Original Article

An Overview About Pediatric Type 1 Diabetes Mellitus

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Abstract

Background: Diabetes mellitus (DM) represents one of the most common metabolic diseases in the world, with rising prevalence in recent decades. Most cases are generally classified into two major pathophysiological categories: type 1 diabetes mellitus (DM1), which progresses with absolute insulin deficiency and can be identified by genetic and pancreatic islet autoimmunity markers, and type 2 diabetes mellitus (DM2), which is the most prevalent form and involves a combination of resistance to the action of insulin with an insufficient compensatory response of insulin secretion. In the last two decades, in parallel with the increase in childhood obesity, there has also been an increase in the incidence of DM2 in young people in some populations. Other forms of diabetes may affect children and adolescents, such as monogenic diabetes (neonatal diabetes, MODY – maturity onset diabetes of the young, mitochondrial diabetes, and lipoatrophic diabetes), diabetes secondary to other pancreatic diseases, endocrinopathies, infections and cytotoxic drugs, and diabetes related to certain genetic syndromes, which may involve different treatments and prognoses. DM1 is considered an immuno-mediated disease that develops as a result of gradual destruction of insulin-producing pancreatic beta cells that eventually results in their total loss and complete dependence on exogenous insulin. Clinical presentation can occur at any age, but most patients will be diagnosed before the age of 30 years

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INTRODUCTION

Diabetes mellitus (DM) represents one of the most common metabolic diseases in the world, with rising prevalence in recent decades. Most cases are generally classified into two major pathophysiological categories: type 1 diabetes mellitus (DM1), which progresses with absolute insulin deficiency and can be identified by genetic and pancreatic islet autoimmunity markers, and type 2 diabetes mellitus (DM2), which is the most prevalent form and involves a combination of resistance to the action of insulin with an insufficient compensatory response of insulin secretion (1).

The natural history of diabetes involves increased risk for acute and severe complications such as diabetic ketoacidosis and hyperosmolar hyperglycemic state, and also chronic microvascular (retinopathy, nephropathy, peripheral and autonomic neuropathy) and macrovascular (coronary atherosclerotic vascular, cerebral and peripheral vascular disease) complications that negatively affect the quality of life and survival of these patients. Approximately 1 million people die every year as a result of diabetes, two-thirds of which in developing countries (2).

Classification of DM in childhood and adolescence

The current classification is based on existing pathophysiological knowledge, including four clinical classes: DM1, DM2, gestational DM, and specific types of DM due to other causes (3).

DM1 corresponds to 90% of cases in children aged less than 15 years, constituting one of the leading pediatric chronic diseases. Unfortunately, diabetes diagnosed in childhood presents an increased risk for complications at an early and productive phase of life, and may lead to a reduction of 10 to 20 years in the average life expectancy, especially in developing countries. In the last two decades, in parallel with the increase in childhood obesity, there has also been an increase in the incidence of DM2 in young people in some populations. Other forms of diabetes may affect children and adolescents, such as monogenic diabetes (neonatal diabetes, MODY – maturity onset diabetes of the young, mitochondrial diabetes, and lipoatrophic diabetes), diabetes secondary to other pancreatic diseases, endocrinopathies, infections and cytotoxic drugs, and diabetes related to certain genetic syndromes, which may involve different treatments and prognoses (4).

Type 1 diabetes mellitus

DM1 is considered an immuno-mediated disease that develops as a result of gradual destruction of insulin-producing pancreatic beta cells that eventually results in their total loss and complete dependence on exogenous insulin. Clinical presentation can

occur at any age, but most patients will be diagnosed before the age of 30 years. The disease process begins months to years before the onset of clinical signs such as polyuria, polydipsia, weight loss, and diabetic ketoacidosis. However, the etiology and natural history of DM1 are not yet completely known, with genetic and environmental factors believed to participate. The genetic effect probably contributes 70 to 75% in the susceptibility to DM1, with environmental factors possibly initiating or stimulating the process that will lead to the destruction of the beta cells and the onset of the disease (5).

Epidemiology

Type 1diabetes may be diagnosed at nearly any age, though peaks in presentation occur between ages 5 to 7 and around puberty. There appears to be seasonal variation with more cases diagnosed in fall and winter. Unlike most autoimmune disorders, type 1 diabetes is slightly more common in boys and men. In the past several decades, type 1 diabetes incidence and prevalence has increased in most age, sex, and race/ethnic groups with some of the fastest growth in young children (6).

