Early Intervention by Family Physicians to Delay Type 1 Diabetes

By Steven Edelman, MD

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KEY TAKEAWAYS

- Type 1 diabetes (T1D) is an autoimmune disease mediated by T cells that target and destroy insulin-producing beta cells. Individuals with genetic risk of T1D will progress at variable rates through 3 stages of immune activation and development of islet autoimmunity. Measuring pancreatic islet cell autoantibodies predicts risk for progression that can take weeks to years before the onset of T1D.
- Screening options available to family physicians can identify persons at risk or in the early stages of T1D, such as first- and second-degree relatives or those with a family history of autoimmune disorders, to ultimately offer proven interventions that may delay or prevent the condition. Screening can reduce emergency room visits, hospitalizations, and intensive care unit admissions for diabetic ketoacidosis, which can be fatal, and can educate and prepare individuals and families for a smoother transition to insulin therapy when necessary.
- Recent advances in technology and understanding of the immune pathogenesis of T1D has resulted in emerging disease-modifying therapies that are changing how family physicians approach delaying and potentially preventing or reversing the disease.

FACULTY

Steven Edelman, MD, Professor of Medicine, University of California, San Diego, Veterans Affairs Medical Center.

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INTRODUCTION

Lauren, a 30-year-old patient, expresses concern that her 34-year-old brother was recently diagnosed with type 1 diabetes (T1D). She is aware that diabetes can be genetic and is concerned not only about her own risk, but also that of her 9- and 11-year-old children.

As recently as 5 years ago, this would have been a short discussion. T1D is an autoimmune disease with a genetic origin triggered by environmental stimuli such as viruses (eg, Coxsackie B, rubella, enterovirus).[1] A blood glucose and C-peptide test would be the best a family physician could offer—to diagnose, but not predict, her or her children's risk. Additionally, there were no disease-modifying therapies (DMTs) approved for human use at that time.

For the first time, family physicians can offer to detect risk for T1D through a simple blood test.[2] Because T1D is an autoimmune disorder characterized by beta-cell destruction, measuring islet cell autoantibodies provides information that correlates to disease risk. If ≥2 autoantibodies are present, the 5-year and 10-year risk are approximately 44% and 70%, respectively, and if glucose intolerance has already developed, the risk is 75% at 5 years, with a lifetime risk of nearly 100%.[2] The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends both general population and targeted screening.[3] The American Diabetes Association (ADA) recommends screening first- and second-degree relatives.[4] Both recommend following with education and monitoring.

Adopting screening protocols provides an opportunity to identify who is likely to develop T1D and, most importantly, offers a therapeutic option to delay or prevent the onset of clinical diabetes. The recent development of new and emerging treatments may potentially change an individual's autoimmune response and delay the onset of T1D for months to years.[1,5] Lauren knows the diagnosis of T1D is life-changing for the entire family; therefore, it is beneficial to delay beta-cell loss as long as possible and maintain normal blood glucose levels to delay a lifestyle of daily insulin therapy and blood-glucose monitoring, diet and exercise restrictions, and adverse effects on education and/or work.

More than 1.45 million Americans are living with T1D. Nearly 64,000 people are diagnosed each year in the United States (US), and it is estimated that 300,000 people in the US are at risk for T1D. In addition, 2.1 million people in the US

are expected to have T1D by 2040.[6] T1D is one of the most common chronic diseases of childhood and two-thirds of cases are diagnosed by age 30 years.[3] Yet anyone at any age can develop T1D. A combination of genetic susceptibility and environmental exposure is thought to determine lifetime risk of developing T1D.[1,5] While genetic susceptibility contributes to the destruction of insulin-producing beta cells, 85% of individuals who develop T1D do not have a family history.[2] This latter fact has implications for determining who to screen for T1D risk.

