Assessment of Vitamin D Status, its Determinants and Relationship with Bone Health in Indian Children and Young Adults with Type-1 Diabetes

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Abstract

Introduction: Recent evidence suggests that vitamin D deficiency and type-1 diabetes (T1D) have a bidirectional cause–effect relationship. The objective of this study is to estimate the prevalence and determinants of vitamin D deficiency in Indian children and young adults with T1D and assess the relationship between vitamin D status and their bone health. **Methods:** It was a single-centre, cross-sectional study. Inclusion: Children, young adults aged 5–25 years with T1D duration >1 year. Exclusion: Already on vitamin D supplementation, conditions affecting bone health. Data collected: Demographic, clinical, anthropometry, biochemical, body composition, DXA, pQCT measurements. **Results:** A total of 453 participants (251 girls) with T1D, mean age = 13.5 ± 4.0 years, disease duration = 5.7 ± 3.9 years. Mean 25-hydroxy vitamin D concentration of study group was 20.4 ± 11.3 ng/mL. One hundred and eleven (24.5%) were deficient in 25-hydroxy vitamin D, 141 (31.1%) were insufficient and 201 (44.4%) were sufficient. 25-Hydroxy vitamin D concentrations had significant negative correlation with BMI Z-score, diastolic blood pressure, fat percentage Z-score and positive correlation with physical activity, haemoglobin concentrations and trabecular density ($P < 0.05$). Risk of developing vitamin D deficiency and insufficiency was significantly lower in subjects with good/intermediate glycaemic control versus poor control ($P = 0.008$). Higher diastolic blood pressure and female gender were significant risk factors for development of vitamin D deficiency. **Conclusion:** Vitamin D deficiency has high prevalence in children and youth with T1D and has detrimental effect on bone geometry of these subjects. Weight reduction increased outdoor physical activity, good glycemic control are some modifiable factors that may prove useful in preventing vitamin D deficiency.

Keywords: Bone health, deficiency, trabecular bone density, type 1 diabetes, Vitamin D

INTRODUCTION

In recent times, an ever-increasing role of vitamin D has been documented in various physiological functions and its sufficiency/deficiency is believed to play an important role in health and disease. Vitamin D plays a pivotal role in calcium and bone metabolism; the manifestations of its deficiency are manifold. The Indian Academy of Pediatrics (IAP) guidelines define vitamin D status as being sufficient (>20 ng/mL), insufficient (12–20 ng/mL) or deficient (<12 ng/mL).[1] Various Indian studies have reported vitamin D deficiency in all age groups (including pregnant and lactating women) ranging from 30% to 90%.[1] A study in healthy Indian school-going children and adolescents from various states, aged 5–18 years, reported 42% to be vitamin D sufficient; 20% and 38% were deficient and insufficient, respectively.[2] Vitamin D deficiency leads to abnormal mineralization of bone matrix, lower bone mineral density (BMD) and often rachitic deformities.

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Type-1 diabetes (T1D) is a chronic disorder characterized by autoimmune destruction of pancreatic beta cells, with subsequent chronic insulin deficiency. Recent evidence suggests that vitamin D deficiency and T1D have a bidirectional cause–effect relationship.[3] Specific effects of vitamin D on genes relevant to T1D and type-2 diabetes as well as the presence of polymorphisms in vitamin D response elements in the promoter regions of diabetes-related genes have been reported.[3] Vitamin D deficiency may predispose to diabetes by modulating autoimmunity, inflammation, insulin sensitivity, adiposity and insulin post-receptor signalling pathways.[3] Vitamin D deficiency promotes the development of insulin resistance even in T1D, which can further accelerate micro/macrovascular complications.[3] Conversely, T1D is reported to cause vitamin D deficiency by enhancing the excretion of vitamin D-binding protein and decreased renal 1α-hydroxylase activity in diabetic nephropathy.[4]