In Egypt, previous study enrolled 1600 patients in the 0-18 years' age group with T1DM over a period of 18 years (1994-2011) in the Nile Delta region in Egypt demonstrated that T1DM incidence in 1996, 2006 and 2011 was 0.7, 2.0 and 3.1/105/year, respectively, while age-adjusted T1DM prevalence in the same years was 1.9, 15.5 and 26.8/105/year, respectively (7)

A study of incidence and prevalence of T1DM in children and adolescents in three Egyptian governorates (Fayoum, North Sinai, and Suez) showed a prevalence rate of 0.7/1000 and an incidence rate of 4.01/100 000 (8).

Risk Factors

Both genetic and environmental factors contribute to the risk of developing type 1 diabetes mellitus (T1DM) (9).

Genetic susceptibility

The lifetime risk of developing T1DM is significantly increased in close relatives of a patient with T1DM (10):

- No family history – 0.4 percent
- Offspring of an affected mother – 1 to 4 percent
- Offspring of an affected father – 3 to 8 percent
- Offspring with both parents affected – reported as high as 30 percent
- Non-twin sibling of affected patient – 3 to 6 percent
- Dizygotic twin – 8 percent
- Monozygotic twin – 30 percent within 10 years of diagnosis of the first twin, and 65 percent concordance by age 60 years

Other risk factors

Risk factors for type 1 diabetes mellitus in children include familial and ethnic risk factors which are most likely the consequences of gene polymorphisms in the major histocompatibility complex (MHC) or other genetic susceptibility regions. Additionally, in genetically susceptible individuals, exposure to one or more environmental agents appears to trigger an immune response that ultimately causes destruction of the insulin-producing pancreatic beta cells. Identification of these factors should lead to a better understanding of the pathogenesis of the disease and aid in developing strategies to prevent T1DM. Reports have linked each of the following factors to an increased risk of T1DM; however, none of these associations have been verified and many have been contradicted by other studies. They include (11):

- Viral infections, particularly enterovirus infections
- Immunizations
- Diet, especially exposure to cow's milk at an early age
- Higher socioeconomic status
- Obesity
- Vitamin D deficiency
- Perinatal factors such as maternal age, history of preeclampsia, and neonatal jaundice. Low birth weight decreases the risk of developing T1DM

Seasonal variation has been suggested in some studies, with a higher reported incidence of T1DM in colder as compared to warmer months, particularly in children. However, another study did not find a seasonal variation in girls and reported a higher incidence in the summer months for boys (12).

Pathophysiology

The pathophysiological model of DM1 was proposed as a gradual deficiency of insulin production resulting from the destruction of pancreatic beta cells due to an autoimmune process mediated by T cells in individuals genetically susceptible to the disease, who were born with a normal number of beta cells but undergo a process of cell destruction, most likely after exposure to precipitating environmental factors. Beta cells are destroyed by an aggressive autoimmune response mediated by factors that include the infiltration of CD4+ and CD8+ T cells, as well as B cells and macrophages, resulting in insulitis. Cellular immunity is accompanied by adaptive immunity and anti-insulin antibodies (IAA) are the first detectable markers of beta cell destruction, followed by the appearance of other types, such as anti-glutamic acid decarboxylase (GADA), transmembrane anti-tyrosine phosphatase (IA-2A), and anti-zinc transporter protein 8 (anti-ZnT8), directed against components of insulin secretory granules, whose presence would suggest the expansion of the destructive process (13).

After the loss of approximately 85 to 95% of the beta cells, the classic symptoms of diabetes mellitus arise and the process of autoimmune aggression ends along with complete elimination of these cells. However, studies suggest that beta cells can persist for a longer period in some individuals with DM1, without ever achieving total destruction, and that other pancreatic

characteristics could have a significant pathogenic role in DM1, such as the size of the pancreas, suggesting that multiple pathogenic mechanisms may lead to loss of pancreatic beta cells in DM1 (14).

Clinical Presentation

Childhood type 1 diabetes mellitus (T1DM) can present in several different ways includes (15):

- Classic new onset of chronic polydipsia, polyuria, and weight loss with hyperglycemia and ketonemia (or ketonuria)
- Diabetic ketoacidosis
- Silent (asymptomatic) incidental discovery

Classic new onset

Hyperglycemia without acidosis is the most common presentation of childhood T1DM in most populations. Patients typically present with the following symptoms:

Polyuria which occurs when the serum glucose concentration rises significantly above 180 mg/dL (10 mmol/L), exceeding the renal threshold for glucose, which leads to increased urinary glucose excretion. Glycosuria causes osmotic diuresis (ie, polyuria) and hypovolemia. Polyuria may present as nocturia, bedwetting, or daytime incontinence in a previously continent child. In children who are not toilet trained, parents may note an increased frequency of wet diapers and/or diapers that are unusually heavy (wet) (16).

