### **REVIEW**

# The emerging landscape of childhood diabetes: unraveling the diagnosis



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- **Practice Points**
- Epidemiology of non-Type 1 diabetes
  - Diagnosing childhood diabetes has become more complex. Rates of Type 2 diabetes (T2D) and medication-induced diabetes are on the rise among children and youth and a better understanding of monogenic diabetes has led to increased recognition of cases.
- Making the diagnosis: pathophysiology & clinical features of non-Type 1 diabetes
  - Clinical features and findings on investigations may overlap across diabetes types (i.e., the presence of obesity or pancreatic autoimmunity).
  - Close attention to the presence or absence of particular clinical risk factors, the natural history of the disease and clinical suspicion should prompt further testing to confirm diabetes type.
- Laboratory investigations
  - Testing for pancreatic autoimmunity, endogenous insulin secretion (i.e., insulin or C-peptide levels), and evidence of insulin resistance (i.e., polycystic ovarian syndrome) and/or obesity-related comorbidities (i.e., persistent dyslipidemia and elevated liver enzymes) can help to distinguish diabetes type.
- Treatment
  - Accurate diagnosis of diabetes type will result in the initiation of the most effective treatment regimen and, in many cases, will optimize patient quality of life. For example, a patient with a confirmed diagnosis of monogenic diabetes can often transition from daily insulin injections to a simpler treatment regimen with an oral hypoglycemic agent.
  - Lifestyle modification in combination with metformin and/or insulin has been the mainstay treatment for pediatric T2D. However, increased recognition of major differences in clinical progression between childhood and adult-onset T2D (i.e., tempo of progression from impaired glucose tolerance to T2D and frequent failure of metformin monotherapy in children and youth with T2D), combined with new results from clinical trials in this age group, indicate further research is needed to identify optimal treatment regimens.



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- Sulfonylureas are often indicated in patients with common forms of monogenic diabetes, as they are most effective in optimizing glycemic control in this patient population.
- Medication-induced diabetes is almost always treated with insulin and/ or lifestyle modification. A better understanding of risk factors for medication-induced diabetes will allow for more effective prevention efforts where the least diabetogenic medications can be initiated in high-risk patients.

**SUMMARY** The diagnosis of diabetes in children has become increasingly complex with the emergence of increased rates of childhood-onset Type 2, monogenic and medication-induced diabetes. Differentiating between different types of childhood diabetes is challenging, requiring a basic understanding of pathophysiology of various diabetes types and their associated clinical risk factors. Overlapping clinical features and conflicting findings on laboratory investigations sometimes complicate the picture. The clinician must pay careful attention to the presence or absence of typical risk factors for Type 2 diabetes, family history of diabetes, laboratory evidence of endogenous insulin production or pancreatic autoimmunity, and the natural progression of the disease, in order to make an accurate diagnosis and choose the most appropriate and effective treatment regimen.

Rising rates of overweight and obesie children and youth have improved understanding of molecular genetics, and the increasing use of diabetogenic medications has changed the diagnostic and treatment approach to the child or adolescent with diabetes. The potential diagnoses extend beyond the most commonly diagnosed Type 1 diabetes (T1D) to what is often referred to as 'non-T1D' (NT1DM), which includes Type 2 diabetes (T2D), monogenic diabetes and medication-induced diabetes (MID). The delineation of these various forms of childhood diabetes is often not straightforward and poses a significant challenge to clinicians.

Overlapping clinical features between T1D and forms of NT1DM contribute to the new complexity of the diagnosis of diabetes in children and youth. Diabetes in childhood 20 years ago was almost exclusively due to T1D, a state of insulinopenia resulting from the autoimmune destruction of pancreatic insulin producing β-cells [1]. Today, T2D accounts for 8-43% of all cases of childhood diabetes [2], monogenic diabetes affects 1-2% of patients with diabetes [3] and MID occurs more frequently with the emergence of new drugs and increasing rates of pediatric organ transplantation and childhood obesity [4].

This review describes the epidemiology, pathophysiology and clinical presentation of the most common forms of NT1DM, T2D, MID and monogenic diabetes, and will provide a diagnostic approach to classifying diabetes type in a child or adolescent with hyperglycemia.

#### **Epidemiology of NT1DM**

Estimates of the prevalence and incidence of childhood T2D probably under, or over, estimate the extent of the true disease burden [5]. The prevalence of T2D reported in the SEARCH for Diabetes in Youth Study in the USA was 0.22 cases per 1000 children <20 years of age with the highest prevalence (0.42 cases per 1000 youth) in the 10-19 years age group [6]. Screening of children and youth belonging to populations at high risk of developing T2D using oral glucose tolerance tests (OGTT) resulted in prevalence rates of T2D ranging from 0.3 to 0.4% [7-9]. Recent national population surveillance studies for new cases of physiciandiagnosed T2D have been conducted in the UK and Canada with minimum incidence rates of 0.53 cases per 100,000 children <17 years of age and 1.55 cases per 100,000 children <18 years of age, respectively [10,11]. The SEARCH study in the USA reported the incidence of T2D to be 8.1 cases per 100,000 and 11.8 cases per 100,000 in children aged 10-14 and 15-19 years, respectively [12].

