Original Article

Prevalence of stunting and determinants of growth failure in children with Type 1 diabetes

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ABSTRACT

Objectives: India is home to highest number of prevalent cases of Type-1 diabetes (T1D) in children. There is scarcity of data on growth failure of children with diabetes, especially those having complications and comorbidities, thus, we conducted this study with the objective to determine the prevalence and predictors of stunting in children with T1D. **Methods:** This cross-sectional study included 350 children and adolescents aged 1–18 years with T1D. Demographic data, anthropometry, diet, sexual maturity rating, and biochemical measurements were performed using standard protocols. Short stature was defined as height for age Z-score <−2. $p<0.05$ was considered statistically significant. **Results:** We report 15.7% prevalence of stunting in our cohort of children with T1D. Stunted children had higher cholesterol, lower hemoglobin, lower midparental height Z-scores, and higher urinary albumin creatinine ratio. Binary logistic regression revealed that pre-existing comorbidities, compromised renal function, longer disease duration, and short mid-parental height were significant predictors of stunting. **Conclusion:** A little under one-sixth of children with T1D had short stature. Monitoring growth in these patients, especially in subjects with short parents, prolonged duration of diabetes, existing comorbidities, and deteriorating renal function are critical.

Keywords: Albumin-creatinine ratio, Children, Insulin-like growth factor 1, Midparental height, Stunting, Type-1 diabetes

Type-1 diabetes mellitus (T1D) is one of the most common chronic pediatric endocrine disorders in which the ß-cells of the pancreas do not produce enough insulin to maintain normal glucose metabolism [1]. The International Diabetes Federation Atlas 10th edition estimates 1,211,900 children and adolescents younger than 20 years to have T1D globally. T1D age-standardized incidences are highest in populations of North European origin and in several countries in the Middle Eastern and North African Region. India and the United States of America have the highest numbers of estimated incident cases of T1D followed by various other populous countries [2]. T1D and its complications, including impaired childhood growth/short stature, thus remain a major concern [3].

A child with short stature or stunting is a child whose height/length is <–2SD (i.e., below the 2.3 percentile) for his/her age and gender. Stunting (low height-for-age) is considered to be a significant indicator of nutritional assessment of children and adolescents and is also an indicator of chronic under nutrition [4].

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Short stature may be a normal variant of growth, such as due to familial short stature and constitutional delay of growth and puberty, however, it may also result due to pathological causes such as poor nutrition, repeated infections, and inadequate psychosocial stimulation [5]. A child with growth failure may suffer from severe irreversible physical and cognitive damage. The detrimental effects of stunting can thus last a lifetime and may even affect the next generation [6].

The central hormone involved in statural growth at each step of development is growth hormone (GH), together with its facilitator, insulin-like growth factor 1 (IGF-1). Change in the/insulin-like(GH/IGF-1) axis in the pediatric population results in compromised growth [7]. A large amount of data has noticeably documented the central role of insulin as one of the main regulators of GH/IGF-1 axis. Insulin controls the expression of GH receptors in the liver and affects IGF-1 and IGF-binding proteins (IGFBPs) synthesis by modulating the GH post-receptor events [8,9]. By impairing this complex regulatory physiology, low portal insulin concentrations documented in children with T1D results in GH hypersecretion, low circulating levels of IGF-1 and IGFBP3, and high circulating levels of IGF-binding protein I (IGFBP-1) [3,10].

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Insulin therapy has been shown to restore GH-binding protein concentrations, though levels remain lesser than those found in normal subjects [3]. In turn, all these variations related to portal insulin deficiency result in an increased risk of developing growth failure [11].

Factors affecting growth in children with T1D include the genetics, environmental factors, age at diagnosis, diabetes duration, pubertal timing, metabolic control, the status of GH, IGFs, and IGFBPs [12]. The main causes for poor height gain are believed to be under-insulinization (poor glycemic control), associated autoimmune disorders (thyroiditis, celiac disease, Addison's disease, pernicious anemia, hyperparathyroidism, hypergonadotropic hypogonadism, alopecia, and vitiligo), compromised renal function, and psychosocial factors [12]. Given the high incidence of T1D in India and scarcity of data on growth failure of children with diabetes, especially those having complications and comorbidities, we conducted this study. The specific objectives of our study were as follows: (1) To determine the prevalence of stunting among children with T1D and (2) to determine factors predicting growth failure in them.

