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ABOUT COVER

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REVIEW

Diagnosis, treatment and prevention of type 2 diabetes mellitus in children and adolescents

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Abstract

During the last two decades, there have been several reports of an increasing incidence of type 2 diabetes mellitus (T2DM) in children and adolescents, especially among those belonging to minority ethnic groups. This trend, which parallels the increases in prevalence and degree of pediatric obesity, has caused great concern, even though T2DM remains a relatively rare disease in children. Youth T2DM differs not only from type 1 diabetes in children, from which it is sometimes difficult to differentiate, but also from T2DM in adults, since it appears to be an aggressive disease with rapidly progressive β-cell decline, high treatment failure rate, and accelerated development of complications. Despite the recent research, many aspects of youth T2DM still remain unknown, regarding both its pathophysiology and risk factor contribution, and its optimal management and prevention. Current management approaches include lifestyle changes, such as improved diet and increased physical activity, together with pharmacological interventions, including metformin, insulin, and the recently approved glucagon-like peptide-1 analog liraglutide. What is more important for everyone to realize though, from patients, families and physicians to schools, health services and policy-makers alike, is that T2DM is a largely preventable disease that will be addressed effectively only if its major contributor (*i.e.*, pediatric obesity) is confronted and prevented at every possible stage of life, from conception until adulthood. Therefore, relevant comprehensive, coordinated, and innovative strategies are urgently needed.

Key Words: Type 2 diabetes; Children; Adolescents; Diagnosis; Treatment; Prevention

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Core Tip: Type 2 diabetes mellitus (T2DM) incidence has increased among children and adolescents during the last two decades, especially for minority groups. Youth T2DM is an aggressive disease, associated with high treatment failure rate and early complications. It can be differentiated from type 1 diabetes in obese youth presenting with hyperglycemia, by using both clinical and laboratory clues. T2DM management is based upon the combined application of lifestyle interventions and pharmacological treatments. Nevertheless, prevention seems to be the only way to effectively deal with this disease and this requires preventing pediatric obesity starting as early as before birth and extending throughout childhood.

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INTRODUCTION

Up to 30 years ago, type 2 diabetes mellitus (T2DM) rarely occurred in the pediatric population and was accordingly referred to as "adult-onset diabetes". Gradually, and especially since the turn of the century, several countries started to report an increasing incidence of T2DM in youth, following an increase in both prevalence and degree of pediatric obesity[1-3]. Currently, T2DM is a complex and costly condition in adults, since almost half a billion people worldwide live with the disease, accounting for 90% of diabetes cases. T2DM in these patients can cause renal insufficiency, blindness, lower limb amputation, cardiovascular disease and other complications, causing substantially higher morbidity and mortality than found in the general population.

T2DM in children and adolescents is even more worrying and complex, since it has been proven to be a particularly aggressive form of disease associated with high therapeutic failure rates and leading to much earlier complications than the "adult-onset" form of the disease[4]. Management of these patients in a timely and efficient manner is essential to prevent or at least delay complications and to improve long-term outcomes. Taking into consideration that worldwide prevalence of pediatric overweight and obesity rates have plateaued at high levels in many countries and continue to rise in others[5] and that there is a time lag between obesity onset and T2DM appearance, a further increase in pediatric T2DM is expected in the coming decades. Consequently, not only management but also prevention of obesity and T2DM in children and adolescents should be a top priority for health services and society alike. Otherwise, the next generation might be the first with children of shorter life expectancy than their parents[6].

The present review focuses on the latest available data on diagnosis, treatment and prevention of T2DM in youth and suggests potential areas for future research.

EPIDEMIOLOGY

A rise in pediatric T2DM prevalence is observed worldwide in parallel with the increasing prevalence of obesity in children[7]. In the United States, for instance, T2DM diagnoses accounted for only 3% of all the diabetes diagnoses in children and adolescents in the early 1990's[8]. In the mid-2000's, this percentage rose to 20%[9] and then increased even further, to almost 30%, in the early 2010's, while at the same time type 1 diabetes mellitus (T1DM) incidence also increased[10]. This percentage is even higher (> 50%) for specific ethnic minorities[10]. Similar trends were also observed in other countries[11-13]. Particularly concerning is the increasing incidences reported in China and India, given the fact that these two countries represent one-third of the world's population[14,15].

Despite this increase, T2DM in children and adolescents remains a rare disease. According to data from the SEARCH for Diabetes in Youth Study, its incidence rate in

the United States was 12.5 cases *per* 100000 in 2011-2012[10]. In the United Kingdom and other European countries, its incidence has been much lower, at < 1 case *per* 100000[16], leading some researchers to question the claims of an "epidemic" of T2DM among youth[17]. In addition, a mismatch between the sharp increase in the incidence of childhood obesity and the less severe increase of T2DM could dispute the causal link between the two conditions. This discrepancy can possibly be explained by the long latency period between the onset of obesity and T2DM appearance, combined with the sharp increase of T2DM in early adulthood[18]. In any case, it is generally accepted that pediatric T2DM is emerging as a serious clinical and public health issue[19].

PATHOPHYSIOLOGY AND RISK FACTORS

T2DM is a heterogeneous metabolic disorder characterized by hyperglycemia, insulin resistance, and relatively impaired insulin secretion. Studies in adults have shown that T2DM is caused by complex interactions between social, behavioral and environmental risk factors that affect genetically-susceptible individuals.

Regarding the role of genes in T2DM development, many pieces of the puzzle are still missing but multiple genes seem to play a role (polygenic disease), leading to a strong genetic predisposition. Indeed, a significantly increased risk of T2DM has been demonstrated in close relatives of an affected individual. Monozygotic twin studies showed that if one twin is affected, the other has a 90% chance of developing diabetes[20]. Further, epidemiological studies have shown that more than one-half of youth with T2DM have at least one affected parent[21]. Similarly, the offspring of a parent with T2DM has an almost 3.5-fold increased risk of developing diabetes compared to the risk of an individual without T2DM parental history, and this risk is 6-fold higher if both parents are affected[22].

The role of genetic predisposition in the pathogenesis of T2DM is also illustrated by the differences in the prevalence of the disease in various racial groups. In the United States, for instance, T2DM is much more common in Native, African and Asian Americans as well as in Pacific Islanders and Hispanic children than in the rest of the pediatric population[10]. Similarly, worldwide incidence and prevalence of pediatric T2DM vary substantially among different countries[23]. Sex is another genetically defined "risk-factor" for T2DM, with adolescent girls being 1.3 to 1.7 times more likely than boys to develop the disease for reasons that are not clear[24]. Further, puberty appears to play a central role in T2DM development, due to the physiologically increased insulin resistance of adolescence. It is, thus, no wonder that 40% of T2DM cases are diagnosed in youth between 10 and 14 years of age and the remaining 60% between 15 and 19 years of age[8].

