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Autoantibodies in Type 1 Diabetes

Robyn Houlden, MD, FRCPC

Introduction

Type 1 diabetes (T1D) is an autoimmune disease characterized by progressive destruction of pancreatic β cells. This process is mediated by both cellular (T lymphocyte) and humoral (autoantibody) immune responses. Although T cells play a central pathogenic role, autoantibodies are the earliest detectable markers of β cell autoimmunity and are instrumental in diagnosing and predicting disease progression.[1] Although T1D develops on a background of genetic risk, most individuals with genetic risk never develop type 1 diabetes. In contrast, virtually all individuals with 2 or more islet autoantibodies eventually develop type 1 diabetes.[2]

Major Islet Autoantibodies in T1D

Several well-characterized islet autoantibodies serve as key markers of T1D, and include[3]

- **Glutamic acid decarboxylase autoantibody (GAD 65 Ab, GADA)** – targets the GAD enzyme.
- **Insulin autoantibody (IAA)** – directed against insulin.
- **Insulinoma antigen-2 autoantibody (IA-2A) (also called islet cell autoantigen 512 [ICA512])** – directed against a tyrosine phosphatase-like protein.
- **Zinc transporter 8 autoantibody (ZnT8A)** – targets the ZnT8 protein on β cells.

Key features of these autoantibodies are summarized in **Table 1**. Measurement of all four autoantibodies is recommended with screening.[4] The prevalence of islet autoantibodies varies by ethnicity and region. For example, studies in India and China show lower frequencies of GADA of ~31 to 41%. ZnT8A and IA-2A frequencies are lower as well.[5] Specific HLA class II haplotypes influence susceptibility and prevalence of certain autoantibodies. For example, GADA is strongly associated with DR3-DQ2.5, and IAA and IA-2A are associated with DR4-DQ8.[6]

Risk Prediction and Disease Progression

The appearance of one or more islet autoantibodies typically precedes the clinical onset of T1D by months to years. The presence of multiple islet autoantibodies significantly increases the probability of progression. In a Diabetes TrialNet study of more than 2,300 older children and young adults (median age 16.2 years) who had a relative with T1D and also had multiple autoantibodies, 35% of individuals with normal glucose tolerance and 70% of those with abnormal glucose tolerance progressed to clinical T1D within five years, while others progressed over a longer time period.[7] A longitudinal cohort study, the Diabetes Autoimmunity Study in the Young (DAISY), followed 2,547 children with a high-risk HLA genotype (HLA-DR3/4) or a first-degree relative with T1D. Children with persistent IAA progressed more rapidly to clinical T1D: 100% progressed by 5.6 years, versus 63% in those with fluctuating IAA levels by 10 years.[8]

Clinical Applications of Islet Autoantibodies

In Latent Autoimmune Diabetes in Adults (LADA), autoantibodies can help distinguish from type 2 diabetes.[9] GADA, ICA, IA 2A, and ZnT8A may all be positive. GADA is especially prevalent in adult-onset autoimmune cases. However, it is important to recognize that approximately 5% of people with T1D are negative for the 4 major islet autoantibodies.[10] This is referred to as seronegative T1D, and may be caused by low autoantibody levels or novel antigens not covered by standard antibody panels.

Autoantibodies can also be used to stage individuals with T1D. A recent 2024 American Diabetes Association Consensus paper identified the following stages[11] **(Table 2)**:

- **At risk (pre-Stage 1):** Individuals have a single islet autoantibody or transient single autoantibody. They have normoglycemia and a normal A1C. They are asymptomatic.
- **Stage 1 diabetes (pre-clinical disease):** Individuals have ≥2 islet autoantibodies. They are asymptomatic and have normal glucose tolerance, but they have impaired C-peptide