Monogenic diabetes accounts for approximately 1-2% of all cases of diabetes [3]; however, many cases remain undiagnosed or misdiagnosed due to a lack of population-level studies and poor access to genetic testing [13]. The minimum population prevalence of monogenic diabetes in adults living in the UK is approximately 108 cases per million people [13]. There are few studies specific to children and youth. In population-based incident surveillance studies performed in Canada and the UK, approximately 10% of pediatric cases of NT1DM were classified as monogenic diabetes [10,11].

Rates of MID may be increasing due to rising rates of childhood obesity [4]. In a case-control study involving children receiving glucocorticoids in combination with either tacrolimus or cyclosporine after renal transplantation, 7% were affected by MID and 50% of those children were obese [14]. A Canadian study reported the prevalence of secondary diabetes to be 1.8% in acute lymphoblastic leukemia (ALL), 3.4% in heart transplant, 2.6% in liver transplant and 1.5% in renal transplant pediatrics patients. In addition, 50% of children with ALL in this study had a BMI greater than the 95th percentile [15]. In our Canadian surveillance study for NT1DM, the minimum incidence of MID was 0.4 cases per 100,000 children <18 years of age [11].

#### Making the diagnosis: pathophysiology & clinical features of NT1DM

Differentiating forms of NT1DM from T1D and from each other can be challenging; however the presence or absence of certain clinical risk factors and signs and symptoms, as well as the results of certain laboratory investigations, can be particularly helpful in making the diagnosis (**Box 1 & Figure 1**). These include:

- Typical risk factors for T2D (i.e., obesity, insulin resistance and ethnic background);
- Family history of diabetes with particular attention to the pattern of inheritance;
- Laboratory evidence of endogenous insulin production;
- Laboratory evidence of pancreatic autoimmunity;
- Natural progression of the disease over time (i.e., insulin requirements).

#### Type 2 diabetes

#### Pathophysiology

Childhood T2D results from a combination of insulin resistance and relative insulin deficiency

secondary to  $\beta$ -cell dysfunction [16]. The progression from normoglycemia to impaired fasting glucose, impaired glucose tolerance (IGT) and frank T2D is strongly influenced by  $\beta$ -cell capacity, which depends on  $\beta$ -cell mass and secretory ability [17], and is influenced by genetic and environmental factors [18]. In a 3-year longitudinal study of obese adolescents with normoglycemia, those who progressed to IGT had lower  $\beta$ -cell secretion at baseline compared with antiprogressors [19]. In hyperglycemic clamp studies involving obese adolescents with T2D, there was marked reduction in both first and second phase insulin secretion. Based on these studies, it has been proposed that youth with T2D have lost approximately 80% of their  $\beta$ -cell function at diagnosis [20]. This is further supported by the fact that some youth with T2D exhibit pancreatic autoimmunity [10,11,21]. Preexisting and subsequent progression of β-cell dysfunction are therefore important factors influencing whether or not an obese child or adolescent develops T2D.

Insulin resistance also plays a critical role in the development of T2D and can precede the onset of T2D by many years. Unique to adolescence is a transient state of insulin resistance during puberty that is more pronounced in females, compared with males, and results in a 32% decrease in insulin sensitivity [1,22,23]. Puberty is therefore a time when all forms of diabetes (i.e., T1D and monogenic diabetes) can present, including T2D. Insulin resistance is strongly linked to ectopic fat deposition, including hepatic steatosis, intramyocellular lipid and visceral adiposity [2,24]. Several studies have demonstrated increased ectopic fat in adolescents with IGT and one study demonstrated a close relationship of hepatic steatosis with decreased insulin secretion and increased insulin resistance [3,4,25-27]. It is not clear why some individuals accumulate more visceral and intramyocellular fat, despite similar lifestyle habits and degree of obesity; however, the role of genetics, diet and the number and function of myocellular mitochondria have been implicated [5,28].

#### **Risk factors & clinical features**

Specific risk factors for T2D during childhood and adolescence include [6,29]:

 Being overweight (BMI: 85–95th percentile for age and gender) or obese (BMI: >95th percentile for age and gender);

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#### Box 1. Key features to consider when diagnosing diabetes type in children and youth.

