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Consensus Statement

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ISPAD Clinical Practice Consensus Guidelines 2024: Type 2 Diabetes in Children and Adolescents

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Summary of What Is New/Different

Updates since the 2022 ISPAD guidelines on this topic include
- Diagnostic algorithms for youth with new onset type 2 diabetes (T2D).
- Algorithms and tables for treatment, management, and assessment of comorbidities and complications.

Recommendations on recently approved pharmacologic therapies for the treatment of youth-onset T2D and management strategies.

Keywords
Management · Type 2 diabetes · Children · Adolescents · Complications

Abstract
Youth-onset type 2 diabetes (T2D) results from genetic, environmental, and metabolic causes that differ among individuals and populations. This chapter builds on the 2022

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ISPAD guidelines and summarizes recent advances in the management of T2D in children and adolescents. Updates include diagnostic algorithm for youth with new onset T2D, algorithms and tables for treatment, management, and assessment of comorbidities and complications and recommendations on recently approved pharmacologic therapies for the treatment of youth-onset T2D and management strategies.

List of Abbreviations

ACE inhibitor:	angiotensin-converting enzyme inhibitor
ALT:	alanine transaminase
ARB:	angiotensin II receptor blocker
AST:	aspartate transaminase
CAN:	cardiac autonomic neuropathy
CGM:	continuous glucose monitoring
CPAP:	continuous positive airway pressure
DBP:	diastolic blood pressure
DHA:	docosahexaenoic acid
DKA:	diabetic ketoacidosis
DPP-4:	dipeptidyl peptidase-4
eGA:	estimated glucose average
eGFR:	estimated glomerular filtration rate
FPG:	fasting plasma glucose
GAD-65:	glutamic acid decarboxylase-65
GLP-1 RA:	glucagon-like peptide-1 receptor agonist
HHS:	hyperosmolar hyperglycemic state
HDL-C:	high-density lipoprotein cholesterol
IAA:	insulin antibody
IA-2:	islet antigen-2
IFG:	impaired fasting glucose
IGT:	impaired glucose tolerance
LDL-C:	low-density lipoprotein-cholesterol
MASLD:	metabolic dysfunction-associated steatotic liver disease
MEN:	multiple endocrine neoplasia
MNSI:	Michigan Neuropathy Screening Instrument
MNT:	medical nutrition therapy
MODY:	maturity onset diabetes of the young
NGSP:	National Glycohemoglobin Standardization Program
OGTT:	oral glucose tolerance test
OSA:	obstructive sleep apnea
PCOS:	polycystic ovary syndrome
PSG:	polysomnogram
SBP:	systolic blood pressure
SDOH:	social determinants of health
SGLT-2:	sodium-glucose co-transporter 2
SMBG:	self-monitoring of blood glucose
SMR:	standardized mortality ratios
TAR:	time above range
TBR:	time below range
TC:	total cholesterol
T1D:	type 1 diabetes
T2D:	type 2 diabetes
TIR:	time in range
TODAY study:	Treatment Options for Type 2 Diabetes in Adolescents and Youth
TG:	triglycerides
TZD:	thiazolidinedione
VLDL:	very low density lipoprotein
Znt8:	zinc transporter 8

Pathophysiology and Risk Factors

Youth-onset T2D results from genetic, environmental, and metabolic causes that differ among individuals and populations. The pathophysiology of youth-onset T2D, although not fully elucidated, is like that of adult-onset T2D, with insulin resistance and impaired insulin secretion contributing to hyperglycemia development. Specific abnormalities include increased hepatic, adipose, and skeletal muscle insulin resistance; relative insulin deficiency due to impaired pancreatic beta (β)-cell function; and also, hyperglucagonemia due to alpha (α)-cell dysfunction [1]. The following observations support a conclusion that youth-onset T2D is a more severe and progressive condition than adult-onset T2D. See Table 1.

The risk factors [9–17] (see Table 2) and the clinical correlates of youth-onset T2D underlie recommended risk-based screening approaches. Whilst obesity is a major risk factor by increasing insulin resistance, it is important to note it is not a universal phenotype in youth-onset T2D. The prevalence of obesity as defined by BMI, is lower in Asian children with T2D than in other ethnicities [12] and notably, in Japanese children with a healthy weight, nonautoimmune T2D phenotype, insulin resistance is mild but coupled with a significantly reduced insulin secretory capacity [18, 19]. Modifiable risk factors remain important prevention targets for youth with T2D.

Screening and Diagnosis of T2D and Prediabetes

Targeted screening to identify youth with T2D should be considered: (1) after onset of puberty or after 10 years of age, (2) in youth who have a BMI ≥85th percentile for age and sex, and (3) if one or more of the following risk factors are present:

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- Family history of T2D in a first- or second-degree relative **[A]**.
- Mother had pregestational T2D or gestational diabetes during pregnancy **[A]**.
- Parents are from higher risk race/ethnicity groups (examples being Native American, Canadian First Nation, Indigenous Australian, Black, Hispanic, Latin American, East and South Asian, Middle Eastern, and Pacific Islander populations) **[A]**.
- Clinical signs of insulin resistance or conditions associated with increased insulin resistance (acanthosis nigricans, fatty liver disease, hypertension, dyslipidemia, polycystic ovary syndrome [PCOS]) **[B]**.
- Child was born small for gestational age or large for gestational age [20] **[B]**.
- Use of atypical antipsychotic agents with rapid weight gain (examples include aripiprazole, risperidone, olanzapine) [21–25] **[B]**.

In some indigenous populations or high risk-groups, consider screening before age 10 or before puberty onset if BMI ≥85th percentile for age and sex and multiple risk factors are present [26, 27] **[E]**.

Screening tests include: HbA1c, fasting glucose, random plasma glucose, or plasma glucose after a 2-h oral glucose tolerance test (OGTT) **[B]**.

If initial (T2D screening) tests are within range, repeat screening should occur at a minimum every 2–3 years **[E]**.

Annual rescreening may be necessary if BMI is increasing, the cardiometabolic risk profile is worsening, PCOS or metabolic dysfunction-associated steatotic liver disease (MASLD) is present, there is a strong family history of T2D, or evidence of prediabetes **[C]**.

Screening for T2D

Comorbidities and microvascular complications may occur early in the course of T2D in youth or be present at diagnosis [28, 29]. As such, early detection and intervention of T2D is likely associated with better outcomes. Universal screening of unhealthy weight youth, in the absence of additional risk factors for T2D, is unlikely to be cost-effective [30] and is not recommended [31].

Diagnosis of Prediabetes

Prediabetes indicates that dysglycemia is present, but criteria are not met for diabetes. IGT and impaired fasting glucose are intermediate stages in the T2D natural history transition from normal glucose homeostasis to overt hyperglycemia [32]. Prediabetes has been used to recognize the high risk for progression to T2D [33]. However, none of the diagnostic criteria for prediabetes have been specifically validated in youth, rather all are extrapolated from adult definitions [34] (Table 3). Recent data suggest a 1-h plasma glucose of >155 mg/dL (8.6 mmol/L) may also indicate an increased risk to progress to T2D [35].

Individuals with IGT may manifest hyperglycemia only when challenged with a substantive glucose load and be predominantly euglycemic with normal or near-normal hemoglobin A1c (HbA1c) levels. At the population level, a small percentage of optimal weight youth have elevated HbA1c and/or fasting glucose concentrations suggesting these adult criteria for prediabetes should be applied with caution especially around puberty [36]. There are notable racial differences for meeting prediabetes criteria using HbA1c cut-points alone with Black youth having the highest risk for overdiagnosis of prediabetes based on HbA1c [37, 38].

Limited longitudinal data are available on the natural history and rate of progression of prediabetes to T2D. A Cochrane database systematic review showed a wide pooled cumulative incidence of T2D in youth, usually associated with IGT at baseline and with follow-up of 1–10 years, of 1%–56% [39]. Pubertal insulin resistance may be associated with dysglycemia with a high rate of return to normoglycemia when insulin sensitivity improves [40]. In 547 youth with overweight and obesity aged 14.5 ± 2.2 years (70% Hispanic) with baseline HbA1cs in the prediabetes range, 76% had a follow-up HbA1c

Table 1. Unique characteristics of youth with impaired glucose tolerance (IGT) and T2D, as compared to adults

- A more rapid decline in β-cell function not attenuated by metformin or glargine [2–4]
- Greater insulin resistance, with significant reductions in insulin sensitivity not explained by race/ethnicity, sex, or body mass index (BMI) [2–4]
- A relative hyperresponsiveness of pancreatic β-cells resulting in higher C-peptide and insulin secretion at similar glucose concentrations even after adjustments for insulin sensitivity [5, 6]
- Poorer response to diabetes medications [7]
- A more rapid development of diabetes complications [8]
- Prediabetes and T2D predominance in females compared to males [9].

Table 2. Risk factors associated with youth-onset T2D

Age	T2D is rare among pre-pubertal children; typical onset mid-puberty [9]
Race/ethnicity	Disproportionally higher incidence in some groups, e.g., Native American, Canadian First Nation, Indigenous Australian, Black, Hispanic, East and South Asian, Middle Eastern, and Pacific Islander populations [9]
Sex and puberty	Generally, incidence is higher in girls than boys [9]
Early life determinants	Intrauterine exposure to maternal gestational diabetes, pregestational diabetes, and maternal obesity [10]
Obesity, excess adiposity and associated conditions	Relationship is modified by race/ethnicity; obesity is less common in Asian youth with T2D [12]
Family history of T2D in first-degree relatives	Likely mediated by shared genetics, lifestyle, and environmental factors. Genetic factors that contribute are like those of adult-onset T2D, with similar or larger effect sizes in youth [11]
Lifestyle factors	Excess caloric intake including sugar-sweetened beverages, increased sedentary behavior, low physical activity, and poor sleep [15, 17]
SDOH	The relationship with SDOH is complex and interactions with obesity and race/ethnic minority status exist [13, 14, 16]

Table 3. Recommended criteria for the diagnosis of prediabetes [B]

Test	Laboratory values
Fasting plasma glucose (FPG) (indicates IFG)	ADA IFG definition: 100–125 mg/dL (5.6–6.9 mmol/L) NICE/IEC/WHO/DC IFG definition: 110–125 mg/dL (6.1–6.9 mmol/L)
2-h plasma glucose (indicates IGT)	>140–199 mg/dL (7.8–11.0 mmol/L) after an OGTT (after 1.75 g/kg (max 75 g) anhydrous glucose dissolved in water)
HbA1c	ADA definition: A1c 5.7–6.4% (39–47 mmol/mol) NICE/IEC/DC definition: 6.0–6.4% (42–47 mmol/L)

ADA, American Diabetes Association; DC, Diabetes Canada; IEC, International Expert Committee; NICE, National Institute for Health and Care; WHO, World Health Organization.

