WILEY ISPAD

ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES

ISPAD Clinical Practice Consensus Guidelines 2018: Type 2 diabetes mellitus in youth

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1 | WHAT'S NEW

The 2018 ISPAD Guidelines have been updated based on published data and evolving expert opinion since the 2014 chapter was published, including treatment target (HbA1c = 7%) and intensification of management recommendations.

2 | EXECUTIVE SUMMARY

2.1 | Screening for T2DM in at-risk youth

1. Undiagnosed type 2 diabetes mellitus (T2DM) is rare in the adolescent population, even among high-risk individuals (A)
2. Generalized population screening of obese youth is unlikely to be cost-effective in most populations (E).
   a. Urinary glucose screening in Japanese and Taiwanese adolescents may be a unique situation with demonstrated cost-effectiveness (A)
3. Testing to identify clinical cases of diabetes should be considered in children and adolescents after the onset of puberty or after 10 years of age, whichever occurs earlier, who have risk factors for diabetes (obesity, intrauterine growth retardation with rapid infant weight gain, first-degree family history of T2DM, maternal history of diabetes or gestational diabetes during child's gestation, high-risk ethnicity, polycystic ovary syndrome). (A)
4. Clinical testing for dysglycemia in obese at-risk youth should occur in the setting of clinical assessment of other obesity-related comorbidities (non-alcoholic fatty liver disease [NAFLD], dyslipidemia, elevated blood pressure [BP], polycystic ovary syndrome) that are more prevalent than dysglycemia (A)

2.2 | Diagnosis and determination of diabetes type

1. T2DM in youth should be diagnosed using American Diabetes Association (ADA) criteria (A)
   a. Diagnosis can be made based on fasting glucose, or 2-hour glucose concentration during an oral glucose tolerance test (OGTT) or hemoglobin A1c (HbA1c) (B)
   b. In the absence of symptoms, testing should be confirmed with a repeat test on a different day
   c. Clinicians should be aware of the weaknesses of each diagnostic test
2. Diabetes autoantibody testing should be considered in all pediatric patients with the clinical diagnosis of diabetes because of the high frequency of islet cell autoimmunity in otherwise "typical" T2DM (B)

a. Pre-pubertal children are unlikely to have T2DM even if obese (A)

b. Antibodies will indicate the diagnosis of T1DM and an earlier need for insulin (A)

c. Antibodies will indicate the need to consider the presence of other associated autoimmune disorders (A)

3. Diabetes autoantibody testing should be considered in overweight/obese pubertal children with a clinical picture of T1DM (A)

4. The presence of clinically relevant comorbidities should be assessed at the time of diagnosis (A), including hypertension, dyslipidemia, elevation of liver enzymes, and elevated urine albumin/creatinine ratio (ACR)

5. Patients should be screened for obstructive sleep apnea (OSA), depression/anxiety, eating disorders, and impairment of cognition at the time of diagnosis (E). The possibility of pregnancy should be considered

2.3 | Initial treatment

1. Lifestyle changes should be recommended at the time of diagnosis of T2DM (A)

2. Initial pharmacologic treatment of youth with T2DM should include metformin and insulin alone or in combination, depending on degree of hyperglycemia and metabolic disturbances, and presence or absence of ketosis/ketoacidosis. B

a. Metabolically stable patients (HbA1c < 8.5 and no symptoms) should be started on metformin. (A)

  i. Begin with 500-1000 mg (or 850 mg when this is the lowest available dose) daily × 7 to 15 days. Titrate once a week over 3 to 4 weeks, depending on patient tolerance, to a maximal dose of 1000 mg BID or 850 mg TID (extended release metformin product may be used where available).

b. In patients with ketosis/ketonuria/ketoacidosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the metabolic abnormality (A).

  i. Once a day intermediate-acting or basal insulin (0.25-0.5 units/kg starting dose) is generally effective in attaining metabolic control

  ii. Metformin can be started along with insulin, once acidosis is resolved (E).

  iii. Transition onto metformin monotherapy can usually be achieved safely over 2 to 6 weeks (A)

3. The goal of treatment should be an HbA1c < 7.0% (<47.5 mmol/mol). (B)

4. Self-monitored blood glucose (SMBG) should be performed regularly. The frequency of SMBG should be individualized, based on the degree of glycemic control and available resources (E). The benefits of continuous glucose monitoring have not been explored in youth-onset T2DM.

3 | SUBSEQUENT TREATMENT

1. If the patient fails to reach target HbA1c of <7% (<47.5 mmol/mol) within 4 months on metformin monotherapy, addition of basal insulin (or intermediate-acting insulin where basal insulin is not available) should be strongly considered. (A)

2. If target is not attained on the combination metformin and basal insulin (up to 1.5 U/kg), prandial insulin should be initiated and titrated to reach target HbA1c < 7% (B)

3. Other pharmacologic agents are generally not approved for use in this population and their role in the management of glycemia in youth-onset T2DM is presently not determined (E)

a. The use of sulfonylurea agents is not recommended due to increased risk for hypoglycemia and more rapid loss of β-cell function (A)

3.1 | Assessment and management of comorbidities and complications

1. Urine ACR should be obtained at the time of diagnosis and annually thereafter: (A)

a. An elevated ACR (>30 mg/g creatinine or 3.39 mg/mmol) should be confirmed on two of three samples.

b. If urine ACR is confirmed to be >30 mg/g or 3.39 mg/mmol and BP is elevated, or if urine ACR is >300 mg/g irrespective of BP, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) should be started and titrated with the goal of BP in the normal range (A)

c. Consider non-diabetes related causes of renal disease especially in the presence of ACR > 300 mg/g (33.9 mg/mmol); consider referral to a renal specialist.

2. BP should be monitored at every visit according to standardized techniques specific for children (A)

a. Elevated BP should be confirmed on 2 additional separate days

  i. Hypertension is defined as an average systolic or diastolic BP > 95th percentile for age, sex, and height, with high normal BP being 90th to <95th percentile.

b. Initial treatment should consist of weight loss, limitation of dietary salt, and increased physical activity. (E)

c. If BP remains above the 95th percentile after 6 months, an ACE inhibitor should be initiated and titrated to achieve BP less than the 90th percentile (A)

d. If the ACE inhibitor is not tolerated due to adverse effects, an ARB, calcium channel blocker, or diuretic can be used. (E)

e. Combination therapy may be required if hypertension does not normalize on single agent therapy. (E)

3. Testing for dyslipidemia should be repeated once glycemic control has been achieved or after 3 months of initiation of medication, and annually thereafter. Initial screening does not require a fasting sample (B)

a. Cholesterol

  i. Goal levels are (B):

    1. LDL-C < 100 mg/dL (2.6 mmol/L)

    2. HDL-C > 35 mg/dL (0.91 mmol/L)

    3. triglycerides <150 mg/dL (1.7 mmol/L)

  ii. If LDL-C is above goal, blood glucose control should be optimized and dietary counseling should be provided using the American Heart Association Step 2 diet

  iii. A repeat lipid profile should be performed fasting in 6 months. (B)

iv. If repeat fasting LDL-C > 130 mg/dL (>3.4 mmol/L): begin medication with an initial goal of <130 mg/dL (<3.4 mmol/L): and an ideal target of <100 mg/dL (2.6 mmol/L (B)

v. Statin therapy has been shown to be safe and effective in adolescents (A)

1. The risks of pregnancy should be re-emphasized

b. Triglycerides

i. If triglycerides are >400 mg/dL fasting (>5.6 mmol/L) or >1000 mg/dL (>11.3 mmol/L) non-fasting: begin medication with a goal of <400 mg/dL (>5.6 mmol/L) fasting (to reduce risk for pancreatitis) (C)

ii. Fibrates are the preferred medication category for hypertriglyceridemia and have been shown to be safe and effective in adolescents (A)

4. Retinal examination should be performed at diagnosis and annually thereafter (A)

5. Evaluation for NAFLD and non-alcoholic Steatohepatitis (NASH) by measuring ALT and AST should be done at diagnosis and annually thereafter (A)

a. Interpretation of ALT should be based upon sex-specific upper limits of normal in children (22 U/L for girls and 26 U/L for boys) and not individual laboratory upper limits of normal. (A).

b. NAFLD/NASH or other causes of chronic hepatitis should be considered for persistently (>3 months) elevated ALT >3 times the upper limit of normal (ULN) (C)

c. Patients should be referred to gastroenterology if liver enzymes remain elevated >3 times ULN despite weight loss and attainment of glycemic control. (E)

6. Patients should be asked about menstrual irregularities, symptoms of hyperandrogenism, depression, anxiety, eating disorders, and sleep disturbance at diagnosis and regularly thereafter. (E). Patients with menstrual irregularities should be tested for hyperandrogenism

7. Patients should be asked about smoking and alcohol use at diagnosis and regularly thereafter and these behaviors should be discouraged. (A).

