



# Evaluation and Management of Youth-Onset Type 2 Diabetes: A Position Statement by the American Diabetes Association

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Although all types of diabetes result in hyperglycemia, the pathophysiology of each type of diabetes is different. These guidelines summarize available data specific to the comprehensive care of youth with type 2 diabetes. The objective is to enrich the recognition of type 2 diabetes in youth, its risk factors, its pathophysiology, its management, and the prevention of associated complications.

## PATHOPHYSIOLOGY

Glucose homeostasis is maintained by a balance between insulin secretion from the pancreatic  $\beta$ -cells and sensitivity to insulin in skeletal muscle, adipose tissue, and liver (1). When insulin sensitivity declines, insulin secretion must increase to maintain glucose tolerance, and, in most youth, decreased insulin sensitivity due to puberty and/or obesity is compensated by increased insulin secretion. However, when  $\beta$ -cells cannot secrete sufficient insulin to compensate for insulin resistance, abnormalities in glucose homeostasis ensue, potentially progressing to prediabetes and type 2 diabetes as  $\beta$ -cell function deteriorates further (2–9). The relationship between  $\beta$ -cell function and insulin sensitivity in adults and youth has been demonstrated to be a hyperbolic function and can be described mathematically as the product of insulin sensitivity and  $\beta$ -cell function, called the disposition index (DI) (1). The DI essentially expresses the amount of insulin being secreted relative to the degree of insulin resistance and is a constant for a given degree of glucose tolerance in any one individual.

Overweight and obesity are major acquired contributors to the development of insulin resistance, particularly in the face of the physiologic insulin resistance characteristic of puberty. Robust pancreatic  $\beta$ -cell compensatory insulin secretion maintains normal glucose homeostasis. However, in adolescents with obesity who develop type 2 diabetes, there is severe peripheral and hepatic insulin resistance, with ~50% lower peripheral insulin sensitivity than peers with obesity without diabetes, along with increased fasting hepatic glucose production and inadequate first- and second-phase insulin secretion, resulting in ~85% lower DI (2). Additional abnormalities in youth with type 2 diabetes include impaired glucose sensitivity of insulin secretion, lower serum adiponectin concentrations, and reduced incretin effect (3,9–13). While upregulation of  $\alpha$ -cell function with hyperglucagonemia has been implicated in the pathophysiology of type 2 diabetes in adults (14,15), there are limited data in youth with type 2 diabetes, with studies showing either hyperglucagonemia or no difference from control subjects without diabetes (3,11,16,17).

Cross-sectional and longitudinal studies in youth with obesity along the spectrum of glycemia from normoglycemia to prediabetes to type 2 diabetes show, as in adults, that  $\beta$ -cell failure with declining insulin secretion relative to insulin sensitivity results in prediabetes and type 2 diabetes in high-risk youth (5–9,18–21). Importantly, however, prior to reaching the American Diabetes Association (ADA)-defined fasting and oral glucose tolerance test (OGTT)-stimulated glycemic cut points for the diagnosis of prediabetes, youth, like adults, already demonstrate declining  $\beta$ -cell function relative to insulin sensitivity (6–8). Also, youth with A1C in the at-risk/prediabetes category ( $\geq 5.7$  to  $< 6.5\%$ ) demonstrate impaired  $\beta$ -cell function compared with those with A1C  $< 5.7\%$  (22). A combination of obesity, genetics,

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For further information on the ADA evidence-grading system and the levels of evidence, please see Table 1 in the American Diabetes Association's Introduction section of the Standards of Medical Care in Diabetes—2018. *Diabetes Care* 2018;41(Suppl. 1):S2, <https://doi.org/10.2337/dci18-SINT01>.

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the hormonal milieu, incretins and/or their effect, and metabolic alterations, such as glucotoxicity and/or lipotoxicity, are likely to contribute to deteriorating  $\beta$ -cell function against the backdrop of insulin resistance, eventually culminating in prediabetes and type 2 diabetes in at-risk youth. Based on the baseline data from the Restoring Insulin Secretion (RISE) study (23,24), there appear to be important differences in insulin sensitivity and  $\beta$ -cell function between youth and adults with similar degrees of dysglycemia, including greater insulin resistance for any degree of adiposity and greater insulin secretion for any degree of insulin resistance in youth compared with adults.

## RISK, SCREENING, AND DIAGNOSIS

### Risk Factors

Nonmodifiable risk factors for youth-onset type 2 diabetes include genetics/epigenetics, manifested as a strong family history of type 2 diabetes in first- or second-degree relatives; being the offspring of a pregnancy complicated by gestational diabetes mellitus (GDM); minority race/ethnicity; and physiologic insulin resistance of puberty. Metabolic evidence of genetic susceptibility can be detected in the first decade of life, manifested as impaired insulin sensitivity and reduced insulin secretion in otherwise healthy youth with a family history of type 2 diabetes (25). This genetic susceptibility, when combined with environmental factors conducive to obesity and a sedentary lifestyle, may ultimately translate to type 2 diabetes. Indeed, in a study of youth with obesity, a genetic risk score for  $\beta$ -cell dysfunction from five single nucleotide polymorphisms was associated with a higher chance of prediabetes and type 2 diabetes (26). Dozens of specific genetic variants linked to type 2 diabetes have been identified in adults (27,28), but these only account for about 10% of its heritability (29,30). Particular genetic variants that predispose to diabetes in youth have been identified in Oji-Cree Native Canadians (31) and African American youth (32), but information in other populations is only now emerging.

Evidence from both animal and human studies suggests that maternal obesity and GDM contribute to obesity and type 2 diabetes in youth (33,34). In the Treatment Options for Type 2 Diabetes

in Adolescents and Youth (TODAY) cohort, one-third were born after a pregnancy complicated by preexisting diabetes or GDM (35). In the SEARCH for Diabetes in Youth (SEARCH) study, a population-based study of the epidemiology of type 1 and type 2 diabetes in youth in the U.S., exposure to maternal GDM or pregestational diabetes and maternal obesity were independently associated with type 2 diabetes in adolescents, with intrauterine exposure to these two risk factors present in 47.2% of type 2 diabetes in the cohort (36). Age of onset of type 2 diabetes was also younger in those exposed to diabetes during gestation.

Incidence and prevalence of type 2 diabetes are highest among youth from a minority race/ethnicity (37), likely as a consequence of many factors, including genetics, metabolic characteristics, cultural/environmental influences, and quality of and access to health care. Several studies have demonstrated significant differences by race/ethnicity in insulin sensitivity and secretion that might heighten the risk of type 2 diabetes (38–42).

Type 2 diabetes typically occurs in adolescents at midpuberty (for example, the mean age of diagnosis was 14 years in the TODAY study) (43), most likely precipitated by the physiologic, but transient, pubertal insulin resistance aggravating the preexisting metabolic challenges of obesity. Cross-sectional and longitudinal studies show that insulin sensitivity declines by 25–30% as youth transition from prepuberty to puberty (44–46). In the presence of normally functioning  $\beta$ -cells, puberty-related insulin resistance is compensated by increased insulin secretion/hyperinsulinemia, such that DI remains normal. In youth who are predisposed to develop prediabetes and/or type 2 diabetes,  $\beta$ -cell compensation is inadequate with progressive decline in the DI, ultimately resulting in dysglycemia (46,47).

In youth-onset type 2 diabetes, the major modifiable risk factors are obesity and lifestyle habits of excess nutritional intake, low physical activity, and increased sedentary behaviors with decreased energy expenditure, resulting in the surplus of energy being stored as body fat. Other potentially modifiable risk factors for type 2 diabetes in adolescents and young adults include chronic

stress and/or depressed mood (48,49) and sleep-related disorders (50–52).

### Risk Assessment and Diagnostic Criteria

#### Recommendations

- Risk-based screening for prediabetes and/or type 2 diabetes should be considered after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents who are overweight (BMI  $\geq$ 85th percentile) or obese (BMI  $\geq$ 95th percentile) and who have one or more additional risk factors for diabetes (see Table 1 for evidence grading).
- If tests are normal, repeat testing at a minimum of 3-year intervals E, or more frequently if BMI is increasing. C
- Fasting plasma glucose, 2-h plasma glucose after 75-g OGTT, or A1C can be used to test for prediabetes or diabetes. B

Risk-based screening for prediabetes and/or type 2 diabetes is timed after the onset of puberty or after 10 years of age, whichever occurs earlier, because the majority of youth-onset type 2 diabetes occurs during puberty, as stated above, and rarely in prepubertal children. However, some youth with obesity may have earlier onset of puberty than usual, necessitating screening before 10 years of age. In addition, in North America almost all youth with type 2 diabetes are overweight/obese, hence the recommendation to screen youth with overweight/obesity. In other parts of the world where youth with type 2 diabetes are not necessarily overweight and/or obese, clinical judgment should guide whom to screen. Although there is no robust evidence-based rationale for the proposed frequency of testing, increasing BMI has been shown to be a predictor of deteriorating glycemia and progression to type 2 diabetes (21). Therefore, clinicians caring for youth with overweight/obesity with continued increase in their BMI should be aware of the need for more frequent screening.