Nevertheless, the rising prevalence of pediatric T2DM observed in recent years cannot be attributed to genetic changes but rather to various environmental factors linked to its pathogenesis[25]. As analyzed in detail in the "Prevention" section below, evidence from several studies suggests that maternal obesity and gestational diabetes mellitus (GDM) increase the risk of obesity and T2DM in the offspring[26]. These, together with other risk factors that abound in the obesogenic environment of modern societies, increase the risk of obesity and visceral fat accumulation in children. It has been demonstrated that increased visceral fat leads to selective insulin resistance through several mechanisms[27]. Initially, euglycemia is preserved through increased insulin production by the pancreatic β-cells. Gradually, in genetically-susceptible individuals with sedentary lifestyle and worsening obesity, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) appear as prediabetic conditions. The resultant hyperglycemia and increased free fatty acid production are toxic for β-cell function (gluco- and lipotoxicity) and progressively, parallel to the worsening insulin resistance, impaired insulin secretion is established[28]. This sequence of events culminates in overt T2DM, with the patient having lost most of his/her pancreatic β-cell function by the time of diagnosis[29]. For reasons largely unknown, the time of progression from insulin resistance to full-blown T2DM is much shorter in adolescents compared to adults, as suggested, for example, by the results of the Treatment Options for T2DM in Adolescents and Youth (TODAY) study[30].

PREDIABETES

Several attempts have been made to identify criteria that will detect patients with prediabetes, *i.e.*, patients that are one step before developing T2DM. The following

criteria have been mostly validated in adult populations but are being used in children and adolescents as well: (1) IFG: Fasting plasma glucose (FPG): ≥ 5.6-6.9 mmol/L; (2) IGT: Plasma glucose: ≥ 7.8-11.0 mmol/L 2 h after a glucose load of 1.75 g/kg (maximum dose: 75 g) in an oral glucose tolerance test (OGTT)[31]; and (3) Hemoglobin A1c (A1C) values between 39 and 47 mmol/mol.

Almost 1 in 5 adolescents in the United States have been found to fulfill one or more of the above criteria, and this percentage was higher in obese subjects of male sex and of minority groups[32]. However, there was little overlap among the subgroups that were diagnosed using abnormal A1C, FPG, or glucose tolerance, thereby throwing the reliability of these criteria for estimating the prevalence of prediabetes in youth into question.

The picture of prediabetes in adolescence is further complicated by the fact that puberty is normally associated with a marked increase in insulin resistance that subsides once adolescence is over. Indeed, in a multi-ethnic prospective cohort of 526 obese youths with IGT, only 8% progressed to T2DM within 3 years, while 65% reverted to normal glucose tolerance[33]. Other factors that might influence progression from a prediabetic state to T2DM are ethnic background and weight changes. For example, in the above study, non-Hispanic black adolescents had a much higher risk of progressing to T2DM compared with white adolescents[33]. Similar studies from Europe have shown an even higher percentage of adolescents converting back to normal glucose tolerance at the end of puberty[34]. Further, expert opinion varies regarding prediabetes management in youth, but lifestyle interventions similar to the ones recommended for patients with established T2DM seem to prevent or delay the development of T2DM[35].

Despite the above limitations, prediabetes conception and especially IFG and IGT are widely used in pediatric populations not only to clarify the natural history of progression to overt T2DM but also as a screening tool for T2DM primary prevention, as described in the "Prevention" section below[35].

CLINICAL PRESENTATION OF T2DM

T2DM in children and adolescents can present clinically in several ways. About one-third of the patients will be identified while not having any of the typical diabetes signs or symptoms. These patients are usually obese individuals in their mid-adolescence who were screened because of one or more positive risk factors or because of glycosuria detected on a random urine test. In addition, they usually have one or more of the typical metabolic syndrome (MetS) characteristics, such as hypertension and dyslipidemia[36].

About one-half of adolescents with T2DM will present with the typical symptoms of hyperglycemia, such as polyuria, polydipsia, and nocturia, just like patients with T1DM. Recent weight loss might also be present but is usually less severe than that observed in T1DM patients[37]. In addition, frequent fungal skin infections, or severe vulvovaginitis due to Candida in adolescent girls can be the presenting complaint[38].

Less than 1 in 10 adolescents diagnosed with T2DM present with diabetic ketoacidosis, namely hyperglycemia, ketonuria, and acidosis[39]. These patients are usually of ethnic minority groups, report polyuria, polydipsia, fatigue, and lethargy, and require admission, rehydration, and insulin replacement therapy. Patients with symptoms such as vomiting can deteriorate rapidly and need urgent evaluation and management. We should keep in mind that a percentage of obese adolescents presenting with diabetic ketoacidosis and diagnosed with T2DM at presentation have T1DM rather than T2DM and will need lifelong insulin treatment[40].

Hyperosmolar hyperglycemic state (also known as hyperosmolar hyperglycemic nonketotic syndrome) is fortunately the rarest presenting clinical picture of children with T2DM. It is characterized by severe hyperglycemia (plasma glucose > 33 mmol/L), increased serum osmolality (> 330 mOsm/kg) and severe dehydration, with little or no ketonuria. It is a medical emergency, with high morbidity and mortality if not adequately treated[41].

DIAGNOSIS

Since T2DM represents one of several different diabetes types, diagnosing a child or adolescent with the disease is a two-step process. Firstly, one has to confirm the diagnosis of diabetes and secondly, to establish that it is diabetes type 2.

According to the American Diabetes Association (ADA), the criteria used to diagnose diabetes in youth are the same as those used in adult populations[42]. There are four possible ways to diagnose diabetes and each, in the absence of hyperglycemia symptoms, must be confirmed on a different day by any one of the other three: (1) FPG ≥ 7.0 mmol/L; (2) 2 h post-OGTT plasma glucose ≥ 11.1 mmol/L. It should be noted that OGTT has poor reproducibility in adolescents, with a concordance rate of < 30% between tests performed a few weeks apart[43]; (3) random plasma glucose ≥ 11.1 mmol/L in the presence of diabetes symptoms. If such symptoms are not present, hyperglycemia diagnosed incidentally or under stress conditions (*e.g.*, acute infection or surgery) may be transitory and should not be regarded as diagnostic of diabetes. In such cases, repeat exam on a subsequent day will help diagnostically; and/or (4) A1C ≥ 48 mmol/mol. This criterion remains controversial since, in some but not all, studies it identifies a population that does not overlap entirely with that identified by FPG or OGTT[44-46]. In addition, A1C must be measured by using a laboratory-based National Glycohemoglobin Standardization Program-certified methodology and not a point-of-care device, in order to be reliable.

It is important to remember that none of the above criteria has ever been validated in pediatric population studies but they have been extrapolated from adult definitions. Such studies in youth would take a substantial period of time, and may prove unfeasible to perform[45].

