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ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes in children and adolescents

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Abstract

Since the 2018 ISPAD guidelines on this topic, follow-up of large cohorts from around the globe have continued informing the current incidence and prevalence of co-morbidities and complications in young adults with youth-onset type 2 diabetes (T2D). This chapter focuses on the risk factors, diagnosis and presentation of youth-onset T2D, the initial and subsequent management of youth-onset T2D, and management of co-morbidities and complications. We include key updates from the observational phase of the multi-center Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial, the SEARCH for Diabetes in Youth (SEARCH) study and new data from the Restoring Insulin Secretion (RISE) study, a head-to-head comparison of youth onset vs adult-onset T2D. We also include an expanded section on risk factors associated with T2D, algorithms and tables for treatment, management, and assessment of co-morbidities and complications, and sections on recently approved pharmacologic therapies for the treatment of youth-onset T2D, social determinants of health, and settings of care given COVID-19 pandemic.

KEYWORDS
type 2 diabetes, pediatrics, obesity, youth

1 | WHAT IS NEW/DIFFERENT

Since the 2018 ISPAD guidelines on this topic, follow-up of large cohorts from around the globe have continued informing the current incidence and prevalence of co-morbidities and complications in young adults with youth-onset type 2 diabetes (T2D). In these 2022 guidelines, we include:

- Key updates from the observational phase of the multi-center Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) clinical trial, the SEARCH for Diabetes in Youth (SEARCH) study and new data from the Restoring Insulin Secretion (RISE) study, a head-to-head comparison of youth onset versus adult-onset T2D
- An expanded section on risk factors associated with T2D
- Algorithms and tables for treatment, management, and assessment of co-morbidities and complications
- Sections on recently approved pharmacologic therapies for the treatment of youth-onset T2D, social determinants of health (SDOH), and settings of care given COVID-19 pandemic

2 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

2.1 | Screening for T2D

- Targeted screening to identify cases of T2D can be considered after onset of puberty or after 10 years of age in youth who have a body mass index (BMI) ≥85th percentile for age and sex and risk factors for T2D. **A**
- Fasting plasma glucose (FPG), 2-h plasma glucose after 75-g oral glucose tolerance test (OGTT), or Hemoglobin A1c (HbA1c) can be used to screen for T2D. **B**
- If tests are normal, repeat screening should occur at a minimum every 3 years. Annual screening may be necessary if (BMI) is increasing, the cardiometabolic risk profile is worsening, there is a strong family history of T2D, or evidence of pre-diabetes. **C**
- Clinical assessment of other obesity-related comorbidities (hypertension (HTN), dyslipidemia, non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), obstructive sleep apnea (OSA)) should be conducted when considering screening for T2D in youth. **A**

2.2 | Diagnosis of T2D

- Symptoms of hyperglycemia and one of the following laboratory values and negative islet autoantibodies. **B**
  - FPG ≥126 mg/dl (7.0 mmol/L)
  - 2-h plasma glucose on an OGTT ≥200 mg/dl (11.1 mmol/L). OGTT: 1.75 g/kg (max 75 g) anhydrous glucose dissolved in water
  - Random plasma glucose ≥200 mg/dl (11.1 mmol/L)
  - HbA1c ≥ 6.5% (48 mmol/mol) by a NGSP-certified device, standardized to the DCCT assay

2.3 | Diabetes education for T2D

- Education should be provided soon after diagnosis in a culturally sensitive and age-appropriate manner and should include diabetes self-management education that is specific for pediatric T2D. **B**
- Education should be given by team members with expertise and knowledge of the unique dietary, exercise, and psychological needs of youth with T2D. **C**
- The education and treatment team for T2D ideally should include a pediatric endocrinologist, certified diabetes educator, a nutritionist, a psychologist and/or social worker, and an exercise physiologist all of whom provide consistent education to families. **E**
- Education content should include the pathophysiology and treatment of T2D in youth, building skills of healthy eating, knowledge about macronutrients, portion sizes, food label reading, blood glucose monitoring and in some cases ketone testing. **E**
- Education should include development of problem-solving skills, risky behaviors reduction (drugs, alcohol, smoking, and vaping), contraceptive counseling and living with diabetes. **E**
- Education should address any negative perceptions that might impact diabetes care. **E**
- Schools should be educated on the management of T2D to optimize support of the young person's diabetes management. **E**

2.3.1 | Diet modification should be advised for the entire family and should focus on

- Eliminating sugar-sweetened soft drinks and juices. **B**
- Reducing the intake of foods made from refined, simple sugars and high fructose corn syrup (HFCS). **B**
- Limiting intake of high-fat and/or calorie dense foods. **B**
- Reducing the intake of processed, prepackaged, and convenience foods. **E**
- Limiting portion sizes. **E**
- Reducing meals eaten away from home. **E**
- Increasing vegetable intake and limited use of fruit as a substitute for high-calorie and low nutrient foods. **E**
- Changing staple foods from enriched white rice and white flour to brown rice and whole grains with lower glycemic index to promote gradual absorption of glucose with meals. **E**

2.3.2 | Diet education

- Teaching families to interpret nutrition fact labels. **E**
- Emphasizing healthy parenting practices related to diet and activity by promoting parental modeling of healthy eating habits, while avoiding overly restricted food intake. **E**
- Encouraging positive reinforcement of all goals achieved (e.g., no or minimal weight gain, reduction in high caloric drinks). **E**

- Promoting meals eaten on schedule, in one place, preferably as a family unit, and with no other activity (television, computer, studying), and minimizing frequent snacking. **E**
- Maintaining food and activity logs as beneficial for raising awareness of food and activity issues and for monitoring progress. **E**

2.3.3 | Exercise education

- Encourage youth to participate in at least 60 min of moderate to vigorous physical activity daily with muscle and bone strength training at least 3 days a week. **B**
- Reduce sedentary time, including watching TV, computer-related activities, texting, and video games to less than 2 h a day. **C**
- Address sedentary time spent doing schoolwork and identifying ways to incorporate physical activity. **E**
- Promote physical activity as a family event, including daily efforts to be physically more active, such as using stairs instead of elevators, walking or bicycling to school and to shop, and doing house and yard work. **E**
- Encourage positive reinforcement of all achievements and avoidance of shaming. **E**

2.3.4 | Sleep recommendations

- Discuss sleep timing, duration and quality. **E**
- Promote adequate quality sleep of 8–11 h a night according to age (9–11 h for children 5–13 years of age and 8–10 h for adolescents 14–17 years). **C**
- Encourage consistent wake up and bedtimes. **E**

2.4 | Glycemic monitoring and targets

- FPG targets are 70–110 mg/dl (4–6 mmol/L). **E**
- Postprandial blood glucose targets are 70–140 mg/dl (4–8 mmol/L). **E**
- HbA1c target is <7% and in most cases can be <6.5%. **E**
- Once glycemic goals have been achieved, limit at home testing depending on treatment regimen. If values consistently rise out of the target range, more frequent testing may be needed. **E**
- During acute illness or when symptoms of hyper- or hypoglycemia occur, youth should perform more frequent testing and contact their diabetes care team for advice. **E**
- Youth on insulin (or sulfonylureas) need to use self-monitoring blood glucose (SMBG) more frequently to monitor for asymptomatic hypoglycemia, particularly at night. **E**
- HbA1c concentration should be measured every 3 months, if possible. **E**

2.5 | Pharmacotherapy

2.5.1 | Initial therapy

- If HbA1c <8.5% (69 mmol/mol) – metformin is the treatment of choice together with healthy lifestyle changes. **A**
- In youth with ketosis/ketonuria/ketoacidosis or HbA1c ≥8.5% (69 mmol/mol), insulin is required initially with once-a-day intermediate-acting or long-acting basal insulin (starting dose 0.25–0.5 units/kg). **B**
- Transition to metformin only can usually be achieved over 2–6 weeks by decreasing the insulin dose by 30%–50% each time the dose of metformin is increased, with a goal of eliminating insulin therapy if this can be achieved with optimal glycemic management. **B**

2.5.2 | Subsequent therapy

- The goal of initial treatment should be to attain an HbA1c of <7.0% (53 mmol/mol) and in some situations <6.5% (48 mmol/mol), if this can be attained without hypoglycemia. **C**
- If a HbA1c of <7.0% (53 mmol/mol) is not attained, consider addition of a second agent. **C**
- The choice of a second agent should consider the degree of glucose lowering required, mechanism of action, cost and payer coverage, regulatory approval, route of administration, dosing regimen, weight loss anticipated, side effects, and impact on comorbidities and complications. **E**
- If HbA1c >10%, initiation or re-initiation of basal insulin is the preferred option. **C**

2.6 | Screening for comorbidities and complications

2.6.1 | Hypertension

- Blood pressure (BP) should be measured starting at diabetes diagnosis and at every subsequent visit, in the seated position, with feet on the floor, arm supported at heart level, after 5 min of rest with an appropriate-sized cuff. **A**
- Ideally, BP should be measured without recent stimulant use, caffeine or smoking. **B**
- BP should be measured with a mercury sphygmomanometer, aneroid sphygmomanometer, or oscillometric device. Abnormal oscillometric values should be confirmed with auscultation. **B**
- Ambulatory blood pressure monitoring (ABPM) can be considered if there is suspicion of white coat HTN or to confirm HTN. ABPM can also be used to assess response to treatment. **B**
- Echocardiographic evaluation is recommended in youth with confirmed HTN to assess for left ventricular target organ injury. **C**

- Initial management should include dietary changes consistent with the Dietary Approaches to Stop Hypertension (DASH) diet. **B**
- Initial pharmacological treatment should be monotherapy with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and the dose should be increased to achieve a BP in the normal range. **A**
- If an ACE inhibitor is not tolerated due to adverse effects (mainly cough), an ARB, calcium channel blocker, or diuretic are alternatives. **E**
- Combination therapy may be required if HTN does not normalize on single agent therapy. However, combining an ACE inhibitor and ARB is not recommended due to an excess of adverse events and no added clinical benefit. **E**
- If HTN is not responsive to initial medical therapy, evaluate for secondary causes of HTN. **E**
- The potential teratogenic effects of ACE inhibitors and ARBs in sexually active adolescent females must be discussed. **E**

2.6.2 | Dyslipidemia

- In youth with T2D, testing for dyslipidemia should occur once glycemic control has been achieved or after 3 months of initiation of medication regardless of HbA1c values, and annually thereafter unless abnormal. **B**
- If cholesterol levels are above goal, optimization of medications to improve blood glucose levels and diet recommendations consistent with the American Heart Association Step 2 Diet and the Cardiovascular Health Integrated Lifestyle Diet (CHILD-2 diet) should be implemented. **B**
- Statins should be initiated in youth with T2D who continue to have LDL-C levels >130 mg/dl (3.4 mmol/L) after a 6-month trial of lifestyle change intervention. **B**
- Statin therapy has been shown to be safe and effective in youth and should be the first pharmacologic intervention. **A**
- Statin treatment should begin at the lowest available dose. **A**
- Obtain a lipid panel 4–12 weeks after initiation and following a change in dose. **B**
- If LDL cholesterol target levels are still not achieved after at least 3 months of regular statin use, then the dose may be further increased by 1 increment (usually 10 mg). Alternatively, a second agent such as a bile acid sequestrant or cholesterol absorption inhibitor can be added. **E**
- Initial treatment of elevated triglycerides (TG) (≥150 mg/dl or ≥1.7 mmol/L) should focus on improving blood glucose levels, limiting dietary fat and simple sugars, and weight loss. **C**
- If LDL-C is <130 mg/dl but TG levels are >400 mg/dl, fibrates should be initiated. **C**
- Concentrated fish oil can be considered but lipids should be carefully monitored as high-dose docosahexaenoic acid (DHA) can increase LDL-C. **C**
- Statin plus fibrate combination therapy is generally not recommended. **E**
- Low HDL-C levels in youth are not managed directly with medication; rather, physical activity, avoidance of smoking and a healthy diet should be encouraged. **E**
- The potential teratogenic effects of statins in sexually active adolescent females must be discussed. **E**

2.6.3 | Nephropathy

- Albuminuria screening using 3 first morning urine collections should occur at diagnosis and annually thereafter. **A**
- If urine albumin/creatinine ratio is confirmed to be >30 mg/g (3 mg/mmol) and BP is elevated or urine albumin/creatinine ratio is >300 mg/g (30 mg/mmol) irrespective of BP, an ACE inhibitor or ARB should be started and BP normalized. **B**
- Causes of renal disease unrelated to diabetes should be considered and consultation with a nephrologist obtained if severely increased albuminuria (albumin/creatinine ratio > 300 mg/g or 30 mg/mmol) or HTN is present. **E**
- A repeat urine albumin/creatinine ratio may be helpful 6 months after the start of ACE inhibitor or ARB blocker to ensure albuminuria is normalized. **E**
- If albuminuria is present, serum potassium concentration and renal function should be evaluated annually. **E**
- Cystatin C measurements as a marker of glomerular filtration rate are currently not recommended as they show high variability and are affected by age, gender, BMI and HbA1c levels. **E**

