Type 1 Diabetes Screening and Diagnosis

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KEYWORDS

• T1D screening • T1D screening programs • T1D staging and risk of progression
• T1D diagnosis

KEY POINTS

- Deciding who and how to screen for T1D has broad clinical and research implications.
- Several screening programs exist with goals of early detection of T1D and possible entry into prevention and/or new-onset trials.
- In pediatric patients at increased risk of T1D, OGTT is the gold standard for disease staging and assisting in predicting risk of progression, especially when incorporated in a T1D risk score.
- Unless overt symptoms of DM are present at diagnosis, testing should be repeated to confirm the diagnosis.

WHO TO EVALUATE FOR TYPE 1 DIABETES

Those with Concerning Signs and/or Symptoms

Type 1 diabetes (T1D) is one of the most common chronic diseases of childhood and adolescence, with an estimated worldwide prevalence of approximately 1.52 million people younger than age 20 living with the condition as of 2022. In 2022, the T1D Index estimated that 35,000 of T1D-related deaths were in undiagnosed people younger than 25 years old.[1] It is critical that health care providers be aware and attentive to the symptoms of T1D to ensure a timely diagnosis. In general, patients with polyuria, polydipsia, nocturia, and/or unexplained weight loss should be screened for T1D. Additional findings may include abdominal pain, nausea, emesis, blurred vision, lethargy, decreased appetite, and irregular breathing. Detection of symptoms is challenging in young patients so close attention should be given to anthropometric data during well and sick visits.

At Risk Based on Family History

The risk of T1D is approximately 0.4% in the overall population. Risk increases if one has a relative with T1D.[2] This information is useful to guide screening patterns and

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Endocrinol Metab Clin N Am ■ (2023) ■–■
https://doi.org/10.1016/j.ecl.2023.09.008 **endo.theclinics.com**
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counseling of families. The estimated lifetime risk depends on which relative has T1D, as further described next.

- Sibling of person with T1D: 6.7% according to data from the nationwide Childhood Diabetes in Finland (DiMe) study.[3]
- Child of mother with T1D: 3.4%, according to data from the Familial Autoimmune and Diabetes (FAD) Study based out of Pittsburgh, Pennsylvania.[4]
- Child of father with T1D: 4.9%, according to data from the FAD.[4]
- Twins with person with T1D:
  - Monozygotic twin: 65% in long-term follow-up studies, according to data obtained from patients identified at the Joslin Diabetes Center, the Barbara Davis Center for Childhood Diabetes, and through the Diabetes Prevention Trial–Type 1 Diabetes.[5]
  - Dizygotic twin: Risk is similar to nontwin siblings, according to patient data from the Joslin Diabetes Center, the Barbara Davis Center for Childhood Diabetes, and the Diabetes Autoimmunity Study in the Young (DAISY).[6]

Potential Universal Screening, Considering New Therapies

The recent Food and Drug Administration (FDA) approval of teplizumab-mzwv (TZIELD) indicated for stage 2 T1D brings into question the consideration of universal screening for T1D. The age and method of screening would likely generate great debate and true universal screening would be challenging. **Fig. 1** provides a pictorial summary of who to screen for T1D.

SCREENING PROGRAMS

The Environmental Determinants of Diabetes in the Young (TEDDY) Study is a consortium responsible for creating and implementing studies to investigate the potential triggers and/or protective factors of T1D in children with higher risk genes. The clinical centers recruit subjects as neonates from the general population and newborn first-degree relatives of someone with T1D. Neonates are enrolled if they have a predetermined risk of T1D of 3% (general population) or 10% (those with first-degree relatives with T1D), based on genetic testing (HLA genotype). Subjects are followed for 15 years or until they develop islet autoimmunity and/or T1D. Participants have blood samples collected every 3 months for 4 years followed by every 6 months until 15 years old. Other samples collected include drinking water, nasal swabs, stools samples, toenail clippings, and urine. Historical data are collected, and diet, illnesses, allergies, vaccinations, psychosocial stressors, gestational events, and toxins. As of 2022, 8667 children have participated to date worldwide of which 435 have been diagnosed with T1D. Notable findings have included the role of non-HLA genetic factors in the development of T1D[7] and the importance of the order of appearance of autoantibodies in predicting the risk of developing T1D.[8]