4 | INTRODUCTION

T2DM in children and adolescents (youth-onset T2DM) has become an increasingly important public health concern throughout the world,[1–10] with unique characteristics and demographics. The incidence of T2DM in adolescents continues to increase in many countries.[11] Similarly, the prevalence of prediabetes, defined in adults as a state of high-risk for progression to diabetes, is increasing quickly in some developing countries with the increase of overweight and obesity.[12] Because of the relatively recent emergence of the problem in children and adolescents, there has been a limited evidence base leading to unique challenges in the diagnosis, management, and monitoring of these individuals. This limited evidence base is further complicated by differences in the characteristics and presentation of the disorder and approaches to treatment in developed and developing countries. In 2014, ISPAD developed guidelines for the diagnosis and management of children and adolescents with T2DM.[13] Since the

publication of the last guidelines, additional studies, including follow-up of individuals in the multi-center randomized controlled TODAY trial and continuation of the population-based SEARCH for diabetes in youth study, have provided further information that contributes substantially to understanding of T2DM. This chapter will discuss the diagnosis and presentation of T2DM, classification of diabetes type, initial and subsequent treatment, monitoring, and assessment and management of associated comorbidities and complications.

5 | DEFINITION, CLASSIFICATION, AND CHARACTERISTICS OF YOUTH-ONSET T2DM

T2DM occurs when insulin secretion is inadequate to meet the increased demand posed by insulin resistance, leading to relative insulin deficiency[14] and is generally associated with other metabolic abnormalities characteristic of insulin resistance (dyslipidemia, hypertension, polycystic ovary syndrome, fatty liver). Unlike T1DM, there is no identified autoimmune process leading to inadequate insulin secretion in T2DM, which appears to result from genetic, environmental, and metabolic causes that may differ between individuals and populations. Insulin secretion depends on disease status and duration and can vary from a delayed but markedly elevated peak in response to a glucose challenge initially, to absolutely diminished secretion over time.[14] Adults with symptoms of diabetes have 50% reduction in insulin secretion at the time of diagnosis and may become insulin dependent within a few years.[15] In adolescents at the time of diagnosis of T2DM, insulin secretion relative to their insulin sensitivity is impaired by ~85%.[16] Moreover, recent data from the TODAY (Treatment Options for T2DM in Adolescents and Youth) study suggest that deterioration in insulin secretion is even more rapid in adolescents than what has been reported in adults.[2,17–20] Furthermore, data from the TODAY[21][2] and SEARCH studies,[22] from studies of First Nations adolescents in Canada[23] and from diabetes registries in Australia[24] indicate that diabetes- and obesity-related comorbidities are prevalent at diagnosis in youth-onset T2D, increase rapidly over time, and are associated with worse morbidity and mortality than T1D diagnosed in the same age group.

The diagnosis of T2DM requires two steps: confirmation of the presence of diabetes followed by determination of diabetes type. The criteria and classification of diabetes are presented in greater detail in the ISPAD Clinical Practice Consensus Guidelines: Definition, Epidemiology, Diagnosis, and Classification of Diabetes (needs reference to that chapter) The diagnostic criteria for diabetes in youth are based on measurement of glycemia and the presence of symptoms.[25] There are four accepted ways to diagnose diabetes and each, in the absence of unequivocal symptoms of hyperglycemia, must be confirmed, on a subsequent day, by any one of the four methods given below.

According to the ADA,[25] diabetes is diagnosed when: (note: none of these criteria have been specifically validated in children and adolescents and are all extrapolated from adult definitions)

- Fasting plasma glucose (FPG) ≥ 7.0 mmoL/L (126 mg/dL)
- Post OGTT 2-hour plasma glucose ≥11.1 mmoL/L (200 mg/dL)
  - 1.75 g/kg (max 75 g) anhydrous glucose dissolved in water[26]

- Symptoms of diabetes and a random plasma glucose ≥200 mg/dL (11.1 mmol/L).
  - Symptoms of diabetes include polyuria, polydipsia, nocturia, and unexplained weight loss.
  - HbA1c ≥ 6.5% (48 mmol/mol)
  - Must utilize a laboratory based, DCCT aligned, National Glycohemoglobin Standardization Program (NGSP) certified methodology
  - Point-of-care measurement of HbA1c is not acceptable for diagnosis
- In the absence of symptoms, hyperglycemia detected incidentally or under conditions of acute physiologic stress may be transitory and should not be regarded as diagnostic of diabetes.
- The OGTT has poor reproducibility in adolescents, with a concordance rate between tests a few weeks apart of less than 30%.[27]
- Although the HbA1c criterion has been accepted by the ADA for the diagnosis of diabetes in adults, this criterion remains controversial, as it identifies a population that does not overlap entirely with that identified by fasting or post-glucose challenge criteria in adults or in youth.[28–30] However, HbA1c ≥ 6.5% (48 mmol/mol) predicts the risk for retinopathy in adults,[25] as well as the glucose criteria.
- Caution should be used in interpreting HbA1c, as the relationship between HbA1c and average glucose concentration can vary between different ethnic/racial populations[31] but appears to be consistent within an individual[32]

After the diagnosis of diabetes is established, diabetes autoantibody testing should be considered where available in all pediatric patients with the clinical diagnosis of T2DM because of the high frequency of islet cell autoimmunity in patients with "clinically" diagnosed T2DM. Studies have shown that autoantibodies are present in 10% to 20% of patients clinically diagnosed with T2DM, depending on the race and ethnicity of the population[15,33–35,36,37] The presence of antibodies predicts rapid development of insulin requirement,[34] as well as risk for development of other autoimmune disorders. Diabetes autoantibody testing should also be considered in overweight/obese pubertal children with a clinical picture of T1DM (weight loss, ketosis/ketoacidosis), some of whom may have T2DM and be able to be weaned off of insulin for extended periods of time with good control.[38,39]

5.1 | Characteristics of individuals with youth-onset T2DM

- Youth onset T2DM occurs most often during the second decade of life, with a median age of diagnosis of 13.5 years. This coincides with the peak of physiologic pubertal insulin resistance and, accordingly, the median age of onset is 1 year later in boys than girls.[26,40]
- Youth-onset T2DM rarely occurs prior to puberty.[26,40]
- Youth with T2DM come from families with a high prevalence of T2DM in first- and second-degree relatives.[26,41]
- Youth onset T2DM occurs in all races, but with a much greater prevalence in populations at overall high risk for type 2 diabetes,

for example, American Indians, Canadian First Nations, Africans and African-Americans, Latinos, East and South Asians, Indigenous Australians and Pacific Islanders. The SEARCH for Diabetes in Youth study found the proportion of T2DM among 10 to 19-year-olds to vary greatly by ethnicity in the United States: 6% for non-Hispanic whites, 22% for Hispanics, 33% for African-Americans, 40% for Asians/Pacific Islanders, and 76% for Native Americans.[4,40] In Europe, there is a greater prevalence in immigrant populations from Asia, North Africa, and the Middle East.[4]

