Review Article

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Diagnostic and Therapeutic Strategies of Type 2 Diabetes Mellitus in Youth

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The incidence of type 2 diabetes mellitus (T2DM) is increasing in youth, largely in correlation with an increase in childhood overweight and obesity. Youth-onset T2DM is a major public health concern worldwide, and tends to show more aggressive features than adult-onset T2DM. Early diagnosis and treatment are important to prevent the occurrence of complications and comorbidities. However, current treatment options are limited and only modestly successful in youth-onset T2DM. Over the last few decades, significant progress has been made in the understanding of youth-onset T2DM. This review summarizes the current understanding of the pathogenesis, diagnosis, and treatment of T2DM in youth. (Ewha Med J 2022;45(3):e3)

Introduction

Type 2 diabetes mellitus (T2DM), previously referred to as *adult-onset diabetes*, is becoming increasingly prevalent in youth worldwide and is largely associated with an increase in childhood obesity [1,2]. According to the Korea School Health Examination Survey, the mean body weight was significantly higher in 2018 than in 2010 for students in most school grades [3]. In the U.S., the incidence of youth-onset T2DM increased by 4.8% per year between 2002 and 2015, with 3,916 youths newly diagnosed with T2DM during that period [4]. Although the prevalence of diabetes in Korean youth is lower than that in the U.S., it almost doubled from 0.2% to 0.4% between 2007 and 2018 [5]. The increase in T2DM in Korean youth started in the early 2000s and was predominant in boys from low-income families [6]. The prevalence of fasting hyperglycemia has also increased from 5.4% to 11.7% in Korean adolescents over the past decade [7]. Deterioration of β-cell function is more rapid in adolescents than in adults [8–10]. Moreover, diabetes-related comorbidities are highly prevalent and rapidly progressing in youth-onset T2DM compared with adult-onset diabetes [11,12]. Although there are limited pharmacologic options for the treatment of T2DM in youth, evidence based on the management of youth-onset T2DM has expanded significantly since 2014 [13]. In this review, we describe the pathogenesis of youth-onset T2DM and discuss the diagnostic and therapeutic strategies for youth with T2DM based on recent consensus guidelines in children and adolescents.

Pathogenesis of T2DM

T2DM is characterized by hyperglycemia caused by insulin resistance and an inadequate compensatory increase in insulin secretion [14]. The etiology of T2DM in youth, similar to that in adults, is multifactorial and includes genetic, environmental, and metabolic factors. Obesity, the main cause of insulin resistance, may partly alter fatty acid metabolism, which interferes with normal glucose metabolism [15]. Adipocyte-secreted factors (such as adiponectin and leptin) and obesity-induced inflammation are likely to be involved in the development of insulin resistance and T2DM [15,16]. In addition to obesity, youth with T2DM often have a family history of T2DM, which is indicative of genetic predisposition. Recent studies have also identified several established genetic risk variants of adult T2DM to be associated with youth-onset T2DM, including *GCK*, *TCF7L2*, *IGF2BP2*, *CDKAL1*, *HHEX*, *HNF1A* [17]. Other clinical risk factors involved in T2DM pathogenesis in youth include maternal diabetes prior to or during pregnancy, low socioeconomic status, sedentary lifestyle, high-risk ethnicity, and female sex [2,14,18]. The onset of T2DM in youth commonly occurs around the onset of puberty, when insulin resistance is normally transiently increased, but an appropriate compensatory increase in insulin secretion is impaired in youth with T2DM, leading to progressive failure of the pancreatic β-cells [17].

Risk-based Screening and Diagnosis of Diabetes

Pediatricians often face challenges in the early diagnosis of diabetes in youth owing to the insidious onset of symptoms, which increases the risk of complications later in life. The American Diabetes Association (ADA) recommends risk-based screening for T2DM or prediabetes in asymptomatic youth with overweight or obesity aged≥10 years (or after the onset of puberty) who have one or more risk factors [19]. These risk factors include maternal or gestational diabetes, family history of T2DM, high-risk ethnicity, signs of insulin resistance, or conditions associated with insulin resistance (such as acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight). Fasting plasma glucose (FPG), 2-hour plasma glucose during a 75-g oral glucose tolerance test (OGTT), and glycated hemoglobin (HbA1c) can be used as screening tests [20]. The diagnosis of diabetes is based on blood glucose levels and the presence of characteristic symptoms such as polydipsia, polyuria, nocturia, and unexplained weight loss [13,19]. The diagnostic criteria for diabetes in youth given by the ADA are the same as those for adults: (1) in youth with classic symptoms of hyperglycemia, diagnosis can be made if random plasma glucose≥200 mg/dL; (2) in the absence of symptoms, hyperglycemia (FPG≥126 mg/dL, 2-hour post-OGTT plasma glucose≥ 200 mg/dL, or HbA1c≥6.5%) should be confirmed by repeat testing on another day [19]. Once the diagnosis of diabetes is established, pancreatic autoantibody testing, especially for glutamic acid decarboxylase 65 autoantibodies and tyrosine phosphatase-related islet antigen 2, is useful in the determination of diabetes type [13,21,22].