Once the diagnosis of diabetes is established, the next important step is to differentiate T2DM from T1DM as well as from other more rare diabetes types. This distinction is not merely of academic importance but of clinical importance as well, since different types of diabetes require a different management approach, at least in the long-term[47]. Since there is considerable overlap between T2DM and T1DM, a combination of history clues, clinical characteristics and laboratory studies must be used in order to reliably make the distinction, which is not always possible at the beginning (Table 1). Such clues include: (1) Age. T2DM patients usually present after the onset of puberty, at a mean age of 13.5 years. By contrast, almost one-half of T1DM patients present before 10 years of age[9]; (2) Family history. A reported 75%-90% of patients with T2DM have an affected first- or second-degree relative[31], while the corresponding percentage for patients with T1DM is less than 10%; (3) Ethnic group. Youth belonging to minority groups such as Native American, African American, Hispanic, and Pacific Islander run a much higher risk of developing T2DM compared to Caucasians[24]; (4) Body weight. Adolescents with T2DM are usually obese [body mass index (BMI) ≥ 95 percentile for age and sex]. In contrast, children with T1DM are usually of normal weight and may report a recent history of weight loss; although, up to 25% are overweight or obese[7]; and (5) Clinical findings. Patients with T2DM usually present with features of insulin resistance and MetS, such as acanthosis nigricans, hypertension, dyslipidemia, and polycystic ovary syndrome (PCOS)[48]. Such findings are rarely encountered in youth diagnosed with T1DM. For instance, a study in the United States showed that up to 90% of youth diagnosed with T2DM had acanthosis nigricans, in contrast to only 12% of those diagnosed with T1DM[49].

In addition to the above history and clinical clues, laboratory tests that can help include those for: (1) Pancreatic autoantibodies. Since T2DM is not immunologically mediated, the identification of one or more pancreatic (islet) cell antibodies in a diabetic obese adolescent supports the diagnosis of autoimmune diabetes[50]. Antibodies that are usually measured include islet cell antibodies (against cytoplasmic proteins in the β-cell), anti-glutamic acid decarboxylase, and tyrosine phosphatase insulinoma-associated antigen 2, as well as anti-insulin antibodies, provided that insulin replacement therapy has not been used for more than 2 wk. In addition, a recently described β-cell-specific autoantibody to zinc transporter 8 is commonly detected in children with T1DM and can aid in their differential diagnosis[51,52]. One should keep in mind, though, that up to one-third of T2DM children can have at least one detectable β-cell autoantibody and, thus, complete absence of diabetes autoimmune markers is not a prerequisite for the diagnosis of T2DM in children and adolescents[53,54]; (2) Ketoacidosis. Since patients with T1DM are more prone to develop ketoacidosis at the time of diagnosis, measurement of venous pH and urinary ketones could help differentiate between T2DM and T1DM, especially in the presence of typical symptoms (*e.g.*, polydipsia, polyuria, and signs of dehydration). Of course, it should be remembered that up to 10% of adolescents with T2DM can have a similar initial clinical presentation[55]; and (3) Insulin and C-peptide levels. A low C-peptide level (< 0.2 nmol/L) detected in newly diagnosed diabetic youth strongly suggests T1DM[56]. Insulin levels can also be used, provided that insulin therapy has not been initiated.

The challenges of differentiating between T2DM and T1DM were demonstrated in a

Table 1 Clinical and laboratory findings of type 1 and type 2 diabetes mellitus and maturity-onset diabetes of the young in children and adolescents

Parameter	T1DM	T2DM	MODY
Prevalence	Common, increasing	Rare, increasing	Rare, stable
Ethnicity	Mainly Caucasian	Mainly minority groups	All
Inheritance	Multigenic	Multigenic	Autosomal dominant
Family history	5%-10% positive for T1DM	75%-90% positive for T2DM	100% positive for MODY
Sex	Male = Female	Male < Female	Male = Female
Age at presentation	Childhood-adolescence	Adolescence	Before 25 yr of age
Body habitus	Usually normal weight	Mostly obese	Various
Acanthosis nigricans	Rare	Very common	Absent
Onset	Usually acute, severe	Usually insidious, rarely acute	Insidious
Ketosis at onset	Common	5%-10%	Rare
Insulin, C-peptide	Decreased or absent	Variable	Detectable
Insulin sensitivity	Normal	Decreased	Normal
HLA-DR3/4 association	Strong	None	None
Pancreatic autoantibodies	85%-100%	< 10%	Rare
Insulin dependence	Permanent	Variable	Rare
Associated disorders	Autoimmune disorders (*e.g.*, Hashimoto, vitiligo, celiac disease)	MetS components (*e.g.*, lipid disorders, hypertension, PCOS, sleep apnea, *etc.*)	Depending on type, may present with exocrine pancreas insufficiency, urogenital malformation, *etc.*

HLA: Human leukocyte antigen; MetS: Metabolic syndrome; MODY: Maturity-onset diabetes of the young; PCOS: polycystic ovary syndrome, T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

multicenter study of 2291 subjects aged < 20 years with recently diagnosed diabetes that were classified based upon presence or absence of β-cell autoimmunity and insulin sensitivity[49]. More than 70% of the patients fell into the traditional autoimmune plus insulin-sensitive T1DM (55%) or non-autoimmune plus insulin-resistant T2DM categories (16%). Almost 20% of the subjects were diagnosed with autoimmunity and insulin resistance, and were considered to be obese individuals with T1DM. The smallest group (10%) comprised insulin-sensitive patients in the absence of pancreatic autoimmunity that could either be patients with type 1B or with monogenic diabetes, thus requiring further testing.

Maturity-onset diabetes of the young (MODY) is the most common form of monogenic diabetes. MODY is a clinically heterogeneous group of disorders characterized by non-insulin dependent diabetes together with lack of pancreatic autoimmunity. It is a congenital disorder with autosomal dominant transmission that is usually diagnosed in childhood or early adulthood. MODY accounts for at least 1.2% of all cases of diabetes in the United States in people aged 20 years and younger and 2.5% in the United Kingdom[57,58]. Eleven different MODY types have been described thus far, caused by mutations in several genes and with the most common types being MODY3 (*HNF-1a* gene mutations) and MODY2 (glucokinase gene mutations)[59]. MODY should be suspected in young (< 25 years) patients presenting with non-insulin-dependent diabetes (detectable C-peptide), usually without the typical comorbidities of obesity and MetS, without pancreatic autoantibodies, but with a strong family history of diabetes for more than one generation (Table 1). Its diagnosis requires genetic testing by direct sequencing of the suspected gene[60].