2.6.4 | Non-alcoholic fatty liver disease

- Liver enzymes (alanine transaminase [ALT], aspartate aminotransferase [AST]) should be measured at diagnosis and annually thereafter, and sooner if abnormal. **B**
- If liver enzymes remain >3 times the upper limit of normal after 6 months refer to a pediatric gastroenterologist for consultation to exclude other causes of elevated liver enzymes, imaging and/or liver biopsy. **B**
- The presence of NAFLD does not preclude the use of metformin. **B**
- Optimizing blood glucose levels and improving weight are required to adequately manage NAFLD. **C**

2.6.5 | Obstructive sleep apnea

- Symptoms of OSA should be assessed at diagnosis and annually thereafter, unless there is excessive weight gain which requires earlier review of OSA symptoms. **C**
- OSA can be initially evaluated using questions about snoring, sleep quality, apnea, morning headaches, daytime sleepiness, nocturia, and enuresis. **E**
- If symptoms are suggestive of OSA, the diagnosis of OSA is made by referral to a sleep specialist and performing a sleep study. **C**

- Nocturnal pulse oximetry can be an initial useful evaluation if there is limited access to a sleep study. **E**

2.6.6 | Polycystic ovary syndrome

- A menstrual history should be taken on every girl with T2D at diagnosis and every subsequent visit. **B**
- PCOS screening should occur at diagnosis in pubertal girls and yearly thereafter with evaluation of menstrual history (primary or secondary amenorrhea) and evidence of hyperandrogenism (hirsutism and/or moderate to severe acne and/or elevated free testosterone level). **B**
- PCOS is diagnosed based on the presence of oligo- or amenorrhea with clinical or biochemical evidence of hyperandrogenism after exclusion of other possible causes. **B**
- Pelvic ultrasound is not recommended for diagnosis of PCOS within 8 years post menarche. **B**

2.6.7 | Retinopathy

- Screen youth with T2D for retinopathy at the time of initial diagnosis and annually by an ophthalmologist or optometrist by comprehensive eye examination with dilated pupils or retinal photography. **A**
- More frequent examinations by an ophthalmologist may be required if retinopathy is present or progressing. **C**
- Management of retinopathy should also include optimization of blood glucose levels as well as treatment of dyslipidemia and HTN if present. **E**

2.6.8 | Neuropathy

- Foot examination (including sensation, vibration sense, light touch and ankle reflexes) at diagnosis and annually is recommended to detect neuropathy. **C**
- Youth with diabetes should be taught proper foot care. **E**
- Management should be individualized according to symptoms and signs; and referral to a neurologist should be considered if there are abnormal neurological signs. **E**

2.6.9 | Psychosocial health

- Youth with T2D should be screened for psychological co-morbidities including depression, diabetes distress, and disordered eating at diagnosis and at regular follow-up intervals. **B**
- Youth identified to have mental health concerns should be offered mental health support either in conjunction with the clinic or through community based mental health programs. **E**
- Providers should avoid stigmatizing language and promote contextualizing and understanding of the complexity of childhood onset T2D which encompasses more than lifestyle-based behaviors. **E**

2.7 | Social determinants of health

- Providers should determine the cultural, social, geographic, and economic barriers to implementing behavioral change and prescribe lifestyle modification in the life context of the youth and family. **E**
- Providers should consider household food security, housing stability and family financial resources when devising a treatment plan with the youth and family. **E**

2.8 | Transition of care

- Counseling should include diabetes self-management, smoking, vaping, alcohol use, pre-conception counseling for all females of child- bearing potential, and diabetes complications. **E**
- Assessment of readiness for transfer should include addressing socioeconomic barriers to healthcare access. **E**
- Provide structured transition protocols with specific and detailed guidance on the transition education content, transition plans, and specific adult provider referrals. **E**
- Transition to subspecialist diabetes care and multidisciplinary team when feasible. **E**

This chapter focuses on the risk factors, diagnosis and presentation of youth-onset T2D, the initial and subsequent management of youth-onset T2D, and management of co-morbidities and complications. This chapter does not cover the management of acute complications of T2D such as diabetes ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) as they are discussed in the ISPAD 2022 Consensus Guidelines Chapter 13 on Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State.

3 | PATHOPHYSIOLOGY AND RISK FACTORS

3.1 | Pathophysiology of T2D and differences between youth and adults

T2D in youth results from genetic, environmental, and metabolic causes that may differ among individuals and populations. Unlike type 1 diabetes (T1D), there is no autoimmune process leading to deficient insulin secretion in T2D. The pathophysiology of youth-onset T2D includes hepatic, peripheral and adipose tissue insulin resistance together with relative insulin deficiency due to impaired pancreatic beta (β)-cell function,[1–3] and hyperglucagonemia due to alpha (α)-cell dysfunction, as well as impaired incretin effect.[4] While youth-onset

T2D shares these pathophysiological features with adult T2D, some unique characteristics have been identified in youth versus adult T2D. Limited longitudinal data in youth with T2D, using the clamp methodology,[5] and the TODAY study, using fasting and OGTT surrogate estimates of insulin sensitivity and β-cell function[6] show that there is a relatively rapid deterioration in β-cell function, on average 20%–35% per year. These data contrast with the ~7%–11% per year decline in β-cell function reported in adults with T2D.[7] Such observations suggest that T2D in these younger individuals is a more severe and rapidly progressive condition than in adults.[1] Against this backdrop, the RISE consortium was formed.[8]

The RISE consortium tested interventions designed to preserve or improve β-cell function in prediabetes or early T2D (<6 months in youth and <1 year in adults) with head-to-head comparisons between youth and adults using shared methodologies to understand similarities and differences in disease pathogenesis between youth and adults.[8] Youth and adults with obesity and either impaired glucose tolerance (IGT) or recently diagnosed T2D were randomized to 3 months of insulin glargine followed by 9 months of metformin, or 12 months of metformin. Hyperglycemic clamps and OGTTs conducted at baseline, after 12 months of medication, and after 3 and 9 months of medication withdrawal assessed β-cell function.

The major similarities and differences between youth and adults with early T2D and IGT can be summarized as follows.

- Compared to adults, youth had around 50% lower insulin sensitivity, using both the hyperglycemic clamp and the inverse of fasting insulin concentration that was not due to race/ethnicity, sex, or BMI.[9,10]
- Youth exhibited hyper-responsiveness of the β-cell to both intravenous and oral glucose ingestion, with higher C-peptide and insulin responses despite similar glucose concentrations. These increased C-peptide and insulin responses in youth exceeded what would be needed to compensate for their markedly lower insulin sensitivity.[9–11] This severe insulin resistance in youth and the hyper-responsiveness of β-cells may play a role in the occurrence of diabetes at this young age.
- In youth, β-cell function deteriorated during treatment and after treatment withdrawal, resulting in worse fasting and 2-h OGTT glucose levels with no difference between the two treatment groups. Thus, neither metformin nor glargine followed by metformin prevented worsening β-cell function in youth. In adults, β-cell function improved during treatment, though similar to youth this was not maintained after treatment withdrawal.[12,13]
- Glycemic worsening was more common among youth than in adults; 17.8% versus 7.5% at month 12, and 36% versus 20% at month 21 respectively.[14] While in both youth and adults, lower baseline β-cell responses predicted glycemic worsening, in youth higher baseline HbA1c and 2-h plasma glucose concentrations were additional predictors of glycemic deterioration. This was also the case in the TODAY study, where baseline HbA1c and β-cell function were predictors of worsening glycemic control and the need for insulin.[6]
- α-cell dysfunction was essentially similar in youth and adults with IGT or recently diagnosed T2D and did not explain the differences in β-cell function and insulin sensitivity between youth and adults.[15]

3.2 | Risk factors

Information gleaned from several large cohort studies suggest that the risk factors associated with youth-onset T2D are similar to those associated with later onset T2D, but key differences exist as discussed below.[16–19] These risk factors and the clinical correlates of youth-onset T2D underlie the currently recommended risk-based screening approaches. Individually, they also serve to alert the provider to the child or adolescent who might be at risk. Risk factors that can be modified remain important targets for T2D prevention in children and young adults.

3.2.1 | Race/ethnicity

Youth-onset T2D occurs in all racial/ethnic groups, but with a disproportionally high incidence and prevalence in Native American, Canadian First Nation, Indigenous Australian, African-American, Hispanic, East and South Asian, Middle Eastern and Pacific Islander populations. Of youth age 10–19 years-old with diabetes in the United States, the SEARCH study reported T2D accounts for 46% of new diabetes cases in Hispanic, 58% in African-American, 70% in Asian and Pacific Islander, and 86% Native American youth, but only 15% of diabetes cases in non-Hispanic white youth.[20] In other countries, the proportion of youth-onset T2D is reported to be 66% in Indigenous Australians[21] and 68.6% in China.[22]

Some of the highest reported prevalence rates of youth-onset T2D is in the First Nations people in Canada (821/100,000 ages 0–18 years) and in northern Australia (670/100,000 age < 24 years), in African-American and Hispanic populations in the US, and in South America (ranging 79–3300 per 100,000).[23–27] Some of the lowest reported prevalence rates are seen in Europe and the United Kingdom (ranging 0.6–1.4 per 100,000),[28–30] where majority populations are white.[28] Prevalence estimates of youth-onset T2D differ by region[23,28] and may be explained by methodological differences in case capture, variations in childhood obesity rates, cultural, environmental, and/or other SDOH.

3.2.2 | Obesity, nutrition, activity, and sedentary time

Obesity is a risk factor for the development of youth-onset T2D and contributes to insulin resistance. Data from the United States suggest a strong inverse relationship between age of diabetes onset and BMI.[31] In accordance, the SEARCH study found the prevalence of obesity and overweight in youth-onset T2D was 79.4% and 10.4% respectively, and similar proportions are reported in European

cohorts.[32,33] However, there is considerable heterogeneity and for some ethnicities the relationship of obesity to age of onset of T2D is less clear. In youth-onset T2D in South Asian urban children, 50% were normal weight (<120% weight for height).[34] In Taiwan, obesity was present in 37.9% and 39.5% respectively for school aged boys and girls with T2D.[35] Japanese children with youth-onset T2D are thinner than Caucasian children with youth-onset T2D.[36] As in adults, weight gain may be poorly tolerated metabolically given ethnic specific differences in body fat distribution on a background of poorer β-cell secretory reserve.[36–38]

The causes of excess adiposity in youth are complex. Dietary factors are important; consumption of energy-dense foods and sugar-sweetened beverages, often with HFCS, are commonly seen in youth with T2D.[39] Although evidence that specifically links HFCS to obesity in children is varied, evidence supports the hypothesis that fructose is especially detrimental to metabolic health and thus increases risk for T2D.[40] In a global ecological study, countries with higher availability of HFCS, have a higher prevalence of T2D in adults, independent of obesity.[40] Disordered eating in the context of obesity may also be contributory. In the TODAY study, 30% of youth with T2D reported binge eating.[41] Low physical activity, increased sedentary time, and excess screen time also contribute to obesity, insulin resistance and diabetes risk.[42,43] Currently, evidence for efficacious interventions targeting lifestyle changes in the prevention of youth-onset T2D are lacking.[44]

3.2.3 | Age, sex, and puberty

The incidence of youth-onset T2D is extremely low among pre-pubertal children and is rarely seen under 10 years of age except in native Americans, First Nations Canadians and Indigenous Australians.[45] The incidence rises gradually at puberty, attributable to the physiological insulin resistance characteristic of puberty.[46] Consistent with this is the observation that the mean age of onset of youth-onset T2D is earlier for girls than boys, corresponding with the age of peak pubertal insulin resistance for each sex.[16,47]

Both prevalence and incidence rates are higher in girls than boys, a sex difference that is not seen in later onset T2D. The prevalence ratio of girls to boys is reported as 6:1 for First Nations youth in Canada, 5:1 for Pima Indian, 3:1 for Mexican Americans and 1.2:1 for Japanese.[35,48,49] Similar sex differences are found in Taiwan but not in studies from China.[22,35,50] These sex differences are not well understood and may be due to differential sex-hormone effects, undiagnosed polycystic ovary syndrome (PCOS) which is a known risk factor for youth-onset T2D (see section on Co-morbidities and Complications below), divergent post pubertal weight gain and behavioral patterns, or sex specific cultural approaches to health.

3.2.4 | Family history and genetics

In youth-onset T2D, an increased familial clustering of diabetes is seen, with a high prevalence of T2D in first- and second-degree relatives, even when monogenic forms are excluded. This observation, supported by the high concordance rates of T2D in identical twins, and the disproportionate prevalence of youth-onset T2D in certain racial and ethnic groups, points to heritability and the impact of the shared environment.[51,52] In healthy white children, detailed hormonal and metabolic investigation revealed a less-favorable metabolic phenotype characterized by reduced insulin sensitivity and reduced compensatory β-cell secretory function in youth with a first-degree relative with T2D.[53] These metabolic differences in those with a family history were demonstrable as early as the first decade of life, supporting the notion of a heritable, susceptible, metabolic phenotype upon which additional stressors (puberty, obesity, sedentary lifestyle, SDOH) may combine and ultimately result in youth-onset T2D.