- In Hong Kong, 90% of youth-onset diabetes is T2DM,[42] 66% among Australian indigenous youth,[43] 60% in Japan, 50% in Taiwan,[7] but only 8% in China.[11]
- In the United States and Europe, nearly all youth with T2DM have body mass index (BMI) above 85th percentile for age and sex,[26] with the median BMI > 99% percentile. In Europe, nearly half of the adolescents with T2DM are extremely obese (BMI > 99.5th percentile).[44,45] However, in Japan, 15% of children with T2DM are not obese,[10,46] in South Asian urban children, half of those with T2DM had normal weight (<120% ideal for height),[8] and half of Taiwanese children with T2DM are not obese.[7]
- Youth onset T2DM has a sex ratio (male: female) that varies from 1:4 to 1:6 in native North Americans to 1:1 in Asians and Libyan Arabs. In some reports from China, the prevalence of T2DM in males is higher than in females.[11]
- In the United States and Europe, youth-onset T2DM is predominately found in populations characterized by low socioeconomic and educational status,[26] while in emerging countries like China and India, more affluent children are more likely to develop T2DM than poorer children.[8,11]
- The presentation of youth-onset T2DM can vary from asymptomatic hyperglycemia detected through screening or during routine physical examination to ketoacidosis in up to 25% of patients[47,48] or hyperglycemic hyperosmolar state.[49] These latter two presentations can entail significant risk for morbidity and mortality if not recognized and appropriately treated.
- Youth-onset diabetes that has occurred in three consecutive generations, appears to be mild, but not responsive to Metformin should raise suspicion of the possibility of a form of monogenic diabetes in the young (MODY). (reference)

5.2 | Autoimmune "T2DM"

Some authors have reported the phenomenon of autoimmune T2DM. This has sometimes been referred to as T1.5DM, T3DM, or double-diabetes. However, these individuals are best understood as having autoimmune T1D presenting in overweight or obese individuals with underlying insulin resistance and associated metabolic abnormalities.

- Youth and adults in United States and Europe who are clinically diagnosed with T2DM are found to have T1D associated auto-antibodies in 15% to 40% of cases, including many who are not receiving insulin 1 year after diagnosis.[35–37]
- Antibody-positive youth with the T2DM phenotype are significantly less overweight, have lower BP, lower triglycerides, higher

HDL-C, are less likely to be female and more likely to be non-minority than otherwise similar antibody negative patients.[37]

- ß-cell function is significantly lower in antibody-positive youth with T2DM phenotype, resulting in more rapid development of insulin dependence.[37,50,51]

5.3 | Uncertainties of classification

The clinician is obliged to weigh the evidence in each individual patient to distinguish between T1DM and T2DM. The reasons for this conundrum are:

- With increasing obesity in childhood, as many as 30% of newly diagnosed T1DM or patients with monogenic diabetes (MODY) may be obese, depending on the rate of obesity in the background population.
- A significant number of pediatric patients ultimately diagnosed with T2DM demonstrate ketonuria or ketoacidosis at diagnosis.[48,52]
- T2DM is common in the general adult population, with a positive family history for diabetes in 15% or greater in minority populations, reducing the specificity of a positive family history.
- Measurement of insulin or C-peptide is not recommended as part of routine evaluation. There is considerable overlap in insulin or C-peptide measurements between T1DM and T2DM at onset of diabetes and over the first year.[40] This overlap may be due to subjects being in the pre-symptomatic or recovery phase of autoimmune-mediated T1DM (the "honeymoon") and the effects of elevated glucose (glucotoxicity) and free fatty acids (lipotoxicity) to impair insulin secretion at the time of testing in both T1DM and T2DM. In addition, the insulin resistance of obesity may raise residual C-peptide levels in obese adolescents with T1D. Therefore, measurements are relatively valueless in the acute phase. However, persistence of C-peptide above the normal level for age is unusual in T1DM after 12 to 14 months.[53]
- Insulin resistance is present in both T2DM and T1DM, though the pathophysiology is different and resistance in T2DM is generally more severe.[54,55]
- Measurement of diabetes autoantibodies is the most rigorous approach to identification of T1DM. However, this measurement may be limited by lack of ready availability of standardized auto-antibody assays, cost, involvement of antibodies not yet identified, and varying rates of antibody positivity in T1DM in different ethnic groups.
- While monogenic diabetes is rare in youth-onset diabetes overall, studies suggest that approximately 5% of individuals in some populations diagnosed with T2DM will have identifiable mutations associated with monogenic diabetes.[56,57] Monogenic diabetes can be confused with either T1DM or T2DM and requires a high-index of suspicion and recognition of autosomal dominant transmission in the family. The identification of monogenic diabetes has important clinical implications (50% likelihood of offspring being affected, better prognosis, fewer employment restrictions, possible avoidance of needing insulin) so that genetic testing should be considered where appropriate and available.

5.4 | Pre-diabetes: Diagnostic criteria (impaired glucose tolerance and impaired fasting glucose)

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. The ADA has designated these physiologic state "pre-diabetes" to recognize the high risk for progression to diabetes in adults.[25]

- Prediabetes is diagnosed according to ADA definitions:
  - IFG: FPG ≥5.6 to 6.9 mmol/L (≥100-125 mg/dL)
  - IGT: Post-challenge plasma glucose is ≥7.8 to 11.1 mmol/L (≥140-199 mg/dL)
  - Hemoglobin A1c 5.7% to 6.4% (40-46 mmol/mol)
    - Laboratory-based, DCCT aligned, NGSP certified methodology
- IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation.[58,59]
- Individuals who meet the criteria for IGT or IFG may be euglycemic in their daily lives, as shown by normal or near-normal HbA1c and those with IGT may manifest hyperglycemia only when challenged with an OGTT. Conversely, some individuals may have elevated HbA1c but have normal OGTT, likely reflecting daily carbohydrate intake exceeding that associated with a standard glucose load.

The relevance of the concept and cut-offs for prediabetes, by definition a state of high risk for progression to diabetes in adults, is unclear in adolescents. However, data in youth demonstrate that β-cell function relative to insulin sensitivity is impaired even below the typically accepted cut points for fasting and the 2-hour glucose concentrations diagnostic of IFG and IGT.[60,61]

- In obese adolescents, pre-diabetes is often transient, with as many as 60% of individuals reverting to normal glucose tolerance within 2 years as the insulin resistance of puberty wanes.[62] Persistent weight gain is a predictor of persistent pre-diabetes and progression to diabetes.[63] Less than 2% of European adolescents with IFG or IGT develop T2DM in the next 5 years,[64,65] though this rate is higher among Latino and African-American youth.[66]
- Among minority adolescents in the United States, those with a laboratory measured HbA1c > 6% (42 mmol/mol) have more than double the rate of progression to diabetes than those with an HbA1c 5.7% to 6% (39-42 mmol/mol).[66]
- Only lifestyle change, with decreased caloric intake and increased physical activity has been shown to be effective for adolescents with pre-diabetes.[67] There is currently no evidence base for the use of medications, such as metformin, for the treatment of prediabetes in adolescents and the low progression rate to diabetes in

this population indicates that many adolescents would be unnecessarily treated.

6 | TREATMENT OF YOUTH ONSET T2D

6.1 | Management differences between T1DM and T2DM

The emergence of T2DM in children and adolescents has required that specialists familiar with the management of T1DM in children and adolescents recognize the vast differences between the treatment challenges of these two disorders.

- Differences in socioeconomic status: Whereas T1DM is distributed throughout the population proportionate to socioeconomic distribution, T2DM in developed countries disproportionately affects those with fewer resources, for example, lower income levels, less educated parents, and less well insured.[26,40] Conversely, in Asia and in other emerging economies, T2DM disproportionately affects the affluent.
- Older age: T1DM occurs throughout childhood, when parental influence is predominant, whereas T2DM occurs typically in adolescence, when peer influence predominates.
- More family experience: Only 5% of families with a child with T1DM have family experience with the disease, while more than 75% of families of the child with T2DM have such experience. Poor weight and glycemia control in these family members is common, with resultant complications and risk for a sense of fatalism.
- Gestational factors: More children with T2DM have either low or high birth weights and were exposed to gestational diabetes compared with those with T1DM .[68,69]
- Associated comorbidities and complications: Unlike T1DM, where diabetes related complications develop after many years of diabetes, many patients with T2DM will have comorbidities, such as fatty liver, sleep apnea, dyslipidemia, and hypertension[22,26,70] at the time of diagnosis and appear to develop microvascular and macrovascular complications at an accelerated rate. Therefore, screening for these abnormalities is recommended at the time of diagnosis and treatment may be required at the time of initiation of therapy for dysglycemia. Reduction in the rate of complications will require especially diligent attention to management of glycemia and aggressive treatment of comorbidities.[15,18,24,71,72] The complication rate of T2DM in European adolescents is lower than in the United States and Australia.[45]
- Lifestyle education: While education on diet and physical activity is important in all youth with diabetes, the need for intensive lifestyle intervention is a dominant feature of therapy in youth with T2DM.[73,74] However, treatment adherence is a great challenge in lifestyle intervention of obese adolescents.[74,75]
- Because of the lower risk for hypoglycemia in T2DM, a lower HbA1c target is achievable in most adolescents with T2DM.