Longstanding diabetes adversely affects bone metabolism and microarchitecture.[4] Besides vitamin D deficiency, various other factors cause impaired bone mineralization and increased fragility in T1D, namely, poor glycaemic control, longstanding diabetes, advanced glycation end products, nephropathy, urinary calcium loss and chronic inflammation.[5] Studies by the author's group have demonstrated short and narrow bones in children with T1D, with significantly lower total body (TB) less head areal BMD *Z*-scores following disease progression and affection of trabecular bone as evidenced from significantly lower trabecular BMD on peripheral quantitative computed tomography (pQCT).[6,7]

Despite India accounting for the largest incidence and prevalence of T1D in children and youth globally, there is scarcity of studies assessing the burden of vitamin D deficiency and insufficiency in T1D and the relationship between bone health and vitamin D status in children with T1D. Hence, this study was planned with the following objectives:

1. To estimate the prevalence of vitamin D deficiency in Indian children and youth with T1D.
2. To identify determinants of vitamin D deficiency in children and youth with T1D.
3. To assess the relationship between vitamin D status and bone health of patients with T1D.

MATERIALS AND METHODS

Study design and subjects

A single-centre, cross-sectional study was conducted between November 2020 and February 2021 at a tertiary-care centre (Pune, India). All patients attending the paediatric T1D clinic were screened for eligibility. All children and young adults with T1D duration of more than a year, aged 5–25 years, were included in this study. Children who were currently on vitamin D supplementation ($n = 26$) or had any condition which could affect bone health were excluded. Thus, out of 530 patients seen at the clinic, 453 children (or their parents) and young adults gave written informed consent/

assent and were included. The remaining 77 either did not fulfil the inclusion criteria or refused to participate. Using the formula, $n = z \times z \times P \times (1 - P)/d \times d$ ($z = 1.96$ for 95% confidence interval, P = prevalence based on previous studies and d = precision), a sample size of 355 was adequate for a power of 0.8 at a significance level of <0.05.

Clinical history and examination

Questionnaires were used to collect the following data: age, gender, diabetes duration, total daily dose of insulin, history of fractures and personal and family history. The activity questionnaire adapted for Indian children and adolescents was used to assess activity.[8] Dietary intake was recorded by a trained nutritionist using the 24-h dietary recall method. For estimation of food intake, participants were interviewed in Hindi, English or Marathi languages using standard cups and spoons. Nutrient intakes were then estimated using the C-diet software.[9] Pubertal status was assessed by a paediatric endocrinologist using Tanner staging for sexual maturity.[10] We classified subjects' pubertal status as Tanner stage 1 as prepubertal, stage 2–4 as pubertal and stage 5 as post-pubertal.[10]

Anthropometry

Height (Seca Portable stadiometer, up to 0.1 cm accuracy) and body weight (Seca 876 Flat scale, up to 100 g accuracy) were measured and BMI was calculated as weight (kg)/height (m²). Waist (WC) and hip circumferences were measured based on the World Health Organization guide to physical measurements and waist:hip ratio was calculated.[11] Weight, height, WC and BMI were converted to *Z*-scores.[11]

Biochemical measurements

A total of 5–8 ml blood was drawn by an experienced phlebotomist after a minimum of 8 h fast. Lipid profile (total cholesterol, triglycerides and HDL-C) was assessed using the enzymatic method and low-density lipoprotein-cholesterol concentrations were calculated by the Friedewald formula.[12] Glycaemic control was assessed by measuring glycosylated haemoglobin (HbA1c) using high-performance liquid chromatography (HPLC, BIO-RAD, Germany). Good/Intermediate glycaemic control and poor glycaemic control were defined as HbA1c below and above 9.5%, respectively.[13] Serum IGF-1 concentrations were measured by a solid-phase enzyme-linked immunosorbent assay (ELISA, Biocheck, Germany) with an intra-assay coefficient of variation (CV) of 4.7% and inter-assay CV of 7.2%. Haemoglobin was estimated by spectrophotometry at a wavelength of 555 nm using a Horiba Yumizen H500 haematology analyser. Serum phosphorous was measured by ultraviolet method. Serum concentrations of total calcium were measured using a calorimetric assay (ISA; AVL List GmbH, Graz, Austria). Urinary spot albumin was assessed by immunoturbidimetry and urinary creatinine by Jaffe's method. The serum concentration of 25-hydroxy vitamin D was measured using radioimmunoassay (DiaSorin, Stillwater, MN, USA). Vitamin D status was classified as

sufficiency (>20 ng/mL), insufficiency (12–20 ng/mL) or deficiency (<12 ng/mL) based on the IAP recommendations on vitamin D and rickets.[1] All children diagnosed with deficiency/insufficiency were supplemented with vitamin D on obtaining the results.

