Brief Communication

Type 2 diabetes in children: Clinical aspects and risk factors

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ABSTRACT

A strong link between obesity, insulin resistance, and metabolic syndrome has been reported with development of a new paradigm to type 2 diabetes mellitus (T2DM), with some evidence suggesting that beta-cell dysfunction is present before the onset of impaired glucose tolerance. Differentiating type 1 diabetes mellitus (T1DM) from T2DM is actually not very easy and there exists a number of overlapping characteristics. The autoantibody frequencies of seven antigens in T1DM patients may turn out to be actually having T2DM patients (pre-T2DM). T2DM patients generally have increased C-peptide levels (may be normal at time of diagnosis), usually no auto-antibodies, strong family history of diabetes, obese and show signs of insulin resistance (hypertension, acanthosis, PCOS). The American Academy of Paediatrics recommends lifestyle modifications ± metformin when blood glucose is 126–200 mg/dL and hemoglobin A1c (HbA1c) <8.5. Insulin is recommended when blood glucose is >200 mg/dL and HbA1c >8.5, with or without ketosis. Metformin is not recommended if the patient is ketotic, because this increases the risk of lactic acidosis. Metformin is currently the only oral hypoglycemic that has been approved for use in children. Knowing these subtle differences in mechanism, and knowing how to test patients for which mechanism (s) are causing their diabetes mellitus, may help us eventually tailor treatment programs on an individual basis.

Key words: Type 2 diabetes mellitus in children, hemoglobin A1c, metformin, obesity

Introduction

Young diabetics who were lean or normal weight have been historically defined as ketosis-resistant diabetics and classified as J type diabetics. These children were diagnosed with good insulin sensitivity in the 1960s and subsequently classified as type 2 diabetes mellitus (T2DM) in children by Dr. M. M. S. Ahuja. These children were treated with insulin and around 30% were treated with sulfonylureas.

Classical type 1 diabetes mellitus (T1DM) is autoimmune in nature and is caused by islet autoantibodies and is seen in young and lean individuals, while classical cases of T2DM presents with insulin resistance in obese and adult patients. The two types, however, predominantly have some overlapping features.

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In general in T1DM, the normal body physique is lean, with the presence of autoimmunity and low pancreatic beta cell function (low C-peptide). Some IDDM patients, however, also present with normal weight, without autoimmunity and pancreatic beta cell dysfunction (low C-peptide). The two diabetes types may be difficult to diagnose in patients solely based on clinical judgment and would require the help of screening of antibodies and other important parameters. These parameters may present confusing results and the patients' diagnosis may change with time or advancement of technologies and parameter value updations. Generally in T2DM, obesity is an important factor to be considered with increased C-peptide levels (may be normal at the time of diagnosis) and no autoimmune disorders. However, there are reported cases where T2DM patients are lean and have normal C-peptide levels.

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Factors contributing to insulin resistance include obesity/sedentary lifestyle, race/ethnicity, and family history. The Bogalusa Heart Study looked at >6500 kids aged 4–17 years, with and without parental diabetes mellitus (DM) from childhood to adulthood. This study showed that children with parental DM had a higher body mass index (BMI) and increased systolic blood pressure (SBP) from childhood, increased fasting insulin and glucose and insulin resistance index from puberty, increased Triglycerides (TGs) and low density lipoprotein, and decreased high-density lipoprotein (HDL) in adulthood.

Puberty is another important factor leading to the development of T2DM. At puberty, increased GH/IGF-1 levels cause insulin resistance and insulin-mediated glucose disposal has been shown to be decreased by 30% in Tanner Stages 2–4 compared with Stage 1 in some hyperinsulinemic-euglycemic clamp studies. A hyperglycemic clamp study showed that both early and late responses to hyperglycemia were enhanced during puberty (leading to hyperinsulinemia). This differs from the hyperinsulinemia seen in early T2DM, where the early phase release of insulin is impaired, and late phases exhibit a compensatory increased insulin release. The other factors include polycystic ovary syndrome and intrauterine factors including gestational DM, low birth weight, and small head circumference.

A study in Pima Indians showed that intrauterine factors are transferred in the family from parents to their children or grandchildren. Children born to mothers with T2DM were more likely to develop DM than their siblings who were born when the mother was nondiabetic. Low birth weight was found to be associated with the thrifty gene hypothesis which explains the increase in fasting insulin and decrease in beta cell function.