Polydipsia due to enhanced thirst because of increased serum osmolality from hyperglycemia and hypovolemia. Despite the hypovolemia, patients may not have the classic signs of dry mucus membranes or decreased skin turgor (16).

Weight loss is a result of hypovolemia and increased catabolism. Insulin deficiency in diabetic children impairs glucose utilization in skeletal muscle and increases fat and muscle breakdown. Initially, appetite is increased, but over time, children are thirstier than hungry, and ketosis leads to nausea and anorexia, contributing to weight loss. Patients with these symptoms usually present in the ambulatory setting appearing slightly ill, with vague complaints, such as weight loss and lethargy, the mean duration of symptoms before presentation is 10 days. The classic symptoms of polyuria and polydipsia are present in more than 90 percent of patients, but these are not always the initial complaints and may become apparent only after obtaining a careful history (eg, nocturia and bedwetting, increased frequency and/or unusually wet diapers, and persistent thirst). Weight loss is a presenting symptom in about half of children (16).

Other presentations include perineal candidiasis, which is a relatively common presenting symptom in young children and in girls. Visual disturbances are common because of alterations in the osmotic milieu of the lens, and to a lesser extent the aqueous and vitreous humors leading to changes in refractive index. Children with longstanding hyperglycemia may present with cataracts (17).

Diabetic ketoacidosis

Diabetic ketoacidosis (hyperglycemia and ketoacidosis) is the second most common form of presentation for T1DM in most populations. Symptoms are similar but usually more severe than those of patients without acidosis. In addition to polyuria, polydipsia, and weight loss, patients with ketoacidosis may present with a fruity-smelling breath and neurologic findings including drowsiness and lethargy. DKA can be misinterpreted as an acute vomiting illness because classic pediatric symptoms of dehydration (decreased urination) are masked by the polyuria that is associated with glycosuria. The reported frequency of diabetic ketoacidosis (DKA) as the initial presentation for childhood T1DM is approximately 30 percent, but varies from 15 to 67 percent. Young children (<six years of age) or those from an adverse socioeconomic background are more likely to have DKA as their initial presentation of T1DM. Among children younger than age three years, more than half had DKA as their initial presentation of T1DM. Children with DKA require hospitalization, rehydration, and insulin replacement therapy (18).

Silent presentation

Some children will be diagnosed with T1DM before the onset of clinical symptoms. This presentation is least common and typically occurs in children who have another close family member with T1DM and are being closely monitored. The diagnosis often is made by either a family member or clinician with a high index of suspicion. Children with an affected close family member also may undergo pancreatic autoantibody screening to assess risk for the disease (19).

Complications

Cataracts, Retinopathy, gastro paresis, renal failure, Hypertension, Premature coronary disease, peripheral vascular disease, Neuropathy and Increased susceptibility to infections have been reported as complications of type 1 diabetes in children and adolescents (20).

Special populations

Infants

A variety of disorders can cause hyperglycemia during infancy. Although autoimmune classic T1DM can occur in the first year of life, neonatal diabetes is uncommonly autoimmune in nature. Neonatal diabetes is a rare disorder caused by one of several genetic defects in pancreatic development or beta cell function (21).

Young children

Younger children are more vulnerable to dehydration compared with older children because they are less able to compensate for pathologic processes by seeking fluids and increasing fluid intake (to replace ongoing urinary losses). In addition, children younger than six years of age are more likely to present with DKA, because health care personnel and families less often suspect diabetes in this age group. This leads to a prolonged duration of illness and more severe metabolic decompensation before diagnosis (6).

Children in this age group also have polydipsia and polyuria, but these symptoms are difficult to detect if the child is in diapers or is nonverbal and unable to communicate thirst. Therefore, it is often difficult to recognize these symptoms of hyperglycemia in young children, especially those younger than two years of age (6).

The history or presence of prolonged or recurrent candidal infection (usually in the diaper area) is an important clue that should raise suspicion about the possibility of diabetes mellitus in young children. Candidal infection was present at diagnosis in a significant proportion of children younger than six years with T1DM, and especially in those younger than two years of age. These patients often have been seen by a clinician for nonspecific complaints before the diagnosis (6).

In this vulnerable age group, a high index of suspicion is required for early diagnosis. When a young child presents for evaluation of dehydration, abdominal pain, or fatigue, the clinician should include diabetes in the differential diagnosis and consider measuring serum glucose and testing for glucosuria (6).