Body composition

Fat and fat-free mass were assessed using Bioelectrical Impedance Analyzer (BIA) (Tanita Model-BC420MA) in standing position after at least 3-h of fasting and voiding before measurements; *Z*-scores were computed using Indian reference data.[14]

DXA

Areal BMD was measured using dual-energy X-ray absorptiometry technique (DXA) by the Lunar iDXA (GE Healthcare, WI) fan beam scanner (encore software – version 16). Total body (TB) and lumbar spine were the sites assessed by a single operator for all patients and bone mineral content (BMC, g), BMD (aBMD, g/cm^2) and bone area (BA, cm^2) were measured. The machine was calibrated daily and calibrations were regularly reviewed by service engineers. The CV for L1–L4 aBMD and L1–L4 BMC was 1% and 2.8%, respectively. Total body less head (TBLH) aBMD had a CV of 0.7%. *Z*-scores for lumbar spine BMD (L1–L4 BMD), TBLH aBMD and lumbar spine bone mineral apparent density for age were computed using reference data for Asians.[15]

Peripheral quantitative computed tomography

The radius of the non-dominant hand was the site of pQCT measurements and was evaluated using the Stratec XCT 2000 equipment (Stratec Inc., Pforzheim, Germany), analysed using an integrated software for Stratec 2000, version 6.2. The distance between the olecranon and the ulnar styloid process of the participant's non-dominant hand was measured using a non-stretchable measuring tape. Using the scout view, reference line was drawn through the middle of the ulnar border of the articular cartilage. Images at 4% and 66% length of radius were obtained during scan.[16,17] At 4% site of the radius using 0.59 mm voxel size, contour and peel modes 2, slice thickness 2.5 mm, trabecular volumetric BMD (vBMD) and bone mass were measured at a threshold of 180 mg/cm^3. Periosteal and endosteal circumferences, cortical vBMD and thickness and strength strain index (SSI) were measured at 66% of radius at a threshold of 711 mg/cm^3, contour mode 3. The CV for the pQCT bone parameters from duplicate scans in children ($n = 10$) ranged from 0.65% to 3%. The CV for total, trabecular and cortical density was 0.7%, 3.0% and 0.8%, respectively. The cortical thickness, periosteal circumference and endosteal circumference measurements had a CV of 2.6%, 0.8% and 1.9%, respectively. Machine-generated *Z*-scores for trabecular density, total density, cortical density and SSI for age were used for analysis.

Statistical analysis

Data were analysed using SPSS 26.0 (IBM SPSS, Bangalore, India). All outcome variables were tested for normality before performing statistical analyses. Mean (SD), median (IQR) and proportions were used for descriptive statistics. One-way ANOVA was used to compare differences in means between the sufficient, insufficient and deficient groups. Correlation analysis was performed using Spearman's correlation coefficient. Multinomial logistic regression was performed to assess factors affecting vitamin D deficiency and insufficiency with reference to vitamin D sufficiency. *P* values <0.05 were considered as statistically significant. Glycaemic control was used as the predictor with poor glycaemic control as the reference category (haemoglobin was not considered in the analysis because HbA1c and haemoglobin demonstrated collinearity). Other predictors of vitamin D deficiency used in the model were age, gender, body mass index, blood pressure, waist circumference, physical activity and dietary intake of calcium and phosphorus.

Ethical Aspect

This study was conducted following institutional ethics committee approval (Ethics Committee Jehangir Clinical Development Centre Pvt Ltd, dated 22nd July 2020) in accordance with the declaration of Helsinki (2013). Written informed consent/assent was obtained from all participants / their parents.

