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Pediatric Diabetes 2014: 15(Suppl. 20): 26–46
doi: 10.1111/pedi.12179
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Pediatric Diabetes

ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Type 2 diabetes in the child and adolescent

Zeitler P, Fu J, Tandon N, Nadeau K, Urakami T, Bartlett T, Maahs D. Type 2 diabetes in the child and adolescent.
Pediatric Diabetes 2014: 15 (Suppl. 20): 26–46.

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Key words: guidelines – ISPAD – type 2 diabetes

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

Screening for T2D in at-risk youth

- Undiagnosed type 2 diabetes (T2D) is very rare in the adolescent population (A).
- Generalized screening of obese youth is unlikely to be cost-effective in most populations (E).
  - Urinary glucose screening in Japanese adolescents may be a specific case with demonstrated cost effectiveness.
- Clinical testing for dysglycemia in obese at-risk youth should occur in the setting of clinical assessment of obesity-related comorbidities [non-alcoholic fatty liver disease (NAFLD), elevated triglycerides, elevated blood pressure (BP)] that are more prevalent than dysglycemia (E)

Diagnosis and determination of diabetes type

- T2D in youth should be diagnosed using American Diabetes Association (ADA) criteria (E)
  - Diagnosis can be made based on fasting glucose, 2-h postchallenge glucose, or hemoglobin A1c (HbA1c).
  - In the absence of symptoms, testing should be confirmed on a different day.
  - Clinicians should be aware of the weaknesses of each diagnostic test.
- Diabetes autoantibody testing should be considered in all pediatric patients with the clinical diagnosis of T2D because of the high frequency of islet cell autoimmunity in otherwise 'typical' T2D (E).
  - Prepubertal children are unlikely to have T2D even if obese (A).
  - Antibodies will indicate the diagnosis of type 1 diabetes (T1D) and an earlier need for insulin (A).
  - Antibodies will indicate the need to consider the presence of other associated autoimmune disorders (A).
- Diabetes autoantibody testing should be considered in overweight/obese pubertal children with a clinical picture of T1D (A).

- The presence of clinically relevant associated complications and comorbidities should be assessed at the time of diagnosis (A).

  - Triglycerides and liver enzymes should be obtained at the time of diagnosis to exclude acute clinically relevant abnormalities (E).
  - Urine albumin/creatinine ratio (ACR) should be obtained at the time of diagnosis.
  - Patients should be screened for obstructive sleep apnea (OSA), pregnancy, and depression at the time of diagnosis (E).

Initial treatment

- Lifestyle change should be initiated at the time of diagnosis of T2D (E).
- Initial pharmacologic treatment of youth with T2D should include metformin and insulin alone or in combination (A).
- Initial treatment is determined by symptoms, severity of hyperglycemia, and presence or absence of ketosis/ketoacidosis (E).

  - Patients with symptoms can deteriorate rapidly irrespective of eventual diabetes type and need urgent assessment and appropriate treatment (E).
  - Metabolically stable patients (HbA1c < 9 and no symptoms) should be started on metformin monotherapy (A).

    (i) Begin with 500 mg daily × 7 d. Titrate by 500 mg once a week over 3–4 wk to the maximal dose of 1000 mg twice-daily (BID) (extended release metformin product may be used where available).

  - Patients who are not metabolically stable require insulin (A).

    (i) Once a day NPH or basal insulin (0.25–0.5 units/kg starting dose) is often effective in attaining metabolic control.
    (ii) Metformin can be started at the same time as insulin, unless acidosis is present.
    (iii) Transition onto metformin monotherapy can usually be achieved safely over 2–6 wk.

- The goal of initial treatment should be HbA1c < 6.5% (B).
- 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).

Subsequent treatment

- If the patient fails to reach target HbA1c of <6.5% within 3–4 months on metformin monotherapy, addition of basal insulin should be strongly considered (A).
- If target is not attained on combination metformin and basal insulin (up to 1.2 U/kg), prandial insulin should be initiated and titrated to reach target HbA1c < 6.5% (B).
- There are limited studies of the use of other pharmacologic agents and they are generally not approved in this population (E).

Assessment and management of comorbidities and complications

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

  (i) An elevated urine ACR should be confirmed on 2 of 3 samples.

    - If elevated urine ACR is confirmed, angiotensin-converting enzyme (ACE) inhibitor should be started and titrated every 3 months until ratio is normal (A).

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

  (i) Elevated BP should be confirmed on 2 additional days.
  (ii) Hypertension is defined as an average systolic or diastolic BP > 95 percentile for age, sex, and height percentiles, with high normal BP being 90 to <95 percentile.

  - Initial treatment should consist of weight loss, limitation of dietary salt, and increased physical activity (E).
  - If BP is above the 95th percentile after 6 months, an ACE inhibitor is initiated and titrated to achieve BP less than the 90th percentile (A).

  (i) If the ACE inhibitor is not tolerated due to adverse effects, an angiotensin receptor blocker, calcium channel blocker, or diuretic can be used (E).
  (ii) Combination therapy may be required if hypertension does not normalize on single agent therapy (E).

- Testing for dyslipidemia should be repeated soon after diagnosis when glycemic control has been achieved and annually thereafter (A).

◦ Cholesterol

(i) Goal levels are:

- Low-density lipoprotein cholesterol (LDL-C) <100 mg/dL (2.6 mmol/L)
- High-density lipoprotein cholesterol (HDL-C) >35 mg/dL (0.91 mmol/L)
- Triglycerides <150 mg/dL (1.7 mmol/L)

(ii) If LDL-C is above goal, blood glucose control should be maximized and dietary counseling should be provided using the American Heart Association (AHA) step 2 diet.

- A repeat fasting lipid profile should be performed in 6 months.

(iii) If repeat LDL-C >130 mg/dL: begin medication with a goal of <130 mg/dL an ideal target of <100 mg/dL (E).

(iv) Statin therapy has been shown to be safe and effective (A).

◦ Triglycerides

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

(ii) Fibrate therapy is the preferred medication category for hypertriglyceridemia and has been shown to be safe and effective (A).

- Examination for retinopathy should be performed at diagnosis and annually thereafter (A).
- Evaluation for NAFLD should be done at diagnosis and annually thereafter (A).