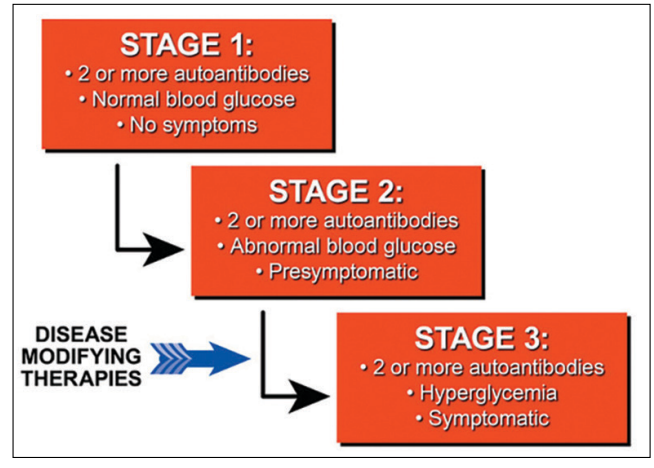
Immune pathogenesis and time course of T1D

T1D is an autoimmune disease conventionally believed to be caused by "killer" or "auto-reactive" T cell-mediated selective destruction of pancreatic insulin-producing beta cells.[7,8] While T cell-mediated autoimmunity is likely triggered by an unknown insult to the beta cells, leading to the eventual production of beta cell-destructive T cells, innate immunity and islet inflammation may be involved as well.[2,6-8] Regardless, destruction leads to a loss of beta-cell mass, with no current evidence that beta cells can regenerate after death. Three key factors are thought to be involved in the progressive development of T1D: the beta-cell mass present early in life (ages 1 to 2 years), which indicates risk and time to onset; the aggressiveness of the self-directed immune response that destroys beta cells; and the loss of beta-cell mass required for T1D onset (85% to 95% loss, with a wide range).[7]

Islet autoimmunity in T1D generally progresses slowly, taking months to years before established clinical onset.[8] The rate of beta-cell destruction varies but is typically more rapid in children than in adults.[3] If the body is unable to stop or slow the T cell destruction of beta cells, then insulin deficiency, hyperglycemia, and T1D results. Understanding the immune processes and the time course of the disease allows us to identify people currently experiencing beta-cell destruction. Knowing how far the autoimmune destruction has progressed can predict the time of onset of clinical T1D.[2]

In 2015, an international community developed a staging system that considers preclinical stages, beginning with autoimmunity and progressing through normoglycemia (Stage 1) and dysglycemia (Stage 2), and culminating in clinical T1D (Stage 3) (**FIGURE 1**).[2] Staging T1D using predictive biomarkers alters the therapeutic approach to T1D, providing opportunities to delay or prevent further disease progression. Indeed, disease-modifying therapies (DMTs) for T1D are now available, and more are being developed.[1] Just as DMTs have transformed treatment options in other autoimmune diseases, multiple DMTs may soon transform how we approach T1D in at-risk and newly diagnosed patients.[5]

FIGURE 1. Early stages of type 1 diabetes[7]



Importance of screening for T1D

Islet autoantibody screening aims to identify whether an individual is presymptomatic, that is, in Stage 1 or Stage 2. After discussing with Lauren the progressive risk for developing T1D for first- and second-degree relatives, the next step is to discuss the benefits and risks of screening or not screening for islet autoantibodies. If desired, she should be offered screening options.

Islet cell autoantibodies serve as the primary biomarkers of T1D risk and can be measured using ultra-low volumes of blood, including capillary samples and dried blood spots.[5,6,9] Insulin autoantibodies (IAA) and glutamic acid decarboxylase (GAD), islet antigen 2 (1A-2A), and zinc transporter 8 (Znt8) antibodies are currently used in the staging system. Stage 1 is defined as the beginning of beta-cell autoimmunity (≥2 islet autoantibodies), where individuals are presymptomatic and normoglycemic. Stage 2 is characterized by beta-cell autoimmunity (≥2 islet autoantibodies) with abnormal blood sugar (dysglycemia) but no symptoms. Stage 3 is beta-cell autoimmunity (≥2 islet autoantibodies), overt hyperglycemia, and symptomatic disease.[2]

The ADA and ISPAD recommend screening for T1D risk in first-degree family members of people with T1D or for research trials.[3,4] The ISPAD further recommends general population screening for all newborns.[3] Indeed, screening strategies are gaining momentum worldwide and believed to be the future standard of care.[3]

The goal of screening is to offer interventions that delay and prevent T1D—a goal we are closer to achieving than ever before. Yet, there are other clinical benefits that drive the need for active screening in clinical practice:

