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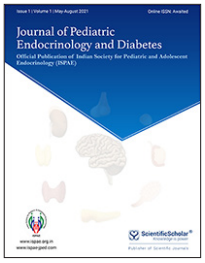

Original Article

Evaluation of bone mineral density in children with type 1 diabetes: A cross-sectional case–control study

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ABSTRACT

Objectives: To compare the bone mineral density (BMD) and vitamin D levels of children with type 1 diabetes (T1D) with normal children.

Material and Methods: Children with T1D, aged 4–18 years, and age- and gender-matched healthy controls, were recruited. Children with chronic systemic disorders and those taking medications that impair BMD were excluded from the study. Dual-energy X-ray absorptiometry, vitamin D, intact parathyroid hormone, calcium, phosphorus, alkaline phosphatase, osteocalcin, and spot urine deoxypyridinoline crosslinks (Pyrilinks-D)/creatinine ratio were estimated in both cases and controls.

Results: Thirty-seven children with T1D with a mean age of 9.7 ± 2.1 years were enrolled and compared with controls. The bone mineral content (BMC) in cases was 24.5 g (20.3–30.6) and in controls 25.5 g (23.5–26.8) ($P = 0.66$) and BMD in cases was 0.68 ± 0.165 g/cm^2 and in controls 0.69 ± 0.149 g/cm^2 ($P = 0.76$). However, the prevalence of low BMD (BMD <-2 Z-score) was seen in only 3 (8%) cases (P – <0.001). Serum 25-hydroxyvitamin D [25(OH)D] levels were also lower in cases 14.1 ng/mL (12.05–14.75 ng/mL) as compared to controls 15.73 ng/mL (13.1–23.2 ng/mL) ($P = 0.01$). Thirty-three (89%) cases and 24 (64%) controls had low 25(OH)D levels (<20 ng/mL). There was no significant difference in the bone turnover markers between cases and controls.

Conclusion: Children with T1D have similar BMD and lower vitamin D levels compared to healthy children.

Keywords: Type 1 diabetes, Bone mineral density, Vitamin D, Osteocalcin

INTRODUCTION

Type 1 diabetes (T1D) is a chronic inflammatory condition associated with decreased insulin secretion resulting from the destruction of pancreatic beta cells. Approximately 85–90% of the diabetes observed in children is due to T1D.[1] The prevalence of vitamin D deficiency is very high in the Indian population. About 50–90% of Indian children suffer from vitamin D deficiency.[2] There are various reasons attributed to the high prevalence of vitamin D deficiency among Indians. Mainly, it is due to the increased urbanization and sedentary behavior with an indoor lifestyle and increased skin melanin content.

Further, various studies show that children with T1D are predisposed to vitamin D deficiency compared to the general population.[3] Few studies even show that there is better glycemic control with vitamin D supplementation.[4,5] Further, vitamin D can modulate the synthesis of various proteins in different tissues of the body. Vitamin D supplementation

improved the insulin secretion and biosynthesis by 1,25-dihydroxyvitamin D [1,25$(OH)_2$].[6]

Potential pathological mechanisms of T1D-related bone damage may include hyperglycemia,[4,7] a defect in IGF-1,[5,8] non-enzymatic glycosylation of type 1 collagen with advanced glycation end products,[6,9] chronic inflammatory state,[7,10] and vitamin D deficiency.[8,11] There is a paucity of the literature regarding bone mineral density (BMD) in children with T1D in India. This cross-sectional case–control study was conducted in our institute to know the magnitude of low BMD and vitamin D deficiency in children who have T1D.