MATERIALS AND METHODS

Study Design and Subjects

This was a single-center, cross-sectional, observational study. Children (1–18 years) with T1D along with their parents who attended the diabetes clinic at a tertiary care hospital in Pune, India, during the study period (October 2020–March 2021) were approached. Since we wanted to assess the effect of complications and comorbidities on growth failure, all patients who attended the clinic during the study period and who agreed to take part in the study were included in the study. The study was approved by the Institutional Ethics Committee of Jehangir Clinical Development Centre Pvt. Ltd. on July 22, 2020. Parents provided written informed consent and children gave assent for the study. Considering a 30% prevalence of stunting in T1D with a precision of 0.05, the sample size of 350 was adequate at a 95% confidence interval [1].

Clinical history and examination: Data on the age of patients, age at diagnosis of diabetes, duration of diabetes, current medications, number of admissions for ketoacidosis, birth weight, history of other illness, family history, type of insulin regimen, and total dose of insulin per day were collected using standardized questionnaires by a pediatrician. Medical history provided by parents was verified from hospital medical records. Tanner staging for sexual maturity was performed by a pediatric endocrinologist. Pubertal staging was classified as pre-pubertal, pubertal, and post-pubertal [13,14]. Physical activity was assessed using validated activity questionnaires adapted for Indian children [15].

Anthropometry: Standing height of patients and parents was measured using a portable stadiometer (Leicester Height Meter, Child Growth Foundation, and UK) to the nearest millimeter and weight was measured using an electronic scale to the nearest 100 g. Body mass index (BMI) was computed by dividing weight in kilograms by height in meter square. Subsequently, the height, weight, and BMI were converted to Z scores using Indian references [16].

Dietary Data

Dietary data were recorded using the 1day dietary recall method on 1 week day and a holiday and a mean were computed. Trained nutritionists interviewed the children along with their primary caregivers to get an accurate estimate of the foods consumed. Nutrient intakes were then computed using the cooked food database software, CDiet [17]. Adequacies of nutrient intakes were estimated by computing the percentage of the recommended dietary allowance (RDA) for Indian children for each nutrient consumed [18].

Biochemical measurements: Glycemic control was evaluated by measuring glycosylated hemoglobin (HbA1c). A fasting blood sample (5 ml) was collected between 7 am and 9 am by a pediatric phlebotomist. HbA1c was measured by high-performance liquid chromatography (BIO-RAD, Germany). Hemoglobin was estimated by spectrophotometry at a wavelength of 555 nm using a Horiba Yumizen H500 hematology analyzer. The fasting blood samples were then assessed for lipid profile (total cholesterol, triglycerides, and HDL-C) using the enzymatic method and low-density lipoprotein-cholesterol concentrations were calculated by the Friedewald formula. The first voided urine sample was collected in a sterile container and urine was assessed for urine microalbumin, creatinine, and urine albumin: creatinine ratio (ACR) which were computed using a ratio of urine albumin to urine creatinine (urinary albumin and creatinine concentrations determined using radioimmunoassay and Jaffe's method, respectively). Samples were not taken during menstrual cycles, fever, after heavy exercise, or marked hyperglycemia. If ACR was in the range between 0 and 30 ug/mg, it was considered normal. Single high value of early morning urinary ACR (above 30 ug/mg) was considered as altered ACR [manuscript in publication]. Serum IGF1 concentrations were analyzed by a solid-phase enzymelinked immunosorbent assay with an intraassay coefficient of variation (CV) of 4.7% and interassay CV of 7.2%. The IGF1 concentrations were then converted into Zscores using available reference data [19].

Statistical Analysis

All statistical analyses were carried out using the SPSS for Windows software program, version 26 (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 for parametric data, Mann–Whitney U-test for non-parametric data, and Chi-square test for categorical variables. For testing relationships between dichotomous-dependent variables and continuous predictors, binary logistic regression analysis was carried out. The dependent variable in the model was stunting while the independent variables were

midparental height Z-scores, tanner stage (classified into two groups as pre-pubertal and in puberty/post-pubertal), diabetes duration, glycemic control (HbA1c), and comorbidities/ complications such as hypothyroidism, altered ACR, and lipids. p<0.05 was considered statistically significant.

RESULTS

Of the 350 children studied, 156 (44.6%) were boys and 194 (55.4 %) were girls. Mean age of the children in the study group was 11.9±3.9 (1.2–18) years and the average duration of diabetes was 5.0±3.4 years. One hundred and ninety-two (54.9%) children had a disease duration of <5 years and the remaining 158 (45.1%) children had disease duration >5 years. The children's mean HbA1c was 10.0±2.1%. The mean total insulin requirement of our cohort was 1.1±0.4 units/kilogram/day and all children were on basal bolus regimen. One hundred and twenty-six (36%) children were pre-pubertal and the remaining 224 (64%) were in puberty or had completed their puberty. Patients' demographics and laboratory findings are illustrated in Table 1.