The laboratory glycemia-based diagnostic criteria for diabetes and prediabetes are the same for youth and adults, regardless of type of diabetes (Table 2) (53). However, these criteria are extrapolated from adults, and the

**Table 1—Risk-based screening for type 2 diabetes or prediabetes in asymptomatic children and adolescents\* in a clinical setting**

Criteria
Testing should be considered in youth* who are overweight ( $\geq 85\%$ ) or obese ( $\geq 95\%$ ) <b>A</b> and who have one or more additional risk factors based on the strength of their association with diabetes:
<ul style="list-style-type: none"> <li>• Maternal history of diabetes or GDM during the child's gestation <b>A</b></li> <li>• Family history of type 2 diabetes in first- or second-degree relative <b>A</b></li> <li>• Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander) <b>A</b></li> <li>• Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight) <b>B</b></li> </ul>

\*After the onset of puberty or after 10 years of age, whichever occurs earlier.

epidemiological studies that formed the basis for both glucose and A1C definitions of diabetes did not include pediatric populations. Therefore, the exact relevance of these definitions for pediatric populations remains unclear until more data become available.

The A1C test is universally available and can be performed any time of the day without need for fasting. However, several studies have questioned its validity in the pediatric population because of poor sensitivity for identifying children with dysglycemia and underestimation of the prevalence of prediabetes and diabetes (54–56). Fasting and OGTT criteria have not been validated in youth, either. Studies using continuous glucose monitoring (CGM) in youth with obesity demonstrated that A1C and OGTT are equally

effective at identifying glycemic abnormalities on CGM, but the glycemic patterns differ (57); abnormal A1C was associated with higher overall and nighttime average glucose on CGM, while abnormal OGTT was associated with more time spent above the normal glucose range during the day. Institution of A1C screening in a large primary care network increased provider adherence to screening recommendations compared with OGTT screening while identifying the same prevalence of type 2 diabetes (58). Furthermore, in this cohort, the progression to clinically confirmed diabetes was substantially more likely for those with A1C  $>6\%$  (18.4%) than for those with levels 5.7–6.0% (1.3%). Therefore, screening with fasting glucose, OGTT, or A1C is an

acceptable approach but should be based on sound clinical judgment, recognition of the strengths and weaknesses of each test, and the facilities and resources available.

### Confirming Diabetes Type

#### Recommendations

- Children and adolescents with overweight/obesity in whom the diagnosis of type 2 diabetes is being considered should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune type 1 diabetes. **B**
- Genetic evaluation to exclude monogenic diabetes should also be based on clinical characteristics and presentation. **B**

As stated above, youth with type 2 diabetes in the U.S. are characteristically overweight and/or obese, in mid- to late puberty, with overrepresentation of minority ethnic/racial groups and females (4,43,59). The clinical presentation varies widely from asymptomatic or minimally symptomatic, diagnosed incidentally during routine laboratory testing, to a severe presentation with symptomatic hyperglycemia, weight loss, metabolic decompensation, diabetic ketoacidosis (DKA), or hyperglycemic hyperosmolar nonketotic (HHNK) syndrome (4).

Obesity is a consistent feature of youth-onset type 2 diabetes in the U.S. However, because of the escalating rates of obesity in the general population, children with both type 1 diabetes and monogenic diabetes are also more likely to be overweight/obese than in the past (60), making the clinical distinction between type 2 diabetes and obese type 1 or monogenic diabetes difficult. This was illustrated in the TODAY study in which, of the 1,206 youth clinically diagnosed with type 2 diabetes and screened for circulating GAD65 and IA2 antibodies, 118 (9.8%) were antibody positive ( $Ab^+$ ) (61). Even though these  $Ab^+$  individuals had clinical characteristics that overlapped with the antibody-negative ( $Ab^-$ ) youth, they were less likely to be obese, have features of metabolic syndrome, have a family history of diabetes, be female, or be from a minority race/ethnicity, indicating a phenotype more similar to their peers with type 1 diabetes. Pathophysiologically,

**Table 2—Criteria for the diagnosis of prediabetes and diabetes**

Prediabetes
A1C 5.7% to $<6.5\%$ (39 to $<48$ mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.
IFG: fasting glucose $\geq 100$ but $<126$ mg/dL ( $\geq 5.6$ but $<7.0$ mmol/L).
IGT: 2-h plasma glucose $\geq 140$ but $<200$ mg/dL ( $\geq 7.8$ but $<11.1$ mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 1.75 mg/kg (max 75 g) anhydrous glucose dissolved in water.*
Diabetes
A1C $\geq 6.5\%$ ( $\geq 48$ mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR
FPG $\geq 126$ mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h plasma glucose $\geq 200$ mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 1.75 mg/kg (max 75 g) anhydrous glucose dissolved in water.*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose $>200$ mg/dL (11.1 mmol/L).

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; max, maximum. \*In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.

Ab<sup>-</sup> youth with obesity are more insulin resistant than Ab<sup>+</sup> youth with obesity, while Ab<sup>+</sup> youth have more severe insulin deficiency (61–64). Fasting and stimulated C-peptide are significantly lower in Ab<sup>+</sup> youth with obesity and diabetes, though with appreciable overlap (63). Moreover, Ab<sup>-</sup> youth are more likely to exhibit features of the metabolic syndrome (elevated systolic blood pressure and ALT), while Ab<sup>+</sup> youth have significantly more frequent ketonuria at initial presentation (61,64). The reported rates of positive pancreatic autoantibodies in youth clinically diagnosed with type 2 diabetes vary from 10% to 75% (4,62), likely depending on the ratio of type 1 and type 2 diabetes in the population. The clinical distinction between youth with type 2 diabetes and youth with obesity and type 1 or monogenic diabetes is further blurred because youth with type 2 diabetes often present with some degree of ketosis, including DKA (65).

The distinction between these forms of diabetes in youth with obesity has important implications for treatment (66), since Ab<sup>+</sup> youth present more like individuals with type 1 diabetes, progressing to insulin requirement more rapidly (61), and are at risk for other autoimmune disorders. Therefore, measurement of pancreatic autoantibodies is recommended in all youth with clinical characteristics of type 2 diabetes. This testing should include GAD65 and IA2 antibodies, along with insulin autoantibody in individuals who have not yet been exposed to exogenous insulin. The benefit of measurement of ZnT8 antibody in individuals with phenotypic type 2 diabetes is not yet clear.

We further recommend that antibodies be measured in a laboratory aligned with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Pancreatic Autoantibody Standardization Program because currently available commercial assays may not be sufficiently sensitive or specific. However, in all cases, clinical judgment and the presence of other risk factors for type 1 diabetes or type 2 diabetes should be considered in making the diagnosis, and the health care team should remain open to reconsidering the initial diagnosis. Since 4.5–8.0% of youth with clinical features suggestive of type 2 diabetes have been found to have monogenic

diabetes, genetic testing for monogenic forms of diabetes should be considered as well (67–69).

## GLYCEMIC TARGETS

### Recommendations

- A1C should be measured every 3 months. **E**
- A reasonable A1C goal for most children and adolescents with type 2 diabetes treated with oral agents alone is <7%. More stringent A1C goals (such as <6.5%) may be appropriate for selected individual patients if they can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes and lesser degrees of  $\beta$ -cell dysfunction and patients treated with lifestyle or metformin only who achieve significant weight improvement. **E**
- A1C targets for youth on insulin should be individualized, taking into account the relatively low rate of hypoglycemia in youth-onset type 2 diabetes. **E**
- Home self-monitoring of blood glucose (SMBG) regimens should be individualized, taking into consideration the pharmacologic treatment of the patient. **E**

Previous target A1C guidelines by the ADA and the International Society for Pediatric and Adolescent Diabetes for youth with type 2 diabetes ranged from <6.5% to <7.0% (70,71) and <7.5% (72), mostly based on expert opinion and extrapolated from youth with type 1 diabetes and adults with type 2 diabetes. However, accumulating evidence provides support for more appropriate goals. The TODAY study showed that hypoglycemia is rare in adolescents with type 2 diabetes, even with insulin therapy (73), suggesting that more stringent A1C targets are acceptable. Also in TODAY, individuals with an A1C of >6.3% after 3 months of metformin or an increasing A1C, even in the nondiabetes range (74), had a substantially increased risk for loss of glycemic control, likely reflecting a greater degree of  $\beta$ -cell dysfunction (75,76). Furthermore, individuals with youth-onset type 2 diabetes have high rates of

complications (77–79), many of which are associated with poor glycemic control, and rapid deterioration with increasing A1C. Finally, youth with type 2 diabetes can be expected to have long disease duration and, therefore, continued risk for accumulation of glycemia-related complications. Taken together, this evidence suggests that a more stringent A1C target can and should be attained in youth with type 2 diabetes.

The evidence is insufficient regarding the value of SMBG and how often testing should be performed by youth with type 2 diabetes not on insulin therapy. Until such data become available, the frequency of SMBG should be individualized, taking into account patient and family burden, the value of the information obtained and how it will be used to adjust therapy, and the associated hypoglycemia risk.