◦ Patients should be referred to gastroenterology if liver enzymes remain elevated despite weight loss and attainment of glycemic control (E).

- Patients should be screened for menstrual irregularities, hyperandrogenism, depression, and OSA at diagnosis and regularly thereafter (E).
- Patients should be screened for smoking and alcohol use at diagnosis and regularly thereafter (E).

Introduction

T2D in children and adolescents (youth-onset T2D) has become an increasingly important public health concern throughout the world (1–17), with unique characteristics and demographics in many countries. Because of the relatively recent emergence of the problem in this age group, 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 2009, ISPAD developed guidelines for the diagnosis and management of children and adolescents with T2D (18). Since the publication of those guidelines, a number of important studies have been designed and completed that contribute substantially to understanding of T2D. This chapter will discuss the diagnosis and presentation of T2D, classification of diabetes type, initial and subsequent treatment, monitoring and assessment, and management of associated comorbidities and complications.

Definition, classification, and characteristics of youth-onset T2D

T2D occurs when insulin secretion is inadequate to meet the increased demand posed by insulin resistance, leading to relative insulin deficiency (19) and is generally associated with other metabolic abnormalities, characteristic of insulin resistance (dyslipidemia, hypertension, polycystic ovary syndrome, fatty liver) (20). Unlike T1D, there is no identified autoimmune process leading to inadequate insulin secretion in T2D (20) and inadequate insulin secretion appears to result from genetic, environmental, and metabolic causes may differ between individuals. Insulin secretion depends on disease status and duration, and can vary from delayed but markedly elevated in response to a glucose challenge initially to absolutely diminished (19). 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 (21). Recent data from the TODAY (Treatment Options for T2DM in Adolescents and Youth) study suggest that the loss of insulin secretion is even more rapid when T2D presents in adolescents (22, 23).

The diagnosis of T2D 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 (24). The diagnostic criteria for diabetes are based on the 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.

Diabetes is diagnosed when:

- Fasting plasma glucose (FPG) is ≥7.0 mmol/L (126 mg/dL).
- Postchallenge plasma glucose is ≥11.1 mmol/L (200 mg/dL).
  - 1.75 g/kg (max 75 g) anhydrous glucose dissolved in water.
- Symptoms of diabetes and a casual plasma glucose ≥200 mg/dL (11.1 mmol/L).
  - Casual is defined as any time of day without regard to time since last meal.
  - Symptoms of diabetes include polyuria, polydipsia, nocturia, and unexplained weight loss.
- HbA1c > 6.5%.
  - Must utilize a laboratory based, DCCT aligned, National Glycohemoglobin Standardization Program certified methodology.
- 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.
- Studies have raised concerns about the reproducibility of the oral glucose tolerance test (OGTT) in obese adolescents, with a concordance rate between repeat OGTTs a few weeks apart of approximately 30% (26).
- 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 postglucose challenge criteria (27). However, HbA1c > 6.5% predicts the risk of retinopathy as well as the glucose criteria. The application of HbA1c criteria for children has not been established and caution should be used when relying solely on HbA1c for diagnosis.

After the diagnosis of diabetes is established, diabetes autoantibody testing should be considered in all pediatric patients with the clinical diagnosis of T2D because of the high frequency of islet cell autoimmunity in patients with otherwise 'typical' clinically defined T2D. Studies have shown that autoantibodies are present in 10–20% of patients clinically diagnosed with T2D, depending on the race and ethnicity of the population (21, 28–32). The presence of antibodies predicts rapid development of insulin requirement (33), 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 T1D (weight loss, ketosis/ketoacidosis), some of whom may have T2D and be able to wean insulin off for extended periods of time with good control (34).

Characteristics of individuals with youth-onset T2D

- Youth-onset T2D occurs most often during the second decade of life, with a median age of diagnosis of 13.5 yr. This coincides with the peak of physiologic pubertal insulin resistance, which may lead to onset of overt diabetes in previously compensated adolescents. Accordingly, the median age of onset is 1 yr later in boys than girls (8, 35).
- Youth-onset T2D rarely occurs prior to puberty (8, 35).
- Youth with T2D come from families with a high prevalence of T2D in first and second degree relatives (35, 36).
- Youth-onset T2D occurs in all races, but at a much greater prevalence in those of non-White European descent, e.g., those of Black African descent, native North American, Hispanic (especially Mexican)-American, Asian, South Asian (Indian Peninsula), and Native Pacific islanders. The SEARCH for Diabetes in Youth population-based study found the proportion of physician diagnosed T2D among 10–19 yr olds to vary greatly by ethnicity in the USA: 6% for non-Hispanic Whites, 22% for Hispanics, 33% for Blacks, 40% for Asians/Pacific Islanders, and 76% for Native Americans (8).
- In Hong Kong, 90% of youth-onset diabetes is T2D (10), in Taiwan 50% (11) and nearly 60% in Japan.
- In the USA and Europe, nearly all youth with T2D have body mass index (BMI) above 85th percentile for age and sex (35). However, this is not true in Asia. In Japan, 15% of children with T2D are not obese (17, 37). In Asian Indian urban children, half of those with T2D had normal weight (<120% ideal for height) (12), and half of Taiwanese children with T2D were not obese (11).
- Youth-onset T2D has a sex ratio (male:female) that varies from 1:4–1:6 in native North Americans to 1:1 in Asians and Libyan Arabs.
- In the USA and Europe, youth-onset T2D is predominately found in populations characterized by low socioeconomic and educational status (35), whereas in emerging countries like China and India, more affluent children are more likely to develop T2D than poorer children.
- The presentation of youth-onset T2D can vary from asymptomatic hyperglycemia detected through screening or during routine physical examination

to ketoacidosis in up to 25% of patients (38) or hyperglycemic hyperosmolar state (39). These latter two presentations can entail significant risk for morbidity and mortality if not recognized and treated.

Autoimmune 'T2D'

Some authors have reported the phenomenon of autoimmune T2D. This has sometimes been referred to as T1.5, T3, or double diabetes. However, it is now becoming clearer that these individuals are best understood as having autoimmune T1D presenting in overweight or obese individuals with underlying insulin resistance.