#### History & physical examination

- Family history of diabetes
- Symptomology polyuria, polydipsia and weight loss
- Lifestyle characterized by high fat intake and minimal physical activity
- Belonging to a high-risk population for Type 2 diabetes
- Recent initiation of a known diabetogenic drug
- Age of onset
- Overweight or obese
- Acanthosis nigricans
- Hypertension

#### Laboratory investigations

- Severe metabolic acidosis and ketosis
- Pancreatic autoimmunity (GAD, IA2, ICA and IAA antibodies)
- Other autoimmunity (i.e., elevated TTG and anti-TPO antibodies)
- Elevated insulin levels prior to insulin therapy
- Endogenous insulin secretion >6 months after diagnosis (i.e., measurable C-peptide in blood or urine)
- Persistent dyslipidemia following stabilization of glycemia
- Elevated liver enzymes
- Low renal threshold for glucose (i.e., glucose measurable in urine when blood sugar <12 mmol/l)</p>

#### Natural history

- Decreasing or minimal insulin requirements (<0.3 units/kg/day) >6 months after diagnosis with a near normal A1c (<7%)
- Complete insulin independence >6 months after diagnosis (especially after significant lifestyle modification)
- Excellent glycemic control after treatment with a sulfonylurea
- A family history of T2D in a first or second degree relative;
- Exposure to maternal diabetes while *in utero*;
- Belonging to a populations such as Hispanic, Aboriginal, South Asian or African who are known to be at higher risk for developing T2D;
- Signs and symptoms of insulin resistance (i.e., polycystic ovarian syndrome, acanthosis nigricans [AN], hypertension, dyslipidemia, nonalcoholic fatty liver disease [NAFLD]);
- Age of peripuberty or puberty.

Greater than 90% of children and youth with T2D are obese making it the single most important risk factor for the development of insulin resistance and T2D [7-12,30]. In a longitudinal study of 117 obese children and youth, those who progressed from normal glucose tolerance to IGT had the largest increase in body weight and those with IGT who reverted to normoglycemia had minimal increases in body weight and a decrease in BMI [10,11,31]. However, as the global rate of childhood obesity increases, obesity may be present in other forms of diabetes. Rates of obese and overweight youth with T1D in the SEARCH study were 13 and 22%, respectively, and youth with T1D had a higher prevalence of being overweight, but not obese, compared with nondiabetic youth [12,30]. Some postulate that body mass plays a critical role in the development and rising incidence of both T1D and T2D, a theory coined by Wilkin and termed the 'accelerator hypothesis'. Wilkin proposes two 'accelerators' of β-cell loss: insulin resistance that hastens apoptosis of the  $\beta$ -cell and enhances immunogenicity; and genes that modulate the rate at which β-cell function declines [3,10,11,13,32,33]. Therefore, obesity, although present in almost all cases of childhood and adolescent T2D, must be considered in the context of other risk factors for T2D.

Genetics play an important role in the pathogenesis of T2D. More that 75% of children and youth with T2D are reported to have at least one relative affected by T2D [4,11,34]. Siblings of children and youth with T2D who are overweight have a fourfold higher risk of having abnormal glucose tolerance when compared with overweight children without an affected

sibling [14,35]. Offspring of parents where one is affected by T2D have a 40% lifetime risk of developing T2D, a number that increases to 70% if both parents have T2D [15,36]. Most genome-wide association studies have been conducted in adults with T2D; however, one gene, *TCF7L2*, has recently been implicated in the development of IGT in obese children [11,37]. Therefore, an immediate or extended family history of T2D is an important risk factor for childhood and adolescent T2D.

Complex interactions between genes and the environment, or 'epigenetics', may also contribute to the interindividual variation in diabetes susceptibility [16,38]. Epigenetic factors include DNA methylations, histone modifications and miRNAs, which are heritable changes in gene function that occur without a change in nucleotide sequence and are affected by environmental and behavioral factors such as age, nutrient intake, sedentary lifestyle, obesity and intrauterine environment [17,38]. Given that T2D is a complex, multifactorial disease, epigenetics probably plays an additional role in its pathogenesis. The most striking evidence for this comes from studies examining exposure to hyperglycemia in utero. Offspring of women with either pregestational T1D or T2D, or gestational diabetes during pregnancy had a fivefold increased odds of developing IGT compared with controls [18,39]. In a case-control study involving African-American, Hispanic



Figure 1. Diagnostic algorithm for diabetes.

DKA: Diabetic ketoacidosis; NT1DM: Non-Type 1 diabetes mellitus.

and non-Hispanic white youth, exposure to maternal diabetes *in utero* resulted in a 5.7 increased odds of developing T2D, and 47% of cases of childhood and adolescent T2D could be attributed to exposure to maternal diabetes *in utero* [19,40].

Racial differences related to genetics, and cultural differences influencing diet and physical activity contribute to the development of T2D in children and youth. The highest incidence of T2D are in ethnic minority groups such as indigenous people, and those who are of African-American and Hispanic descent [10-12,20]. However, up to 25% of youth with T2D are of Caucasian ethnicity [10,11,21]. Mechanisms are probably related to differences in  $\beta$ -cell function where obese African-American and Hispanic youth require a greater early insulin response to maintain normoglycemia as compared with similarly obese Caucasian children and youth [41]. Therefore, children and youth of ethnic minorities may develop T2D earlier because of this increased  $\beta$ -cell demand resulting in earlier β-cell failure.