Autoantibody	Approximate Prevalence at Diagnosis	Comments
GAD65 antibody (GADA)	~70–80%	Most common in adolescents and adults; less frequent in very young children. Strong association with slower progression.
Insulin autoantibody (IAA)	~40–60% overall; >70% in young children (<5 years)	Often the first autoantibody to appear in childhood. Frequency falls with increasing age at onset. It is present in 90% in children progressing to T1D before age 5 and drops to 40–50% in those older than 15. IAA must be measured within 2 weeks of beginning treatment with insulin. After that point, antibodies may be produced in response to exogenously administered insulin.
IA-2 antibody (IA-2A)	~50–70%	More frequent in children/teens; associated with rapid progression and higher risk of diabetic ketoacidosis (DKA).
Zinc transporter 8 antibody (ZnT8A)	~60–80%	Detected in both children and adults; adds diagnostic sensitivity, especially if GADA/IAA/IA-2A are absent.

Table 1. Major islet autoantibodies in T1D*; courtesy of Robyn Houlden, MD, FRCPC*

secretion compared with autoantibody-negative individuals. First-phase or early insulin secretion is impaired in response to intravenous or oral glucose administration; however, fasting insulin levels remain normal. This stage carries an approximate 70% risk of progression to Stage 3 T1D within 10 years and approaches a 100% risk over time.

- **Stage 2 diabetes (pre-clinical disease):** Individuals have ≥2 islet autoantibodies and dysglycemia or glucose intolerance. Individuals are asymptomatic. Impaired early phase insulin secretion results in increasing postprandial glucose values. Fasting glucose and A1C levels typically remain in the normal range.
- **Stage 3 diabetes (clinical disease):** Individuals have ≥1 islet autoantibody and meet diagnostic criteria for diabetes. Individuals are typically symptomatic. Most individuals continue to have significant insulin secretion, although the degree of preserved secretion varies. As a result, C-peptide is often not helpful at the time of diagnosis for distinguishing between T1D and T2D. Autoantibodies may disappear over time.[12]

Rationale for Screening for Diabetes-related Autoantibodies

Screening for islet autoantibodies, followed by appropriate metabolic monitoring, may reduce the likelihood of individuals presenting with severe hyperglycemia or diabetic ketoacidosis (DKA) with Stage 3 T1D. In high-income countries (North American, Western Europe, Australia), around 20 to 30% of children and adolescents with new onset of T1D present in DKA.[13] In adults, the rate is lower (typically 10 to 15%), since symptom recognition tends to be faster.[14] In low- and middle-income countries, rates can be much higher, often 40 to 80%, due to limited awareness and delayed access to care. Some sub-Saharan African studies report DKA in 70 to 80% of new diagnoses.[15] Several screening and monitoring programs have shown a significant decrease in the percentage of individuals presenting with DKA.[16]

Screening may also create an opportunity to provide early support and diabetes education allowing more time to accept a diagnosis of T1D.[17] Finally, screening and monitoring may facilitate access to disease-modifying therapy or clinical trials. For example, the anti-CD3 antibody teplizumab has been approved by Health Canada to delay progression from Stage 2 to Stage 3 T1D with a median delay of approximately 2 years.[18]

Whom to Screen

Two approaches to screening have been used in research and clinical settings.

Population-based screening initiatives such as the Fr1da study in Bavaria (Germany) and the Autoimmunity Screening for Kids (ASK) program in

Stage of TID	Islet Autoantibody Status	Glycemic Status
At risk (pre-stage T1D)	Single autoantibody or transient single autoantibody	Normoglycemia
Stage 1 T1D (presymptomatic)	≥2 autoantibodies	Normoglycemia
Stage 2 T1D (presymptomatic)	≥2 autoantibodies	Glucose intolerance or dysglycemia*
Stage 3 TID	≥1 autoantibody	Persistent hyperglycemia**