- Youth and adults in USA and Europe who are clinically diagnosed with T2D are found to have T1D-associated autoantibodies in 15–40% of cases, including many who are not receiving insulin 1 yr after diagnosis (28–31).
- Antibody positive youth with the T2D 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 (21, 28, 32).
- ß-cell function is significantly less in antibody positive youth with T2D phenotype, resulting in more rapid development of insulin dependence (28, 31, 32).

Uncertainties of classification

The clinician is obliged to weigh the evidence in each individual patient to distinguish between T1D and T2D. The reasons for this conundrum are:

- With increasing obesity in childhood, as many as 30% of newly diagnosed T1D (or monogenic diabetes) patients may be obese, depending on the rate of obesity in the background population.
- A significant number of pediatric patients with T2D demonstrate ketonuria or ketoacidosis at diagnosis (2).
- T2D 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.
- There is considerable overlap in insulin or C-peptide measurements between T1D and T2D at onset of diabetes and over the first year or so (8). This overlap is due to the recovery phase of autoimmune-medicated T1D (the honeymoon) and the effects of elevated glucose (glucotoxicity) and free fatty acids (FFAs) (lipotoxicity) to impair insulin secretion at the time of testing in both T1D and T2D. In addition the insulin resistance of obesity raises residual C-peptide levels in obese adolescents with T1D. Such measurements are thus relatively valueless in the acute phase. However, persistence of c-peptide above the normal level for age would be unusual in T1D after 12–14 months (36).
- Insulin resistance is present in both T2D and T1D, though the pathophysiology is different and resistance in T2D is generally more severe (40, 41).
- Measurement of diabetes autoantibodies is the most rigorous approach to identification of T1D. However, this measurement may be limited by lack of ready availability of standardized autoantibody assays, cost, involvement of antibodies not yet identified, and varying rates of antibody positivity in T1D in different ethnic groups

Prediabetes: diagnostic criteria (impaired glucose tolerance and impaired fasting glycemia)

There are individuals whose glucose levels do not meet the criteria for diabetes, but are too high to be considered normal. The ADA had designated this physiologic state prediabetes to recognize the high risk of progression of these individuals to diabetes (25).

- Impaired glucose tolerance (IGT) and impaired fasting glycemia (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes.
- IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation. IFG is a measure of disturbed carbohydrate metabolism in the basal state, whereas IGT is a dynamic measure of carbohydrate intolerance after a standardized glucose load (42).
- Individuals who meet the criteria for IGT or IFG may be euglycemic in their daily lives, as shown by normal or near-normal glycated hemoglobin levels, and those with IGT may manifest hyperglycemia only when challenged with an OGTT.
- Some individuals may have elevated glycated hemoglobin levels but have normal OGTT, likely reflecting daily carbohydrate intake exceeding that associated with a standard glucose load.
- In obese adolescents, prediabetes is often a transient state, with as many as 60% of individuals reverting to normal glucose tolerance within 2 yr. Persistent weight gain is a predictor of persistent prediabetes and progression to diabetes (43).
- Prediabetes is diagnosed when:
  - IFG: FPG is 5.6–6.9 mmol/L (100–125 mg/dL)
  - IGT: Postchallenge plasma glucose 7.8–11.1 mmol/L (140–199 mg/dL)

- HbA1c 5.8–6.4%
  - Must utilize a laboratory based, DCCT aligned, National Glycohemoglobin Standardization Program certified methodology.

Treatment of youth-onset T2D

1 Management differences between T1D and T2D

The emergence of T2D in children and adolescents has required that specialists familiar with the management of T1D in children and adolescents recognize the vast differences between the treatment challenges of these two disorders.

- Differences in socioeconomic status: While T1D is distributed throughout the population proportionate to socioeconomic distribution, T2D in developed countries disproportionately affects those with fewer resources, e.g., lower income levels, less educated parents, less well-insured (35). Conversely, in Asia and emerging economies, T2D disproportionately affects the affluent.
- Older age: T1D occurs throughout childhood, when parental influence is predominant, whereas T2D occurs typically in adolescence, when peer influence predominates.
- More family experience: Only 5% of families with a child with T1D have family experience with the disease, whereas more than 75% of families of the child with T2D have such experience. The failure of these family members to control weight and glycemia is common, with resultant complications in the family members and risk for a sense of helplessness.
- Prevalence of associated comorbidities and complications early in the course of disease: Unlike T1D, where diabetes-related complications develop after many years of diabetes, the majority of patients with T2D will have comorbidities, such as fatty liver, sleep apnea, hypertension (35) at the time of diagnosis and appear to develop microvascular and macrovascular complications at an accelerated rate. Therefore, the treatment of these associated disorders is often required at the time of initiation of therapy for dysglycemia. Reduction in the rate of complications may require especially diligent attention to comorbidities (21, 23, 44, 45).
- Lifestyle education: While education on diet and physical activity is important on all youth with diabetes, the need for intensive lifestyle intervention is a dominant feature of therapy in youth with T2D.

2 Management goals

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

3 Education [See also the ISPAD Clinical Practice Guidelines for diabetes education (46)]

Initial and on-going education for T2D 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 North American populations and are available for public use on the TODAY public website [portal.bsc.gwu.edu/web/today].

- The education and treatment team for T2D ideally should include a nutritionist, psychologist and/or social worker, and exercise physiologist (46).
- Education in T2D places greater emphasis on behavioral, dietary, and physical activity changes than is generally required for T1D.
- Education should be given by team members with expertise and knowledge of the unique dietary, exercise, and psychological needs of youth with T2D.
- Education should be provided in a culturally sensitive and age-appropriate manner.
- Because nearly all youth with T2D are adolescents, the ISPAD Guidelines for Adolescent Care are appropriate to the education of youth and families with T2D.
- The entire family will need education to understand the principles of treatment of T2D and to understand the critical importance of the lifestyle changes required for the entire family to successfully manage a youth with T2D.
- 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 'type' of diabetes.

4 Behavioral change

Lifestyle change is the cornerstone of treatment of T2D and clinicians should initiate a lifestyle modification program, including nutrition and physical activity,

for children and adolescents at the time of diagnosis of T2D (47). The interventions include promoting a healthy lifestyle through behavior change, including nutrition, exercise training, weight management, and smoking cessation. Lifestyle intervention can have a beneficial effect on the incidence of diabetes in patients with impaired glucose tolerance and effectively decrease the incidence of T2D in high-risk patients (48, 49).