Recently, the First Genome-Wide Association Study (GWAS) for T2D in Youth identified seven genome-wide significant findings in a multi-ethnic cohort, including variants in or near *TCF7L2*, *MC4R*, *CDC123*, *KCNQ1*, *IGF2BP2*, *PHF2*, and *SLC16A11* that had previously been identified in GWAS studies in adult T2D, with similar or increased effect sizes. Two novel loci were identified in *PHF2* and *CPEB2* but, overall, the results suggest that the genetic landscape of youth and adult onset T2D overlap.[54] Other than a private genetic variant identified in Oji-Cree Native Canadians that predisposes to T2D in youth,[55] currently the evidence does not support a different genetic predisposition or increased burden of risk associated genes in youth-onset T2D compared to T2D in adults. Additional studies to assess the effect of gene–environment interactions and epigenetic modifiers may underscore variations in susceptibility and the earlier onset of T2D in youth.

3.2.5 | Early life determinants: nutrition, maternal diabetes and obesity

Intrauterine exposures to maternal diabetes (both pre-gestational and gestational diabetes [GDM]) and maternal obesity/fetal over-nutrition are associated with development of T2D in offspring.[56,57] Notably, in the TODAY cohort, one-third of youth with T2D were born to mothers with pre-existing diabetes or GDM.[16] In a multi-ethnic US case control study of youth-onset T2D, exposure to maternal GDM or pre-gestational diabetes and maternal obesity were independently associated with T2D in adolescents (OR 5.7 and 2.8 respectively), and adjustments for socioeconomic factors and other perinatal factors did not alter these associations.[58] Evidence from other populations including First Nation Canadian Youth, Pima Indians and families with monogenic diabetes, suggest that the risk of an earlier age of onset of diabetes inferred by in-utero exposure, is over and above any inherited genetic risk.[56,59,60] Maternal under-nutrition, intrauterine growth retardation, and low birthweight are also associated with an increased risk of obesity and T2D in later life in some populations.[61] The early post-natal environment, and the timing of catch-up growth in underweight offspring, may also impact this overall risk; weight gain during the first 4 months of life is associated with an increased risk of overweight at age 7 years.[62] Mitochondrial damage, endoplasmic reticulum stress, and epigenetic modifications may underlie these observations, but many mechanistic questions remain.[63]

TABLE 1 Risk based screening for T2D in Children and Adolescents

Screening tests in youth should be considered after the onset of puberty or age 10 years, whichever is earlier, in youth with BMI≥85th percentile for age and sex with one or more of the following:
• Family history of T2D in the first- or second-degree relative.
• Race/ethnicity (Black, Native American, African, Latin American, Asian, Middle Eastern Pacific Islander, Australian Indigenous, Canadian First Nations).
• Signs of insulin resistance (acanthosis nigricans, HTN, dyslipidemia, polycystic ovary syndrome), low birth weight (small for gestational age) or high birth weight.
• Maternal history of T2D or gestational diabetes during the child's gestation.
• Current use of weight promoting atypical antipsychotic agents.[74–78]

TABLE 2 Diagnosis of pre-diabetes in Children and Adolescents

Diagnosis	Laboratory values
Impaired fasting glucose (IFG)	Fasting plasma glucose (FPG) 100–125 mg/dl (5.6–6.9 mmol/L)
Impaired glucose tolerance (IGT)	2-h plasma glucose is >140–199 mg/dl (7.8–11.0 mmol/L) after an OGTT (after 1.75 g/kg (max 75 g) anhydrous glucose dissolved in water).
Elevated A1c	HbA1c 5.7%–6.4% (39–47 mmol/mol) obtained from a laboratory based, diabetes control and complications trial (DCCT) aligned, National Glycohemoglobin Standardization Program certified methodology.

Maternal weight before and during pregnancy has been described as a possible 'checkpoint' for prevention of T2D. Mid-pregnancy maternal BMI and glycemia are independently and additively associated with direct adiposity measures in 10–14 year old children.[64] Furthermore, gestational glucose intolerance categories, that do not meet the threshold for GDM, were associated with increased risk of weight, obesity and severe obesity in the offspring in late adolescence.[65] It has been suggested that some pre-conceptual weight loss may modify obesity-related factors transmitted via the intrauterine environment.[66] Breastfeeding may be protective against prediabetes and metabolic syndrome in offspring exposed to GDM in utero. Compared with GDM offspring who were not breastfed, GDM offspring who were breastfed had lower odds of persistent prediabetes and metabolic syndrome.[67]

3.2.6 | Cardio-metabolic risk factors and psychological health

HTN, dyslipidemia, NAFLD, PCOS and OSA are co-morbidities often seen in youth with T2D. The presence of these conditions in childhood may also identify individuals at increased risk to develop youth-onset T2D. A bi-directional relationship between psychological health, particularly depressive disorders, and T2D is also seen. These relationships are discussed in the section on Co-morbidities and Complications.

4 | SCREENING AND DIAGNOSIS OF PRE-DIABETES AND TYPE 2 DIABETES

4.1 | Screening for T2D

Early detection and intervention of T2D can prevent or delay microvascular complications and is associated with better outcomes in adults,[68] though evidence is lacking in youth. Screening of the general population or of the population of all overweight/obese youth for T2D is unlikely to be cost-effective. In the United States, the country with the highest prevalence of youth-onset T2D, screening based on fasting and post-challenge glucose in high-risk youth with obesity identified <1% with T2D.[69,70] The utility of screening of specific populations where there are higher rates of T2D in youth also remains unclear. Urinary glucose screening of 1,500,000–3,000,000 school age children in Japan between 1975–2015 only identified 301 students with T2D.[71,72]

Risk based screening for youth is recommended, see Table 1.[68] Testing can be considered in specific high-risk populations before age 10 under appropriate clinical circumstances.[45,73]

4.2 | Diagnosis of pre-diabetes

There are individuals whose glucose levels do not meet the criteria for diabetes but are too high to be considered normal. Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes, Table 2.[68] Pre-diabetes has been used to recognize the high risk for progression to T2D chronic kidney disease and cardiovascular disease in the adult population. It should be noted none of the diagnostic criteria have been specifically validated in youth and are all extrapolated from adult definitions.[79]

The World Health Organization (WHO) definition of IGT is consistent with the ADA definition; however, the WHO definition of IFG, 6.1–6.9 mmol/L (110–125 mg/dl), differs from the ADA definition.[80] It is important to note individuals who meet the criteria for IGT or IFG may manifest hyperglycemia only when challenged with a substantive glucose load and may be euglycemic in their daily lives, as shown by normal or near-normal HbA1c levels. Additionally, 2.2% of normal weight youth had elevated HbA1c and fasting glucose concentrations suggesting these adult criteria should be applied with caution.[81] Notably, there were differences by race/ethnicity; 7.1% of normal weight black youth have an HbA1c ≥5.7%, and only 1.3% of Hispanic and 0.1% of white youth have an HbA1c in the prediabetes range.[81]

Very few longitudinal data are available on the natural history and rate of progression of prediabetes to T2D. A Cochrane Database Systematic Review showed that the pooled cumulative incidence of T2D

TABLE 3 Criteria for the diagnosis of T2D in Children and Adolescents.

Symptoms of hyperglycemia, one of the following laboratory values and negative islet autoantibodies[a]. B
• FPG ≥126 mg/dl (7.0 mmol/L)
• 2-h plasma glucose on an OGTT ≥200 mg/dl (11.1 mmoL/L). OGTT: 1.75 g/kg (max 75 g) anhydrous glucose dissolved in water
• Random plasma glucose ≥200 mg/dl (11.1 mmol/L)
• HbA1c ≥ 6.5% (48 mmol/mol) by a NGSP-certified device, standardized to the DCCT assay.

[a]Hyperglycaemic symptoms include polyuria, polydipsia, nocturia, unexplained weight loss and general fatigue. In the absence of unequivocal hyperglycemia symptoms, laboratory testing should be confirmed using a different test from the same sample or on a different day.

in youth, usually associated with IGT at baseline and with follow-up of 1–10 years, is 1%–56%.[64] There is a high rate of spontaneous remission of prediabetes in youth with obesity once the insulin resistance of puberty wanes.[82] There was regression from prediabetes to normoglycemia within a follow-up period of 1–4 years from 45% to 81%.[64] In 547 overweight/obese youth aged 14.5 ± 2.2 years (70% Hispanic), with baseline HbA1c in the prediabetes and T2D range, 76% had a follow-up HbA1c available at a median of 12–22 months. The percent with diabetes-range HbA1c was 4% in youth with baseline HbA1c values of 5.7%–5.9%, 8% with baseline HbA1c of 6.0%–6.4%, and 33% with baseline HbA1c of ≥6.5%.[83]

Lifestyle change, with decreased caloric intake and increased physical activity, is shown to be effective for youth with pre-diabetes.[84] However, even when a high-quality lifestyle intervention, which was provided by appropriate and adequately trained personnel with ample funding in the TODAY study, there was not a sustained change in behavior.[85] Owing to insufficient data and recent data from the RISE study, the use of metformin and/or insulin in youth with prediabetes is not currently recommended.[86]

4.3 | Diagnosis of diabetes

4.3.1 | Clinical presentation

The presentation of youth-onset T2D can vary from asymptomatic hyperglycemia detected through screening at the time of a routine physical examination to DKA in up to 25% of patients[87–89] or HHS.[90] These latter two presentations can entail significant risk for morbidity and mortality if not recognized and appropriately treated. Increasing rates of DKA at presentation of new onset T2D have been reported during the COVID-19 pandemic.[91–93]

4.3.2 | Laboratory investigations

The diagnosis of T2D requires two steps: confirmation of the presence of diabetes followed by determination of diabetes type (Table 3). Diabetes in youth should be diagnosed using the ADA or ISPAD criteria.[68,94] HbA1c is universally available, can be performed any time of day, but should utilize a laboratory based, DCCT aligned, NGSP certified methodology and not a point-of-care method. Point-of-care HbA1c testing should be reserved for assessment of glycemic control in the clinic.[68] In the absence of unequivocal hyperglycemia symptoms, laboratory testing should be confirmed using a different test from the same sample or on a different day. The presence of clinically relevant comorbidities should be assessed at the time of diagnosis or once glycemic control has been achieved and include evaluation for HTN, dyslipidemia, NAFLD, and renal impairment (Table 6).

None of the diagnostic criteria for diabetes have been specifically validated in youth and are all extrapolated from adult definitions.[79] Marked discordance between HbA1c and plasma glucose levels should raise the possibility of HbA1c assay interference. Studies using continuous glucose monitoring (CGM) in youth with obesity show that HbA1c and OGTT are equally effective at identifying glycemic abnormalities on CGM, but the glycemic patterns differ, with abnormal HbA1c associated with higher average glucose and abnormal OGTT associated with more frequent peaks.[95] The OGTT has poor reproducibility in youth with concordance rates of less than 30% between tests performed a few weeks apart.[96] A recent analysis by the National Health and Nutrition Examination Survey (NHANES) data supports using HbA1c for screening of high-risk youth.[70]

4.3.3 | Evaluation of autoimmunity

Islet autoantibody testing for Glutamic Acid Decarboxylase (GAD), Islet antigen-2 (IA-2), Zinc Transporter 8 (ZnT8) and Insulin (IAA), in those who have not received insulin treatment, should be done, where available, in all youth with the clinical diagnosis of T2D because of the high frequency of islet autoimmunity in youth with clinically diagnosed T2D. Studies have shown that autoantibodies are present in 10%–20% of youth clinically diagnosed with T2D.[97–101] The presence of antibodies predicts rapid development of insulin requirement,[98] as well as risk for development of other autoimmune disorders. Diabetes autoantibody testing should also be confirmed in overweight/obese pubertal children with a clinical picture of T1D (weight loss, ketosis/ketoacidosis), some of whom may have T2D and can be weaned off of insulin for extended periods of time with optimal glycemic control.[102,103] Youth with hyperglycemia and the presence of islet auto antibodies are best classified as having T1D.

4.3.4 | Evaluation of monogenic diabetes

Approximately ~2.5%–6.5% of individuals in some populations diagnosed with T2D have identifiable mutations associated with monogenic diabetes (MODY).[104,105] Distinguishing between T2D and MODY has important clinical implications (50% likelihood of offspring being affected, better prognosis, fewer employment restrictions and possible avoidance of needing insulin) so that genetic testing should be considered where appropriate and available.

Youth-onset T2D that appears to be mild, is not associated with classical T2D risk factors or co-morbidities and is not responsive to metformin should raise suspicion of the possibility of a form of MODY. Please refer to ISPAD 2022 Consensus Guidelines Chapter 4 on Monogenic Diabetes.

5 | MANAGEMENT

5.1 | Education

Diabetes education is very important and should focus on behavioral changes (diet and physical activity), use of medications and side effects, and SMBG.[106–108] Dedicated extra time and the use of an interpreter will be required for education sessions if the young person and their families come from different language speaking areas or countries. Written education materials are useful but are limited in pediatric T2D. The materials used to provide diabetes education in the TODAY clinical trial were specifically designed to be age and culturally appropriate for English- and Spanish-speaking North American populations and are available for public use in both English and Spanish on the TODAY public website (portal.bsc.gwu.edu/web/today). They have also been modified and made available by the American Diabetes Association as a program called Be Healthy TODAY; Be Healthy for Life (http://www.diabetes.org/living-with-diabetes/parents-and-kids/children-and-type-2/). Specific strategies and issues to consider when educating Indigenous groups were described in the recent Australasian guidelines for youth with T2D and include engagement of youth/families/communities, language considerations, use of a whole family approach, and addressing psychosocial health, food security and social welfare.[78] Also see the ISPAD 2022 Clinical Practice Guidelines Chapter 6 on Diabetes Education in Children and Adolescents. Care providers should acknowledge that the initial uncertainty in the diagnosis of diabetes type in some youth can be confusing and anxiety-provoking for the youth and family. The anxiety can be minimized by emphasizing the importance of normalizing blood glucose using whatever therapy is appropriate to the metabolic circumstances of the specific individual, regardless of the eventual 'type' of diabetes.