(12–22 months later) [40]. Progression to T2D as indicated by HbA1c was 4% in those with baseline HbA1c 5.7%–5.9% and 8% in youth with a baseline HbA1c 6.0–6.4% [41]. Overall, youth with HbA1c in the prediabetes range have low short-term rates of progression to T2D [42, 43].

Lifestyle change, with decreased caloric intake and increased physical activity, may be effective for improving insulin sensitivity and glucose lowering in youth with prediabetes [44–46]. However, there are currently insufficient data to support the metformin, glucagon-like peptide-1 receptor agonist (GLP-1 RA) and/or insulin use to prevent the progression of prediabetes in youth [47].

Diagnosis of T2D

Recommended criteria for the diagnosis of T2D: symptoms of hyperglycemia and ONE of the following laboratory values [**B**].

- HbA1c ≥6.5% (48 mmol/mol)
- FPG ≥126 mg/dL (7.0 mmoL/L)
- Random plasma glucose ≥200 mg/dL (11.1 mmol/L)
- 2-h plasma glucose on an OGTT ≥200 mg/dL (11.1 mmoL/L). OGTT: 1.75 g/kg (max 75 g) anhydrous glucose dissolved in water.

When measuring HbA1c utilize a laboratory based, Diabetes Control and Complications Trial (DCCT) aligned, National Glycohemoglobin Standardization Program (NGSP) certified method [**B**].

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In the absence of unequivocal hyperglycemia symptoms (including polyuria, polydipsia, nocturia, unexplained weight loss and general fatigue), utilize TWO of the criteria above or confirmatory testing on a different day. The following support the diagnosis of T2D **[B]**.

- BMI ≥85th percentile
- Signs of insulin resistance
- Associated metabolic comorbidities (dyslipidemia, MASLD, hypertension, PCOS)
- Family history of T2D
- Negative (absent) pancreatic autoantibodies.

The presentation of youth-onset T2D ranges from asymptomatic (detected during routine screening), to symptomatic hyperglycemia, to metabolic decompensation (diabetes ketoacidosis [DKA] or hyperglycemic hyperosmolar state [HHS]) [48]. HHS is significantly more common in youth with T2D than type 1 diabetes (T1D) and is associated with greater morbidity and mortality than DKA [49]. Thus, it is critical to measure serum osmolality in those with metabolic decompensation and suspected T2D.

Diagnostic testing encompasses fasting glucose, 2-h/random plasma glucose, and HbA1c, all of which assess glycemia. The OGTT often has poor reproducibility when repeated in the same individual [50] and the HbA1c is often more practical to obtain and correlates well with both fasting and 2-h glucose [51]. These have led the ADA to move the HbA1c to the top of the diagnostic testing hierarchy [52]. HbA1c is unreliable in patients with hemoglobinopathies, within 3 months of transfusion or with increased red cell turnover.

Pancreatic autoantibodies are recommended in the evaluation of youth-onset T2D. Testing should include glutamic acid decarboxylase-65 (GAD-65), islet antigen-2 (IA-2), zinc transporter 8 (ZnT8) and insulin antibody (IAA), the latter in those who have not yet been treated with insulin. If all four antibodies are unavailable, GAD should be the primary antibody measured and if negative should be followed by IA-2 and/or ZnT8. Immunoassay and the gold-standard radio-binding assays should be used to measure pancreatic autoantibodies. Though immunofluorescence assays may still be available, they are not recommended due to low sensitivity and specificity [53].

Up to 12% of youth with clinical diagnosis of T2D can have pancreatic autoimmunity [54]. Youth with a clinical phenotype of T2D and single antibody positivity (sometimes referred to as "double-diabetes" or "double-diabetes") have been shown to have early insulin requirement [54–56], although data regarding the clinical course and most ideal treatment in patients with diagnosed diabetes and single antibody positivity are limited. When pancreatic autoantibodies are not available, family history, response to treatment, clinical progression and associated metabolic comorbidities can help confirm a T2D diagnosis.

Differential Diagnoses

Type 1 Diabetes

The diagnosis of T1D should be considered in youth with diabetes with the following clinical features: **[B]**

- BMI <85th percentile
- Age of diabetes onset of <10 years of age
- Pre-pubertal at diabetes onset
- Absence of risk factors and clinical features of T2D
- DKA or cerebral edema at presentation.

Although the incidence of T2D is increasing worldwide, T1D remains most common type of diabetes in youth [57]. Moreover, obesity is common in most of the westernized world and equally affects those with T1D [58]. Thus, careful consideration of risk factors, including that T2D rarely presents prior to pubertal onset, and further testing for pancreatic autoantibodies helps differentiate between T1D and T2D. Figure 1 can be used to assist in determination of initial diagnosis of diabetes type.

Monogenic Diabetes

The diagnosis of maturity onset diabetes of the young (MODY) should be considered in youth with the following clinical features: **[B]**

- BMI <85th percentile
- Family history of diabetes in one parent and first-degree relatives of that affected parent
- Absence of other risk factors and clinical features of T2D
- Absence of pancreatic autoantibodies
- Features such as genitourinary tract abnormalities, renal cysts, pancreatic atrophy, hyperuricemia or gout (HNF1B MODY)
- Stable isolated fasting hyperglycemia in the range of 100–150 mg/dL (5.5–8.5 mmol/L) (GCK MODY)
- History of neonatal diabetes.

Monogenic diabetes, diagnosed by genetic testing, is much less common than T1D or T2D [59]. However, it is likely underdiagnosed and because it often is associated with milder hyperglycemia and is familial in nature, may be misdiagnosed as T2D, particularly in youth who otherwise fit the clinical picture of T2D. The

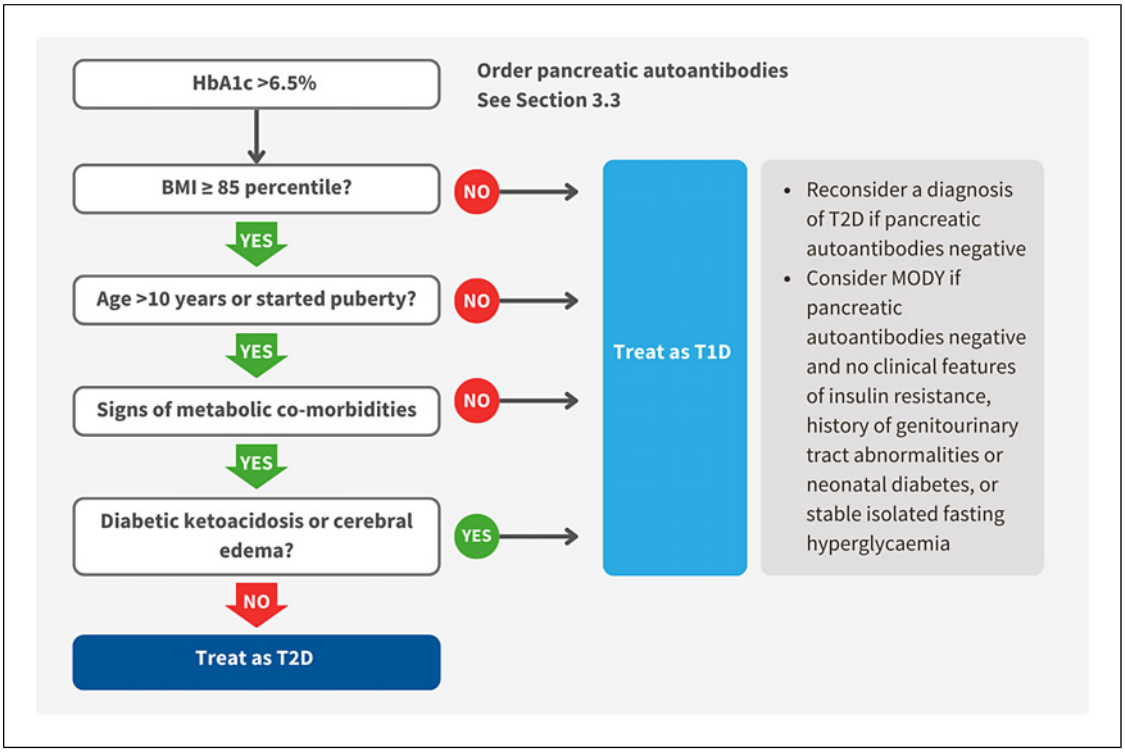

Fig. 1. Diagnosis of new onset diabetes in youth.

ProDiGY collaboration, which includes over 3,000 youth with presumed T2D (including participants from the TODAY and SEARCH studies), found a 2.8% frequency of MODY-positive genetic testing [60]. Monogenic diabetes is important to differentiate from other types of diabetes due to differences in treatment and expected clinical course. The diagnosis should be made more easily now that genetic testing is more readily available and the price has decreased. Tools, such as the MODY calculator [61], can be useful in assessing risk, but require validation across populations and age groups.

Management

Diabetes education should be started at the time of diagnosis and as part of ongoing management and should be focused on lifestyle changes (Table 4), medications, and self-monitoring of blood glucose (SMBG) if applicable [62, 63]. Education materials should be age and culturally appropriate, focused on educating both the youth and their families, and including extended family members if possible.