## LIFESTYLE MANAGEMENT

### Diabetes Education and Self-Management Skills

#### Recommendation

- All youth with type 2 diabetes and their families should receive comprehensive diabetes self-management education/support that is specific to youth with type 2 diabetes and is culturally competent. **B**

It has been well established that diabetes education is necessary, but not sufficient, to enhance self-management in people with diabetes (80,81). The majority of these studies, however, focused on adults with type 2 diabetes and/or youth with type 1 diabetes. Since the population of youth with type 2 diabetes is more likely to be of minority ethnic/racial background than those with type 1 diabetes, and materials developed for adults may not address issues of development in youth, culturally appropriate programs specific to youth with type 2 diabetes and their families are necessary. Unfortunately, there are no randomized clinical trials of education and support programs for youth with type 2 diabetes. Nonetheless, descriptive reports suggest that programs that focus on building knowledge and skills appropriate to this population are important in ensuring adequate self-management.



In the TODAY trial (81), the diabetes education program included content about type 2 diabetes physiology and treatment, building skills of healthy eating habits, carbohydrate counting, portion sizes, reading food labels, glucose monitoring, and ketone testing, as well as problem solving, risk reduction, and living with diabetes. Full mastery of the program was achieved in an average of 5.5 90-min sessions. Factors associated with shorter time to mastery included more recent diagnosis and not having to use a translator, while sex, primary language of the youth and family, individual versus group sessions, or site of delivery were not. These program materials are available from the ADA as “Be Healthy Today” (82). Given the lack of clinical trials of various educational approaches, it is unclear that this program is superior to other approaches. Nonetheless, the program provides effective, engaging materials for youth with type 2 diabetes that were designed specifically for this population. Until comparative trials of various approaches are completed, diabetes education using these materials is appropriate (83).

### Psychosocial Factors

#### Recommendations

- Providers should assess social context, including potential food insecurity, housing stability, and financial barriers, and apply that information to treatment decisions. **E**
- Use patient-appropriate standardized and validated tools to assess diabetes distress and mental/behavioral health in youth with type 2 diabetes, with attention to symptoms of depression and disordered eating behaviors, and refer to specialty care when indicated. **B**
- When choosing glucose-lowering or other medications for youth with overweight/obesity and type 2 diabetes, consider medication adherence and treatment effects on weight. **E**
- Starting at puberty, preconception counseling should be incorporated into routine diabetes clinic visits for all females of childbearing potential. **A**

- Patients should be screened for smoking and alcohol use at diagnosis and regularly thereafter. **C**

The ADA position statement on the provision of psychosocial care for people living with diabetes recognizes the profound influence of psychosocial factors on health outcomes and well-being (84). The recommendations herein are consistent with those outlined in that position statement, an important resource for more detailed information about life-course issues and assessment of psychosocial comorbidities.

Most youth with type 2 diabetes come from racial and ethnic minority groups, have low socioeconomic status, and have a family history of diabetes (37,85,86). Families often experience multiple stressors including food insecurity, employment and housing instability, and difficulties with access to treatment; youth also may have been exposed to early adversity, which has been shown to affect health over time (87). Providers should personalize approaches to diabetes management to minimize barriers to care, enhance adherence, and maximize response to treatment by taking into consideration the sociocultural context of the patient and their family.

Youth with type 1 diabetes have high rates of diabetes distress and psychiatric symptoms and diagnoses (in particular, depression and disordered eating behaviors) necessitating ongoing surveillance of mental and behavioral health. Evidence about psychiatric disorders and symptoms in youth with type 2 diabetes is limited (88–92), but given the sociocultural context and the medical burden, as well as preexisting obesity-associated comorbidities together with type 2 diabetes, ongoing surveillance of mental health/behavioral health is also indicated in youth with type 2 diabetes.

Symptoms of depression and disordered eating are common in youth with type 2 diabetes and associated with poorer glycemic control (89). The prevalence of clinically significant symptoms of depression among youth with type 2 diabetes was reported to be 8.6% in the SEARCH cohort of youth with type 1 and type 2 diabetes (89) and 14.8% in the TODAY cohort of youth with type 2 diabetes (93). In addition, more than 25% of females and males in the SEARCH

cohort of youth with type 2 diabetes reported symptoms of disordered eating behaviors, such as skipping insulin, vomiting, and using diet pills or laxatives, and these behaviors were associated with poorer glycemic control in females (89). Binge eating rates in the TODAY cohort were high (26%) and were associated with more severe obesity, psychological symptoms of disordered eating, and symptoms of depression (94).

More research is needed to evaluate rates of diagnosable psychiatric disorders, trauma, victimization, and psychotropic drug use in youth with type 2 diabetes. It also is important to elucidate the relationships among obesity, psychiatric disorders, and medication regimens because many of the drugs prescribed for diabetes and psychiatric disorders are associated with weight gain and increased concerns about eating, shape, and weight (95,96).

Finally, in accord with the ADA’s *Standards of Medical Care in Diabetes—2018* (97), preconception counseling should be provided starting at puberty for all girls of childbearing potential in order to increase understanding of risk related to diabetes and improve health prior to conception. In the TODAY study (98), despite counseling on pregnancy reduction designed specifically for youth with type 2 diabetes, 10.2% of the females in the cohort became pregnant over an average of 3.8 years of study participation. Of note, 26.4% of pregnancies ended in a miscarriage, stillbirth, or intrauterine death, and 20.5% of the live-born infants had a major congenital anomaly. These data confirm the importance of educating young women with type 2 diabetes to time their pregnancies to reduce risks to themselves and their offspring. More research regarding pregnancy outcomes in youth with type 2 diabetes is needed.

### Lifestyle Modification, Weight Management, Exercise, and Nutrition

#### Recommendations

- Youth with overweight/obesity and type 2 diabetes and their families should be provided with developmentally and culturally appropriate comprehensive lifestyle programs that are integrated with diabetes management aiming to achieve 7–10% decrease in excess weight. **C**

- Given the necessity of long-term weight control and lifestyle management for children and adolescents with type 2 diabetes, lifestyle intervention should be based on a chronic care model and offered in the context of diabetes care. **E**
- Youth with diabetes, like all children, should be encouraged to participate in at least 30–60 min of moderate to vigorous physical activity at least 5 days per week (and strength training on at least 3 days per week) **B** and should be encouraged to decrease sedentary behavior. **C**
- Nutrition for youth with type 2 diabetes, like all children, should focus on healthy eating patterns that emphasize consumption of nutrient-dense, high-quality foods and decrease consumption of calorie-dense, nutrient-poor foods, particularly sugar-added beverages. **B**
- The utility of pharmacotherapy for weight reduction in youth with type 2 diabetes remains limited in the absence of approved, effective, and safe medications and the lack of clinical trials in youth with type 2 diabetes. **B**

Lifestyle modification programs that incorporate evidence-informed behavioral strategies to promote changes in diet and physical activity (99) are a cornerstone of treatment for adults with type 2 diabetes because the resulting reductions of 5–7% of initial body weight are associated with improvements in blood glucose levels and other risk parameters. Much less is known about the impact of lifestyle interventions in youth with type 2 diabetes, although 90% are overweight or obese. Family-based behavioral weight management programs in school-aged children without diabetes have a modest, but positive, impact on weight and cardiometabolic risk factors but are less effective in adolescents and children with more severe obesity (100–102). Intensive weight management, when compared with usual treatment, can have sustained benefits over a 2-year period for ethnically and racially diverse inner-city children and adolescents with an average BMI >35 (102,103). Although BMI changes in treated youth

were modest (103), those who received usual care showed increases in BMI over the period of observation, while the intervention group had continued improvements in body composition and insulin resistance relative to those who did not receive weight management.

The most pertinent evidence regarding the impact of lifestyle interventions for youth with type 2 diabetes comes from the TODAY study (104), where the goal was to achieve 7–10% decrease in percent overweight. The addition of lifestyle intervention to metformin monotherapy was not associated with durable metabolic control beyond that of metformin alone. Youth receiving metformin plus lifestyle intervention showed short-term, but not sustained, weight loss and improvements in body composition relative to those in the two other intervention groups (105). While 31% of youth who received lifestyle intervention achieved the preplanned goal of a decrease of  $\geq 7\%$  in percent overweight through 24 months of intervention, this result did not differ significantly from that obtained with metformin monotherapy and no predictors of successful weight loss were identified. However, irrespective of treatment assignment, sustained weight losses  $\geq 7\%$  of excess body weight were associated with improvements in A1C, HDL, and C-peptide (105), indicating that obesity management remains a crucial goal.

Components of a comprehensive pediatric lifestyle intervention are well established (106,107), including those for youth with severe obesity (108). These include the involvement of family at a developmentally appropriate level and evidence-based behavioral strategies to facilitate enduring changes in nutrition and physical activity. Guidelines for physical activity and nutrition are based on those recommended by the American Academy of Pediatrics (2007) (107) and the Endocrine Society (2017) (106). Youth with type 2 diabetes frequently have severe obesity, and it is particularly important that behavior change goals for diet and activity incorporate stepwise, achievable targets developed in conjunction with the youth and family members, as appropriate.

Youth with type 2 diabetes will face increasing severity of obesity and diabetes complications as they age (109–111).

An important first step is to integrate diabetes care and education, such as the approach used in the TODAY trial, with ongoing lifestyle intervention for obesity management (106) to maximize the impact of medical and lifestyle interventions over time. Comprehensive chronic care models have been recommended for youth with obesity and chronic illness (112,113).