6.2 | Management goals

- Education for diabetes self-management
- Normalization of glycemia while minimizing hypoglycemia
- Weight loss
- Reduction in carbohydrate and calorie intake
- Increase in physical activity and exercise capacity
- Control of comorbidities and complications, including hypertension, dyslipidemia, nephropathy, sleep disorders, and hepatic steatosis

6.3 | Education

See also the ISPAD Clinical Practice Guidelines for diabetes education.[76] Initial and on-going education for T2DM should focus on behavioral changes (diet and activity), as well as education on administration of oral hypoglycemic agents and insulin as needed. The materials used to provide diabetes education in the TODAY 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 ADA 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/)

- Education should be given by team members with expertise and knowledge of the unique dietary, exercise, and psychological needs of youth with T2DM. The education and treatment team for T2DM ideally should include a nutritionist, psychologist and/or social worker, and exercise physiologist.[76]
- Education in T2DM places greater emphasis on healthy lifestyle habits including behavioral, dietary and physical activity changes than is generally required for T1DM.
- Education should be provided in a culturally sensitive and age-appropriate manner
- Because nearly all youth with T2DM are adolescents, the ISPAD Guidelines for Adolescent Care are appropriate to the education of youth and families with T2DM.[77]
- The entire family will need education to understand the principles of treatment of T2DM and to understand the critical importance of the lifestyle changes required of the entire family to successfully manage a youth with T2DM.
- Care providers should acknowledge that the initial uncertainty in the diagnosis of diabetes type in some patients can be confusing and anxiety-provoking for the youth and family. The anxiety can be minimized by emphasizing the importance of normalizing blood glucose metabolism using whatever therapy is appropriate to the metabolic circumstances of the specific individual, regardless of the eventual "type" of diabetes.
- Contraceptive counseling should be included, as well as a discussion of typical failure rates and the importance of using the contraceptive method consistently and correctly to avoid unplanned pregnancy in diabetes.

6.4 | Behavioral change

Lifestyle change is the corner-stone of treatment of T2DM and clinicians should initiate a lifestyle modification program, including nutrition and physical activity, for children and adolescents at the time of diagnosis of T2DM.[78] The interventions include promoting a healthy lifestyle through behavior change, including nutrition, exercise training, weight management, and smoking cessation.

- The family and child should understand the medical implications of obesity and T2DM.
- Clinicians must understand the health beliefs and behaviors of the family/community to design an effective behavioral plan.
- Changes should be made in small achievable increments and with the understanding that these changes need to be permanent.
- The patient and family should be trained to monitor the quantity and quality of food, eating behavior, and physical activity on a regular basis.
- As in any behavioral change, a dynamic and sustainable reward system is essential for success.

6.5 | Dietary management

Involvement of a nutritionist/dietitian with knowledge and experience in nutritional management of youth with diabetes is necessary and experience with the unique characteristics of youth with T2DM is desirable. Dietary recommendations should be culturally appropriate, sensitive to family resources, and should be provided to all caregivers. 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. More specific dietary recommendations are given in the ISPAD Guidelines for dietary management and by the American Academy of Pediatrics.[79]

6.5.1 | Dietary modification should focus on

- Eliminating sugar-sweetened soft drinks and juices. 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 patients limit carbohydrate and energy intake,[80] but evidence that NNS can provide sustained reduction in weight or insulin resistance is lacking.
- Increasing fruit and vegetable intake.
- Reducing the use of processed, prepackaged, and convenience foods.
- Reducing the intake of foods made from refined, simple sugars and high fructose corn syrup.
- Portion control.
- Reducing meals eaten away from home.
- Asian diets that primarily consist of high-carbohydrate meals, and in some regions, high animal protein intake, should be modified, with increased portions of fresh vegetables and decreased portions of carbohydrate rich noodles, white rice, and starches.
- Changing staple foods from enriched white rice and white flour to brown rice and whole grain items with lower glycemic index to promote gradual and sustainable absorption with meals.
- Changing family diet behaviors:

  - Limiting availability of high-fat, high-calorie dense food and drink.
  - Teaching families to interpret nutrition fact labels.
  - Emphasizing healthy parenting practices related to diet and activity by promoting parental modeling of healthy eating habits, but avoiding overly restricted food intake.
  - Encouraging positive reinforcement of all goals achieved (eg, no or minimal weight gain, reduction in high caloric drinks) and avoiding blame for failure.
  - 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.
  - Collaboration with the family to consider cultural food preferences and the use of food during family events and cultural festivals.
  - Maintaining food and activity logs as beneficial for raising awareness of food and activity issues and for monitoring progress.

6.6 | Exercise management

Exercise is an important part of the diabetes management plan. Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, contribute to weight loss, and improve well-being[81–83] Youth with T2DM should be encouraged to engage in moderate-to-vigorous exercise for at least 60 minutes daily; this can be completed in several shorter segments. Specific, negotiated, and enjoyable exercise prescriptions should be developed for each patient 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 patient.

Exercise management should include:

- Collaborative development of an achievable daily exercise program to break the entrenched sedentary lifestyle characteristic of youth with T2DM,
- Reduction in sedentary time, including TV, computer-related activities, texting, and video games.[84] Screen time should be limited to less than 2 hours a day. 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.[84–86]
- Promotion of stable household routines, particularly increasing sleep duration and reducing TV viewing.[86,87]
- Addressing sedentary time spent doing school work and identifying ways to incorporate physical activity as breaks.
- 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,

- Encouragement of positive reinforcement of all achievements and avoidance of shaming.

6.7 | 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.[88] Additional research is needed to develop and examine the efficacy of interventions specifically targeting tobacco use among youth with T2DM within healthcare settings. Patients should be asked at each visit if they are smoking and counseled against initiation of smoking. Those youth who are smoking should be counseled on the importance of smoking 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.

6.8 | Glycemic monitoring

- SMBG
  - SMBG should be performed regularly. The frequency of SMBG should be individualized and include a combination of fasting and postprandial glucose measurements with a frequency based on the medication(s) used, the degree of glycemic control present, and available resources. Unlike in T1DM, the evidence that SMBG has an impact on glycemic control in individuals with T2DM is limited.
  - Once glycemic goals have been achieved, limited at home testing is needed and a few fasting and post prandial values a week are generally satisfactory. If values rise out of the target range consistently, more frequent testing should be recommended to identify the possible need for change in therapy.
  - During acute illness or when symptoms of hyper- or hypoglycemia occur, patients should perform more frequent testing and be in contact with their diabetes care team for advice.
- Patients on insulin or sulfonylureas need to use SMBG more frequently to monitor for asymptomatic hypoglycemia, particularly at night.
- HbA1c concentration should be determined at least twice a year and quarterly, if possible.
- The potential benefit of continuous glucose monitoring is being investigated in this population.

6.9 | Pharmacologic therapy

The aims of therapy in youth-onset T2DM are to improve glycemia, to prevent acute and chronic complications, to prevent metabolic decompensation, to improve insulin sensitivity, to improve endogenous insulin secretion if possible, to restore glucagon and incretin physiology, and to provide exogenous insulin when necessary. Furthermore, the choice of therapeutic approach should consider the effect on comorbidities and cardiovascular risk. While many oral hypoglycemic agents are approved for use in adults, only metformin is approved for use in youth in the majority of countries. Sulfonylureas are approved for use in adolescents in some countries; other oral agents are described below for information, recognizing that some adolescents may benefit from their use. However, newer agents are generally more expensive than the core therapies and evidence for their efficacy and safety in youth is limited or currently non-existent. Many clinical trials of anti-hyperglycemic agents are underway in youth-onset T2DM, but recruitment is slow and results are not expected for a few more years.