RESULTS

A total of 453 children and young adults aged 5–25 years with T1D were included in the study. Two hundred and two (44.6%) were boys and 251 (55.4%) were girls. The mean age of the children in the study group was 13.5 ± 4.0 years and the average duration of diabetes was 5.7 ± 3.9 years. The mean HbA1c was 10.1 ± 2.3%. The mean total insulin requirement in our cohort was 1.1 ± 0.3 units/kg/day. One hundred and twenty-two (26.9%) children were pre-pubertal, 156 (34.4%) children were in puberty and 175 (38.6%) children/youth were post-pubertal. The number of obese and overweight children in our study was 15 (3.3%) and 57 (12.6%), respectively. Ten subjects (2.2%) had a history of fracture (radius-4, olecranon-1, humerus-1, fibula-2, tibia + fibula-2). Most fractures occurred following falls while playing, one fracture involving the tibia and fibula occurred following a road traffic accident. None of the patients had more than one instance of fracture. Patients' demographics and laboratory findings have been illustrated in Table 1a. As seen in Tables 1a and b, the subjects with vitamin D deficiency had higher BMI *Z*-score, fat mass percentage, diastolic blood pressure and lower haemoglobin, trabecular density and moderate–vigorous physical activity as compared to the sufficient group.

The mean 25-hydroxy vitamin D concentration of study group was 20.4 ± 11.3 ng/ml. One hundred and eleven (24.5%) were deficient in 25-hydroxy vitamin D, 141 (31.1%) were insufficient and 201 (44.4%) were sufficient. As shown in Table 2, 25-hydroxy vitamin D concentrations had significant negative correlation with BMI *Z*-score (−0.116, *P* < 0.05), diastolic blood pressure and fat percentage *Z*-score. The 25-hydroxy vitamin D

Table 1a: Demographic, clinical, body composition and laboratory findings of the study population			
Parameter	Deficiency (*n*=111) Mean (SD)	Insufficiency (*n*=141) Mean (SD)	Sufficiency (*n*=201) Mean (SD)
Clinical, anthropometric, physical activity and dietary data			
Age (years)	13.7 (3.8)	13.7 (3.9)	13.2 (4.1)
Proportion of females (%)	81 (32.2%)	70 27.8%)	100 (39.8%)
Proportion of males (%)	30 (14.8%)	71 (35.1%)	101 (45.9%)
Duration of illness (years)	5.7 (4.0)	5.6 (3.6)	5.7 (4.0)
Height (*Z*-score)	−0.5 (1.1)	−0.7 (1.1)	−0.6 (1.1)
Weight (*Z*-score)	−0.3 (1.1)	−0.6 (1.0)	−0.6 (1.0)
BMI (*Z*-score)*	−0.1 (1.0)	−0.3 (0.9)	−0.4 (0.9)
Waist (*Z*-score)	−1.0 (1.0)	−1.9 (1.4)	−1.2 (1.1)
Systolic blood pressure (mmHg)	107.6 (13.3)	108.5 (13.9)	105.4 (12.1)
Diastolic blood pressure (mmHg)*	67.6 (11.0)	66.4 (11.7)	64.3 (9.7)
Insulin requirement (U/kg/day)	1.1 (0.3)	1.0 (0.3)	1.1 (0.3)
Dietary intake of calcium (mg/day)	384.5 (212.3)	386.9 (207.6)	413.9 (232.9)
Dietary intake of phosphorus (mg/day)	889.1 (317.1)	934.0 (332.4)	981.4 (355.3)
Total sleep duration (min/day)	524.0 (52.0)	519.4 (57.0)	524.8 (47.8)
Total moderate–vigorous activity (min/day)*	38.5 (29.8)	43.9 (35.0)	47.6 (32.4)
Effective sunlight exposure (min/day)	16.6 (26.8)	32.9 (46.2)	31.8 (41.4)
Biochemistry			
HbA1c (%)	10.3 (2.5)	10.0 (2.2)	10.0 (2.2)
IGF 1 (ng/mL)	151.1 (78.6)	140.8 (71.5)	147.4 (111.5)
25-Hydroxy vitamin D (ng/mL)	8.4 (2.4)	15.7 (2.2)	30.3 (9.5)
Serum calcium (mg/dL)	9.1 (0.4)	9.3 (0.4)	9.2 (0.3)
Serum phosphorus (mg/dL)	3.9 (0.8)	3.9 (0.5)	4.2 (1.0)
Albumin–creatinine ratio (μg/mg)	69.0 (272.7)	53.0 (185.9)	62.1 (293.2)
Haemoglobin (g/dL)*	13.1 (1.3)	13.1 (2.0)	13.5 (1.5)
Total cholesterol (mg/dL)	161.0 (36.4)	160.2 (37.6)	157.1 (33.0)
HDL (mg/dL)	49.7 (11.7)	49.7 (11.5)	49.2 (10.5)
LDL (mg/dL)	90.1 (37.9)	90.7 (38.9)	91.4 (29.2)
Triglyceride (mg/dL)	106.0 (170.6)	98.6 (148.6)	82.1 (42.6)
VLDL (mg/dL)	21.2 (34.1)	19.7 (29.7)	16.4 (8.5)
Body composition			
Fat percentage*	22.4 (9.5)	18.6 (9.5)	17.7 (9.5)
Fat percentage (*Z*-score)*	−0.02 (0.8)	−0.2 (0.9)	−0.3 (0.9)
Lean body mass percentage	29.2 (8.0)	29.7 (8.7)	28.6 (9.1)

