doi.org/10.58931/cdet.2025.3346

About the Author

M. Constantine Samaan, MD

Dr. M. Constantine Samaan is Professor and Head, Department of Pediatrics, Queen's University and Pediatric Endocrinologist, Kingston Health Sciences Centre. He is the holder of the Queen's Chair in Pediatric Research and Education. Dr. Samaan provides tertiary care for children and adolescents with endocrine disorders. Dr. Samaan's program of translational research is in pediatric diabetes and obesity. He has received funding from several agencies including the Canadian Institutes of Health Research.

Affiliations: Department of Pediatrics, Division of Pediatric Endocrinology, Queen's University, Kingston, ON

Youth-Onset Type 2 Diabetes: A Review

M. Constantine Samaan, MD

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.

Correspondence

M. Constantine Samaan, MD
Email: constantine.samaan@queensu.ca

Financial Disclosures

C.S.: None declared.

References

1. Patel TJ, Ayub A, Bone JN, Hadjiyannakis S, Henderson M, Nour MA, et al. Incidence trends of type 2 diabetes mellitus, medication-induced diabetes, and monogenic diabetes in Canadian children, then (2006–2008) and now (2017–2019). Pediatr Diabetes. 2023;2023:5511049. Published 2023 Nov 14. doi:10.1155/2023/5511049
2. Fazeli Farsani S, van der Aa MP, van der Vorst MM, Knibbe CA, de Boer A. Global trends in the incidence and prevalence of type 2 diabetes in children and adolescents: a systematic review and evaluation of methodological approaches. Diabetologia. 2013;56(7):1471–1488. doi:10.1007/s00125-013-2915-z
3. Salama OE, Rawal Y, Irabor P, Kassim H, Pylypjuk C, Sellers EAC, et al. In-utero exposure to maternal diabetes and DNA methylation alterations in the Next Generation birth cohort. Clin Epigenetics. 2025;17(1):165. Published 2025 Oct 3. doi:10.1186/s13148-025-01972-3
4. Dabelea D, Mayer-Davis EJ, Lamichhane AP, D'Agostino RB Jr, Liese AD, Vehik KS, et al. Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: the SEARCH Case-Control Study. Diabetes Care. 2008;31(7):1422–1426. doi:10.2337/dc07-2417
5. Leunissen RWJ, Kerkhof GF, Stijnen T, Hokken-Koelega A. Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. JAMA. 2009;301(21):2234–2242. doi:10.1001/jama.2009.761
6. Luo Y, Luo D, Li M, Tang B. Insulin resistance in pediatric obesity: from mechanisms to treatment strategies. Pediatr Diabetes. 2024;2024:2298306. Published 2024 Jun 28. doi:10.1155/2024/2298306
7. Bacha F, Gungor N, Lee S, Arslanian SA. In vivo insulin sensitivity and secretion in obese youth: what are the differences between normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes? Diabetes Care. 2009;32(1):100–105. doi:10.2337/dc08-1030
8. Cioana M, Deng J, Nadarajah A, Hou M, Qiu Y, Chen SSJ, et al. The prevalence of obesity among children with type 2 diabetes: a systematic

