA-IR). HOMA-IR was calculated using the following formula: fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5.

Dual-energy X-ray absorptiometry

Bone mineral density (BMD unit: grams/cm^2), bone mineral content (BMC unit: grams), and whole-body composition including lean body mass and fat mass were evaluated for all subjects using a Lunar Prodigy (General Electric, GE Healthcare, Madison, WI, USA). All patients underwent dual-energy X-ray absorptiometry (DEXA) within one week after the initial diagnosis. BMDs (g/cm^2) at the level of lumbar spine segments L1–L4 (LS), femur neck (FN), and total body (TB) were measured with a whole-body scan. To adjust for body size, bone mineral apparent density (BMAD) was calculated using the following formula: BMAD = BMD (LS) × 4/(π × width) [13]. Z-scores for BMD at each site were calculated using data on healthy Korean children and adolescents (262 girls and 252 boys) after adjusting for height-for-age [9, 14]. Subjects were carefully repositioned before every scan to minimize errors associated with changes in measurement geometry. Scans were taken by a single experienced operator. Variation coefficients for repeated measurement were < 1 % of LS, FN, and TB. Ethical approval for this study was obtained from Ajou University Hospital Ethics Committee (AJIRB-MED-MDB-17-117). Written informed consent was obtained from all subjects and their parents.

Statistical analysis

Statistical analysis was performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Parameters (BMD Z-scores for LS, FN, TB, and whole-body composition) with normal distribution were evaluated with Kolmogorov–Smirnov test. One-way analysis of covariance (ANCOVA) was performed to assess differences between patients and controls after adjusting for age, sex, BMI, and Tanner stage. Pearson's correlation analysis was performed to determine the relationship between BMD Z-scores at each site and other clinical variables. When we found a significant association with BMD Z-scores at each site, linear regression was performed for multivariate analysis with stepwise variable selection, including age, BMI SDS, HbA1c, and HOMA-IR. Statistical significance was defined at $p < 0.05$. All results are given as mean ± SD, unless otherwise stated.

Results

The clinical characteristics of all subjects are shown in ▶ **Table 1**. The mean age of all subjects was 12.9 ± 2.4 years (range, 8.3–18.3 years). Age, sex distribution, height SDS, weight SDS, or BMI SDS was not significantly different between the 2 groups. Mean HbA1c level and HOMA-IR of patients were 95 ± 3 mmol/mol and 9.7 ± 6.4, respectively. Serum C-peptide and insulin levels were 4.42 ± 2.25 ng/ml and 19.4 ± 10.4 IU/l, respectively. Of 17 patients with T2D, 8 patients were treated with hypoglycemic drugs at the time of initial diagnosis and 3 patients needed to take basal insulin and hypoglycemic drugs. Six patients were only treated with diet and exercise interventions.

▶ **Table 1** Comparison of clinical characteristics between patients with type 2 diabetes mellitus and obese controls in children and adolescents.

Variable	T2D (n = 17)	Obese controls (n = 59)	p-Value
Age (years)	13.5 ± 2.0	12.8 ± 2.5	0.202
Sex (M/F)	10/7	33/26	0.529
Pubertal status			0.353
Tanner stage 1	1	8	
Tanner stage 2	3	10	
Tanner stage 3	1	10	
Tanner stage 4	4	15	
Tanner stage 5	8	15	
Height SDS	0.46 ± 1.02	0.52 ± 1.08	0.854
Weight SDS	1.83 ± 1.67	1.67 ± 0.68	0.409
BMI SDS	1.89 ± 0.57	1.77 ± 0.46	0.462

T2D: Type 2 diabetes mellitus.

▶ **Table 2** Bone mineral density (BMD) Z-scores for lumbar spine, femur neck, and total body in patients with type 2 diabetes and obese controls.

Variable	T2D (n = 17)	Obese controls (n = 59)	p-Value†
BMD_{ht} Z-scores*			
Lumbar spine	−0.14 ± 1.51	0.27 ± 0.80	0.123
Femur Neck	0.09 ± 1.09	0.65 ± 0.95	0.011
Total body	0.36 ± 0.89	0.72 ± 0.84	0.069
BMAD Z-scores	−0.41 ± 1.16	0.32 ± 0.92	0.012
Lean body mass Z-scores	0.45 ± 1.12	1.21 ± 1.20	0.001
Fat mass Z-scores	4.69 ± 2.59	3.33 ± 2.73	0.125

* The Z-scores for BMD at each site were calculated using data on healthy Korean children and adolescents after adjusting for height-for-age.; † One-way analysis of covariance (ANCOVA) was performed to assess differences between patients and controls after adjusting for age, sex, BMI and Tanner stage.; T2D: Type 2 diabetes mellitus; BMAD: Bone mineral apparent density.

Bone mineral density

After adjusting for age, sex, BMI SDS, and Tanner stage, BMD_{ht} Z-scores for LS or TB were not significantly different between patients and controls. However, BMD_{ht} Z-scores for FN and BMAD Z-scores for lumbar spines were significantly lower in type 2DM patients than those in healthy obese controls (▶ **Table 2**). All subjects except one had bone density above −2.0 Z-scores. Low bone density of LS (Z-score: < −2) was only found in one patient with T2D (Z-score: −3.17).

