

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

[Insulin Antibody 0099228](#)

- Use to determine presence of antibodies to endogenous or exogenous insulin analogues
- Testing not recommended for patients receiving insulin >2 weeks, as insulin antibody formation may occur

[Zinc Transporter 8 Antibody 2006196](#)

- Useful to establish autoimmune etiology in previously diagnosed T1DM

[Islet Cell Cytoplasmic Antibody, IgG 0050138](#)

- 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

- American Diabetes Association. Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018; 41 Suppl 1: S1-S159
- Bingley P. Clinical applications of diabetes antibody testing. J Clin Endocrinol Metab. 2010; 95(1): 25-33
- de Leiva A, Mauricio D, et al. Diabetes-related autoantibodies and gestational diabetes. Diabetes Care. 2007; 30 Suppl 2: S127-33
- Handelsman Y, Bloomgarden Z, et al. American Association of Clinical Endocrinologists and American College of Endocrinology - Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015; 21 Suppl 1: 1-87
- Insel R, Dunne J, 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): 1964-74
- Lampasona V, Petrone A, et al. Non Insulin Requiring Autoimmune Diabetes (NIRAD) Study Group. Zinc transporter 8 antibodies complement GAD and IA-2 antibodies in the identification and characterization of adult-onset autoimmune diabetes: Non Insulin Requiring Autoimmune Diabetes (NIRAD) 4 Diabetes Care. 2010; 33(1): 104-8
- Monogenic Forms of Diabetes: Neonatal Diabetes Mellitus and Maturity-onset Diabetes of the Young. National Institutes of Health. Bethesda, MD [Accessed: Feb 2016]
- Nambam B, Aggarwal S, et al. Latent autoimmune diabetes in adults: A distinct but heterogeneous clinical entity. World J Diabetes. 2010; 1(4): 111-5
- Nilsson C, Ursing D, et al. Presence of GAD antibodies during gestational diabetes mellitus predicts type 1 diabetes. Diabetes Care. 2007; 30(8): 1968-71
- Stenström G, Gottsäter A, et al. Latent autoimmune diabetes in adults: definition, prevalence, beta-cell function, and treatment Diabetes. 2005; 54 Suppl 2: S68-72

Indications for Insulin Antibody Testing	
<ul style="list-style-type: none"> • 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 	
T1DM	<ul style="list-style-type: none"> • Patient should have diagnosed DM <ul style="list-style-type: none"> ○ Antibody testing is not useful for the diagnosis of DM ○ Patients should ideally be receiving insulin ≤ 2 weeks <ul style="list-style-type: none"> ▪ Testing not recommended for patients receiving insulin >2 weeks, as insulin antibody formation may occur (false-positive result possible) • Most useful in newly diagnosed DM in children <18 years to establish autoimmune etiology (ADA, 2017; AACE, 2015) • May be useful in difficult adult cases when it is unclear if patient has T1DM or T2DM (Bingley, 2010)
T2DM	<ul style="list-style-type: none"> • No indication for routine evaluation or management (Insel, 2015)
Screening	<ul style="list-style-type: none"> • Not recommended for screening family members of patients with T1DM (so-called risk prediction) except in research settings (ADA, 2017)

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