review and meta-analysis. JAMA Netw Open. 2022;5(12):e2247186. Published 2022 Dec 1. doi:10.1001/jamanetworkopen.2022.47186
9. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325.
10. Klingensmith GJ, Pyle L, Arslanian S, Copeland KC,Cuttler L, Kaufman F, et al. The presence of GAD and IA-2 antibodies in youth with a type 2 diabetes phenotype: results from the TODAY study. Diabetes Care. 2010;33(9):1970–1975. doi:10.2337/dc10-0373
11. Tfayli H, Bacha F, Gungor N, Arslanian S. Islet cell antibody-positive versus -negative phenotypic type 2 diabetes in youth: does the oral glucose tolerance test distinguish between the two? Diabetes Care. 2010;33(3):632–638. doi:10.2337/dc09-0305
12. Shah AS, Barrientos-Pérez M, Chang N, Fu JF, Hannon TS, Kelsey M, et al. ISPAD Clinical Practice Consensus Guidelines 2024: Type 2 diabetes in children and adolescents. Horm Res Paediatr. 2024;97(6):555–583. doi:10.1159/000543033
13. Cioana M, Deng J, Hou M, Nadarajah A, Qiu Y, Chen SSJ, et al. Prevalence of hypertension and albuminuria in pediatric type 2 diabetes: a systematic review and meta-analysis. JAMA Netw Open. 2021;4(4):e216069. Published 2021 Apr 1. doi:10.1001/jamanetworkopen.2021.6069
14. Cioana M, Deng J, Nadarajah A, Hou M, Qiu Y, Chen SSJ, et al. Prevalence of Polycystic Ovary Syndrome in Patients With Pediatric Type 2 Diabetes: A Systematic Review and Meta-analysis. JAMA Network Open. 2022;5(2):e2147454-e.
15. Hu C, Cioana M, Saini A, Ragganandan S, Deng J, Nadarajah A, et al. The prevalence of non-alcoholic fatty liver disease in pediatric type 2 diabetes: a systematic review and meta-analysis. Front Adolesc Med. 2024;2. doi:10.3389/fradm.2024.1303375
16. Cioana M, Deng J, Nadarajah A, Hou M, Qiu Y, Chen SSJ, et al. Global prevalence of diabetic retinopathy in pediatric type 2 diabetes: a systematic review and meta-analysis. JAMA Netw Open. 2023;6(3):e231887. Published 2023 Mar 1. doi:10.1001/jamanetworkopen.2023.1887
17. Matsuura N, Amemiya S, Sugihara S, Urakami T, Kikuchi N, Kato H, et al. Metformin monotherapy in children and adolescents with type 2 diabetes mellitus in Japan. Diabetol Int. 2018;10(1):51–57. Published 2018 Jun 27. doi:10.1007/s13340-018-0361-3
18. Jones KL, Arslanian S, Peterokova VA, Park J-S, Tomlinson MJ. Effect of metformin in pediatric patients with type 2 diabetes: a randomized controlled trial. Diabetes Care. 2002;25(1):89–94. doi:10.2337/diacare.25.1.89
19. Zeitler P, Hirst K, Pyle L, Linder B, Copeland K, Arslanian S, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. N Engl J Med. 2012;366(24):2247–2256. doi:10.1056/NEJMoa1109333
20. Laffel LM, Danne T, Klingensmith GJ, Tamborlane WV, Willi S, Zeitler P, et al. Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial. The Lancet Diabetes & Endocrinology. 2023;11(3):169–181. doi:10.1016/S2213-8587(22)00387-4
21. Tamborlane WV, Barrientos-Perez M, Fainberg U, Frimer-Larsen H, Hafez M, Hale PM, et al. Liraglutide in Children and Adolescents with Type 2 Diabetes. N Engl J Med. 2019;381(7):637–646. doi:10.1056/NEJMoa1903822
22. Tamborlane WV, Bishai R, Geller D, Shehadeh N, Al-Abdulrazzaq D, Vazquez EM, et al. Once-Weekly Exenatide in Youth With Type 2 Diabetes. Diabetes Care. 2022;45(8):1833–1840. doi:10.2337/dc21-2275
23. Arslanian SA, Hannon T, Zeitler P, Chao LC, Boucher-Berry C, Barrientos-Perez M, et al. Once-Weekly Dulaglutide for the Treatment of Youths with Type 2 Diabetes. N Engl J Med. 2022. doi:10.1056/NEJMoa2204601
24. Tamborlane WV, Laffel LM, Shehadeh N, Isganaitis E, Van Name M, Ratnayake J, et al. Efficacy and safety of dapagliflozin in children and young adults with type 2 diabetes: a prospective, multicentre, randomised, parallel group, phase 3 study. Lancet Diabetes Endocrinol. 2022;10(5):341–350. doi:10.1016/S2213-8587(22)00052-3
25. Shankar RR, Zeitler P, Deeb A, Jalaludin MY, Garcia R, Newfield RS, et al. A randomized clinical trial of the efficacy and safety of sitagliptin as initial oral therapy in youth with type 2 diabetes. Pediatr Diabetes. 2022;23(2):173–182. doi: 10.1111/pedi.13279
26. Tamborlane WV, Laffel LM, Weill J, Gordat M, Neubacher D, Retlich S, et al. Randomized, double-blind, placebo-controlled dose-finding study of the dipeptidyl peptidase-4 inhibitor linagliptin in pediatric patients with type 2 diabetes. Pediatr Diabetes. 2018;19(4):640–648. doi: 10.1111/pedi.12616