- Prevent diabetic ketoacidosis (DKA) and its morbidity and mortality. DKA is present at diagnosis in 30%

to 60% of US children, with a significantly higher incidence in African American and Hispanic children.[10,11] DKA is associated with increased mortality, longer hospitalizations, higher insulin requirements, shorter remission periods, and worse long-term glycemic control. Population screening and follow-up is associated with significantly less DKA and hospitalizations at diagnosis.[12]

- Preserve C-peptide secretion, a marker of insulin production, that yields better long-term metabolic control and reduced risk for complications.[13]
- Allow children, parents, and individuals time to adjust to the diagnosis, learn about diabetes management, and make a smoother transition to insulin therapy. Diabetes education and counseling can reduce the anxiety that may accompany multiple islet autoantibody test results.[14]
- Allow more time for the advancement of better devices, such as hybrid and fully closed loop systems and other adjunctive therapies.[3]
- Advance preventive and treatment therapies through clinical trial recruitment.[3,4]

Screening process, frequency, and monitoring

Autoantibody screening for T1D risk is available now to family physicians and their patients through 2 programs supported by the JDRF (formerly the Juvenile Diabetes Research Foundation): TrialNet (for relatives aged 2–45 years) or T1Detect (for those with no family history), as well as through regional screening programs. These programs use the recommended panel of autoantibodies so as not to miss a predictive biomarker: IAA, GDA, islet 1A-2A, and Znt8 antibodies. Average clinical sensitivity and specificity of assays are 96% and 97%, respectively, and correctly identify 95% of high-risk individuals with ≥2 autoantibodies.[8]

Clinicians can also order this screening panel from commercial laboratories (Mayo Laboratories, LabCorp, Quest Diagnostics), remembering that cost to the patient depends on insurance coverage. Interpretation and patient discussion guidance is available at JDRF.org.

The optimal frequency of testing in genetically high-risk individuals such as Lauren and her children is continuously under evaluation. The JDRF provides an ASK THE EXPERT resource for the latest information. Current monitoring guidelines for individuals who have been screened are based on antibody test results[5]:

- A negative autoantibody test. Rescreen if the individual becomes symptomatic. Since children are at greatest risk, screening at 2 to 3 years and 5 to 7 years can be valuable.[5] If the individual is older than 18 years of age, risk of developing T1D is low but not absent. Consider future rescreening if a family member has a history of another autoimmune disorder.
- One positive antibody test. Rescreen while monitoring for T1D symptoms. Check glycated hemoglobin (A1c) for normality (<5.7%) and perform a metabolic test within 6 months to exclude clinical T1D diabetes (eg, oral glucose tolerance test [OGTT], fasting plasma glucose [FPG], random blood glucose [BG]).
- Positive for ≥2 autoantibodies. Rescreen. Discuss disease staging and monitoring. Counsel about risk and timeline for moving through Stage 2 (abnormal glycemia) to Stage 3 T1D (symptomatic disease). Educate on signs and symptoms of T1D and DKA.
    - Stage 1: Normal glycemia. Check A1c for normality (<5.7%) and perform a metabolic test within 6 months to exclude clinical T1D diabetes (eg, OGTT, FPG, random BG).
    - Stage 2: Confirm dysglycemia with 1 or more of the following:
        - –FPG 100-125 mg/dL
        - –2-hour plasma glucose 140-199 mg/dL
        - –A1c 5.7%-6.4%
        - –An OGTT is required for staging individuals into clinical trials
        - –Perform ongoing monitoring: 6 to 12 monthly A1c tests and 2-hour postprandial or random glucose testing in children. Continuous glucose monitoring (CGM) or self-monitoring of blood glucose data can provide real-time data for early detection
    - Stage 3: Diagnose clinical diabetes using ADA criteria. Refer for diabetes self-management education, mental health professional counseling, and diabetes clinical specialist (see Diabetes.org)[4]

New era of disease-modifying interventions

Actions to prevent, delay, or even reverse the progressive beta-cell destruction in T1D can maintain beta-cell volume and function to reduce lifelong exogenous insulin dependency and associated acute and long-term complications. Recent discoveries and improvements in immunotherapy development may change our approach to T1D, just as refined therapies to treat autoimmune and inflammatory diseases like rheumatoid arthritis are now common in family practice.[1] Several newer DMTs targeting islet-specific immune pathways are being investigated in ongoing clinical trials.[3]