6.9.1 | Initial treatment

Initial treatment of youth with T2DM should include metformin and/or insulin alone or in combination. The specifics of the initial treatment modality are determined by symptoms, severity of hyperglycemia, and presence or absence of ketosis/ketoacidosis. As in T1DM, those with symptoms, particularly vomiting, can deteriorate rapidly and need urgent assessment and treatment.

1. If the patient is metabolically stable—HbA1c < 8.5% (69.4 mmol/mol) and no symptoms—metformin is the treatment of choice together with healthy lifestyle changes. Begin with 500 to 1000 mg daily × 7 to 14 days. Titrate by 500 to 1000 mg every 1 to 2 weeks, depending on patient tolerability, over 3 to 4 weeks until the maximal dose of 1000 mg BID, 850 mg TID (or 2000 mg once a day of extended-release metformin where available) is reached.
2. In patients with ketosis/ketonuria/ketoacidosis or HbA1c > 8.5% (69.4 mmol/mol), insulin will be required initially. A variety of insulin regimens are effective, but once-a-day intermediate or basal insulin (0.25-0.5 units/kg starting dose) is often effective in attaining metabolic control, while entailing minimal patient burden and being well-tolerated by the patients. The primary adverse effect of insulin is weight gain. The risk of hypoglycemia should also be considered, but is uncommon in adolescents with T2DM due to their insulin resistance. Metformin can generally be started at the same time as insulin, unless acidosis is present.
3. Transition onto metformin can usually be achieved over 2 to 6 weeks by decreasing the insulin dose 30% to 50% each time the metformin 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 T2DM can be successfully weaned off insulin and treated with metformin alone.[38,39]

6.9.2 | Subsequent therapy

The goal of initial treatment should be to attain an HbA1c of less than 7.0% (53 mmol/mol),[89] and in some situations <6.5% (47.5 mmol/mol).[90] This can almost always be accomplished with metformin and basal insulin, alone or in combination. Long-term glycemic control is more likely when therapy is intensified to maintain the HbA1c target (treat-to-target) rather than waiting for the HbA1c to rise before intensifying therapy (treat-to-failure).[91]

- If the patient fails to reach target HbA1c of <7.0% (53 mmol/mol) or <6.5% (47.5 mmol/mol) within 4 months on metformin monotherapy, addition of basal insulin should be considered.
- If target is not attained on combination metformin and basal (up to 1.5 U/kg/day), initiation of prandial insulin should be considered, with titration to reach target HbA1c < 7.0% (53 mmol/mol) or <6.5% (47.5 mmol/mol).
- Use of other oral or injected agents known to be effective in adults with T2DM for youth with T2DM may be beneficial in addition to, or instead of, metformin and insulin, but there are limited studies of the use of these agents and they are generally approved only for patients >18 years of age. These agents have not been specifically studied in young adults between 18 and 25 years, but it is presumed their safety and effectiveness are similar to that reported for older adults.

6.10 | Metformin

Metformin acts through AMP kinase in liver, muscle, and fat and improves glycemia through reducing hepatic glucose production by decreasing gluconeogenesis, and by stimulating peripheral glucose uptake in some but not all studies. Additionally, an initial anorexic effect may promote limited and likely unsustained weight loss.

- There is little to no risk of hypoglycemia with monotherapy.
- Intestinal side effects (transient abdominal pain, diarrhea, nausea) may occur, but can be minimized in most patients with slow dosage titration over 3 to 4 weeks and instructions to always take the medication with food. The side effects may also be attenuated by the use of extended release formulations.
- The risk of lactic acidosis with metformin is extremely low. Metformin should not be given to patients in ketoacidosis, with renal impairment, cardiac or respiratory insufficiency, or who are receiving radiographic contrast materials. Metformin should be temporarily discontinued during a gastrointestinal illness.[89]
- Metformin may normalize ovulatory abnormalities in girls with polycystic ovary syndrome (PCOS) (ovarian hyperandrogenism) and increase pregnancy risk.[92]
- Metformin is approved for use during pregnancy.
- Recent studies in adults indicate increased prevalence of B12 deficiency in adults taking metformin, but the implications for adolescents are unclear; no cases of B12 deficiency were reported in the TODAY study.[93] Nevertheless, periodic monitoring of B12 should be considered.

6.11 | Other available agents

6.11.1 | Sulfonylurea and meglitinides (not approved for use in those <18 years in all countries)

These agents bind to receptors on the K+/ATP channel complex causing K+ channels to close, resulting in insulin secretion. Meglitinides bind to a separate site from sulfonylureas on the K+/ATP channel complex. Sulfonylurea sites equilibrate slowly and binding persists for prolonged periods; thus, traditional sulfonylureas have prolonged effects. Meglitinides[94] have an intermediate equilibration and binding

duration and are prescribed for rapid enhancement of insulin secretion before meals. Overall, use of sulfonylureas in adults is associated with a 1.5% to 2% decrease in HbA1c.

- The major adverse effects of sulfonylureas are:
  - Hypoglycemia: may be severe and prolonged depending on the agent used
  - Weight gain
- There has been a single pediatric clinical trial of a sulfonylurea (glimepiride), which showed no superior efficacy to metformin and a greater degree of weight gain and hypoglycemia.[95]
- Sulfonylureas may accelerate the loss of beta-cell function and eventual loss of control on oral therapy alone.[96]

6.11.2 | Thiazolidinedione (TZD) (not approved for use in those <18 years of age)

TZDs bind to nuclear peroxisome proliferator activator receptors (PPAR gamma), which are ubiquitous orphan steroid receptors particularly abundant in adipocytes. These agents increase insulin sensitivity in muscle, adipose, and liver tissue, with a greater effect on muscle glucose uptake than biguanides. Long-term treatment in adults is associated with a reduction in HbA1c of 0.5% to 1.3%. The side effects of TZDs include weight gain, anemia, fluid retention (including congestive heart failure),[94,97] and possible association with bladder cancer.[98] Liver toxicity associated with earlier members of this family have not been found with the newer TZDs. Rosiglitazone was under substantial marketing restriction in the United States and Europe due to concerns for an increased risk for congestive heart failure and myocardial infarction. Although these restrictions have been lifted, the future of TZDs in therapy for T2DM in adults or youth remains unclear.

In the TODAY study, therapeutic failure rates were the lowest in the group receiving metformin plus rosiglitazone (38.6%) vs metformin alone (51.7%) vs metformin plus lifestyle (46.6%).[17] Thus, addition of rosiglitazone to metformin decreased the risk for progression to insulin requirement by 23%.

6.11.3 | α-Glucosidase inhibitors (not approved for use in those <18 years of age

α-glucosidase inhibitors (acarbose, miglitol) reduce the absorption of carbohydrates in the upper small intestine by inhibiting breakdown of oligosaccharides, thereby delaying absorption in the lower small intestine. This reduces the postprandial rise of plasma glucose. Long-term therapy is associated with 0.5% to 1% (5.5-10.9 mmol/mol) reduction in HbA1c. Because of their mechanism of action, these agents have been particularly widely used and successful in countries where carbohydrates make up a substantial part of the diet.[99] There have been no trials of α-glucosidase inhibitors in youth, but the frequent side effect of flatulence makes these agents unattractive to most adolescents.

6.11.4 | Incretin mimetics (glucagon-like peptide-1 [GLP-1] receptor agonists) (not approved for use in those <18 years of age)

GLP-1 is secreted by L-cells in the small intestine in response to food, increasing insulin secretion proportionate to BG concentrations,

suppressing glucagon, prolonging gastric emptying, and promoting satiety. They are rapidly degraded by dipeptidyl peptidase- IV (DPP-IV); both native GLP-1 and the injected mimetic have a serum half-life of 2 minutes. However, pharmaceutical alterations in the GLP-1 agonists have resulted in longer-acting injected agents given twice-daily, once daily, or once-weekly subcutaneous injections. Clinical trials in adults have shown reduced fasting and post-prandial BG, weight loss, and lower HbA1c (0.5%-0.8%), as well as reduction in cardiovascular and renal events in high-risk patients.[100,101] Adverse effects include nausea, vomiting, diarrhea, and infrequent dizziness, headache, and dyspepsia. The side effects generally decrease over time. Besides a single publication of the pharmacodynamics and the pharmacokinetics of liraglutide in adolescents with T2DM,[102] there are no published studies of efficacy and safety of incretin mimetics in youth T2D, but several are currently underway.

