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Current Perspectives on Management and Treatment Pediatric Type 2 Diabetes Mellitus

Mouritzen Ulrik*

Department of Pediatrics, Division of Pediatric Endocrinology, McMaster Children's Hospital, McMaster University, Hamilton, Canada

Abstract

The prevalence of type 2 diabetes mellitus (T2DM) in children and adolescents is on the rise, and the increase in prevalence of this disorder parallels the modern epidemic of childhood obesity worldwide. T2DM affects primarily post-pubertal adolescents from ethnic/racial minorities and those from socioeconomically disadvantaged backgrounds. Youth with T2DM often have additional cardiovascular risk factors at diagnosis. T2DM in youth is more progressive in comparison to adult onset T2DM and shows lower rates of response to pharmacotherapy and more rapid development of diabetes-related complications. Lifestyle modifications and metformin are recommended as the first-line treatment for youth with T2DM in the absence of significant hyperglycemia. Assessment of pancreatic autoimmunity is recommended in all youth who appear to have T2DM. Pharmacotherapeutic options for youth with T2DM are limited at this time. Liraglutide, a GLP-1 agonist, was recently approved for T2DM in adolescents 10 years of age and older. Several clinical trials are currently underway with youth with T2DM with medications that are approved for T2DM in adults. Bariatric surgery is associated with excellent rates of remission of T2DM in adolescents with severe obesity and should be considered in selected adolescents.

Keywords: Type 2 diabetes mellitus; Youth; Adolescents

Introduction

Type 2 diabetes (T2D) is increasing in youth, driven by the obesity epidemic that is affecting millions of children around the world. T2D is a serious disorder with multiple complications that appear early in the course of the disease. Since T2D in young people has been only recognized over the past few years, knowledge of its natural history is lacking, and there are only few studies examining treatments beyond metformin and insulin. Even in case of the latter two medications, randomized controlled trials are very few, and knowledge is still accumulating in this field [1].

Metformin alone was no different from metformin plus LSI in improving metabolic outcomes, and higher failure rates in black participants were noted. Combination therapy of metformin plus rosiglitazone offered better success rates especially in girls but was associated with more weight gain. Despite intensive LSI, the rates of clinically important weight loss were achieved in only 24.3% in the metformin group, 31.2% in the metformin plus LSI groups, and in only 16.7% in the metformin plus rosiglitazone group. This study revealed that, even with intensive LSI and pharmacotherapy, a significant number of T2D patients fail to achieve adequate glycemic control. In addition, the treatment options available to youth with T2D are limited when compared to adults, with insulin and metformin being the main agents used. Furthermore, rosiglitazone has been associated with unfavorable cardiac effects that lead to limited use in adult patients with T2D [2], although this has been recently questioned, but this limits its use in youth at this point. In this review, we will discuss the diagnosis and treatment of T2D in teens in view of the results of TODAY study.

Clinical presentation of T2D in children and adolescents

The average age of T2D diagnosis in youth is around 13.5 years, with female predominance. This age of presentation is likely to be related to a time of puberty-mediated insulin resistance in combination with increased weight.

The clinical presentation can be diverse. T2D can be detected while screening asymptomatic youth because of belonging to a high-risk population. These risk factors include being overweight or obese, family history in a first or second degree relative of T2D, being from certain ethnic groups known to have higher risk of T2D, and history of in-utero exposure to obesity or hyperglycemia [3].

Additional risk factors that warrant screening for T2D include the presence of insulin resistance, for example, Acanthosis nigricans, dyslipidemia and hypertension, polycystic ovarian syndrome (PCOS), non-alcoholic fatty liver disease, and history of antipsychotic medication use. The cost-benefit analysis for having a screening program for the general population is unjustified because of the low yield noted on several studies.

Screening in high-risk groups is recommended to start at the age of 10 years or when puberty starts if it is sooner than that, using fasting plasma glucose every 2 years. Oral glucose tolerance test can also be used but has poor reproducibility and is more expensive [4].

Some children and adolescents present with diabetes-related symptoms including polyuria, polydipsia, tiredness, blurred vision, vaginal moniliasis, and weight loss. They may also present with acute metabolic decompensation including ketosis, diabetic ketoacidosis, and hyperglycemic hyperosmolar nonketotic state.

Laboratory diagnosis of T2D in children and adolescents

The laboratory diagnosis of T2D in children uses the blood glucose cut-offs that are identical to adults and involves measuring fasting or random plasma glucose or a formal oral glucose tolerance test. HbA1c

***Corresponding author:** Mouritzen Ulrik, Department of Pediatrics, Division of Pediatric Endocrinology, McMaster Children's Hospital, McMaster University, Hamilton, Canada, E-mail: MouritzenUlrik@ac.cn

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is not recommended in the pediatric age group as a diagnostic test as is the case in adults but is used for follow-up in established T2D to determine glycemic control.

One area of difficulty in confirming the diagnosis of T2D is its overlapping picture with type 1 diabetes (T1D) and less so with familial diabetes (MODY). Because the general population is becoming overweight and many families do have a history of diabetes and as up to 33% of T2D youth have ketonemia at diagnosis, the distinction between T1D and T2D is challenging in this subset of patients [5]. Pancreatic autoantibody testing is positive in 10–75% of T2D patients, and this may indicate that these patients with "autoimmune type 2 diabetes" are in fact overweight type 1 diabetes patients, as clamp studies have revealed that those with antibodies are more insulin resistant and have reduced insulin production capacity. However, this is not fully clarified as some children who phenotypically seem to have bona fide T2D have antibodies, and one additional possibility is that islet injury due to glucotoxicity and lipotoxicity exposes cellular antigens that lead to an immune response as a secondary phenomenon.

