

Original Article:**Growth and skeletal maturation in children with type 1 diabetes mellitus**

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ABSTRACT

Objective: To study growth and skeletal maturation in children with type 1 diabetes mellitus (T1DM).

Methods: We prospectively studied the anthropometric data of 56 children with T1DM at our tertiary care teaching hospital. Height was re-measured at one year to assess height velocity. A plain radiograph of the left hand was obtained for assessment of skeletal maturation. Glycosylated haemoglobin and thyroid stimulating hormone were measured in all the patients.

Results: Short stature [height standard deviation score (HtSDS) <-2] was seen in 15/56 (27%) patients. A negative correlation was observed between HtSDS at recruitment and duration of T1DM ($r = -0.347$, $p = 0.009$). Ten of the 25 patients followed up over one year had impaired (< 3rd centile) height velocity (HV). A negative correlation was observed between glycosylated haemoglobin ($r = -0.664$, $p < 0.001$) and HV. The proportion of patients with an impaired HV was more in those with an age of onset more than 7.5 yrs (42% Vs 14%, $p = 0.005$). A delayed bone age was observed in 10/37 (27%) patients assessed for skeletal maturation. It correlated negatively with the body mass index standard deviation score ($r = -0.484$, $p = 0.002$).

Conclusion: Poor glycaemic control causes impaired growth in patients with T1DM. Further, T1DM may also be associated with delayed skeletal maturation.

Key words: Juvenile diabetes, Growth, Puberty, Bone age

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INTRODUCTION

Type 1 diabetes mellitus (T1DM) is the most common form of diabetes seen in children.¹ Chronic diseases in childhood can cause impaired growth and delayed puberty.^{2,3} Published data on the effect of T1DM on growth have yielded conflicting results. In children with T1DM, growth could be influenced by metabolic control, pubertal stage, and age of the child at diagnosis.⁴⁻⁸ In contrast, other studies⁹⁻¹¹ have concluded that there is no impairment in final height, irrespective of metabolic control.

Poor access to health care and poor financial resources results in suboptimal management of T1DM. Moreover, most patients in India, including those seen in our hospital do not perform daily home glucose monitoring and are not adequately trained to alter their doses of insulin based on pre-meal glucose values and on calorie counting. Hence, the level of metabolic control achieved is frequently inadequate. There are sparse published data from India on growth in T1DM. Hence there was a need to design a study addressing the aspect of growth in Indian children with T1DM.

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MATERIAL AND METHODS

A longitudinal observational study was conducted in our tertiary care teaching hospital in South India, from March 2011 to August 2012. Patients younger than 20 years, diagnosed with diabetes mellitus as per American Diabetes Association (ADA) criteria¹² and requiring insulin for their management were defined as T1DM. Patients with untreated hypothyroidism and co-existing chronic illness other than T1DM were excluded. The study was cleared by the Institutional Ethics Committee.

Written informed consent was obtained from all participants/parents/guardians. A detailed history was taken and complete physical examination was carried out. Weight was measured (in kg) on a beam balance with minimal clothing to the nearest of 0.1 kg. Height was recorded (in cm) using a stadiometer with head held in Frankfurt plane to the nearest of 0.1 cm. The height standard deviation score (HtSDS) was calculated using web based calculator (<https://web.emmes.com/study/ped/resources/htwtcalc.htm>.) which is based on the Centre for Disease Control growth charts.¹³ Patients with HtSDS less than -2 were defined as having short stature. Height was measured again at 1 year to assess the height velocity (HV) in girls aged 13 years or below and boys aged 15 years or below at the end of the 1 year period of follow-up. The HV was plotted on Tanner's HV chart.¹⁴ Patients with HV standard deviation less than third centile on the above chart were considered to have impaired height velocity. Body-mass index (BMI;kg/m²) was calculated using the formula weight (kg)/[height (metres)]². BMI standard deviation score (BMISDS) was calculated using web based calculator (<http://stokes.chop.edu/web/zscore/>). Patients with BMISDS less than -2 were considered to have malnutrition.

All the patients were tested for HbA_{1c} twice during the study period, i.e, at recruitment and six months later using commercially available high performance liquid chromatography (HPLC) kit (Bio-Rad D-10, California, USA). Thyroid stimulating hormone (TSH) was measured by immunoradiometric assay (IRMA) using IRMAK-9 kits [Board of Radiation and Isotope Technology (BRIT), Mumbai, India] for all the patients at recruitment. Patients were diagnosed to have primary hypothyroidism if the TSH was greater than 5 mU/L or patients were already on replacement with levothyroxine at recruitment.

