Brief Communication

Growth disorders in type 1 diabetes: an Indian experience

Anju Virmani

Senior Consultant Diabetologist and Endocrinologist, Department of Pediatrics, Apollo, Max, Pentamed and SL Jain Hospitals, New Delhi, India

ABSTRACT

Though children with type 1 diabetes mellitus (T1DM) are often tall at the time of diagnosis, they may experience growth retardation, pubertal delay or both, which may be due to poor glycemic control, associated diseases or chronic complications. Factors affecting growth include: gender, genetic environment, age at diagnosis, diabetes duration, puberty, metabolic control, and status of growth hormone (GH), insulin-like growth factors (IGFs), and IGF binding proteins (IGFBPs). Insulin regulates expression of hepatic GH receptors, affects IGFs and IGFBPs synthesis by modulating GH postreceptor events, and significantly increases IGF-I bioactivity. Low portal insulin seen in T1DM leads to GH hypersecretion, low circulating IGF-I and IGFBP-3, and high circulating IGFBP-1. Newly diagnosed T1DM patients have decreased GHBP which can be restored with insulin therapy. Growth velocity should be appropriate for the age of the child/adolescent, and the mid-parental height. Height, weight and blood pressure (BP) should be measured and plotted on a growth chart at least 2–3 times a year. Puberty should also be assessed annually. Following precautions are to be taken in T1DM children: checking for pubertal onset and ensuring it is not delayed, testing early when growth falters (hypothyroidism/celiac disease/puberty/other conditions), aiming for best possible metabolic control (multidose regimens, regardless of type of insulin), and encouraging dietary calcium and protein, exposure to sunlight, Vitamin D supplements and exercise.

Key words: Type 1 diabetes mellitus, growth disorders, growth velocity

Introduction

The Indian experience with paediatric diabetes is important to learn from, not only because of the high burden of diabetes (likely prevalence 5 million diabetic children and adolescents; of which 3–4 million face poverty along with diabetes) but also because of problems like death before diagnosis (due to missed diagnosis), poor management because of low awareness and high costs, limited availability of insulin and poor cold chains in rural areas, limited availability of blood glucose strips, yet greater family support, as in many developing countries of Asia and Africa. In developing countries, medical training pays little attention to chronic disorders and long term care, since the focus is mainly on infections and other acute illnesses, vaccinations, reproductive issues, and nutrition. Other major limitations are poor infrastructure and low public expenditure on health, leading to significant out-of-pocket expenses by individuals.[1] Poor care and delayed or no prevention strategies lead to more complications. Due to these inadequacies in the medical care system, the patient and family are trapped in a vicious cycle of increased acute and chronic complications, thus further elevating costs, mortality, absenteeism from work and hence decrease in income, employability, and quality of life, further pushing the family into indebtedness and poverty.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.155405

Why Monitor Growth?

Monitoring growth is useful for monitoring the general health of the child/adolescent, and is a test which is practically free. A clinic just needs to paint the height bar on the wall and acquire a right angled head board to be able to measure heights. What is critical is measuring correctly,

Corresponding Author: Dr. Anju Virmani, Diabetologist and Endocrinologist, Apollo, Max, Pentamed and SL Jain Hospitals, New Delhi, India. E-mail: virmani.anju@gmail.com

and recording correctly, so that the all-important growth velocity (GV) can be tracked, plotted on a growth chart. According to the International Society for Paediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines (2014), monitoring of growth and physical development and the use of growth charts are essential in the continuous care of children and adolescents with type 1 diabetes mellitus (T1DM).

What are the Growth Disorders Possible in Diabetes?

Though children with type 2 (T2DM) and T1DM are often tall at the time of diagnosis, they may experience growth retardation, pubertal delay (thus effect on pubertal growth spurt), or both later, whether due to poor glycemic control, associated diseases or chronic complications. Children with prepubertal onset of T1DM are taller than those with onset at puberty. Factors affecting growth include: gender, genetic endowment, age at diagnosis, diabetes duration, puberty, metabolic control, and status of growth hormone (GH), insulin-like growth factors (IGFs), and IGF binding proteins (IGFBPs). In the author's experience with data from AIIMS Diabetes of the Young clinic (1988–1995), the frequency of growth retardation was 11–14%, similar to the incidence of other chronic complications like proteinuria, hypertension, retinopathy, dyslipidemia and thyroid disorders (8–15%).[2] More recently (2006), 16% of the T1DMs in the ICMR registry data from the author's clinic had growth retardation.

Insulin is a major regulator of the GH/IGF axis. It regulates expression of hepatic GH receptors, affects IGFs and IGFBPs synthesis by modulating GH postreceptor events, and significantly increases IGF-I bioactivity. Low portal insulin seen in T1DM leads to GH hypersecretion, low circulating IGF-I and IGFBP-3, and high circulating IGFBP-1. Newly diagnosed T1DM patients have decreased GHBP, which can be restored with insulin therapy.