MANAGEMENT

Even if studies regarding long-term outcome of adolescent patients with T2DM are scarce, they show that youth T2DM is a particularly aggressive form of disease associated with early emergence of complications, not only in absolute terms[30,61,62] but also compared to youth with T1DM[63] or to adults with T2DM[4]. In addition, adolescents with T2DM exhibit a faster rate of deterioration of β-cell function[64] and greater extent of insulin resistance than adults with similar adiposity, presenting a decreased response to insulin sensitizers and a high therapeutic failure rate[65,66]. It is, therefore, essential to manage these patients timely and efficiently, in order to avoid or delay complications and to improve long-term outcomes.

Only a few studies have evaluated the management of T2DM in the pediatric age group. The largest among them is the TODAY study, which showed that oral agent monotherapy failed to maintain glycemic control in almost half of the patients evaluated, within a year of the treatment initiation[67]. According to similar evidence from other studies, it seems that the best approach to manage adolescents with T2DM is a combination of non-pharmacologic and pharmacologic interventions, with close monitoring and follow-up[68]. This approach is consistent with the Consensus Guidelines published in 2013 by the American Academy of Pediatrics, Pediatric Endocrine Society, Academy of Nutrition and Dietetics, and American Academy of Family Physicians[69], updated in 2018 by the International Society for Pediatric and Adolescent Diabetes (ISPAD)[19], and in 2020 by the ADA[70].

The best health services for an adolescent with T2DM can be provided by a multidisciplinary team consisting of an endocrinologist, a nurse educator, a dietitian, a mental health professional, and an exercise physiologist. In countries with limited resources, primary care physicians can manage these patients based on published guidelines[69]. Under these circumstances, at least, patients with poor glycemic control should be referred to an endocrinologist and a diabetes educator. It must be emphasized that most of the non-pharmacological interventions that are needed to manage T2DM in youth require active involvement of the entire family, if they are to be successful. In addition, all youth with T2DM and their families must receive comprehensive diabetes self-management education and support.

Management goals

The goals of managing an adolescent with T2DM are the following: (1) To achieve and maintain near-normal glycemic levels with minimal hypoglycemic episodes; (2) To improve body weight, insulin sensitivity and possibly insulin secretion, in order to achieve better glycemic control and improved overall health; (3) To identify and manage the disease in a timely manner and, if necessary, comorbidities and complications such as hypertension, dyslipidemia, hepatic steatosis, nephropathy, and retinopathy; and (4) To prevent or delay, as much as possible, macrovascular complications of T2DM, such as cardiovascular disease and stroke.

These goals can be achieved through the successful implementation of non-pharmacologic and pharmacologic measures. In extreme cases, surgical intervention should be considered.

NON-PHARMACOLOGIC INTERVENTIONS

It is well established that increased fat mass and especially visceral fat is responsible for many of the features that characterize children with MetS and overt T2DM[71]. In adults with T2DM, weight loss has been shown to reduce peripheral insulin resistance and to increase insulin secretion by the β-cells[72]. Similarly, in obese children without T2DM, a BMI decrease of ≥ 0.5 kg/m^2 was shown to improve insulin sensitivity, while the opposite was true for BMI increase[73]. In a study with adolescent patients with T2DM that were treated for 1-4 mo with very low-calorie diets, both BMI and A1C dropped and pharmacologic agents were discontinued in all but 1 of the 20 patients[74]. Obviously, such restrictive diets are very difficult to implement for longer periods of time and can lead to significant nutrient deficiencies in children and adolescents.

The goal for children and adolescents with T2DM should be a 7%-10% reduction in BMI for those that have completed linear growth, or a BMI < 85th percentile for age and sex for those that are still growing[68]. For the latter, weight maintenance could be enough, since it would lead to BMI reduction as the child grows taller. However, since most youth diagnosed with T2DM are in their mid-adolescence and present with severe obesity, weight reduction rather than maintenance should be the long-term

goal. A sensible approach is to start with weight maintenance for some months as the first step and continue with weight loss at a rate of 0.5-1 kg *per* month. For older adolescents that have completed puberty, the recommended weight loss rate is the same as for adults, *i.e.* 0.5-1 kg *per* week. One should keep in mind that this goal can prove quite challenging for many obese adolescents and their families, and changes in both diet and physical activity have to be implemented.

Diet

In order to avoid macro- or micronutrient deficiencies, specific dietary intervention programs should be carried out by an experienced nutritionist/dietitian with knowledge and experience in nutritional management of youth with diabetes. Consultation with a dietitian is particularly important for patients who fail to achieve adequate glycemic control and require treatment intensification. The whole family must be encouraged to make gradual dietary changes consistent with healthy eating recommendations, and healthy parenting practices related to diet and activity should be applauded. Dietary recommendations must be adjusted to each family's possible cultural or financial constraints and should focus on the following[75,76]: (1) elimination of sugar-sweetened soft drinks and fruit juices; (2) reduced consumption of processed and prepackaged foods; (3) decreased intake of refined, simple sugars and corn syrup; (4) reduced saturated and total fat intake; (5) increased fruit and vegetable intake; (6) increased consumption of fiber-rich foods, such as whole grain products and legumes; (7) preferable consumption of foods with low glycemic index; (8) better portion control; and (9) elimination of meals eaten away from home or while screen watching.

It is also important to remember that patients are more likely to follow a diet that is adapted to their preferences and habits and, therefore, dietary interventions must be individualized and have goals that are both measurable and achievable. In order to assess progress and to keep both the patient and the family motivated, frequent visits to the dietitian (*e.g.*, every 4 wk) are recommended[77].

Physical activity

Increased physical activity has a significant role in the management of youth with T2DM, since it not only helps in weight reduction but also increases insulin sensitivity and improves blood glucose control[78,79]. Youth with T2DM should be instructed to gradually increase their physical activity towards a goal of 1 h daily. Exercise must include moderate-to-vigorous aerobic activities and, in addition, strength training at least three times a week. In addition, the patient should engage in daily efforts to be more active physically, such as walking to school instead of taking the school bus, using stairs instead of elevators, doing house and yard work, and so on. At the same time, nonacademic screen time (*e.g.*, television, video games, social media) must be decreased to less than 2 h a day and other sedentary behaviors should be kept to a minimum[70]. Just like dietary changes, physical activity interventions have to be individualized for each patient and family, and should be enjoyable and achievable.

PHARMACOLOGICAL AGENTS

For several years, the only agents approved by the United States' Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of T2DM in children and adolescents were metformin and insulin. Metformin is a biguanide that increases insulin-mediated glucose uptake in the peripheral tissues and decreases hepatic glucose production, thereby promoting decrease of plasma glucose levels[80]. In addition, it has been shown to help in modest weight loss, albeit with only a temporary effect[81]. On the other hand, insulin therapy is used in the initial management of T2DM patients who present with severe hyperglycemia and ketosis or ketoacidosis or in patients that have mixed features of T1DM and T2DM, as described below.