- The family and child should understand the medical implications of obesity and T2D.
- Clinicians must have an understanding of 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.

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 T2D 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 (50). More specific dietary recommendations are given in the ISPAD Guidelines for dietary management.

Dietary modification should include:

- Initial focus on eliminating sugar-containing soft drinks and juices. Complete elimination of these drinks and substitution of water, diet soft drinks, and other calorie-free beverages can result in substantial weight loss (51). Food and Drug Administration (FDA)-approved non-nutritive sweeteners (NNS) may help consumers limit carbohydrate and energy intake as a strategy to manage blood glucose or weight (52).
- Increasing fruit and vegetable intake (53).
- Reducing the use of processed, prepackaged, and convenience food.
- Reducing the intake of foods made out of refined, simple sugars such as processed candy and high fructose corn syrup.
- Portion control. Food and snacks should be served in a plate or bowl and not eaten directly from a box or can.
- 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 to lower glycemic index and promote gradual and sustainable energy elevations with meals.
- Changing family diet behaviors:
  - Limiting availability of high-fat, high caloric density food and drink in the home.
  - Teaching families to interpret nutrition fact labels.
  - Emphasizing healthy parenting practices related to diet and activity by promoting parental modeling of healthy eating habits and avoiding overly restricted food intake.
  - Encouraging positive reinforcement of all goals achieved (e.g., no or minimal weight gain, reduction in high caloric drinks) and avoiding blame for failure.
  - Promoting that meals should be eaten on schedule, in one place, preferably as a family unit, and with no other activity (television, computer, studying).
  - Collaboration with the family to take into account 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 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 (54–56). Youth with T2D should be encouraged to engage in moderate-to-vigorous exercise for at least 60 min 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 T2D.

- Reduction in sedentary time, including TV, computer-related activities, texting, and video games (57). Screen time should be limited to <2 h a day. Use of electronic entertainment and communication devices (EECDs) 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 (57–59).
- Promotion of stable household routines, particularly increasing sleep duration and reducing TV viewing (59–61).
- 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.

7 Smoking and tobacco use.

While cigarette smoking is harmful to all youth, those with special healthcare needs are especially vulnerable to the negative health consequences of smoking as a result of their compromised health status and disease, as well as treatment-related complications (62).

Additional research is needed to develop and examine the efficacy of interventions specifically targeting smoking among youth with T2D 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.

8 Glycemic monitoring

- SMBG
  - Unlike in T1D, the evidence that SMBG has an impact on glycemic control in the individual with T2D is limited.
  - 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 degree of glycemic control and available resources.
  - Once glycemic goals have been achieved, limited at home testing is needed and, at most, a few fasting and postprandial values a week are satisfactory. If values rise out of the target range consistently, more frequent testing should be recommended for 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 monitor for asymptomatic hypoglycemia.
- HbA1c concentration should be determined at least twice a year and quarterly if insulin is being used or metabolic control is unsatisfactory.

9 Pharmacologic therapy (see Fig. 1)

The aim of therapy in youth-onset T2D is to decrease insulin resistance, increase endogenous insulin secretion, or provide exogenous insulin. While a number of oral hypoglycemic agents are available and approved for use in adults, only metformin and insulin are 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, they are generally more expensive than the core therapies and evidence for their use in youth is limited to non-existent at this time. Several clinical trials of newer oral hypoglycemic agents are underway in youth-onset T2D, but are recruiting slowly and results are not expected for many years.

- Initial treatment

Initial treatment of youth with T2D 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 T1D, those with symptoms, particularly vomiting, can deteriorate rapidly and need urgent assessment and treatment.

  - If the patient is metabolically stable (HbA1c < 9 and no symptoms), metformin monotherapy is the treatment of choice. Begin with 500 mg daily × 7 d. Titrate by 500 mg once a week over 3–4 wk until the maximal dose of 1000 mg BID (or 2000 mg once a day of extended release metformin product where available) is reached.
  - If the patient is not metabolically stable, insulin will be required at least initially. A variety of insulin regimens are effective, but once a day NPH 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

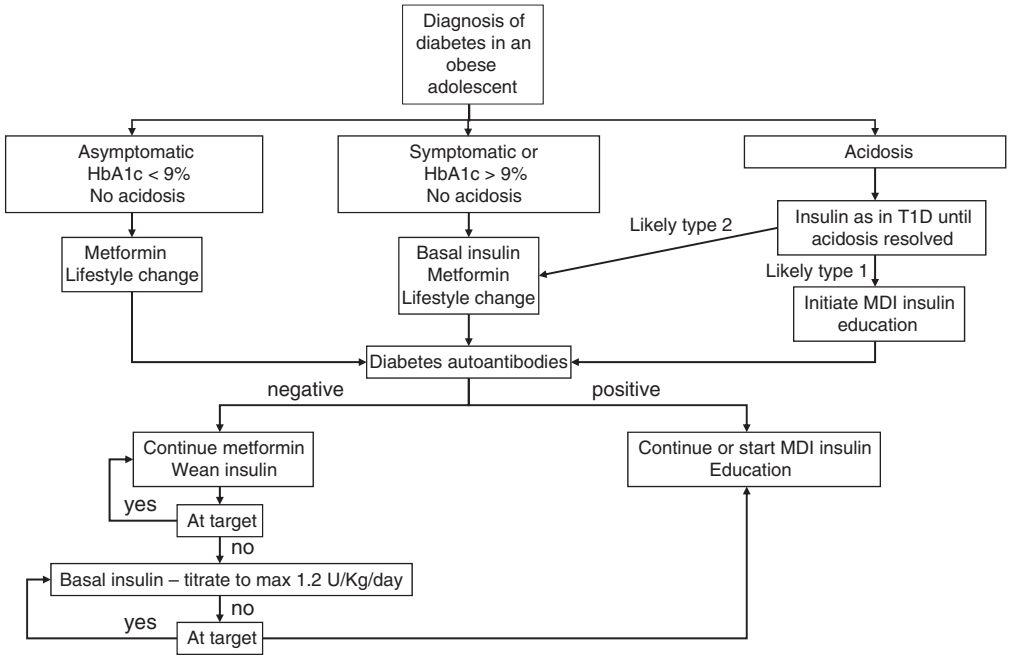

Fig. 1. Approach to initial and subsequent treatment of youth with type 2 diabetes.

well tolerated by the patients. Metformin can generally be started at the same time as metformin, unless acidosis is present.