Lifestyle Management

Promotion of a Healthy Diet

To promote healthy parenting practices related to diet and activity, it is essential to involve a nutritionist/dietitian with experience in nutritional management of youth with T2D. Families and the person living with diabetes should be taught to interpret nutrition fact labels and make dietary changes consistent with healthy eating recommendations, including personalized counseling for weight reduction. Additional dietary recommendations are provided in Table 4 and the International Society for Pediatric and Adolescent Diabetes (ISPAD) 2022 Consensus Guidelines Chapter 10 for Nutritional Management in Children and Adolescents with Diabetes [64].

Increasing Physical Activity and Limiting Sedentary Time

Exercise is an important part of the diabetes management plan. Regular exercise improves blood glucose levels, reduces cardiovascular risk factors, contributes to weight loss, and improved sense of well-being [65, 66]. Any behavior change recommendations must establish realistic goals and consider the families' health

Table 4. Lifestyle recommendations for youth with T2D

Diabetes education should be started at the time of diagnosis and should focus on the following
Promotion of a healthy diet • Use culturally sensitive and family-centered approaches to healthy eating **[B]** • Teach families and the person with diabetes to interpret nutrition fact labels **[B]** • Promote parental modeling of healthy eating habits, while avoiding overly restricted food intake **[E]** • Reduce or eliminate all high calorie drinks and replace with water or calorie-free beverages **[C]** • Promote meals eaten on schedule, in one place, preferably as a family unit, and with no other activity (television, computer, studying), and minimizing frequent snacking **[E]** • Decrease portion sizes **[B]** • Encourage vegetable and fiber intake to improve satiety **[B]** • Choose roasted, grilled, boiled, or baked over fried foods **[E]** • Limit high fat and high calorie food, processed food, and pre-packaged food **[B]** • Maintain food and activity logs as beneficial for raising awareness of food and activity issues and for monitoring progress **[E]**
Increasing physical activity and limiting sedentary time • Encourage youth to build up to 60 min of moderate to vigorous physical activity daily with muscle and bone strength training at least 3 days per week **[B]** • Reduce sedentary time, including screen-time, computer-related activities, texting, and video games to less than 2 h per day **[B]** • Promote physical activity as part of daily living such as using stairs instead of elevators, walking or bicycling to school and to shops, and doing house and yard work **[E]** • Encourage positive reinforcement of all achievements and avoidance of shaming **[E]** • Encourage exercise as part of family-based activities **[E]**.
Optimizing sleep routines • Encourage adequate sleep duration according to age: 9–11 h for children 5–13 years of age and 8–10 h for adolescents and young adults **[B]** • Encourage consistent bed and wake up times and avoiding naps **[E]** • Reduce use of electronic devices prior to going to sleep **[E]**.
Mitigation of risky behaviors • Assess use of drugs tobacco, alcohol, and vaping and refer to cessation programs if needed **[E]** • Assess sexuality, sexual activity and offer pre-conception counseling **[E]**.

beliefs and behaviors [67]. Recommendations are provided in Table 4 and the ISPAD Guidelines for Exercise in Children with Diabetes [68]. Reducing sedentary time is also an important goal in the management of T2D in youth [69].

Optimizing Sleep Routines

Inadequate sleep is associated with insulin resistance in children and adolescents and contributes to the T2D development [70, 71]. Sleep timing, duration, and quality should be discussed with youth and their families, promoting sleep hygiene [69, 70, 72] (see Table 4).

Recognition and Mitigation of Risky Behaviors

Youth with T2D should be screened for the use of tobacco, electronic cigarettes, vaping, recreational drugs and alcohol consumption at each visit and counseled against their use by providing resources for support. Sexual history should be obtained and preconception counseling should be included for all females of child-bearing potential. It is important to assess exposure to cigarette smoke in the home because of the adverse effects of second hand smoke and to discourage youth from smoking [73]. Deleterious effects of alcohol misuse in the setting of diabetes and risk for fatty liver disease, as well as hypoglycemia should be discussed [74].

Glucose Monitoring and Hypoglycemia

Glucose monitoring by SMBG or continuous glucose monitoring (CGM) is recommended for youth with T2D who
- require insulin [**A**]
- when there are symptoms of hyper- or hypoglycemia [**A**]
- during acute illness [**E**]
- when there is suboptimal diabetes management [**E**]
- when there are changes in treatment regimen [**E**]

The choice of blood glucose monitoring device should be made based on an individual's and family's circumstances, desires, and needs [**E**].

Glucose monitoring should include a combination of fasting and postprandial glucose measurements with a frequency based on the medication(s) used, the HbA1c value, cost, preferences, and available resources.

Rates of hypoglycemia in youth with T2D on insulin therapy are lower than in youth with T1D with an incidence rate of 9 events per 5.3 patient-years, [75]. Slightly higher rates of hypoglycemia (but no severe hypoglycemia) were reported in youth when sodium-glucose co-transporter 2 (SGLT-2) inhibitors in combination with insulin compared to placebo [76]. If insulin is used, monitoring and treatment for hypoglycemia should be taught. Glucagon should not be routinely prescribed unless patient is on short-acting insulin and experiencing recurrent hypoglycemia. Treatment of hypoglycemic episodes in youth with T2D is the same as that for children T1D. See ISPAD Clinical Practice Consensus Guidelines 2022: Assessment and management of hypoglycemia in children and adolescents with diabetes [77].

Growing evidence in adults with T2D supports use of CGM, irrespective of treatment modality [78]. Standardized, single-page glucose reports from CGM devices, such as the ambulatory glucose profile, should be considered as a standard summary. Time in range, glycemic variability (%), glucose management indicator (previously called estimated HbA1c), and estimated glucose average can be used for assessments of glycemic status. Additionally, time below range, time above range (TAR), and time in tight range of glucose values between 70 and 140 mg/dL are useful parameters for the evaluation of medication response. No specific CGM targets have been defined for T2D.

A recent study reported that 10-day CGM use did not impact short-term or long-term glycemic levels in youth with T2D; however, most participants reported behavioral changes such as reviewing blood glucoses and increased insulin administration, and overall improved diabetes management and wanted to continue using CGM [79]. A small pilot study using CGM in 15–19-year-old youth with T2D, showed a modest improvement of HbA1c for participants that wore the CGM >85% of the time and who expressed high satisfaction with the CGM device [80].

Glycemic Targets

- HbA1c should be measured every 3 months **[E]**.
- A recommended optimal target for most youth with T2D is HbA1c of <6.5% (48 mmol/L) **[E]**.

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- A higher HbA1c target may be considered <7% (53 mmol/mol) in youth at the initiation of therapy or in instances where the standard target is assessed as being detrimental to the overall well-being of the person with diabetes or their caregivers (i.e., significant hypoglycemia) **[E]**.
- FPG targets are 70–110 mg/dL (4–6 mmol/L) **[E]**.
- Postprandial blood glucose targets are 70–140 mg/dL (4–8 mmol/L) **[E]**.
- If using CGM, align with established CGM targets used for T1D as no targets for T2D have been established (>70% between 3.9 and 10 mmol/L [70–180 mg/dL] <4%: <3.9 mmol/L [70 mg/dL]) **[E]**.

Glycemic goals should be individualized. Glycemic status, via a HbA1c concentration, should be measured every 3 months, if possible. A lower HbA1C goal in youth with T2D when compared with those recommended in T1D is justified by a lower risk of hypoglycemia and a higher risk of complications in youth-onset T2D [67, 81]. An A1C target for youth with T2D is<6.5% [48 mmol/mol]) is recommended if this can be achieved without significant hypoglycemia [82]. A higher target may be considered at initiation of therapy or in instances where the standard target is assessed as being detrimental to the overall well-being of the person with diabetes or their caregivers [83].

Pharmacologic Management

Initial Therapy

Initial therapy in youth with T2D (Fig. 2).

- If initial HbA1c <8.5% (69 mmol/mol) – metformin is the treatment of choice together with healthy lifestyle changes **[A]**.
- In youth with initial HbA1c ≥8.5% (69 mmol/mol) and without ketosis/acidosis, initial management includes basal insulin (starting dose 0.25–0.5 units/kg) along with metformin therapy **[B]**.
- If DKA/acidosis or HHS is present, both long acting and short-acting insulin should be started initially **[A]**.

For youth with stable glycemia, defined as an HbA1c <8.5% (69 mmol/mol) without ketosis or acidosis, metformin is the first-line therapy of choice together with lifestyle recommendations as outlined in Table 4 [84, 85]. Half of adolescents with T2D can maintain effective glycemia management through metformin monotherapy and as such is justified for initial therapy [86]. In youth HbA1c ≥8.5% (69 mmol/mol), insulin will be required initially. Metformin