TrialNet is an international multidisciplinary network of scientists whose overarching goal is to cure diabetes. There are more than 100 participating locations worldwide. Relatives of people with T1D or those who have tested positive for at least one T1D-related autoantibody can receive free risk screening through TrialNet in the Pathway to Prevention risk screening study. The testing is performed either with an in-home test kit or in a laboratory and tests for five autoantibodies. Those with one diabetes-related autoantibody are advised to repeat antibody testing in 1 year. Those with two or more autoantibodies are advised to have an oral glucose tolerance test (OGTT) performed to determine if dysglycemia is present and whether they qualify for available prevention studies. Prevention studies through TrialNet are aimed at

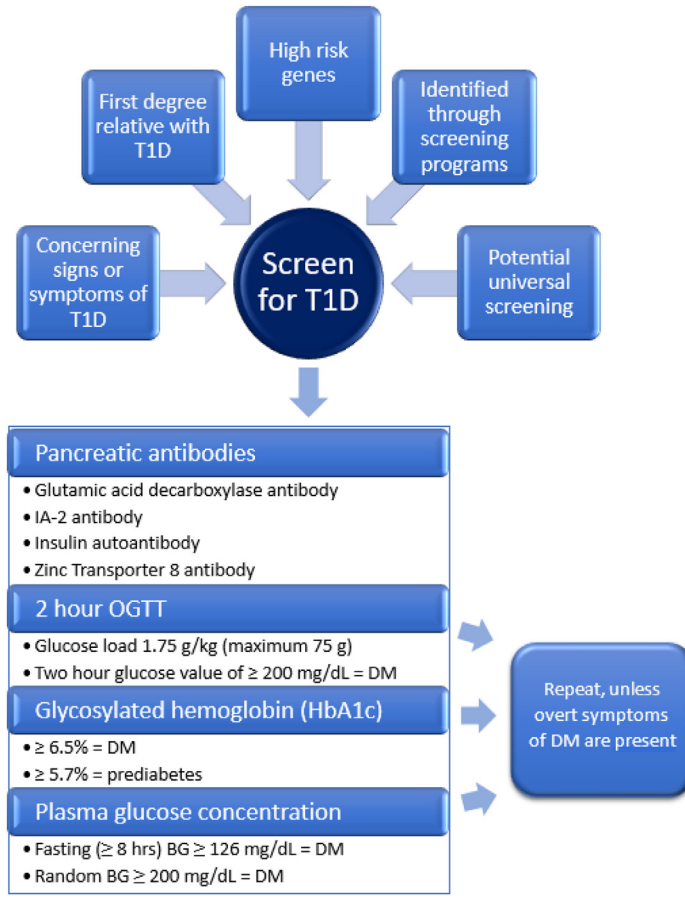

Fig. 1. Screening for T1D. BG, blood glucose; DM, diabetes mellitus.

slowing or preventing diabetes in people who are in early stage T1D, defined as having two or more T1D-related autoantibodies. Studies are also ongoing for those with newly diagnosed T1D, with the goal of maximally preserving the person's insulin production. Participants who develop T1D during a TrialNet prevention study can join the Long-Term Investigative Follow-up in TrialNet (LIFT) study for ongoing monitoring. Participants who completed a new-onset study are also eligible to join the LIFT study. Those participating in LIFT have a visit at a TrialNet location yearly to complete a health status questionnaire and laboratory evaluations. TrialNet is unique in that it is following participants with T1D in all phases: before, during, and after being diagnosed with T1D.

T1Detect is a population awareness and education program created by the Juvenile Diabetes Research Foundation. T1Detect's goals are to make the public aware of the importance of T1D screening, how to obtain screening, and what to do with the results of the screening.

Autoimmunity Screening for Kids (ASK) is a research program located at the Barbara Davis Center for Diabetes at the University of Colorado. This program offers free screening for T1D and celiac disease to all children in the United States, ages 1 to 17 years old. Goals of ASK include early detection of T1D, monitoring and education

of children at increased risk of T1D, trialing therapies to prevent diabetes, and maximizing treatment and monitoring of children with undiagnosed celiac disease. Participants who live more than 15 miles from a screening site can perform at-home screening.