An X-ray of left hand and wrist (postero-anterior view) was obtained at recruitment for assessment of bone age as per Tanner and Whitehouse score.¹⁵ The difference between the individual patient's chronological age and bone age was calculated. A bone age below the third centile for chronological age was considered as delayed.

Statistical analysis

Data were recorded on a predesigned proforma and managed using Microsoft Excel 2007 (Microsoft Corp, Redmond, USA). Continuous variables were presented as mean \pm standard deviation if normally distributed. Otherwise they were expressed as median (inter-quartile range-IQR). Pearson's coefficient was calculated to assess correlation between two different continuous variables. Statistical analysis for the categorical variables was performed by computing the frequencies (percentages) in each category. The difference in proportions between groups was tested for significance by the Chi-square test. All tests were two-tailed; a p-value less than 0.05 was considered as significant. Statistical software SPSS version 15 (SPSS Inc., Chicago, IL) was used for statistical analysis.

RESULTS

Fifty six patients who were 3-19 years old were enrolled in the study. There were 32 (57%) males; 71% of the patients with T1DM were

older than 10 years of age. Their clinical and laboratory data are summarized in Table 1.

In the present study, 14 (25%) patients (6 males) had primary hypothyroidism, were on replacement therapy with levothyroxine and were euthyroid at recruitment. The mean TSH of the study population was 2.4 ± 1.2 mU/L. Sixteen patients (28.5%; 10 males) had malnutrition at recruitment.

Height and height velocity

Of the 56 patients, 15 (27%) patients had short stature (HtSDS < -2) while 6 of these 15 had extreme short stature (Ht SDS < -3). The median (IQR) Ht SDS of the study population was -1.15 (-2.0 to -0.03). HtSDS was found to correlate negatively with the duration of T1DM ($r = -0.347$, $p = 0.009$). The age of onset, glycosylated haemoglobin at enrolment and the BMI SDS score did not correlate with Ht SDS.

The Ht SDS of patients did not differ between the two genders (Table 2) or between the patients with or without malnutrition [-0.73 (-1.82 to 0.25) Vs -1.29 (-2.15 to -0.09), $p =$

Table 1: Clinical and laboratory data in 56 children

Parameter	Observations
Age (years)*	12.5 ± 4.1
Age of onset (years)†	9.25 (5.87 to 12.58)
Duration of T1DM (years)†	2.1 (0.6 to 5)
HtSDS‡	-1.15 (-2.0 to -0.03)
BMI SDS‡	-1.30 (-2.40 to -0.50)
HV (cm/year)‡	5 (3 to 6)
Mean HbA1c (%)*	11.6 ± 2.3
Bone age (years)§	10.6 ± 3.5
CA-BA (years)§	0.7 (-0.3 to 2.25)

* data are expressed as mean \pm standard deviation

† data are expressed as median (interquartile range)

‡ tested in 25 patients (18 males)

§ tested in 37 patients (21 males)

T1DM = type 1 diabetes mellitus; HtSDS = height standard deviation score; BMI SDS = body mass index standard deviation score; HV = height velocity; CA-BA = Chronological age - bone age; HbA1c = glycosylated haemoglobin. Mean HbA1c = average of the two HbA1c values of each patient obtained during the study period

0.369]. Further, the Ht SDS was similar in patients with and without primary hypothyroidism [-0.97 (-2.72 to -0.39) Vs -1.2 (-2.0 to 0.12), $p = 0.791$].

The proportion of patients with short stature (HtSDS < -2SD) did not differ in subgroups of patients based on gender (male Vs female), age of onset (<5 years Vs >5 years), duration of T1DM (<5 years Vs >5 years), level of glycaemic control (HbA_{1c} <10% Vs >10%), BMISDS (> -2 Vs < -2) or hypothyroidism (not present Vs present).

Five patients (3 males) had attained final height i.e., bone age of 18 years for boys and 16 years for girls with no further growth being observed during the one year of follow up. The median final Ht SDS of these boys and girls was -0.80 [inter quartile range (IQR) -2.36 to -0.29] and -1.04 (IQR -1.58 to -0.5) respectively. Of the total study population, 8 patients (14%, 5 males) had newly detected T1DM with duration of T1DM less than 3 months at the time of recruitment. The median Ht SDS of these patients was -0.62 (IQR -1.89 to -0.32).

