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

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<tr>
<th>Indications for Insulin Antibody Testing</th>
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<tr>
<td>• Do not order individual antibody tests; order at least 2 antibodies if pursuing testing</td>
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<tr>
<td>• For most cases, use GAD in combination with ≥1 of the following antibodies: IA-2, IAA, ICA, ZnT8</td>
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T1DM

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<th>Patient should have diagnosed DM</th>
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<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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<td>• Most useful in children or in adults without traditional risk factors for T2DM</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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<td>• May be useful in difficult adult cases when it is unclear if patient has T1DM or T2DM</td>
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T2DM

| No indication for routine evaluation or management |
| Acceptable only for first-degree relatives of a proband with T1DM or in research settings |

Limited Use

| Differentiate LADA from T2DM |
| 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


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