The Fr1da Study was created in 2015 at the Helmholtz Diabetes Center Institute of Diabetes Research. It is the world's largest population-based screening for T1D in children. All children ages 2 to 10 years old who live in Bavaria, Germany are eligible for islet autoantibody testing. Children with a first- or second-degree relative with T1D can receive autoantibody testing between 1 and 21 years old. Children can participate twice in the study if they are within the included age ranges. The main goal of the Fr1da study is to diagnose T1D in children while they are in a presymptomatic stage to prevent diabetic ketoacidosis, improve early onset education, assist with creating standards for early diagnosis of T1D, and detect children who may benefit from immune-based therapies. Two other relevant studies currently being conducted at the Helmholtz Diabetes Center Institute of Diabetes Research are Freder1k and SINT1A. Freder1K is a free and optional newborn screening program completed within the first week after birth to determine the infant's genetic predisposition of T1D. SINT1A is a prevention study for infants with increased risk of T1D, investigating the efficacy of a probiotic *Bifidobacterium infantis*. Freder1k and SINT1A are part of the Global Platform for the Prevention of Autoimmune Diabetes (GPPAD), which is a European platform aimed at identifying infants with increased genetic risk of T1D and performing prevention trials. GPPAD research sites are in Belgium, Germany, Poland, Sweden, and the United Kingdom, with the coordination center being located at Helmholtz Munich.

Fig. 2 provides a summary of some of the T1D screening programs available.

WAYS TO SCREEN ASYMPTOMATIC PARTICIPANTS

- The HLA complex is involved in the immune process of antigen presentation and is therefore critical in the pathogenesis of T1D. The combination of specific alleles of HLA class II genes confers about 50% of the genetic risk of T1D. The highest risk of T1D is linked to DR4-DQ8 and DR3-DQ2 haplotypes, whereas DR2 is protective of T1D. Less than 10% of people with high-risk HLA haplotypes develop T1D.[9] Other genes that confer increased risk of T1D include insulin, PTPN22, and CTLA4.[10]
- Islet cell autoantibodies have an important role as principal markers of pancreatic autoimmunity in T1D. These autoantibodies recognize antigens involved in the secretory machinery of pancreatic β cells.[11]
  - Glutamic acid decarboxylase antibody (GADA): Glutamic acid decarboxylase, particularly GAD65, is found in the cytoplasm of synaptic-like microvesicles. GAD65 is a critical enzyme involved in the synthesis of γ-aminobutyric acid (GABA). GABA is a main inhibitory neurotransmitter in the central nervous system. Despite multiple tissues using GABAergic systems, expression of GAD65 in humans has only been confirmed in pancreatic islet cells and in the central nervous system. The regulation of the GABAergic systems in the brain and pancreas differs. In the human pancreas, GAD65 is found mostly in β cells and in a minority of cells. GADA is the classic antibody detected in patients with latent autoimmune diabetes of the adult.[11]
  - IA-2 antibody (IA-2A): IA-2 is a receptor-type tyrosine phosphatase-like protein that is found on the membrane of secretory granules. Its biologic role is not completely understood, but it seems to ultimately influence insulin secretion,

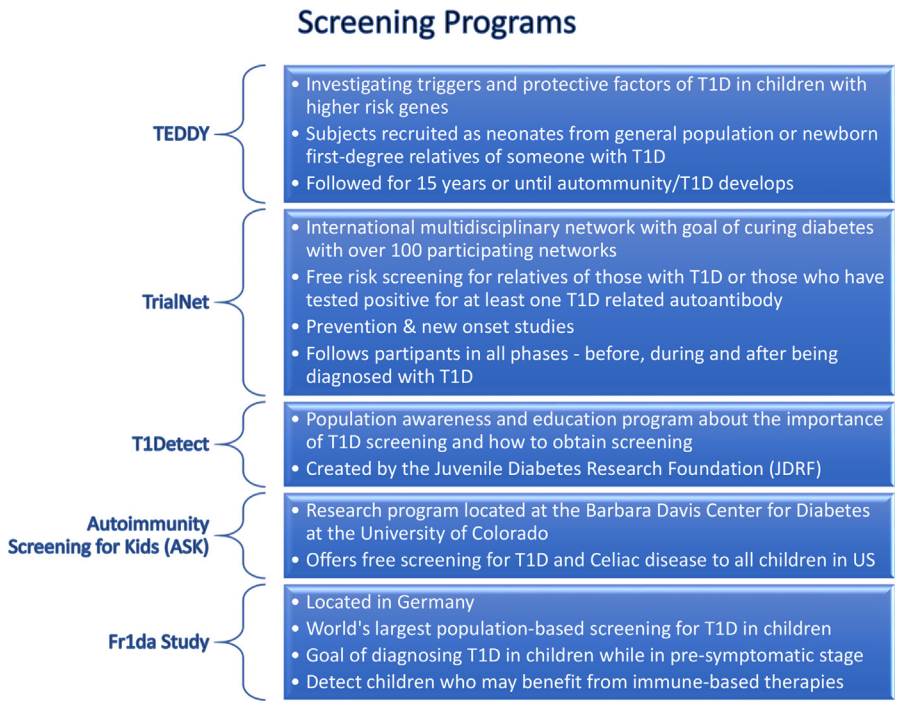

Fig. 2. Screening Programs.