Table 2. Stages of T1D*; courtesy of Robyn Houlden, MD, FRCPC*

*2024 American Diabetes Association (ADA) Consensus Guidelines define as at least two of the following or meeting the same single criteria at two time points within 12 months: fasting plasma glucose 5.6–6.9 mmol/L; 120-min Oral Glucose Tolerance Test (OGTT) 7.8–11.0 mmol/L: OGTT values >11.1 mmol/L at 30, 60, and 90 min; A1C 5.7–6.4% or longitudinal > 10% increase in A1C from the first measurement with stage 2 T1D; capillary blood glucose (CGM) values >7.8 mmol/L for 10% of time over 10 days' continuous wear and confirmed by at least one other non-CGM glucose measurement test listed

** ADA Consensus Guidelines define as measured and confirmed by one or more of the following: one random venous glucose > 11.1 mmol/L with overt symptoms; 120-min OGTT >11.1 mmol/L and/or two random venous glucose >11.1 mmol/L and/or fasting plasma glucose >7 mmol/L and/or A1C >6.5%; CGM values >7.8 mmol/L for 20% of time over 10 days' continuous wear and confirmed by at least one other non-CGM glucose measurement test listed

Colorado, USA have shown the practical benefits of offering islet autoantibody testing to the general pediatric population. The Fr1da Study screened >90,000 children aged 2 to 5 years during routine pediatric visits.[19] The prevalence of multiple islet autoantibodies was ~0.3%. Children identified with presymptomatic T1D were enrolled in structured monitoring programs with regular glucose tolerance testing and education for the families. At clinical diagnosis, only ~5% of screened children presented with DKA compared with ~20 to 40% in unscreened children in the same region. They also had lower A1C and higher residual C-peptide, suggesting milder disease onset and better preserved β-cell function.

The ASK program targeted children aged 2 to 17 years, and offered islet autoantibody testing regardless of family history.[20] Around 1.7% of participants tested positive for ≥2 autoantibodies, similar to expected population prevalence. Families who receive positive results were offered close monitoring and education. ASK demonstrated high acceptability and demonstrated families valued early risk information. Children identified at risk who later developed Stage 3 T1D had substantially lower rates of DKA than those diagnosed without prior screening.

Family-based screening programs focus on first- and second-degree relatives of people with T1D through the age of 45 years. Antibody testing is most important during early childhood, as the rate of progression from multiple autoantibodies to clinical disease is more rapid in younger individuals. The most notable program is TrialNet Pathway to Prevention.[21] TrialNet has screened over 250,000 relatives worldwide, identifying many at presymptomatic stages. Relatives identified as autoantibody-positive are monitored regularly, significantly lowering the risk of DKA at diagnosis and allowing timely intervention. The 2025 ADA Standards of Care in Diabetes recommend that autoantibody-based screening for presymptomatic T1D should be offered to those with a family history of T1D or otherwise known elevated genetic risk.[22] In Canada, individuals with a relative with T1D can undergo autoantibody screening free of charge through Diabetes TrialNet (**https://www.trialnet.org/**) and Autoimmune Type 1 Diabetes Early Detection Program (**https://www.revvity.com/ca-en/category/autoimmune-type-1-diabetes-early-detection-program**).

Family-based programs maximize efficiency by focusing on high-risk groups, making them cost-effective and easier to integrate into existing healthcare systems. Population-based programs reach the majority of children who will eventually develop T1D, since ~85 to 90% of new diagnoses occur in those without a family history.[23] Although more resource-intensive, they are the only way to systematically identify this large group at risk. Both models have demonstrated that screening and follow-up substantially reduces the frequency and severity of DKA at onset, allow earlier initiation of insulin in a planned and less traumatic setting, and open the door to preventive therapies. **(Table 3)**

Monitoring of Islet Autoantibody Positive Individuals

The 2024 ADA Consensus Guidelines for monitoring islet autoantibody positive adults recommends the following management of single islet antibody positive adults[11]:

- Confirm persistent positivity with a second test
- Ensure other islet autoantibodies are negative.
- Annual metabolic monitoring may be considered if additional risk factors are present:
  - o First-degree relative with T1D
  - o Elevated genetic risk
  - o Dysglycemia (e.g., impaired fasting glucose or glucose tolerance)
  - o History of stress-induced hyperglycaemia
- If no additional risk factors, suggest monitoring every 3 years, similar to T2D at-risk adults.