6.11.5 | DPP-IV Inhibitors (not approved for use in those <18 years of age)

DPP-IV inhibitors inhibit the enzyme that breaks down GLP-1, resulting in higher concentrations of GLP-1 and effects similar to those of GLP-1 mimetics, though unlike GLP-1 mimetics, they have no effect on gastric emptying, satiety or weight loss. DPP-IV inhibitors are administered orally once or twice daily and long-term therapy in adults is associated with 0.5% (5.5 mmol/mol) reduction in HbA1c. There have been no published studies of DPP-IV inhibitors in youth, but several are currently underway.

6.11.6 | Sodium-Glucose Co-transporter 2 (SGLT2) inhibitors (not approved for use in those <18 years of age)

SGLT-2 inhibitors inhibit renal tubular reabsorption of glucose, leading to increased urinary glucose loss, reduction in serum glucose, and weight loss. The use of SLGT 2 inhibitors in adults is associated with reduction in HbA1c approaching that seen with metformin.[91] Furthermore, SGLT2 inhibitors have been shown to have beneficial effects on weight loss, BP, renal function, and cardiovascular outcomes in adults.[103–106] Adverse effects include small increases in prevalence of genitourinary infections, particularly among women and uncircumcised men.[107] Canagliflozin has been associated with increased rates of lower extremity amputations in adults at risk for vascular compromise[108] and there have been reports of euglycemic diabetic ketoacidosis in patients on SGLT2 inhibitors.[109] There have been no studies of SGLT2 inhibitors in youth, but several are currently underway.

6.12 | Gastric surgery

Bariatric surgery may be considered for adolescents with obesity-related comorbidities, including T2DM, particularly when patients have been unsuccessful with medical therapy alone. Recent results from a large US consortium of pediatric bariatric surgery centers has demonstrated remission of T2DM and other comorbidities in nearly all youth, with attainment of HbA1c targets exceeding that seen with medical therapy.[110,111] Currently metabolic surgery is considered for adolescents with T2DM and BMI > 35 kg/m^2 who have uncontrolled glycemia and/or comorbidities despite lifestyle and pharmacologic treatment. Although the morbidity and mortality rates in adults have

decreased over the last 5 years, this treatment should be undertaken only in centers of excellence with an established and experienced surgical, nutritional, behavioral, and medical support and outcome data collection program.

7 | T2DM AND INSULIN RESISTANCE: COMORBIDITIES AND COMPLICATIONS

Insulin resistance is a physiologic abnormality, defined as an impaired response to the physiologic effects of insulin, including effects on glucose, lipid, and protein metabolism, and on vascular endothelial function. Insulin resistance is increased during mid-puberty, pregnancy, aging, and the luteal phase of the menstrual cycle, in individuals of some ethnicities, and in those with increased total and visceral adiposity, high fat diet, and sedentary behavior.

Several events in development may be associated with increased risk for the insulin resistance syndrome, including premature adrenarche,[112] being born small for gestational age (SGA) or to a pregnancy complicated by maternal obesity.[113] The development of obesity and inactivity during childhood also increases the likelihood of insulin resistance.

The insulin resistance syndrome is a collection of abnormalities that are increased in prevalence in insulin-resistant individuals. These abnormalities include:

- Dysglycemia (IFG, IGT, T2DM)
- Lipid abnormalities (increased triglycerides, decreased HDL-C, small, dense LDL-C particles)
- Endothelial dysfunction (increased mononuclear cell adhesion, plasma cellular adhesion molecules, decreased endothelial-dependent vasodilatation)
- Increased procoagulant factors (plasminogen activator inhibitor-1 and fibrinogen)
- Hemodynamic changes (increased sympathetic nervous system activity, increased renal sodium retention)
- Inflammation (increased C-reactive protein, cytokines.)
- Increased plasma uric acid
- Increased hepatic and intramyocellular lipid deposition
- Mitochondrial dysfunction
- Ovarian hyperandrogenism
- Sleep-disordered breathing.

Because of these insulin resistance-related abnormalities, individuals with insulin resistance have a higher risk of developing overt T2DM, cardiovascular disease, hypertension, polycystic ovary syndrome, NAFLD, nephropathy, OSA, and some types of cancer. In contrast to the definition of metabolic syndrome (MetS) in adults,[114] there is no standard definition of metabolic syndrome for use in the pediatric population and more than 46 different pediatric metabolic syndrome definitions have been used.[115,116] Indeed, the concept of defining the MetS in childhood has been criticized due to absence of epidemiologic data associated any definition with cardiovascular risk.[117] In 2007, the International Diabetes Federation published its definition of the MetS in children and adolescents based on

extrapolation from adult data.[118] This panel recommended the following criteria:

1. for children 6 to <10 years old, obesity (defined as ≥90th percentile of waist circumference), followed by further measurements as indicated by family history;
2. for age 10 to <16 years, obesity (defined as waist circumference ≥ 90th percentile), followed by the adult criteria for triglycerides, HDL-C, BP, and glucose. For youth ≥16 years of age, the panel recommends using the existing International Diabetes Federation criteria for adults.

When this definition is used, MetS is rapidly increasing in prevalence with rising childhood obesity and sedentary lifestyles worldwide. In western countries, the incidence of childhood obesity has more than doubled over the past generation. Studies show that the prevalence of metabolic syndrome in obese youth ranges from 19% to 35%, compared with <2% in normal-weight groups. The odds of developing metabolic syndrome in obese boys and girls were 46-67 and 19-22 times greater, respectively, than for normal-weight youth.[119] A recent study showed that the prevalence of metabolic syndrome was 27.6% in obese Chinese children, compared to 0.2% in normal weight children.[120] Similar findings have been reported from India.[121]

Co-morbidities characteristic of insulin resistance are commonly present at diagnosis or appear early in the course of T2DM and should be screened for sooner than in T1DM, where these disorders are generally seen as complications of long-standing diabetes rather than as co-morbid conditions.[122] A more complete discussion of screening for complications/co-morbidities is presented in the ISPAD Guidelines for microvascular, macrovascular, and other complications.[123,124]

7.1 | Obesity

Obesity has deleterious associations with morbidity independent of insulin resistance and diabetes.[125–127] In addition, weight loss and exercise both improve insulin resistance and glycemia. Shifts up or down in BMI category during childhood are associated with increases and decreases in cardiovascular risks markers.[128] Therefore, assessment of BMI and pattern of weight gain should be considered a routine part of monitoring in youth with T2DM.[129]

7.2 | Hypertension

Hypertension is associated with endothelial dysfunction, arterial stiffness, and increased risk of both cardiovascular and kidney disease.[130] Moreover, tight BP control in adults with T2DM in the UK Prospective Diabetes Study (UKPDS) improved microvascular and macrovascular disease at least as much as control of glycemia.[131] Hypertension was present in 13.6% of 699 US youth in the TODAY study at a median duration of diabetes of 7 month,[26] progressing to 33.8% during average follow-up 3.9 years.[18] Male sex and higher BMI significantly increased the risk for hypertension in the TODAY cohort. Eppens et al.[132] reported even higher rates in Australia, with 36% of youth with T2DM having hypertension within 1.3 years of T2DM

diagnosis. Moreover, the SEARCH Study, which included US youth with longer diabetes duration, found hypertension in 65% of youth with T2DM.[133] Hypertension in T2DM is related to renal sodium retention and resulting volume expansion, increased vascular resistance related to reduced nitric-oxide-mediated vasodilatation, and increased sympathetic stimulation by hyperinsulinemia. In addition, there is a possible genetic predisposition to hypertension in T2DM related to associated increased activity of the renin-angiotensin system.