With the exception of orlistat, weight loss medications are not approved for use in youth. The Endocrine Society guidelines for pediatric obesity (106) review the limited evidence for effectiveness of current weight-loss medications and recommends that their use be restricted to the research setting. More research into possible pharmacologic approaches to augment lifestyle interventions and their role in type 2 diabetes in youth is urgently needed.

## PHARMACOLOGIC APPROACHES TO GLYCEMIC MANAGEMENT

### Recommendations

- Initiate pharmacologic therapy, in addition to lifestyle therapy, at diagnosis of type 2 diabetes. **A**
- In incidentally diagnosed or metabolically stable patients (A1C <8.5% and asymptomatic), metformin is the initial pharmacologic treatment of choice if renal function is normal. **A**
- Youth with marked hyperglycemia (blood glucose  $\geq 250$  mg/dL, A1C  $\geq 8.5\%$ ) without acidosis at diagnosis who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with basal insulin while metformin is initiated and titrated. **B**
- In patients with ketosis/ketoacidosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the hyperglycemia and the metabolic derangement. Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued. **A**
- In individuals presenting with severe hyperglycemia (blood glucose  $\geq 600$  mg/dL), assess for HHNK syndrome. **A**

- In patients initially treated with insulin and metformin who are meeting glucose targets based on home blood glucose monitoring, insulin can be tapered over 2–6 weeks by decreasing the insulin dose 10–30% every few days. **B**
- If the glycemic target is no longer met using metformin alone, or if contraindications or intolerable side effects of metformin develop, basal insulin therapy should be initiated. **B**
- If the combination of metformin plus basal insulin is ineffective at achieving or maintaining glycemic targets, more intensive approaches to insulin therapy may be initiated. **E**
- The use of nonapproved medications in youth with type 2 diabetes is not recommended outside of research trials. **B**

In the clinical setting, only a minority of youth with type 2 diabetes are on lifestyle management alone (114,115) because it is often inadequate for achieving and maintaining the desired level of glycemic control and BMI improvement, with the percentage of patients remaining on lifestyle intervention alone declining further by 1 year (115). Therefore, in most cases, the addition of pharmacologic intervention early in the disease is warranted. As in adults, the pharmacologic intervention should be a stepped process. However, since only metformin and insulin are currently approved for the treatment of diabetes in patients under 18 years old, the approach in youth is more limited.

**Initial Treatment**

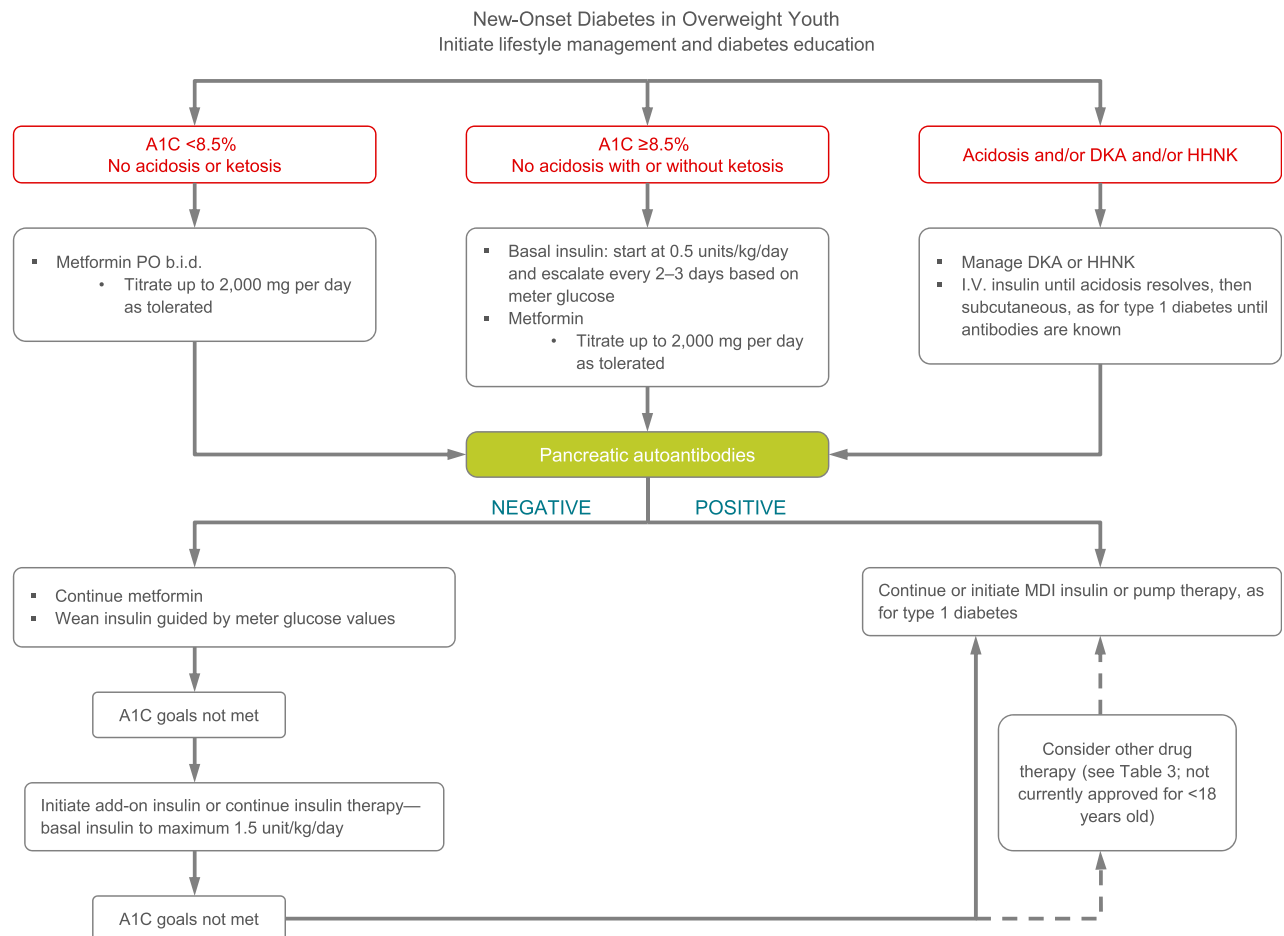
Initial treatment of youth-onset type 2 diabetes should include metformin and/or insulin alone or in combination, based on the metabolic status of the patient.

Initial treatment of the youth with obesity and diabetes must take into account that diabetes type is often uncertain in the first few weeks of treatment owing to overlap in presentation and that a substantial percentage of youth with type 2 diabetes will present with clinically significant ketoacidosis (65). Therefore, immediate therapy should address the hyperglycemia and associated metabolic derangements irrespective of ultimate diabetes type, with adjustment of therapy once metabolic compensation has been established and subsequent information, such as antibody results, becomes available.

Figure 1 provides an approach to initial treatment.

**Metformin**

Metformin is the preferred drug for initial treatment of type 2 diabetes in adults and youth. In the TODAY study, 48.3% of youth with type 2 diabetes who were



**Figure 1**—Management of new-onset diabetes in overweight youth suspected to have type 2 diabetes based on risk factors listed in Table 1. MDI, multiple daily injections.

enrolled, with less than 2 years (median 8 months) of diabetes duration, maintained adequate glycemic control (A1C <8.0%) on metformin alone for up to 6 years (104). However, youth were more likely than adults to require additional pharmacologic treatment to meet glycemic targets, with the other 51.7% of youth on metformin requiring insulin by 4 years, with a median time to treatment failure of 11.8 months.

Asymptomatic youth with presumptive type 2 diabetes who present in a stable metabolic state and have A1C <8.5% should be started on metformin as initial therapy if renal function is normal. Asymptomatic patients with A1C  $\geq$ 8.5% may also be given an initial trial of metformin monotherapy at the discretion of the health care provider, especially if the patient and family situation suggest the promise of excellent adherence to lifestyle change recommendations.

The recommended approach to metformin initiation is to start with a dose of 500–1,000 mg/day and gradually escalate it every 1–2 weeks, depending on patient tolerability, to the recommended therapeutic dose of 1,000 mg b.i.d. Slower dosage escalation may be needed if gastrointestinal side effects occur and, in some cases, the maximum dose may not be achievable. Extended-release metformin may have fewer gastrointestinal side effects and be more convenient for the patient, but there are no studies in youth comparing extended-release metformin to the standard metformin preparation.

#### **Metformin Plus Insulin**

Youth with marked hyperglycemia (blood glucose  $\geq$ 250 mg/dL and/or A1C  $\geq$ 8.5%) without acidosis at diagnosis but who are symptomatic with polyuria, polydipsia, nocturia, and/or weight loss should be treated initially with basal insulin while concurrently initiating and titrating metformin. In patients with ketosis/ketoacidosis at diagnosis, treatment with subcutaneous or intravenous insulin should be initiated to rapidly correct the hyperglycemia and the metabolic derangement. Once acidosis is resolved, metformin should be initiated while subcutaneous insulin therapy is continued (116). In individuals presenting with severe hyperglycemia (blood glucose  $\geq$ 600 mg/dL), assess for HHNK syndrome.