If a therapeutic intervention is to preserve beta-cell volume and function, it needs to be used as early as possible in the course of the disease. The majority of agents use

single immunosuppressive drugs such as methotrexate and cyclosporin, targeting T cells or B cells in new-onset T1D.[15,16] Treatment with cyclosporin A produced remission in children with T1D, but clinical remission was lost once cyclosporin was stopped.[16] A single course of low-dose antithymocyte globulin slowed decline of C-peptide and lowered A1c in new-onset T1D for at least a year.[17] Short-course rituximab, an anti-CD20 monoclonal antibody targeting B cells, slowed the fall of C-peptide by 8.2 months in new-onset T1D, but the C-peptide decline was the same as controls at 2 years.[18]

In addition to research in immunosuppressive therapy, trials of agents targeting the general inflammatory process, such as the TNF-a blocker golimumab, are ongoing in adults and children with newly diagnosed T1D and Stage 2 T1D (phase 2 trial, NCT02846545).[1] Targeting specific inflammatory pathways is thought to be the best anti-inflammatory approach, but so far there has been little success in restoring immune tolerance in T1D.

Studies in non-obese diabetic (NOD) mice demonstrated that early treatment with anti-CD3 monoclonal antibodies targeting T cells induced remission if used around the time of disease onset.[19] Anti-CD3 monoclonal antibodies are currently the most extensively studied immunologic approach to T1D as more specific and less toxic T cell–directed therapies show promise.[1]

The anti-CD3 monoclonal antibody teplizumab modifies CD8+ T lymphocytes, which are thought to kill beta cells.[20,21] Early phase 2 studies in young adults and children with T1D using a short course of teplizumab for 6 to 14 days within the first 6 weeks of diagnosis showed improvements in C-peptide responses for at least 2 years after treatment.[22] Furthermore, the average area under the curve (AUC) for C-peptide was significantly greater in the drug-treated group at each 6-month time interval. Improved clinical parameters included significantly reduced A1c and insulin requirements when compared to untreated controls.

A follow-up study examined whether 2 courses of teplizumab administered 1 year apart reduced the decline in C-peptide at 2 years.[23] Because the effects of treatment varied and were not permanent in the previous study, the investigators also set out to identify individuals as responders (for whom the effect lasted 3 years) or nonresponders. Teplizumab reduced loss of C-peptide 2 years later and C-peptide AUC at year 2 was 75% greater compared with controls. The strongest differentiator between responders and nonresponders was in metabolic features—responders had lower A1cs and insulin use at baseline. In addition, responders had fewer numbers of T cell subsets. Results of these and other studies have shown that teplizumab therapy reduces loss of beta-cell function in recent-onset T1D for as long as 5 years.[24]

Teplizumab for preventing/delaying T1D

These earlier studies led to the recognition that intervening early in Stage 2 T1D with anti-CD3 monoclonal antibodies—specifically teplizumab—could possibly prevent or delay the onset of T1D (Stage 3). In a landmark study published in 2019, teplizumab delayed the onset of T1D by an average of 3 years in nondiabetic at-risk relatives aged 8 to 45 years.[25] Relatives of people with T1D had at least 2 autoantibodies and abnormal results on an OGTT—in other words, they were in Stage 2. The percentage of diabetes-free persons in the teplizumab group was double (57%) that of the placebo group (28%). Treatment with teplizumab delayed the time to diagnosis of T1D; 19 (43%) of 44 participants on teplizumab and 23 (72%) of the 32 who received placebo were diagnosed with T1D. Median time to diagnosis was 48.4 months in the teplizumab group and 24.4 months in the placebo group (HR: 0.41; 95% CI: 0.22-0.78, P=0.006). The greatest effect of teplizumab treatment occurred in the first year, as only 3 of 44 (7%) in the treatment group were diagnosed compared with 14 of 32 (44%) in the placebo group. In a subgroup analysis, the presence of HLA-DR4 and absence of HLA-DR3 were associated with more robust responses to teplizumab. Additionally, participants who did not have Znt8 antibodies responded better.

Treatment involved a 14-day outpatient course of teplizumab delivered intravenously with dosing based on body surface area. Safety analysis revealed spontaneous rash (36% of participants) and transient lymphopenia as the 2 primary adverse events. As in previous trials in individuals with T1D, lymphocyte count decreased to a nadir on the fifth day. Lymphopenia resolved by day 45 in all but one participant, for whom it resolved on day 105. Rates of infection were similar in the 2 groups.