The Consensus Guidelines recommend the following management of multiple autoantibody positive adults:

- Educate individuals on the importance of ongoing monitoring to prevent DKA.
- Provide written instructions with emergency contacts for symptoms of T1D or hyperglycemia.
- Confirm persistent multiple islet autoantibodies status with second test
- If confirmation is not possible, a single positive test for multiple islet autoantibodies is enough to initiate metabolic monitoring.
- If a previously multiple islet autoantibodies adult reverts to single or negative, continue monitoring.
- Provide self-monitoring of blood glucose tools for use during illness or symptoms.
- Monitor A1C annually. Adjust frequency based on age, autoantibody profile and glycemic trends

- If normoglycemia persists for 5+ years, monitoring every 2 years may be sufficient.

The ADA Consensus Guidelines provide detailed information on recommended monitoring for children and adolescents and readers are encouraged to refer to these when caring for this age group.[11]

Feature	Family-Based Screening (e.g., TrialNet)	Population-Based Screening (e.g., Fr1da, ASK)
Target group	First- and second-degree relatives of individuals with T1D	All children in a defined population, regardless of family history
Risk enrichment	~15-fold higher risk than general population	Includes majority of children who will develop T1D (85–90% of cases occur without family history)
Yield of multiple autoantibodies (≥2)	~3–5% of screened relatives	~0.3–0.5% of screened general children
Number needed to screen (NNS) to detect ≥2 IAb	Lower (more efficient due to enriched risk)	Higher (requires large-scale testing)
Major programs	TrialNet Pathway to Prevention (international, >250,000 relatives screened)	Fr1da (Germany) – >90,000 children screened; ASK (Colorado, USA) – 25,000+ screened and ongoing
Clinical outcomes at diagnosis	Lower diabetic ketoacidosis (DKA) rates compared to background population; diagnosis often anticipated	Dramatic reduction in DKA (e.g., 5% in Fr1da vs ~20–40% unscreened); lower A1C, higher C-peptide at onset
Access to monitoring and prevention	Structured follow-up; direct pipeline to prevention trials	Monitoring and education offered; enables access to prevention if therapy is available
Advantages	Cost-efficient, high-yield, lower resource burden; strong research infrastructure	Captures the majority of future T1D cases; population-wide health equity (doesn't miss those without family history)
Limitations	Misses ~85–90% of future T1D cases (no family history)	More resource-intensive; requires coordination with public health, schools, or primary care; cost-effectiveness still under study
Health system implications	Easier to implement in research or specialized settings; lower upfront costs	Potentially transformative for early diagnosis at the population level, but needs scalable infrastructure and funding

Table 3. Family-Based vs Population-Based Screening Programs in T1D*; courtesy of Robyn Houlden, MD, FRCPC*

Conclusion

Islet autoantibodies are important biomarkers used to identify individuals at risk of developing T1D. These autoantibodies target proteins found in the insulin-producing beta cells of the pancreas, signaling an autoimmune response. Screening for multiple islet autoantibodies, including GADA, IAA, IA-2, and ZnT8, can help detect early immune activity before clinical symptoms appear. The presence of two or more autoantibodies significantly increases the risk of progression to T1D. Early identification through autoantibody screening enables closer monitoring and reduces the risk of DKA and hyperglycemia with Stage 3 T1D. Screening may also create an opportunity to provide early support and diabetes education allowing more time to accept a diagnosis of T1D; and facilitate access to disease-modifying therapy or prevention trials. Family-based screening and population-based screening approaches have demonstrated clinical benefits. Guidelines are available to inform monitoring of single and multiple islet antibody positive individuals.

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