Once glycemic stability is achieved, insulin may not be needed. Limited

data suggest that adolescents with type 2 diabetes who present initially with DKA, ketosis, or symptomatic hyperglycemia can be managed successfully with metformin alone, at least initially after a short course of insulin therapy to establish glycemic stability (117). For example, in the TODAY study, more than 90% of the subjects screened for study participation were initially controlled adequately on metformin alone regardless of prior insulin therapy (117). However, these TODAY participants were frequently contacted and closely monitored by the research staff, a situation that may not be feasible in a clinical setting. Whether or not early treatment with insulin provides unique benefits in youth with type 2 diabetes remains questionable. The recently completed RISE Pediatric Medication Study in youth with obesity with impaired glucose tolerance or recent-onset type 2 diabetes did not demonstrate benefits of 3 months of basal insulin glargine followed by 9 months of metformin compared with metformin alone for 12 months in preserving or restoring  $\beta$ -cell function (118). It remains to be determined if longer periods of insulin treatment may prove beneficial in preserving  $\beta$ -cell function.

#### **Ongoing Therapy**

When the individualized glycemic target can no longer be met with metformin alone, or if metformin intolerance or renal insufficiency develops, insulin therapy should be initiated. This can be done alone or in combination with metformin, unless metformin is contraindicated. Because studies indicate that adherence with insulin therapy is a challenge in youth with type 2 diabetes (73,119), starting with a single daily dose of a long-acting insulin analog (glargine [Lantus, Basalglar, Toujeo], detemir [Levemir], or degludec [Tresiba]) may be preferred. Premixed insulins may be appropriate in some circumstances.

If the combination of metformin at the maximum tolerated dose (up to 1,000 mg b.i.d.) plus basal insulin at a maximum dose of 1.5 units/kg/day is ineffective at achieving the glycemic target, medication adherence should be actively addressed. When combined metformin and basal insulin therapy does not achieve targets, and in the absence of other approved drugs to treat diabetes in youth (<18 years old), higher doses of

long-acting insulin or initiation of multiple daily injections of basal and premeal rapid-acting insulin should be considered, though adherence to the latter may be a barrier.

Because severe insulin resistance is characteristic of youth with type 2 diabetes, basal insulin doses above 1.5 units/kg/day may be required to achieve adequate glycemic control, particularly for those youth with elevated A1C and glucotoxicity and youth who are in mid-to late puberty. In these circumstances, it may be appropriate to use more concentrated insulin preparations (U-300 glargine [Toujeo], U-200 Tresiba, U-200 Humalog, U-500 regular) to avoid large-volume injections that may further diminish medication adherence.

The most significant adverse effect of insulin therapy in type 2 diabetes, as in type 1 diabetes, is hypoglycemia. Although the incidence of hypoglycemia in youth with type 2 diabetes is low, even with insulin therapy (73), patients treated with insulin should be educated about avoidance, recognition, and treatment of hypoglycemia and should be instructed on the use of glucagon for treatment of severe hypoglycemia. Also, since insulin may result in weight gain, involvement of a nutritionist in patient care and education is essential when insulin is initiated.

#### **Other Therapies**

Other than insulin and metformin, there are currently more than 25 medications in 10 general classes that are commercially available and FDA-approved for treatment of type 2 diabetes in adults in the U.S. (Table 3). It should be noted, however, that none of these are currently approved for use in youth (<18 years old), and while some of these agents have undergone or are currently undergoing pharmacokinetic, pharmacodynamics, and safety/tolerability testing in small pediatric studies, no efficacy or long-term safety results have yet been reported in youth.

Although the TODAY study demonstrated that the addition of rosiglitazone to metformin improved the durability of glycemic control (treatment failure rate 38.6% for metformin plus rosiglitazone vs. 51.7% for metformin alone) with no increased rate of adverse events over a 3–6 year period in youth with recent-onset type 2 diabetes, it is premature to recommend its widespread use in



**Table 3—Drugs for treating type 2 diabetes in adults (not including insulin or insulin analogs) but not yet approved in youth except for metformin**

Drug class	Available drugs in this class	Mechanism of action	Significant adverse effects	Approved in patients <18 years old
Biguanides	Metformin	Decreases insulin resistance; reduces hepatic glucose production; increases peripheral glucose uptake; decreases gastrointestinal absorption of glucose	Gastrointestinal Lactic acidosis	Yes
Sulfonylureas	Glipizide Glimepiride Glyburide	Stimulates secretion of insulin from the $\beta$ -cell	Hypoglycemia Weight gain	No
Meglitinides	Repaglinide Nateglinide	Stimulates glucose-dependent secretion of insulin from the $\beta$ -cell	Hypoglycemia URI Diarrhea Headache	No
$\alpha$ -Glucosidase inhibitors	Acarbose Miglitol	Delays absorption of glucose by intestines by inhibiting breakdown of complex sugars	Flatulence Diarrhea Abdominal cramps	No
GLP-1 agonists	Exenatide Liraglutide Dulaglutide Lixisenatide Albiglutide Semaglutide	Incretin effect; slows gastric emptying; enhances postprandial insulin biosynthesis; improves $\beta$ -cell function; decreases appetite	Acute pancreatitis C-cell hyperplasia/ medullary thyroid carcinoma Nausea/vomiting Hypoglycemia Diarrhea Headache	No
DPP-4 inhibitors	Saxagliptin Sitagliptin Alogliptin Linagliptin	Inhibits DPP-4 enzyme, reducing endogenous GLP-1 breakdown	Acute pancreatitis URI UTI Nasopharyngitis Headache	No
Amylin analog	Pramlintide	Inhibits postprandial glucagon secretion; delays gastric emptying; improves satiety	Hypoglycemia Nausea Anorexia Abdominal pain	No
Thiazolidinediones	Rosiglitazone Pioglitazone	PPAR- $\gamma$ inhibitor; increases insulin sensitivity in liver, muscle, and adipose tissue; decreases hepatic glucose output	Edema Weight gain Anemia Elevated liver enzymes	No
SGLT-2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin	Allows more glucose to be excreted in the urine and hence lowers blood glucose	Euglycemic ketoacidosis UTI Candidal vulvovaginitis	No
Bile acid sequestrant	Colesevelam	Mechanism for glucose lowering is unknown	Gastrointestinal (gas, nausea, diarrhea, abdominal pain) Weakness Muscle pain	No
Dopamine-2 agonist	Bromocriptine (quick release)	Modulates hypothalamic regulation of metabolism; increases insulin sensitivity	Nausea/vomiting Fatigue Dizziness Headache	No

DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; PPAR, peroxisome proliferator-activated receptor; SGLT2, sodium-glucose cotransporter 2; URI, upper respiratory infection; UTI, urinary tract infection.

youth with type 2 diabetes, especially since its use is not approved in the pediatric population. Even though many of the newer agents approved in the adult population are promising and may have particular benefits in younger individuals with diabetes, we cannot recommend widespread use of these medications until additional studies are completed. Unfortunately,

implementation and completion of such studies have been slow and many barriers have been identified (111). Therefore, we recommend that the use of these medications in youth with type 2 diabetes be avoided outside of research trials. However, collaboration among investigators, pharmaceutical sponsors, and governmental regulators is urgently needed to expand

treatment options for this population of patients.

### METABOLIC SURGERY

#### Recommendations

- Metabolic surgery may be considered for the treatment of adolescents with type 2 diabetes who are markedly obese (BMI >35 kg/m<sup>2</sup>)

and who have uncontrolled glycemia and/or serious comorbidities despite lifestyle and pharmacologic intervention. **A**

- Metabolic surgery should be performed only by an experienced surgeon working as part of a well-organized and engaged multidisciplinary team including surgeon, endocrinologist, nutritionist, behavioral health specialist, and nurse. **A**

Bariatric or metabolic surgery, including Roux-en-Y gastric bypass, vertical sleeve gastrectomy, laparoscopic adjustable gastric banding, laparoscopic gastric plication, and biliopancreatic diversion, has been shown to significantly reduce weight, BMI (120), and cardiovascular comorbidities (121) in adults with obesity and is now considered a standard component of care for adults with morbid obesity. Metabolic surgery is also an effective strategy for prevention (122,123) and treatment of type 2 diabetes in obese and severely obese (BMI  $\geq 30$  kg/m<sup>2</sup>) adults (124–129) and is now endorsed as part of the algorithm for treating type 2 diabetes in adults (127).

Over the last decade, weight-loss surgery has been increasingly performed in adolescents with obesity, but the long-term experience remains limited. The current guidelines for metabolic surgery in adolescents generally include BMI  $>35$  kg/m<sup>2</sup> with significant comorbidities or BMI  $>40$  kg/m<sup>2</sup> with or without comorbidities (106,130–140). The Endocrine Society Clinical Practice Guideline on Pediatric Obesity discusses bariatric surgery for the management of pediatric obesity in detail, and interested readers can refer to it (106). Briefly, positive outcomes of metabolic surgery have included remission of type 2 diabetes, improvements in glucose homeostasis in youth without diabetes, improvement in surrogate markers of insulin sensitivity and secretion, resolution of sleep apnea, improvements in nonalcoholic fatty liver disease (NAFLD), and improvements in cardiovascular disease (CVD) risk factors, among others (106,134–141). Direct comparison between the medical management of youth with type 2 diabetes and bariatric surgery outcome, both short- and long-term, is very limited. A recent study compared

youth with type 2 diabetes from the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS) cohort who had undergone a bariatric surgical procedure with youth with medically treated type 2 diabetes from the TODAY cohort. During 2 years, A1C decreased from 6.8% to 5.5% in Teen-LABS and increased from 6.4% to 7.8% in TODAY, BMI decreased by 29% in Teen-LABS and increased by 3.7% in TODAY, elevated blood pressure decreased from 45% to 20% of participants in Teen-LABS and increased from 22% to 41% in TODAY, and dyslipidemia decreased from 72% to 24% in Teen-LAB versus no appreciable change in TODAY (142).