Traditionally the development of T2DM is attributed to insulin resistance which leads to increased secretion of pancreatic insulin causing beta cell failure and thus clinical DM. This thought process may underemphasize the role of beta-cell dysfunction.

However, there is a new paradigm to the development of T2DM according to which there is some evidence that beta-cell dysfunction is present before the onset of impaired glucose tolerance. The increase in insulin secretion in the early stages of T2DM is not a marker for proper functioning of beta cells. Late hyperinsulinemia may, in fact, be a result of inadequate beta cell response to hyperglycemia that in itself is a result of early impaired insulin release.

Childhood obesity has more than doubled in children and quadrupled in adolescents in the past 30 years. A worldwide increase in the prevalence of pediatric obesity has been reported. The burden of the disease in the US, in children aged 6–11 years, increased from 7% in 1980 to nearly 18% in 2012. Similarly, the percentage of obese adolescents, aged 12–19 years, increased from 5% to nearly 21% over the same period. In 2012, more than one-third of children and adolescents were overweight or obese.[1-3]

Pediatric obesity has immediate or long-term health effects. Immediate health effects include high risk for cardiovascular disease (CVD) (high cholesterol or high blood pressure), prediabetes, bone and joint problems, sleep apnea, and social and psychological problems (stigmatization and poor self-esteem). Long-term health effects include heart disease and T2DM, amongst others. Besides, published literature reveals that overweight and obesity are associated with increased risk for many types of cancers.

Prevalence of metabolic syndrome in children and adolescents, with varying degrees of obesity, has been studied in number of published studies. According to these studies patients should have at least three of the following criteria: BMI >97th percentile, TG levels >95th percentile, HDL cholesterol level <5th percentile, SBP or diastolic blood pressure >95th percentile and impaired glucose tolerance test (IGTT).

A strong link between obesity, insulin resistance, and metabolic syndrome has been reported. An increase in the prevalence of metabolic syndrome in children is directly correlated with increased insulin resistance. The maximum prevalence of metabolic syndrome in children was seen in Hispanics followed by Caucasians, African-Americans and Asian Indians.

The percentage of children with IGTT increased directly with the severity of obesity, even after adjusting for sex, race, and Tanner stage. The results of CARDIA study on 4576 young adults showed a weight-independent association between fasting insulin and hypertension (HTN). According to a scientific statement released by American Heart Association in the year 2003 increased left ventricular mass, an independent risk factor for CVD is visible in childhood in obese children.

In the changing diabetes in children program, the autoantibody frequencies of seven antigens in T1DM patients were evaluated. After obtaining the autoantibody titers it was concluded that many patients considered as T1DM patients were actually T2DM patients (pre-T2DM).

Both genetic and environmental components are involved in the majority of T2DM patients. T2DM has a polygenic inheritance and the development of T2DM is attributed to diabetogenic genes. For example, a mutation in insulin receptor gene leads to insulin resistance and thus clinical T2DM. Both insulin sensitivity and insulin secretion are impaired and intra-abdominal obesity is believed to cause insulin resistance.

Differentiating T1DM from T2DM is actually not very easy and there exists a number of overlapping characteristics. Few differentiating factors exist; T1DM patients have an increased incidence of other autoimmune disorders, usually low insulin/C-peptide levels (may be normal during "honeymoon phase") and are usually nonobese. On the other hand, T2DM patients generally have increased C-peptide levels (may be normal at time of diagnosis), usually no auto-antibodies, have a strong family history of diabetes, are usually obese and show signs of insulin resistance (HTN, acanthosis, PCOS).

Acanthosis nigricans has been initially thought to be a result of rubbing of skin folds together. Currently it is thought to be an effect of IGF-1. However, one study has shown that acanthosis was directly associated with increased fasting insulin levels, increased insulin/glucose ratio, increased insulin responses and decreased glucose disposal rates during hyperglycemic clamps. These effects were more in obese patients with acanthosis than those without.[4]

Though the genetic basis of occurrence of T2DM is common to all diabetic patients there are distinguishing characteristics for each diabetic patient. Several studies demonstrate that not all people with T2DM are insulin resistant and certain subgroups of T2DM patients have impaired insulin secretion, but not insulin resistance. However, these are not classified as T1DM as they are not ketosis-prone and won't die without insulin. Besides, compensatory responses to insulin resistance are different in different ethnic groups; viz. African Americans show decreased hepatic extraction of insulin and Hispanics show increased 2nd phase secretion of insulin. In pediatric patients, hyperglycaemic hyperosmolar non-ketosis (HHNK) is a common presentation of T2DM. Also, pediatric HHNK does not seem to be associated with concurrent infections/stresses like commonly seen in adult HHNK. African American children appear to be more likely to present in DKA than other races.[5,6]