5.1.1 | Diet

Diet modification for youth with T2D should focus on education for youth and their families (and if possible, extended family). Elimination of sugar-sweetened soft drinks and juices should be emphasized. Complete elimination of these drinks and substitution of water and other calorie-free beverages can result in substantial weight loss. FDA-approved nonnutritive sweeteners (NNS) may help youth limit carbohydrate and energy intake,[109] but evidence that NNS can provide sustained reduction in weight or insulin resistance is lacking. Other changes include eliminating intake of foods made from refined, simple sugars and HFCS, and an emphasis on decreasing portion sizes and increasing vegetable intake. One study found a very-low-energy diet was associated with weight loss and elimination of insulin therapy in small number of youth with T2D.[110] Currently, there are no data to support very low calorie, low carb diet, keto diet or intermittent fasting in youth-onset T2D.

Families should also be taught to interpret nutrition fact labels. The goal should be to emphasize healthy parenting practices related to diet and activity by promoting parental modeling of healthy eating habits, while avoiding overly restricted food intake. Promoting meals eaten on schedule, in one place, preferably as a family unit, and with no other activity (television, computer, studying), and minimizing frequent snacking is also helpful.

Involvement of a nutritionist/dietitian with knowledge and experience in nutritional management of youth with diabetes is necessary. A nutritionist/dietitian with experience concerning the unique characteristics of youth with T2D is desirable. The family should be encouraged to make dietary changes consistent with healthy eating recommendations, including individualized counseling for weight reduction, reduced carbohydrate and total and saturated fat intake, increased fiber intake, and increased physical activity. Additional dietary recommendations are provided in the ISPAD 2022 Consensus Guidelines Chapter 10 for Nutritional Management in Children and Adolescents with Diabetes.

5.1.2 | Physical activity

Exercise is an important part of the diabetes management plan. Regular exercise improves blood glucose levels, reduces cardiovascular risk factors, contributes to weight loss, and improve well-being.[111,112] Youth with T2D like all children, should be encouraged to participate in at least 60 min of moderate to vigorous physical activity daily with muscle and bone strength training on at least 3 days a week; this can be completed in several shorter segments. Specific, negotiated, enjoyable and achievable exercise prescriptions should be developed for each youth and family that are sensitive to family resources and environment. A family member or friend should be identified who is available to participate in physical activity with the youth. Promotion of physical activity as a family event, including daily efforts to be physically more active, such as using stairs instead of elevators, walking or bicycling to school and to shop, and doing house and yard work may also be helpful. The efficacy of exercise and lifestyle modification in youth-onset T2D may be less than expected and failure in improvement of fitness, HbA1c levels or weight may have a physiologic basis.[113]

Recommendations for youth should also include limiting sedentary time, including TV, computer-related activities, texting, and video games to less than 2 h a day.[114] Use of electronic entertainment and communication devices such as video games, computers, and smart phones are associated with shortened sleep duration, excess body weight, poorer diet quality, and lower physical activity levels.[114–116] Specific recommendations are given in the ISPAD 2022 Consensus Guidelines Chapter 14 for Exercise in Children and Adolescents with Diabetes.

5.1.3 | Sleep

Sleep timing, duration and quality should be discussed with youth and their families.[116,117] Adequate sleep should be advised according to age with 9–11 h for children 5–13 years of age and 8–10 h for adolescents 14–17 years.[78]

5.1.4 | Smoking and alcohol

While cigarette smoking is harmful to all youth, those with special healthcare needs are especially vulnerable to the negative health consequences of tobacco as a result of their compromised health status and disease, as well as treatment-related complications.[118] Additional research is needed to develop and examine the efficacy of interventions specifically targeting tobacco use among youth with T2D within healthcare settings. Youth should be asked at each visit if they are smoking, vaping or using other recreational drugs and counseled against initiation and the importance of cessation and provided resources for support. Similarly, the deleterious effects of the misuse of alcohol in the setting of diabetes and risk for fatty liver disease, as well as for hypoglycemia, should be discussed at each visit.

5.1.5 | Glycemic monitoring and targets

SMBG should be individualized and include a combination of fasting and postprandial glucose measurements with a frequency based on the medication(s) used, the HbA1c value, and available resources. Unlike in T1D, the evidence that SMBG has an impact on glycemic control in individuals with T2D is limited. The potential benefit versus cost of continuous glucose monitoring in this population also remains unclear.

5.1.6 | Pharmacologic therapy

The aims of therapy in youth-onset T2D are to improve glycemia; to prevent acute and chronic complications; to prevent metabolic decompensation; to improve insulin sensitivity; to improve endogenous insulin secretion and glucagon and incretin physiology, if possible; and to provide exogenous insulin when necessary while reducing the burden of chronic disease management. Furthermore, the choice of therapeutic approach should consider individual preferences, route of administration, potential side effects and the impact on comorbidities and cardiovascular risk. While many anti-hyperglycemic agents are approved for use in adults, until recently therapy in youth was limited to metformin in most countries and sulfonylureas in some. However, an increasing number of clinical trials of agents in youth-onset T2D have been completed or are nearing completion, resulting in the availability of more efficacy data and regulatory approval for two Glucagon-like peptide-1 (GLP-1) receptor agonists. All available agents are described below in Table 4, recognizing that some youth may benefit from their use off-label. However, newer agents are generally more expensive than the core therapies and, with few exceptions, evidence for their efficacy and safety in youth remains limited.

5.2 | Pharmacotherapy

5.2.1 | Initial treatment

Initial treatment of youth with T2D should include metformin and/or insulin alone or in combination determined by symptoms, severity of hyperglycemia, and presence or absence of ketosis/DKA. As in T1D, those with symptoms, particularly vomiting, can deteriorate rapidly and need urgent assessment and treatment. As part of the initial assessment and treatment in all youth for which the diagnosis of T2D is considered, islet autoantibodies should be obtained (Figure 1).

For youth with stable glycemia stable, defined as an HbA1c <8.5% (69 mmol/mol), metformin is the treatment of choice together with healthy lifestyle changes.[102,103] In youth with ketosis/ketonuria/DKA or HbA1c ≥8.5% (69 mmol/mol), insulin will be required initially. A variety of insulin regimens are effective, but once-a-day intermediate-acting or long-acting basal insulin (starting dose 0.25–0.5 units/kg) is often effective in attaining metabolic control, while minimizing burden. The primary adverse effect of insulin is weight gain. The risk of hypoglycemia should also be considered, but is uncommon. Metformin should be started at the same time and the dose titrated unless acidosis is present. Transition to metformin alone can usually be achieved over 2–6 weeks by decreasing the insulin dose by 30%–50% each time the metformin dose is increased, with a goal of eliminating insulin therapy if this can be achieved without loss of glycemic control. Data from the TODAY study indicate that 90% of youth with T2D can be successfully weaned off insulin and treated with metformin alone with attainment of glycemic targets.[102,103]

5.2.2 | Subsequent therapy (3+ months after diagnosis)

The goal of initial treatment should be to attain an HbA1c of less than 7.0% (53 mmol/mol).[119] In some situations a target of <6.5% (48 mmol/mol) is appropriate[120] if this can be attained without hypoglycemia, which is true for most youth with T2D. Long-term glycemic control is more likely to be achieved when therapy is intensified as needed to maintain the HbA1c target (treat-to-target) rather than waiting for the HbA1c to rise before intensifying therapy (treat-to-failure).[121] If the HbA1c target of <7.0% (53 mmol/mol) (ADA target) or <6.5% (48 mmol/mol) is not attained, the latter supported by data from TODAY within 4 months on metformin monotherapy,[120] addition of a second agent should be considered Figure 1 and Table 4. Choice of a second agent should consider degree of glucose lowering

TABLE 4 Non-insulin anti-hyperglycemic medications for the treatment of T2D.

Medication	Mechanism of action	Benefits	Adverse effects	Names and dosing	Special considerations	Percent HbA1c lowering[a]
Medications approved in youth						
Biguanides (Metformin)	Acts through AMP kinase in liver, muscle, and fat Reduces hepatic glucose production by decreasing gluconeogenesis and by stimulating peripheral glucose uptake	Oral, no risk of hypoglycemia An initial anorexic effect and may promote limited weight loss	Transient abdominal pain, diarrhea, nausea. Side effects attenuated by extended-release formulation. Lactic acidosis rarely reported	Begin with 500–1000 mg daily for 7 days. Titrate by 500 mg every 1–2 weeks, depending on tolerability, until the maximum tolerated dose or 1000 mg BID or 850 mg TID of the standard metformin preparation or 2000 mg once a day of extended-release metformin Liquid form available Standard preparations can be crushed Take metformin with food	Avoid in DKA, if eGFR <30 ml/min, cardiac or respiratory insufficiency, or receiving radiographic contrast materials. Caution in gastrointestinal illness with risk for dehydration.[119] Metformin may normalize ovulatory abnormalities in girls with PCOS and increase pregnancy risk.[122]	1%–2%
Glucagon-like peptide-1 (GLP-1) receptor agonist	GLP-1 is secreted by L-cells in the small intestine in response to food, increasing insulin secretion proportionate to blood glucose concentrations, suppressing glucagon, prolonging gastric emptying, and promoting satiety.	Subcutaneous Clinical trials in adults have shown reduced fasting and postprandial BG, weight loss, lower HbA1c and reduction in cardiovascular, renal events and mortality.[123–125] An oral form approved in adults	Initially nausea, vomiting, diarrhea, and infrequent dizziness, headache, and dyspepsia. C cell hyperplasia and risk for thyroid carcinoma in those with MEN	Current pediatric approved formulations are given as either once daily or weekly subcutaneous injections Liraglutide (Victoza 0.6–1.8 mg daily SC). Start with lower doses and increase to maximum tolerated dose. Extended release Exenatide, 2 mg once-weekly SC injection Dulaglutide once weekly SC, trial in children in progress (NCT02963766)	Discontinue if pancreatitis suspected. Do not use in combination with a DPP-4 inhibitor. Risk of hypoglycemia when used in combination with insulin (see product information)	0.5%–0.8% Ellipse trial showed Liraglutide group had 1% and 1.5% HbA1c lowering at 26 and 52 weeks, respectively.[126] Exenetide (Bydureon) 2 mg once a week lowered A1c by 0.85% A1c compared to placebo.[127]
Medications currently not approved in youth						
Sodium-Glucose Co-transporter 2 (SGLT-2) inhibitor	Inhibits renal tubular reabsorption of glucose, leading to increased urinary glucose loss, reduction in serum glucose, and weight loss.	Oral Weight loss, BP reduction, improved renal function, and cardiovascular outcomes in adults.[128–131]	Increased prevalence of genitourinary infections, particularly among women and uncircumcised men.[132] Potential risk of euglycemic diabetic ketoacidosis,[133] caution in youth with prior episode of DKA	Canaglifozin 100–300 mg/day Empagliflozin 10-25 mg/day Dapagliflozin 10 mg/day Ertugliflozin 15 mg/day Synjardy is a combination of empagliflozin and metformin	Consider discontinuing before surgical procedure to avoid potential DKA. Risk of volume depletion. Risk of hypoglycemia when used in combination with insulin (see product information)	1%–2%. Dapagliflozin use in youth with T2D did not show benefit relative to metformin ± insulin; although sub-analysis showed a 1.1% A1c lowering in youth that reported consistent use.[134]

(Continues)

TABLE 4 (Continued)

Medication	Mechanism of action	Benefits	Adverse effects	Names and dosing	Special considerations	Percent HbA1c lowering[a]
				Canaglifozin, trial in progress in children (NCT03170518).		
Thiazolidinedione (TZD)	Binds to nuclear PPAR gamma, ubiquitous orphan steroid receptors abundant in adipocytes. Increases insulin sensitivity in muscle, adipose, and liver tissue, with a greater effect on muscle glucose uptake than biguanides.	Oral Increases insulin sensitivity in muscle, adipose, and liver tissue, muscle glucose.	Weight gain, anemia, fluid retention (including congestive heart failure when used in combination with insulin).[135,136] Possible association with bladder cancer and fracture risk women.[137]	Pioglitazone: 15 mg can increase to 30 mg/day. 45 mg/day dose available, but limited additional benefit and increased side effects.	Can be useful in youth given their severe insulin resistance and normal cardiac function, particularly when metformin is not tolerated. Liver toxicity has not been seen with newer TZDs; instead may be beneficial in NAFLD.[138]	0.5%–1.3%
Dipeptidyl-peptidase 4 (DPP-IV) Inhibitor	Inhibit the enzyme that breaks down GLP-1, resulting in higher concentrations of GLP-1.	Oral Reduce fasting and postprandial BG. Unlike GLP-1 agonists no effect on gastric emptying, satiety or weight loss.	Upper respiratory infections, nasopharyngitis	Sitagliptin 100 mg/day Alogliptin 25 mg/day Saxagliptin 5 mg/day Linagliptin 5 mg/day	Should not be used in combination with GLP-1 agonist	0.5% Sitagliptin use in youth with T2D did not show benefit relative to metformin monotherapy.[139]
α-Glucosidase inhibitor (Acarbose, miglitol)	Reduces the absorption of carbohydrates in the upper small intestine by inhibiting breakdown of oligosaccharides, thereby delaying absorption in the lower small intestine.	Oral Reduce postprandial glucose rise	Flatulence Diarrhea Abdominal cramps	Must be given with meals Acarbose 25–100 mg three times a day. Miglitol 100 mg three times a day.	Particularly successful in countries where carbohydrates make up a substantial part of the diet.[140]	0.5%–1%
Sulfonylurea and Meglitinides	Sulfonylureas bind to receptors on the potassium/ATP channel complex causing potassium channels to close, resulting in insulin secretion. Meglitinides bind to a separate site from sulfonylureas on the potassium/ATP channel complex.	Oral Anti-hyperglycemic	Mild or severe hypoglycemia Weight gain May accelerate the loss of β-cell function.[141]	Meglitinides are prescribed for rapid enhancement of insulin secretion before meals[135] 1 mg taken once per day with breakfast or the first main meal of the day. -Max dose is 8 mg.		1.5%–2% A single pediatric clinical trial of a sulfonylurea (glimepiride) showed no superior efficacy to metformin and a greater degree of weight gain and hypoglycemia.[142]

[a]Indicates percent HbA1c lowering from adult studies unless specified in the table.