Both the FDA and EMA, based on the promising results of the Evaluation of Liraglutide in Pediatrics with Diabetes clinical trial[82], approved the use of liraglutide for the treatment of T2DM in youth in 2019. Liraglutide is a glucagon-like peptide-1 (GLP-1) analog that acts by increasing glucose-dependent insulin secretion from pancreatic β-cells following ingestion of a meal, thereby ensuring an appropriate insulin response and avoidance of hyperglycemia. It may also promote modest weight loss, due to delayed gastric emptying and central effects on appetite[82]. A problem of the GLP-1 analogs treatment is the need for daily subcutaneous injection, which may be solved in the near future by long-acting analogs requiring only once-weekly

administration or oral preparations for adolescents.

Many other anti-hyperglycemic agents have been approved for use in adults but none in youth with T2DM, except for sulfonylureas (*e.g.*, glimepiride) in some countries[83]. Therefore, such drugs should not be used in adolescents outside research trials until more data regarding their safety and efficacy are available. For instance, the TODAY clinical trial showed that administration of rosiglitazone (a thiazolidinedione) with metformin failed to improve the lipid profile and the cardiovascular risk in youth with T2DM[30]. Clinical trials with adolescents are underway, testing the safety and efficacy of agents belonging to various drug categories. A detailed description of all the anti-hyperglycemic agents used in adult patients with T2DM is beyond the scope of this review.

Initial treatment

Some obese adolescents with T2DM will present with diabetic ketoacidosis and several others will present with features of both T1DM and T2DM. For this reason, immediate therapy should address hyperglycemia and possible metabolic derangements, irrespective of ultimate diagnosis[68]. According to the Consensus Guidelines published by the ADA and ISPAD, initial treatment of youth with T2DM should include metformin and insulin, either alone or in combination[19,68,70]. The decision on the initial treatment is individualized, as follows (Figure 1): (1) If the patient has no symptoms and A1C is < 69.4 mmol/mol, metformin is the treatment of choice, accompanied by lifestyle modifications. The initial dose is 500 mg once a day (taken with meals) and can be gradually increased by 500 mg every week, depending on patient tolerability, up to the maximal dose of 1000 mg BID or 850 mg TID (or 2000 mg once a day of extended-release metformin, if available). This slow titration can reduce gastrointestinal side effects; (2) If the patient has marked hyperglycemia (A1C ≥ 69.4 mmol/mol and/or blood glucose ≥ 13.9 mmol/L) together with related symptoms (polyuria, polydipsia, nocturia, weight loss) but without ketoacidosis, combination therapy with basal insulin and metformin is suggested; and (3) Patients who present with ketosis or ketoacidosis should initially be treated with insulin alone without metformin. A variety of insulin regimens is being used but once-a-day intermediate or basal insulin (0.25-0.5 U/kg starting dose) is often effective and well tolerated by the patient. Metformin should be added only after ketoacidosis has subsided and glucose levels have reached near-normal with insulin therapy. Since many youth with T2DM can be successfully weaned off insulin and treated with metformin alone[84], a gradual transition can usually be achieved over 2-6 wk by decreasing the insulin dose each time metformin is increased, simultaneously ensuring that glycemic targets are met.

The goal of treatment is to achieve an A1C of < 53 mmol/mol in most adolescents with T2DM and < 47.5 mmol/mol in others, for example those with shorter diabetes duration and less severe obesity[19,68,70]. Just like lifestyle modifications, treatment goals can initially be individualized. If, for example, the above targets seem unrealistic for a specific individual or if there is increased hypoglycemia risk, one can start with a higher target (*e.g.*, A1C < 64 mmol/mol) and then gradually decrease it[69]. In addition to A1C levels, FPG levels can be used as an indication of adequate therapy, with FPG < 7.2 mmol/L as a general goal.

A1C is typically measured every 3 mo. Self-monitoring of blood glucose can be done at home with a glucometer, at least three times *per* day in children who are on insulin therapy, whose dosage or treatment regimen is changing, or who are not meeting goals for glycemic control[69]. Use of continuous glucose monitoring could be considered in patients failing to attain glycemic targets and in those on a multiple daily injection regimen, although our knowledge on its use in adolescents with T2DM is just starting to evolve[85].

Intensification of therapy

Patients who fail to achieve adequate glycemic control require re-evaluation of their management. The initial steps include more intense efforts for lifestyle modifications, review of medication adherence, and dealing with possible barriers, as well as more frequent blood glucose measurements. If all these measures fail, a change in medication is the next step (Figure 1).

For patients who fail to achieve glycemic control 3-6 mo after intensification of lifestyle measures and monotherapy with metformin at the maximal tolerated dose (up to 1000 mg BID), basal insulin can be added, with liraglutide as an acceptable alternative. The advantage of insulin is the much greater clinical experience we have with its use in diabetic children and adolescents but, at the same time, one has to consider that it can cause weight gain and hypoglycemia, and requires frequent dose adjustment. Liraglutide, on the other hand, is a rather new anti-diabetic agent for teens

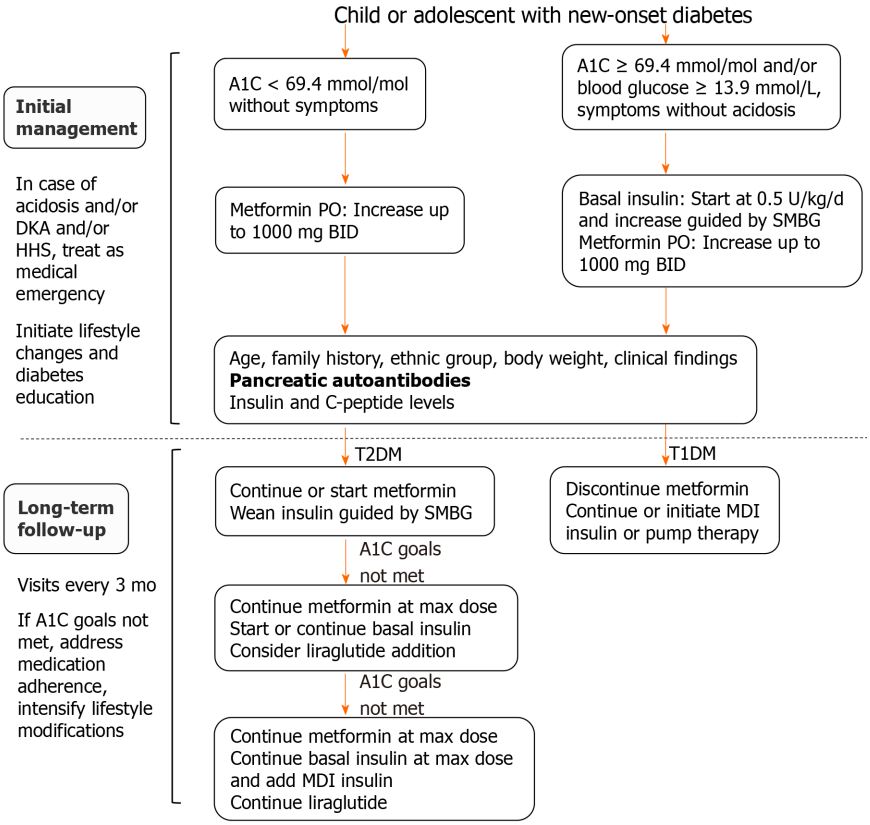

Figure 1 Management of new-onset diabetes in obese youth. A1C: Hemoglobin A1c; BID: Twice *per* day; DKA: Diabetic ketoacidosis; HHS: Hyperosmolar hyperglycemic state; IV: Intravenous; MDI: Multiple dose injection; PO: Per os; SC: Subcutaneous; SMBG: Self-monitored blood glucose; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus.

but there are no long-term data on its use and it might be more costly than insulin. It seems, though, to be at least as effective as basal insulin and may help obese diabetic youth to lose weight; it also has an easy dosing scheme[86].