concentrations also had significant positive correlation with physical activity, haemoglobin concentrations and trabecular density (0.210, *P* < 0.05).

Table 3 presents a multinomial logistic regression model describing factors affecting vitamin D deficiency [Table 3a] and and vitamin D insufficiency [Table 3b] with reference to vitamin D sufficiency. We found that the risk of development of vitamin D deficiency and insufficiency was significantly lower in subjects with good/intermediate glycaemic control as compared to those with poor control (*P* = 0.008). Higher diastolic blood pressure and female gender were significant risk factors for the development of vitamin D deficiency.

DISCUSSION

From our cross-sectional study on Indian children and youth with T1D, we found that 24.5% were deficient, 31.1% were insufficient and 44.4% were sufficient in vitamin D. The mean 25-hydroxy vitamin D concentration of study group was 20.4 ± 11.3 ng/ml. 25-Hydroxy vitamin D concentrations had significant negative correlation with BMI and fat percentage *Z*-scores. 25-Hydroxy vitamin D concentration also had significant positive correlation with haemoglobin levels and trabecular bone density at radius. We found that the risk of development of vitamin D deficiency and insufficiency was significantly lower in subjects with good/intermediate glycaemic control (HbA1c <9.5%, ADA definition) as compared to subjects with poor control (*P* = 0.008). Higher diastolic blood pressure and female gender were significant risk factors for the development of vitamin D deficiency in Indian children and youth with T1D.

The prevalence of vitamin D deficiency in T1D is sizeable. Global results on prevalence have shown mixed results in comparison with healthy population. Similar to our study, a multistate study on healthy Indian school-going children

Table 1b: DXA and pQCT findings of the study population

Parameter	Deficiency (*n*=111) Mean (SD)	Insufficiency (*n*=141) Mean (SD)	Sufficiency (*n*=201) Mean (SD)
DXA			
L1–L4 BMD (g/cm²)	0.8 (0.1)	0.8 (0.1)	0.7 (0.1)
L1–L4 BMC (g)	31.0 (13.1)	30.4 (13.2)	29.1 (13.2)
L1–L4 area (cm²)	35.6 (8.2)	36.2 (8.6)	35.1 (8.8)
L1–L4 (*Z*-score)	−1.2 (1.0)	−1.3 (1.0)	−1.2 (1.0)
TBLH BMD (g/cm²)	0.7 (0.1)	0.7 (0.1)	0.6 (0.1)
TBLH BMC (g)	979.8 (370.0)	991.1 (395.1)	960.7 (414.7)
TBLH area (cm²)	1,337.9 (275.6)	1,357.4 (308.2)	1,325.3 (327.2)
TBLH (*Z*-score)	−1.6 (0.9)	−1.5 (0.8)	−1.5 (0.9)
pQCT			
SSI (mm³)	158.4 (48.0)	160.6 (57.2)	176.4 (64.4)
Trabecular area (mm²)	101.6 (20.8)	107.0 (26.4)	110.4 (30.8)
Trabecular density (mg/cm³)*	140.6 (35.9)	147.0 (32.9)	156.9 (37.5)
Cortical area (mm²)	47.6 (12.6)	49.4 (13.5)	52.3 (14.7)
Cortical density (mg/cm³)	1,064.8 (72.1)	1,064.5 (61.2)	1,063.9 (61.5)
Cortical thickness (mm)	1.5 (0.4)	1.6 (0.3)	1.6 (0.4)
Periosteal circumference (mm)	35.4 (3.0)	35.2 (3.9)	36.5 (4.1)
Endosteal circumference (mm)	25.5 (3.4)	24.9 (3.6)	26.1 (3.5)

