Management of Pediatric Type 2 Diabetes: A Practical Overview of Current Guidelines and Emerging Therapies

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Introduction

Type 2 Diabetes Mellitus (T2DM) can no longer be considered an adult chronic disease. The diagnosis of pediatric T2DM is based on the laboratory criteria of fasting plasma glucose ≥7.0 mmol/L; 2-hour plasma glucose on a 75 g oral glucose tolerance test (OGTT) ≥11.1 mmol/L; random plasma glucose ≥11.1 mmol/L; or A1c ≥6.5% per Diabetes Canada.[1] It is important to note that these criteria are based on extrapolations from adult data, and have not been specifically validated in youth. The International Society for Pediatric and Adolescent Diabetes (ISPAD) adds that the diagnosis should not be made on these laboratory criteria alone, but should include symptoms of hyperglycemia and negative islet auto-antibodies.[2]

A Canadian national surveillance study of pediatric T2DM completed in 2010, has demonstrated a minimum incidence of youth-onset T2DM of 1.54 per 100,000 children per year with significant regional variation; the highest incidence was 12.45 per 100,000 children per year in Manitoba.[3] Youth-onset T2DM disproportionately affected Canadian children from high-risk ethnic groups, with 44% of new diagnoses occurring in the Indigenous, Asian, African and Caribbean populations.[3]

Over the past twenty years, youth-onset diabetes has been rising. In the United States, according to the SEARCH for Diabetes in Youth Study, there has been an annual increase of 7.1% observed across all age, sex, race and ethnic groups.[4] The COVID-19 pandemic has added further escalation in the incidence of youth-onset worsening disease severity at presentation.[5] New cases in the United States rose by 77.3% in the initial year following the COVID-19 pandemic, vs in the two years pre-pandemic. Furthermore, 21% of youth presented with diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome vs previous estimates of 9% pre-pandemic.[5] The SEARCH for Diabetes in Youth Group projects that the number of youths with T2DM will increase from 28,000 to 48,000 youth today, to 220,000 youth by 2060, with widening racial and ethnic disparities among youth with T2DM.[6]

Navigating the Heavy Burden of Youth-Onset T2DM

Several pivotal studies show that youth-onset T2DM has a more aggressive clinical course than adult-onset T2DM.

1. **The RISE consortium:** Pancreatic β-cell failure progresses more rapidly in youth than in adults despite early treatment with metformin and/or glargine.[7] Glycemic worsening occurred in 17.8% of youth vs 7.5% of adults within 12 months (P=0.008) and in 36% of youth vs 20% of adults within 21 months (P=0.002).[7]
2. **The TODAY study group:** Youth with T2DM develop microvascular and macrovascular complications with shorter disease duration than youth with T1DM and adults with T2DM.[8] With a mean diagnosis at age 13.3 ± 1.8 years, the cumulative incidence of any microvascular complication was 50% by 9 years and 80% by 15 years of disease duration. The cumulative incidence of hypertension was 67.5%; dyslipidemia was 51.6%; diabetic kidney disease was 54.8%; and peripheral neuropathy was 32.4%.[8] The prevalence of retinopathy increased from 13.7% to 51.0% between 5 years to 12 years of disease duration.[9] Risk factors for the development of complications included minority race or ethnic group, hyperglycemia, hypertension, and dyslipidemia.[8]
3. **The SEARCH group:** Microvascular and macrovascular complications are statistically higher in youth with T2DM versus those with T1DM: diabetic kidney disease (absolute difference [AD]: 14.0%); retinopathy (AD: 3.5%); peripheral neuropathy (AD: 9.2%); arterial stiffness (AD: 35.9%); and hypertension (AD: 11.5%).[10]
4. **The SEARCH group:** There remains high all-cause mortality among youth and young adults with T2DM beyond that which occurs in youth with T1DM, and the general population.[11]

Lessons from these studies suggest an urgent need for improvements in our approach to managing youth-onset T2DM.