For adolescents who fail to achieve adequate glycemic control despite intense lifestyle interventions and combination therapy of metformin (at maximal tolerated dose) with basal insulin (at a dose ≤ 1.5 U/kg/d), either liraglutide or prandial rapid-acting insulin can be added. Both approaches are acceptable, but liraglutide (at a starting dose of 0.6 mg/d) has the advantage of a single daily injection compared to the three injections required for prandial insulin. This is a rather important point to remember, considering the poor adherence of diabetic youth to insulin therapy[87].

It should be noted that adolescents with T2DM might have severe insulin resistance and, thus, basal insulin doses above 1.5 U/kg/d may be needed to achieve adequate glycemic control, particularly for those with higher A1C and glucotoxicity and those in mid- to late puberty[68]. If intense lifestyle interventions together with combination therapy of metformin, insulin, and liraglutide at maximal doses fail, bariatric surgery is a reasonable option.

SURGICAL THERAPY

Weight loss surgery is a rather new therapeutic approach for severely obese adolescents (BMI ≥ 120% of the 95th percentile for age and sex) with T2DM and/or other serious comorbidities and who fail to achieve glycemic control despite intensive lifestyle and pharmacologic intervention[68,75]. Several different techniques have been employed, such as gastric bypass, sleeve gastrectomy and adjustable banding, with good safety and efficacy results, if performed in experienced centers. T2DM usually subsides after surgery and remains in remission for some years, but relevant long-term data are lacking. As an example, in a multicenter, prospective study of bariatric surgery in severely obese adolescents with T2DM, diabetes resolved after surgery in 95% and remained in remission in 90% of a subgroup of them at 5 years later[88]. In the recent Teen-Longitudinal Assessment of Bariatric Surgery/TODAY study comparison,

adolescents treated with bariatric surgery demonstrated better glycemic control compared to age-, sex- and BMI-matched patients managed with medical therapy alone, but 30% of them required readmission and/or reoperation[89]. It is obvious that long-term follow-up and further research are needed regarding eligibility criteria, possible short- and long-term benefits and risks, as well as the optimal timing of bariatric surgery for obese youth with T2DM; thus far, the data are promising.

SCREENING FOR COMORBIDITIES AND COMPLICATIONS

When diagnosed with T2DM, many adolescents have already developed one or more of the MetS components, such as hypertension, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea, and PCOS[1]. These comorbidities, together with hyperglycemia and increased insulin resistance, rapidly aggravate the adolescent's health status and accelerate the appearance of microvascular complications such as nephropathy, retinopathy, and neuropathy, as well as of macrovascular complications and cardiovascular disease. Therefore, screening for and management of comorbidities and complications both at the time of diagnosis and in the course of the disease are essential components of T2DM management in youth (Table 2)[70,90].

Screening for hypertension should start as early as possible after T2DM diagnosis, since 15%-30% of obese adolescents with T2DM are diagnosed with high blood pressure (BP), with some being hypertensive already at diagnosis[91]. BP should be measured with an appropriately sized cuff at all routine health visits. If the BP remains elevated despite lifestyle interventions, anti-hypertensive therapy must be initiated, such as by prescription of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker[68,70]. Regarding dyslipidemia, all pediatric patients with T2DM should undergo lipid profile assessment at the time of diagnosis (after hyperglycemia has been controlled) and every year thereafter. Non-pharmacologic interventions can improve lipid levels to some extent. If these measures fail and low-density lipoprotein cholesterol remains elevated [≥ 130 mg/dL (≥ 3.36 mmol/L)], pharmacologic treatment (*e.g.*, a statin) can be started[70]. Youth with T2DM should also be screened annually for NAFLD, along with measurement of aminotransferase levels and possibly liver ultrasonography. Weight reduction is the only established treatment for this comorbidity[70].

Microvascular disease is the hallmark of hyperglycemia in both adults and children with T2DM and the relative risk increases with worse glycemic control and disease duration. In a children population-based cohort study, major complications related to microvascular dysfunction (*i.e.*, dialysis, blindness, or limb amputation) started to manifest 10 years after the T2DM diagnosis[92]. Regarding nephropathy, youth with T2DM should be screened annually for albuminuria by measuring the urine albumin-to-creatinine ratio in a random urine sample. Treatment with an ACE inhibitor is recommended for patients with increased albuminuria and elevated BP[70]. Diabetic retinopathy must be excluded by annual screening of youth *via* dilated eye examination and/or retinal imaging. Annual screening for diabetic neuropathy is also indicated, beginning at diagnosis, and includes a careful neurologic examination of the sensory nerves[70].

Regarding macrovascular complications, several lines of evidence suggest that children and adolescents with T2DM are at high risk of atherosclerosis and premature ageing of their cardiovascular system. Indeed, they have increased carotid intima media thickness, arterial stiffness, and left ventricular wall thickness compared to obese non-diabetic or normal weight controls[93-96]. Further, it was shown that adults with T2DM who were diagnosed between 15 and 30 years of age have double cardiovascular mortality compared to patients of similar age with T1DM of similar duration[63]. In order to reduce macrovascular disease, youth with T2DM should be screened and aggressively treated if found to have hypertension or dyslipidemia. In addition, smoking avoidance or cessation should be strongly encouraged. Better glycemic control should also be a target even though it has not yet been formally linked with improved cardiovascular outcome in T2DM youth. Routine screening of asymptomatic diabetic children and adolescents with electrocardiography, echocardiography, or stress testing is not recommended[70].