*Significant difference between deficient and sufficient group. SD=standard deviation, BMI=body mass index, HbA1c=glycated haemoglobin, IGF 1=insulin-like growth factor 1, HDL=high-density lipoprotein, LDL=low-density lipoprotein, VLDL=very low-density lipoprotein, BMD=bone mineral density, BMC=bone mineral content, TBLH=total body less head, SSI=stress–strain index

Table 2: Correlation of 25-hydroxy vitamin D concentrations with various clinical, anthropometric, biochemical, DXA and pQCT-derived parameters

Parameters	Spearman's correlation coefficient (rho)	Parameters	Spearman's correlation coefficient (rho)
Age (years)	−0.08	Fat percentage	−0.200*
Duration of illness	−0.028	Fat percentage (*Z*-score)	−0.149*
Height (*Z*-score)	0.033	Fat mass	−0.183*
Weight (*Z*-score)	−0.066	Fat-free mass	−0.022
Body mass index (*Z*-score)	−0.128*	Muscle mass	−0.044
Waist circumference (*Z*-score)	−0.063	L1–L4 BMD (g/cm²)	−0.086
Systolic blood pressure (mmHg)	−0.088	L1–L4 BMC (g)	−0.061
Diastolic blood pressure (mmHg)	−0.157*	L1–L4 Area (cm²)	−0.031
Insulin requirement (U/kg/day)	0.03	L1–L4 (*Z*-score)	0.012
HbA1c (%)	−0.017	TBLH BMD (g/cm²)	−0.046
Insulin-like growth factor 1 (ng/ml)	−0.062	TBLH BMC (g)	−0.034
Haemoglobin (g/dL)	0.112*	TBLH Area (cm²)	−0.014
		TBLH (*Z*-score)	0.037
Serum calcium (mg/dL)	0.038	SSI (mm³)	0.086
Serum phosphorus (mg/dL)	0.086	Trabecular area (mm²)	0.092
Urinary albumin creatinine ratio (µg/mg)	−0.012	Trabecular density (mg/cm³)	0.198*
Total daily moderate and vigorous activity (min/day)	0.110*	Cortical area (mm²)	0.098
Total cholesterol (mg/dL)	−0.035	Cortical density (mg/cm³)	−0.024
High-density lipoprotein (mg/dL)	−0.011	Cortical thickness (mm)	0.065
Low-density lipoprotein (mg/dL)	0.004	Periosteal circumference (mm)	0.119
Triglycerides (mg/dL)	−0.034	Endosteal circumference (mm)	0.064
Very low-density lipoprotein (mg/dL)	−0.034	Effective sunlight exposure (min/day)	0.121
Daily sleep duration (h)	−0.002		

*Significant correlation at *P*<0.05. BMD=bone mineral density, BMC=bone mineral content, TBLH=total body less head, SSI=stress–strain index

and adolescents aged 5–18 years reported that only around 42% were vitamin D sufficient. Of the remaining 58%, 20% were deficient and 38% were insufficient. They also reported

overall mean 25-hydroxy vitamin D concentration of the study population as 45.8 ± 23.9 nmol/L (18.3 ± 9.5 ng/mL).[2] The comprehensive national nutrition survey has reported 18% of

