

Diabetes-Associated Autoantibodies

Diabetes mellitus (DM) refers to a group of metabolic disorders characterized by hyperglycemia that results from defects in insulin secretion, insulin action, or both. Type 1 DM (T1DM) is less common than type 2 DM (T2DM) and is characterized by insulin deficiency, often resulting from the autoimmune-mediated destruction of insulin-producing cells. The detection of diabetes-associated autoantibodies confirms an autoimmune etiology for that individual.

Indications for Insulin Antibody Testing

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- Do not order tests individually; order two or more antibodies if pursuing testing¹
- For most cases, order GAD in combination with ≥1 of the following antibodies: IA-2, IAA, ICA, ZnT8

T1DM	<ul style="list-style-type: none"> • Patient should have been previously diagnosed with DM <ul style="list-style-type: none"> ◦ Antibody testing is not useful for the diagnosis of DM ◦ Patients should ideally be receiving insulin ≤2 weeks <ul style="list-style-type: none"> ▪ Testing not recommended for patients receiving insulin >2 weeks, as insulin antibody formation may occur (false-positive result possible) • Most useful in children or in adults without traditional risk factors for T2DM <ul style="list-style-type: none"> ◦ Traditional risk factors include BMI ≥25 kg/m², first-degree relative with diabetes, high-risk race/ethnicity, physical inactivity, etc. (for a full list of traditional risk factors, see Table 2.3 in the Standards of Medical Care in Diabetes—2020). • May be useful in difficult adult cases to help differentiate between T1DM or T2DM³
T2DM	No indication for routine evaluation or management ¹
Screening	Acceptable only for first-degree relatives of a proband with T1DM or in research settings
Limited Use	<ul style="list-style-type: none"> • Differentiate LADA from T2DM⁴ • Rule out autoantibodies as a cause of DM in patients with suspected genetic DM types (eg, monogenic DM, maturity onset diabetes of the young [MODY])

GAD, glutamic acid decarboxylase antibody; IA-2, islet antigen-2; IAA, insulin antibody; ICA, islet cell cytoplasmic antibody; LADA, latent autoimmune diabetes of the adult; ZnT8, zinc transporter 8 antibody

Tests to Consider

Glutamic Acid Decarboxylase Antibody 2001771

Method: Semi-quantitative Enzyme-Linked Immunosorbent Assay

Use in combination with another insulin antibody test to determine autoimmune DM.

Islet Antigen-2 (IA-2) Autoantibody, Serum 3001499

Method: Quantitative Enzyme-Linked Immunosorbent Assay

Useful to establish autoimmune etiology in previously diagnosed T1DM.

Insulin Antibody 0099228

Method: Semi-Quantitative Radioimmunoassay

- Determine presence of antibodies to endogenous or exogenous insulin analogues
- Testing not recommended for patients receiving insulin >2 weeks, as insulin antibody formation may occur

Islet Cell Cytoplasmic Antibody, IgG 0050138

Method: Semi-Quantitative Indirect Fluorescent Antibody

Useful to establish autoimmune etiology in previously diagnosed T1DM.

Zinc Transporter 8 Antibody 2006196

Method: Semi-Quantitative Enzyme-Linked Immunosorbent Assay

Useful to establish autoimmune etiology in previously diagnosed T1DM.

See [Related Tests](#)



Prevalence

1.25 million in the United States

Age of Onset

Most common in children but can develop in individuals of any age, especially in late 30s or early 40s

Symptoms

- Excessive thirst, hunger, and urination
- Fatigue, nausea, blurred vision
- Unexplained weight loss
- Obesity is rare upon initial diagnosis
- May have other autoimmune disorders

Physiology

- Caused by autoimmune-mediated destruction of insulin-producing beta cells of the islets of Langerhans in the pancreas
- Five major autoantibodies of diagnostic interest
 - Glutamic acid decarboxylase (GAD)
 - Insulin antibodies (IAA)
 - Islet antigen-2 (IA-2)
 - Islet-cell antibodies (ICA)
 - Zinc transporter 8 (ZnT8)
- Antibodies may be present in individuals years before the onset of clinical symptoms
 - Presence in individuals with diabetes confirms an autoimmune etiology

Test Interpretation

Sensitivity/Specificity

Moderate sensitivity, high specificity in newly diagnosed T1DM

- Presence of antibodies may decrease with long-term disease
- Insulin antibody testing loses specificity once patient has been on exogenous insulin for >2 weeks

Results

- Presence of multiple insulin antibodies (GAD, IA-2, IAA, ICA, and ZnT8) is predictive of T1DM
- If one autoantibody is found, others should be assayed; the risk of T1DM increases (>90%) if an individual tests positive for two or more autoantibodies
- For further risk stratification, *HLA-DR* or *HLA-DQ* genotyping may be helpful

Limitations

- Negative test results do not rule out autoimmune diabetes; autoantibody response varies by individuals
- Presence of a single autoantibody in the absence of clinical symptoms has low predictive value (1-2% in healthy individuals)
- Not all individuals with antibodies will develop T1DM
- Do not use to monitor or diagnose T1DM
- IAA test does not differentiate between antibodies specific for endogenous and exogenous forms of insulin

References

1. Insel RA, Dunne JL, Atkinson MA, et al. [Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association](#). *Diabetes Care*. 2015;38(10):1964-1974. PubMed

2. American Diabetes Association. [Standards of Medical Care in Diabetes–2020](#). Arlington County, VA. [Published: Jan 2020; Accessed: Mar 2020]

3. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. [American Association of Clinical Endocrinologists and American College of Endocrinology - Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015](#). *Endocr Pract.* 2015;21 Suppl 1(Suppl 1):1-87. PubMed

4. Pieralice S, Pozzilli P. [Latent Autoimmune Diabetes in Adults: A Review on Clinical Implications and Management](#). *Diabetes Metab J.* 2018;42(6):451-464. PubMed



Additional Resources

National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. [Monogenic Diabetes \(Neonatal Diabetes Mellitus & MODY\)](#). [Accessed: Apr 2020]

Nilsson C, Ursing D, et al. [Presence of GAD antibodies during gestational diabetes mellitus predicts type 1 diabetes](#). *Diabetes Care.* 2007;30(8):1968-1971. PubMed

Related Information

[Diabetes Mellitus](#)

Related Tests

[Hemoglobin A1c 0070426](#)

Method: Quantitative Capillary Electrophoresis

[Glucose Tolerance Test 0020542](#)

Method: Quantitative Enzymatic

[Glucose, Plasma or Serum 0020024](#)

Method: Quantitative Enzymatic

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