Table 2 Routine monitoring of children and adolescents with type 2 diabetes for comorbidities and chronic complications

Evaluation	Test performed	Testing frequency
Hypertension	BP measurement with appropriately-sized cuff	At the time of diagnosis and at each routine visit; more frequently if elevated
Dyslipidemia	Non-fasting or fasting lipid panel	At diagnosis once glycemic control is achieved. Annually thereafter, more frequently if abnormal
NAFLD	Liver transaminases	At diagnosis and annually thereafter
Retinopathy	Dilated eye examination or retinal imaging	At diagnosis and annually thereafter, or as per ophthalmologist's advice
Nephropathy	In a spot specimen urine albumin-to-creatinine ratio	Repeat annually. If abnormal, repeat on at least two occasions during the next 3-6 mo
Neuropathy	Foot examination (pulses and ankle reflex); sensory testing for vibration (tuning fork) and sensation (10-g monofilament)	Repeat annually. If abnormal, refer to neurologist
Psychosocial assessment	Screen for depression, eating disorders, risk-taking behaviors, or other psychosocial dysfunction	Repeat at each routine visit or as needed. If abnormal, refer to mental health professionals

BP: Blood pressure; NAFLD: Non-alcoholic fatty liver disease.

THE IMPORTANCE OF PATIENT'S ADHERENCE

Despite efforts of medical services, evidence shows that only a few patients with T2DM have an acceptable lifestyle modification and medication adherence level in the long-term. For example, data in adult populations have shown that adherence to dietary recommendations is < 65% and even lower (< 30%) to physical activity recommendations[97]. In addition, adherence to treatment with oral hypoglycemic agents and insulin therapy ranges between 36%-93% and between 20%-80%, respectively[97]. Several factors, such as complexity of treatment, have been implicated in low adherence in adults with T2DM[98]. What seems to be very important in both adult and adolescent populations though, is psychological factors such as depression and anxiety[99,100]. Therefore, it is important to support these young patients both emotionally and socially if we are to improve adherence and glycemic control. In addition, family support together with pairing the medication regimen with daily routines have been suggested by adolescents themselves to be important strategies for medication adherence improvement[101].

PREVENTION

According to Hippocrates of Kos (460-377 BC) "preventing is better than treating". In the case of pediatric T2DM with the difficult management and early serious complications, this could not be more true. As detailed above, there are several risk factors that increase the likelihood of early T2DM development. Some of them, such as genetic predisposition and ethnicity, cannot be altered, while others are potentially modifiable and could, therefore, be targets for preventive initiatives (Figure 2).

Mounting evidence indicates that youth T2DM follows the Developmental Origins of Health and Disease concept, according to which various events during critical periods, such as *in utero* or early years of life, predispose the developing organism to health or disease later in life[102]. Therefore, a primordial prevention approach aiming at modifiable risk factors, starting as early as before birth and extending throughout childhood, can have the greatest impact on preventing T2DM.

Intrauterine life

Both cohort- and registry-based studies have shown that maternal overweight and obese status are associated with T2DM in offspring, irrespective of various confounding pre-existing or pregnancy-related conditions[103-106]. In one of the largest such studies, for instance, Lahti-Pulkkinen *et al*[104] found that children born to obese or overweight women had a 3.5- and 1.4-fold higher incidence of T2DM respectively, compared to those born to normal-weight women. Further, several studies have linked high pregravid BMI or increased weight gain early in pregnancy to increased risk of childhood obesity in the offspring[107-109], which predisposes to early T2DM develop-

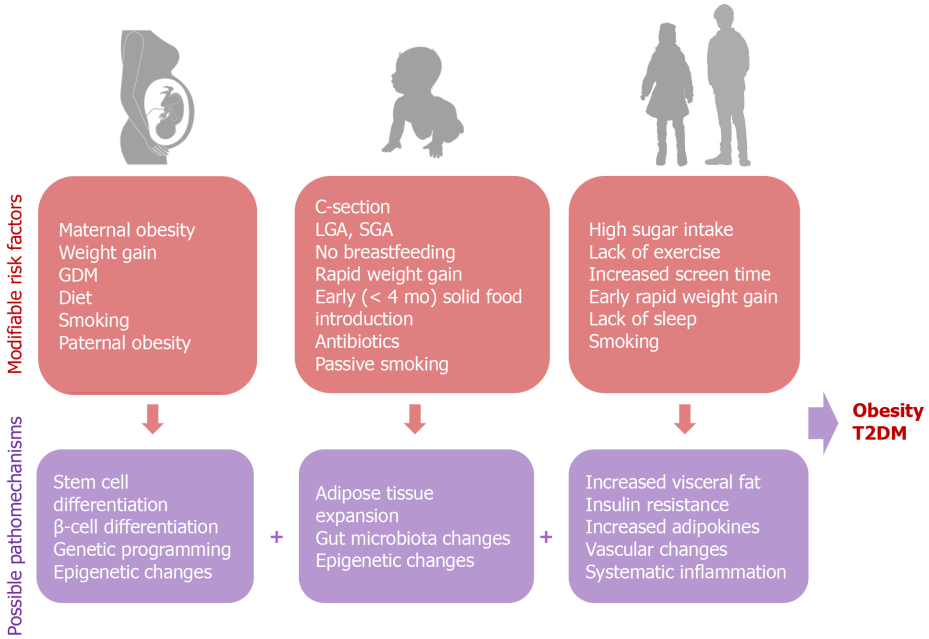

Figure 2 Modifiable risk factors and possible pathomechanisms in different age groups, leading to obesity and pediatric type 2 diabetes mellitus. C-section: Cesarian section; GDM: Gestational diabetes mellitus; LGA: Large-for-gestational age; SGA: Small-for-gestational age; T2DM: Type 2 diabetes mellitus.

ment. These results show that one of the earliest points of youth T2DM prevention is the reduction of overweight and obese status during pregnancy.

Obesity during pregnancy also increases the risk of GDM in the mother. Compared with normal-weight women, obese mothers have more than a 3-fold increased risk of developing GDM[110]. A substantial body of evidence, both in minority groups and in the general population, has shown that offspring of women with GDM are at increased risk of T2DM and obesity, irrespective of the mother's weight status during pregnancy[105,111]. In addition, not only overt GDM but also prediabetic conditions during pregnancy have been linked to glucose abnormalities and insulin resistance in the offspring[112]. Protection of the fetus from a diabetic intrauterine environment is, therefore, of paramount importance to prevent prediabetic conditions and T2DM in childhood and adolescence. Other risk factors such as maternal diet[113], maternal smoking[114], and even paternal obesity[115] should also be considered (Figure 2).

Addressing obesity and diabetes during pregnancy will not only protect youth from T2DM but could also prove beneficial at the population level by mitigating the so-called "vicious cycle of diabetes and obesity", first described by Pettitt and Knowler[116]. According to this concept, obese and diabetic pregnant women confer to their offspring the predisposition for developing obesity and T2DM, and the offspring, in turn, when at reproductive age, will give birth to another generation of obese diabetic individuals, thus perpetuating a transgenerational cycle of disease[117].