The prevalence of stunting in our cohort of children with type 1 diabetes was 15.7%, that is, 55 children (height-for-age Z score<–2) were stunted and 295 (84.3%) children were within reference range for height. The prevalence of stunting with respect to disease duration, comorbidities, altered albumin-creatinine ratio, lipid profile, and glycemic control is shown in Fig. 1. The number of children having stunting and disease duration ≤5 years was 18 (5.1%) and those having disease duration >5 years were 37 (10.6%). Children having stunting had higher cholesterol, lower hemoglobin, and lower midparental height Z-scores. Furthermore, urinary ACR which is a marker of compromised renal function was higher in children who were stunted (Table 1).

While performing logistic regression analysis, we considered children with T1D with or without stunting as the dependent variable while diabetes duration, physical activity and dietary intake (energy percentage of as per recommended daily allowance), midparental height Z-scores, tanner stage, comorbidities, urinary ACR, serum cholesterol, HbA1c, and IGF-1 Z-scores as the independent variables. Binary logistic regression revealed that children with comorbidities (such as hypothyroidism, vitiligo, and celiac disease), children having compromised renal function, longer disease duration, children who had achieved puberty, and children with short midparental height were significant predictors of stunting (p<0.05). Variables such as physical activity and dietary intake of energy, cholesterol concentrations, HbA1c, and IGF-1 concentrations were not significant predictors (p>0.05) (Table 2).

DISCUSSION

We report 15.7% prevalence of stunting in our cohort of Indian children and youth with T1D. Stunted patients had higher cholesterol, lower hemoglobin, lower mid-parental height, and higher ACR. Diabetes duration, midparental height, altered renal function, puberty, and presence of comorbidities were significant predictors of stunting.

Stunting is a prevalent cause of concern in rural and sub-urban populations of India [20-24]. According to the Global Nutrition Report 2018, India is home to 46.6 million stunted children under 5 years, a third of the world's total number of stunted children [25]. However, there is little literature describing stunting among Indian children with T1D. A study by

Table 1: Clinical/laboratory findings of patients classified by stature

Parameter	Stunting (n=61)	No stunting (n=345)	p-value
Age (years)	13±3.5	11.6±4	0.020*
Diabetes duration (years)	7.4±4	4.5±3.1	0.000*
Height Z scores (15.7% stunted)	–2.7±0.6	–0.6±0.9	0.000*
Weight Z scores	–1.8±0.8	–0.6±0.9	0.128
BMI Z scores	–0.6±0.9	–0.4±0.9	0.000*
Midpaternal height Z scores	–1.3±0.8	–0.8±0.7	0.000*
Physical activity (min/week)	292.5±224.9	301.5±226.5	0.788
PercentRDA_energy (%)	68.9±27.3	72.8±31.8	0.391
PercentRDA_protein (%)	104.6±54.1	115.9±60.6	0.204
PercentRDA_zinc (%)	66.9±52.3	67.9±47.4	0.884
Insulin (unit/kg/day)	1.2±0.4	1.1±0.3	0.168
Creatinine (mmol/L)	0.1±0.0	0.1±0.0	0.048*
HbA1c (mmol/L)	13.8±0.8	13.4±0.8	0.308
Vitamin D (ng/ml)	19.7±9.1	18.9±9.1	0.576
Hemoglobin (g/dl)	12.9±1.3	13.4±1.5	0.020*
Total cholesterol (mmol/L)	4.3±1.0	3.9±0.9	0.004*
LDL cholesterol (mmol/L)	1.0±1.0	1.0±0.8	0.366
Albumin Creatinine ratio (ug/mg)	242.1±698.1	29.3±76.7	0.000*

***p<0.05, all normal variables are mentioned as mean±standard deviation, all non-normal variables are expressed as median (interquartile range) (BMI: Body mass index, HbA1c: Glycated hemoglobin, LDL: Low-density lipoprotein, NS: Not significant)**

