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 (GAD) antibody in combination with another insulin antibody test listed below
- Most useful to establish autoimmune etiology in previously diagnosed type 1 DM (T1DM)
- Do not use to differentiate T1DM from type 2 DM (T2DM), for most cases

Test Description

Glutamic Acid Decarboxylase (GAD) 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)
- Semiquantitative radioimmunoassay

Insulin Antibody (IAA)
- Semiquantitative radioimmunoassay

Zinc Transporter 8 (ZnT8) Antibody
- Semiquantitative ELISA

Islet Cell Cytoplasmic Antibody (ICA), IgG
- Semiquantitative indirect fluorescent antibody

Tests to Consider

Primary tests
Insulin antibody tests

Glutamic Acid Decarboxylase Antibody 2001771
- Use in combination with another insulin antibody test to determine autoimmune DM

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 T1DM
- If either GAD or IAA is negative, then IA-2 will be added

IA-2 Antibody 0050202
- Useful to establish autoimmune etiology in previously diagnosed T1DM

Related tests

Diagnose and monitor DM and prediabetes

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

Disease Overview

T1DM

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 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, ZnT8, and ICA) is highly suggestive of T1DM
- If one autoantibody is found, others should be assayed
  - Risk of T1DM 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 T1DM
- Do not use to monitor or diagnose T1DM
- Insulin antibody RIA test does not differentiate between antibodies specific for endogenous and exogenous forms of insulin

References


Indications for Insulin Antibody Testing

- Do not order individual antibody tests; order at least 2 antibodies if pursuing testing (Insel, 2015)
- For most cases, use GAD in combination with ≥1 of the following antibodies – IA-2, IAA, ZnT8, ICA

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<tr>
<th>T1DM</th>
<th>T2DM</th>
<th>Screening</th>
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<td>Patient should have diagnosed DM&lt;br&gt;○ Antibody testing is not useful for the diagnosis of DM&lt;br&gt;○ Patients should ideally be receiving insulin ≤2 weeks&lt;br&gt;  ▪ Testing not recommended for patients receiving insulin &gt;2 weeks, as insulin antibody formation may occur (false-positive result possible)&lt;br&gt;○ Most useful in newly diagnosed DM in children &lt;18 years to establish autoimmune etiology (ADA, 2017; AACE, 2015)&lt;br&gt;○ May be useful in difficult adult cases when it is unclear if patient has T1DM or T2DM (Bingley, 2010)</td>
<td>No indication for routine evaluation or management (Insel, 2015)</td>
<td>Not recommended for screening family members of patients with T1DM (so-called risk prediction) except in research settings (ADA, 2017)</td>
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### Indications for Insulin Antibody Testing

**Limited Use**
- Latent autoimmune DM (LADA) in adults
  - Differentiate LADA from T2DM (Lampasona, 2010; Stenström, 2005; Nambam, 2010)
- 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 T1DM (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

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