Longitudinal assessment of height velocity could be done in 25 patients. Their median (IQR) HV was 5 (3-6) cm. Ten of these 25 patients (7 males) followed-up over one year had impaired height velocity (HV < 3rd centile). Of the various disease variables, a negative correlation was seen between the HbA1c ($r = -0.664$, $p < 0.001$) and HV. The age of onset, duration of T1DM and the BMI SDS did not show correlation with the HV.

No difference was observed between the HV of boys and girls (Table 2). The HV also did not differ in subgroups of patients with BMI SDS greater than -2 and those with BMI SDS less than -2 (5.07 ± 1.95 cms vs. 3.91 ± 0.91 cm, $p = 0.062$) or in patients with and without primary hypothyroidism (4.73 ± 1.93 cm Vs 5.12 ± 1.18 cm, respectively, $p = 0.612$).

Table2: Comparison of clinical and laboratory data between male and female genders

Parameter	Male (n= 32)	Female (n=24)	p-value
Age (years)*	12.34 ± 4.05	12.63 ± 4.23	0.792
Age of onset (years)†	8.13 (5.2 to 12.5)	9.6 (7.33 to 13.01)	0.513
Duration of T1DM (years)†	2 (0 to 5.7)	2.21 (0.81 to 4.46)	0.751
HtSDS†	-1.18(-2.0 to 0.03)	-1.07 (-2.04 to 0.05)	1.0
BMI SDS†	-1.67 (-2.4 to -0.58)	-1.06 (-2.3 to 0.19)	0.217
HV (cm/year)‡	5 (3 to 6)	6 (3 to 6)	0.836
Mean HbA1c (%)*	11.9 ± 2.4	11.3 ± 2.2	0.354
Bone age (years)§	9.8 ± 3.5	11.6 ± 3.3	0.128
CA-BA (years)§	1.2 (0.21 to 2.4)	0.25(-0.65 to 1.93)	0.156

* data are expressed as mean ± standard deviation

† data are expressed as median (interquartile range)

‡ tested in in 25 patients (18 males)

§ tested in 37 patients (21 males)

T1DM = type 1 diabetes mellitus; HtSDS = height standard deviation score; BMI SDS = body mass index standard deviation score; HV = height velocity; CA-BA = difference in chronological age - bone age; HbA1c = glycosyated haemoglobin. Mean HbA1c = average of the two HbA1c values of each patient obtained during the study period

The proportion of patients with impaired height velocity (HV <3rd centile) was more in patients with an age of onset > 7.5 years (42% Vs 14%, p=0.005) and HbA1c more than 12 (83% Vs 26%, p=0.023). The proportion of patients with impaired height velocity, however, did not differ in other subgroups categorized by gender, presence and absence of malnutrition and with or without primary hypothyroidism.

Bone age

Bone age was assessed in 42 patients with T1DM. Five patients with a chronological age of 16 years or more in girls and 18 years or more in boys had attained adult skeletal age and thus were not included in the final analysis. Hence, only 37 patients were analyzed for bone age characteristics. A bone age less than 3rd centile or more than 97th centile for chronological age was considered significant. Delayed bone age delay was seen in 10 (27%) patients (6 males), while significant advancement was seen in 2 (5.4%) patients (both females). In comparison to the chronological age the bone age was delayed by a median (IQR) of 0.7 (-0.3 to 2.35) years. Age of onset, duration of T1DM and glycemic control did not correlate with the bone age

delay. A negative correlation was seen between the extent of bone age delay and the BMI SDS (r= -0.484, p=0.002).

The proportion of patients with delayed bone age did not differ in subgroups of patients categorized by sex (male vs. females), age of onset (<7.5 years Vs >7.5 years), duration of disease (<5 years Vs >5 years), HbA1c (<10 Vs >10), BMI SDS (< -2 Vs > -2), hypothyroidism [present (adequately treated) Vs not present].

DISCUSSION

Childhood is a phase of life characterized by the unique processes of growth. Thus, in the management of T1DM in children, the issue of growth needs to be addressed along with micro vascular and macro vascular complications. The question of whether linear growth is impaired in diabetic children is still debated. Several studies have shown that T1DM can cause impaired growth.^{5,7,8} In contrast, other studies⁹⁻¹¹ have shown no effect of T1DM on growth.