Insulin resistance is also associated with metabolic syndrome, cardiovascular disease, polycystic ovarian syndrome (PCOS), NAFLD, hypertension and dyslipidemia [42]. Similar to adults, 'clustering' of these cardiovascular risk factors has been described in the pediatric population [43]. In a Canadian cohort of children and youth with newly diagnosed T2D, 73% presented with AN, a clinical sign of insulin resistance, and 45 and 28% presented with dyslipidemia and hypertension, respectively, at diagnosis [11]. A total of 12% of females had PCOS at diagnosis. Therefore, the presence of one or more of these features on clinical history, physical exam or laboratory investigations in a child or adolescent with hyperglycemia should prompt consideration of T2D.

T2D in childhood generally presents during pubescence, however, recent studies report that 4–8% of children with T2D present before the age of 10 years [11,12]. Thus, T2D must be considered even in prepubertal children, especially when other risk factors for T2D are present.

#### Monogenic diabetes

#### Pathophysiology

Monogenic diabetes is an autosomal dominant transmitted form of NT1DM first described in the 1970s [44] and, with improved understanding of molecular genetics, is now known to be a group of clinically heterogeneous forms of β-cell dysfunction. To date, ten different gene mutations causing monogenic diabetes have been identified [3]. The most common mutations occur in genes encoding glucokinase (GCK) enzyme and nuclear transcription factors HNF-1A and -4A, which account for approximately 70% of all cases of monogenic diabetes [45]. HNF-1A and -4A are transcription factors that interact within a complex network to regulate gene transcription and are critical to the normal development and functioning of the  $\beta$ -cell. HNF-1A mutations are also associated with a low renal threshold for glucose and HNF-4A mutations are often accompanied by abnormal lipid and lipoprotein profiles [45]. Mutations in genes encoding HNF-1A and -4A result in a progressive defect in insulin secretion with onset of diabetes usually in the second to fifth decade of life; however, this may also occur during childhood and adolescence.

The GCK gene encodes the GCK enzyme that acts as the glucose sensor in the  $\beta$ -cell by catalyzing the phosphorylation of glucose to glucose-6-phosphate, the rate-limiting step in cellular glucose uptake. A mutation in the gene encoding for GCK results in a raised threshold level of glucose that is required for the stimulation of insulin secretion. As a result, patients with a GCK mutation present clinically with asymptomatic, mild, stable, lifelong fasting hyperglycemia that is often identified on routine screening, such as during pregnancy. The  $\beta$ -cells retain the ability to secrete insulin under higher glucose conditions, thus the complications of diabetes do not occur. GCK mutations are highly prevalent in children with incidental hyperglycemia. In 172 Italian families meeting the diagnostic criteria for monogenic diabetes, 63.4% had confirmed GCK mutations versus 6.9% with confirmed HNF-1A mutations [46].

Discussion of other forms of monogenic diabetes is beyond the scope of this review due to rarity and characteristic signs of presentation. Briefly, these include neonatal diabetes (occurrence before 6 months of age) caused by various mutations including the Kir6.2 ATP-sensitive potassium channel or sulfonylurea receptor 1 subunits in the ATP-sensitive potassium channel [47], and diabetes associated with severe insulin resistance related to mutations in the insulin receptor, downstream mediators of insulin action or adipocyte function (characterized by significant AN and very elevated insulin levels ± lipodystrophy) [48].

#### Risk factors & clinical features

Specific risk factors for monogenic diabetes include:

- At least one parent with diabetes;
- Diabetes affecting multiple generations in an autosomal dominant inheritance pattern;
- Not severely overweight or obese and clinical signs or laboratory investigations consistent with insulin resistance;
- Caucasian or not belonging to a population at high-risk of developing T2D.

Offspring of an individual with monogenic diabetes will have a 50% probability of inheriting the same mutation [49] and, therefore, a family history of diabetes following an autosomal dominant inheritance pattern and at least one parent with diabetes are important indicators of monogenic diabetes. A history of at least one affected parent with diabetes is reported in 90% of cases of monogenic diabetes versus 61 and 19% in T2D and T1D, respectively [50]. Furthermore, a family history of onset of diabetes at a young age (typically before 25 years) should prompt further investigation into monogenic diabetes [51].

Although some risk factors for T2D and monogenic diabetes may be similar, differentiating features may provide direction to the diagnosis. Individuals with monogenic diabetes have an overall lower degree of obesity compared with those with T2D [50]. Furthermore, features of insulin resistance are often absent in monogenic diabetes. In a Canadian cohort of children with a clinical diagnosis of monogenic diabetes, only 7% had AN on clinical exam and comorbidities such as hypertension, dyslipidemia and PCOS were absent, and 71% were Caucasian [11]. It is important to note that monogenic diabetes does not necessarily have a lower population prevalence in non-Caucasian ethnic groups, but rather, the prevalence of T2D is much higher in non-Caucasian ethnic groups resulting in monogenic diabetes accounting for a lower proportion of all diabetes in these populations.