Table 2: Binary logistic regression to determine the predictors of stunting

Parameter	OR	Wald	Sig	95% CI for EXP (B)	
				Lower	Upper
Duration of diabetes	1.452	20.75	0.000*	1.237	1.704
Midparental height Z-scores	3.597	12.307	0.000*	1.76	7.352
Tanner stage	0.154	8.172	0.004*	0.043	0.555
Children having comorbidities (hypothyroidism, vitiligo, and celiac disease)	4.297	3.594	0.05*	0.952	19.404
Albumin: creatinine ratio	5.751	8.216	0.004*	1.739	19.022
Cholesterol	0.652	0.271	0.603	0.13	3.269
Vitamin D	0.731	0.441	0.507	0.29	1.844
HbA1c	1.61	0.886	0.347	0.597	4.344
IGF1_zscores	0.702	2.247	0.134	0.443	1.115
Sports duration (weekly/min)	1	0.01	0.921	0.998	1.002
PercentRDA_energy	0.999	0.024	0.878	0.98	1.018
Constant	0.004	14.2	0		

*p<0.05. HbA1c: Glycated hemoglobin, IGF1: Insulin-like growth factor1, PercentRDA_energy: Percentage Recommended Dietary Allowance

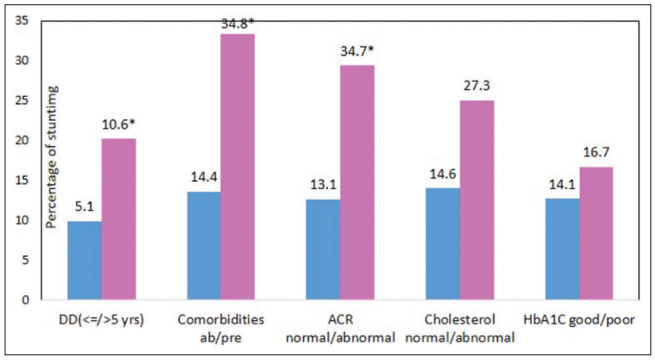

Figure 1: Prevalence of stunting with respect to disease duration, comorbidities, altered albumin-creatinine ratio, lipid profile, and glycemic control

Khadilkar *et al*. reported significantly higher (27.1%) prevalence of stunting among children with diabetes [26]. Despite the study being conducted in same center, the differences in results may be attributed to timing of the study (2011–2012), sample size, and poor availability of resources required for comprehensive diabetes care. Further, over 50% of the children in the earlier study were on mixed spilt regimen unlike patients in the present study who were all on basal bolus regimen. Similar to our results, a study from Baghdad, Iraq, found 15.1% prevalence of stunting among children with T1D [27]. In another study, from Rwanda (Africa), 136 children with T1D were assessed reported the prevalence of stunting to be 30.9%, which was higher as compared to our study [12]. However, as in our study, they also did not find any association between stunting and glycemic control.

We report duration of diabetes, existing comorbidities, and altered ACR as significant predictors of stunting among children with T1D. A study conducted in Sudanese children with diabetes concluded that retardation in physical growth and pubertal development was positively correlated with the duration of diabetes before the onset of puberty and glycated hemoglobin (HbA1c) concentrations [28]. A review article describes that coexistence of T1D with other autoimmune diseases impairs glucose metabolism and deteriorates diabetes control [29]. Although children with diabetes are often tall at the time of diagnosis, they may experience growth retardation, pubertal delay (thus effect on pubertal growth spurt), or both later, either due to poor glycemic control, associated diseases or chronic complications [12]. In our study, we did not find a role of glycemic control in causing stunting in children with T1D. Similar results have been reported in a study conducted in Royal Children's Hospital (RCH), Melbourne, Australia, which concluded no significant association between metabolic control and linear growth of children with T1D [30]. In contrast to our results, a study conducted in Jeddah Kingdom of Saudi Arabia from June to August 2017 showed that there was no association between the duration of diabetes and the height, weight, or BMI Z-scores. Besides, they also report a correlation between HbA1c levels and height Z-scores. This may be explained by exclusion of children with hypothyroidism, celiac disease, and familial short stature [5].

There are very few studies from India that have reported the prevalence of stunting among children with T1D. Our study concluded that longer duration of disease, altered ACR, existing comorbidities, and lower midparental height are important predictors of stunting in subjects with T1D. Lack of data from children of different socioeconomic classes, single-centric data, and lack of longitudinal follow-up are the limitations of our study. Furthermore, in our study, children had poorly controlled diabetes, thus our results may not be applicable to children with good control.

CONCLUSION

Our study suggests that a little under one-sixth of children with T1D had short stature. Monitoring growth in these patients, especially in subjects with short parents, prolonged duration of diabetes, existing comorbidities, and deteriorating renal function are critical.

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AUTHORS' CONTRIBUTIONS

All authors contributed to conceptualization, data collection, data analysis, and writing of manuscript.

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