secretory granule synthesis/homeostasis, and beta-cell expansion. IA-2 expression is found at the mRNA and protein levels in several neuroendocrine cells, splenocytes, and the thymus. In the pancreas, IA-2 is only found in pancreatic islets (β, α, and δ cells) and is not seen in pancreatic exocrine tissue.[11]

- Insulin autoantibody (IAA): Insulin is contained within secretory granules and in humans is almost only expressed in the pancreatic β cells. At the mRNA and protein levels, insulin expression is also seen in thymic medullary epithelial cells. There are associations between specific polymorphic variants in the insulin gene and increased risk of T1D.[11]
- Zinc Transporter 8 antibody (ZnT8A): ZnT8 is found on the membrane of secretory granules. It seems to be essential for the accumulation of zinc into secretory granules and the appropriate maintenance of stored insulin. Polymorphisms of ZnT8 have been associated with increased risk of T2D, impaired glucose homeostasis, and altered rate of conversion of proinsulin to its mature hormone. ZnT8 expression in humans is mainly in the pancreas, at the mRNA and protein level. Within pancreatic islet cells, it is mainly found in beta cells.[11]

DISEASE STAGING AND RISK OF PROGRESSION

Almost all children with multiple islet cell autoantibodies eventually develop stage 3 T1D. Disease staging and ongoing monitoring is critical in this population.[12]

The 2-hour OGTT is the gold standard for T1D disease staging once multiple islet cell autoantibodies are present. Stage 1 is the presence of at least two autoantibodies with normal blood glucose levels and no symptoms. Stage 2 is the presence of at least two autoantibodies with abnormal glucose tolerance and typically no symptoms. Stage 3 is

the presence of two autoantibodies, abnormal blood glucose values diagnostic of diabetes mellitus (DM), and typically symptoms of diabetes. Stage 4 is established T1D. The OGTT also aids in determining the risk of disease progression, either on its own or when used in risk score calculations. Most prevention trials require an OGTT for disease staging before being considered for inclusion. Alternatives to OGTT for disease staging and determining risk of progression include glycosylated hemoglobin (HbA_{1c}), continuous glucose monitoring (CGM), random venous plasma glucose, and self-monitoring of blood glucose, especially outside of a research setting.[12]

HbA_{1c} has limitations when it comes to making an early diagnosis of T1D in the pediatric population. T1D can progress rapidly in this population. There is also the possibility of an underlying condition that may affect red blood cell turnover (eg, hemoglobinopathy), which may falsely lower the HbA_{1c} in this group.[12] In the high-risk pediatric population, an HbA_{1c} greater than or equal to 5.7% has a low sensitivity (<50%) and variable specificity to diagnose impaired glucose tolerance. In this same population, HbA_{1c} greater than or equal to 6.5% has a very low sensitivity (24%–34%) and high specificity (98%–99%) to make a diagnosis of T1D. This was obtained from data from the DPT-1, TEDDY, TRIGR, and TrialNet Natural History studies. Across these studies, the positive predictive value of an HbA_{1c} greater than or equal to 6.5% to predict development of T1D in this group ranged from 50% to 94%. Adjusting the current thresholds of HbA_{1c}, particularly in the high-risk pediatric population, may improve its utility in making an early diagnosis of diabetes.[13] An HbA_{1c} in the normal range but that is increasing has shown some utility in making an early diagnosis of T1D.[14]

CGM has utility in monitoring patients at increased risk of developing T1D.[12] However, CGM usage is limited by cost and the lack of widespread accessibility. Average sensor glucose levels and increased glycemic variability are CGM metrics that are used to predict progression to clinical diabetes in high-risk patients. TA140 is the time spent with glucose levels greater than 140 mg/dL with a CGM. In data obtained from the Autoimmunity Screening for Kids (ASK) Study, autoantibody-positive children with TA140 greater than 10% had an 80% risk of progression to clinical diabetes in 1 year. In that same cohort, children who progressed to clinical diabetes within a median time range of 6 months were found to have significantly higher average CGM glucose levels, increased glycemic variability (including standard deviation, coefficient of variation, mean of daily differences, and mean amplitude of glycemic excursions), and increased time spent greater than 160 mg/dL.[15]