- BP should be measured with an appropriate-sized cuff at every clinic visit, and values compared to the normal ranges for sex, height and age.
- Initial treatment of BP consistently at, or above, the 95th percentile on three occasions should consist of efforts at weight loss, limitation of dietary salt, and increased physical activity.
- If, after 6 months, BP is still above the 95th percentile, initiation of an ACE inhibitor or ARB should be considered to achieve BP values that are less than the 90th percentile[134,78,130,135] If the ACE inhibitor is not tolerated due to adverse effects (mainly cough), an ARB, calcium channel blocker, or diuretic are alternatives.
- Combination therapy may be required if hypertension does not normalize on single agent therapy. However, combination ACE inhibitor and ARB are not recommended due to an excess of adverse events and no added clinical benefit.[136] Evaluation of hypertension not responsive to initial medical therapy should also include a renal ultrasound and echocardiogram.[130]

7.3 | Nephropathy

Albuminuria (either micro- or macro-) is present at the time of diagnosis in a substantial number of adolescents with T2DM and prevalence increases with duration of diabetes. In the TODAY study, microalbuminuria was found in 6.3% of 699 T2DM youth at baseline at a median disease duration of 7 months and prevalence rose to 16.6% by 36 months[18,26]; higher levels of HbA1c were significantly related to risk of developing microalbuminuria. Similar findings have been reported in smaller studies of US minority and Indian, Canadian First Nation and Maori youth[70,137,138] and macroalbuminuria was reported in 16% of First Nation youth after relatively short disease duration.[139] In a study in Manitoba, Canada, youth with microalbuminuria were nine times as likely to develop renal failure as those without microalbuminuria.[140] Thus, the presence of albuminuria in youth was highly predictive of the future risk of renal failure. The prevalence of micro- and macroalbuminuria is higher and the progression of nephropathy is accelerated in youth-onset T2DM compared to T1DM in all populations examined. In a Japanese cohort of 1065 patients diagnosed with T2DM prior to age 30 years, 31 (3%) developed renal failure requiring dialysis at a mean age of 35 years. Factors influencing progression were diabetes duration, HbA1c, and diastolic BP. Moreover, the incidence of nephropathy for those diagnosed age 10 to 19 years was double that of individuals in the same population with T1DM, even when accounting for duration of disease.[141]

- Albuminuria should be evaluated at diagnosis and annually thereafter
- The definition of microalbuminuria used by the ADA is either:
  - Albumin-to-creatinine ratio 30 to 299 mg/g (3.39-33.79 mg/mmol) in a spot urine sample (preferred)
  - Timed overnight or 24-hour collections with albumin excretion rate of 20 to 199 mcg/min.
- An elevated value can be secondary to exercise, smoking, menstruation and orthostasis. Therefore, the diagnosis of persistent abnormal microalbumin excretion requires documentation of two of three consecutive abnormal values obtained on different days.
  - Repeat testing should be done in the AM immediately after rising, as orthostatic proteinuria is common in adolescents and is considered benign.
- Non-diabetes-related causes of renal disease should be considered and consultation with a nephrologist obtained if macroalbuminuria (ACR > 300 mg/g) is present.
- If urine ACR is confirmed to be >30 mg/g (3.39 mg/mmol) and BP is elevated, or if urine ACR is >300 mg/g (33.9 mg/mmol) irrespective of BP, ACE inhibitor or ARB should be started and BP normalized (A)

7.4 | Dyslipidemia

Hypertriglyceridemia and decreased HDL-C are the hallmarks of the dyslipidemia characteristic of obesity, insulin resistance and T2D. In the TODAY study, 79.8% of T2DM youth had a low HDL-C and 10.2% had high triglycerides within a few months of diagnosis[26] and the SEARCH study found that 73% of 2096 US youth with T2DM of longer duration had a low HDL and 60% to 65% had hypertriglyceridemia.[142] In a Canadian First Nations population of 99 youth with T2DM, total cholesterol, LDL-C, triglycerides and apoB level greater than the National Health And Nutritional Evaluation Study (NHANES) 75th percentile were found in in 60%, 41%, 43%, and 43%, respectively, and low HDL-C in 35%.[139] In 68 Australian youth with a duration of T2DM of less than 3 years, elevated total cholesterol was found in 32% and hypertriglyceridemia in 53%.[132] Finally in Taiwan, hypercholesterolemia was present in 27% youth with T2DM.[7] Additional findings include elevated VLDL, elevated Lp_a, and increased small dense LDL-C particles. Decreased lipoprotein lipase activity, increased lipoprotein allocation and increased lipoprotein oxidation render the lipoproteins more atherogenic.

- In youth with T2DM, testing for dyslipidemia should be assessed once glycemic control has been achieved or after 3 months of initiation of medication, and annually thereafter.[78,130] Initial screening does not need to be done fasting.
- Goal levels are:
  - LDL-C < 100 mg/dL (<2.6 mmol)
  - HDL-C > 35 mg/dL (0.91 mmol/L)
  - triglycerides <150 mg/dL (1.7 mmol/L)
- If LDL-C is above goal,
  - blood glucose control should be maximized and dietary counseling should be provided (7% saturated fat, <200 mg cholesterol) and exercise encouraged.[130]

- A repeat lipid profile should be performed in 6 months.
- If repeat LDL-C > 130 mg/dL (>3.4 mmol/L): begin medication with a goal of <130 mg/dL (<3.4 mmol/L) and an ideal target of <100 mg/dL (<2.6 mmol/L).
- Statin therapy has been shown to be safe and effective in children as in adults and should be the first pharmacologic intervention,[123] although long term safety data are not available.
- Statin treatment should begin at the lowest available dose and dose increases should be based on monitoring of LDL-C levels and side effects.
- 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.
- Routine monitoring of liver enzymes is not required with statin therapy.
- Elevated triglycerides can increase the risk for pancreatitis.
  - If the triglycerides are >150 mg/dL (>1.7 mmol/L), efforts to maximize blood glucose control, limit dietary fat and simple sugars and achieve desirable weight should be emphasized.
  - If fasting triglycerides are >400 mg/dL (5.6cmmol/L) or non-fasting triglycerides >1000 mg/dL (11.3 mmol/L) treatment with a fibric acid should be considered due to significantly increased risk for pancreatitis, with a goal of <150 mg/dL (<1.7 mmol/L).
- Low HDL-C levels in youth are not managed directly with medication, but physical activity and healthy diet should be encouraged.

7.5 | Atherosclerosis and vascular dysfunction

Hyperglycemia, dyslipidemia, and hypertension 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 T2DM. 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.[143,144] In addition, youth with T2DM have increased intima media thickness, serum markers of endothelial damage, left ventricular hypertrophy,[145,146] cardiac dysfunction, reduced maximal exercise capacity[55] and increased arterial stiffness,[147] all of which predict early cardiovascular morbidity and mortality.

7.6 | Polycystic ovary syndrome (PCOS)

PCOS is increasingly recognized in adolescent girls with obesity. Adolescents with PCOS have ∼40% reduction in insulin-stimulated glucose disposal compared to body composition matched non-hyperandrogenic control subjects.[148] There are limited data on the exact prevalence of PCOS in youth with T2DM, but a study of 157 adult women of reproductive age with T2DM found the PCOS prevalence to be high at 8.3%.[149] A lack of periods can increase long term risk of endometrial cancer and PCOS increases lifetime risk for cardiovascular disease.[150]

- A menstrual history should be taken on every girl with T2DM at diagnosis and at each visit.
- An evaluation for PCOS should be considered if there is primary or secondary amenorrhea, hirsutism and or significant acne.
- PCOS is diagnosed based on the presence of oligo- or amenorrhea with biochemical or clinical evidence of hyperandrogenism, without or without evidence for polycystic ovaries.[92]
- Decreasing insulin resistance with weight loss, exercise and metformin improves ovarian function and increases fertility.
- Girls receiving diabetes treatment should also be counseled that fertility may improve as a result and appropriate birth control should be used when desired to prevent pregnancy.

