doi.org/10.58931/cdet.2025.3346

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Youth-Onset Type 2 Diabetes: A Review

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Introduction

Type 2 diabetes (T2D) was once considered a disease of adults. However, the obesity pandemic has helped its transition to the pediatric population. While type 1 diabetes remains the most common type of pediatric diabetes in Canada, the incidence of youth-onset T2D has increased by 60% in recent years.[1] Canada has one of the highest prevalences of youth-onset T2D in the world,[2] with approximately 50% of new cases annually occurring in Indigenous children,[1] with the remaining 50% of cases occurring in other ethnic groups, including Caucasians.

As a relatively new disease in youth, there is a lack of natural history data for youth-onset T2D to predict long-term outcomes. However, its aggressive nature in youth suggests that these patients will likely have a significant burden of disease related to cardiometabolic risk, comorbidities, and complications.

In this paper, we highlight current knowledge on the pathophysiology of youth-onset T2D, diagnostic criteria, the impact of obesity on diabetes risk, comorbidities and complications, and current treatments.

Pathophysiology of Youth-onset T2D

While the exact pathophysiology of youth-onset T2D is incompletely understood, genetic, epigenetic, and environmental factors all drive its genesis. A strong genetic component exists, often reflected in a significant family history of diabetes, with some families affected by both type 1 and type 2 diabetes. Youth-onset T2D is more common in females than males, and certain ethnic/racial groups are at higher risk of developing T2D than others (see below).

Fetal exposure to an adverse in-utero environment drives the fetal epigenetic programming for ex-utero cardiometabolic risk. Research in Pima Indians, who have the highest rates of T2D in the world, show that in-utero exposure to normoglycemia versus hyperglycemia was associated with an increased risk of developing T2D in the latter group.[3,4] Additionally, fetal exposure to maternal obesity and being born small- or large-for-gestational-age also increases the risk of T2D.[4,5]

The impact of environmental factors, including endocrine disrupting chemicals, in epigenetic programming of risk in youth-onset T2D remains unclear.

Obesity as a Risk Factor for Youth-onset T2D

Obesity is a major driver of youth-onset T2D. The increased body mass and adiposity, especially during puberty, lead to insulin resistance through mechanisms involving glucotoxicity, lipotoxicity, and inflammation, all of which impact insulin action. The insulin resistance in youth with T2D is higher than that seen in adults with comparable body mass index (BMI) levels and is independent of race/ethnicity and sex.[6]

Skeletal muscle insulin resistance is an early and important event in obesity, as skeletal muscle accounts for up to 75% of post-prandial glucose update. Hepatic insulin resistance leads to increased hepatic glucose output. In addition, adipose tissue expansion is associated with inflammation and increased lipolysis that leads to insulin resistance.

In youth with T2D, insulin resistance is coupled with a heightened islet responsiveness to glucose, and elevated insulin and C-peptide levels at diagnosis in many cases. However,

Treatment	Intervention	HbA1c Reduction	Impact on Weight	Effect On Lipids/ Blood Pressure
Lifestyle	Behavioural and psychological approaches, dietary advice, physical activity, sleep hygiene	0.5–1%	↓ modestly (if adherent)	↓ TG, ↑ HDL-C
Biguanide	Metformin	0.8–1%	↓ mild or neutral	↓ TC, LDL-C, TG; ↑ HDL-C
GLP-1 receptor agonists	Liraglutide, Exenatide, Dulaglutide, Semaglutide	0.6–1.5%	↓ or neutral	↓ TG
SGLT-2 inhibitors	Empagliflozin, Dapagliflozin	0.7–1%	↓ modestly or neutral	↓ BP
DPP-4 inhibitors	Sitagliptin, Saxagliptin, Linagliptin, Alogliptin	0.2–0.4%	Neutral	Neutral
Thiazolidine diones	Pioglitazone, Rosiglitazone	0.5–1%	↑ weight	↓ TG, ↑ HDL-C, neutral LDL
α-Glucosidase inhibitors	Acarbose	0.50%	Neutral	Neutral
Sulfonylureas	Glimepiride, Gliclazide	1%	↑ weight	Neutral
Insulin	Basal ± bolus insulin	>2%	↑ weight	Neutral
Metabolic/ Bariatric surgery	Sleeve gastrectomy, Roux-en-Y	Normalization in most cases	↓ ↓ weight	↓ LDL-C, TG, ↑ HDL-C

Table 1. Treatment modalities and their impact on glycemic control and cardiometabolic health outcomes in youth-onset type 2 diabetes; *courtesy of M. Constantine Samaan, MD*

Abbreviations: BP: blood pressure; **DPP-4:** dipeptidyl peptidase-4; **GLP-1:** glucagon-like peptide 1; **HDL-C:** high-density lipoprotein cholesterol; **LDL-C:** low-density lipoprotein cholesterol; **SGLT-2:** sodium-glucose cotransporter-2; **TG:** triglycerides

these patients lose 20-35% of insulin production capacity annually, and many require insulin in late adolescence or early adulthood. This aggressive decline in islet function is not mitigated by insulin or metformin.[7]

While obesity is a major risk factor for youth-onset T2D, it is not a universal phenotype. Approximately one in eight patients do not have obesity.[8] For example, some Japanese children have normal body mass levels yet have a clear phenotype of T2D. These cases may have defects in insulin production or abnormalities with metabolic organ insulin response or signalling that contribute to T2D occurrence. What is classified as T2D in youth today likely encompasses several subtypes that are driven by different pathophysiologic mechanisms, which require further elucidation.