Navigating Disease Management

Current pharmacologic management strategies are centered around a limited number of clinical studies: metformin,[12] glimepiride,[13] the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study,[14] the ELLIPSE trial of liraglutide,[15] meta-analysis of GLP-1RAs,[16] DINAMO,[17] and the pediatric arm of the Restoring Insulin SEcretion (RISE) Study.[18]

There are a number of challenges in procuring evidence-based data for the treatment of youth-onset T2DM, including the high cost of operating randomized, placebo-controlled trials; lack of inclusive patient engagement of ethnic minority groups; barriers in access to clinical trial sites; strict study entry criteria; and the high prevalence of psychosocial challenges that impact patient participation. Advocates in the field urge for the consideration and early adoption of off-label antidiabetic agents.[19]

Current guidelines from Diabetes Canada (2018),[1] ISPAD (2022)[2] and the American Diabetes Association (ADA) (2023)[20] have been developed based on the current literature and clinical expertise. The objective of youth-onset T2DM glycemic control is to achieve target A1c of <7%.[2,20] Lower A1c (<6.5%) can be targeted for select populations: (a) recently diagnosed patients to preserve their beta function; (b) youth who are able to achieve significant weight loss by lifestyle changes; and (c) youth managed on metformin only.[2,20]

Culturally sensitive, family-based lifestyle modification in a safe healthcare setting free of stigma, shame and blame is first-line treatment for T2DM. In selecting pharmacotherapy, it is critical to balance achieving optimal glycemic control (A1c <7%) and the prevention of complications with avoidance of over-insulinization and the prevention of weight gain.

Navigating Diabetes Education

Youth-onset T2DM is best managed by a multidisciplinary pediatric team with expertise in this cohort's unique dietary, exercise and psychological needs. The treatment team should ideally include a pediatric endocrinologist, certified diabetes educator, dietitian, psychologist, and/or social worker, and an exercise physiologist if resources permit.[2] Important considerations for diabetes education delivery include:

1. A family-centered approach that focuses on the family's involvement; sharing responsibility and self-management with family monitoring and support using nonjudgmental, motivational and supportive conversations;
2. Education using culturally appropriate material in the patient's/family's first language;
3. Interpreter services and workforce diversity to optimize communication;
4. Encouragement of self-management guided by the patient's/family's level of confidence and motivation;

5. Consideration of group education to assist with motivation and social networking;[22]
6. Consideration of hybrid in-person and virtual models of care to improve access to care for patients living in remote communities;[22,23]
7. Education content should also extend to schools to optimize support of diabetes management among youth.[2]

Pharmacotherapy

Initial management: metformin and insulin

Metformin is used as the first-line drug of choice in youth with A1c <8.5%, with minimal symptoms, and no ketosis or acidosis, at a starting dose of 500 mg/day, gradually increasing to 2,000 mg/day over four weeks in order to minimize potential gastrointestinal (GI) side effects. In youth with ketosis, A1c ≥8.5%, and no signs of acidosis, metformin paired with long-acting basal insulin (a starting dose of 0.25–0.5 units/kg) is often effective in attaining metabolic control, while minimizing excessive weight gain. The use of prandial fast-acting insulin is now reserved for youth with T2DM presenting in diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS) upon transition off intravenous (IV) continuous insulin infusion.

Data emerging from the TODAY study indicates that 90% of youth presenting with T2DM can be successfully weaned off insulin and treated with metformin alone.[8] Transition off insulin can usually be achieved over two-to-six weeks by reducing the insulin dose in 30–50% increments as the metformin dose is increased.[2,20]

Subsequent therapy

If the A1c target of <7.0% is not achieved within three-to-four months on metformin monotherapy, additional second-line agents should be considered (Table 1). While polypharmacy may not appear to be the optimal treatment approach in youth who struggle with compliance, it is the experience of many pediatric endocrinologists that patients and their families are motivated by the possibility of avoiding insulin.[19]

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA)

The most recent ADA and ISPAD guidelines recommend the consideration of GLP-1RAs if glycemic targets are not met with metformin monotherapy (with or without insulin) in children ≥10 years of age.[2,20] Diabetes Canada has not yet made this recommendation.[1] There was clear benefit in A1c reduction reported in the ELLIPSE trial assessing the safety and efficacy of liraglutide.[15] This was corroborated in a meta-analysis of seven studies of GLP-1RAs[16] and the AWARDS-PEDS study of dulaglutide.[24] Semaglutide was assessed for the treatment of obesity in the STEP TEENS trial; however no data was collected in those with youth-onset T2DM.[25] In adults with T2DM, GLP-1RAs have been demonstrated to be both cardio- and reno-protective, while such impact has yet to be assessed in youth. Given the previously stated data regarding severe complications in youth-onset T2DM, it is vital to consider early adoption of GLP-1RAs.

Health Canada has approved liraglutide for use in youth age >12 years, whereas semaglutide has not yet received this approval.

Sodium-glucose cotransporter-2 inhibitors (SGLT2is)

SGLT2is (dapagliflozin, empagliflozin and canagliflozin) are not yet Health Canada approved for youth-onset T2DM. Phase 3 results of a clinical trial of dapagliflozin in children and young adults with T2DM determined that dapagliflozin safely lowers glucose in this population (decreased A1c by 0.62% vs placebo).[26] Empagliflozin also showed clinically significant reductions in A1c of 0.84% vs placebo at 26 weeks of treatment; however, hypoglycemia was noted as an adverse event in 77% of participants.[17] These agents represent a potential treatment option for youth-onset T2DM.