Evaluation

Particular attention is paid to home glucose monitoring to learn the patterns of glucose variability and their relation to life circumstances such as school, exercise, and physical stresses such as illness and menses. Insulin dose adjustment is performed with child and family input, as appropriate. Hemoglobin A1C is typically measured at clinic visits as a measure of average glucose over the prior two to three months. The American Diabetes Association recommends Hemoglobin A1c be less than 7.5%, although large population studies suggest only 20% to 25% of children and adolescents achieve this. Diabetes organizations in other developed countries may suggest lower Hemoglobin A1c targets and are somewhat more successful at achieving these targets. Continuous glucose monitoring (CGM) has become more common in children and adolescents, and measures of "time in range" and glucose variability are likely to be even more valuable than Hemoglobin A1c, although insurance does not universally cover CGM and is not always desired by patients (22).

Screening for thyroid disorders is performed at regular intervals and screening for celiac disease is typically done as well, although the frequency is not established. Regular screening for lipid disorders, microalbuminuria, and retinopathy are recommended based on the duration of diabetes. Assessment of mental health and psychosocial factors are also important. Islet cell antibodies are not usually measured to make the diagnosis of type 1 diabetes. These antibodies are only found in about 5% of children and are not specific markers. One should obtain a baseline lipid profile. In addition, urinary albumin should start at age 12 as these children are susceptible to end-stage renal disease (23).

Treatment / Management

Contact between the child and family and medical team between in-office visits is frequent, at least initially, while treatment is adjusted and the family learns the daily management tasks of caring for a child with diabetes. The patient and family make long-term day to day treatment decisions. Insulin delivery is by multiple daily injections (MDI) or an insulin pump to simulate endogenous insulin physiology. Multiple daily injections include basal insulin once or twice daily, and bolus insulin typically is given at meals three or more times daily and is based on carbohydrate content and current blood glucose (18).

Insulin pumps deliver rapid-acting insulin only and provide a basal rate of insulin that is either programmed or automatically adjusted based on continuous glucose monitor input in some pumps, and mealtime insulin is typically calculated based on mealtime inputs of carbohydrate and current blood glucose. The provider will also screen for associated disorders (e.g., thyroid disease, celiac disease, dyslipidemia), ensure screening for complications of chronic hyperglycemia (e.g., retinopathy, neuropathy, nephropathy), and ongoing healthcare maintenance such as influenza vaccine. Strategies should be established to allow the parent to achieve the best glycemic management. Behavior intervention has been found to help with medication compliance and improve outcomes. The parent should be educated about hypoglycemia, the signs, and its management (24).

A recent study revealed that probiotic supplementation before age 3 in infants with type 1 diabetes led to a reduction in the development of pancreatic islet cell autoimmunity. A dietary consult is an essential component of diabetes management. Current consensus recommends the following (25):

- Carbohydrates should provide 50-55% of the daily energy intake, but simple carbohydrates like sucrose should not make up more than 10% of the total.
- Fats should provide about 30% of the daily energy intake
- Protein should provide 10-15% of the daily energy intake.

Current Guidelines

American Diabetes Association (ADA) Guidelines summary for type 1 diabetes in children and adolescents included the following (26):

- When glycosuria/hyperglycemia is noted, consult with an endocrinologist
- Differentiate between type 1 and type 2 disease
- Children usually require intense insulin regimens, with multiple daily injections
- Assess A1c every 3 months
- The blood glucose should be monitored 5-10 times every day
- Continuous blood glucose monitors should be recommended for children
- Monitor for ketones when the child is ill or has an infection
- Optimize nutrition
- Daily exercise for 60mins is recommended; check blood glucose before and after exercise to detect hypoglycemia and hyperglycemia
- Remain compliant with medication; insulin omission is a leading cause of DKA

- Screen for albuminuria after age 10
- Ensure the child has annual eye exams at age 10 and annually thereafter
- Monitor BP; of high use ACE inhibitors
- Monitor LDL cholesterol and if abnormal, treat with diet; if that fails, use a statin.
- Maintain A1C to less than 7.5%
- Carry sugar snacks in case of hypoglycemia
- Monitor thyroid function if there is growth variability
- Screen for celiac disease
- Educate about harms of smoking

COVID-19 and Pediatric Type 1 Diabetes Mellitus

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) worldwide pandemic has been devastating particularly for older adults and those from vulnerable groups, including racial and ethnic minority populations. Additionally, people with certain underlying medical conditions, including diabetes, are also at increased risk of severe illness from coronavirus disease 2019 (COVID-19). Some children experience significant disease, and pediatric deaths have been reported (27).