MATERIAL AND METHODS

This cross-sectional case-control study was conducted in the pediatric endocrinology outpatient clinic, Department of Pediatrics, JIPMER, in collaboration with the department of endocrinology from January 2019 to March 2021, after obtaining approval from the Institute Ethics Committee (Human Studies) (JIP/IEC/2018/432). The sample size was calculated using the OpenEpi online tool, based on the BMD of the previous study (where mean BMD for cases was −1.07 and controls was −0.33) and at a 95% confidence interval, 80% power, and 1:1 ratio of cases and controls, the calculated sample size was 37 cases and 37 controls.[9,12] Children between 4 and 18 years who are non-obese having diabetes according to the WHO criteria (symptoms plus random plasma glucose ≥200 mg/dL or fasting plasma glucose ≥126 mg/dL or 2 h plasma glucose ≥200 mg/dL during oral glucose tolerance test (OGTT) or HbA1c ≥6.5%) and who require insulin to maintain normal blood glucose were considered as T1D for our study purpose. Our study included age- (±6 months) and sex-matched healthy children as controls. All children with chronic kidney disease with glomerular filtration rate <60 mL/min/1.73 m^2, vitamin D and calcium supplementation, parathyroid disorders, celiac disease, proven monogenic diabetes, obese children with body mass index (BMI) >95th percentile for age and sex, children on drugs such as antitubercular therapy, glucocorticoids, antiepileptics like phenytoin, and other drugs which affect the BMD were excluded from the study.

Anthropometric parameters such as weight were measured using an electronic weighing machine with a precision of ± 10 g, and height was measured by a stadiometer with a precision of ± 1 mm. The duration of sun exposure (hours/day) and time spent on screens (hours/day) was assessed by 24 h recall method. Dietary intake of calcium intake (mg/day) was measured by the 24 h recall method, using a calcium calculator developed by the Osteoporosis Foundation. Physical activity score was assessed in the form of a questionnaire and graded from 1 (requiring assistance from others) to 5 (unrestricted activities). In children with T1D, duration of diabetes; type of insulin therapy; daily prescribed insulin dose; and complications such as diabetic neuropathy, retinopathy, nephropathy, and diabetic ketoacidosis were recorded at the time of enrollment. The presence or absence of lipodystrophy and hypothyroidism was also noted in cases.

The following investigations were done in cases and controls – dual-energy X-ray absorptiometry (DXA) scan at the lumbar spine from L1 to L4 (Hologic QDR Discovery DXA fan-beam scanner), serum calcium, albumin, phosphorus, alkaline phosphatase (ALP), 25-hydroxyvitamin D [25(OH)D], intact parathyroid hormone (iPTH), creatinine, osteocalcin, and spot urine Pyrilinks-D (deoxypyridinoline crosslinks) to creatinine ratio. 25(OH)D and iPTH were estimated by the chemiluminescence method (ADVIA Centaur). Serum osteocalcin and urine Pyrilinks-D were also assessed by chemiluminescence (Immulite 1000 by Siemens). The reportable range, assay sensitivity, intra-assay, and interassay coefficient of variation of 25(OH)D, iPTH, serum osteocalcin, and urine Pyrilinks-D are given in Table 1.

Low BMD was defined as per "International Society of Clinical Densitometry" as BMD <−2 Z-score, adjusted for age, gender, and body size and BMD Z-score was calculated for enrolled children.[10,13]

Statistical analysis

The statistical analysis was carried out with IBM SPSS software version 19. According to the Kolmogorov–Smirnov measure, continuous variables with a normal distribution were expressed as mean ± SD and then analyzed using an independent *t*-test. Continuous variables which followed a non-normal distribution were expressed as median, IQR, and analyzed using the Mann-Whitney U test. Categorical variables were expressed as proportions. Pearson test for continuous variables with normal distribution and Spearman test for continuous variables with non-normal distribution were used as correlation tests.

RESULTS

Thirty-seven children with T1D and 37 healthy children fulfilling the inclusion criteria were assessed for eligibility and enrolled. The mean age of children with T1D was 10 (±3.14) years and that of controls was 9.78 (±2.1) years. Fourteen (38%) cases were underweight (weight Z-score <−2), 9 (24%) were stunted (height Z-score <−2), and 17 (46%) had thinness (BMI Z-score <−2). No children in the control group had altered anthropometric values. There was no significant difference in calcium intake, physical activity, and duration of sun exposure between cases and controls. However, screen time was significantly more in controls (2.24 h/day) as compared to cases (1.89 h/day) ($P < 0.009$).