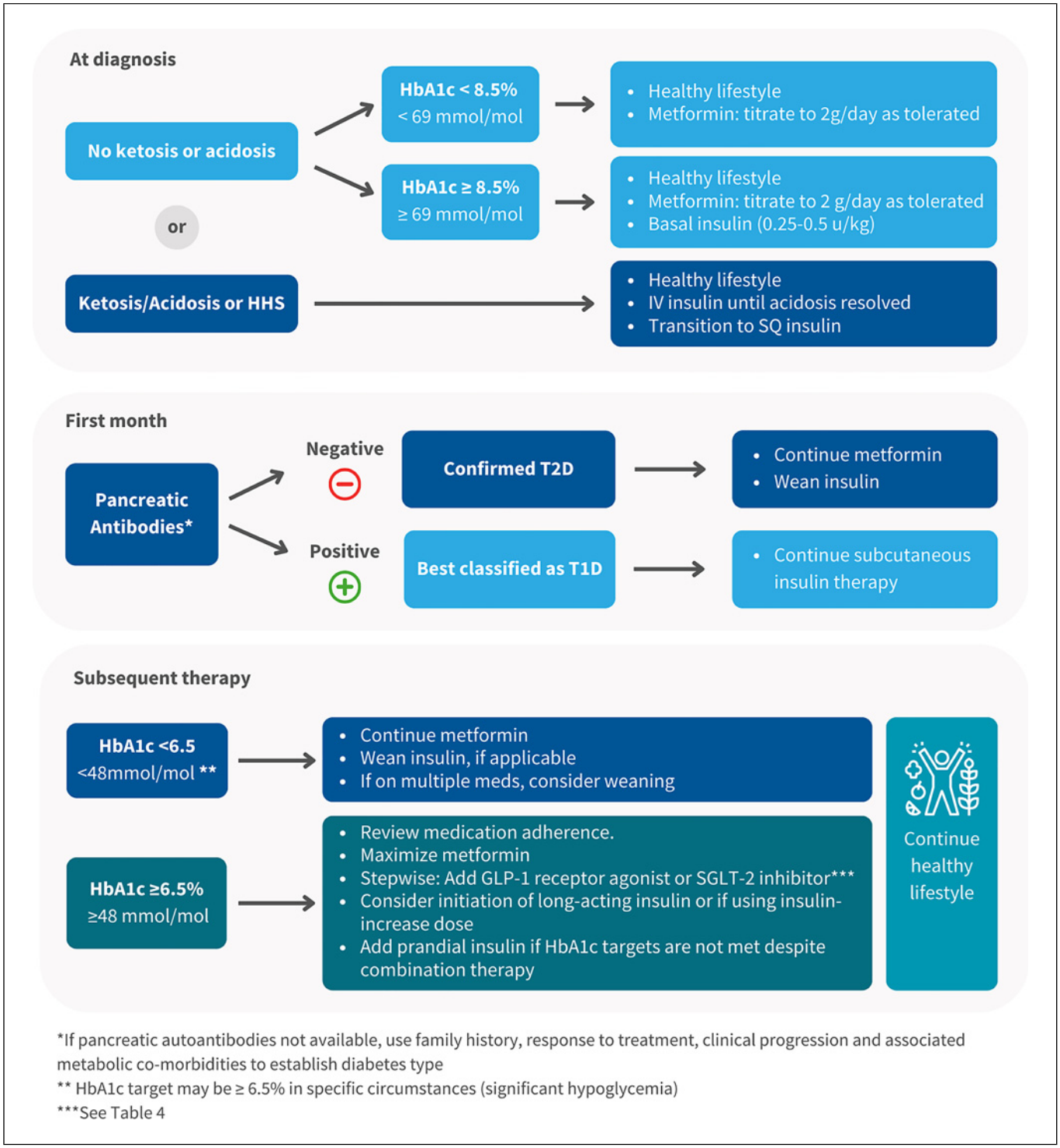

Fig. 2. Evaluation and management of new onset T2D.

should be started concurrently, and the dose titrated to maximum tolerated up to 2,000 mg daily. If ketosis, acidosis and/or HHS are present, IV insulin should be started.

Various indicators can predict loss of glycemic levels on metformin monotherapy, such as reduced insulin secretion, impaired insulin processing (elevated proinsulin/insulin ratio), an increasing proinsulin level overtime. From a clinically useful standpoint, the TODAY study demonstrated that an HbA1c of ≥6.3% after 48 months [82] or a rise in HbA1c of 0.5% predicts loss of optimal glycemic management within a relatively short period of time [87]. Long-term glycemic management is more likely to be achieved when therapy is intensified as needed to maintain the HbA1c target (treat-to-target) rather than waiting for the HbA1c to rise before intensifying therapy (treat-to-failure) [88].

Short-acting insulin should be weaned if started as soon as blood glucose values stabilize. The primary adverse effect of short-acting insulin is weight gain and hypoglycemia. Data from the TODAY study indicated that 90% of youth with T2D can be successfully weaned off insulin and managed with metformin alone with attainment of glycemic targets [84, 85].

Subsequent Therapy (2–3+ Months after Diagnosis)

- Maintenance therapy should be guided by an active approach to maintain the HbA1c targets (treat-to-target) **[E]**.
- If a HbA1c of <6.5% (53 mmol/mol) is not attained, GLP-1 RA and/or SGLT-2 inhibitor medications should be considered [A] and customized to the individual T2D youth needs, preferences and access to these agents **[E]**.
- Significant and sustained increases in HbA1c despite combination therapy will require insulin therapy. Basal insulin should be maximized and short acting add if glycemic targets still not achieved) **[E]**.

If after treatment is initiated a HbA1c target of <6.5% (48 mmol/mol) is not attained, addition of a GLP-1 RA or SGLT-2 inhibitor should be considered. See Figure 2 and Table 5. Before adding additional medications, patient engagement and barriers should be assessed. The choice of therapeutic approach should consider individual preferences, degree of glucose lowering required, mechanism of action, cost and payer coverage, regulatory approval, route of administration, dosing regimen, potential side effects and the impact on comorbidities and cardiovascular risk.

Recent multicenter randomized controlled studies evaluating newer medications from 20 to 26 weeks, with some studies extending to 52–54 weeks in youth with T2D have been published [76, 94–96, 99, 101, 110]. The studies involved adolescents from diverse ethnic backgrounds enabling the generalization of each drug's effectiveness (Table 5). Currently, the following drugs have received approval for the management of adolescents: GLP-1 RA (liraglutide, exenatide, dulaglutide, semaglutide) and SGLT-2 inhibitors (empagliflozin and dapagliflozin).

Clinical considerations for additional therapy:

- Elevated A1c. Consider adding GLP-1 RA and/or SGLT-2 inhibitor. Basal insulin may be necessary if HbA1c is >8.5%.
- Weight management. Consider GLP-1 RA and/or SGLT-2 inhibitors. Though it should be noted, studies in youth with T2D have not shown significant BMI lowering compared to placebo [76, 94–96, 99, 101, 110].
- Severe insulin resistance. Consider adding pioglitazone, which has been shown to improve insulin sensitivity in adults.
- Reservations about needle-based treatments. Consider SGLT-2 inhibitor therapy.
- Difficulty swallowing pills. Consider combination medications (i.e., metformin/empagliflozin combination).
- Concomitant cardiovascular complications. Consider GLP-1 RA options if cardiovascular complications [111].
- Concomitant cardiovascular and/or renal complications. Consider SGLT-2 inhibitor based on adult studies [112].
- MASLD. Consider adding pioglitazone, which has been shown to improve MASLD in adults [113, 114]. GLP-1 RA may also be helpful in MASLD [115, 116].

If the glycemic target is not attained on a combination therapy, add basal insulin at a dose of up to 1.5 units/kg/day. Initiation of prandial insulin (short- or rapid-acting insulin) once to three times a day should be considered, with titration to reach HbA1c targets while monitoring for hypoglycemia. Patients who have completely lost endogenous insulin secretion eventually progress to intensive insulin treatment, such as multiple daily injections of insulin or insulin pump therapy, similar to that used in patients with T1D. Once glycemia has stabilized, consider weaning short-acting insulin.

Bariatric Surgery

- Bariatric surgery should be considered in youth 12 years and older with a BMI ≥35 kg/m^2 or 120% of the 95th percentile (whichever is lower) **[A]**.
- Metabolic surgery should be undertaken only in centers of excellence with an established and experienced surgical, nutritional, behavioral, and a medical support team and outcome data collection program and ensure appropriate capacity and consent **[A]**.

Table 5. Medications for use in T2D

Medication (Brand Name)	Approval and potential adverse effects	Dosing	ETD between groups (treatment vs. placebo) if available and percent HbA1c lowering within the treatment group	Impact on metabolic parameters
Biguanides (glucophage, Metformin®)	Approved in youth Can cause transient abdominal pain, diarrhea, nausea, all attenuated by the extended-release formulation Avoid in DKA, if eGFR <30 mL/min, cardiac or respiratory insufficiency, or receiving radiographic contrast materials	Oral once, twice or three times daily Starting dose 500 mg Can increase to 2,000 mg	HbA1c ↓ of 0.8% at 16 weeks [89], 0.8% at 24 weeks and 0.46% at 52 weeks, respectively [90]	Weight: an initial anorexic effect that may promote limited weight loss Lipids: TC, LDL-C, TG ↓, HDL-C ↑ BP: SBP ↓
Glucagon-like peptide-1 [GLP-1] receptor agonists • GLP-1 RA can have side effects including nausea, vomiting, diarrhea, and infrequently dizziness, headache, and dyspepsia • Discontinue if pancreatitis suspected. GLP-1 RA should not be used in combination with a DPP-4 inhibitor • In patients with MEN, these medications have a risk of C-cell hyperplasia and thyroid carcinoma • Adult trials show reduction in cardiovascular, renal events, and mortality [91–93]. There are no data in children				
liraglutide (Victoza®)	FDA approved in youth aged 10 years and older Higher dose Liraglutide, Saxenda® 3 mg is approved for weight loss in youth aged >12 years with obesity	SC once daily Start with 0.6 mg Can increase to maximum tolerated dose (1.2 or 1.8 mg) daily [95].	ETD: 1.06% and 1.3% at 26 and 52 weeks HbA1c ↓ of 0.64% and 0.5% at 26 and 52 weeks [94]	Weight/BP: no difference compared to placebo at week 26 Lipids: VLDL and TG ↓ at week 26, but no difference observed at week 52 [94]
Exenatide (Bydureon®)	FDA approved in youth aged 10 years and older	SC once weekly Single dose (2 mg), no titration available	ETD: 0.85% at 24 weeks HbA1c ↓ of 0.36% at 24 weeks [95]	Weight/BP: no difference compared to placebo [95] Lipids: no data
Dulaglutide (Trulicity®)	FDA approved in youth aged 10 years and older	SC once weekly Start with 0.75 mg, increase to 1.5 mg as tolerated	ETD: 1.5% at 26 weeks HbA1c ↓ of 0.9% and 0.6% at 26 and 52 weeks [96]	Weight/BP: no difference compared to placebo [96] Lipids: TC, LDL-C and TG ↓ in the dulaglutide groups
Sodium-glucose co-transporter 2 (SGLT-2) inhibitors • SGLT-2 inhibitors can increase risk for ketosis and euglycemic DKA though rates of these side effects were low in pediatric T2D studies to date. As a result, caution is recommended in youth who may have ever presented with ketoacidosis or DKA. • Adult trials show weight loss and reduction in cardiovascular disease and renal protection [97, 98]. There are no data in children				
empagliflozin (Jardiance®)	FDA approved in youth 10 years and older Metformin-Empagliflozin combination approved age 10 years and older	Oral once daily Starting dose is 10 mg Can increase to 25 mg/day	ETD: 0.84% at 26 weeks HbA1c ↓ of 0.17% and 0.04% at 26 and 52 weeks, respectively [76]	Weight/BP: no difference compared to placebo [76] Lipids: no data
dapagliflozin Farxiga® (US) and Forxiga® (EU)	FDA approved for youth 10 years and older Approved by the EMA in children 10 years or older	Oral once daily Starting dose is 5 mg Can increase to 10 mg/day	ETD: 0.75% at 24 weeks [99]; 1.03% at 26 weeks [100] HbA1c ↓ of 0.25% at 24 weeks [99] HbA1c ↓ of 0.62 at 26 weeks [100]	BMI/weight/BP: no difference compared to placebo [99, 100] Lipids: no data