The median (IQR) of Ht SDS of our cohort was -1.15 (-2.0 to -0.03). Thus our patients were on an average shorter than what is expected

for normal children in the population suggesting that diabetes does impair growth. Indeed one fourth of our study population had short stature ($< -2SD$) and among them 40% had severe short stature ($< -3SD$). In the present study, a negative correlation was observed between the duration of T1DM and the Ht SDS. Also, for other chronic complications of diabetes (e.g., retinopathy, neuropathy, nephropathy), the duration of diabetes exposure has a major impact.¹⁶ Even though the HbA_{1c} at recruitment did not correlate with the Ht SDS in the present study, this does not rule out a role for past level of control which could have influenced growth. HbA_{1c} only reflects metabolic control over the preceding 2-3 months, whereas, growth is a continuous process which occurs over a long period of time. The role of poor metabolic control in retardation of growth was affirmed by the HV observed during follow-up showing a negative correlation to the mean individual HbA_{1c} during this period ($r = -0.664$, $p < 0.001$). Similar observations were reported in another study.⁷ A negative linear relationship was seen between HbA_{1c} and the HV ($r = -0.117$, $p = 0.001$). The reason why the present study showed that T1DM could impair growth, while three other studies⁹⁻¹¹ did not report so, could be related to the higher mean HbA_{1c} in our patients ($11.60 \pm 2.31\%$). This reflects the fact that most of our patients belong to the lower socioeconomic level, who were attending a “free diabetes camp” and were availing free insulin supply and none of them could afford to do daily self monitoring of blood glucose. Unfortunately, these circumstances are typically like those found in most diabetes care settings in India and other developing countries. Hence, the results from developed countries showing no effect of T1DM on growth cannot be applied to developing countries like India.

The cause of short stature in T1DM could be multifactorial. At molecular level, the state of insulinopenia deprives an individual of the

direct and indirect somatotrophic effects of insulin mediated by acting through insulin receptors and the cross talk with type I insulin like growth factor (IGF) receptors.^{17,18} The state of insulinopenia produces a state of growth hormone (GH) resistance characterized by elevated GH, decreased hepatic production of insulin like growth factor-1 (IGF-1) and insulin like growth factor binding protein (IGFBP-3).¹⁹ Baxter et al reported that insulin regulates the number of growth hormone (GH) receptors in the rat liver. They proposed that the low IGF levels and growth retardation observed in T1DM may be attributable to a deficiency in this action of insulin.²⁰ Thus, growth being a cumulative phenomenon, increasing duration of T1DM deprives an individual of the direct somatotrophic action of insulin for a longer time, causes GH resistance with low circulating levels of IGF-1, IGFBP-3 and results in patients with short stature as seen in the present study.

In the present study, only five patients had attained final height. The median final Ht SDS of boys was -0.80 (IQR -2.36 to -0.29) whereas that of girls was -1.04 (IQR -1.58 to -0.5). This finding is similar to another study⁵ where 72 patients were studied and the mean final Ht SDS of the boys and girls was -1.63 ± 0.44 and -1.72 ± 0.79 respectively.⁵

In the present study, the proportion of patients with impaired height velocity was more in the subgroup of patients with age of onset over 7.5 years. (42% Vs 14%, $p = 0.005$). Children who are prepubertal or in the early stages of puberty are the most vulnerable to growth suppression.⁷ The impaired HV seen in patients with onset of T1DM during peripubertal years could be possibly due to the low levels of IGF-1 seen in older diabetic children when compared to younger diabetic children or age matched healthy controls.²¹

Among other factors affecting growth in children, the presence of hypothyroidism or of

poor nutrition *per se* must also be considered. In the present study, 25% of the patients had co-existing hypothyroidism. The American Diabetes Association (ADA) has recommended screening for hypothyroidism, both at diagnosis of T1DM and annually thereafter. Hence, all patients were diagnosed on screening and put on adequate replacement therapy. They were euthyroid both at recruitment and on follow-up. No patient presented with classical symptoms of hypothyroidism. As a possible consequence, the Ht SDS score and the proportion of patients with short stature were similar in both treated hypothyroid and non-hypothyroid T1DM patients. Thus, the presence of hypothyroidism was unlikely to confound the observed correlation between poor metabolic control and older age of onset with impaired growth.