The median duration of diabetes in cases was 10 (2–36) months. The median insulin dose was 1 U/kg (0.9–1.2). The mean HbA1c was 9.46 ± 2%. Five (13%) diabetic children had autoimmune thyroiditis and 7 (19%) children had lipodystrophy.

The bone health parameters and their categorization in cases and controls are given in Table 2. Three (8%) children with T1D were found to have low BMD (BMD <–2 Z-score). In contrast, none in the control group had low BMD. Serum 25(OH)D was significantly lower in cases, and serum iPTH was substantially higher than controls. Low serum 25(OH)D was found in 33 children with diabetes (89%), whereas 24 (65%) controls were also had low 25(OH)D levels (P = 0.01). There was no significant difference in the serum calcium, phosphorus, ALP, osteocalcin, and urine Pyrilinks-D levels between cases and controls.

There was no significant correlation between bone mineral content (BMC) and other bone turnover variables such as serum osteocalcin, urine Pyrilinks-D, serum vitamin D, serum phosphorus, serum calcium, and ALP. The duration of the disease, HbA1c, the daily dose of insulin, screen time, and the presence of hypothyroidism too did not show a significant correlation with BMC.

During the COVID pandemic (March 2020–December 2020), none of the children with T1D enrolled in our study had COVID pneumonia. Two out of 37 cases had DKA. Procurement of insulin was from a nearby pharmacy store in all the cases and none had discontinued any medication.

DISCUSSION

Bone mineral acquisition in childhood determines the quality of bone in adolescents and adults. Prevention of insult to the formation of bone and osteoprotection is crucial in childhood. Poor quality of bone is responsible for the low impact fracture and growth faltering.[11,14] Early identification of low BMD is of paramount importance for early initiation of treatment. Treatment strategies proposed for low BMD in children with T1D include calcium supplementation, vitamin D supplementation, and bisphosphonates.

Studies have reported mixed results regarding bone health. Some observed no difference between T1D and normal controls,[12-18] whereas few studies showed low BMD in children with T1D.[2,3,12] We did not find any significant difference in BMD between cases and controls. This may be due to the lesser duration of diabetes in our study population. Only 3 (8%) cases had low BMD for age (Z-score

Table 1: Performance characteristics of bone health markers.

Parameter	Reportable range	Assay sensitivity	Intra-assay coefficient of variation (%)	Inter-assay coefficient of variation (%)
25(OH) Vitamin D (ng/mL)	4.5–150	4.2	<7	<11
Intact parathyroid hormone (pg/mL)	4.6–2000	4.6	<5	<7
Serum osteocalcin (ng/mL)	2–200	0.55	<4	<10
Urine Pyrilinks-D (nmol)	7–300	6	<15	<20

Table 2: Differences in bone health parameters in cases and controls.

Variable	Cases (n=37)	Controls (n=37)	P-value
Bone mineral content in grams (Median, IQR)	24.5 (20.3–30.6)	25.5 (23.5–26.8)	0.661
Bone mineral density in g/cm^2 (Mean, SD)	0.68±0.165	0.69±0.149	0.769
Bone mineral density Z-score			
<–2	3 (8%)	-	<0.001
≥–2	34 (92%)	37 (100%)	
25[OH] Vitamin D in ng/mL (Median, IQR)	14.1 (12.05–14.75)	15.73 (13.1–23.29)	0.010
S.25[OH] Vitamin D (ng/mL)			
≤12	9 (24%)	10 (27%)	0.039
12–20	24 (65%)	14 (38%)	
>20	4 (11%)	13 (35%)	
Intact parathyroid hormone, pg/mL (Median, IQR)	28.1 (18.6–32.4)	21.6 (14.6–29.4)	0.048
Calcium (mg/dL) (Mean±SD)	9.4±0.57	9.07±0.54	0.118
Phosphorus (mg/dL) (Mean±SD)	4.19±0.46	4.28±0.55	0.431
Alkaline phosphatase (IU/L) (Mean±SD)	222±96	230±62	0.695
Urine Pyrilinks-D/creatinine ratio (nmol deoxypyridinoline/mmol creatinine) (Median, IQR)	20.1 (14.4–26.5)	17.8 (14.7–21.0)	0.563
Serum osteocalcin (ng/mL) (Median, IQR)	18.2 (3.5–25.3)	10.8 (3.5–20.2)	0.222