Complications and Comorbidities

Youth-onset T2DM is associated with poor glycemic control and early micro- and macrovascular complications [23,24]. Insulin resistance-related comorbidities, such as hypertension, dyslipidemia, and non-alcoholic fatty liver disease, may also be present at the time of T2DM diagnosis, which can accelerate the occurrence of micro- and macrovascular

complications [25–27]. Therefore, screening for and management of complications and comorbidities is recommended at the time of T2DM diagnosis in youth and regularly thereafter [13,19]. Blood pressure measurement, assessment of random urine albumin-to-creatinine ratio, foot examination, dilated eye examination, liver transaminases, and lipid screening (preferably after optimizing glycemia) should be performed at diagnosis. Other comorbidities associated with pediatric obesity, such as obstructive sleep apnea, polycystic ovary disease, and psychosocial concerns, also should be screened on a regular basis [13,19].

Current Management of Youth-onset T2DM

The management of youth-onset T2DM should include lifestyle changes, education for diabetes self-management, and pharmacological treatment [19]. Lifestyle changes, including a healthy diet and increased physical activity, are the cornerstone of treatment and should be initiated at the time of T2DM diagnosis [28]. Healthy eating recommendations include reduced high-carbohydrate and high-fat intake, increased fiber intake, and decreased consumption of calorie-dense foods, especially sugar-containing drinks [19,29]. The recommended distribution of macronutrients is carbohydrates 45%–50% of energy, fat<35% of energy (saturated fat<10%), and protein 15%–20% of energy [30]. Additionally, aerobic and/or resistance exercises are considered to have a positive effect on insulin sensitivity [31]. Youth with T2DM should be encouraged to engage in at least 1 hr of moderate-to-vigorous physical activity daily and to reduce sedentary time [13,19]. For pharmacologic treatment, only three drug classes have currently been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of youth-onset T2DM: metformin, insulin, and glucagon-like peptide (GLP)-1 analogues. According to the Consensus Guidelines of the ADA and International Society for Pediatric and Adolescent Diabetes (ISPAD), the initial treatment of T2DM in youth should include metformin and insulin, either alone or in combination: (1) in asymptomatic patients with HbA1C<8.5%, metformin is the treatment of choice; (2) in patients with HbA1C≥8.5% together with related symptoms without acidosis, combination therapy with metformin and basal insulin is suggested; (3) in patients with acidosis, including diabetic ketoacidosis or hyperglycemic hyperosmolar nonketotic syndrome, intravenous insulin alone should be initiated without metformin, and metformin should be added after acidosis is resolved in combination with continued subcutaneous insulin therapy [13,19]. Many youths with T2DM can successfully discontinue insulin treatment and switch to metformin monotherapy after a 2–6 weeks transition period by decreasing the insulin dose while metformin is increased [32] (Fig. 1).

For most youth with T2DM, the goal of initial treatment is to attain an HbA1c of <7.0%, and <6.5% may be appropriate for patients who have had diabetes for a short period of time, lesser degrees of β-cell dysfunction, and those who achieved significant weight improvement [19]. A higher target of HbA1C (e.g., <7.5%) can be considered in patients with an increased risk of hypoglycemia [19]. Glycemic status should be measured every three months. If patients fail to achieve adequate glycemic control with metformin at the maximally tolerated dose (up to 2,000 mg/day), basal insulin can be added, with subcutaneous liraglutide, a GLP-1 analog, as an acceptable alternative [33]. For patients who fail to meet glycemic targets despite combination therapy with metformin and basal insulin, either liraglutide or prandial insulin can be added. Bariatric surgery may be considered in young patients with T2DM who have severe obesity (body mass index>35 kg/m^2) and those who have uncontrolled hyperglycemia and/or serious comorbidities despite intense lifestyle interventions together with combination therapy with