Overall, studies in both adults and adolescents suggest that those who undergo bariatric surgery earlier in the course of diabetes (that is, at a younger age or with higher baseline  $\beta$ -cell function) have a higher remission rate despite similar weight loss (143). Initial diabetes remission rates in adults range between 40% and 70%, whereas in adolescents the reported initial rates are as high as 68–100% (144). The long-term durability of these remissions is unknown and will require longer follow-up.

Short-term and long-term complications of metabolic surgery need to be taken into consideration. In Teen-LABS, 13% of adolescents required a second operative procedure and another 13% required an endoscopic procedure because of a complication (145). In the recent Teen-LABS/TODAY comparison, 30% of the youth with diabetes undergoing surgical intervention required readmission and/or reoperation (142). Postoperative nutritional complications (vitamin B<sub>12</sub>, thiamine, and vitamin D deficiency) are also prevalent. Long-term follow-up and further research is required to better understand the mechanisms by which metabolic surgery improves type 2 diabetes and the short-term and long-term benefits and risks of this procedure in youth. Quality of life and economic (cost-benefit) analyses will also be important components of ongoing follow-up and research (146,147).

## PREVENTION AND MANAGEMENT OF DIABETES COMPLICATIONS

Youth-onset type 2 diabetes is associated with significant microvascular and

macrovascular risk burden and a substantial increase in the risk of cardiovascular morbidity and mortality at an earlier age than those individuals diagnosed later in life (148). The higher complication risk in earlier-onset type 2 diabetes is likely to be related to prolonged lifetime exposure to hyperglycemia and other atherogenic risk factors, including insulin resistance, dyslipidemia, hypertension, and chronic inflammation. These diabetes comorbidities also appear to be higher than in youth with type 1 diabetes despite shorter diabetes duration and lower A1C (149). In addition, the progression of vascular abnormalities appears to be more pronounced in type 2 diabetes diagnosed earlier in life compared with type 1 diabetes of similar duration, including ischemic heart disease and stroke (150,151).

## Nephropathy

### Recommendations

- Blood pressure should be measured at every visit. **A**
- Blood pressure should be optimized to reduce risk and/or slow the progression of diabetic kidney disease. **A**
- If blood pressure is  $>95$ th percentile for age, sex, and height, increased emphasis should be placed on lifestyle management to promote weight loss. If blood pressure remains above the 95th percentile after 6 months, antihypertensive therapy should be initiated. **C**
- Initial therapeutic options include ACE inhibitors or angiotensin receptor blockers. Other blood pressure-lowering agents may be added as needed. **C**
- Protein intake should be at the recommended daily allowance of 0.8 g/kg/day. **E**
- Urine albumin/creatinine ratio (UACR) should be obtained at the time of diagnosis and annually thereafter. An elevated UACR ( $>30$  mg/g creatinine) should be confirmed on two of three samples. **B**
- Estimated glomerular filtration rate (eGFR) should be determined at the time of diagnosis and annually thereafter. **E**

- In nonpregnant youth with diabetes and hypertension, either an ACE inhibitor or an angiotensin receptor blocker is recommended for those with modestly elevated UACR (30–299 mg/g creatinine) **D** and strongly recommended for those with UACR >300 mg/g creatinine and/or eGFR <60 mL/min/1.73 m<sup>2</sup>. **E**
- For those with nephropathy, continued monitoring (yearly UACR, eGFR, serum K) may aid in assessing adherence and detecting progression of disease. **E**
- Referral to nephrology is recommended in case of uncertainty of etiology, worsening UACR, or decrease in eGFR. **E**

Diabetic kidney disease is diagnosed in the presence of elevated albumin excretion and decreased eGFR and is the leading cause of end-stage renal disease (152). Elevated UACR or albuminuria, defined as >30 mg/g creatinine, and hyperfiltration, defined as an eGFR between 120 mL/min/1.73 m<sup>2</sup> and 150 mL/min/1.73 m<sup>2</sup> (153,154), are early abnormalities that indicate increased risk of progression to diabetic kidney disease (154,155). Overt nephropathy is defined as persistent proteinuria ≥500 mg/day or UACR ≥300 mg/g creatinine and an eGFR <60 mL/min/1.73 m<sup>2</sup>.

Albuminuria and hyperfiltration detected early in youth with type 2 diabetes may occur because of obesity before the onset of diabetes (156) and can be related to early vascular dysfunction (157). In TODAY, the prevalence of microalbuminuria was 6.3% at randomization (mean 7.8 months since diagnosis of diabetes) and increased to 16.6% over 3 years (79). This coincided with progression of dyslipidemia (from 4.5% at baseline to 11%) and hypertension (from 11.6% at baseline up to 33%) (78,79) despite standardized therapy for these comorbidities. The main determining factor in albuminuria progression was A1C, with 17% higher risk of developing albuminuria per 1% increase in A1C (79), consistent with findings in other studies (149). Modifiable risk factors include obesity, dyslipidemia, hypertension, and glycemia (152). In some ethnic groups, particularly Pima Indians and First Nations people in Canada, the

risk of nephropathy is much higher in youth with type 2 diabetes (158–161).

Spot UACR is generally recommended for screening of urinary albumin excretion, with an abnormal value confirmed on two of three consecutive tests obtained on different days within a 3- to 6-month period. Results can be affected by orthostatic proteinuria, marked hyperglycemia, exercise, menstruation, recent intercourse, and sample contamination. eGFR can be calculated from serum creatinine and the patient's height using the Schwartz equation. However, recent studies suggest that this underestimates hyperfiltration, which is highly prevalent in youth with type 2 diabetes, and a combined estimation using serum creatinine and serum cystatin C is preferable when available (162).

In addition to optimizing glycemia, control of hypertension is important to prevent and slow the progression of nephropathy. Therapeutic options include the use of ACE inhibitors or angiotensin receptor blockers (152,163–165). If not tolerated, a calcium channel blocker or diuretic or combination therapy may be required if hypertension does not normalize on single-agent therapy.

## Neuropathy

### Recommendations

- Youth with type 2 diabetes should be screened for the presence of neuropathy by foot examination at diagnosis and annually. The examination should include inspection, assessment of foot pulses, pinprick and 10-g monofilament sensation tests, testing of vibration sensation using a 128-Hz tuning fork, and ankle reflexes. **C**
- Prevention should focus on achieving glycemic goals. **C**

Diabetic neuropathy can manifest as distal polyneuropathy (DPN), mononeuropathy, and/or autonomic neuropathy. Mononeuropathies are uncommon. DPN is usually the earliest clinically apparent manifestation of neuropathy in persons with diabetes and most commonly presents with paresthesia, numbness, or pain in the feet. DPN generally affects the small myelinated fibers first with burning or stabbing pain and reduced or absent thermal and pinprick sensation. It then progresses to larger

myelinated fibers with numbness, tingling, and poor balance along with reduced or absent reflexes, vibration perception, and monofilament sensation. The “gold standard” for the diagnosis of DPN includes careful neurologic examination to rule out other potential causes of neuropathy and nerve conduction velocity studies. The Diabetes Control and Complications Trial (DCCT), which used a combination of examination by a neurologist, nerve conduction velocity testing, and autonomic neuropathy testing, clearly showed that improved glycemic control reduced the incidence of diabetic neuropathy, both DPN and autonomic, by 44–60%.

However, most large prospective studies have not been able to include the gold standard of nerve conduction studies and have utilized less invasive and less expensive approaches to the diagnosis of diabetic neuropathy. The most commonly used is the Michigan Neuropathy Screening Instrument (MNSI). The MNSI is a self-administered questionnaire (MNSIQ) and an examination (MNSIE) for foot abnormalities, distal vibration perception, and ankle reflexes; the MNSI has been validated in adults with type 1 diabetes as a screening tool for neuropathy (166–169). It should be noted, however, that the MNSIE does not include an assessment of small-fiber dysfunction.

Evidence of diabetic neuropathy using the MNSI was found in 26% of youth with type 2 diabetes in the SEARCH study (168) and in 21% of an Australian cohort using thermal (small fiber) and vibration (large fiber) threshold testing (149). In addition, more than half of the cohort had evidence of autonomic neuropathy (pupillary reactivity) after a median duration of diabetes of 1.3 years (149). In an Indian cohort of mean age 16 years at diagnosis, the prevalence of neuropathy increased from 3% in those with diabetes duration <5 years to 49% in those with duration >15 years (170). In the SEARCH study, the prevalence of abnormal MNSI was significantly higher in youth with type 2 diabetes compared with those with type 1 diabetes after adjustment for age and sex. This association was no longer significant after adjustment for the covariates of diabetes duration, waist circumference, blood pressure, HDL cholesterol, and microalbuminuria (168). In the Australian cohort, the prevalence of

peripheral and autonomic neuropathy in adolescents with type 2 diabetes was similar to that of the type 1 diabetes cohort despite shorter diabetes duration (1.3 vs. 6.8 years) and lower A1C (7.3% vs. 8.5%) (149). In adolescents with type 1 diabetes, data from the DCCT support the importance of intensive glycemic therapy and reduction of A1C for the prevention of diabetic neuropathy (171,172). So far, such data do not exist in youth with type 2 diabetes.