- Transition onto metformin monotherapy can usually be achieved safely over 2–6 wk by decreasing the insulin dose 30–50% each time the metformin is increased with a goal of eliminating insulin therapy. Data from the TODAY study indicate that 90% of youth with T2D can be successfully treated initially with metformin alone (34)
- If the glucose values remain in the diabetic range during titration of metformin and insulin, the diagnosis of T2D should be reconsidered and lifestyle changes reinforced.

The goal of initial treatment should be to attain HbA1c of <6.5%. This can almost always be accomplished with metformin and basal insulin, alone or in combination. If SMBG values remain in the diabetic range during titration, or the patient fails to reach HbA1c below 6.5%, the diagnosis of T2D should be reconsidered and the need for intensification of therapy should be assessed.

Subsequent therapy

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) (63).

- If the patient fails to reach target HbA1c of <6.5% within 3–4 months on metformin monotherapy, addition of basal insulin should be strongly considered.
- If target is not attained on combination metformin and basal insulin (up to 1.2 U/kg), prandial insulin should be initiated and titrated to reach target HbA1c < 6.5%.
- Use of other oral or injected agents in youth may be beneficial in addition to or instead of metformin and insulin, but there are very limited studies of the use of these agents and they are generally not approved in the population.

Metformin. Metformin acts through adenosine monophosphate (AMP) kinase in liver, muscle, and fat tissue, with a predominant action on the liver.

- Hepatic glucose output is reduced by decreased gluconeogenesis.
- Insulin stimulated glucose uptake is increased in muscle and fat.
- An initial anorexic effect may promote limited weight loss.
- There is little to no risk of hypoglycemia with metformin monotherapy.
- Long-term use is associated with a 1–2% reduction in HbA1c.
- Intestinal side effects (transient abdominal pain, diarrhea, and nausea) may occur. These can be eliminated in most patients with slow dosage titration over 3–4 wk, and instructions to always take the medication with food. The side effects may 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 with renal impairment, cardiac or respiratory insufficiency, or who are receiving radiographic contrast materials. Metformin should be temporarily discontinued during a gastrointestinal illness.
- Metformin may normalize ovulatory abnormalities in girls with polycystic ovarian syndrome (PCOS) (ovarian hyperandrogenism) and increase pregnancy risk.
- Metformin is now approved for use during pregnancy.

Insulin. Despite hyperinsulinemia and insulin resistance, supplemental insulin is generally effective in reducing hyperglycemia and attaining glycemic targets. If there is inadequate glycemic control on oral agents, a long-acting (basal) insulin analog without peak effects or once-daily NPH may provide satisfactory therapy without the burden of meal-related injections (64). Metformin should be continued to improve insulin sensitivity and the combination of metformin and once daily insulin is successful at maintaining target glycemia in the majority of youth for extended periods of time. However, if HbA1c target is not reached and postprandial hyperglycemia persists, rapid or short-acting insulin can be added.

The primary adverse effects of insulin are:

- Hypoglycemia: hypoglycemia is very uncommon in youth with T2D despite sometimes very elevated dose of insulin (65).
- Weight gain: weight gain can be substantial in this population when insulin therapy is initiated unless there is careful attention and adherence to dietary measures. Emphasis on diet and exercise is extremely important.

Other available agents. Sulfonylurea and meglitinide/repaglinide (*may not be approved for use in those <18 yr in all countries*)

- These agents bind to receptors on the K+/ATP channel complex causing K+ channels to close, resulting in insulin secretion. Meglitinide and repaglinide bind to a separate site on the K+/ATP channel complex.
  - Sulfonylurea sites equilibrate slowly and binding persists for prolonged periods; thus, traditional sulfonylureas have prolonged effects.
  - Meglitinide/repaglinide has an intermediate equilibration and binding duration and are prescribed to rapid enhancement of insulin secretion before meals.
- Use of sulfonylureas in adults is associated with a 1.5–2% decrease in HbA1c.
- The major adverse effects of sulfonylureas are:
  - Hypoglycemia: may be severe and prolonged depending on the agent used. Hypoglycemia appears to be more common in youth-onset T2D.
  - 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 (66).
- Sulfonylureas may accelerate the loss of beta-cell function and eventual loss of control on oral therapy alone (63).

Thiazolidinedione (*TZD*) (*not approved for use in those <18 yr of age*)

TZDs increase insulin sensitivity in muscle, adipose, and liver tissue, with a greater effect on muscle glucose uptake than biguanides. TZDs bind to nuclear peroxisome proliferator activator receptors (PPAR gamma), which are ubiquitous orphan steroid receptors particularly abundant in adipocytes. This activation ultimately increases the formation of proteins involved in the nuclear-based actions of insulin, including cell growth, adipose cell differentiation, regulation of insulin receptor activity, and glucose transport into the cell. The binding of the thiazolidinediones to PPAR gamma receptors is ubiquitous, affecting muscle cell growth and migration in response to growth factors, including arterial walls smooth muscle.

- Long-term treatment in adults is associated with a reduction in HbA1c of 0.5–1.3%.
- There has been a randomized clinical trial of rosiglitazone, but the results have never been published.
- In the TODAY study, addition of rosiglitazone to metformin decreased the risk of progression to insulin requirement by 23% (22).
- Different TZDs have differing effects on lipid profiles, with pioglitazone having a more beneficial effect on LDL than rosiglitazone.
- The side effects of TZDs include weight gain, anemia, and fluid retention (including congestive heart failure) (67, 68). Liver toxicity associated with earlier members of this family has not been found with the newer TZDs.
- Rosiglitazone was under substantial marketing restriction in the USA and Europe due to concerns for an increased risk for congestive heart failure and myocardial infarction (68, 69).
- Although these restrictions have now been lifted, the future of TZDs in therapy for T2D in adults or youth remains unclear.

α-*Glucosidase inhibitors* (*not approved for use in those <18 yr 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 0.5–1% reduction in HbA1c (70).
- Because of their mechanism of action, these agents have been particularly widely used and successful in emerging economies where carbohydrates make up a substantial part of the diet.
- There have been no trials of α-glucosidase inhibitors in youth.
- The frequent side effect of flatulence makes these agents unacceptable to most adolescents.

