

Puberty and type 1 diabetes

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ABSTRACT

Various data on type 1 diabetes mellitus (T1DM) have showed that the incidence of T1DM peaks at puberty. However, diabetes control and complications could be adversely affected by the physiological changes of puberty. In early years of insulin therapy, severe growth retardation with pubertal delay, like in Mauriac syndrome, have been reported. Insulin and leptin are metabolic factors, circulating in the periphery, which participate in the hypothalamic control of metabolism and reproduction. Insulin may be an important regulator of leptin in humans. Increased levels of advanced glycation end products suppress activation of the gonadotropin-releasing hormone (GnRH) pulse generator, resulting in pubertal delay. Glycemic control deteriorates during puberty as the lean body mass doubles mainly over a period of 25 years, which increases insulin requirement. There is also an increase in insulin resistance over the period of puberty. In normal individuals, fasting and postprandial insulin concentrations reach a peak in both sexes in mid to late puberty. Puberty, at all stages, has the worst insulin resistance. It has been observed that an excessive GH secretion in T1DM during puberty has significant effects on ketogenesis. Adolescent T1DM tends to decompensate very rapidly and develop ketoacidosis when the late night insulin dose is omitted. Adolescence is a critical developmental phase that presents unique challenges and opportunities to individuals with diabetes, their families and their healthcare providers.

Key words: Adolescence, puberty, type 1 diabetes mellitus

INTRODUCTION

Various type 1 diabetes mellitus (T1DM) registries have showed that the incidence of T1DM increases with age, in childhood and peaks at puberty. Furthermore, studies have shown that the pubertal growth and sexual maturation are dependent on intricate physiological mechanisms, which work in unison. Chronic diseases like diabetes can disturb physiology, thus affecting linear growth and pubertal development. However, diabetes control and complications could be adversely affected by the physiological changes of puberty.

As per the epidemiological data revealed by the International Diabetes Federation Atlas 2013 (6th edition), there are

approximately 5,00,000 known cases of children with T1DM (0–14 years) worldwide. Approximately, 50–60% cases are diagnosed before the age of 15 years.^[1] In the 19th century, the typical age of onset of menarche for girls was 16 years while currently it is reported to be 12.5 years.

In early years of insulin therapy, severe growth retardation with pubertal delay, like in Mauriac syndrome, have been reported in patients with insulin-dependent diabetes mellitus (IDDM), but these conditions are now rare due to improvements in insulin delivery and glycemic control. Mauriac syndrome is characterized by dwarfism, obesity and hepatomegaly in patients with IDDM. It is associated with poor control of T1DM in adolescents. Main symptoms are obesity, hepatomegaly, Cushingoid facies and elevated transaminases. It is typically associated with growth failure and delayed pubertal maturation.^[2] Due to IDDM, the onset of puberty is less commonly delayed but increased incidence of irregularities in menstrual cycle and secondary amenorrhea in girls have been reported.

Insulin and leptin are metabolic factors, circulating in the periphery, which participate in the hypothalamic control

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of metabolism and reproduction. Insulin receptors act on gonadotropin-releasing hormone (GnRH) neurons. Lack of insulin may cause delayed puberty through disruption of normal GnRH neuronal function. Leptin also activates GnRH neurons, potentiating the effect of insulin and inhibition of hypothalamic neuropeptide Y.^[3] Leptin levels are lower in newly diagnosed T1DM compared with healthy children and adequately insulin-treated young adult (Tanner stage 5) patients after adjustment for gender and body mass index (BMI). Insulin may be an important regulator of leptin in humans. Thus, the long-term adaptations of the reproductive axis to metabolic parameters are dependent on coordinated insulin and leptin signals.^[4]

A German study of pubertal delay in children with T1DM reported significant delay in pubertal onset and age at menarche though ultimately sexual maturity, (i.e. Tanner stage 5) was attained at a normal age. It was also found that pubertal delay increases with glycated hemoglobin (HbA1c), prepubertal duration and BMI; thus glycemic control is considered to be the most readily modifiable factor.^[5]