Early life

In order to prevent youth T2DM, one should clearly focus on intrauterine life, but postnatal exposures seem to play an equally important role. Diet and environment during the first 1000 d of each individual, from conception to the second birthday, have gained much attention as a window of opportunity for T2DM prevention[118]. For instance, breastfeeding has been shown to have a strong protective effect against early-onset T2DM in various populations[119,120]. In addition, it seems that breastfeeding for ≥ 6 mo mitigates the risk of an *in utero* diabetes exposure, regarding childhood adiposity and fat distribution[121], as well as prediabetes and MetS development[122], suggesting a specific protective effect among high-risk offspring.

Both high and low birth weight[123,124], preterm birth[125], as well as rapid weight gain during the first months of life[126,127] have been linked to increased risk of obesity later in life and to insulin resistance and glucose metabolism disturbances, thus predisposing to T2DM. Several other early life risk factors, such as Cesarean section[128], antibiotic exposure[129], secondhand smoking[130], and early (< 4 mo of age) solid food introduction[131], have been linked to increased obesity risk. Even if a direct link to glucose abnormalities and T2DM development has not been established, preventive

initiatives including these factors could prove helpful in preventing pediatric obesity and thus T2DM (Figure 2).

From their first birthday on, children can and should eat their meals at the family table. Following the diet and physical activity recommendations for children of this age is important to avoid later obesity. Especially important seems to be the preschool period since, as Geserick *et al*[132] showed, rapid weight gain between 2 and 6 years of age is associated with a much higher risk of overweight or obesity status in adolescence, thereby increasing the risk of early T2DM.

Childhood and adolescence

Measures to tackle T2DM in childhood and adolescence are based on obesity prevention, given the etiological connection between increased body fat and MetS and T2DM. Programs to limit childhood obesity are mainly school-based and seem to yield the best results in children younger than 12 years, although robust conclusions cannot be drawn given the heterogeneity of relevant studies. Food choices in this age group can be improved by measures that involve parents and teachers alike, such as healthier school meals, taxes on simple sugars, and restriction of unhealthy food advertisements aimed at children. Nutritional interventions should be combined with programs targeting increased physical activity in order to achieve the best long-term outcome[133,134].

For adolescents, interventions include improving eating habits, increasing physical activity, and restricting sedentary and screen time. In this age group, school-based interventions have proven more effective when the adolescents were addressed directly[135]. Behavior-oriented prevention programs have shown limited long-term effects thus far[136]. Further, interventions to improve the current obesogenic environment could prove essential in the fight against pediatric obesity and T2DM. Several environmental and social factors, such as length of the street the children live on, accessibility to playgrounds and sports facilities, population density and socioeconomic status of the neighborhood, influence children's BMI, even if only to a limited extent[137,138].

Screening for prediabetes

Primordial prevention is important, as described above. Equally important can be primary prevention through screening strategies aiming to identify prediabetes in youth and avert progression to T2DM. To date, no studies in a pediatric age group have examined if early diagnosis improves T2DM long-term outcome. However, there is indirect evidence from adult studies showing that lifestyle interventions can delay or even prevent the onset of T2DM[139].

Since generalized population screening of obese youth is unlikely to be cost-effective in most populations, the ADA and ISPAD recommend screening only high-risk individuals[68,70,140]. These include asymptomatic overweight or obese children and adolescents after the onset of puberty or at ≥ 10 years of age (whichever occurs first) if they have one or more of the following risk factors: (1) family history of T2DM in a first- or second-degree relative; (2) minority race/ethnic group (Native American, African American, Hispanic, Asian American, Pacific Islander); (3) maternal history of diabetes or GDM during the child's gestation; and/or (4) conditions or signs associated with insulin resistance (*i.e.* hypertension, dyslipidemia, acanthosis nigricans, PCOS, small-for-gestational age status at birth).

According to ADA recommendations, this screening should be repeated at least every 2-3 years, or earlier if BMI is increasing, and should be done by measuring A1C and FPG or by performing an OGTT. Abnormal results must be confirmed either by the same test on a different day or by performing a different test.

FUTURE PERSPECTIVES

Pediatric T2DM incidence has increased considerably and is expected to rise even further in the decades to come. According to a study that was based on data from the SEARCH for Diabetes in Youth Study, the number of youth with T2DM in 2050 is likely to increase 4-fold compared to the levels in 2010, with substantially larger numbers among minority youth[141]. This trend, if verified, will lead to a much heavier economic and societal burden, with many young adults having serious health conditions.

In order to avoid such an adversity, more measures have to be taken in the near future regarding both management and prevention of pediatric obesity and T2DM.

Regarding treatment, clinical trials of various anti-hyperglycemic agents used in adults from different categories, such as sodium-dependent glucose cotransporters inhibitors and dipeptidyl peptidase-4 inhibitors, are underway in pediatric populations and results are expected in the coming years. For instance, there are ongoing phase 3 studies of canagliflozin (NCT03170518), dapagliflozin and saxagliptin (NCT03199053) as well as of linagliptin and empagliflozin (NCT03429543) in patients with T2DM of ages between 10 and 18 years. The first results regarding empagliflozin pharmacokinetic characteristics in teens have already been published[142]. Further, studies in pediatric patients are needed with GLP-1 analogs designed for once-weekly dosing that are already available for use in adults as well as oral preparations, in order to help adolescents with poor adherence to liraglutide.

Even more important than improving pediatric T2DM management is optimizing its prevention. In order to develop effective preventive approaches, we need to elucidate mechanisms linking genetic, epigenetic, social, environmental and other risk factors with T2DM pathogenesis. To achieve this and to move from association to causation, better studies have to be designed, such as longitudinal cohorts starting even before birth. Such an example is the EarlyBird cohort which recruited 307 healthy children in the United Kingdom at 5 years of age and followed them throughout childhood, and which very recently showed that pancreatic β-cell defects predate insulin resistance in the onset of prediabetes[143].

In addition, future research should focus on questions regarding why some adolescents demonstrate durable control of their disease and others do not[144], and why T2DM is a more aggressive disease in adolescence compared to adulthood. Such studies will help to improve the overall understanding of youth T2DM as well as screening, prevention, and treatment strategies for such patients.

CONCLUSION

Pediatric T2DM is still a rare disease but recent reports indicate an increasing prevalence around the world, possibly following the increasing prevalence and severity of obesity in children and adolescents. Despite extensive research in the field over the last two decades, many knowledge gaps remain regarding the optimal management of obese children and adolescents with T2DM. The current approach is based on lifestyle interventions, including of diet and physical activity, on one hand, and pharmacologic treatment with metformin, insulin, and liraglutide in various combinations, on the other. What is important for everyone to realize, though, is that T2DM is a largely preventable disease if we manage to tackle its major risk factor, which is obesity. If families, schools, physicians, health services, policy makers and society altogether accept the obese child as the new "normal" and do not act promptly, no management approaches will be able to protect the next generation from many years of serious health problems and low-quality life.

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