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

GLP-1 is rapidly secreted by L-cells in the small intestine into the circulation 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 min. In recent years, pharmaceutical alterations in the GLP-1 agonists have resulted in longer acting agents.

- Incretin mimetics are given as BID, once daily, or once-weekly subcutaneous injections.
- Clinical trials in adults have shown reduced fasting and postprandial BG, weight loss, and lower HbA1c (0.5–0.8%).
- Adverse effects include nausea, vomiting, diarrhea, and infrequent dizziness, headache, and dyspepsia. The side effects generally decrease over time.
- There have been no published studies of incretin mimetics in youth, but several are currently underway.

DPP-IV inhibitors (*not approved for use in those <18 yr 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.

- DPP-IV inhibitors are administered orally once daily.
- Long-term therapy in adults is associated with 0.5% reduction in HbA1c.
- Unlike GLP-1 mimetics, they have no effect on gastric emptying, satiety, or weight loss.
- There have been no published studies of DPP-IV inhibitors in youth, but several are currently underway.

Sodium-glucose co-transporter-2 (*SGLT-2*) *inhibitors* (*not approved for use in those <18 yr 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 first of these agents have been approved for use in T2D in adults.

- Short-term use of SLGT-2 inhibitors is associated with reduction in HbA1c approaching that seen with metformin. There have been no long-term studies of HbA1c reduction.
- Weight loss in the range of a few kilograms has been reported in short-term studies.
- Adverse effects include small increases in prevalence of urinary infections, particularly among uncircumsized men.
- There have been no studies of SGLT-2 inhibitors in youth.

10 Gastric surgery

Bariatric surgery may be considered for adolescents with obesity-related comorbidities, including T2D (71), particularly when patients have been unsuccessful with medical therapy alone. Recent results from a large US consortium of pediatric bariatric surgery centers have demonstrated remission of T2D and other comorbidities in nearly all youth, with attainment of HbA1c targets exceeding that seen with medical therapy (72). However, Roux-en-Y gastric bypass, the traditional surgical procedure for weight loss, can have significant morbidity and mortality. Newer techniques, which appear to be safer, include gastric banding and sleeve gastrectomy. Although the morbidity and mortality rates in adults have decreased over the last 5 yr, this treatment is still uncommon in children and should be undertaken only in centers with an established and experienced surgical team and outcome data collection program.

T2D 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, protein metabolism, and on vascular endothelial function. Insulin resistance can occur in many tissues, including hepatic, muscle, and adipose tissue, and in

some areas of the brain. However, not all tissues are insulin resistant, as some tissues continue to respond to hyperinsulinemia, such as the ovary and the sympathetic nervous system innervating muscle. Finally, within tissues there can be mixed insulin resistance and retained insulin sensitivity, such as the combination of hepatic resistance to insulin's metabolic effects, resulting in increased hepatic glucose output, yet retained insulin response in suppression of sex hormone-binding globulin production, resulting in increased free sex steroids and in stimulation of insulin-like growth factor 1 (IGF-1) production, resulting in mitogenic effects (73).

Insulin resistance is increased during mid-puberty, pregnancy, aging, and the luteal phase of the menstrual cycle, in those of non-Caucasian race/ethnicity, 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 of the insulin resistance syndrome. Premature adrenarche (pubic hair appearing before the age of 8 yr) in girls may be the first signs of hyperandrogenism as a component of PCOS, a disorder associated with insulin resistance (74, 75). Children born small for gestational age (SGA) are at increased risk of insulin resistance related to decreased intrauterine growth, pancreatic development, and lean muscle mass and are also at increased risk of premature adrenarche. Infants born to a pregnancy complicated by maternal obesity, and in particular maternal T2D or gestational diabetes, are more likely to be born large for gestational age (LGA) and to have an increased risk of insulin resistance (76). 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 (impaired fasting glucose, impaired glucose tolerance, T2D)
- Lipid abnormalities (increased triglycerides, decreased HDL-C, small, dense LDL-C particles)
- Endothelial dysfunction (increased mononuclear cell adhesion, plasma cellular adhesion molecules and asymmetric dimethylarginine, 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, white blood cells (WBCs), etc.]
- Increased plasma uric acid
- Increased hepatic and intramyocellular lipid deposition
- Mitochondrial dysfunction
- Ovarian hyperandrogenism
- Sleep-disordered breathing.

As a result of these insulin resistance-related abnormalities, individuals with insulin resistance have a higher risk of developing overt T2D, cardiovascular disease, hypertension, PCOS, NAFLD, nephropathy, OSA, and some types of cancer. This recognition that insulin resistance is associated with a cluster of abnormalities differs from the concept of the metabolic syndrome (MetS), which are five specific insulin resistance-related criteria (obesity, elevated BP, impaired fasting glucose, high triglycerides, low HDL-C) chosen originally by the Adult Treatment Panel III, based on increased risk of cardiovascular disease in adults (77).

In contrast to the definition of MetS in adults, there is still no standard definition of MetS for use in the pediatric population and more than 46 different pediatric MetS definitions have been used (78). In 2007, the International Diabetes Federation published its definition of the MetS in children and adolescents (79). This panel recommends the following criteria:

1 For children 6 to <10 yr old, obesity (defined as $\geq$90th percentile of waist circumference), followed by further measurements as indicated by family history.
2 For age 10 to <16 yr, obesity (defined as waist circumference $\geq$90th percentile), followed by the adult criteria for triglycerides, HDL-C, BP, and glucose. For youth ≥16 yr 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 MetS in obese youth ranges from 19 to 35%, compared with $<2\%$ in the normal-weight groups. The odds of developing MetS in obese boys and girls were 46–67 and 19–22 times greater, respectively, than for normal-weight youth (80).

Co-morbidities characteristic of insulin resistance are commonly present at diagnosis or appear early in the course of T2D and should be screened for sooner than in T1D, where these disorders are generally seen as complications of long-standing diabetes rather than as comorbid conditions (81–83). A more complete discussion of screening for complications/comorbidities is presented in the ISPAD Guidelines for microvascular and macrovascular complications (84).

Obesity

Obesity has deleterious associations with morbidity independent of insulin resistance and diabetes (85–94). 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 (95), and youth in the USA with T2D have a mean BMI *Z*-score of 2.15 (35). Therefore, the assessment of BMI and pattern of weight gain should be considered a routine part of monitoring in youth with T2D.