Table 5 (continued)

Medication (Brand Name)	Approval and potential adverse effects	Dosing	ETD between groups (treatment vs. placebo) if available and percent HbA1c lowering within the treatment group	Impact on metabolic parameters
Other medications studied in children				
sitagliptin (Januvia®)	Upper respiratory infections, nasopharyngitis	Oral once daily Dose is 100 mg/day Combination available with metformin	ETD: 0.19% at 20 weeks (nonsignificant) HbA1c: ↓0.01% lowering at 20 weeks [101]	Weight/BP: No difference compared to placebo [101] Lipids: no data
alogliptin (Nesina®, Vipidia®)	Upper respiratory infections, nasopharyngitis	Oral once daily Dose is 25 mg/day	Results in youth pending	Weight/lipids/BP: no data
saxagliptin (Onglyza®)	Upper respiratory infections, nasopharyngitis	Oral once daily Dose is 5 mg/day	ETD: 0.44% at 26 weeks (nonsignificant) HbA1c: ↑ 0.6% at 26 weeks [100]	Weight/BP: no difference compared to placebo [100] Lipids: no data
linagliptin (Tradjenta®)	Upper respiratory infections, nasopharyngitis	Oral once daily Dose is 5 mg/day	ETD: 0.34% at 26 weeks (nonsignificant) HbA1c: ↓0.33% at 26 weeks and 0.8% at 52 weeks [76]	Weight/BP: no difference compared to placebo [76] Lipids: no data
Thiazolidinedione (pioglitazone, Actos®) rosiglitzone, Avandia®)	Pioglitazone is the preferred TZD due to overall fewer cardiovascular side effects in adults compared to rosiglitazone [102, 103] Risk of weight gain if used in combination with insulin In the TODAY study no significant side effects reported with rosiglitazone therapy [86] Liver toxicity has not been seen with newer TZDs; instead, may be beneficial in MASLD [104]	Oral once daily A 45 mg/day dose is available but limited additional benefit and increased side effects Starting dose 15 mg, can increase to 30 mg/day Can be useful in youth given their severe insulin resistance and normal cardiac function particularly when metformin is not tolerated	Associated with the lowest therapeutic failure when rosiglitazone was combined with metformin (38.6%) vs. metformin alone (51.7%) vs. metformin plus lifestyle (46.6%) [86]	Weight: ↑ [86] Lipids/BP: no significant change
α-Glucosidase inhibitoracarbos (acarbose, Precose® miglitol, Glyset®)	Reduce postprandial glucose rise Particularly successful when carbohydrates are substantial part of diet [105] Can lead to flatulence, diarrhea, abdominal cramps	Oral up to three times a day with meals Acarbose 25–100 mg with each meal Miglitol 100 mg three times a day	No data	Weight/BP/Lipids: No data

Table 5 (continued)

Medication (Brand Name)	Approval and potential adverse effects	Dosing	ETD between groups (treatment vs. placebo) if available and percent HbA1c lowering within the treatment group	Impact on metabolic parameters
Sulfonylurea and Meglitinides (glimepiride: Amaryl®) approved for children in Japan [106].	Mild or severe hypoglycemia Weight gain May accelerate β-cell function loss [108, 109] Glimepiride, a new sulfonylurea, stimulates insulin release before meals and has additional pancreatic effects including decreased liver glucose production and enhanced peripheral tissue insulin sensitivity [102]	Oral once daily Starting dose: 1 mg taken once daily with breakfast or the first main meal of the day Can increase to 8 mg per day	Glimepiride showed no HbA1c lowering with a greater degree of weight gain and hypoglycemia [107]	Weight: ↑ in Glimepiride vs. metformin group Lipids: No difference in Glimepiride compared to metformin [107] BP: no data

BP, blood pressure; DPP-4, dipeptidyl peptidase-4; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; ETD, estimated treatment difference compared to placebo; FDA, Food and Drug Administration; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MEN, multiple endocrine neoplasia; TG, triglycerides; SBP, systolic blood pressure; SC, subcutaneous; TC, total cholesterol; TZD, thiazolidinedione; VLDL, very low-density lipoprotein.

Metabolic bariatric surgery can be considered in youth with T2D and BMI ≥35 kg/m^2 [117]. A large US consortium of pediatric bariatric surgery centers compared their HbA1c and comorbidity outcomes to matched individuals managed with metformin alone, metformin and lifestyle or metformin and rosiglitazone in the TODAY study and showed greater and more sustained lowering of HbA1c with surgery and improvement/normalization of other comorbidities (dyslipidemia, hypertension, kidney disease) in nearly all youth [118, 119]. There is still a lack of long-term post bariatric surgery data (>10–15 years) in relation to re-operations, complications, bone health, nutritional deficiencies and diabetes recurrence. Additionally, outcome data comparing vertical sleeve gastrectomy, the most widely performed bariatric surgery to medications, especially newer GLP-1 RA and SGLT-2 inhibitors, is lacking.

Setting of Care

Until recently, diabetes education and diabetes care were largely provided in person, and telehealth (defined as telecommunication techniques for providing healthcare) was used less due to lack of equipment, infrastructure, and payer reimbursement [120, 121]. The COVID-19 pandemic brought telehealth to the forefront of diabetes education for youth with T1D to safely seek care [122]. To date, there are no published studies evaluating outcomes of telehealth or telemonitoring in youth with T2D. One study found capillary blood collection kits, suitable for home use, provided similar HbA1c results to those obtained from venous specimens [123], providing an alternative to in clinic testing. Providers need to take into consideration the reported benefits (inconvenience of travel and parking, minimize time away from work and/or school) and barriers (lack of point of care testing, lack of internet or poor mobile phone connectivity) related to telehealth in youth with T2D [81].

Screening and Management of Diabetes Comorbities and Complications

Hypertension

- BP should be measured at every diabetes with an appropriately sized cuff and BP values should be compared to the reference ranges for age, sex, and height of optimal weight youth **[B]**.
- Management and treatment approach should be based upon age and BP thresholds (see Fig. 3) **[C]**.

BP should be measured at every diabetes visit. In youth <13 years, BP values should be compared to the reference ranges for age, sex, and height of optimal weight youth [124]. In youth ≥13 years, a simplified BP classification regardless of sex and height can be

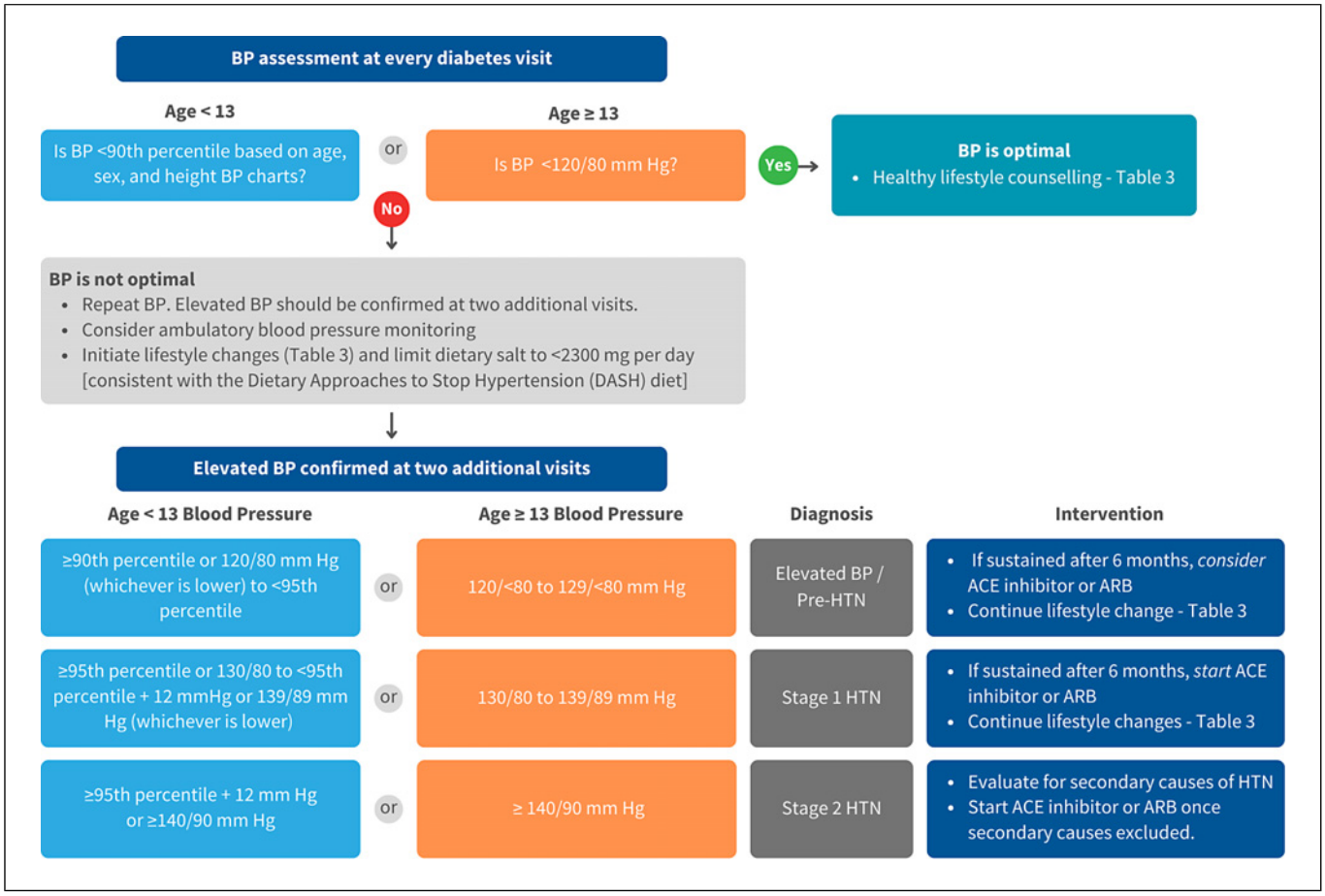

Fig. 3. Blood pressure evaluation and management in youth with T2D.