Maturity Onset Diabetes of the Young (MODY) is often called as monogenic diabetes. There are three MODY subtypes and insulin secretion dynamics in these subtypes is different. A number of features differentiate MODY from T2DM; out of which the most considered ones are inheritance and age of onset. Contrary to MODY which is monogenic, T2DM is polygenic in inheritance. MODY usually occurs in children and adolescents (usually <25 years) while T2DM occurs in people of 40–60 years of age. MODY is multi-generational with 80–95% penetrance, and the patients are not-obese with dysmetabolic syndrome, while T2DM is rarely multi-generational with 10–40% penetrance, and the patients are usually obese with dysmetabolic syndrome.

Double diabetes is a new terminology also known as "type 1.5" and is characterized by the occurrence of hyperglycemia in overweight/obese children and adolescents with the combination of markers typical of both T1DM and T2DM. It may occur when a child with T2DM has autoantibodies to ß-cells or when a child with T1DM becomes overweight/obese. The term was first introduced by Libman and Becker and coworkers, and also called hybrid diabetes, type 1.5 diabetes or Latent Autoimmune Diabetes in Youth. The disease has overlapping phenotype of both T2DM and T1DM. In adults, these subjects are usually defined as affected by latent autoimmune diabetes of adults.

The American Academy of Pediatrics recommends lifestyle modifications ± metformin when blood glucose is 126–200 mg/dL and hemoglobin A1c (HbA1c) <8.5. Insulin is recommended when blood glucose is >200 mg/dL and HbA1c >8.5, with or without ketosis. Metformin is not recommended if the patient is ketotic, because this increases the risk of lactic acidosis. The American Diabetes Association (ADA) recommends dietary modifications and exercise as initial therapy. If the goals are not achieved, the patient should be then prescribed with metformin as monotherapy. If normal blood sugar levels are still not achieved then insulin therapy should be initiated and insulin should be started immediately if the patient presents with DKA. Metformin is currently the only oral hypoglycemic that has been approved for use in children.

Lifestyle modifications are very efficacious, but metformin decreases the rate of progression to DM. Modifications in lifestyle, like watching less TV and playing less video-games, have been reported to show a significant decrease in BMI, triceps skinfold thickness, waist circumference, and waist-to-hip ratio. Programs to eliminate soft drinks and candy machines from schools and serve healthier lunches should be promoted.[7] Early insulin therapy plays an important role in adults and is thought to possibly reverse some of the glucotoxicity that damages beta cells and other insulin-sensitive tissues. There is some evidence suggesting that T2DM may be

more aggressive in young people, so early insulin therapy should be strongly considered.

The American Pediatric Surgery Association Clinical Task Force on Bariatric Surgery recommend bariatric surgery in patients who fail to lose weight after 6 months of organized attempts, patients with near-mature physiologic status of Tanner Stage 3 or above, patients with BMI ≥ 40 with major life-threatening comorbidities or BMI ≥ 50 with minor but life-altering comorbidities. The patients after surgery should have commitment to medical and psychological evaluation pre/post-surgery, commitment to avoid pregnancy for at least 1 year post-surgery, ability and intent to adhere to post-surgery nutritional guidelines, supportive family environment, ability to provide informed assent (patient) and consent (family). However, bariatric surgery has some potential disadvantages like interference with linear growth, no sufficient data available about future reproductive capability, increased impact of decreased nutrient absorption when patient is still growing, and long term effects on adolescents are not known.

Summary

The more we learn about DM, the more it appears to be a continuum of disorders, evidenced by how hard it is sometimes to differentiate T1DM and T2DM. This is also evidenced by a variety of clinical pictures, and subtle laboratory nuances when mechanisms are studied. Children developing T2DM may help us understand how this continuum works, and may help us explore some of the genetic differences that result in the spectrum of disorders that are classified as diabetes. Knowing these subtle differences in mechanism, and knowing how to test patients for which mechanism (s) are causing their DM, may help us eventually tailor treatment programs on an individual basis.

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