Diabetes control has a major impact on adult height, with near-adult height correlating negatively with DM duration and mean glycated hemoglobin.[3] Let us look at two contrasting populations to understand the impact. A cohort of 22,651 German and Austrian T1DM achieved a mean adult height of -0.16 ± 1.0 standard deviation score, that is, normal adult height.[3] On the other hand, a group of 72 Sudanese children were found to have significant reduction in pubertal growth spurt and in final adult height, with average age at menarche 15.1 year, and average age of full sexual maturation in boys 17.2 years.[4] A similar contrast in a single case: A girl from a lower socioeconomic family who had diabetic ketoacidosis at age 18 months, presented at age 8 year with poor height gain. With better glycemic control, height gain improved, then she developed diarrhoea and pain in abdomen, at which time celiac disease (CD) was diagnosed. With support in the form of insulin and glucostrips from Changing Diabetes in Children and Yog Dhyan Foundation, she had normal puberty and her present height is 156 cm compared with mid parental height of 153 cm.

Growth velocity

As discussed above, the main criterion is GV, which should be appropriate for the age, sex, pubertal status, and the mid-parental height (MPH). Height, weight and blood pressure (BP) should be measured and plotted on a growth chart at least 2–3 times a year. Puberty should also be assessed annually. In a well-controlled child, growth should be normal for MPH.

Causes of poor growth

The main causes of poor height and weight gain are under-insulinization (poor glycemic control), autoimmune disorders (thyroiditis, CD, Addison's disease, pernicious anaemia, hypoparathyroidism, hypergonadotropic hypogonadism, alopecia and vitiligo), improper renal function, and psychosocial factors. Poor glycemic control may be due to low SES, inadequate dosage, poor family support, emotional issues, and other factors causing compliance issues.[5] Eventually, these lead to short stature, delayed puberty, poor bone health, and other problems. Excess weight gain results from over-insulinization and a high intake of fats and carbohydrates. Care givers should aim for best possible metabolic control by multi-dose regimens, regardless of type of insulin.

Thyroid disorders

The most frequent autoimmune problems associated with DM are thyroid disorders, more so in girls and with longer DM duration.[6] Hypothyroidism is far more common than hyperthyroidism. ISPAD Clinical Practice Consensus Guidelines 2014 recommend screening of thyroid function by measurement of TSH and anti-thyroid peroxidase antibodies at the diagnosis of diabetes, and then every 1–2 years in asymptomatic individuals without goitre or in the absence of thyroid autoantibodies. However, in resource constrained situations, the high cost of thyroid antibodies should be kept in mind, as also the fact that treatment decisions would be taken on the basis of TSH rather than antibody levels.

Celiac disease

Celiac disease is being increasingly diagnosed. However, clinical manifestations can be extremely variable, including

diarrhoea, abdominal pain, constipation, vomiting, weight loss, short stature, anemia, osteopenia, muscular atrophy, peripheral neuropathy, or completely asymptomatic.[7,8] The ISPAD Clinical Practice Consensus Guidelines 2014 suggest screening for CD by measurement of tissue transglutaminase (tTG) antibodies every 2 years in asymptomatic children. Management of CD is itself very difficult, more so with co-existent diabetes, so the diagnosis should not be made lightly. It is important to confirm the diagnosis with biopsy findings as tTG may be false positive, e.g. due to giardiasis.[9]

Rare co-morbidities of T1DM include Addison's disease (due to autoimmunity or adrenal tuberculosis) and pernicious anaemia. In Addison's disease, symptoms include decreased insulin need, hyperpigmentation, lethargy, weight loss, decreased serum sodium and increased potassium levels. The recommendation that adrenal cortex autoantibodies be monitored every 5 years is impractical in many instances; therefore a high index of suspicion is very important. Diagnosis can be done by low 8 am cortisol level or low cortisol response to ACTH. Treatment includes lifelong steroid replacement. Pernicious anaemia is a rarity in children, and therefore there are no clear recommendations about monitoring for it.

Some of the extreme forms of T1DM include Mauriac syndrome and ketosis-resistant diabetes. Mauriac syndrome is characterized by severe under-insulinization, severe growth failure, pubertal delay, hepatomegaly, and elevated transaminases and serum lipids levels. The ketosis-resistant diabetic patients characteristically have intermediate C-peptide levels, may survive with little/no insulin for short periods, need high doses of insulin for glycaemic control, and experience frequent chronic complications. Fortunately, both these conditions are becoming rare.

Delayed puberty can be caused by all the conditions which slow down growth, and in turn delayed puberty causes short stature. Regular monitoring for progression of secondary sexual characteristics is needed after the age of 10 years. The first sign of puberty in girls is breast budding: This should appear latest by age 13 years, and menarche should not be delayed beyond 3 years of onset of breast buds, or beyond age 16 years. The first sign of puberty in boys is increased testicular volume, and should occur by age 14 years. If a specific cause for delay is diagnosed, it should be treated. If necessary, replacement should be started after the age of 13–15 years, in low doses and built up gradually. In girls, oral estrogen can be started in the dose of 1–2 mcg/day and increased slowly, with later addition of progesterone. In boys 50 or 100 mg testosterone intramuscular monthly can be started.