Because "diabetes" (generally grouping together type 1 diabetes and type 2 diabetes) and chronically elevated hyperglycemia have been associated with worse outcomes in adults with COVID-19, the pediatric community has voiced great concerns about risk and outcomes for children with diabetes (3).

A foundation of pediatrics is caution about the extrapolation of adult practice to children. Many publications report poor outcomes from COVID-19 and diabetes without emphasizing that data reported are from adults, frequently older adults with additional comorbidities. Moreover, there have been warnings related to COVID-19 and immunosuppression leading to confusion, predominately outside the medical community, about the difference between immunocompromised and autoimmune. In sum, these worries have led to increases in frequency and severity of diabetic ketoacidosis (DKA), due in part to families being reluctant to enter health care settings, especially in areas where COVID-19 cases cluster (18).

Data scarcity regarding many aspects of how COVID-19 is affecting children with both new-onset and established diabetes has magnified these concerns. In this issue of Diabetes Care, Rabbone et al. (28) describe cross-sectional data from Italy, an early pandemic epicenter. This team examined diabetes diagnoses as well as reports of DKA and SARS-CoV-2 infection in children with new-onset and established type 1 diabetes from 20 February to 14 April 2020. They compare data on new presentations and DKA rates to data from the same period in 2019. They report 23% fewer new-onset cases during this time, with more children with new-onset disease presenting in DKA; they speculate that the observed decrease may be due to fear of presentation to health care facilities, implying that observed rates might rebound in a subsequent observation period. They also note that differences in exposure to other seasonal viruses associated with precipitating type 1 diabetes might have affected presentation rates (28)

Two additional reports in this issue also address whether SARS-CoV-2 infection affected new pediatric type 1 diabetes diagnosis rates. Interestingly, one posits an increase and the other documents no change. Unsworth et al., (29), report data from five U.K. regional inpatient units collected from late March to early June 2020. One of the five units reported an increase from two to ten cases, and a second reported an increase from four to ten cases; the other three units reported no change. As in the Rabbone et al. (28) report, many of the newly diagnosed children had severe DKA. The U.K. group states that these data point to an increase in incidence of pediatric type 1 diabetes of up to 80%. However, the report does not provide information on the total denominator of unit or hospital admissions, typical variability in case numbers, whether this increase is statistically significant over time, or how many newly diagnosed children regionally are typically treated at these hospitals versus other area facilities (19).

The authors then theorize that a higher type 1 diabetes incidence could be related to SARS-CoV-2 infection of the pancreas and cite data showing angiotensin-converting enzyme 2 (ACE2) receptor expression in β-cells from a 2010 article by Yang et al. However, this assertion is based on immunofluorescence analysis of a single organ donor with limited methodologic details provided regarding reagent validation or even antibody source. Thus, at present, the presence and the level of ACE2 expression in β-cells remains controversial. Moreover, analysis of pancreata from individuals infected with SARS-CoV-2 is not available to support the notion of direct β-cell infection (19).

Additionally, rapid viral-mediated increases in incidence are not very plausible, as fulminant autoimmune-mediated diabetes does not acutely present after infection. Rather, exposures to viruses that may trigger type 1 diabetes generally predate clinical onsets by months to years. The higher incidence rates observed in two regional inpatient units are more likely due to other factors (30).

In contrast, Tittel et al. (31) examined country-wide electronic medical record data from the Diabetes-Prospective Follow-up registry (DPV). Based on population-level data from 216 of 217 DPV clinics, the rate of new-onset pediatric type 1 diabetes observed across Germany from mid-March to mid-May 2020 did not differ significantly from predicted rates based on data collected over the last decade (31)

Regarding these previous articles, there was no compelling evidence that the pandemic is leading to dramatic short-term adverse changes in incidence of pediatric type 1 diabetes. Changes in viral exposure, including novel exposures to SARS-CoV-2 and fewer exposures to normally prevalent pediatric communicable diseases due to public health mitigation measures, could potentially shift future incidence rates and observed diabetes endotypes (19).

A recent U.S. multicenter study reported outcomes in sixty-four adults and children with type 1 diabetes, and confirmed or suspected COVID-19. However, only six patients presented with new-onset type 1diabetes. Reports from China and Italy describe a number of children presenting with newonset type 1 diabetes or severe DKA during the COVID-19 pandemic, apparently unrelated to infection. This prompted concerns of delayed presentation, but we suggest that a number of these cases may be attributed to prior SARS CoV-2 exposure. In accordance with previous reports, high rate of severe DKA was observed, but delayed presentation did not appear to be a significant factor, with relatively short symptom duration in the majority of children (32).

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