The ADA recommends that assessment for symmetric DPN should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All patients should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation (173). Since it appears that youth with type 2 diabetes develop DPN at least as frequently as adults, youth with type 2 diabetes should be screened at the same frequency: at diagnosis and annually.

### Retinopathy

#### Recommendations

- Screening for retinopathy should be performed by dilated funduscopy or retinal photography at or soon after diagnosis and annually thereafter. **C**
- Optimizing glycemia is recommended to decrease the risk or slow the progression of retinopathy. **B**
- Less frequent examination (every 2 years) may be considered if there is adequate glycemic control and a normal eye exam. **C**

Diabetic retinopathy refers to changes in the small vessels of the retina with the occurrence of hemorrhages, microaneurysms, exudates, or abnormal vessels. The prevalence of retinopathy in youth with type 2 diabetes is reported to be between 2% and 40%, depending on the methodology used, the age of the participants, and the duration of diabetes. The prevalence is higher with greater duration of the disease, although retinopathy has been reported at diagnosis (149,170,174). In the TODAY study, the prevalence of early retinopathy by digital fundus photography at a mean age of 18.1 years and mean duration of diabetes

of 4.9 years was 13.7%, with no evidence of macular edema or proliferative retinopathy (77). Retinopathy was associated with older age (19.1 vs. 17.9 years), longer duration of diabetes (5.6 vs. 4.7 years), and higher A1C (8.3% vs. 6.9%). Moreover, the odds ratio for retinopathy increased with increasing A1C, age, and duration of diabetes (77). In the SEARCH study, the prevalence of retinopathy using retinal photography was 42% at a mean age of 21 years and mean duration of type 2 diabetes of 7.2 years (175). A1C and LDL cholesterol were significantly higher among those with retinopathy compared with those without. In Pima Indians, retinopathy was detected only after age 20 years and only after 5 years of diabetes duration (158). However, by 30 years of age, retinopathy had developed in 45% of this population (158).

### NAFLD

#### Recommendations

- Evaluation for NAFLD (by measuring ALT and AST) should be done at diagnosis of type 2 diabetes and annually thereafter. **B**
- Referral to gastroenterology should be considered for persistently elevated or worsening transaminases. **B**

The prevalence of dysglycemia in youth with NAFLD is higher than in those without NAFLD (176). In a multicenter cohort of youth with NAFLD, primarily of Hispanic descent, a third of the children with NAFLD had abnormalities in glucose metabolism; 23.4% had prediabetes and 6.5% had type 2 diabetes (176). Moreover, type 2 diabetes in youth is associated with greater NAFLD histologic severity than in adults, which may imply a heightened risk of progression to fibrosis, cirrhosis, and hepatic failure (176,177). Therefore, it is particularly important to evaluate for NAFLD in youth with obesity and type 2 diabetes. For screening, transaminase levels are a clinical tool that is widely available and has a good sensitivity for the detection of more advanced stages of hepatitis or fibrotic changes, but these tests are not disease specific; therefore, other causes of chronic liver disease should be ruled out (178,179). Recently, population-based cutoffs lower than those used

in clinical laboratories have been advocated to indicate abnormality (180). Among the noninvasive diagnostic tests, MRI/MRS are currently the preferred imaging modalities, though of limited clinical application (181). Liver ultrasound, though a widely available clinical tool, is operator dependent and detects liver fat >30% with sensitivity of 80%, but sensitivity is lower with lower degrees of fatty infiltration and the presence of morbid obesity. Hence, its value in the early diagnosis of NAFLD is limited (181). Among the noninvasive modalities, elastography is useful in evaluating advanced fibrosis and cirrhosis (181) and is gaining wider acceptance. Liver biopsy remains the gold standard for diagnosis and staging of liver disease and the only way to differentiate between nonalcoholic steatohepatitis and hepatic steatosis. Treatment options for NAFLD remain limited, with weight loss being most effective. Therapeutic agents tested in randomized clinical trials in youth include metformin, vitamin E, and cysteamine, with no clear established benefit on histologic outcomes or sustained reduction in ALT (182–184).

### Obstructive Sleep Apnea

#### Recommendation

- Screening for symptoms of obstructive sleep apnea (OSA) should be done at each visit, and referral to a pediatric sleep specialist for evaluation and a polysomnogram, if indicated, is recommended. OSA should be treated when documented. **B**

Sleep disturbance (insufficient or disrupted sleep, circadian rhythm dysregulation) and OSA are increasingly recognized as being associated with obesity (185–189), insulin resistance in adults and children (52,190–195), and type 2 diabetes in adults (196–199), as well as risk for future CVD (200). Experimental sleep restriction results in decreased glucose clearance and postprandial glucose elevation (193,201), decrease in glucose effectiveness, and variable decrease in insulin sensitivity (190,192,202). OSA may influence glycemic regulation in individuals with diabetes; in adults with type 2 diabetes, treatment of OSA with



continuous positive airway pressure has been associated with improvement in the glycemic profile (203), decreased A1C, and improvement in insulin sensitivity indices (204) as well as inflammation (205) in some, but not all, studies. Further study is needed.

### Polycystic Ovary Syndrome

#### Recommendations

- Evaluate for polycystic ovary syndrome (PCOS) in female adolescents with type 2 diabetes, including laboratory studies when indicated. **B**
- Oral contraceptives for treatment of PCOS are not contraindicated for girls with type 2 diabetes. **C**
- Metformin in addition to lifestyle modification is likely to improve the menstrual cyclicity and hyperandrogenism in girls with type 2 diabetes. **E**

PCOS affects 5–10% of females in the reproductive age-group and is characterized by hyperandrogenism and amenorrhea or oligomenorrhea secondary to chronic anovulation (206,207). The prevalence of PCOS is significantly higher in adolescent girls with obesity compared with adolescent girls without overweight/obesity (208), but the prevalence in adolescent girls with type 2 diabetes is not well studied. Insulin resistance with compensatory hyperinsulinemia are metabolic features in both adult women with PCOS with and without overweight/obesity (209) and in adolescent girls with PCOS compared with control subjects of similar age, body composition, and abdominal adiposity (210). In adolescent girls with PCOS and obesity, this increased insulin resistance when combined with impaired  $\beta$ -cell function predisposes to prediabetes and type 2 diabetes (211), with higher prevalence of impaired glucose tolerance (30%) and type 2 diabetes (3.7%) (212). Therefore, it is important to obtain a menstrual history and evaluate female adolescents with type 2 diabetes for signs and symptoms of hyperandrogenism (irregular menses, hirsutism, acne) and to initiate appropriate diagnostic evaluation for PCOS if indicated (213,214). In the TODAY cohort, 21% of adolescent girls who were  $\geq 1$ -year postmenarche had irregular menses. Those with irregular menses

versus regular menses had higher total testosterone, free androgen index, BMI, and AST and lower sex hormone-binding globulin and estradiol (215). Treatment of PCOS in adolescents includes lifestyle changes (216–218), the use of oral contraceptive pills (OCPs), and insulin sensitizers, such as metformin (213). However, the use of some OCPs has been associated with unfavorable effects on indices of insulin sensitivity (219) and lipid profile (220). The use of metformin therapy for 3–12 months was associated with decrease in serum androgens, improvement in lipid profile, induction of ovulation, and improvement in glucose tolerance and insulin sensitivity (216,221,222). Therefore, in girls with type 2 diabetes and PCOS, treatment with metformin in addition to lifestyle modification is likely to improve the metabolic dysfunction associated with PCOS and may improve menstrual cyclicity and hyperandrogenism (213,218). However, for the girls in the TODAY study, all of whom received metformin, there was no treatment group (metformin alone, metformin plus lifestyle, and metformin plus rosiglitazone) effect on menses or sex steroids at 12 and 24 months and no association of sex steroids with surrogate estimates of insulin sensitivity or secretion (215). Despite the potential negative effects of OCPs, which may not be shared by all OCPs, on metabolic status and cardiovascular risk, hormonal contraceptive therapy is more effective at addressing the symptoms of hyperandrogenism and anovulation and is not contraindicated in female youth with type 2 diabetes (213).