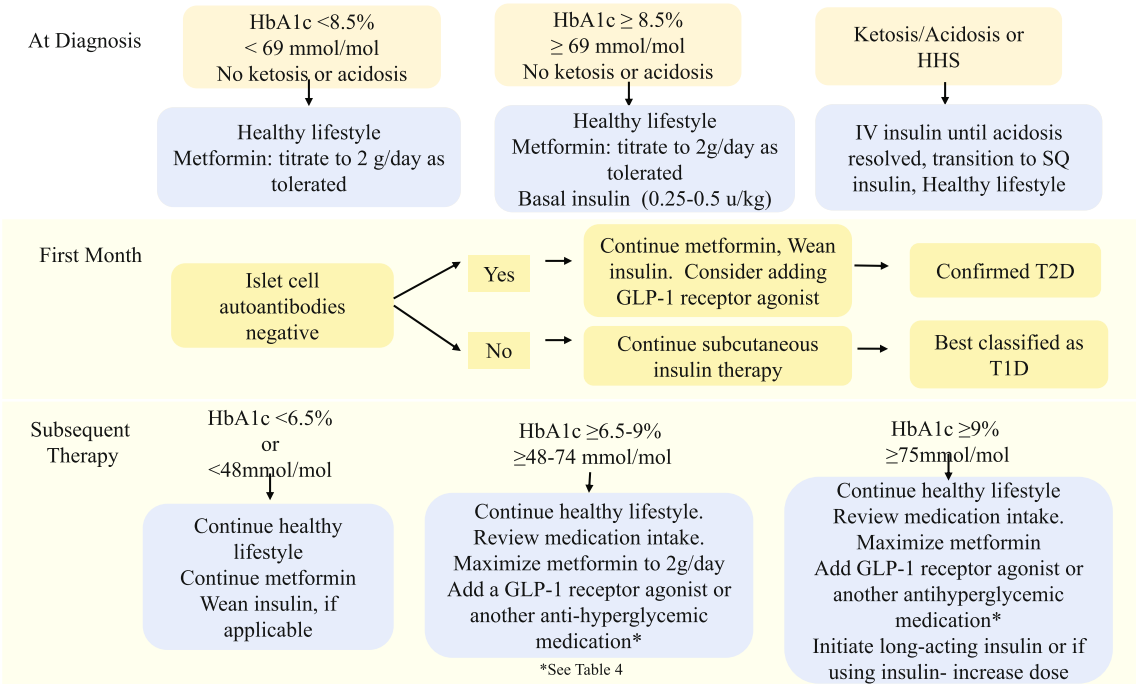

FIGURE 1 Management of T2D in Children and Adolescents. Initial management and subsequent therapy. Adapted from ADA Position Statement "Evaluation and Management of Youth-Onset Type 2 Diabetes". GLP-1, glucagon like peptide-1.

required, mechanism of action, cost and payer coverage, regulatory approval, route of administration, dosing regimen, weight loss anticipated, side effects, and impact on comorbidities and complications. With higher HbA1c values (Figure 1), initiation or re-initiation of basal insulin is the preferred option. The starting dose of basal insulin is 0.25–0.5 units/kg and the dose is titrated based on results of SMBG. If the glycemic target is not attained on a combination metformin and basal insulin at a dose of up to 1.5 units/kg/day, initiation of prandial insulin should be considered, with titration to reach a target HbA1c <7.0% (53 mmol/mol) or <6.5% (47.5 mmol/mol) provided the youth does not experience hypoglycemia.

5.2.3 | Additional treatment considerations

Medications for youth-onset T2D should be initiated in collaboration with a pediatric endocrine subspecialist. At each visit regular medication use should be assessed, especially before adding additional medications. Affordability of medications should also be considered. If side effects from medications occur, lowering the dose to the highest tolerated dose is acceptable.

Metformin

- Recent studies in adults indicate increased prevalence of vitamin B12 deficiency in adults taking metformin, but no cases of vitamin B12 deficiency were reported in the TODAY study.[143] Periodic monitoring of serum vitamin B12 levels should be considered especially in children on vegetarian diets.
- Gastrointestinal side effects are the main limiting factor for using Metformin even with the extended- release preparations.

Glucagon-like peptide-1 (GLP-1) receptor agonists

- Efficacy of the daily GLP-1 agonist, Liraglutide, in youth-onset T2D was studied in the Ellipse trial,[126] which demonstrated placebo-subtracted HbA1c lowering of 1% and 1.5% at 26 and 52 weeks, respectively. This glycemic reduction was accompanied by a small decrease in BMI z-score. Liraglutide (Victoza 0.6–1.8 mg a day) subsequently received approval by the FDA for use in youth 12–17 years of age.
- Higher dose Liraglutide (Saxenda 3 mg a day) has been approved for use in youth >12 years of age for weight loss.
- Recently, extended release exenatide (Bydureon BCise 2 mg) was approved as a once-weekly injection for youth 10–17 years of age based on data from the BCB114 study showing superiority to placebo in lowering HbA1c with a between-group difference of 0.85 percentage points ($p = 0.012$).[127]
- A clinical trial of another weekly GLP-1 receptor agonist (Dulaglutide) at a once-weekly dose of 0.75 mg or 1.5 mg was superior to placebo in improving glycemic control. The HbA1c lowering was −0.6 percentage points in the 0.75-mg group and −0.9 percentage points in the 1.5-mg group, $p < 0.001$ for both comparisons versus placebo and will likely result in FDA approval of another GLP-1 receptor agonist.
- It is unknown whether the long-term reductions in cardiovascular and renal events with GLP-1 receptor agonists will also be seen in youth, but the high prevalence and rapid accumulation of comorbidities and complications in youth-onset T2D make the potential

impact of these agents worth considering when choosing additional therapy (Table 4).

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

The use of SGLT 2 inhibitors in adults is associated with reduction in HbA1c approaching that seen with metformin.[121] Initial studies with dapagliflozin showed a 1.1% A1c lowering in those who reported consistent medication use compared to placebo.[134]

Thiazolidinedione (TZD)

- In the TODAY study, therapeutic failure rates were lowest in the group receiving metformin plus rosiglitazone (38.6%) versus metformin alone (51.7%) versus metformin plus lifestyle (46.6%).[144] Thus, addition of rosiglitazone to metformin decreased the risk for progression to insulin requirement by 23%.
- No significant side effects were identified in those treated with rosiglitazone and this agent could be useful in youth given their severe insulin resistance and normal cardiac function, particularly when metformin is not tolerated.
- Pioglitazone is the preferred TZD choice due to overall less cardiovascular side effects in adults compared to rosiglitazone.
- Higher risk of weight gain especially if used in combination with insulin can be a limiting factor for using a TZD.

5.2.4 | Bariatric surgery

Bariatric surgery should be considered for youth with obesity-related comorbidities, including T2D, particularly when medical therapy alone has been unsuccessful. A large US consortium of pediatric bariatric surgery centers compared their results to matched individuals treated with medical therapy in TODAY and showed greater and more sustained lowering of HbA1c with surgery and improvement/normalization of other comorbidities (dyslipidemia, HTN, kidney disease) in nearly all youth.[145,146] There is still a lack of long-term post bariatric surgery data (>10–15 years) in relation to re-operations, complications, bone health and nutritional deficiencies.

Currently, metabolic surgery is considered for post-pubertal youth with T2D and BMI ≥35 kg/m^2 who have uncontrolled glycemia and/or comorbidities despite lifestyle and pharmacologic treatment. Metabolic surgery should be undertaken only in centers of excellence with an established and experienced surgical, nutritional, behavioral, and medical support team and outcome data collection program. Additionally, the adolescent must be able to provide informed consent; that is, a full understanding of the procedure, risks/ benefits and the need for long-term follow-up.

5.3 | Setting of care

Until recently, diabetes education and diabetes care were largely provided in person, and telehealth was used less due to lack of equipment, infrastructure, and payer reimbursement.[147,148] In 2020, the COVID-19 pandemic brought telehealth to the forefront of medical care including diabetes education. Telehealth, defined as the use of any telecommunication techniques for providing health care by any health care professional, has emerged as a way for youth to safely seek care while maintaining social distancing and minimizing the risk of the virus transmission.[149] In a rapid review study including adults with T2D or T1D, women with diabetes in pregnancy and youth with T1D, virtual telehealth care for glycemic management elicited similar or superior HbA1c outcomes when compared with usual care, particularly for adults with T2D over a median follow up of 9 months. To date, there are no published studies evaluating outcomes of telehealth or tele-monitoring in youth with T2D. One study found capillary blood collection kits, suitable for home use, provided similar HbA1c results to those obtained from venous specimens,[150] providing an alternative to in clinic testing. Following the COVID-19 pandemic, it is likely that telehealth will be permanently integrated into practice. Providers need to take into consideration the reported benefits and barriers related to telehealth in youth with T2D, see Tables 5 and 6.

TABLE 5 Benefits and barriers to telehealth and telemonitoring in children and adolescents with T2D.

Benefits	Barriers
Telehealth avoids the costs, time, and inconvenience of travel and parking, helping to minimize time away from work and/or school.[149]	Lack of appropriate institutional infrastructure, technological support, and consistent payer reimbursement.
Individual, family, and provider satisfaction can be high.[151,152]	Lack of internet or mobile phone connectivity, or inexperience with technology
Telehealth services combined with advanced diabetes technology offer practical, convenient, and cost-effective alternatives to in-person quarterly visits as shown in pediatric T1D.[108]	Language/culture barrier and lack of interpreter services for foreign language speakers
In some youth, telehealth may decrease anxiety because they are seen in their familiar home environment.[147]	Limitations to upload glucose monitoring data and point of care HbA1c, physical examination, weight, and BP monitoring.[151,153]

6 | CO-MORBIDITIES AND COMPLICATIONS

6.1 | Hypertension

HTN is associated with endothelial dysfunction, arterial stiffness, left ventricular hypertrophy and diastolic dysfunction in youth at risk of or affected by T2D.[154–158] Of 699 U.S. youth enrolled in the TODAY study the prevalence of HTN at baseline was 11.6% and increased to 67.5% after 12 years of follow up.[159,160] Similarly, the SEARCH for Diabetes in Youth study found HTN in 27% (95% CI 18–36) of youth with T2D who

TABLE 6 Recommendations for screening of comorbidities/complications, social determinants of health, and high-risk behaviors.