Hypertension

Hypertension is associated with endothelial dysfunction, arterial stiffness, and increased risk of both cardiovascular and kidney disease (96). Moreover, tight BP control in adults with T2D in the UK Prospective Diabetes Study (UKPDS) improved microvascular and macrovascular disease at least as much as control of glycemia (97). Hypertension was present in 13.6% of 699 US youth in the TODAY study at a median duration of diabetes of 7 months (35) progressing to 33.8% during average follow-up of 3.9 yr (23). Male sex and higher BMI significantly increased the risk of hypertension in the TODAY cohort. Eppens et al. (98) reported even higher rates in Australia, with 36% of youth with T2D having hypertension within 1.3 yr of T2D diagnosis. Moreover, the SEARCH for Diabetes in Youth Study (SEARCH) study, which included US youth with longer diabetes duration, found hypertension in 65% of US youth with T2D (99, 100). Hypertension in T2D 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 T2D related to the associated angiotensin converting enzyme genotype and resulting increased activity of the renin-angiotensin system (101).

- BP should be measured with an appropriate sized cuff at every clinic visit, and normalized 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 should be considered to achieve BP values that are less than the 90th percentile (102).
    - Of note, major congenital malformations have been reported with first trimester exposure to ACE inhibitors in non-diabetic women.
- If the ACE inhibitor is not tolerated due to adverse effects (mainly cough), an angiotensin receptor blocker is often used as second line therapy (47, 102–105).
- Combination therapy may be required if hypertension does not normalize on single agent therapy, and may include calcium channel blockers or diuretics.
- Work-up of the hypertension should also include a renal ultrasound and an echocardiogram (96).

Nephropathy

Albuminuria (either micro- or macro-) is present at the time of diagnosis in a substantial number of adolescents with T2D and prevalence increases with duration of diabetes (24). In the TODAY study, microalbuminuria was found in 6.3% of 699 T2D youth at baseline at a median disease duration of 7 months and prevalence rose to 16.6% by 36 months (23, 35); 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 (15, 106) and macroalbuminuria was reported in 16% of First Nation youth after 10 yr (107, 108). In a study in Manitoba, Canada, those with microalbuminuria as youth were nine times as likely to develop renal failure as those without microalbuminuria (109). 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 T2D compared to T1D in all populations examined. In a Japanese cohort of 1065 patients diagnosed with T2D prior to age 30 yr, 31 (3%) developed renal failure requiring dialysis at a mean age of 35 yr (110). Factors influencing progression were diabetes duration, HbA1c, and diastolic BP. Moreover, the incidence of nephropathy for those diagnosed at age 10–19 yr was double that of individuals in the same population with T1D, even when accounting for duration of disease (111).

- Micro- and macroalbuminuria may be present at the time of diagnosis.
- Albuminuria should be evaluated at diagnosis and annually thereafter.
- The definition of microalbuminuria used by the ADA is either:
    - Albumin-to-creatinine ratio 30–299 mg/g in a spot urine sample (preferred).
    - Timed overnight or 24-h collections with albumin excretion rate of 20–199 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 excluded and consultation obtained, especially if macroalbuminuria (ACR > 300 mg/g) is present.
- ACE inhibitors are the agents of choice because of the beneficial effects of ACE inhibitors on preventing diabetic nephropathy, even if BP is normal (2).
- Albumin excretion should be monitored at 3- to 6-month interval and therapy titrated to achieve as normal an albumin-to-creatinine ratio as possible.

Dyslipidemia

Hypertriglyceridemia and decreased HDL-C are the hallmarks of the dyslipidemia characteristic of insulin resistance and T2D. In the TODAY study, 79.8% of T2D youth had a low HDL-C and 10.2% had high triglycerides within a few months of diagnosis (35) and the SEARCH study found that 73% of 2096 US youth with T2DM of longer duration had a low HDL and 60–65% had hypertriglyceridemia (112). Among Pima Indians in the US, 18% had evidence of hypercholesterolemia at T2D diagnosis (107). In a Canadian First Nations population of 99 youth with T2D, total cholesterol, LDL-C, triglycerides, and apoB level greater than the NHANES 75th percentile were found in 60, 41, 43, and 43%, respectively, and low HDL-C in 35% (108). In 68 Australian youth with a duration of T2D of <3 yr, elevated total cholesterol was found in 32% and hypertriglyceridemia in 53% (98). Finally in Taiwan, hypercholesterolemia was present in 27% youth with T2D (11). Additional findings include elevated very low-density lipoprotein (VLDL), elevated lipoprotein (a) (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.

- Testing for dyslipidemia should be performed soon after diagnosis when blood glucose control has been achieved and annually thereafter (113–115).
- Goal levels are:
  - LDL-C <2.6 mmol (100 mg/dL)
    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 using the AHA step 2 diet (dietary cholesterol <200 mg/d, saturated fat <7% of total calories, and <30% calories from fat) and exercise encouraged (114).
- A repeat lipid profile should be performed in 6 months.
  - If LDL-C remains elevated, further intervention is warranted:
    - LDL-C 100–129 mg/dL: maximize non-pharmacologic treatment.
    - LDL-C >130 mg/dL: begin medication with a goal of <130 mg/dL and an ideal target of <100 mg/dL
- Statin therapy has been shown to be safe and effective in children as in adults and should be the first pharmacologic intervention (84), although long-term safety data are not available.
- Statin treatment should begin at the lowest available dose and dose increases should be based on LDL-C levels and side effects.
- If there is any persistent complaint of significant muscle pain/muscle soreness, the medication should be discontinued to see if symptoms resolve.
- The use of statins in sexually active adolescent females must be very carefully considered and the risks explicitly discussed, as these drugs are not approved in pregnancy.
- Current recommendations are to not manage elevated triglyceride levels directly with medication for cardiovascular disease prevention.
- If the triglycerides are >150 mg/dL, efforts to maximize blood glucose control, limit dietary fat and simple sugars, and achieve desirable weight should be emphasized.
- If fasting triglycerides are >400–600 mg/dL, treatment with a fibric acid medication should be considered due to significantly increased risk of pancreatitis, with a goal of <150 mg/dL.
- Low HDL-C levels in youth are not managed directly with medication, but physical activity and healthy diet should be encouraged.