Diagnosis of Youth-onset T2D

The diagnosis of T2D in youth uses the same biochemical diagnostic criteria as adults, with HbA1c of ≥6.5%, fasting glucose of ≥7.0 mmol/L, and a random or a 2-hour glucose of ≥11.1 mmol/L post Oral Glucose Tolerance Test using 1.75 g/kg of glucose up to a maximum of 75 g are all diagnostic.[9] Many patients are asymptomatic at diagnosis; in these cases, confirmation requires two of the above tests or repeat testing on a different day. Negative pancreatic antibody levels support the diagnosis of T2D, in addition to clinical features such as overweight status, signs of insulin resistance, existing comorbidities, and a positive family history of T2D.[10,11]

Targeted versus universal screening for T2D in youth is currently recommended due to considerations such as cost effectiveness, feasibility, and clinical impact. T2D screening is advised for youth who have an age- and sex-based BMI ≥85TH percentile and who are older than 10 years of age or are in puberty with one or more additional risk factors.

The risk factors include: a family history of T2D in first- or second-degree relatives, maternal history of diabetes (including gestational diabetes), high-risk ethnic backgrounds such as Indigenous, Pacific Islander, Black, Hispanic, Latin American, South Asian, and Middle Eastern, along with other groups that include being born small- or large-for-gestational-age, having clinical signs of insulin resistance, (e.g., acanthosis nigricans), metabolic dysfunction associated steatotic liver disease (MASLD), hypertension, dyslipidemia, polycystic ovary syndrome (PCOS), and youth on atypical antipsychotics that are associated with weight gain.[12]

Children younger than 10 years from Indigenous or other risk groups may need screening if their age- and sex-based BMI ≥85TH percentile or if they develop cardiometabolic risk factors.

Comorbidities and Complications

Youth-onset T2D is an aggressive disease, often accompanied by multiple, and at times simultaneous, comorbidities early in the course of the illness. At diagnosis, patients may present with obesity, MASLD, dyslipidemia, hypertension, obstructive sleep apnea, and PCOS. The progression of complications is more rapid in youth compared to adults.

Hypertension and proteinuria are present in approximately 1:4 and 1:5 pediatric T2D cases, respectively.[13] PCOS occurs in approximately 1:4 female patients[14], while MASLD occurs in 1:3 patients increasing to 1:2 patients when multiple diagnostic modalities are implemented. The Middle East reports the highest prevalence of MASLD.[15]

Retinopathy can appear early in 1:14 patients, and its risk escalates rapidly such that within five years of diagnosis, 1:4 have some degree of retinopathy.[16]

Treatment Options for Youth-onset T2D

In the early years after T2D was first recognized as a pediatric disease, treatment strategies focused on lifestyle interventions, such as eliminating sugar sweetened beverages and adding basal insulin to achieve adequate glycemic control. As evidence emerged regarding the aggressive nature of youth-onset T2D, the focus shifted toward a combination of lifestyle intervention plus pharmacotherapy targeting both T2D and its associated comorbidities and complications. The treatment goal is to maintain HbA1c below 6.5%. Treatment is guided by need, patient preferences, regulatory approval, drug mechanism of action, method of administration, adherence considerations, and availability of therapies.[12]

Table 1 summarizes current and potential treatments for youth with T2D.[12] Lifestyle intervention is foundational for all patients. The recommendations should be tailored to individual families and delivered through culturally sensitive

approaches. Lifestyle intervention remains an important cornerstone for treating T2D comorbidities including MASLD, dyslipidemia, and hypertension, in addition to improving insulin sensitivity.[12]

For patients with an HbA1c <8.5% at diagnosis, metformin is the first line pharmacotherapy for patients alongside lifestyle intervention.[17-19] In the TODAY study, the combination of metformin and rosiglitazone was more effective in preventing treatment failure, defined as an HbA1c of ≥8% 6 months after starting treatment, compared to metformin alone or metformin plus lifestyle intervention. However, an analysis of adult studies of rosiglitazone demonstrated a potential risk of adverse cardiovascular outcomes, which limited its use in children.[19]

For patients with an HbA1c ≥8.5% at diagnosis, insulin therapy is warranted in combination with metformin. Basal insulin therapy starts with 0.25-0.5 units/kg/day, and higher doses may be needed based on response. Rapid-acting insulin is added if hyperglycemia persists. If the patient presents with diabetic ketoacidosis (DKA), insulin therapy is initiated immediately, and metformin is introduced after resolution of DKA and stabilization of the glucose levels.[12]

Maintenance therapy is designed to achieve and sustain an HbA1c target of <6.5%. If this goal is not met, treatment may include glucagon-like peptide -1 receptor agonist (GLP-1RA) or sodium-glucose cotransporter-2 (SGLT-2) inhibitors, while dipeptidyl peptidase-4 (DPP-4) inhibitors appear to offer limited benefit.[20-26]

Bariatric surgery has been used to treat youth-onset T2D. While not widely used, it can result in reduced body mass and improved glycemic control, and, in some cases, diabetes remission. This surgery should be performed only in centres with specialized expertise.[12]

In summary, youth-onset T2D is rising in prevalence and represents more aggressive disease than adult-onset T2D or pediatric type 1 diabetes, with several comorbidities and a faster progression of complications compared to adults. Lifestyle intervention is a cornerstone of treatment as it can improve insulin sensitivity and help manage T2D-related comorbidities. While several pharmacotherapies can lower HbA1c, not all treatments impact weight or cardiometabolic risk factors such as blood pressure or lipid levels and some are not easily accessible. It is critical to assess these patients for the presence of comorbidities and complications, alongside ongoing research to clarify long-term outcomes and to define therapeutic entry points for managing diabetes and its associated comorbidities and complications.

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Financial Disclosures

C.S.: None declared.

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