Comorbidity/ complication	Intervals for screening	Screening test
Hypertension	Starting at diabetes onset and at every diabetes related clinical encounter	BP measurement using appropriately sized cuff
Dyslipidemia	Yearly starting at diabetes onset (ideally after glycemic control achieved or within 3 months of diagnosis)	Fasting lipids
Nephropathy	Yearly starting at diabetes onset	Albumin to creatinine ratio
NAFLD	Yearly starting at diabetes onset	ALT, AST
OSA	Yearly starting at diabetes onset	Symptoms: snoring, sleep quality, apnea, morning headaches, daytime sleepiness
PCOS	Yearly (unless there is menstrual irregularity) starting at diabetes onset in pubertal females	Menstrual cycle history and evidence of hyperandrogenism
Retinopathy	Yearly starting at diabetes onset	Comprehensive eye examination with dilated pupils or retinal photography
Neuropathy	Yearly starting at diabetes onset	Symptoms of numbness, pain, cramps and paresthesia and tests of vibration sense, light touch, and ankle reflexes
Psychosocial health	Starting at diabetes onset and then every diabetes related clinical encounter	Symptoms of depression and disorder eating; and use validated screening questionnaires or referral for further evaluation
Social determinants of health	Starting at diabetes onset and then every diabetes related clinical encounter	Assess food security, financial concerns, social/ school and community support
Smoking, vaping, drugs and alcohol use	Starting at diabetes onset and then every diabetes related clinical encounter	Clinical assessment on history
Pre-conception counseling	Starting at diabetes onset and then every diabetes related clinical encounter	History of sexual activity

TABLE 7 Blood Pressure Classification and Management in children and adolescents with T2D

Diagnosis	Age < 13 years (use age, gender and height BP charts)	Age ≥ 13 years	Initial Treatment	Subsequent Treatment
Normal	<90th percentile	<120/80 mm Hg	Healthy lifestyle Monitor BP at every visit	Healthy lifestyle Monitor BP at every visit
Elevated BP or prehypertension	≥90th percentile or 120/80 mm Hg (whichever is lower) to <95th percentile	120/<80–129/ <80 mm Hg	Weight loss, limitation of dietary salt to <2300 mg per day (consistent with the Dietary Approaches to stop hypertension [DASH] diet) and increased physical activity. Table 8	If sustained after 6 months, consider pharmacological therapy
Stage 1 HTN	≥95th percentile or 130/80 to <95th percentile +12 mmHg or 139/89 mm Hg (whichever is lower)	130/80 to 139/89 mm Hg		If sustained after 6 months, start ACE inhibitor or ARB.
Stage 2 HTN	≥95th percentile +12 mm Hg or ≥140/90 mm Hg	≥ 140/90 mm Hg		Evaluate for secondary causes of HTN and start pharmacological therapy once confirmed

had diabetes for 1.5 years[161] with incident HTN developing in an additional 35.6% at 7 year follow-up.[162] Using ambulatory BP monitoring HTN was present in 49.3% of Canadian youth with T2D.[163] The age adjusted prevalence of HTN in young adults with T2D in the SEARCH study was twofold higher (21.6%, 95% CI 17–1–26.9) compared to those with T1D (10.1%, 95% CI 8.6–11.9).[164] Higher rates of HTN in youth with T2D have been associated with male sex, higher BMI and older age. In the TODAY study males had 87% higher risk of developing HTN compared to females.[159] In general, BP lowering medications have historically been underutilized in youth with T2D[18,165] despite randomized control trials in adults unequivocally demonstrating that lowering BP reduces micro- and macrovascular complications and mortality.[166–168]

In youth <13 years, BP values should be compared to the reference ranges for age, sex, and height of normal weight youth[169] (Table 7). In youth ≥13 years, a simplified BP classification regardless of sex and height can be used. HTN should be confirmed at two additional visits. Initial

TABLE 8 Dietary approaches to stop hypertension (DASH) diet recommendations

Food group	Number of servings per day
Fruits and vegetables	4–5
Low fat milk products	≥2
Whole grains	6
Fish, poultry, and lean red meats	≤2
Legumes and nuts	1
Oils and fats	2–3
Added sugars and sweets (including sugar sweetened beverages)	≤1
Dietary sodium	<2300 mg per day

management should include dietary changes consistent with the Dietary Approaches to Stop Hypertension (DASH) diet (Table 8). Initial pharmacological treatment should be monotherapy with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) and the dose increased to achieve a BP in the normal range.[170–172].

The use of ACE inhibitors or ARBs in sexually active adolescent females must be carefully considered and the risks explicitly discussed, as these drugs are potentially teratogenic and not approved in pregnancy. Evaluation of HTN not responsive to initial medical therapy should include evaluation of secondary causes of HTN.[170]

6.2 | Dyslipidemia

The typical pattern of dyslipidemia in youth with T2D is characterized by high plasma TG concentrations, low HDL-C, and an increased concentration of atherogenic small dense LDL-C particles.[173] This occurs secondary to adipose insulin resistance resulting in increased free fatty acid release with an influx to the liver resulting in the overproduction of TG rich lipoproteins. A diet rich in saturated fat and carbohydrates exacerbates dyslipidemia in T2D.

In the TODAY clinical trial, 79.8% of T2D youth had a low HDL-C and 10.2% had high TG within a few months of T2D diagnosis.[16] High LDL-C defined as >130 mg/dl (3.4 mmol/L) or use of lipid-lowering medication rose from 4.5% at baseline to 10.7% over 36 months in the trial.[174] At long term follow-up of the cohort when diabetes duration was 13.3 ± 1.8 years, 51.6% had dyslipidemia.[160] Dyslipidemia rates are higher in T2D compared to T1D despite shorter diabetes duration. Elevated LDL-C and elevated TG were present in 8.6% and 50.0% of Canadian youth with T2D at a mean diabetes duration of 2.3 years compared to 3.5% and 7.5% of youth with T1D who had diabetes for 7.2 years.[163] The SEARCH study also found a greater prevalence of high TG, apoB and small dense LDL particles in youth with T2D compared to youth with T1D with continued worsening overtime in youth with T2D.[175–178] Higher rates of dyslipidemia and diabetes related complications by young adulthood[164] are the primary reason LDL-C treatment thresholds in youth with T2D are more aggressive compared to T1D.

Clinical trials focused on lipid lowering in youth-onset T2D have not been conducted. However, in a multinational study of youth with T1D (ages 10–16 years) statin use for at least 2 years was associated with reductions in total LDL-C and TG concentrations.[179] Combined insulin and metformin resulted in improvement in non-HDL-C and HDL concentrations in a retrospective study of 301 youth with T2D.[180] A randomized controlled trial of Liraglutide versus placebo in youth with T2D ages 10–17 years showed a decrease in VLDL-C and TG levels in the Liraglutide group at week 26 (ratio of change between Liraglutide and placebo, 0.82; 95% CI 0.72–0.94 and 0.83; 95% CI 0.72–0.95, respectively), but no differences at week 52.[126] Metabolic weight loss surgery in youth with T2D is associated with near normalization of lipids soon after surgery with sustained improvements observed beyond 5 years.[145,181,182] Given that dyslipidemia in youth tracks into adulthood[183] and dyslipidemia in youth with T2D is associated with retinopathy, neuropathy and nephropathy,[184] it is expected that lowering lipid levels will reduced future diabetes-related complications.

In youth with T2D, testing for dyslipidemia should occur once the HbA1c target has been achieved or after 3 months of initiation of medication regardless of the degree of control achieved. Annual testing should occur thereafter unless initial screening results are abnormal.[170] Initial screening can be done non-fasting with measurement of non-HDL-C.[185] Figure 2. If cholesterol levels are above goal, HbA1c should be optimized and lifestyle management should be intensified consistent with the American Heart Association Step 2 Diet and the Cardiovascular Health Integrated Lifestyle Diet (CHILD-2 diet).[170] Table 9. Statin initiation in youth with T2D who do not meet LDL targets after a 6 month trial of lifestyle change intervention aligns with overall recommendations for dyslipidemia in youth.[170] Statin therapy has been shown to be safe and effective in children ages 8 years and older with familial hypercholesterolemia. As such, statins should be the first pharmacologic intervention.[170] Statin treatment should begin at the lowest available dose. Obtain a lipid panel 4–12 weeks after initiation and following a change in dose. If LDL cholesterol target levels are still not achieved with at least 3 months of consistent use, then the dose may be further increased by one increment (usually 10 mg). Alternatively, a second agent such as a bile acid sequestrant or cholesterol absorption inhibitor can be added.

Side effects of statins include hepatic enzyme elevation and muscle toxicity. Concerns that statins may cause cognitive dysfunction is currently not supported by evidence in adults.[186] The use of statins in sexually active adolescent females must be carefully considered and the risks explicitly discussed, as these drugs are potentially teratogenic and not approved in pregnancy. Families should be counseled about potential medication interactions with statins. An LDL-C > 190 mg/dl (4.9 mmol/L) should prompt suspicion of familial hypercholesterolemia.

Initial treatment of elevated TG should optimize blood glucose control and weight and limit dietary fat and simple sugars (Table 9). Fasting TG >400 mg/dL (4.6 mmol/L) or non-fasting TG >1000 mg/dl

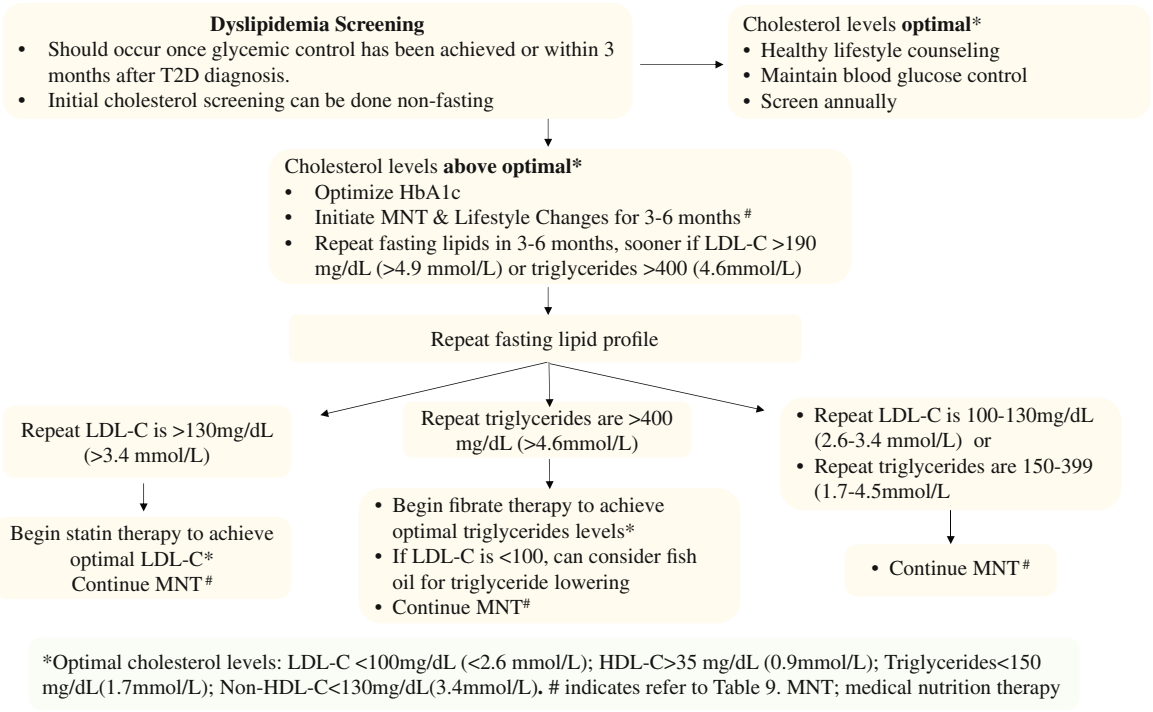

FIGURE 2 Dyslipidemia screening and treatment in youth with T2D. Figure includes initial screening, management, and subsequent therapy. MNT, medical nutritional therapy

TABLE 9 Medical nutrition therapy and lifestyle management for dyslipidemia

Medical nutrition therapy and lifestyle management for dyslipidemia
Limit total fat to 25%–30% of daily caloric intake
Limit saturated fat to <7% of daily caloric intake
Limit cholesterol to <200 mg cholesterol of daily caloric intake
Avoid trans-fat intake
For LDL-C levels above optimal, consider adding plant sterol and stanol ester supplementation up to 2 grams/day and adding water-soluble fiber psyllium at a dose of 6 g/day for children 2–12 years of age, and 12 g/day for children ≥12 years of age
For triglyceride levels above optimal, consider reducing sugar intake, replacing simple carbohydrates with complex carbohydrates, avoiding sugar-sweetened beverages, and increasing dietary fish to increase omega-3 fatty acid intake
Encourage at least 1 h of moderate-to-vigorous physical activity daily while limiting sedentary screen time to <2 h/day.[170]

(11.3 mmol/L) should prompt evaluation of secondary causes of hypertriglyceridemia and treatment with a fibric acid should be considered due to significantly increased risk for pancreatitis. Concentrated fish oil can be considered but LDL-C should be carefully monitored as high-dose docosahexaenoic acid (DHA) can increase LDL-C.[170] Statin plus fibrate combination therapy is generally not recommended. Low HDL-C levels in youth are not managed directly with medication, but physical activity, avoidance of smoking and a healthy diet should be encouraged.

6.3 | Atherosclerosis and vascular changes

Hyperglycemia, dyslipidemia, and HTN are contributors to the acceleration of atherosclerosis in T2D, along with oxidative stress, glycation of vascular proteins, and abnormalities in platelet function and coagulation. Defective endothelium-dependent vasodilatation is an additional factor accelerating atherosclerosis in T2D. Endothelial dysfunction is an early sign of increased risk for cardiovascular disease, is predictive of cardiovascular events and occurs in obese children relative to their level of obesity and degree of insulin resistance.[187] In addition, youth with T2D have increased intima media thickness, left ventricular hypertrophy,[188] diastolic dysfunction, reduced maximal exercise capacity,[189] and increased arterial stiffness,[190] all of which predict early cardiovascular morbidity and mortality. Echocardiogram evaluation is recommended in youth with confirmed HTN to assess for left ventricular target organ injury.[169] Routine monitoring of vascular function is not currently recommended.