used (Fig. 3). If there is concern about transient, stress-related high blood pressure (white coat hypertension) ambulatory blood pressure monitoring should be considered Table 6. Ambulatory blood pressure monitoring can also be used to assess response to treatment. If BP is elevated, initial management should include dietary changes consistent with the Dietary Approaches to Stop Hypertension (DASH) diet [125], weight management if appropriate, and physical activity (Table 4). Initial pharmacological treatment should be monotherapy with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) at the lowest possible dose to achieve a BP <120/80 [126–128]. The teratogenic effects of ACE inhibitors or ARBs in sexually active females must be explicitly discussed. Evaluation of hypertension not responsive to initial medical therapy should include evaluation of secondary causes of hypertension [126].

Dyslipidemia

- Lipids should be measured yearly starting at diabetes onset (after optimal glycemic levels are achieved or within 3 months of diagnosis) **[B]**.
- Management and treatment approach should be based upon LDL-C and triglyceride thresholds (see Fig. 4) **[B]**.

Lipid screening in youth with T2D should occur once the HbA1c target has been achieved or after 3 months of initiation of medication regardless of HbA1c. Annual screening should occur thereafter unless initial screening results are abnormal [126]. Initial screening can be done non-fasting and non-HDL-C calculated [129] (Fig. 4). If cholesterol levels are above goal, HbA1c should be optimized, nutrition counseling provided (Table 7), and physical activity encouraged [126]. After 3–6 months if youth with T2D

Table 6. Recommendations for screening of associated comorbidities/complications

Comorbidity/ complication	Intervals for screening	Screening test
Hypertension	Every diabetes related clinical encounter starting at diabetes onset	Blood pressure measurement using appropriately sized cuff. Values should be compared to the reference ranges for age, sex, and height of optimal weight youth. Figure 3
Dyslipidemia	Yearly starting at diabetes onset (after optimal glycemic management is achieved or within 3 months of diagnosis)	Lipid profile including LDL-C and triglycerides. Figure 4
Nephropathy	Yearly starting at diabetes onset	Urine albumin-to-creatinine ratio, Assess estimated GFR at diagnosis and for youth with worsening kidney function
MASLD	Yearly starting at diabetes onset	ALT or AST
Obstructive sleep apnea	Yearly starting at diabetes onset	Ask about snoring, sleep quality, apnea, morning headaches, daytime sleepiness
Polycystic ovary syndrome	Yearly (unless there is menstrual irregularity) starting at diabetes onset in pubertal females	Ask about menstrual irregularities and examine for evidence of hyperandrogenism (clinical and/or biochemical)
Retinopathy	Yearly starting at diabetes onset	Comprehensive eye examination with dilated pupils or retinal photography
Neuropathy	Yearly starting at diabetes onset	Symptoms of numbness, pain, cramps and paresthesia and tests of vibration sense, light touch, and ankle reflexes
Mental health	Every diabetes related clinical encounter starting at diabetes onset	Depression and disordered eating with and referral for further evaluation if needed
SDOH	Every diabetes related clinical encounter starting at diabetes onset	Food security, financial concerns, social/school, and community support

ALT, alanine transaminase; AST, aspartate transaminase; MASLD, metabolic dysfunction-associated steatotic liver disease; specific details regarding how to screen and follow-up are described in the individual sections below.

do not meet LDL targets, regardless of HbA1c, a statin, at the lowest available dose, should be initiated [126]. Atorvastatin can be considered as first-line therapy given it lowers LDL-C by about 40%, has a favorable safety profile in youth [130], and is available as a generic formulation. A repeat lipid panel should be obtained 4–12 weeks after initiation or following a dose change of a statin. If LDL cholesterol target levels of <100 mg/dL (2.6 mmol/L) are still not achieved with at least 3 months of consistent use, then the dose may be further increased by one increment (usually 10 mg). Alternatively, a second agent such as ezetimibe, a cholesterol absorption inhibitor, can be added. Side effects of statins include hepatic enzyme elevation and muscle toxicity and should be checked before and 4–12 weeks after initiating a statin. An LDL-C >190 mg/dL (4.9 mmol/L) should prompt suspicion of familial hypercholesterolemia.

Initial management of elevated TG should optimize blood glucose levels and weight, limit dietary simple sugars, Table 7, and encourage physical activity [126]. Fasting TG >400 mg/dL (4.6 mmol/L) or non-fasting TG >1,000 mg/dL (11.3 mmol/L) should prompt evaluation of secondary causes of hypertriglyceridemia and treatment with a fibrate should be considered with a goal of <400 mg/dL (4.6 mmol/L) due to significantly increased risk for pancreatitis. Concentrated fish oil can be considered but LDL-C should be carefully monitored as high-dose docosahexaenoic acid (DHA) can increase LDL-C [126]. Statin plus fibrate combination therapy is generally not recommended in children.

The potential teratogenic effects of statins and fibrates in sexually active adolescent females must be explicitly discussed. Low HDL-C levels in youth are not managed directly with medication, but physical activity, avoidance of smoking and a healthy diet should be encouraged.

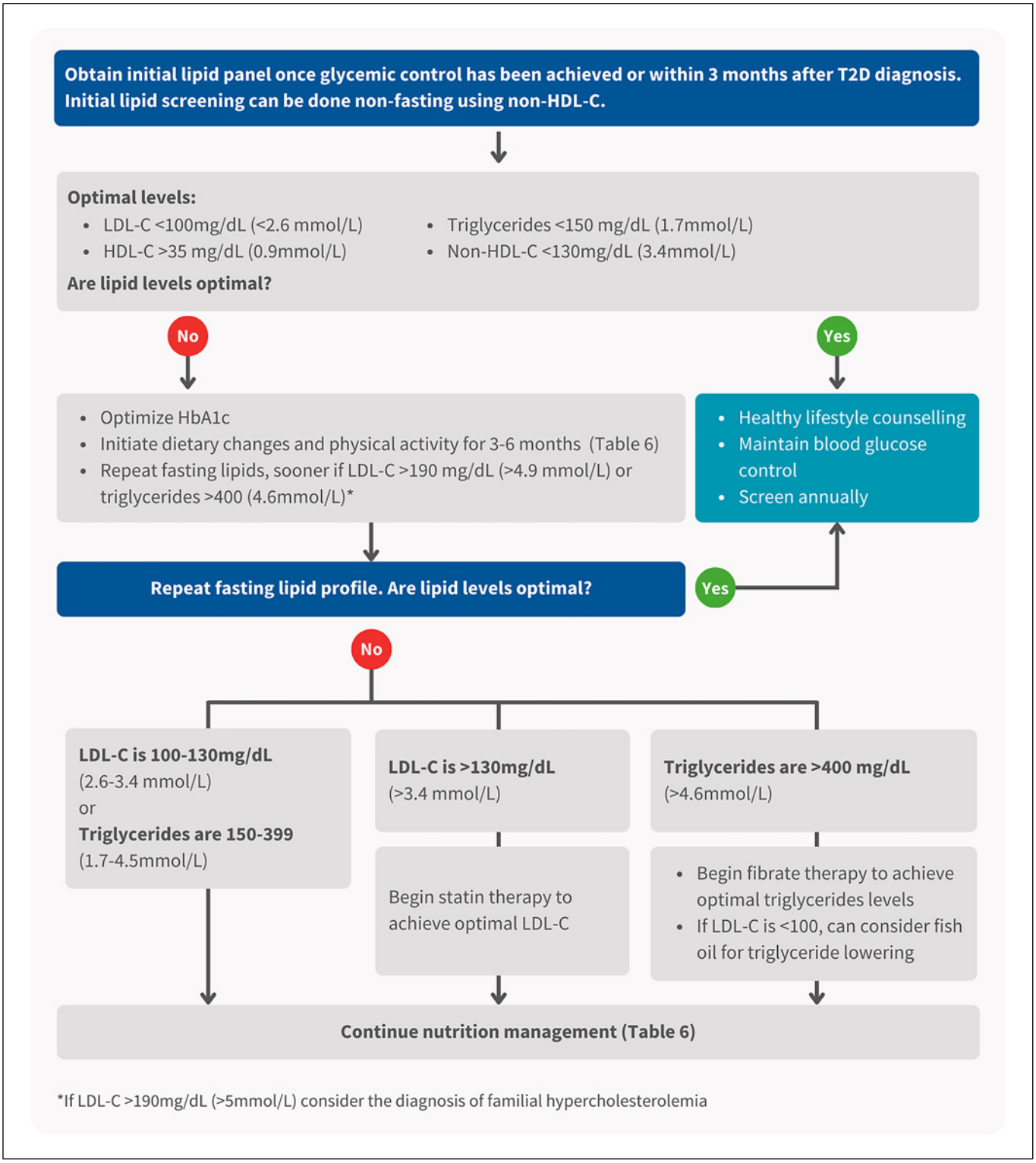

Fig. 4. Lipid evaluation and management in youth with T2D.