Correlation analysis

Univariate and multivariate analyses were performed to investigate the correlation between several variables (age, HbA1c, HOMA-IR, and BMI SDS) and BMD_{ht} Z-scores at multiple sites. There were no significant correlations between these variables and BMD BMD_{ht} Z-scores.

Discussion

In this study, BMD_{ht} Z-scores of LS and TB in adolescents with newly developed T2D were similar to those in healthy obese controls after adjusting for potential confounders. However, BMD_{ht} Z-scores for FN and BMAD in patients with T2D were significantly lower than those in controls. HbA1c or insulin resistance was not associated with BMD Z-score.

It is well known that glucose and insulin levels can cause alterations in bone mineral metabolism in patients with types 1 and 2 DM [15]. There have been many studies on BMD in T2D in adults with inconsistent results. A meta-analysis has reported that patients with T2D have about 25–50 % SD higher BMD compared to normal control subjects [16]. In a recent review article on adults, most studies have reported increased BMD in patients with T2D compared to healthy control subjects [17]. Thirteen studies revealed decreased BMD while 8 studies found no difference in BMD between patients and healthy controls [17]. These contradicting findings might be due to large variations in ethnicity, methods used for measuring BMD, sample size, and duration of disease. In our study, BMDs of LS and TB except FN in patients with T2D were not significantly different from those in the control group. It is currently unclear why BMDs of FN only are lower in patients with T2D than those in controls. A previous study has reported that the higher the ratio of cortical and trabecular bone (distal radius > femoral neck > lumbar spine), the lower the BMD Z-score (lumbar spine > femoral neck > distal radius) in women with T2D [6]. Nakamura et al. [18] have also reported that T2D patients have significantly lower cortical bone thickness, but not trabecular BMD, compared to non-diabetic controls. These results suggest that selective loss of cortical bone might have influenced different bone density at multiple bony sites.

Higher BMI has been identified as a strong determinant of higher BMD [19]. Thus, a comparison between patients and BMI-matched controls may be important. In our study, patients with T2D in the early period after diagnosis showed no differences in BMD in comparison with BMI-matched controls, although many studies reported higher BMD in DM patients after adjusting for BMI [16]. There have been no reports on BMD in pediatric patients with T2D. Afghani et al. [20] have compared BMDs of children with impaired glucose tolerance to those in children with normal glucose tolerance. They reported that BMD was not significantly different between pre-diabetic overweight children and normal overweight controls.

The pathogenesis of bone disease in patients with T2D includes multiple factors. The early phase is characterized by hyperinsulinemia or insulin resistance whereas the late phase is characterized by the development of vascular complications [21]. In an experimental study, insulin can stimulate osteoblast proliferation and insulin-mediated signals in osteoblasts can activate bone resorption markers [22]. In addition to direct effects of insulin on bone, hyperinsulinemia could mediate bone metabolism by changing the IGF-1 axis [23]. Although results regarding the effect of insulin resistance or hyperinsulinemia on BMD have been inconsistent, Abrahamsen et al. have reported that low insulin sensitivity is correlated with high BMD in healthy men [24]. A recent study by Arikan et al. [25] has reported that insulin resistance has a negative effect on BMD in patients with type 2 DM. In our study, insulin resistance was not significantly associated with BMD in patients with T2D.

Patients with T2D have an increased risk of fracture regardless of increased or normal BMD [26]. In the Rotterdam study [27], adults above 55 years of age with T2D have increased risk of nonvertebral fracture (hazard ratio: 1.33). Although several mechanisms have been proposed for diabetes-related bone fracture, the exact mechanism remains largely unclear. Petit et al. [28] have reported that older men with T2D have smaller total bone area at the tibia than controls based on peripheral quantitative computed tomography. In the MINOS study [29], small bone width is associated with incident fractures in elderly men. In a recent study, disc height has been found to be lower in patients with T2D than that in controls [30]. Decreased bone size may be associated with fracture because decreased bone strength can result in inability to withstand mechanical loads. In our study, BMAD of the lumbar spine in patients with T2D was significantly lower than that in controls. Thus, the size of bone should be taken into account when analyzing BMD in patients with T2D.

Our study has several limitations stemming from its case-control study design. First, we did not evaluate markers related to bone metabolism, calcium intake, or physical activity. Thus, it was difficult to determine causality. Second, the sample size was very small because the prevalence of T2D in younger individuals was low in Korea. In spite of these limitations, to the best of our knowledge, this is one of the first studies to measure BMD and body composition in children and adolescents with newly developed T2D.

In conclusion, our study revealed that BMD_{ht} Z-scores at multiple sites except FN in children and adolescents with T2D were not different from those in obese controls. Longitudinal and large cohort studies are needed in the future to validate the association between diabetes and bone metabolism using more accurate methods to assess bone width such as peripheral quantitative computerized tomography.

Conflict of Interest

The authors declare that they have no conflict of interest. We confirm that we have read the Journal's position on issues involving ethical publication and affirm that this report is consistent with those guidelines.

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