Teplizumab was approved by the US Food and Drug Administration in November 2022. Teplizumab is a CD3-directed antibody indicated to delay the onset of Stage 3 T1D in adults and pediatric patients aged ≥ 8 years with Stage 2 T1D.[26] This approval represents the beginning of the use of DMTs to delay or possibly prevent T1D diabetes.

DMTs to slow, stop, or reverse T1D

A growing body of evidence suggests that many patients with T1D retain beta cells long after diagnosis and likewise retain the ability to produce C-peptide.[27] DMTs can change the course of newly diagnosed T1D by preserving and/or restoring beta-cell mass; reducing insulin need; and subsequently reducing mortality, morbidity, and the burden of diabetes management. Finding clinically effective single or combination DMT that can rebalance the immune system and preserve or regenerate beta cells can change the way clinicians

approach and treat T1D. Several promising clinical trials in new-onset T1D include:

- The PROTECT trial, which is determining whether 2 courses of teplizumab administered 6 months apart slows the loss of beta cells and preserves beta-cell function in children and adolescents 8 to 17 years who have been diagnosed with Stage 3 T1D in the previous 6 weeks. Recruitment is complete and results are expected in 2023 (Identifier: NCT03875729)
- The CLVer trial, which uses hybrid closed-loop therapy and verapamil for beta-cell preservation in new-onset T1D. Verapamil has been shown to protect and strengthen beta cells and slow their destruction in T1D. Children and adolescents 7 to 17 years with diagnosis in the past 4 weeks are being enrolled (Identifier: NCT04233034)
- The Ver-A-T1D trial, which is designed to determine C-peptide response to 360 mg verapamil sustained release added to an insulin regimen in newly diagnosed adults (Identifier: NCT04545151)
- The TOPPLE study, which is testing the safety of a plasmid vector to stop beta-cell destruction in adults with T1D diagnosed in the last 4 years (NCT04279613)
- The BANDIT trial, which examines the potential for JAK inhibitors, currently approved for other autoimmune diseases, to stop beta-cell destruction in T1D. Trial results are expected in 2023 (Identifier: NCT04774224)

Practice implications

The nature of family practice means that the family physician is on the frontline of changing the paradigm for approaching those at risk for and treating T1D. Just as Lauren's example implies, identifying individuals at risk for T1D and coordinating a treatment and follow-up care plan for families will become common in family practice. Currently, this rapidly expanding field involves being prepared to:

- Inform at-risk patients of the current state of research and opportunities for screening, staging, and treating if necessary. JDRF.org contains materials for distribution and review
- Determine who should be screened
  - First- and second-degree relatives of a person with T1D
  - Individuals who have family members with autoimmune disorders associated with T1D such as celiac disease, Crohn's disease, thyroiditis, rheumatoid arthritis, and systemic lupus
  - Individuals with type 2 diabetes who appear to be misdiagnosed. Measure the presence of glutamic acid decarboxylase (GAD) antibodies if the patient is normal weight for an adult. Elevated GAD can indicate late autoimmune diabetes of adults (LADA). Decide on the screening options you feel comfortable with recommending/performing using recommended laboratories or screening programs[28]
- Stage patients using laboratory results. Discuss the meaning and value of staging and follow-up steps, if any. Monitor using suggested tests if ≥2 autoantibodies are detected
- Discuss options to treat or not treat. Direct family members to organizations with important educational information (**TABLE 1**)
- Decide on practice capacity to administer a 14-day course of teplizumab infusions or refer patients to a specialty practice for treatment and follow-up

Rapidly changing and innovative technology, along with advances in DMTs, will soon provide more options for individuals at risk for and with early-onset T1D. This is an incredibly exciting and hopeful time for families and family physicians. ●

TABLE 1. Type 1 diabetes resources

Patient information:

- JDRF.org
  - T1Detect (screening for relatives age 2–45)
  - TrialNet.org (screening with no family history)
- Diabetes.org: camps for children with diabetes
- TCOYD.org
- diaTribe.org
- Type1tested.com
- Healthcare professional information: jdrf.org/t1d-resources/hcp/?. Includes: ask the expert, screening guidelines, education; TCOYD.org/cme-enduring
  - tzieldhcp.com

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