Table 7. Nutrition management for dyslipidemia [A]

For any abnormal lipid values: • Limit total fat to 25–30% of daily caloric intake • Limit saturated fat to <7% of daily caloric intake • Limit cholesterol to <200 mg cholesterol of daily caloric intake • Avoid trans-fat intake.
For LDL-C levels above optimal: Add the following: • Water-soluble fiber psyllium at a dose of 6 g/day for children 2–12 years of age, and 12 g/day for children ≥12 years of age • Consider plant sterol and stanol ester supplementation up to 2 g/day.
For triglyceride levels above optimal: Add the following: • Reduce sugar intake • Replace simple carbohydrates with complex carbohydrates • Avoid sugar-sweetened beverages • Increase dietary fish to increase omega-3 fatty acid intake.

Nephropathy

- Urine albumin-to-creatinine ratio should be assessed yearly starting at diagnosis [**B**].
- Estimated GFR should be assessed at diagnosis and monitored in youth with worsening kidney function [**E**].
- Once albuminuria is confirmed, treatment should include an ACE inhibitor, ARB, and consideration of a SGLT-2 inhibitor [**B**].
- A repeat urine albumin/creatinine ratio may be helpful 6 months after the start of ACE inhibitor or ARB blocker to ensure albuminuria is normalized [**E**].
- Causes of renal disease unrelated to diabetes should be considered and consultation with a nephrologist obtained if severely increased albuminuria (albumin/creatinine ratio > 300 mg/g or 30 mg/mmol), HTN is present or estimated GFR is worsening [**E**].

Albuminuria, either moderately increased albuminuria or severely increased albuminuria, may be found at diagnosis of T2D and the prevalence increases with duration of diabetes [131]. Higher HbA1c is associated with a higher risk of developing albuminuria [132–135]. The presence of albuminuria in youth is highly predictive of the future risk of renal failure [136].

For nephropathy screening, urinary albumin-to-creatinine ratio should occur at diagnosis and annually thereafter. Elevated urinary albumin-to-creatinine ratio is documented when two of three first morning urine collections are >30 mg/g (3 mg/mmol). For those with nephropathy, annually urinary albumin/creatinine ratio, eGFR, and serum potassium should be monitored [137, 138].

There are emerging validated formulas to assess eGFR in youth with T2D who are likely to have hyperfiltration (elevated eGFR> 135 mL/min/m^2) at early stages of diabetic nephropathy or lower eGFR (values <90 mL/min/m^2) [74, 133, 139, 140]; however, they require further validation. Pending additional information on the applicability of different eGFR equations in this patient population, clinicians should consider use of the modified the Schwartz equation [141] except when serum creatinine is rapidly changing.

If urine albumin/creatinine ratio is confirmed to be >30 mg/g (3 mg/mmol) and BP is elevated or if urine albumin/creatinine ratio is > 300 mg/g (30 mg/mmol) irrespective of BP, ACE inhibitor or ARB should be started and BP normalized [74, 142]. In cases of confirmed albuminuria where BP is normal, consider management with an SGLT-2 inhibitor given the studies in adults demonstrating renal benefit [97, 98, 143]. Combination therapy with either an ACE inhibitor or ARB and SGLT-2 inhibitor may be needed if there is a need to optimize BP, glycemia, and albuminuria. Causes of renal disease unrelated to diabetes should be considered and consultation with a nephrologist obtained if severely increased albuminuria (albuminuria-albumin/creatinine ratio >300 mg/g or 30 mg/mmol) and HTN is present. A repeat urine albumin/creatinine ratio may be helpful 6 months after the start of treatment to ensure albuminuria is normalized [72, 144].

Metabolic Dysfunction-Associated Steatotic Liver Disease

- Liver enzymes (ALT, AST) should be measured at diagnosis and annually thereafter, and sooner if abnormal [**B**].

(Continued on following page)

(continued)

- If liver enzymes remain >3 times the upper limit of normal after 6 months refer to a pediatric gastroenterologist for consultation to exclude other causes of elevated liver enzymes, imaging and/or liver biopsy **[B]**.

MASLD is characterized by accumulation of fat (in at least 5% of hepatocytes) in the absence of other causes of liver disease. Liver biopsy is the gold standard test for diagnosis of all stages of MASLD [145]. Proton magnetic resonance spectroscopy [146, 147] as a noninvasive imaging test, is equivalent in diagnosing MASLD and evaluating liver fat content quantitatively [148]. The evaluation of liver fibrosis in children with MASLD such as transient elastography by FibroScan®, ultrasound shear wave elastography or enhanced liver fibrosis test, is promising but accuracy and normative data in youth is needed [149]. Magnetic resonance elastography for stiffness is mostly used in research settings [150].

Liver enzymes (ALT, AST) should be evaluated at diagnosis and evaluated annually thereafter unless abnormal. If liver enzymes remain >3 times the upper limit of normal over 6 months, referral should occur to a pediatric gastroenterologist to exclude other causes of liver enzyme elevation, imaging and/or liver biopsy.

Optimizing blood glucose levels and healthy lifestyle interventions are likely to improve MASLD [151, 152]. The presence of MASLD does not preclude the use of metformin. Although most T2D medications improve liver enzymes, only glitazones and GLP-1 RA improved histologic features of MASLD in adult studies [153].

Sleep and Obstructive Sleep Apnea

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

The prevalence of OSA in youth-onset T2D has not been well documented [154, 155]. Youth with T2D should be screened for symptoms of OSA at diagnosis and annually thereafter. OSA can be initially evaluated by symptoms including frequent snoring, labored breathing during sleep, apnea, sleep enuresis, headaches on awakening, daytime sleepiness, nocturia, attention-deficit/hyperactivity disorder and learning problems [156]. If symptoms are suggestive of OSA, the diagnosis of OSA is confirmed either through a polysomnogram (PSG) or by referring the individual to a sleep specialist for a more comprehensive evaluation. When PSG is unavailable, initial monitoring can be performed using a clinically validated portable sleep monitor such as a pulse oximeter. There are no screening questionnaires to accurately predict a diagnosis of OSA in children [157].

Continuous positive airway pressure (CPAP) is the most effective treatment and widely regarded as the gold standard for addressing moderate to severe OSA in patients. However, merely 5% of adults with T2D diagnosed with OSA receive CPAP therapy within 1 year following their diagnosis [158]. Although the effects of CPAP therapy on overall glycemic management remain inconsistent, CPAP has potential advantages on lowering blood pressure, decreasing inflammatory markers, reducing daytime sleepiness, enhancing quality of life, and minimizing healthcare resource utilization [159]. Besides CPAP, weight loss achieved through lifestyle changes, medication, or bariatric procedures have shown effectiveness in decreasing OSA severity and improving glycemic status among individuals with unhealthy weight and T2D [160].

Polycystic Ovarian Syndrome

- PCOS screening should occur at diagnosis in pubertal girls and yearly thereafter with evaluation of menstrual history (primary amenorrhea or menstrual irregularities according to time post menarche) and evidence of hyperandrogenism (hirsutism and/or moderate to severe acne and/or elevated free testosterone level) **[B]**.
- PCOS is diagnosed based on the presence of menstrual irregularities with clinical or biochemical evidence of hyperandrogenism after exclusion of other possible causes **[B]**.
- Pelvic ultrasound or anti-mullerian hormone evaluation is not recommended for diagnosis of PCOS within 8 years post menarche **[B]**.

The prevalence of PCOS in adolescents with T2D is ~20% which is 2–5 times higher than in adolescents without T2D [161, 162]. A menstrual history should be taken in every girl with T2D at diagnosis and every

diabetes follow-up encounter [81]. PCOS screening should occur if there are menstrual irregularities. Screening includes evaluation of the two diagnostic criteria (menstrual irregularities according to time post-menarche [including primary amenorrhea] and hyperandrogenism [hirsutism, severe acne, and/or total/free testosterone]). PCOS diagnosis during adolescence is based on the presence of both menstrual irregularities and hyperandrogenism after exclusion of other conditions that mimic PCOS [163]. Pelvic ultrasound or anti-mullerian hormone is not recommended for diagnosis of PCOS in adolescents within 8 years post menarche [163, 164]. Adolescents with only one of these features (menstrual irregularities or hyperandrogenism) can be considered "at risk" for PCOS and require management of the symptoms and ongoing follow-up [163].

The management of adolescents "at risk" of PCOS or with PCOS include reinforcement of healthy lifestyle, combined oral contraceptive pills for menstrual irregularity and/or hyperandrogenism and metformin (if not on metformin for diabetes) for management of metabolic features and cycle regulation [163, 164]. Hirsutism can be managed with cosmetic therapies including laser and light therapies [164]. Antiandrogens should be considered when response to treatment with combined oral contraceptive pills and cosmetic therapy is suboptimal after 6 months [163, 164].

Retinopathy

- Screen youth with T2D for retinopathy at the time of diagnosis and annually by an ophthalmologist or optometrist by comprehensive eye examination with dilated pupils or retinal photography **[C]**.
- More frequent examinations by an ophthalmologist may be required if retinopathy is present or progressing **[C]**.

Diabetic retinopathy (DR) is the leading cause of blindness in adults with T2D and DR is reported at high prevalence in pediatric and youth-onset T2D studies, including the SEARCH multicenter, population-based prospective cohort study (56% DR prevalence after 12.5-year diabetes duration) and TODAY study (49% prevalence after 12 years diabetes duration) [165, 166]. A recent meta-analysis found the prevalence of DR differed according to diabetes duration with 1% (less than 2.5 years), 9% (2.5–5 years), and 28% (more than 5 years); and no differences in prevalence according to sex, race, or obesity. Fundoscopy in this meta-analysis was less sensitive than 7-standard-field stereoscopic photos for detecting DR (0.5% vs. 13.5%) [167].

Screening for DR with fundus photography or mydriatic ophthalmoscopy performed by optometrist or ophthalmologist is required at the time of diagnosis, yearly and more frequently if retinopathy is present or progressing [81, 140]. Seven standard-field stereoscopic photos are a more sensitive screening method, if available [167]. Strategies like eye examination by optometrist/ophthalmologist at the same time of the diabetes follow-up [168] and the use of artificial intelligence to assess DR with an in clinic retinal camera seem promising in improving outcomes [169, 170]. The presence of any DR requires a referral to an ophthalmologist for management as well as optimization of glucose management and treatment of comorbidities including dyslipidemia and hypertension if present [81].