## Medication-induced diabetes Pathophysiology

MID develops secondary to therapy with diabetogenic medications such as glucocorticoids, atypical antipsychotics, chemotherapeutic agents (e.g., L-asparaginase) and immunosuppresants (e.g., tacrolimus and cyclosporine). Mechanisms leading to hyperglycemia include direct pancreatic toxicity, interference with insulin secretion and the development of insulin resistance secondary to weight gain [52]. Cyclosporine and L-asparaginase are directly toxic to pancreatic  $\beta$ -cells [53,54] and glucocorticoids, in addition to inducing insulin resistance, may also decrease insulin secretion [55]. Medications used to treat CNS disorders such as atypical antipsychotics and antiseizure medications can also lead to weight gain and insulin resistance with eventual hyperglycemia and diabetes [56,57]. The degree of insulin deficiency can be so severe that the initial presentation of MID is diabetic ketoacidosis (DKA) [14,58] and can therefore be confused with T1D.

#### **Risk factors & clinical features**

Specific risk factors for MID may include:

- Recent initiation of a medication known to be diabetogenic (family history of diabetes);
- Obese or overweight;
- Insulin resistance.

Glucocorticoid administration is the most commonly reported treatment in MID, documented in 95% of newly reported cases either alone (53%) or in combination with other medications such as tacrolimus (21%) and L-asparaginase (16%) [4].

The literature in both adults and children describing risk factors for MID is conflicting. Observational studies in adults indicate that older age, greater BMI and non-Caucasian ethnicity increase the risk of developing posttransplantation MID [59,60]; however, a systematic review did not replicate these findings [61]. In a case-control study of children who received renal transplantation and were treated with glucocorticoids in combination with either cyclosporine or tacrolimus, 50% were obese and a positive family history of T2D was the most important risk factor for the development of MID post-transplantation [14]. Canadian studies have shown similar results where 50% of children with ALL and MID were obese [15] and among incident cases of MID, 53% were obese and 52% had a positive family history of T2D [4]. Despite the reported rates of obesity in this population, compared with children and youth with T2D, overall rates of obesity and a family history of T2D are lower among children with MID. In addition, these children

are more likely to be of Caucasian ethnicity and less likely to have AN and obesity-related comorbidities such as dyslipidemia, hypertension or PCOS [4]. Clinicians should, however, consider risk factors such as BMI and family history when initiating medical treatment for children requiring immunosuppression in order to minimize the potential for added morbidity from hyperglycemia.

#### Laboratory investigations

Laboratory investigations can be helpful in differentiating diabetes type in children and youth. In those who present acutely with typical symptoms of polyuria, polydipsia and weight loss, the first step is to establish the presence or absence of DKA. In the symptomatic hyperglycemic child with DKA, the most likely diagnosis is T1D, particularly if the child is <10 years of age, nonobese and does not have a family history of T2D. A diagnosis of T1D is further suggested when there is the presence of one or more pancreatic autoantibody (glutamic acid decarboxylase, IA2, insulin or islet cell antibodies), or very low endogenous insulin secretion (i.e., serum C-peptide levels) more than 1 year after diagnosis, after the 'honeymoon' period. Lastly, presence of other autoimmunity, such as TTG antibodies (celiac disease) or anti-TPO antibodies (hypothyroidism), may be more consistent with a diagnosis of T1D.

The clinical presentation of T2D can vary from being asymptomatic to having moderate symptoms of polyuria, polydipsia, blurry vision and monilial vaginitis in females, to being critically ill with DKA or hyperglycemic hyperosmolar nonketosis (HHNK) [62]. In an asymptomatic obese or overweight child or youth being screened for T2D, laboratory investigations typically reveal hyperglycemia and elevated insulin and C-peptide levels both with fasting and after a glucose challenge (OGTT). In an acutely symptomatic patient with T2D, insulin and C-peptide levels may not be significantly elevated due to acute β-cell toxicity and may not be useful in directing one to a diagnosis. Measurements taken after stabilization of the acute hyperglycemia provide more useful information. Additionally, many children and youth with T2D also have evidence of obesity-related comorbidities such as dyslipidemia, elevated alanine transferase above 90 IU/l indicating NAFLD, or clinical and laboratory evidence of PCOS in females. In the Canadian surveillance study for T2D, 37% of children and youth with a new diagnosis of T2D had at least one comorbidity and 13% had three or more comorbidities at diagnosis [11]. Therefore, evidence of obesity-related comorbidities on laboratory investigations should prompt consideration of T2D.

Up to 20% of children with T2D have been described to have evidence of pancreatic autoimmunity [12] and these children, when compared with similar children with T2D and negative pancreatic autoimmunity, have more severe insulin deficiency and  $\beta$ -cell failure, and less insulin resistance [21]. It has been postulated that these children might have autoimmune T1D against a background of obesity. Observation of the natural history of the disease where a rapid response to insulin treatment and periods of complete insulin independence in the presence of typical risk factors for T2D make a diagnosis of T2D more likely [63]. Furthermore, 10% of cases of T2D may present with DKA and, therefore, can be misdiagnosed as T1D. If the child or youth initially presented with DKA or HHNK and has minimal insulin requirements (i.e., <0.3 units/kg/days) and a near normal A1c (<7%) 1 year after diabetes onset, a diagnosis of NT1DM should be considered, especially if the child is overweight or obese and has a positive family history of T2D.