Table 3a: Regression model describing factors affecting vitamin D deficiency

Parameter	*B*	Sig.	Exp (*B*)	95% Confidence interval for Exp (*B*)	
				Lower bound	Upper bound
Age (years)	−0.01	0.71	0.98	0.90	1.07
Gender*	0.8	0.01	2.34	1.33	4.10
BMI (kg/m²)	0.02	0.67	1.02	0.92	1.12
Total moderate–vigorous activity daily	−0.01	0.53	0.99	0.98	1.00
Dietary calcium intake (mg/day)	−0.01	0.47	0.99	0.99	1.00
Dietary phosphorous intake (mg/day)	−0.01	0.21	0.99	0.99	1
Waist circumference (cm)	0.01	0.65	1.01	0.96	1.05
Diastolic blood pressure* (mmHg)	0.03	0.02	1.03	1.00	1.06
Glycaemic control*	−0.04	0.01	0.96	0.57	1.60

*Statistically significant at *P*<0.05

Table 3b: Regression model describing factors affecting vitamin D insufficiency

Parameter	*B*	Sig.	Exp (*B*)	95% Confidence interval for Exp (*B*)	
				Lower bound	Upper bound
Age (years)	0.034	0.396	1.035	0.956	1.121
Gender	−0.103	0.676	0.903	0.558	1.46
BMI (kg/m²)	0.004	0.936	1.004	0.914	1.102
Total moderate–vigorous activity daily	−0.003	0.489	0.997	0.99	1.005
Dietary calcium intake (mg/day)	0	0.497	1	0.998	1.001
Dietary phosphorous intake (mg/day)	−0.001	0.218	0.999	0.999	1
Waist circumference (cm)	−0.014	0.504	0.986	0.946	1.028
Diastolic blood pressure (mmHg)	0.016	0.224	1.016	0.99	1.042
Glycaemic control*	−0.121	0.008	0.886	0.56	1.403

*Statistically significant at *P*<0.05

school-age children aged 5–9 years and 24% of adolescents aged 10–19 years with vitamin D deficiency.[18] A 13-year nationwide Danish study showed no difference in 25-hydroxy vitamin D levels between children newly diagnosed with T1D and their healthy siblings. The study included 1803 participants and eliminated genetic confounding.[19] Another study also demonstrated that youth with T1D had similar 25-hydroxy vitamin D concentrations, after controlling for race/ethnicity. In addition, vitamin D deficiency and insufficiency were equally common in youth with and without diabetes after adjusting for race/ethnicity and socio-economic status.[20]

The prevalence of vitamin D deficiency/insufficiency in children and adolescents with T1D ranges from 19% to 90.6%.[21,22] Unlike our study, various studies have shown that, overall, patients with T1D had lower levels of 25-hydroxy vitamin D than controls. A meta-analysis pooled data from 12 studies and showed that patients with T1D had lower concentrations of 25-hydroxy vitamin D than controls. However, they also reported that the association was not statistically significant in the subgroup aged >14 years.[23] A Korean study reports that mean 25-hydroxy vitamin D concentration was considerably lower, and vitamin D deficiency was more prevalent in children with T1D than in healthy controls. They concluded that polymorphisms in vitamin D metabolism may contribute to susceptibility to T1D in Korean children.[24] A case-control study from India concluded that children with T1D have lower 25-hydroxy vitamin D concentrations compared to healthy children.[25] Some studies have shown prevalence similar to healthy population, while others have shown a higher prevalence in T1D. This discrepancy in results probably stems from variations in the age of study participants, timing of performing study (at diagnosis vs. later after onset of T1D), sample size, method of performing 25-hydroxy vitamin D assay, country of residence and cut-offs used to define vitamin D sufficiency. Irrespective, the prevalence of vitamin D deficiency in T1D is not low.