Dipeptidyl peptidase 4 inhibitors (DPP4is)

DPP4is are not yet Health Canada approved for youth-onset T2DM. Systematic reviews and recent clinical trials of linagliptin do not show any advantage of DPP4is for glycemic improvement in youth-onset T2DM.[17,27]

Thiazolidinediones (TZDs)

TZDs are not yet Health Canada approved for youth-onset T2DM. The addition of TZD (rosiglitazone) to metformin decreased the risk for progression to insulin requirement by 23% in youth in the TODAY study.[14] This class of medication has been associated with a high risk of weight gain; this has limited its widespread off-label adoption in the pediatric population. Some experts report that it can be considered viable for patients who cannot tolerate metformin or for those for whom the cost of the newer agents is prohibitive.[19]

Combination medications

Tirzepatide is a dual GLP-1RA and glucose-dependent insulinotropic peptide (GIP) receptor agonist that has been shown to cause substantial weight loss in adults, with improvement in A1c of 1.07%.[28] An ongoing clinical trial is being conducted to demonstrate the

Class	Mechanism of action	Names and dosing	HbA1c impact	Impact on weight management	Cost
GLP-1RA	1. Increasing insulin secretion 2. Suppressing glucagon 3. Prolonging gastric emptying and promoting satiety	**Liraglutide** (1.8 mg SC daily)	ELLIPSE trial: reduction of 0.64% in HbA1c; 63.7% of patients in liraglutide group achieved HbA1c values <7.0%	ELLIPSE trial: mean difference of 1.3 kg after 26 weeks	High; variable coverage in Canada depending on province
		Semaglutide (1.0 mg SC daily)	No pediatric data available	STEP-TEENS trial: BMI from baseline to week 68 was -16.7% estimated difference; 73% had weight loss of 5% or more	
		Dulaglutide (0.75 or 1.5 mg SC weekly)	AWARDS-PEDS: reduced HbA1c by 0.9%	No significant change in body weight noted at 26 weeks of treatment	
		Exenatide (2 mg SC weekly)	Reduced HbA1c by 0.85%	No significant change in body weight noted at 24 weeks of treatment	
SGLT2i	Inhibits renal tubular reabsorption of glucose, leading to increased urinary glucose loss, reduction in serum glucose, and weight loss	**Canaglifozin** (100–300 mg/day) **Dapagliflozin** (10 mg/day) **Empagliflozin** (10–25 mg/day) **Ertugliflozin** (15 mg/day)	**Dapapgliflozin**: Reduced HbA1c by 0.5% at 24 weeks **Empagliflozin**: Reduced HbA1c by 0.85%	DINAMO trial: No impact on weight	Moderate
DPP4i	Inhibits the enzyme that breaks down GLP-1, resulting in higher concentrations of GLP-1	**Linagliptin** (5 mg/day)	DINAMO trial: No impact on HbA1c	DINAMO trial: No impact on weight	Moderate
TZD	1. Binds to nuclear PPAR gamma, ubiquitous orphan steroid receptors abundant in adipocytes 2. Increases insulin sensitivity in muscle, adipose, and liver tissue	**Pioglitazone** (15 mg/day; can increase to 30 mg/day) 45 mg/day dose available	0.5–1.3% HbA1c reduction	Weight gain noted	Low to Moderate

Table 1: Summary of current pediatric literature in use of off-label second-line anti-hyperglycemic agents.
Adapted from ISPAD 2022 guidelines.

metabolic and weight reduction effects of tirzepatide in adolescents (National Library of Medicine, NCT number: NCT05260021).

Bariatric Surgery

Bariatric Surgery in the post-pubertal adolescent population can be an effective tool for the remission of T2DM.[2,20] Five years after bariatric surgery, adolescents were 1.27 times more likely to have remission of T2DM vs adults five years post-surgery.[29]

Nutrition

The involvement of a dietitian for initial T2DM education and subsequent management is key to achieving target glycemic control and working toward remission. Nutritional therapy should be aimed at youth and their family including all those involved in creating the child's food environment. A balanced approach is recommended; there are no data to support very low calorie, low carbohydrate or ketogenic diets, nor

intermittent fasting, in youth with T2DM. Diet modification should incorporate:[1,2,20]