6.4 | Nephropathy

Albuminuria, either moderately increased albuminuria or severely increased albuminuria (formerly called microalbuminuria and macroalbuminuria, respectively)[191] may be found at diagnosis of T2D and the prevalence increases with duration of diabetes. A recent systematic review and meta-analysis including nearly 2500 youth with a wide range of T2D duration (0–15 years) showed 21% of youth had moderately increased albuminuria. The prevalence for severely increased

albuminuria in 736 youth was 3.9%. Pacific Islander, Indigenous youth in North America and Asian had higher rates of albuminuria compared to non-Hispanic White youth.[192]

In the TODAY study, moderately increased albuminuria was found in 6.3% of 699 youth with T2D at baseline at a median diabetes duration of 7 months and rose to 16.6% by 3 years and to 18% by 7 years.[16,159,193] Similarly, the SEARCH longitudinal study reported moderately increased albuminuria in 9% of 143 youth with T2D at baseline and 18% after 7 years of follow-up.[194] Recently, the TODAY follow-up study showed a cumulative incidence of diabetic nephropathy of 54.8% at a mean diabetes duration of 13.3 years.[160] Higher levels of HbA1c were associated with a higher risk of developing albuminuria.[159,160,193,194] Other factors that influence progression of renal disease include minority race or ethnic group, lower insulin sensitivity, higher BMI, higher BP and dyslipidemia.[160,193,194] The presence of albuminuria in youth is highly predictive of the future risk of renal failure according to a linkage study including 342 individuals with T2D from Manitoba, Canada.[195]

The prevalence of moderately and severely increased albuminuria is higher and the rate of albuminuria progression is accelerated in youth-onset T2D compared to T1D (15.4% vs. 6%).[164,194,195] Youth with T2D compared to T1D are 2–4 times more likely to develop renal failure.[195,196] Youth with relatively short T2D duration and microalbuminuria compared those without microalbuminuria have increased cardiovascular risk factors and left ventricular diastolic dysfunction.[197]

Albuminuria screening should occur at diagnosis and annually thereafter using three first morning urine collections. An elevated spot value can be secondary to contamination, exercise, smoking, menstruation, infection and orthostasis. Therefore, the diagnosis of persistent abnormal albumin excretion requires documentation of two of three consecutive abnormal values obtained on different days. Urine same collection should be done in the morning immediately after rising, as orthostatic proteinuria, considered benign, is common in youth.

If urine albumin/creatinine ratio is confirmed to be >30 mg/g (3 mg/mmol) and BP is elevated or if urine albumin/creatinine ratio is >300 mg/g (30 mg/mmol) irrespective of BP, ACE inhibitor or ARB should be started and BP normalized.[198,199] Causes of renal disease unrelated to diabetes should be considered and consultation with a nephrologist obtained if severely increased albuminuria (macroalbuminuria-albumin/creatinine ratio >300 mg/g or 30 mg/mmol) or HTN is present. A repeat urine albumin/creatinine ratio may be helpful 6 months after the start of treatment with an ACE inhibitor or ARB blocker to ensure albuminuria is normalized.[78,200] If albuminuria is present, serum potassium and renal function should be evaluated annually. Renal function can be evaluated using estimated glomerular filtration rate (eGFR). There are emerging validated formulas to assess eGFR in youth with T2D who are likely to have hyperfiltration at early stages of diabetic nephropathy.[193,198,201] Cystatin C measurements as another marker of glomerular filtration rate are currently not recommended as they show high variability and are affected by age, gender, BMI and HbA1c levels.[202] It also important to optimize diabetes control, improve weight and treat dyslipidemia.[78,160]

6.5 | Non-alcoholic fatty liver disease

NAFLD is the most common cause of chronic liver disease in youth. NAFLD is usually a silent condition characterized by accumulation of fat (in at least 5% of hepatocytes) detected by imaging or liver biopsy in the absence of other causes of liver disease. NAFLD can progress to a more severe form of NAFLD called non-alcoholic steatohepatitis that can occur with or without advanced fibrosis and can progress to cirrhosis. Liver biopsy is the gold standard test for diagnosis of all stages of NAFLD.[203] The evaluation of liver fibrosis in children with NAFLD using non-invasive imaging tests, such as transient elastography by FibroScan®, ultrasound shear wave elastography or enhanced liver fibrosis test, is promising but the interpretation of the results is challenging due to the lack of validated accuracy data.[204] Other imaging tests such as magnetic resonance elastography for stiffness and magnetic resonance imaging proton density fat fraction for fat content have been less evaluated and are more expensive and less accessible.[203,204] Currently, these later modalities are used in research settings.

Children with biopsy-proven NAFLD have a higher prevalence of IFG, IGT and T2D compared to youth without NAFLD of similar age, gender and adiposity.[205] Studies in Italy and in the United States estimated a 20%–30% prevalence of prediabetes or diabetes in youth with biopsy-proven NAFLD.[205,206] In a population-based cohort study in Israel, normoglycaemic youth with NAFLD diagnosed by biopsy or imaging tests have an approximately 3-fold increased risk for T2D in young adulthood compared to youth without NAFLD, after adjustment for BMI.[207] In youth with NAFLD, the presence of diabetes is a factor associated with risk of progression, increasing the odds of developing NASH and with a higher risk of progression to cirrhosis.[206] A meta-analysis in adults with T2D showed a 55.5%, 37%, and 17% prevalence of NAFLD, NASH and advanced fibrosis, respectively.[208]

Healthy lifestyle interventions that promote weight loss are more likely to improve NAFLD.[209] A meta-analysis including 106 randomized controlled trials (4 of these trials were conducted in children) showed limited data on effective medications for NAFLD and no specific treatment recommendations.[210] A systematic review evaluating the efficacy of T2D medications in 2617 individuals with NAFLD with or without diabetes showed that whilst most T2D medications improve liver enzymes only glitazones and GLP-1 receptor agonists, Liraglutide and Semaglutide improved histologic features of NAFLD. This systematic review also highlighted the need for longer duration trials with other GLP-1 receptor agonists and SGLT-2 inhibitors and liver biopsy as the endpoint.[211]

Liver enzymes (alanine transaminase [ALT], aspartate aminotransferase [AST]) should be evaluated at T2D diagnosis with ALT and AST evaluated annually thereafter, perhaps sooner if abnormal. If liver enzymes remain >3 times the upper limit of normal over 6 months, then referral should occur to a pediatric gastroenterologist to exclude other causes of liver enzyme elevation, imaging and/or liver biopsy. The presence of NAFLD does not preclude the use of metformin. Optimizing blood glucose levels and improving weight are required to adequately manage NAFLD.

6.6 | Obstructive sleep apnea

OSA is highly prevalent in adults with T2D, but the prevalence in pediatric T2D has not been well documented using objective measurements such as sleep studies which are the gold standard for evaluation of OSA.[212,213] Poor sleep quality, daytime sleepiness and high risk of OSA evaluated by sleep questionnaires occurs in 26%, 51%, and 28% of overweight/obese youth with or at risk of T2D.[214]

Severe OSA in adults is associated with a greater risk of incident diabetes[215] and adults with T2D who develop OSA are at increased risk of cardiovascular disease, peripheral neuropathy, chronic kidney disease and all-cause mortality compared with adults without OSA.[216] Evaluation of OSA in adults with T2D is strongly recommended by The International Diabetes Federation Taskforce on Epidemiology and Prevention.[217] OSA in children without diabetes is associated with features of metabolic syndrome and insulin resistance.[218,219] Longitudinal data on children with OSA are limited, and it is not known whether treatment of OSA can attenuate any metabolic risk.

Youth with T2D should be screened for symptoms of OSA at diagnosis and annually thereafter, unless there is excessive weight gain which requires earlier review of OSA symptoms. OSA can be initially evaluated using general questions about snoring, sleep quality, apnea, morning headaches, daytime sleepiness, nocturia, and enuresis. There are no screening questionnaires to accurate predict the diagnosis of OSA in children.[78,220] If symptoms are suggestive of OSA, the diagnosis of OSA is made by referral to a sleep specialist and performing a sleep study. Nocturnal pulse oximetry can be an initial useful evaluation if there is limited access for a sleep study.

6.7 | Polycystic ovary syndrome

Youth with PCOS have insulin resistance compared to body composition matched girls without PCOS.[221] Obese youth with PCOS have more insulin resistance, lipid abnormalities and hyperandrogenism compared to healthy weight youth with PCOS.[222] A study including 493 girls aged 11–21 years with PCOS (oligomenorrhea and hyperandrogenism) found an incidence of T2D among overweight or obese girls of 22.6/1000 person years[223] compared to an incidence of 15.8/1000 person years in 1136 young women aged 15–44 years with PCOS with and without obesity.[224] The TODAY study reported that girls with T2D who were more than 1 year post-menarche have a higher frequency of irregular menstrual cycles (three or fewer periods in the previous 6 months) compared to previous data in healthy girls.[225] Irregular menstrual cycles in this study were associated with higher plasma testosterone and AST levels. Decreasing insulin resistance with healthy lifestyle, weight loss and metformin improves ovarian function and increases fertility.

A menstrual history should be taken on every girl with T2D at diagnosis and every diabetes follow-up encounter. PCOS screening should occur at diagnosis in pubertal girls and yearly after that with evaluation of menstrual history (primary or secondary amenorrhea) and evidence of hyperandrogenism (hirsutism and/or moderate to severe acne and/or free testosterone measurement). PCOS is diagnosed based on the presence of oligo- or amenorrhea with clinical or biochemical evidence of hyperandrogenism (free testosterone) after exclusion of other possible causes. Free testosterone is preferred as total testosterone may be normal due to low sex hormone binding globulin. Pelvic ultrasound is not recommended for diagnosis of PCOS within 8 years post menarche.[226]

6.8 | Diabetic retinopathy

Diabetic retinopathy (DR) is a leading cause of blindness in adults. DR stages include non-proliferative DR (from very mild to severe), proliferative DR and macular edema. Other eye disorders like glaucoma and cataract are also common in adults with diabetes. A meta-analysis including 7604 adults with T2D showed that the presence of proliferative DR or macular edema is associated with increased risk of cardiovascular disease independent of other risk factors.[227] The risk of retinopathy in young-onset T2D (diagnosed between 15 and 40 years) was two-fold higher than older-onset T2D after adjustment for diabetes duration, HbA1c and other risk factors.[228]

The DR incidence rate for youth onset T2D is reported as 19.6 cases per 1000 person years.[228] The prevalence of non-proliferative DR diagnosed by digital fundus photographs was 13.4% in youth and young adults (mean age 22.1 years) after a mean diabetes duration of 7.9 years in the SEARCH study.[164] A similar prevalence was seen in the TODAY study where 13.7% of youth, mean age 18 years, had non-proliferative DR after a mean diabetes duration of 4.9 years.[229] More than half of Asian Indians had non-proliferative DR after a mean diabetes duration of 11.8 years.[230] In the TODAY study, the severity of the retinal disease increased to moderate–severe, including proliferative DR, from 0% to 8.8% after 13 years and 3.5% developed macular edema. Overall prevalence of DR after 13 years was 51%.[160]

The prevalence of DR is higher in youth with T2D as compared to T1D of similar diabetes duration (7.9 years) even after adjustment for HbA1c, central obesity and BP over time.[164] Despite this higher prevalence of DR in youth with T2D, these youth are less likely to have eye screening compared to youth with T1D.[231] In one study, 42.2% of participants with T2D had not had an eye exam after 6 years of diabetes diagnosis.[231]

At the time of initial diagnosis youth with T2D should have a comprehensive eye examination with dilated pupils or retinal photograph performed by an ophthalmologist or optometrist. More frequent examinations by an ophthalmologist are required if retinopathy is present or progressing. Management of retinopathy should also include optimization of blood glucose levels as well as treatment of dyslipidemia/HTN if present. Current injectable therapies for diabetic macular edema and proliferative DR have not been extensively trialed in youth T2D.

6.9 | Neuropathy

Diabetes affects the peripheral sensorimotor system leading to peripheral neuropathy and the autonomic nervous system impacting

nerves in the gastrointestinal, genitourinary, and cardiovascular systems (cardiac autonomic neuropathy, CAN).

The majority of peripheral neuropathies are asymptomatic. Peripheral neuropathy increases the risk of foot complications including amputation. Assessment for peripheral neuropathy in the clinic should include a careful history and assessment of pin prick or temperature (small fiber function) and vibration sense using a 128-Hz tuning fork (large fiber function).[232] All youth should have a 10 g monofilament testing to identify feet at risk for ulceration and amputation. Other methods used include the Michigan Neuropathy Screening Instrument (MNSI) and biothesiometer.[232] Assessments should be done at baseline and then annually. Youth should be taught proper foot care. Management should be individualized according to symptoms and signs; and referral to neurologist should be considered if abnormal neurological signs are detected.