Bone health

Another aspect of growth, frequently neglected, is bone health. As Charles Dent famously said, "Senile osteoporosis is a pediatric disorder". Vitamin D deficiency (VDD) is extremely common even in sunny countries like India, with near universal prevalence in urban areas, more so in people with dark complexions (as most Asians and Africans are) and little sun exposure.[10] Lower Vitamin D levels are associated with T1DM and microalbuminuria (MAU^+), with VDD independently associated with diabetic nephropathy.[11,12] Unfortunately, the other components for good bone health-calcium, protein, and exercise – are also often lacking for various reasons in patients with T1DM. Poor glycemic control and delayed puberty worsen this situation. Thus low cost high benefit interventions such as universal low dose Vitamin D supplementation, encouragement of adequate dietary intake of calcium and protein (best in low fat dairy products), and encouragement of regular active play and exercise should be emphasized. It is important to keep in mind that Vitamin D testing is expensive and not routinely needed.[13,14]

Summary

Regardless of the type of clinic attended by the young person with diabetes, care givers must ensure provision of certain low (or no) cost measures on a regular basis. These include:

- Measuring height and weight at every encounter
- Plotting these on the same growth curve for the individual child
- Monitoring BP at least annually
- Checking for pubertal onset and ensuring it is not delayed
- Testing early when growth falters (hypothyroidism/CD/puberty/other conditions)
- Aiming for best possible metabolic control (multidose regimens, regardless of type of insulin), and
- Encouraging dietary calcium and protein, exposure to sunlight, Vitamin D supplements and exercise.

References

1. Virmani A, Ushabala P, Rao PV. Diabetes mortality in a tertiary referral hospital in India. Lancet 1990;335:1341.
2. Virmani A, Shah P, Setia S, Singh GR. Why must Indian diabetic children continue to have retarded growth? Acta Paediatr 1995;84:354-5.
3. Bonfig W, Kapellen T, Dost A, Fritsch M, Rohrer T, Wolf J, *et al*. Growth in children and adolescents with type 1 diabetes. J Pediatr 2012;160:900-3.e2.
4. Elamin A, Hussein O, Tuvemo T. Growth, puberty, and final height in children with Type 1 diabetes. J Diabetes Complications 2006;20:252-6.
5. Kota SK, Meher LK, Jammula S, Kota SK, Modi KD. Clinical profile

of coexisting conditions in type 1 diabetes mellitus patients. Diabetes Metab Syndr 2012;6:70-6.
6. Dosi RV, Tandon N. A study on prevalence of thyroid auto-immunity in type 1 diabetes mellitus. J Indian Med Assoc 2010;108:349-50, 5.
7. Bhattacharya M, Kapoor S, Dubey AP. Celiac disease presentation in a tertiary referral centre in India: Current scenario. Indian J Gastroenterol 2013;32:98-102.
8. Bhadada SK, Kochhar R, Bhansali A, Dutta U, Kumar PR, Poornachandra KS, *et al*. Prevalence and clinical profile of celiac disease in type 1 diabetes mellitus in north India. J Gastroenterol Hepatol 2011;26:378-81.
9. Aktay AN, Lee PC, Kumar V, Parton E, Wyatt DT, Werlin SL. The prevalence and clinical characteristics of celiac disease in juvenile diabetes in Wisconsin. J Pediatr Gastroenterol Nutr 2001;33:462-5.
10. Mutlu A, Mutlu GY, Özsu E, Çizmecioglu FM, Hatun S. Vitamin D deficiency in children and adolescents with type 1 diabetes. J Clin Res Pediatr Endocrinol 2011;3:179-83.
11. Verrotti A, Basciani F, Carle F, Morgese G, Chiarelli F. Calcium metabolism in adolescents and young adults with type 1 diabetes mellitus without and with persistent microalbuminuria. J Endocrinol Invest 1999;22:198-202.
12. Moyer-Mileur LJ, Slater H, Jordan KC, Murray MA. IGF-1 and IGF-binding proteins and bone mass, geometry, and strength: Relation to metabolic control in adolescent girls with type 1 diabetes. J Bone Miner Res 2008;23:1884-91.
13. Balasubramanian K, Rajeswari J, Gulab, Govil YC, Agarwal AK, Kumar A, *et al*. Varying role of Vitamin D deficiency in the etiology of rickets in young children vs. adolescents in northern India. J Trop Pediatr 2003;49:201-6.
14. Puri S, Marwaha RK, Agarwal N, Tandon N, Agarwal R, Grewal K, *et al*. Vitamin D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi: Relation to nutrition and lifestyle. Br J Nutr 2008;99:876-82.

Cite this article as: Virmani A. Growth disorders in type 1 diabetes: an Indian experience. Indian J Endocr Metab 2015;19:64-7.

Source of Support: Nil, **Conflict of Interest:** None declared.