Random venous plasma glucose is an easy and low-cost tool that is used in monitoring high-risk patients.[12] In the Type 1 Diabetes Prediction and Prevention Project (DIPP), for those children with stage 1 T1D, the median time to diagnosis after a random plasma glucose greater than or equal to 140 mg/dL was 1 year (vs 0.7 years in those with impaired glucose tolerance during a 2-hour OGTT and 5.2 years in those with impaired fasting glucose).[16]

Self-monitoring of blood glucose is limited by the inability to confirm abnormal glucose values in real time. Pediatric data are insufficient regarding its functionality in predicting progression to clinical diabetes in high-risk patients.[12]

RISK CALCULATIONS AND TYPE 1 DIABETES RISK SCORES

- Islet autoantibodies and risk of progression: In genetically at-risk pediatric patients, progression to stage 3 T1D within 10 years in those with multiple autoantibodies is 69.7%, one autoantibody is 14.5%, and no autoantibodies is 0.4%. Progression to clinical disease is quicker in those who develop islet autoantibodies younger than 3 years of age.[17]

- HbA_{1c} and risk of progression: In genetically at-risk pediatric patients with multiple islet autoantibodies, increase in HbA_{1c} over time can aid in predicting progression to stage 3 T1D. Over a 3- to 12-month period, a 10% increase in HbA_{1c} in this population increases the risk of progression to clinical disease by 5.7 times.[18]
- Diabetes Prevention Trial-Type 1 Risk Score (DPTRS): This score was created from data obtained from Diabetes Prevention Trial-Type 1 (DPT-1) and validated in the TrialNet Natural History Study (TNNHS), both of which included autoantibody-positive participants who were relatives of patients with T1D. Metrics included in the DPTRS calculation are C-peptide, values from 2-hour OGTT, age, and body mass index. A threshold of nine on the DPTRS score is highly predictive of those who will progress to stage 3 T1D within 2 years. The 2-year risk of progression was found to be 88% in this population. Because this threshold is typically reached well before diagnosis (on average >9 months before when diagnosis typically made), stimulated C-peptide levels are also higher in this population.[19]
- DPTRS60: This score was modified from the DPTRS and includes data obtained from a 1-hour OGTT versus the standard 2-hour OGTT. The DPTRS60 had a similar prediction rate of T1D at 5-year follow-up compared with DPTRS and was superior to a 2-hour glucose.[20]
- T1D Diagnostic Index60 (Index60): This is a pure metabolic index derived from 2-hour OGTT data from participants in DPT-1 and TNNHS. An Index60 value greater than or equal to 2.0 has potential utility in detecting the earlier stages of T1D.[21]
- M_{120}: This is a T1D disease prediction model based on a single blood sampling at 120 minutes during an OGTT. M_{120} includes sex, age, body mass index, HbA_{1c}, IA-2A status, and OGTT metrics. M_{120} was found to be at least as accurate as DPTRS, DPTRS60 or Index60 in the TrialNet population, while being more practical to obtain.[22]

CURRENT DIAGNOSTIC TOOLS USED IN MAKING THE DIAGNOSIS OF STAGE 3 TYPE 1 DIABETES

- Plasma glucose concentration:
  - Fasting (for at least 8 hours) value greater than or equal to 126 mg/dL in the presence of symptoms concerning for DM or confirmed on repeat testing.
  - Random value greater than or equal to 200 mg/dL in the presence of symptoms concerning for DM or confirmed on repeat testing.
- HbA_{1c} greater than or equal to 6.5%, confirmed on repeat testing. HbA_{1c} greater than or equal to 5.7% is consistent with prediabetes.
- 2-hour OGTT, using a glucose load of 1.75 g/kg (75 g maximum). Two-hour glucose value of greater than or equal to 200 mg/dL, confirmed on repeat testing.
- Fasting insulin level and C-peptide level may help distinguish between T1D and T2D at diagnosis.
- Blood or urine ketone levels to detect developing diabetic ketoacidosis.
- Islet cell autoantibodies:
  - GADA
  - IA-2 antibody (IA-2A)
  - IAA
  - ZnT8A
- Genetic testing for monogenic diabetes when the evaluation suggests that another form of diabetes is likely, such as when:

- Islet autoantibodies are not present.
- There is an autosomal-dominant family history of DM.
- Diagnosis of DM is made within the first 6 to 12 months of life.
- History of hyperinsulinism and associated hypoglycemia in infancy.
- Low insulin requirements or prolonged honeymoon period.
- Evaluation suggestive of T2D but patient is not obese and lacks signs of insulin resistance.
- Other extrapancreatic features are present.