1. Eliminating sugar-sweetened soft drinks and juices
2. Reducing the intake of foods made from refined, simple sugars and high-fructose corn syrup
3. Limiting intake of high-fat and/or calorie dense foods
4. Reducing the intake of processed, prepackaged and "convenience" foods
5. Understanding healthy portions sizes
6. Reducing meals eaten away from home and in fast food restaurants
7. Increasing vegetable and fruit intake
8. Replacing enriched white rice and white flour with brown rice and whole grains with a lower glycemic index to promote the gradual absorption of glucose with meals
9. Healthy parenting practices and promoting parental modelling of healthy eating habits, while avoiding an overly restrictive food intake
10. Encouraging healthy meal practices such as eating on schedule, in one place, preferably as a family unit, and with no other activity (use of computers or studying)
11. Use of educational materials on nutrition; healthy plate models that include ethnically diverse foods

Ongoing patient assessment for unhealthy eating habits is recommended given the increased risk for eating disorders in youth with T2DM.[30] It is advisable to incorporate the use of regular screening questions for all youth regardless of gender and BMI, in particular, in youth reporting body dissatisfaction; history of dieting; history of depression; poor glycemic control; missed clinical appointments; recurrent episodes of DKA; recurrent hypoglycemia secondary to intentional medication overdose; and dietary manipulation.[31]

Nutritional recommendations should also be provided under the practical lens of household food security, housing stability, access to fresh water, barriers to accessing fruits and vegetables due to climate change, and family financial resources.

Physical Activity

Regular daily physical activity is an integral part of all diabetes management plans for improving glycemic control, reducing cardiovascular (CV) risk factors, contributing to weight loss, and improving mental health. Youth are encouraged to target 60 minutes of moderate to vigorous physical activity daily, with strength training at least three days per week.[2] Key considerations for youth with T2DM include:

1. Promote physical activity as a family event, including daily efforts to increase body movement, such as using stairs instead of elevators, walking or cycling to school and shopping outings, and doing house and yard work
2. Encourage physical activity with positive reinforcement and avoid the use a punitive measure as a means to address the intake of high-fat and/or calorie dense foods
3. Reduce sedentary on-screen time to less than two hours per day

Physical activity targets should be specific, negotiated, enjoyable, and sensitive to family resources.[2] Clinical assessment of physical activity should include an understanding of the youth's community, physical environment and neighborhood walkability scores. There is also emerging data to suggest that technology-based interventions such as active video games can improve dyslipidemia and result in weight loss.[32] Effort should also be made to draw on cultural traditions when trying to promote physical fitness.[33] Recent publications have supported the use of Bhangra dancing, for example, to improve cardiovascular respiratory profiles, dyslipidemia and insulin resistance.[34]

Psychosocial Considerations

Psychosocial factors constitute a major challenge in implementing pharmacotherapy and lifestyle behaviour change in youth with T2DM.[4] Youth-onset T2DM disproportionately affects visible ethnic minorities living in poverty,[35] individuals in food insecure households,[36] and those exposed to structural racism.[37] Treatment recommendations should be individualized to consider the cultural, social, geographic and economic barriers to implementing behavioural change.

Youth with T2DM should be screened for psychological comorbidities including depression, anxiety, weight stigma, diabetes distress, and disordered eating at diagnosis and at regular follow-up intervals.[2,38] These factors can create a barrier to lifestyle modifications leading to sedentary lifestyles, disturbed sleep patterns, poor medication adherence, and excessive snacking. The selection of weight-neutral antidepressant medications is recommended when treating depression or other mental health conditions in adolescents with T2DM.[2]

This highlights the importance of the early inclusion of social worker support, the creation of pathways for accessing support groups, and psychologists.

