Diabetes-Associated Autoantibodies

Indications for Ordering

- If pursuing antibody testing to determine autoimmune diabetes mellitus (DM), perform at least 2 antibody tests
  - In most cases, use glutamic acid decarboxylase antibody (GAD) in combination with another antibody test listed below
- Most useful to establish autoimmune etiology in previously diagnosed type 1 DM
- Do not use to differentiate type 1 from type 2 DM, for most cases

Test Description

- **Glutamic Acid Decarboxylase Antibody**
  - Semiquantitative enzyme-linked immunosorbent assay (ELISA)
- **Glutamic Acid Decarboxylase Antibody (GAD65) and Insulin Antibodies with Reflex to IA-2 Antibody**
  - Quantitative radioimmunoassay/quantitative ELISA
- **IA-2 Antibody (IA-2)**
  - Quantitative radioimmunoassay
- **Insulin Antibody (IAA)**
  - Quantitative radioimmunoassay
- **Zinc Transporter 8 Antibody (ZnT8)**
  - Semiquantitative ELISA
- **Islet Cell Cytoplasmic Antibody, IgG (ICA)**
  - Semiquantitative indirect fluorescent antibody

Tests to Consider

Primary tests

- Insulin antibody tests
  - **Glutamic Acid Decarboxylase Antibody 2001771**
  - **Glutamic Acid Decarboxylase Antibody (GAD65) and Insulin Antibodies with Reflex to IA-2 Antibody 2002862**
    - Panel test most useful to establish autoimmune etiology in previously diagnosed type 1 DM
    - If either GAD or IAA is negative, then IA-2 will be added
  - **IA-2 Antibody 0050202**
  - **Insulin Antibody 0099228**
    - Use to determine presence of antibodies to exogenous insulin analogues
    - Testing not recommended for patients receiving insulin >2 weeks, as insulin antibody formation may occur
  - **Zinc Transporter 8 Antibody 2006196**
  - **Islet Cell Cytoplasmic Antibody, IgG 0050138**

Related tests

- **Hemoglobin A1c 0070426**
- **Glucose Tolerance Test 0020542**
- **Glucose, Plasma or Serum 0020024**

Disease Overview

**Type 1 DM**

Prevalence

- Most common metabolic disease of childhood
  - 1/400-600 children and adolescents
  - ~5-10% of all diagnosed cases of diabetes in adults

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 when individual is first diagnosed
- 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
  - GAD
  - IA-2
  - IAA
  - ZnT8
  - ICA
- 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 type 1 DM
- 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, ZnT8, and ICA) is highly suggestive of type 1 DM
- If one autoantibody is found, others should be assayed
  - Risk of type 1 DM increases (>90%) if an individual tests positive for 2 or more autoantibodies
- For further risk stratification, HLA DR/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 type 1 DM
- Do not use to monitor or diagnose type 1 DM
- Insulin antibody RIA test does not differentiate between antibodies specific for endogenous and exogenous forms of insulin

References

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<tr>
<th>Indications for Insulin Antibody Testing</th>
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<td><strong>Do not order individual antibody tests; order at least 2 antibodies if pursuing testing (Insel, 2015)</strong></td>
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<tr>
<td><strong>For most cases, use GAD in combination with ≥1 of the following – IA-2, IAA, ZnT8, ICA</strong></td>
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<th>Type 1 DM</th>
<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 newly diagnosed DM in children &lt;18 years to establish autoimmune etiology (ADA, 2016; AACE, 2015)</td>
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<td>May be useful in difficult adult cases when it is unclear if patient has type 1 or 2 DM (Bingley, 2010)</td>
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| Type 2 DM | No indication for routine evaluation or management (Insel, 2015) |

| Screening | Not recommended for screening family members of patients with type 1 DM (so-called risk prediction) except in research settings (ADA, 2016) |

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<th>Limited Use</th>
<th>Latent autoimmune DM in adults (LADA)</th>
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<td>Differentiate LADA from type 2 DM (Lampasona, 2010; Stenström, 2005; Nambam, 2010)</td>
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| Genetic testing | Identify patients with DM for whom a genetic etiology is suspected (eg, monogenic DM, maturity onset diabetes of the young [MODY]) (Bingley, 2010; NIH, 2016) |
|                | Lack of antibodies suggests these genetic disorders |

| Gestational diabetes mellitus (GDM) | Screen women with history of GDM to identify those at high risk for progression to type 1 DM (Nilsson, 2007; de Leiva, 2007; Bingley, 2010) |
|                                      | No evidence to suggest test results alter outcomes or improve care when compared to intermittent hemoglobin A1c testing |

GAD = glutamic acid decarboxylase antibody, IA-2 = islet antigen-2, IAA = insulin antibody, ZnT8 = zinc transporter 8 antibody, CA = islet cell cytoplasmic antibody, DM = diabetes mellitus