CLINICAL IMPLICATIONS AND RECOMMENDATIONS

- Who should be evaluated for T1D (summarized in **Fig. 1**)?
  - Everyone with concerning signs or symptoms, especially polyuria, polydipsia, nocturia, and/or unexplained weight loss, in whom a delay in diagnosis can have serious adverse effects.
  - Those at increased risk based on family history, particularly first-degree relatives of someone with T1D.
  - Participants identified through screening programs, such as TEDDY, TrialNet, ASK, and Fr1da.
  - Those at high risk based on genetic profile, such as HLA haplotype and other genes that confer increased risk of T1D (insulin, PTPN22, and CTLA4).
  - Those at high risk based on the presence of multiple islet autoantibodies (GADA, IA-2A, IAA, ZnT8A).
  - Consideration for universal screening with the recent FDA approval of teplizumab-mzwv for stage 2 T1D. More broad screening efforts would also allow for earlier entry into ongoing prevention and new-onset T1D studies.
  - The FDA-approved immunotherapy drug teplizumab-mzwv for the delay of T1D in at-risk individuals. TrialNet's Teplizumab Prevention Study was the first to show a clinical T1D diagnosis can be delayed an average of 2+ years in people at high risk.[23] Teplizumab-mzwv is a CD3-directed antibody indicated to delay the onset of stage 3 T1D in adults and pediatric patients aged 8 years and older with stage 2 T1D. Other studies to try to prevent or cure T1D that had some modest effect include using verapamil, abatacept, rituximab, alefacept, antithymocyte globulin, golimumab, imatinib, plasmid vector, and Vertex (Vx-880).
- Goals of early evaluation and screening programs for T1D:
  - Prevent diabetic ketoacidosis and associated severe complications.
  - Smoother transition to initiation of insulin for the patient and the entire family.
  - Possibility of inclusion in prevention and new-onset T1D trials.
  - Potential treatment with teplizumab-mzwv for the treatment of stage 2 T1D.
- Disease staging and risk of progression to stage 3 T1D:
  - OGTT is the gold standard and typically required for entry into a prevention study.
  - Caution should be taken in relying on the HbA_{1c} alone to diagnose early onset T1D, especially in high-risk patients. Change over time in HbA_{1c} is more informative in the early stages of T1D.
  - CGM metrics, particularly TA140, is useful in predicting disease progression.
  - A random plasma glucose is a low cost and more easily accessible option with informative value.
  - T1D risk scores, which usually incorporate OGTT, can increase the ability to predict T1D progression. Examples of risk scores include DPTRS, DPTRS60, Index60, and M_{120}.

- Making the diagnosis of stage 3 T1D:
  - Most tests should be repeated to confirm the diagnosis, unless overt clinical symptoms are present.
  - Fasting plasma glucose greater than or equal to 126 mg/dL, random plasma glucose greater than or equal to 200 mg/dL, HbA_{1c} greater than or equal to 6.5%, and 2-hour glucose value of greater than or equal to 200 mg/dL on OGTT are typically used to make the diagnosis of DM.
  - Ancillary testing to assist in making a precise diagnosis: fasting insulin and C-peptide levels, blood or urine ketones, islet cell autoantibodies, and genetic testing.

CLINICS CARE POINTS

- If a patient has polyuria, polydipsia, nocturia, and/or unexplained weight loss, recommend evaluating for T1D.
- For new-onset T1D or if unsure of type of diabetes, recommend screening with islet cell antibodies (GADA, IA-2A, IAA, ZnT8A) and C-peptide.
- Those with first-degree relatives with T1D and/or high-risk genes should be screened for T1D.
- Those with stage 2 T1D may be candidates for therapy with teplizumab-mzwv.
- When making a diagnosis of T1D, most tests need to be repeated unless there are overt symptoms present.

DISCLOSURE

The authors have no financial relationships with any of the individuals, organizations, or products mentioned in this article.

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