Prevalence of neuropathy as assessed by MNSI and the Semmes–Weinstein monofilament examination in 677 youth with T2D at mean age of 14 years in the TODAY study was 1%.[16] Additionally, none of the participants were found to have neuropathy using biothesiometer to assess vibration test at the great toe in 388 youth with T2D at mean age of 23 years and diagnosed before 16 years of age at a tertiary diabetes care center in India.[233]

Risk of neuropathy increases with duration of diabetes. In the population-based cohort of 342 youth with T2D from Canada, the crude prevalence of neuropathy was 7.6% at 6.5 years duration of diabetes.[234] In the SEARCH study including 272 youth with T2D and using the MNSI, age-adjusted prevalence of neuropathy was significantly higher in youth onset T2D than T1D (17.7% vs. 8.5%) despite similar duration of diabetes (7.9 years) and glycemic control.[164] In a clinic-based longitudinal cohort including 354 Australians with T2D (15–30 years old), biothesiometer Z scores were significantly increased in individuals with T2D in comparison to individuals with T1D of the same age and despite a shorter duration of diabetes (11.6 vs. 14.7 years) and similar glycemic control.[235]

In the TODAY trial, the only prospective follow-up study in youth onset T2D, the cumulative incidence of peripheral diabetic neuropathy was 32.4% at 15 years follow-up[160] from 1% at baseline (duration of diabetes <2 years).[16] Age-adjusted incidence of neuropathy according to duration of diabetes was reported as 11 per 1000 patient years for duration <14 years and 66 per 1000 patient years for duration >15 years from clinic data from an Indian tertiary diabetes care center.[233] The risk factors associated with peripheral neuropathy in youth are older age, male sex, longer duration of diabetes, smoking and lower HDL-C.[236]

Cardiac autonomic neuropathy (CAN) an independent predictor of cardiovascular mortality is seen in youth onset T1D and T2D. In early stages CAN is asymptomatic and is detected only by decrease heart rate variability with deep breathing. Advanced disease maybe associated with resting tachycardia and orthostatic hypotension. In the SEARCH study, CAN was defined as the presence of ≥3 of 5 abnormal heart rate variability indices.[237] CAN was present in 17% of youth and young adults with T2D and was associated with elevated TG levels and increased urinary albumin excretion.[237] In the TODAY study, 8% of participants had CAN when evaluated after 7 years in the study and was related to higher HbA1c over time.[238] Assessments of CAN are currently limited to research studies in youth.

6.10 | Mortality

There are limited long-term mortality data that correspond to the recent increase in incidence of youth onset T2D, as follow up of these individuals is not yet long enough. Estimates can be drawn from results of studies including young adults with T2D. An Australian study examined mortality in those with the age of onset ranging from 15 to 30 years and found that youth with early onset T2D had a 3-fold increased in all-cause mortality compared to the general Australian population, a much higher mortality impact than that seen for the older onset groups.[165] Decreasing the age at diabetes diagnosis by 10 years is associated with a 20%–30% increased risk of all-cause mortality and a 60% increased risk of cardiovascular disease mortality according to an Australian national registry study analyzing data of >700,000 adults with T2D.[239]

These longer-term data are in accordance with the short-term mortality risk evaluated in the SEARCH study, including 1518 individuals diagnosed with T2D before 20 years of age who were followed up over a median of 5.3 years. The standardized mortality ratio of 2.4 was significantly higher than expected for individuals with T2D, compared to the US population; however, at this younger age (15–19 years) T2D was not identified as the cause of death.[240]

An Australian study including 354 individuals with T2D with age of onset 15–30 years has reported a significantly excess mortality, higher hazard for death, which occurred at a relatively younger age and at a shorter duration of diabetes as compared to 471 individuals with T1D with similar age of onset.[235] With similar HbA1c levels as T1D, the T2D cohort had more CVD deaths and less favorable cardiovascular risk factors.[235] Overall survival at 10 and 20 years was reported as 91.4% and 77.5%, respectively in the T2D group ($n = 342$) compared with 99.5 and 97.6% in the T1D ($n = 1011$) group ($p < 0.0001$) from Canada.[234]

Modeled data suggest a decrease in life expectancy of 14 years in men and 16 years in women who have onset of T2D between 20 and 40 years age.[241] These appalling statistics highlight the need to prevent diabetes, if possible, and reinforce management of risk factors in youth with T2D.

6.11 | Psychosocial health

Youth onset T2D disproportionately affects youth facing structural disadvantages, including living in poverty,[16,18,163,164,242] in food insecure households, and being a racialized minority.[243,244] In this context, mental health comorbidities including depression and anxiety are frequent among youth living with T2D. The prevalence of depression with T2D is reported to be between 15% and 38%, with some studies reporting higher depressive symptoms in females.[245–247] The SEARCH study[248]

and Pediatric Diabetes Consortium[247] independently reported that youth with T2D reported 50% higher depression scores and ~10% lower quality of life, compared to their peers living with T1D. In one study, neuropsychiatric diagnoses such as depression, attention deficit hyperactivity disorder, schizophrenia, bipolar, and neurodevelopment disorders were found in 19% of youth-onset T2D at diabetes presentation.[249] In addition, youth with T2D report feelings of significant shame and blame for having developed T2D, and distress related to the deep experiential understanding of long-term diabetes complications due to the intergenerational burden of T2D within their families.[250]

Symptoms of depression are associated with inconsistent medication administration,[251,252] reduced readiness to adopt self-help behaviors,[253] and higher rates of complications and morbidity[254,255] associated with diabetes. In a cohort of Canadian youth with T2D preliminary data have shown an indirect link between adverse mental health and early evidence of renal dysfunction.[256] Although depression and anxiety have not been linked directly to blood glucose and HbA1c levels, their association with health-related behaviors such as regular medication use,[257,258] readiness for behavioral change,[253] disordered eating[41,259,260] and worse sleep hygiene[261,262] are expected to indirectly impact diabetes outcomes. Mental health co-morbidity is associated with all cause hospitalization and mortality[263,264] in adults living with T2D, suggesting a potential role for mental health supports to improve outcomes of youth with T2D.

Youth with T2D with lower levels of stress and distress, and evidence of higher levels of resiliency more often report readiness to adopt self-help behaviors,[253] and a sense of mastery protected against depression and anxiety in a large population of youth and adults in Norway.[265] Future therapeutic approaches for youth with T2D need to account for the cultural, socioeconomic, and psychological variables which impact health-related behaviors.[198] Early studies of interventions in groups of female youth at risk for T2D based on mindfulness[266,267] and cognitive behavioral therapy[267] have shown some promise in improving mental health and health behaviors.

Several screening tools used primarily in research settings have identified youth with T2D as having higher levels of stress and distress and may be incorporated into clinical care with appropriate psychological supports. These include the Diabetes Distress Scale, the PHQ-9, the Kessler distress score (K6), Unger resiliency scales, and the Psychological Stress Score (PSS14). The use of psychotropic medications, including atypical antipsychotic agents that increase weight and insulin resistance, may also contribute to diabetes risk.[74–77]

Youth with T2D should be screened for psychological co-morbidities including depression, diabetes distress, and disordered eating at diagnosis and at regular follow-up intervals. Youth identified to have mental health concerns should be offered mental health supports either in conjunction with the clinic or through community-based mental health programs. Providers should specifically consider household food security, housing stability and family financial resources when devising a treatment plan with the youth and family. Providers should avoid stigmatizing language and promote contextualizing and understanding of the complexity of childhood onset T2D which encompasses more than lifestyle-based behaviors.

7 | SOCIAL DETERMINANTS OF HEALTH

The COVID-19 pandemic has illuminated existing and profound global health inequities, providing a stark reminder of the impact of the SDOH.[268] SDOH is broadly defined as the conditions in which people are born, grow, live, work, and age, that influence health outcomes and are molded by the gradients of money, power, and resources across regions. The strong relationship between obesity and adverse SDOH factors is well accepted, and it is now increasingly recognized that SDOH can impact the onset, prognosis, and course of T2D.[269] Notably, adverse SDOH are over-represented in youth-onset T2D cohorts.[28,270–272]

SDOH research in youth-onset T2D has largely been observational in nature. Of all the SDOH domains, socio-economic status (SES), a multidimensional construct of income, education and occupation, appears to have the largest measurable associations with T2D, and SES is linked to almost all the established SDOH domains. In the United States and Europe, the prevalence of youth-onset T2D is rising fastest in low socio-economic population groups, and the prevalence of poverty is greater than 30% in many youth-onset T2D cohort studies from this region.[48,270] In the SEARCH study, low SES was associated with greater difficulty maintaining healthy diet behaviors; lower educational attainment was associated with less regular use of a DASH diet, and non-white males from lower-income households had the highest intake of sugar-sweetened beverages. Additionally, >80% of youth with T2D had experienced a SDOH-related barrier to quality health care.[17] In contrast, in countries like China and India with rising affluence, it is the children in higher SES strata and urban areas that are likely to develop youth-onset T2D.[22,273]

The food environment, access to affordable healthy and nutritious food, associate with both diabetes risk and diabetes outcomes.[269] In particular, the presence of food insecurity, that is the unreliable availability of nutritious food and the inability to consistently obtain food, may be relevant to youth-onset T2D. The relationship of food insecurity to diabetes is complex; however, the low cost and high palatability of low-quality high energy dense foods may etiologically link poverty, obesity, and diabetes.[269] In the SEARCH study, 29% of youth with T2D had experienced inability to access nutritious food. By using longitudinal data in the Taiwan National Health Insurance scheme, a large study reported associations of imputed food insecurity with an increased likelihood of diabetes-related ambulatory care visits in schoolchildren.[274] However, a recent population-based cohort study of Canadian children did not find an independent risk of food insecurity on incident diabetes; an association suggesting food insecurity and diabetes is likely mediated by other factors.[275]

Overall evidence supports SDOH as an underlying risk factor for the development of youth-onset T2D; however, the relationship is complex and interactions with obesity and ethnic minority status is poorly understood. As SES is linked to virtually all the established SDOH, knowledge of the financial stability of the youth's family/household, including the presence of food or housing insecurity, parental occupation/employment and education, may provide the clinician with the best overall marker of a child's or adolescent's

SDOH-related risk of health disparity. That said, large gaps exist with respect to high-quality evidence for effective interventions that specifically address SDOH on youth-onset T2D incidence and outcomes. Evidence now supports the need for a comprehensive research agenda aimed at the individual, organizational, and policy level, focused on the understanding and amelioration of the effects of the SDOH on youth-onset T2D. Providers should specifically consider household food security, housing stability and family financial resources when devising a treatment plan with the youth and family.

8 | TRANSITION OF CARE FOR EMERGING ADULTS WITH T2D

Epidemiological studies from the United States[276] and Canada[277] have shown that, in comparison to their peers with T1D, young adults with T2D have increased loss to follow-up and worsening HbA1c levels at transition to adult services.[277] With higher rates of comorbidities, and increased risk of early complications,[164,234] adverse pregnancy outcomes,[278,279] and overall mortality[240] for individuals with T2D, youth living with T2D require specific, focused, purposeful transition planning to improve long-term health outcomes.[280] The significant social, educational, geographic and economic challenges in youth with T2D add to the complexity of transition[281] with many youth and caregivers impacted by poverty, geographic isolation, and lower educational attainment.[16,276] These unique medical and socioecological aspects of T2D support a need to develop and evaluate programs specific to the lived realities of these emerging adults. Clinical practice guidelines recommend transition to an adult diabetes specialist care provider[78,280,282] or multidisciplinary team.[78] This is complicated if health insurance lapses during the transition time.

Transition preparation should be started in early adolescence at around 14–15 years of age[283] with youth and their caregivers and at minimum 1 year prior to transition. Transition content should include counseling on diabetes self-management, health risky behaviors, preconception counseling for females of childbearing potential, and diabetes complications.[284] Youth with T2D should be transitioned to subspecialist diabetes care and a multidisciplinary team when feasible and appropriate. Diabetes providers need to develop structured transition protocols with specific and detailed guidance on the transition education content, transition plans, and specific adult provider referrals.[284]

9 | SUMMARY AND CONCLUSIONS

Youth-onset T2D is a growing public health concern worldwide that presents with unique characteristics, demographics and disease progression compared to adult-onset T2D. Because of the relatively recent emergence of T2D in youth, evidence is evolving regarding the optimal means of diagnosis, management and monitoring of these youth.

The full impact of the COVID-19 pandemic on T2D in youth has yet to be determined but initial studies show an increase in obesity and T2D globally, more acute presentations at diabetes onset (i.e., DKA), and have illuminated existing and profound global health inequities, providing a stark reminder of the impact of the SDOH on youth with T2D. However, the pandemic has highlighted the need to consider alternative modes to reach youth and their families including telehealth. Undoubtedly, in the years ahead, we will learn more about the impact of the COVID-19 pandemic on youth-onset T2D.

In the near future, the results of clinical trials in youth of lifestyle and mental health interventions and pharmacological agents already approved for adults with T2D will inform us about alternatives and simplified management of youth with T2D. Since the last guidelines, two GLP-1 agonists have already been approved. There is hope that additional therapies will not only aid in optimizing glycemic control, but slow disease progression and reduce long term co-morbidities and complications.

There is a critical need to better understand the unique pathophysiology of T2D in youth and the interplay of genetics, puberty and the environment and, importantly, how to prevent T2D or improve long-term health impact.

CONFLICT OF INTEREST

Philip S. Zeitler: Consulting: Eli Lilly, Boehringer-Ingelheim, Merck, Daichi-Sankyo, Janssen, Novo-Nordisk. Jencia Wong: Advisory Board and Speaker Bureau: Sanofi Aventis and Eli Lilly. The remaining authors have no conflicts of interest to disclose.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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