Neuropathy (Peripheral and Cardiac Autonomic Neuropathy)

- Foot examination (including sensation, vibration sense, light touch, and ankle reflexes) at diagnosis and annually is recommended to detect neuropathy **[C]**.
- Youth with diabetes should be taught proper foot care **[C]**.
- Referral to a neurologist should be considered if there are abnormal neurological signs **[E]**.
- Cardiac autonomic neuropathy (CAN) management should include optimization of diabetes management, lifestyle, and management of other cardiovascular risk factors. There are limited data on pharmacological treatments for CAN in T2D youth **[E]**.

Diabetic neuropathy includes peripheral neuropathy or abnormalities in the peripheral somatic nerves (large and small fibers) and autonomic neuropathy or abnormalities in the autonomic nervous system including CAN, gastrointestinal neuropathy, urogenital neuropathy, and hypoglycemic autonomic failure (hypoglycemic unawareness). Table 8 includes details of the evaluation of peripheral neuropathy and CAN [81, 140, 171].

There is increasing evidence of the higher prevalence of CAN (defined as ≥2 abnormal heart rate variability measures) in youth with T2D compared with youth with T1D (47% vs. 27%) [81, 174]. CAN was associated with aortic stiffness in participants from the SEARCH study at 23 years of age [175]. Additionally, CAN is associated with higher risk of cardiovascular events and all-cause

Table 8. Evaluation of peripheral and cardiac autonomic neuropathy

Peripheral neuropathy	
History	Foot pain, burning, electric shocks, stabbing, hyperalgesia, numbness, tingling, poor balance, and weakness
Physical examination	General examination of each foot Ankle reflexes of each foot Light touch, proprioception, pin prick and thermal sensation starting distally at the dorsum of each foot Vibration perception using 128-Hz- tuning fork starting distally at the first metatarsophalangeal joint of each foot 10 g monofilament applied to the dorsum of the great toe of each foot 10 times
Screening tools	Michigan Neuropathy Screening Instrument [172] Toronto Clinical Neuropathy Score [173] Neuropathy disability score
Cardiac autonomic neuropathy	
Signs	Resting tachycardia and postural hypotension (a postural decrease of at least 20 mm Hg in systolic blood pressure or at least 10 mm Hg in diastolic blood pressure within 3 min of standing). These signs should prompt formal testing with heart rate variability
Heart rate variability	Evaluated by 10 min continuous electrocardiogram; mainly used in research settings in adolescents
Cardiovascular reflex tests	Heart rate response to deep breathing, standing and Valsalva maneuver Diastolic BP response to sustained handgrip

mortality according to a meta-analysis including individuals with T1D and T2D [176]. There are limited data on evaluation and management of CAN in youth with T2D, therefore management is guided by data in adults [174, 177].

The overall prevalence of peripheral neuropathy in T2D is 31.5% among youth and adults and therefore significant [178]. Higher prevalence in this study was observed with longer diabetes duration and the use of Michigan Neuropathy Screening Instrument (MNSI) compared to neurological symptom score and neuropathy disability score [178]. Data from the TODAY study including 674 participants showed an increase in peripheral neuropathy (evaluated by MNSI) from 1 to 32.4% over 15-year follow-up [179]. The prevalence of peripheral neuropathy assessed by MNSI in youth with T2D increased from 19% to 36% according to diabetes duration (5–10 years vs. >10 years duration, respectively), and it is much higher than the prevalence in youth with T1D which is 2.6–11% [180–182].

Other risk factors for developing peripheral neuropathy according to the TODAY and SEARCH studies included poor diabetes management, older age, higher BMI, smoking, dyslipidemia, higher plasminogen activator inhibitor-1, higher high sensitive C-reactive protein, higher SBP, and hypertension [179, 180].

Mental Health

- Screen for symptoms of depression, anxiety and diabetes distress using validated screening questionnaires **[B]**.
- In cases where mental health concerns are identified, refer to a mental health provider for evaluation and management **[E]**.

Youth-onset T2D disproportionately affects youth facing structural disadvantages, including youth living in poverty [181, 183–186], and in food insecure households [187, 188]. In this context, children with T2D have been shown to have higher mental health comorbidities compared to children with T1D and children without diabetes [189]. In addition, poor mental health has been reported as the leading cause of hospital admission for youth diagnosed with T2D [190]. The prevalence of depressive symptoms in youth with T2D is reported to be ~20% [191–193] with one study reporting 18.9% of youth endorsing self-harm [194]. High levels of diabetes distress [195], associated with depression and anxiety have also been reported in youth living with T2D often with a female predominance.

Although depression and anxiety have not been shown to be directly associated with glycemic management [196], their association with health-related behaviors such as readiness for behavioral change [197], disordered eating

[198–200], and worse sleep hygiene [201–203] are expected to indirectly impact diabetes outcomes. Diabetes distress has been shown to correlate with glycemic management although the mechanism remains unclear [195, 204]. However, in a young adult study lower medication engagement and healthcare follow-up has been linked to unmet social needs and lack of support revealing the complex relationships between stress, depression, anxiety, and the role of social circumstances [205]. In addition, youth with T2D report feelings of significant shame and blame for having developed T2D, and distress related to the deep experiential understanding of long-term diabetes complications due to the intergenerational burden of T2D within their families [206, 207].

Early intervention studies of female youth at risk for T2D based on mindfulness [208–210] and cognitive behavioral therapy [210, 211] have shown some promise in improving mental health and health behaviors. Lower levels of stress and distress are associated with higher levels of resiliency and more readiness to adopt self-help behaviors [197]. In a large population of youth and adults in Norway, a sense of mastery, defined as a sense of having control over the forces that affect one's life, protected against depression and anxiety including in people with diabetes [212]. Future therapeutic approaches for youth with T2D need to account for the cultural, socioeconomic, and psychological variables which impact health-related behaviors [74].

Youth with T2D should be screened for psychological comorbidities including depression, anxiety, and diabetes distress, at diagnosis and regular follow-up intervals. Several screening tools used primarily in research settings may be incorporated into clinical care with appropriate psychological supports. These include the Diabetes Distress Scale, the PHQ-9, the shorter PHQ-2 [213], the Kessler distress score (K6), Unger resiliency scales, and the Psychological Stress Score (PSS14). In addition to mental health screening, programs caring for youth with T2D should have access to either program or community based mental health supports to provide to youth who are endorsing mental health struggles.

Life Expectancy and Mortality

Limited studies examining mortality rates suggest youth with T2D experience significantly higher mortality than youth without T2D, youth diagnosed with T1D, and adults diagnosed with T2D. Global estimates of age standardized mortality rates for youth-onset T2D (age 15–39 years) in 204 countries suggest a modest increase over time from 1990 to 2019 from 0.74 (95% CI 0.72–0.75) to 0.77 (95% CI 0.76–0.78), disproportionately affecting women <30 years and populations living in countries with low and middle sociodemographic indices [214]. A recent systematic review revealed crude mortality rates in youth-onset T2D of 1.0–6.6/1,000 person years with the highest rates reported in the Pima Indian population (18.6/1,000 person years) [215].

Follow-up of the SEARCH for diabetes in youth cohort (mean duration of diabetes 6.6 years, median follow-up 8.5 years) reported 1.5 times higher standardized mortality ratios (SMRs) for youth-onset T2D (SMR 2.3, 95% CI 1.7–3.0) compared to T1D (SMR 1.5, 95% CI 1.2–1.8) [216]. Excess mortality was highest among racial and ethnic minorities and those younger than 25 years at time of death. Of note only 9.1% of deaths in youth with T2D had diabetes related factors as the underlying cause, with external factors (injury, assault, motor vehicular accident) being the most common cause of death.

Higher rates of mortality have been associated with younger age at diagnosis, with one Australian study reporting a 10 year decrease in age at diagnosis is associated with a 20–30% increased risk of all-cause mortality and a 60% increased risk of cardiovascular disease [217]. Similarly, a meta-analysis of ~1.3 million youth diagnosed with T2D from 26 observational studies reported for each 1-year increase in age at diagnosis there is a 4% decreased risk of all-cause mortality after controlling for current age [218]. Taken together, these concerning statistics highlight the need to prevent or delay the diagnosis of T2D and reinforce management of comorbidities and complications in youth with T2D.

Summary and Conclusions

Youth-onset T2D is a growing public health concern worldwide that presents with unique characteristics, demographics and progression compared to adult-onset T2D. There is a critical need to better understand the unique pathophysiology of T2D in youth and the interplay of genetics, puberty, and the environment. Health care professionals must appreciate the cultural, social, geographic, and economic barriers to implementing behavioral change and lifestyle modification in the life context of the youth and family. Large gaps persist with respect to high-quality evidence for effective interventions to address identification and addressing social determinants of health (SDOH) on youth-onset T2D incidence and outcomes. Evidence now supports the need for a comprehensive research agenda aimed at the individual, organizational, and policy level, focused on the understanding and amelioration of the effects of the SDOH on youth-onset T2D.

For pediatric heath care professionals engaged in the care of T2D youth, evidence is rapidly evolving regarding the optimal diagnosis, management and monitoring of these youth. Ongoing data and experience from clinical trials and care-approaches will not only aid in optimizing glycemic management, but slow condition progression and reduce long-term co-morbidities and complications. It is anticipated that these insights will inform personalized, precision medicine-based approaches to implement in an emerging population experiencing unacceptable rates of morbidity and mortality.

Conflict of Interest Statement

There are no conflicts of interest to report.

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Author Contributions

A.S.S., M.B.-P., N.C., J.-F.F., T.S.H., M.K., A.S.P., O.P.-H., T.U., B.W., J.W., and F.H.M. drafted one or more sections of the manuscript and summarized literature about pediatric T2D. A.S.S., M.B.-P., N.C., J.-F.F., T.S.H., M.K., A.S.P., O.P.-H., T.U., B.W., J.W., and F.H.M. reviewed and edited the manuscript drafts. A.S.S. coordinated revisions of the manuscript based on input from ISPAD membership, the coauthors and ISPAD guidelines editors and ISPAD forum comments.

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