Laboratory tests can also be helpful in differentiating T1D from monogenic diabetes. Pancreatic autoantibodies and measures of endogenous insulin production aid in discrimination between T1D and monogenic diabetes [64]. McDonald *et al.* reported that <1% of subjects with a confirmed genetic diagnosis of monogenic diabetes had pancreatic autoantibodies [65]. However, a pediatric survey showed that 17% of patients with a confirmed genetic diagnosis of monogenic diabetes tested positive for pancreatic antibodies [66]. Therefore, the presence of pancreatic autoantibodies should not preclude a diagnosis of monogenic diabetes if there is a high index of suspicion.

Other laboratory investigations may aid in the identification of children and youth with diabetes who would benefit from molecular genetic testing. Patients with *GCK* monogenic diabetes have a lifelong, mild fasting hyperglycemia (5.5–8.0 mmol/l), a small glucose increment on OGTT and A1c levels that are almost always <8% [67,68]. Recent studies have shown that high-sensitivity C-reactive protein levels are lower in *HNF-1A* monogenic diabetes compared with T1D, T2D and other forms of monogenic diabetes [69,70]. *HNF-1A* monogenic diabetes is also associated with a low renal threshold for glucose [71]. Besser *et al.* showed that urinary C-peptide creatinine ratio value of  $\geq$ 0.2 nmol/mmol is highly specific (96%) and sensitive (97%) in differentiating *HNF-1A* and -4A from T1D in patients who are more than 5 years from diagnosis of their diabetes [64].

Molecular genetic testing is the gold standard for diagnosing monogenic diabetes, but is expensive and not often readily available. Guidelines for molecular genetic testing for monogenic diabetes suggest only testing patients who present with diabetes before the age of 25 years, have a strong family history of diabetes and have evidence of insulin independence [51]. It has been shown, however, that strict adherence to these guidelines results in >50% of patients with monogenic diabetes actually being tested [13]. Shields and colleagues have recently developed a validated clinical prediction model that helps to determine an individual's probability of having monogenic diabetes and provides an approach to determining whether molecular genetic testing should be pursued [50,101]. The authors suggest, in patients not receiving insulin within 6 months of diagnosis, molecular genetic testing be initiated if the post-test probability of having monogenic diabetes is >25%. In individuals treated with insulin within 6 months of diagnosis, the implications of a positive genetic test are highly significant (i.e., insulin therapy discontinued and therapy with an oral sulfonylurea initiated) and, therefore, molecular genetic testing should be initiated if the post-test probability is >10% [50]. Urinary C-peptide creatinine ratio and pancreatic antibody testing are also suggested in order to further inform decision-making.

#### Treatment

#### Type 2 diabetes

The long-term goals are to achieve glycemic control by improving insulin sensitivity and slowing  $\beta$ -cell failure; and to prevent the development of diabetes-related complications such as nephropathy, retinopathy, neuropathy and cardiovascular disease. To achieve this, a multifaceted management approach is necessary and should include:

 Family-based behavioral lifestyle therapy to prevent continued weight gain, induce weight loss when appropriate and promote healthier lifestyle behaviors;  Pharmacotherapy, when necessary, to optimize glycemic control and treat existing comorbidity such as hypertension, dyslipidemia, nephropathy and NAFLD.

Some important points to consider related to the treatment of children and youth with T2D are:

- Current management guidelines are not evidence-based owing to a paucity of published treatment studies for T2D in this age group. As such, most recommendations are extrapolated from adult guidelines, clinical experience and treatment guidelines for pediatric T1D [62];
- Similar to T1D, children and youth with T2D should be managed within the context of a multidisciplinary pediatric diabetes healthcare team, including an endocrinologist, diabetes nurse educator, nutritionist and mental health professional (social worker or psychologist). The involvement of an expert in physical activity and behavior modification is also helpful [5];
- Management of pediatric T2D should be ageappropriate, culturally sensitive and familycentered where lifestyle and health behaviors of the entire family are addressed [24];
- More than 50% of adolescents with T2D are lost to follow-up at diabetes care programs [72];
- Initial management of pediatric T2D varies considerably among pediatric endocrinologists [11,73].

#### Acute management

Children and youth with T2D who are critically ill with DKA or HHNK require immediate medical stabilization, preferably in a tertiary care pediatric center. HHNK is associated with significant morbidity and mortality with a case fatality rate of 37% and the most common cause of mortality is multiorgan failure [74]. Management HHNK is beyond the scope of this review; however, the reader is referred to recently published recommended guidelines for treatment of pediatric HHNK [75].

