Diabetes-Associated Autoantibodies

Diabetes mellitus (DM) is 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

<table>
<thead>
<tr>
<th>Indications for Insulin Antibody Testing</th>
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<tbody>
<tr>
<td><strong>T1DM</strong></td>
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<tr>
<td>Patient should have diagnosed DM</td>
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<tr>
<td>Antibody testing is not useful for the diagnosis of DM</td>
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<td>Patients should ideally be receiving insulin ≤2 weeks</td>
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<td>• Testing not recommended for patients receiving insulin &gt;2 weeks, as insulin antibody formation may occur (false-positive result possible)</td>
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<tr>
<td>Most useful in children or in adults without traditional risk factors for T2DM (ADA, 2019)</td>
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<td>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—2019).</td>
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<tr>
<td>May be useful in difficult adult cases when it is unclear if patient has T1DM or T2DM (AACE, 2015)</td>
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| **T2DM Screening**                        |
| No indication for routine evaluation or management (Insel, 2015) |
| Acceptable only for first-degree relatives of a proband with T1DM or in research settings (ADA, 2019) |

| **Limited Use**                           |
| Differentiate LADA from T2DM (Pieralice, 2018) |
| 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

DIABETES MELLITUS TYPE 1 OVERVIEW

**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 of these antibodies 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 prolonged 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 in 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

American Diabetes Association. **Standards of Medical Care in Diabetes—2019.** Arlington County, VA [Accessed: Apr 2019]


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