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 T2D. Endothelial dysfunction is an

early sign of increased risk of cardiovascular disease, is predictive of cardiovascular events (81) and occurs in obese children relative to their level of obesity and degree of insulin resistance. In addition, youth with T2D have left ventricular hypertrophy (116), cardiac dysfunction, reduced maximal exercise capacity (41), and increased arterial stiffness (117) all of which predict early cardiovascular morbidity and mortality.

Polycystic ovarian syndrome

PCOS is increasingly recognized in adolescents as part of the insulin resistance syndrome. Adolescents with PCOS have ~40% reduction in insulin-stimulated glucose disposal compared to body composition matched non-hyperandrogenic control subjects (118). There are limited data on the exact prevalence of PCOS in youth with T2D, but a study of 157 adult women of reproductive age with T2D found the PCOS prevalence to be high at 8.3% (119). A lack of periods can increase long-term risk of endometrial cancer and PCOS increases lifetime risk of cardiovascular disease (120).

- A menstrual history should be taken on every girl with T2D at diagnosis and at each visit.
- A work-up for PCOS should be considered if there is primary or secondary amenorrhea, hirsutism, and significant acne.
- PCOS is diagnosed based on the presence of oligo- or amenorrhea with biochemical or clinical evidence of hyperandrogenism, with or without evidence for polycystic ovaries (121).
- 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.

Non-alcoholic fatty liver disease

Hepatic steatosis is present in 25–50% of adolescents with T2D and more advanced forms of NAFLD, such as non-alcoholic steatohepatitis (NASH), are increasingly common and associated with progression to cirrhosis, portal hypertension, and liver failure (122–124). NAFLD is now the most frequent cause of chronic liver disorders among obese youth (125), and is the most common reason for liver transplantation in adults in USA. In USA, Hispanics have the highest prevalence of NAFLD, followed by non-Hispanic Whites, whereas the prevalence among African-American is much lower (124, 126). However, these prevalence estimates are based on liver enzyme elevations and are likely an under estimate of the prevalence of hepatic steatosis in T2D youth, as steatosis is more common that elevated liver enzymes and liver enzymes can be normal despite having steatosis (127).

NAFLD is associated with insulin resistance leading to a resistance in the antilipolytic effect of insulin in the adipose tissue with an increase of FFAs. The increase of FFAs induces mitochondrial dysfunction and development of lipotoxicity. Moreover, in subjects with NAFLD, ectopic fat also accumulates in the myocardium and pancreas (128). Presence of the MetS in obese adolescents predicts IGT and NAFLD (41) and the presence of T2D independently predicts progression to fibrosis (129).

Weight loss improves NAFLD and metformin has been shown to improve liver enzymes and liver steatosis in youth in insulin-resistant adolescents (41). In the TODAY study, permanent medication reductions/discontinuation due to elevated liver enzymes was lowest in the metformin plus rosiglitazone group (65). Thus, T2D therapies that improve insulin resistance appear to improve NAFLD, and therefore are the standard approach to youth with both NAFLD and T2D. However, due to the potential for progression to NASH, fibrosis, and cirrhosis, ongoing monitoring of liver enzymes is recommended in youth with T2D, with referral for biopsy if enzymes remain markedly elevated despite weight loss and/or diabetes therapies.

Systemic inflammation

Elevated C-reactive protein, inflammatory cytokines, and WBC counts in obese adolescents have been associated with increased risk of cardiovascular disease in adults (92, 93). Inflammation plays a critical role in the pathogenesis of diabetes-related chronic kidney disease (130), diabetic retinopathy (131), β-cell dysfunction (132, 133), and other diabetes-related diseases. Several inflammatory cytokines secreted by obese adipose tissue, including TNFα and IL-6, impair insulin signaling in insulin-responsive organs, and new molecules that affect both local and systemic inflammation have been identified (134). In addition, a role for activated immune cells is emerging (135, 136).

Obstructive sleep apnea. OSA is common in obese youth, but the prevalence in pediatric T2D has not yet been well documented. However, it is likely high, as the prevalence of OSA in adults with T2D is between 70 and 90% (137, 138). OSA not only causes poor sleep quality and daytime sleepiness, but 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 T2D consider the presence of OSA (139).

- OSA can be screened for in youth with T2D using 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.

Depression

Youth with T2D are at increased risk of major clinical depression (140–144), which is associated with poor adherence to diabetic treatment recommendations. 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 T2D 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 healthcare providers experienced in addressing depression in youth (140).

Additional health problems related to obesity and T2D

- Orthopedic problems resulting in diminishing physical activity (145, 146)
- Pancreatitis
- Cholecystitis
- Pseudotumor cerebri
- Deep tissue ulcers

Adults in their 40s with youth-onset T2D 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%) (147). In addition, all of these endpoints were markedly higher than a similarly aged group of participants with T1D, despite similar glycemic control and a longer duration of diabetes in the T1D group. It has been estimated that youth and young adults with T2D lose approximately 15 yr from average life expectancy and may experience severe, chronic complications by their 40s (148). 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

Screening for T2D 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 (149). General guidelines to justify a screening test and as applied to T2D 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 USA, screening based on fasting and postchallenge glucose in high risk minority adolescents at the peak age of T2D diagnosis identified <1% with T2D (88). Whether there is sufficient prevalence of undiagnosed T2D 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 T2D 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.
  - Prediabetes has been identified in at-risk youth, but there is currently no evidence that interventions beyond that which would be delivered to the at-risk youth anyway (weight loss, exercise, and diet change) are efficacious.
  - Hypertension, dyslipidemia, and microalbuminuria have been identified in youth with prediabetes, but also in obese youth without diabetes. Therefore, this argues for monitoring and appropriate treatment of hypertension, dyslipidemia, and microalbuminuria in at-risk youth, not 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-h postchallenge glucose, and HbA1c) are sufficiently sensitive and specific to function, given the low prevalence of T2D 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.

There are currently a single set of recommendations for screening and case-finding, which were issued by the ADA in 2000. However, concerns about these guidelines persist. 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 screening for T2D outside of research settings is not cost-effective in most populations. Urinary glucose screening in Japanese youth may be a unique exception.

Conflicts of interest

The authors have declared no conflicts of interest.

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