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, which often results 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 tests for ≥2 antibodies if pursuing testing[1] - For most cases, order GAD in combination with ≥1 of the following antibodies: IA-2, IAA, ICA, ZnT8	
T1DM	Patient should have been previously diagnosed with DM - Antibody testing is not useful for the diagnosis of DM - Patients should be receiving insulin ≤2 wks, ideally - Testing is not recommended for patients receiving insulin >2 wks, as insulin antibody formation may occur (false-positive result possible) Most useful in children or in adults without traditional risk factors for T2DM - Traditional risk factors include excess weight/obesity (BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian individuals), a first-degree relative with diabetes, being a 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[2] It may be useful in difficult adult cases to help differentiate between T1DM or T2DM[3]
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	- Differentiate LADA from T2DM[4] - Rule out autoantibodies as a cause of DM in patients with suspected genetic DM types (eg, monogenic DM, 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; MODY, maturity-onset diabetes of the young; ZnT8, zinc transporter 8 antibody

Diabetes Mellitus Type 1 Overview

Prevalence

1.25 million in the United States

Featured ARUP Testing

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

- Use to determine presence of antibodies to endogenous or exogenous insulin analogues
- Testing is 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

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 at initial diagnosis)
- Possible co-occurring 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:
  - GAD
  - IAA
  - IA-2
  - ICA
  - ZnT8
- Antibodies may be present in individuals years before the onset of clinical symptoms.
  - A presence in individuals with diabetes confirms an autoimmune etiology.

Test Interpretation

Sensitivity/Specificity

Moderate sensitivity, high specificity in newly diagnosed T1DM

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

Results

- The 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 testing 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.

2. American Diabetes Association. Standards of Care in Diabetes–2023. [Published: Jan 2023; Accessed: Apr 2023]

3. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan-2022 update. Endocr Pract. 2022;28(10):923-1049.

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.

Related Information

Diabetes Mellitus - Type 1, Type 2, and Gestational