### CVD

#### Recommendation

- Intensive lifestyle interventions focusing on weight loss, dyslipidemia, hypertension, and dysglycemia are important to prevent overt macrovascular disease in early adulthood. **E**

### Dyslipidemia

#### Recommendations

- Lipid testing should be performed when initial glycemic control has been achieved and annually thereafter. **B**

- Optimal cholesterol goals are LDL  $< 100$  mg/dL (2.6 mmol/L), HDL  $> 35$  mg/dL (0.905 mmol/L), triglycerides  $< 150$  mg/dL (1.7 mmol/L). **E**
- If LDL cholesterol is  $> 130$  mg/dL, blood glucose control should be maximized and dietary counseling should be provided using the American Heart Association Step 2 diet. **E**
- If LDL cholesterol remains above goal after 6 months of dietary intervention, initiate therapy with statin, with goal of LDL  $< 100$  mg/dL. **B**
- If triglycerides are  $> 400$  mg/dL (4.7 mmol/L) fasting or  $> 1,000$  mg/dL (11.6 mmol/L) nonfasting, optimize glycemia and begin fibrate, with a goal of  $< 400$  mg/dL (4.7 mmol/L) fasting (to reduce risk for pancreatitis). **C**

Although there have been no long-term studies of the outcome of cholesterol-lowering therapy in youth with type 2 diabetes, studies in youth with familial hypercholesterolemia have shown reduction in carotid intima-media thickness (IMT) with the use of statins (223,224), with similar efficacy and side effects as in adults. However, in a recent multicenter, multinational study of youth with type 1 diabetes, statin use did not have a significant effect on carotid IMT despite reductions in total LDL cholesterol and triglyceride concentrations (225). Although longitudinal, interventional data with statins in youth-onset type 2 diabetes are not yet available, statin therapy in youth with type 2 diabetes who do not meet LDL targets following lifestyle change intervention is considered a reasonable approach and aligned with overall recommendations for dyslipidemia (226), given that dyslipidemia in youth tracks into adulthood and is anticipated to confer increased cardiovascular risk. Similarly, though there have been no studies of the use of fibrates in youth with type 2 diabetes and hypertriglyceridemia to prevent pancreatitis, extrapolation from studies in adults supports the use of these agents for severe hypertriglyceridemia in adolescents. Adolescent girls treated with statins or fibrates should receive counseling on potential

risk to the fetus and be encouraged to use effective birth control.

### Cardiac Function Testing

#### Recommendation

- Routine screening for heart disease with electrocardiogram, echocardiogram, or stress testing is not recommended in asymptomatic youth with type 2 diabetes. **B**

Macrovascular disease involves coronary, cerebral, and peripheral arterial disease. In adults, type 2 diabetes is associated with doubling of risk for CVD, including coronary heart disease and stroke as well as increased risk of heart failure, after adjusting for age, sex, smoking status, BMI, and systolic blood pressure (227). Diabetes duration is implicated as a major risk factor for CVD (228,229), though there may also be a worsened risk of CVD with early onset of type 2 diabetes (228,230). While overt cardiovascular events are not expected in youth with type 2 diabetes, epidemiological and clinical studies show that the atherosclerotic process starts during childhood (231), with strong relationships between childhood obesity, elevated blood pressure, low HDL cholesterol, and coronary artery disease in adulthood (232–235). Furthermore, studies of vascular function have demonstrated subclinical vascular disease in adolescents with obesity and type 2 diabetes, including elevated aortic pulse wave velocity, a marker of vascular stiffness (236), and increased carotid IMT, a structural measure of atherosclerosis, compared with normoglycemic youth with and without overweight/obesity (237). In the SEARCH study, youth with type 2 diabetes had worse arterial stiffness than those with type 1 diabetes, attributed to greater central adiposity and hypertension but not related to duration of diabetes or glycemic control (238). In studies of obese youth with and without type 2 diabetes, carotid IMT was significantly related to glycemia, while aortic pulse wave velocity was related to insulin resistance and inflammation (239). In addition, total body and abdominal adiposity were significant determinants of coronary artery calcifications in these youth (239). In TODAY, echocardiographic evaluation revealed a relationship of BMI and blood pressure

with adverse cardiac measures (240), though there was a protective effect of cardiorespiratory fitness on functional measures of cardiac structure and function in this group of largely sedentary youth (241). Overall, studies to date indicate significant vascular dysfunction and greater risk of progression to overt CVD in youth with obesity and type 2 diabetes. The vascular dysfunction may begin prior to the diagnosis of type 2 diabetes as a result of obesity and insulin resistance.

In adults, type 2 diabetes is associated with an increased risk of mortality, with cardiac disease as a major cause of death (242); the excess mortality is related to worse glycemic control, impaired renal function, and younger age at diabetes diagnosis (243). Youth-onset type 2 diabetes appears to be associated with an earlier onset of complications and an increased mortality risk compared with type 1 diabetes (109,244,245). In a Swedish study, type 2 diabetes diagnosed between 15 and 34 years of age was associated with a higher standardized mortality ratio than type 1 diabetes (2.9 and 1.8, respectively), with an increased hazard ratio for males versus females ( $P = 0.0002$ ) (244). Similarly, an epidemiological study from Australia reported a significant mortality excess over 15–30 years of follow-up in individuals diagnosed with type 2 diabetes between 15 and 30 years of age compared with type 1 diabetes, with a hazard ratio of 2.0 (95% CI 1.2–3.2), despite shorter average disease duration (26.9 vs. 36.5 years,  $P = 0.01$ ) and similar glycemic control (109). The mortality excess was related to an excess of cardiovascular deaths in those with type 2 diabetes (50% vs. 30%,  $P < 0.05$ ). In First Nations individuals, increased mortality with type 2 diabetes is reported in relation to end-stage renal disease (159) and is significantly higher than in individuals with youth-onset type 1 diabetes (245). In a large cohort of 354 patients with type 2 diabetes diagnosed between 15 and 30 years of age compared with a duration-matched cohort of 1,062 patients diagnosed between 40 and 50 years old, the negative effect of diabetes on morbidity (albuminuria and neuropathy scores) and mortality was greatest for those diagnosed at a young age. Standardized mortality adjusting for duration was highest, at any

chronological age, for those diagnosed between 15 and 30 years of age (246). Taken together, these data raise significant concern regarding the long-term outcome of youth-onset type 2 diabetes and support the importance of aggressive management of glycemia and CVD risk factors in these youth.

### TRANSITIONING FROM PEDIATRIC TO ADULT CARE

#### Recommendation

- Youth with type 2 diabetes should be transferred to an adult-oriented diabetes specialist when deemed appropriate by the patient and provider. **E**

The process of transferring the pediatric patient to an adult health care provider is a challenge that has only recently received attention in the literature but is now recognized to be “important and should begin well before patients are transferred” (247). Both the Society for Adolescent Medicine (248) and the American Academy of Pediatrics, along with other associations (249), have position statements related to transition of care for those with chronic diseases and special medical needs that emphasize the importance of a gradual and collaborative process starting a year or longer before the actual transition is to occur. Published literature on this subject recommends progressive implementation as eight developmentally linked steps (250,251).

The ADA, in partnership with the other organizations of the ADA Transitions Working Group (252), developed position statements in 2011 (252), in 2014 (253), and in 2018 (254). Even for youth with type 1 diabetes, deficiencies and gaps in the transition process have been demonstrated in observational cross-sectional research. These gaps are summarized in recent reviews (250,252,255) and include minimal empirical evidence about the best approaches, differences in the style and approach to health care delivery between pediatric and adult health care providers, lack of well-defined criteria of readiness for transition or tools to assess readiness, gaps in health insurance coverage, changing social structure as adolescents enter young adulthood, differences in learning styles of the patient

and teaching styles of the provider, and lack of health care provider training related to transition of care.

Despite the prevailing evidence of the need for better transition of care, there are no controlled studies of the effectiveness of such programs in patients with youth-onset type 2 diabetes. Patients with type 1 diabetes have reduced dropout from medical care, increased number of visits, and reduced pregnancy loss, DKA, and severe hypoglycemia during the transition period using a “navigator” to assist young adults (18–30 years old) (256–258).

Since emerging adults with type 2 diabetes express similar concerns related to transition from pediatric to adult health care providers (259), the same principles discussed above and steps to facilitate transition that apply to those with type 1 diabetes should be considered in type 2 diabetes.

## CONCLUSIONS

Even though our knowledge of youth-onset type 2 diabetes has increased tremendously over the last two decades, robust and evidence-based data are still limited regarding diagnostic and therapeutic approaches and prevention of complications. The current-day information indicates that there are fundamental differences in insulin sensitivity and  $\beta$ -cell function between youth and adults with prediabetes and type 2 diabetes, which could possibly explain why some youth develop type 2 diabetes decades earlier than adults (23,24,260,261). Youth are more insulin resistant and have  $\beta$ -cells that are hyperresponsive to stimulation compared with adults (23,24,260,261). Puberty-related physiologic insulin resistance, particularly in obese youth, may play a role in this heightened insulin resistance. It remains an enigma, though, why some individuals with youth-onset type 2 diabetes demonstrate durable control and others do not (74). Furthermore, type 2 diabetes appears to be more aggressive in youth than adults, with a faster rate of deterioration of  $\beta$ -cell function (76) and poorer response to glucose-lowering medications (104). Future research should probe the mechanisms responsible for this youth–adult contrast in the various aspects of type 2 diabetes. Lastly, complications in youth with type 2

diabetes appear early, resulting in higher rates of morbidity and mortality compared with type 1 diabetes. Preexisting obesity and its comorbidities might play a key role in amplifying the complications of youth-onset type 2 diabetes. Intervention/prevention strategies for type 2 diabetes should not be limited to youth with dysglycemia only, but youth with obesity at large.

In closing, the present guidelines are based on current data, experience, opinion, and gained “wisdom.” However, we anticipate that future guidelines will change as more scientific data emerge to support evidence-based recommendations.

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