<–2). Our observation was in concordance with the study from Chile, which reported the prevalence of 6% among children with T1D.[16,19] Further, Parthasarathy *et al.* reported that Indian children with diabetes were shorter and lighter but had adequate mineralization of bone as compared to the reference population. Furthermore, the duration of diabetes did not impact BMD in their study.[17,20]

Vitamin D reduces the autoimmune destruction of the β-cells by immunomodulatory effect and enhances insulin production and secretion by regulating calcium flux and calcium-independent mechanisms. Hence, vitamin D deficiency is considered as a risk factor for developing T1D and found to be low even at the onset of diabetes.[2] As compared to the previous studies,[18,19,21,22] our study showed significantly lower 25(OH)D levels in children with T1D than normal ($P < 0.05$). We observed a higher prevalence of vitamin D deficiency (89%) in children with T1D than few other studies.[20,23] Majority (64%) of controls had low serum levels of 25(OH)D levels in this study, comparable to a study conducted in a healthy pediatric population from India.[21,24] In our study, there was no significant correlation between vitamin D levels and duration of sun exposure, calcium intake, time spent on screen, HbA1c levels, duration of disease, and physical activity score in cases.

In our study, PTH levels were significantly elevated ($P < 0.05$) in children with T1D compared to the healthy controls. The high iPTH levels are probably due to low serum 25(OH)D levels in cases. However, there is no significant difference between the two groups in terms of serum calcium, phosphorus, and ALP levels. Smaller sample size could be a reason for the insignificant difference between the two groups. The previous studies showed mixed results pertaining to these biochemical parameters. Few studies showed comparable results to our study[22,23,25,26] and few other studies had contradicting results.[19,22]

Bone turnover markers predict the increased fracture risk and rapid bone loss, independent of BMD. Serum osteocalcin is a specific marker for bone formation. Finally, we did not find any significant difference in bone turnover markers between the two groups. There is no association of bone turnover markers with BMC, like a study performed by Kayath *et al.*[23,26] A few studies in the past observed a positive association of BMD with bone formation markers and a negative association with bone resorption markers.[9,12,24,27]

Varied results were observed in the previous studies concerning predictors of BMD and vitamin D deficiency in children with T1D. A study done by Madsen *et al*. who showed that BMD in T1D children was negatively associated with HbA1c, insulin pump treatment, and screen time, and there was no significant association between physical activity, sex, and puberty.[24] Fuusager *et al*. observed that poor glycemic control (HbA1c >7.5%) within the latest year was negatively correlated with BMD Z-scores ($P = 0.04$).[14,17] However, Mosso *et al*. did not find any correlation between BMD and the age at onset of the disease, disease duration, level of physical activity, and clinical parameters in children with T1D.[16,19] In our study, there was no significant correlation between BMC and other bone turnover variables such as serum osteocalcin, urine Pyrilinks-D, serum vitamin D, serum phosphorus, serum calcium, and ALP. The duration of the disease, HbA1c, the daily dose of insulin, screen time, and presence of hypothyroidism too did not show a significant correlation with BMC.

Our study gives valuable input to the prevalence of vitamin D deficiency and BMD in children with T1D compared to normal children in our population. The shorter duration of follow-up and not measuring volumetric bone density are the limitations of this study. This being an observational cross-sectional study, the effect of vitamin D supplementation and calcium supplementation in improving bone health could not be assessed, and prospective longitudinal studies will be necessary for the future.

CONCLUSION

Children with T1D had significantly low serum 25(OH)D and almost equivalent BMD as compared to their healthy counterparts. There was no correlation between bone turnover markers, HbA1c, and disease duration with bone mineral content.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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