7.7 | Non-alcoholic fatty liver disease

Hepatic steatosis is present in 25% to 50% of adolescents with T2DM and more advanced forms of NAFLD, such as NASH, are increasingly common and associated with progression to cirrhosis, portal hypertension, and liver failure.[151,152] NAFLD is the most frequent cause of chronic liver disorders among obese youth[153] and is the most common reason for liver transplantation in adults in the United States. In the United States, Hispanics have the highest prevalence of NAFLD, followed by non-Hispanic Whites, while the prevalence among African-American is much lower.[154] However, these prevalence estimates are based on liver enzyme elevations and are likely an underestimate of the prevalence of hepatic steatosis in T2DM youth, as steatosis is more common than elevated liver enzymes and liver enzymes can be normal despite having steatosis.[155] Newer imaging methods for analysis of liver fat and inflammation are emerging and may become more standard in coming years.[156] Presence of the metabolic syndrome in obese adolescents predicts IGT and NAFLD[55] and the presence of T2DM independently predicts progression to fibrosis.[157]

Weight loss improves NAFLD and metformin has been shown to improve liver enzymes and liver steatosis in youth in insulin resistant adolescents.[55,158] In the TODAY study, permanent medication reductions/discontinuation due to elevated liver enzymes was lowest in the metformin plus rosiglitazone group.[93] Thus, T2DM therapies that improve insulin resistance appear to improve NAFLD and, therefore, are the standard approach to youth with both NAFLD and T2DM. However, due to the potential for progression to NASH, fibrosis and cirrhosis, ongoing monitoring of liver enzymes is recommended in youth with T2DM, with referral for imaging and/or biopsy if enzymes remain >3 times ULN despite weight loss and/or diabetes therapies.

7.8 | Obstructive sleep apnea

OSA is common in obese youth, but the prevalence in pediatric T2DM has not yet been well documented. However, it is likely high, since the prevalence of OSA in adults with T2DM is between 70% and 90%.[159,160] OSA not only causes poor sleep quality and daytime sleepiness, but in adults it has clinical consequences, including hypertension, left ventricular hypertrophy and increased risk of renal and cardiovascular disease.

- The International Diabetes Federation Taskforce on Epidemiology and Prevention strongly recommended that health professionals working in adult T2DM consider the presence of OSA.[161]
- OSA can be screened for in youth with T2DM using questions about snoring, sleep quality, apnea, morning headaches, daytime sleepiness, nocturia, and enuresis.
- If symptoms are suggestive, the diagnosis of OSA is made by formal sleep study and referral to a sleep specialist.

7.9 | Depression, anxiety, eating disorders, cognition

Youth with T2DM are at increased risk for a number of major mental health challenges, including major clinical depression,[162–165] which is associated with poor adherence to diabetic treatment recommendations.[162,164,166] Current evidence suggests the early presence of depressive symptomatology, higher distress scores and anxiety, equivalent to or greater than that seen in T1DM and older onset T2DM.[167] Signs include depressed mood, markedly diminished interest or pleasure, increased or decreased appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness and recurrent thoughts of death.

- Youth with T2DM should be assessed for depression at diagnosis and periodically thereafter, particularly in those with frequent emergency department visits or poor glycemic control.
- Identified patients should be referred to appropriate mental health care providers experienced in addressing depression in youth.[162]

There is also increasing evidence of a high prevalence of anxiety disorders, eating disorders,[168,169] social isolation and impaired cognitive function in youth with T2DM and their caregivers.[170] The assessment and treatment of these disorders should be considered part of the comprehensive care of youth with T2DM.

7.10 | Cardiovascular risk in youth-onset T2D

Adults in their 40s with youth-onset T2DM have a marked excess of macrovascular disease, with a high prevalence of ischemic heart disease (12.6%), stroke (4.3%), the composite end point of any macrovascular disease (14.4%) and death (11%).[24] In addition, these endpoints were markedly higher than a similarly aged group of participants with T1DM, despite similar glycemic control and a longer duration of diabetes in the T1DM group. It has been estimated that youth and young adults with T2DM lose approximately 15 years from average life expectancy and may experience severe, chronic complications by their 40s.[171] Furthermore, emerging evidence suggests that early onset of T2DM may be associated with more aggressive development of microvascular and macrovascular complications than T2DM appearing at later ages.[21,172–174] Therefore, a comprehensive management plan that includes early and aggressive control of diabetes complications and cardiovascular risk factors is needed to reduce lifetime risk of morbidity and early death. This risk for accelerated cardiovascular disease in young adults argues for transition of these patients to multidisciplinary adult medical providers who can provide expertise in

comprehensive monitoring and treatment of diabetes and related complications.

8 | POPULATION SCREENING FOR T2DM IN HIGH-RISK YOUTH

As opposed to identification of diabetes in a specific youth in whom there is a moderate or high level of clinical suspicion for diabetes, screening refers to broad based testing of a population or testing of individuals meeting certain general criteria. While the former is necessary in the evaluation of individual patients, the latter is only justifiable in certain circumstances.[175] General guidelines to justify a screening test and as applied to T2DM in youth are as follows:

- The condition tested for is sufficiently common to justify the cost of the testing.
  - It is not clear that this is the case in most populations. In the United States, screening based on fasting and post-challenge glucose in high-risk minority adolescents at the peak age of T2DM diagnosis identified <1% with T2DM.[176] Whether there is sufficient prevalence of undiagnosed T2DM in specific populations of adolescents to justify testing remains unclear.
  - If the disorder has low prevalence, most abnormal tests will be false positives and require additional testing, which must be included in the determination of cost.
- The condition tested for is serious in terms of morbidity and mortality.
  - Unquestionably true of T2DM in adolescents because of the association with increased cardiovascular risk factors and renal dysfunction.
- The condition tested for has a prolonged latency period without symptoms, during which abnormality can be detected and treatment can prevent morbidity.
  - Early detection of T2DM is likely associated with better outcome, though specific published support for this presumption is lacking in youth.
  - Pre-diabetes has been identified in at-risk youth, but there is currently no evidence-based interventions beyond those which would be delivered to the at-risk youth anyway (weight loss, exercise, diet change).
  - Hypertension, dyslipidemia, and microalbuminuria have been identified in youth with pre-diabetes, but also in obese youth without diabetes. Therefore, there is an argument for monitoring and appropriate treatment of hypertension, dyslipidemia, and microalbuminuria in at-risk youth, rather than focusing on identification of dysglycemia.
- A test is available that is sensitive (few false negatives) and accurate with acceptable specificity (minimal number of false positives).

  - None of the currently available tests (fasting glucose, random glucose, 2-hour post-challenge glucose, HbA1c) are sufficiently sensitive and specific to function well given the low prevalence of T2DM, even in high-risk populations

- There remains substantial uncertainty in the normal ranges and meaning of abnormal values in each of these measures of glycemia in youth.

Guidelines issued by the ADA in 2000,[177] the American Academy of Pediatrics in 2013[78] and by the Endocrine Society in 2017[129] all recommend screening for diabetes in the clinical setting in at-risk obese youth after age 10. However, accumulating data indicate that screening to identify diabetes in asymptomatic youth has a low yield and further research is required to determine the optimal strategy for testing, including the frequency of testing. Therefore, for now, the best evidence suggests that population screening for T2DM outside of research settings is not cost-effective in most populations. Urinary glucose screening of youth in Japan and Taiwan may be evidence-based exceptions.[178,179]

9 | SUMMARY AND CONCLUSIONS

Youth-onset T2DM has emerged as an important health problem in youth, disproportionately affecting socioeconomic minorities in North America and Europe and increasingly prevalent in emerging economies, such as India, China, Malaysia, and parts of South America. Since the last set of ISPAD guidelines in 2014, there has been substantial progress in our understanding of the disorder and growing recognition that youth-onset T2DM, while sharing aspects of pathophysiology with T2DM occurring later in life, also has important unique features - rapid onset and progression, highly prevalent and rapidly progressing comorbidities, challenging socioeconomic features in most countries, and close association with puberty, a life-stage during which management of chronic disease is especially difficult. Furthermore, youth-onset T2DM has more rapid development of complications and cardiovascular risk than either youth-onset T1D M or adult-onset T2DM, leading to higher morbidity and mortality rates.

Unfortunately, this elevated risk for poor outcome is not always appreciated by families, primary care providers, or diabetes specialists, for whom familiarity with adult onset T2DM and the lack of insulin dependence may generate a false complacency. These features combine to make youth-onset T2DM a particularly challenging disorder and suggest that, given the complex needs of youth with T2DM, such patients should be managed by diabetes providers experienced in the disorder and its associated comorbidities and, where possible, in specialized multi-disciplinary centers. Furthermore, transition to adult care is period of high-risk for worsening of control and adherence and loss of follow-up and should be undertaken thoughtfully.

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