The HtSDS showed no correlation with the BMI SDS. Further, mean HtSDS and proportion of patients with short stature were also similar between malnourished and well nourished groups- thus arguing against nutrition playing a role in determining stature in our cohort. Alternatively, this may also be due to lack of power of this study to analyze the role of nutritional status on height due to the small sample size.

Contrary observations from some studies^{22,23} in which newly detected T1DM patients were found to be taller than controls, the present study did not find the same.^{22,23} In a study²³ the mean HtSDS of the newly detected T1DM boys and girls was 0.46 and 0.49 respectively.²³ In the present study, there were 8 cases of newly detected T1DM and the median HtSDS was -0.62 (IQR -1.89 to -0.32). A Study²⁴ of pairs of identical twins, with one twin being affected by T1DM showed that when the affected twin had onset of T1DM less than 19 years of age, that individual was likely to be shorter than his twin sibling.²⁴ On the other hand, when the

onset of T1DM was over the age of 25 years, the affected twin was likely to be taller than his unaffected sibling. This observation may explain why the patients in the present study were on average shorter when compared to their healthy population peers (on the CDC growth chart), as all the patients were less than 20 years of age and had a median (IQR) age of onset of T1DM at 9.25 (5.87 to 12.58) years.

Skeletal maturation assessment showed that 27% (n=10) of our patients had delayed bone age (<3rd centile). Bone age lagged behind chronological age by 0.7 (-0.3 to 2.25) years. This observation was similar to that reported in another study²⁵ where it was observed that T1DM causes delayed skeletal maturation.²⁵ Of the total study population only 2 showed significant advancement of skeletal maturation (>97th centile). This observation is probably not exceptional in that given the normal distribution of bone age, 3% of the general population would in any case be expected to have that degree of advancement of bone age.

The proportion of patients with delayed bone age did not differ in subgroup of patients with or without hypothyroidism. Similarly, the mean chronological age-bone age difference did not differ among patients with or without hypothyroidism. This could be attributed to the detection of hypothyroidism by screening, followed by prompt treatment rendering all the patients euthyroid before they became symptomatic.

Insulin has anabolic action on bone development as shown by *in vivo* and *in vitro* studies.^{26,27} Similarly, the anabolic action of IGF-1 on bone has been observed.²⁸ While anabolic effects of insulin and IGF-1 on bone are evident, there is no information on the molecular mechanisms for delayed skeletal maturation observed in the clinical studies on T1DM. It may be noted that skeletal maturation only reflects the overall maturation of the body

as a whole, rather than being any specific property of the skeleton. X-rays of ossification centres only provide a window to view the otherwise intangible concept of physiological maturation of the whole body. It may be that the catabolic environment fostered by the lack of insulin and GH resistance may have an impact on the tempo of maturation of all systems.

In our cohort, a strong negative correlation was observed between BMISDS and the difference between chronological age and bone age, implying thereby that the lower the BMI, more is the difference between chronological age and bone age and *vice versa*. This reveals the well known negative impact of nutritional status on the skeletal maturation.²⁹ Nutrition of children with uncontrolled T1DM is invariably poor, partly due to the calorie wastage resulting from glycosuria and partly due to the prevalent catabolism. The mean BMI SDS score in the present study was -1.30 (-2.40 to -0.50) and 28.5 % of the patients had malnutrition. Apart from the nutritional aspect, it remains to be seen whether there is any other specific role for insulin deficiency in the delayed skeletal maturation evident in children with T1DM.

The limitations in the present study include, a small sample size, a relatively short duration of follow up, heterogeneity of the study cohort in terms of duration of T1DM i.e., some patients were newly detected while others had variable duration, some had already attained final height while others had already attained complete sexual maturation, limited strength of the analysis with regards to the influence of disease variables on growth and puberty. Patients were not followed up to the attainment of final height. A uniform cohort of new onset T1DM with follow up till final height and complete sexual maturation would have shown the influence of disease variables on growth and development.

Chronic poor glycaemic control causes impaired growth in patients with T1DM. Ht SDS

correlates inversely with the duration of T1DM while growth velocity correlates inversely to the mean glycated haemoglobin. Hence, good metabolic control may be essential for normal growth in patients with T1DM. Children with onset of T1DM during peripubertal period had impaired height velocity. Further, T1DM causes delayed skeletal maturation in about quarter of the patients. This delay was associated with poor nutrition.

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