Management of T2D in children and adolescents

The treatment of T2D requires a family-focused plan delivered by a multidisciplinary team with expertise in dealing with T2D in youth and taking into account the significant differences between T2D and T1D. Success in treating T2D requires addressing the main mechanisms that lead to its development, including insulin resistance and β-cell failure. The evidence for benefit of bariatric surgery in teens with T2D is currently limited, and there are no data to justify its use out of research settings, but this is a fast-moving field [6].

The multidisciplinary team includes a combination of physicians, diabetes nurse educators, dietitians, physical activity specialists, social workers, psychologists, and behavioral therapists and may also require the involvement of additional medical subspecialties to address its comorbidities and complications.

The management plan should be intensive with frequent contacts with family and teen and personalized to the individual patient taking into account the family's financial resources and being receptive and respectful of ethnic and cultural attributes of the family. Engaging the patient and family early and frequently is critical to minimize attrition, which is a common problem in this population [7].

Pharmacotherapy

While LSI is important to provide the basis for acquiring healthy behaviors in T2D, the success rates of maintaining glycemic targets based on LSI alone are low, and starting pharmacotherapy at diagnosis is appropriate.

Metformin

Metformin is the first line therapy for youth with T2D. It is a biguanide that lowers blood glucose levels via several mechanisms including reducing hepatic glucose output by inhibiting gluconeogenesis, increasing insulin-stimulated glucose uptake in muscle and adipose tissue, inhibiting inflammation in cells by inhibiting the NFκB pathway which, when active, interferes with insulin signaling, increasing fatty acid oxidation in muscle and inhibiting fatty acid synthesis in fat and liver by upregulating AMPK activity, enhancing the secretion of GLP-1 from gut.

A randomized clinical trial using metformin for 16 weeks in children showed significant improvement of HbA1c, but was used for few years in TODAY study with no major adverse effects. Metformin has an initial anorexic effect and may result in modest weight loss [8]. It lowers HbA1c by 1-2% and is to be taken with food to minimize its gastrointestinal side effects including nausea, vomiting, diarrhea, and abdominal pain.

There are slow release preparations that have less gastrointestinal side effects and are taken once daily, which may improve compliance, and pediatric trials are ongoing to evaluate their efficacy. Importantly, metformin use is rarely associated with hypoglycemia.

Metformin needs to be avoided in renal impairment, liver disease, cardiac or respiratory insufficiency, and when using radiographic contrast media. Metformin may also improve ovarian function, and this increases the chances of pregnancy.

The usual maintenance dose is 1000 mg twice daily, with a starting dose of 250–500 mg, to be increased every few days to reach full dose within 3-4 weeks. If side effects develop, the patient can be reassured that these are transient and to continue titration with lower dose increments.

The goal of insulin therapy is to reverse the acute metabolic decompensation noted in some patients at presentation and may be used for few weeks at diagnosis along with metformin and then is withdrawn gradually. In some cases, it is not possible to come off insulin, and, in one study, only 28% of those started on insulin managed to wean down treatment, and, of those who successfully came off insulin [9], the majority restarted therapy due to deterioration of metabolic control. In addition, insulin is usually needed few years after the initial diagnosis on a maintenance basis due to β-cell failure.

Insulin may be the only prescribed agent in adolescents with T2D in several institutions. The main side effects of insulin include weight gain and hypoglycemia.

Complications of T2D

Youth with T2D have a more aggressive disease than adult T2D and pediatric T1D, with complications noted early in the course of the disease.

The incidence of nephropathy in Pima Indians, a population with the highest rate of T2D in the world, is the same across different age groups, and retinopathy was more common when T2D is diagnosed at an older age. In addition, over the course of the TODAY stud, one-third of patients were hypertensive, one in six had proteinuria, and none had retinopathy [10].

In another study, retinopathy was noted in 4% of T2D, proteinuria and hypertension in 36%. In the latter study, peripheral and autonomic neuropathy occurred at 21 and 57% of T2D teens, respectively. It has also been shown that renal disease and retinopathy may occur early in the course of the disease, and, by early adulthood, many of these complications were already causing morbidities. This indicates the need for aggressive screening for complication in T2D youth at diagnosis and regularly afterwards, and collaboration with nephrology, ophthalmology, and neurology services is a must.

Conclusions

T2D in youth is an emerging disease and is more aggressive than T1D, the more common diabetes form in children. The complications seen in T2D are extensive, and many patients have adverse health problems related to diabetes at diagnosis. Due to its novelty, this disease

is not fully understood, and treatment options beyond metformin and insulin are limited.

Over the coming years, randomized controlled trials are needed to test new and old treatments including combination therapies to define the best treatment options for these patients. Further understanding of the natural history of disease-related comorbidities is required to determine optimal screening times and frequencies and define appropriate interventions to limit their effects.

Unfortunately, this will take time, which is something these youth do not have as they battle this disease. There is a need to further define the mechanisms that cause T2D and its comorbidities and complications, so that targeted therapies may be implemented.

Conflict of Interest

The author declares that there is no conflict of interests regarding the publication of this paper.

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