Children and youth with T2D can present with dehydration, ketosis (without DKA or HHNK) and severe hyperglycemia. Insulin therapy should be initiated immediately in these children so as to normalize blood sugars and other metabolic derangements and alleviate the  $\beta$ -cell toxicity that occurs with severe hyperglycemia. Once the metabolic derangements have resolved, consideration can be given to initiating an oral hypoglycemic agent such as metformin [62].

#### Long-term management

Lifestyle modification, including behavior change related to healthier nutrition and increased physical activity, is the cornerstone of T2D management. Although further studies are required to evaluate the long-term safety and efficacy of dietary regimens in children and youth with T2D, dietary interventions have been successful in improving A1c levels and allowing for the weaning of antidiabetic agents such as insulin and metformin [76-78]. Regular exercise is associated with significant improvement in insulin sensitivity, even when it is not associated with changes in lean body mass or abdominal fat mass [79]. Therefore, both dietary and exercise modification are currently recommended for the treatment of pediatric T2D and, ideally, should be done in consultation with a nutritionist and exercise specialist [80]. The overall goal is to stabilize weight gain with continued normal linear growth; however, weight loss is often desirable especially in the postpubertal child [80].

Unfortunately, only 10% of children and youth with T2D achieve adequate glycemic control with lifestyle modification alone and therefore require medical therapy [72]. Pharmacotherapy in pediatric T2D is currently approved for metformin, although insulin is required for some, and other agents have been used clinically in some cases. Insulin therapy should be initiated at diagnosis in patients with symptomatic hyperglycemia, ketosis or DKA, and/or a very elevated A1c [62]. For patients with an A1c <8.5%, treatment options include aggressive lifestyle modification therapy alone or in combination with metformin or short-term insulin therapy. In a 16-week randomized placebo-controlled trial in youth with newly diagnosed T2D, those treated with metformin had significantly lower A1c values compared with those treated with placebo (7.5 vs 8.6%) and there were no reported safety issues or adverse effects of metformin therapy. Furthermore, there was moderate weight loss with a reduction of 1.5 kg and a BMI decrease of -0.05 [81]. Short-term use (<16 weeks) of premixed 70/30 insulin given twice per day in a group of youth with poorly controlled T2D was associated with a significant improvement in A1c, an effect that persisted 1 year after insulin was discontinued without the use of additional medication and no significant change in BMI or occurrence of hypoglycemia [63].

Metformin therapy should be initiated at a low dose of 500 mg twice daily and titrated to a maximum dose of 2000 mg per day. Adverse effects include gastrointestinal discomfort and diarrhea occurring in up to 50% of patients [82] and can be minimized by administering the medication with meals. Insulin regimens should be tailored to the individual based on degree of glycemia, patient preference and likelihood of compliance [62]. The use of long-acting insulin analogs (i.e., detemir or glargine) once daily (dose 0.30-0.40 units/kg/day) have been suggested as a starting point, however, if this does not optimize glycemic control, other insulin regimens (i.e., premixed, multiple daily injections and continuous subcutaneous insulin infusion) should be considered [62]. Adverse effects of insulin therapy include weight gain and hypoglycemia [82]. Weaning of antidiabetic medications as glycemia normalizes, A1c stabilizes and lifestyle habits improve can be considered on an individual basis, but regular monitoring is required, as the need for reinstitution of therapy over a relatively short-term period is high [83].

The Treatment Options for T2D in Adolescents and Youth (TODAY) study group have recently reported the results of a randomized, controlled trial comparing metformin alone, metformin plus rosiglitazone and metformin plus an intensive lifestyle intervention program [84]. The primary outcome of the study was loss of glycemic control (or treatment failure) defined as an A1c level of  $\geq 8\%$  for 6 months and/ or sustained metabolic decompensation requiring insulin therapy. In the overall multiethnic cohort (n = 699), 46% experienced loss of glycemic control over an average of 3.86 years of follow-up and a median time to treatment failure of 11.5 months. In the separate study groups, rates of treatment failure were 51.7, 38.6 and 46.6% in the metformin alone, metformin plus rosiglitazone and metformin plus lifestyle interventions, respectively. Another key finding was that non-Hispanic black youth exhibited the highest treatment failure rate to metformin therapy, indicating this may be a poor first-line treatment agent in this population. Overall, the results of this study highlight a major difference between adult and pediatric patients with T2D in that, for the majority of children and youth with T2D, currently accepted treatment

strategies (in particular metformin and lifestyle change) are not particularly effective and these youth will require multiple oral agents or insulin therapy within a few years of diagnosis [85]. Further studies are required to identify optimal treatment approaches for this age group that may need to be tailored to individual ethnic groups based on differences in underlying physiology, environmental and cultural influences.