We report a negative correlation between 25-hydroxy vitamin D levels with body mass index and fat percentage. Studies of obese adults and children demonstrate that body fat mass is inversely correlated with serum 25-hydroxy vitamin D levels. The inverse relationship of BMI and 25-hydroxy vitamin D concentrations is explained by decreased bioavailability of vitamin D due to its sequestration into a larger pool of adipose tissue.[3]

A study from north India has reported vitamin D deficiency to be associated with moderate anaemia among young children and concluded that the effect was independent of iron deficiency.[26] It is hypothesized that by suppressing pro-inflammatory cytokines and directly inhibiting hepcidin expression, vitamin D may be effective in mobilizing iron

stores and enhancing erythropoiesis and haemoglobin synthesis.[27] To the best of our knowledge, ours is the first study to report positive correlation between serum 25-hydroxy vitamin D levels and haemoglobin in children and youth with T1D; however, in a previous study, we have shown that anaemic subjects with T1D had significantly lower 25-hydroxy vitamin D levels than those with normal haemoglobin.[28]

A systematic review of observational studies concluded that the relationship between vitamin D status and BP in children and adolescents varied between the studies and mainly pointed towards the lack of association.[29] However, an Indian study has shown a negative correlation of 25-hydroxy vitamin D levels with diastolic blood pressure ($r = -0.1$).[30] A study has demonstrated an inverse relationship between serum 25-hydroxy vitamin D and diabetes, metabolic syndrome, insulin resistance and beta-cell function but the association between vitamin D deficiency with elevated diastolic blood pressure in subjects with T1D is still not known.[31] A study on vitamin D status in children and adolescents with T1D from Tehran also reported a higher prevalence of vitamin D deficiency in female gender like our study. The hypotheses attributed for the same were difference in sun exposure, concealing clothes for religious reasons and higher vitamin D requirements for bone growth during the faster pubertal growth spurt in girls.[21]

We report glycaemic control as a significant predictor for the development of vitamin D deficiency. There are conflicting results regarding the impact of glycaemic control on vitamin D deficiency in children with T1D. Some studies have reported inverse association between 25-hydroxy vitamin D level and HbA1c, while a few have shown that concentration of 25-Hydroxy vitamin D was not influenced by HbA1c and disease duration.[21,32] Even supplementation studies with vitamin D in children with T1D have shown conflicting results. A study reported that subjects with T1D under vitamin D supplementation exhibited a better metabolic control and a lower insulin requirement than non-supplemented children, suggesting a role of vitamin D treatment in glycaemic control and insulin sensitivity.[33]

The bone phenotype of subjects with T1D is characterized by low BMD, disruption of the microarchitecture, increased fracture risk and low bone turnover status. A review article reports that on pQCT measurement of subjects with T1D, a reduced vBMD affecting the trabecular compartment is found.[34] A study from our centre also reported that trabecular vBMD and total vBMD were lower in children with T1D.[7] Altered parathyroid hormone–vitamin D axis is one of the possible mechanisms to explain this association. It causes low bone turnover and leads to reduced bone mineralization affecting the bone geometry and increases the fracture risk. The efficacy of vitamin D on T1D-related bone damage has been examined only minimally in animal models, and to the best of our knowledge, ours is the first study to report significant positive correlation between 25-hydroxy vitamin D levels and trabecular density in Indian children and youth with T1D.[4]

The limitations of our study are cross-sectional study design causing lack of longitudinal follow-up, data from single-centre causing confounding effect of environmental factors and a small proportion of patients with HbA1c below 7.5% due to which the good and intermediate glycaemic control categories had to be combined. However, large sample size, availability of data on dietary intake, effective sunlight exposure and bone geometry using pQCT are the strengths of our study.

Conclusion

Vitamin D deficiency has high prevalence in children and youth with T1D and has detrimental effect on bone geometry of these subjects. Weight reduction increased outdoor physical activity and good glycaemic control is a modifiable factor that may prove useful in preventing vitamin D deficiency. Longitudinal intervention with vitamin D supplementation may be needed to study its effect on bone health of subjects with T1D.

Authors' contribution

All authors played a role in the conceptualization, execution, analysis and writing of the manuscript and all agree and accept responsibility for the contents of the manuscript submitted to this journal.

Conflicts of interest

There are no conflicts of interest.

Data availability statement

Data will be shared on reasonable request to Dr. Anuradha Khadilkar (anuradhavkhadilkar@gmail.com).

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