Complications/ Comorbidities	Screening Test	Screening Interval	Initial Treatment
Hypertension	Blood pressure using appropriately sized cuff	At every visit	• Aim for weight loss • Diet: limitation of dietary salt to <2300 mg/day, initiate DASH diet • Increase physical activity to 1 hour daily • Start ACE inhibitor or ARB if no improvement within 6 months • Referral to pediatric nephrology as required
Dyslipidemia *(high plasma triglycerides, low HDL-C, and high LDL-C)*	Fasting lipid profile	Yearly, starting at 3 months after diagnosis	• Optimize HbA1c <7% • Diet: limit saturated fats, avoid trans fats, improve fiber intake, lower intake of simple sugars and sugar sweetened beverages, increase intake of omega-3 • Increase physical activity to 1 hour daily • Monitor lipid levels every 3–6 months • Start statins to lower LDL-C if no improvement after 6 months of dietary modification • Start fibrates to lower triglycerides if no improvement after 6 months of dietary modification
Nephropathy	Urine albumin to creatinine ratio (ACR)	Yearly, starting at diagnosis	• Elevated spot value occur secondary to contamination, exercise, smoking, menstruation, infection and orthostasis. • Document 2–3 a.m. urine ACR immediately after rising • Consultation with pediatric nephrology if persistently elevated ACR >30 mg/mmol
Retinopathy	Comprehensive eye examination with dilated pupils or retinal photography by optometrist or ophthalmologist	Yearly, starting at diagnosis	• Optimize HbA1c <7% • Ensure treatment of dyslipidemia and hypertension if present • Ongoing close follow-up with ophthalmologist
Neuropathy	Clinical history of symptoms (numbness, pain, cramps, and paresthesia); tests of vibration sense, light touch, and ankle reflexes	Yearly, starting at diagnosis	• Optimize HbA1c <7% • Ensure treatment of dyslipidemia, optimize HDL-C • Counsel on avoidance of smoking and smoking cessation (if applicable) • Referral to pediatric neurologist if symptomatic
NAFLD	ALT, AST	Yearly, starting at diagnosis	• Optimize HbA1c <7% • Consider optimizing diabetes medications; glitazones and GLP-1RA can improve liver enzymes • Consider need for liver ultrasound • Consult pediatric gastroenterologist if ALT and AST >3 times normal reference range over 6 months to exclude other causes of liver enzyme elevation via imaging and/or liver biopsy
OSA	Clinical history of snoring, sleep quality, apnea, morning headaches, daytime sleepiness	Yearly, starting at diagnosis	• Confirm diagnosis with referral to a sleep specialist for sleep study; nocturnal pulse oximetry can be an initial useful evaluation if there is limited access for a sleep study
PCOS	Clinical history of menstrual cycle irregularity and evidence of hyperandrogenism	Yearly at diagnosis in post-pubertal girls	• Optimize HbA1c <7% • Diet: engage in dietary changes towards weight loss • Increase physical activity to 1 hour daily • Start OCP to assist with menstrual irregularity and symptoms of hyperandrogenism as adjunctive therapy
Psychosocial Health	Clinical history of depression, disordered eating, food security, smoking, vaping, drugs, alcohol use, sexual activity, school support and family financial concerns	At every visit	• Engage regular follow-up and monitoring with social worker and mental health resources

Table 2: Navigating complications and comorbidities associated with youth onset T2D. *Courtesy of Dr. Sanjukta Basak.*

Navigating Additional Barriers to Management

Other factors unique to youth include pubertal insulin resistance, which often leads to prescribing large doses of insulin; this, in turn, promotes weight gain. In addition, the development of the adolescent brain is associated with compliance challenges. Often, youth with T2DM have multiple family members with T2DM and diabetes-related complications, creating additional logistical barriers as they manage multiple family appointments, and the added costs of diabetes medications and supplies. Youth may face additional challenges of caring for family members while trying to manage their own diabetes. Youth with diabetes may also present with additional comorbidities such as polycystic ovary syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD), hypertension, obstructive sleep apnea (OSA), and dyslipidemia, which can lead to further setbacks in coping with disease and quality of life burdens. From a financial perspective, there is a scarcity of Health Canada-approved medications for use in pediatric T2DM, leading to barriers in coverage by provincial healthcare plans and extended health care benefits.

Navigating Co-Morbidities Associated with Youth-Onset T2DM

Centralizing the care of T2DM patients and diabetes-related complications is the optimal approach for successful patient engagement and outcomes. As pediatric education centres evolve toward specialized pediatric T2DM clinics, it is critical to ensure that pathways for screening and investigation, as well as for the management of hypertension, dyslipidemia, nephropathy, retinopathy, NAFLD, OSA, PCOS, and referrals, are developed for efficient patient care (Table 2).

Conclusion

Youth-onset T2DM is clinically complex and aggressive, with a high burden of disease. Poor glycemic control and high rates of complications in youth-onset T2DM persist despite management with metformin and insulin. It is important to balance achieving optimal glycemic control (A1c <7%) with the prevention of complications from over-insulinization, and the prevention of weight gain. Limited Health Canada-approved tools exist for the treatment of pediatric T2DM. We need to consider safe, early adoption of off-label medications for this patient population.

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Research Studies/Clinical Trials: Neurocrine Biosciences, Ultragenyx, Pfizer, Rhythm Pharmaceuticals

Speaking Honoraria: Canadian Diabetes & Endocrinology Today, Pfizer, Canadian Pediatric Endocrine Group Meeting, Eli Lily

Advisory Boards: Novo Nordisk Pediatric Expert Obesity National Advisory Board, Growth Hormone Pediatric Endocrinology National Advisory Board

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