#### Monogenic diabetes

The treatment of monogenic diabetes varies depending on the specific gene affected. Patients with a confirmed GCK mutation will have lifelong fasting hyperglycemia that does not deteriorate over time and does not lead to the development of diabetes-related complications [86]. As such, medical therapy is almost always unnecessary [87] and approximately 85% of patients can be treated with diet alone [45]. Monitoring during pregnancy for those affected is recommended; however, to evaluate the growth of the fetus exposed to higher in utero glycemia [88]. Diabetes due to HNF-1A and -4A mutations can initially be treated with dietary modification; however, most patients will eventually require pharmacological treatment. Furthermore, this group of patients is at risk for developing diabetes-related complications. Patients with HNF-1A and -4A mutations are extremely sensitive to sulfonylureas and therefore this particular class of oral hypoglycemic agents should be considered first-line therapy. In these patients, low-dose sulfonylureas decrease blood sugar fourfold more than metformin [89] and glycemic control is often better than what can be achieved with insulin therapy [90]. Therefore, correct classification of monogenic diabetes can have a significant impact on the quality of life because patients can safely transfer to treatment with a low-dose oral hypoglycemic agent and wean off insulin completely [91]. It is recommended that molecular classification be confirmed prior to withdrawal of insulin. In children and youth with monogenic diabetes and obesity or overweight, strategies for lifestyle modification outlined in Box 2 are also very important to ensure optimal glycemic control and prevention of diabetes- and obesity-related complications.

#### Medication-induced diabetes

Ideally, the treatment of MID should involve discontinuation of the diabetogenic medication implicated in order to alleviate the  $\beta$ -cell toxicity and prevent medication-induced weight gain and

the development of insulin resistance. In children and youth with complex disease, such as those requiring immunosuppression after organ transplantation, exposure to diabetogenic medications is often inevitable. Where possible, risk factors for developing MID should be assessed early and choice of pharmacotherapy should be tailored so that risk for MID and its related morbidity is minimized. Dietary modification and physical activity (as outlined in Box 2) should be instituted based on what is realistic and feasible for the child or youth in the context of his/her underlying illness. In the event of severe hyperglycemia or mild-to-moderate hyperglycemia that does not respond to lifestyle modification, insulin therapy should be initiated in order to maximize nutrition and minimize morbidity, such as ketosis and infection. Metformin therapy is not a viable treatment option in this complex patient population because of its contraindication for use in the presence of liver, cardiac and renal insufficiency.

#### **Conclusion & future perspective**

Accurately diagnosing diabetes type in children and youth has become increasingly complex with the emergence of pediatric T2D, improved understanding of monogenic forms of diabetes and the increasing use of drugs that are known to be diabetogenic. Furthermore, a backdrop of rising rates of the overweight and obese in the general population of children and youth confounds the overall clinical picture. A systematic clinical approach to the child or youth with hyperglycemia is necessary with close attention to the presence or absence of typical risk factors for T2D (i.e., obesity and insulin resistance), family history and in particular, the inheritance pattern of diabetes, evidence of preserved endogenous insulin production (i.e., C-peptide levels, minimal insulin requirements and/or insulin independence) and, most importantly, the natural progression of the disease. The clinical picture may have many overlapping features between the various types of diabetes and, therefore, laboratory investigations and approach to treatment should also be guided by clinical suspicion.

Pediatric T2D is a relatively new phenomenon and studies to date show that the disease in childhood and adolescence differs considerably from our experience in adults. As such, more clinical studies are needed to better understand disease pathophysiology and how it relates to treatment effectiveness, particularly in different ethnic groups who have already been shown to have



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Box 2. Strategies for lifestyle modification in pediatric Type 2 diabetes, monogenic diabetes and medication-induced diabetes.

**Dietary modification** 

- Reduction or elimination of sugar-containing beverages and high-fat, high-caloric foods by limiting their availability in the home
- Healthier food choices with at least five servings of vegetables and fruits per day
- Regular meals (including breakfast) and meal times
- Portion control
- Self-monitoring to raise awareness and monitor progress

#### Physical activity

- At least 60 mins of moderate-to-intense physical activity per day
- Decreasing sedentary activities such as time spent in front of televisions, computers and video games ('screen time') to <2 h per day
- Instituting efforts to increase daily habitual physical activity, such as using the stairs, walking or biking, and participating in household chores
- Maintain activity logs to raise awareness and monitor progress Data taken from [60,76]

varying responses to treatment. New drugs are emerging such as those targeting the action of the incretin hormone glucagon-like peptide-1, which enhances glucose-dependent secretion of insulin in addition to slowing gastric emptying and increasing satiety [92]. Rigorous studies in children and youth of these promising treatment modalities are necessary, as it is clear from previous research that response to therapy differs in this age group from older adults with T2D. Research related to monogenic diabetes is ongoing and major strides have been made in the last decade on understanding the genetic basis of the disease and subsequently translating and applying this knowledge directly to the treatment of the patient. As our understanding of monogenic diabetes improves, so will our ability to diagnose the disease accurately and provide the most effective treatment to optimize patient quality

of life. Finally, there are many more questions to be answered related to MID and as such, large, multicenter prospective studies of this patient population are necessary to understand risk factors associated with MID and how this information can be used to minimize the morbidity associated with MID and maximize the efficacy of treatment.

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