Increased levels of advanced glycation end products suppress activation of the GnRH pulse generator, resulting in pubertal delay.^[6] An Egyptian study revealed pubertal disorders in T1DM boys with poor glycemic control. Around 25% of the boys were found to be sexually immature. Follicle stimulating hormone, luteinizing hormone and testosterone were lower in the T1DM boys compared with the nondiabetic group. T1DM boys also showed lower growth parameters (weight, height, and BMI) than the controls.^[7] A survey was conducted under the Changing Diabetes in Children (CDiC) program at Kolkata, India involving 47 children with age ≥ 10 years (33 girls and 14 boys). The mean age of boys was 13.1 years and the mean age of girls was 13.2 years. At visit 1, mean HbA1c of both males and females was 10.7%. At last visit (1–2 years after first visit), mean HbA1c of males was found to be 10.0% and that of females was found to be 9.1%. Mean age of menarche was 13.2 years. Mean age of menarche in nondiabetic girls is 12.4–13.6 years. Majority of the girls had reached Tanner stages 4/5. One-third of the boys attained Tanner Stage 4/5.^[8]

Studies have shown that glycemic control often deteriorates during adolescence and HbA1c levels may be higher than at any other time. In the Diabetes Control and Complications Trial, adolescents, both in the intensive and conventional treatment groups, had 1% higher HbA1c compared with the adults, despite similar therapeutic approaches, with higher doses of insulin.

Glycemic control deteriorates during puberty as the lean body mass doubles mainly over a period of 2–5 years, which increases insulin requirement. Second, there is an increase in insulin resistance over the period of puberty. Third, certain behavioral changes and psychosocial issues occurring during adolescence further worsen glycemic control.

In normal individuals, fasting and postprandial insulin concentrations reach a peak in both sexes in mid to late puberty. Hyperinsulinemic clamp techniques show decrease in insulin sensitivity by 30% during mid-puberty when compared with prepubertal and adult subjects. In IDDM, the same pattern of increase in insulin resistance was observed, but much greater than in normal subjects, at all stages of puberty. Puberty, at all stages, has the worst insulin resistance.^[9] There is increased amplitude of pulses than in normal subjects, at all stages of puberty. Growth hormone (GH) affects insulin action at a postreceptor level, and the excessive GH release during puberty in subjects with IDDM might lead to the observed changes in insulin resistance.

Hepatic GH receptor is partially insulin-dependent, and there is decreased portal delivery of insulin in T1DM. Thus, hepatic production of insulin-like growth factor 1 (IGF-1) also decreases. An IGF-1 bioavailability is also reduced due to decreased insulin-like growth factor-binding protein 3 (IGFBP-3) and increased IGFBP-1, which occurs with waning insulin levels. Decreased activity of IGF-1 increases GH secretion (negative feedback), thus causing insulin resistance.^[10]

Insulin requirements are generally greater between 5 AM and 8 AM compared to earlier in the night and if these requirements are not met, a rise in blood sugar values may occur towards early morning, referred to as the “Dawn phenomenon”. The extent of this overnight increase in insulin resistance correlates directly with mean GH concentrations. Dawn phenomenon is maximal in mid-to-late puberty when GH secretion is at its greatest and can be largely obliterated by suppressing GH secretion.

It's been observed that an excessive GH secretion in T1DM during puberty has significant effects on ketogenesis. Rise in β -hydroxybutyrate and acetoacetate levels, between 2 AM and 3 AM, observed in puberty can be obliterated with suppression of GH. Hence, adolescent T1DM tends to decompensate very rapidly and develop ketoacidosis when the late night insulin dose is omitted.

Recent data suggests greater risk for vascular complications in those with diabetes during puberty, compared with young people who develop diabetes after puberty. A Berlin retinopathy study showed that the median time free from retinopathy was 12.1 years in children diagnosed before 10 years of age versus 6.6 years in those diagnosed in the age group 10–18 years.^[11]

In Finland, data linkage between Kidney Disease Register and Finnish Diabetes Register has provided further insights into the role of puberty in diabetic nephropathy outcomes. Patients diagnosed before 5 years of age or postpuberty had greater time to end stage renal disease than those diagnosed in the age group 10–14 years.^[12]