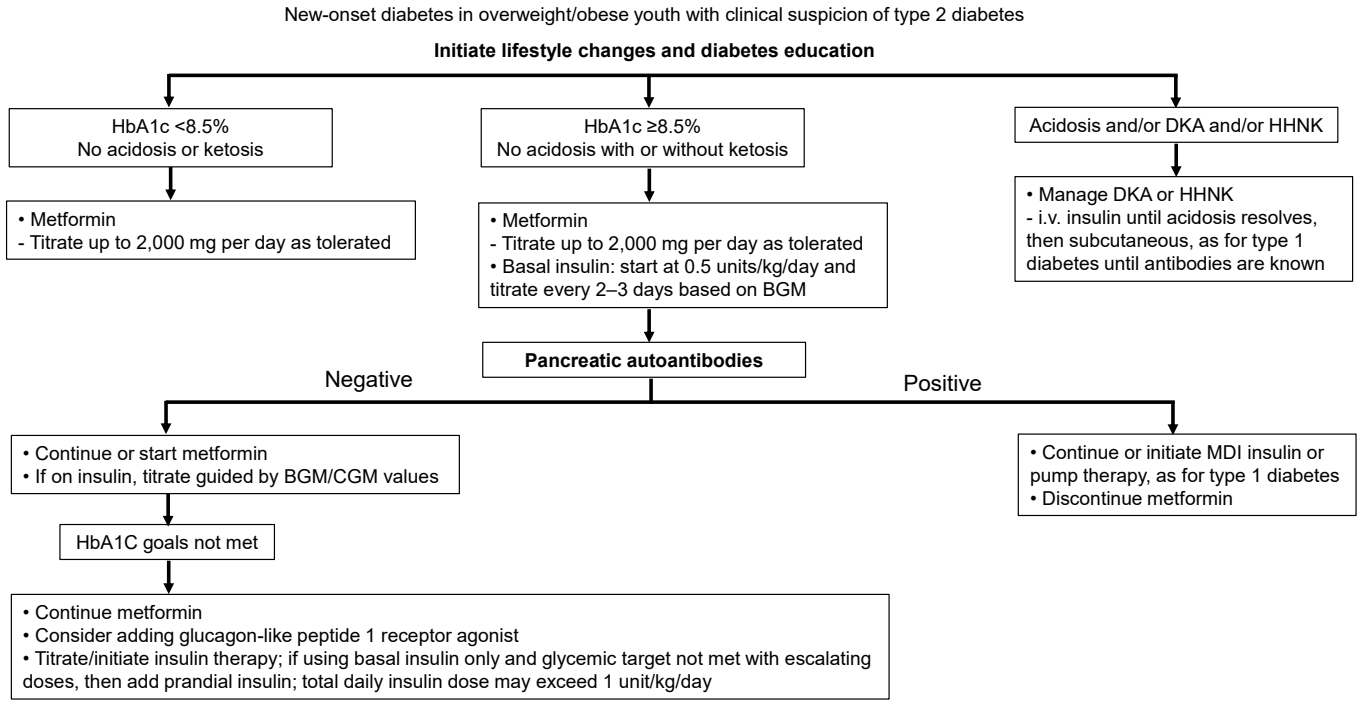

Fig. 1. Management of overweight or obese youth with new-onset diabetes. Adapted from the American Diabetes Association (ADA) position statement in 2022 with License for Non-Commercial Reuse [19]. HbA1c, glycated hemoglobin; DKA, diabetic ketoacidosis; HHNK, hyperosmolar hyperglycemic nonketotic syndrome; BGM, blood glucose monitoring; CGM, continuous glucose monitoring; MDI, multiple daily injections.

metformin, insulin, and liraglutide at maximal doses [19].

Ongoing Clinical Trials in Youth with T2DM

Clinical trials of various categories of anti-hyperglycemic agents used in adults, are underway in pediatric populations (Table 1). For example, phase III studies using GLP-1 analogs designed for once-weekly subcutaneous injections (NCT 05260021) and oral preparations (NCT 04596631) are recruiting young people with T2DM. Phase III studies of sodium-glucose cotransporters-2 (SGLT2) inhibitors are also ongoing in patients with T2DM aged 10–17 years: ertugliflozin (NCT 04029480) and canagliflozin (NCT 03170518). Furthermore, there are ongoing phase III studies using dipeptidyl peptidase-4 (DPP-4) inhibitors, including dapagliflozin and saxagliptin (NCT 03199053) and linagliptin and empagliflozin (NCT 03429543) in youth with T2DM.

Conclusion

Youth-onset T2DM is a relatively recent public health problem resulting from the obesity epidemic in many countries. While sharing a similar pathophysiology with adult-onset diabetes, T2DM in youth has the unique characteristics of rapid progression and rapid development of complications. Early detection and treatment are crucial to prevent serious comorbidities and complications. As current treatment options are not as effective in youth as they are in adults, various pathophysiology-based treatments, including GLP-1 analogs, SGLT2, and DPP-4 inhibitors, are being investigated. Further research regarding the pathogenesis of youth-onset

Table 1. Ongoing clinical trials in youth with type 2 diabetes

NCT	Phase	Drug (route)	Categories	Age of participants
05260021	III	Tirzepatide (weekly SC)	GLP-1 analog	10–18 years (child, adult)
04596631	III	Semaglutide (oral)	GLP-1 analog	10–17 years (child)
04029480	III	Ertugliflozin (oral)	SGLT2 inhibitors	10–17 years (child)
03170518	III	Canagliflozin (oral)	SGLT2 inhibitors	10–17 years (child)
03199053	III	Dapagliflozin, Saxagliptin (oral)	DPP-4 inhibitors	10–18 years (child, adult)
03429543	III	Linagliptin, Empagliflozin (oral)	DPP-4 inhibitors	10–17 years (child)

The National Clinical Trial (NCT) numbers denote ClinicalTrial.gov identifiers.
SC, subcutaneous; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose transporter-2; DPP-4, dipeptidyl peptidase-4.

T2DM is warranted to provide a basis for the development of new therapeutic and preventive strategies.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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