The effect of gender on vascular complications is intriguing, with females at an increased risk of developing retinopathy and nephropathy in childhood and adolescence, while males are at an increased risk when they reach adulthood. Moreover, young adult women with T1DM are at a greater cardiovascular risk as they experience a loss of cardiovascular protection that is otherwise seen in their nondiabetic counterparts, with some evidence that the risk begins in adolescence.^[13-15]

Secular trends in adiposity and change in body composition may add to the risk of complications. Studies have shown that BMI >+2 standard deviation score (SDS) posed a two-fold higher risk of microalbuminuria and the development of retinopathy.^[13]

Girls with diabetes, in particular, are at greater risk for excessive weight gain and adiposity during puberty, which may exacerbate insulin resistance and further impact on complication risk. Adolescent girls with T1DM are more prone to hyperandrogenism or polycystic ovary syndrome phenotype, potentially adding to cardiovascular risk.^[13]

In peripubertal girls with T1DM, lower sex hormone-binding globulin and high free androgen index associated with higher BMI SDS and higher total daily insulin per kg bodyweight supporting the known relationship of SHBG with insulin resistance. Ovarian function is reported to be altered in adolescent girls with T1DM, but relates to disturbance in ovarian androgen production. Estrogen levels are not different between T1DM and their normal counterparts in Tanner stages 2–5.^[13]

The Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT) is currently underway, which will provide important information on the effect of angiotensin converting enzyme inhibitors and/or statins on micro- and macro-vascular outcomes.^[16]

Metformin is being used with emerging evidence of benefit on vascular function and insulin resistance in adolescents with T1DM. Exercise program tailored to increase insulin sensitivity and cardiac function in T1DM may help to counteract the adverse hormonal environment impacting on diabetes complications. The development of other diseases associated with diabetes can occur during adolescence, and these may lead to the erratic and brittle control. Other autoimmune diseases are most likely. Antibodies to thyroid tissue have been reported in 10–50% of people with diabetes under the age of 25 years. Hypothyroidism or thyrotoxicosis are rarer (<5%) as are coexistent asymptomatic Coeliac and Addison's disease. Adolescent behavior typically involves challenging authoritative figures, nonconformity, and efforts at establishing autonomy, rebellious, pleasure-seeking and privacy traits alongwith heightened awareness of self-image and peer pressure. Adolescents with T1DM have been found to suffer from anxiety and depression, two-to three-fold higher compared with their peers without diabetes. They merit independent attention; and also constitute important barriers to adequate blood glucose control.^[13]

Involving adolescents in decision making regarding the insulin regimen that best suits their daily schedules, meal plans, exercise and sleep habits is potentially beneficial. Gradual transition of the responsibility to self-care from the parent (s) to the child is important. The possibilities and hazards of teenage pregnancy should be kept in mind.^[2]

Two cases of teenage pregnancy in females with T1DM were reported by CDiC, Kolkata. One case is of a 17 year old female suffering with T1DM from 8 years; having known primary hypothyroidism for 1-year, on irregular treatment for 3 years, married for 1-year and was diagnosed to be pregnant after 8 weeks of amenorrhea with thyroid stimulating hormone (TSH) level of 65 miu/mL and HbA1c level of 8.8%. She was hospitalized for a short period. The risks of pregnancy were explained to the family, but the family, along with the patient, decided to continue the pregnancy. Subsequent HbA1c levels in pregnancy were reported to be 8.7% and 8.6% respectively, TSH was 3.4. The patient delivered a “healthy” baby of 4.3 kg.

Another case was of a 16-year-old female who was diagnosed with T1DM since 2007 and was on premixed insulin (30/70) 42 units daily. She also has a family history of DM, being present in her father. Her serial HbA1c values were 12% in October 2013 and 12.2% in March 2014. She reported to the hospital on 3rd July 2014 with amenorrhea for 2 months. Her last menstrual period was reported to be in May 2014. Presently she has not returned for follow-up for last 2 months despite repeated phone calls.

SUMMARY

Adolescence is a critical developmental phase that presents unique challenges and opportunities to individuals with diabetes, their families and their healthcare providers. Successful treatment of T1DM is of particular importance during puberty for the achievement of normal growth and sexual maturation and also to reduce the risk of long term vascular complications.

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