MAYO CLINIC LABORATORIES

Test Definition: TSI

Thyroid-Stimulating Immunoglobulin, Serum

Overview

Useful For

Second-order testing for autoimmune thyroid disease, including:
-Differential diagnosis of etiology of thyrotoxicosis in patients with ambiguous clinical signs or contraindicated (eg, pregnant or breast-feeding) or indeterminate thyroid radioisotope scans
-Diagnosis of clinically suspected Graves disease (eg, extrathyroidal manifestations of Graves disease: endocrine exophthalmos, pretibial myxedema, thyroid acropachy) but normal thyroid function tests
-Determining the risk of neonatal thyrotoxicosis in a fetus of a pregnant female with active or past Graves disease
-Differential diagnosis of gestational thyrotoxicosis versus first-trimester manifestation or recurrence of Graves disease
-Assessing the risk of Graves disease relapse after antithyroid drug treatment

A combination of TSI / Thyroid-Stimulating Immunoglobulin, Serum and THYRO / Thyrotropin Receptor Antibody, Serum is useful as an adjunct in the diagnosis of unusual cases of hypothyroidism (eg, Hashitoxicosis).

Method Name

Recombinant Bioassay

NY State Available

Yes

Specimen

Specimen Type

Serum

Ordering Guidance

This test is used for second-order testing for autoimmune thyroid disease.

For suspected cases of autoimmune hypothyroidism, the first-order testing is TPO / Thyroperoxidase Antibodies, Serum.

For suspected cases of autoimmune thyroid disease, first-order testing includes TPO and THYRO / Thyrotropin Receptor Antibody, Serum.

Specimen Required

Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Collection Container/Tube:
Preferred: Red top
Acceptable: Serum gel
Submission Container/Tube: Plastic vial
Specimen Volume: 0.5 mL

Collection Instructions: Centrifuge and aliquot serum into a plastic vial.

Forms

If not ordering electronically, complete, print, and send a General Request (T239) with the specimen.

Specimen Minimum Volume

0.3 mL

Reject Due To

Gross hemolysis	Reject
Gross lipemia	OK
Gross icterus	OK

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Serum	Frozen (preferred)	60 days	
	Ambient	24 hours	
	Refrigerated	7 days	

Clinical & Interpretive

Clinical Information

Autoimmune thyroid disease is characterized by the presence of autoantibodies against various thyroid components, namely the thyrotropin (formerly thyroid-stimulating hormone: TSH) receptor (TSHR), thyroid-peroxidase (TPO), and thyroglobulin (Tg), as well as an inflammatory cellular infiltrate of variable severity within the gland. Among the autoantibodies found in autoimmune thyroid disease, TSHR autoantibodies are most closely associated with disease pathogenesis. All forms of autoimmune thyrotoxicosis (Graves disease, hashitoxicosis, neonatal thyrotoxicosis) are caused by the production of TSHR-stimulating autoantibodies. The role of the TPO and Tg autoantibodies in either autoimmune thyrotoxicosis or autoimmune hypothyroidism is less well established; they may merely represent epiphenomena. Detectable concentrations of anti-TPO antibodies are observed in most patients with autoimmune thyroid disease (eg, Hashimoto thyroiditis, idiopathic myxedema, and Graves disease).

Autoantibodies that bind and transactivate the TSHR lead to stimulation of the thyroid gland independent of the normal feedback-regulated TSH stimulation. These TSHR autoantibodies also are known as long-acting thyroid-stimulator or thyroid-stimulating immunoglobulins (TSI). Some patients with Graves disease also have TSHR-blocking antibodies, which do not transactivate the TSHR. The balance between TSI and TSHR-blocking antibodies, as well as their individual titers, are felt to be determinants of Graves disease severity. At least 20% of patients with autoimmune hypothyroidism also have evidence either of TSHR-blocking antibodies or, less commonly, TSI.

TSHR autoantibodies may be found before autoimmune thyrotoxicosis becomes biochemically or clinically manifest. Since none of the treatments for Graves disease aim at the underlying disease process, but rather ablate thyroid tissue

or block thyroid hormone synthesis, TSI may persist after apparent cure.

TSI are IgG antibodies and can, therefore, cross the placental barrier causing neonatal thyrotoxicosis.

First-order tests for autoimmune thyroid disease include TPO / Thyroperoxidase Antibodies, Serum (most suited for suspected cases of autoimmune hypothyroidism) and THYRO / Thyrotropin Receptor Antibody, Serum. Thyrotropin receptor antibody (TSHR-antibody) is a binding assay that detects both TSI and TSHR-blocking autoantibodies; it can be used instead of this TSI assay for most applications, as long as the results are interpreted in the clinical context. The TSHR-antibody test has a shorter turnaround time than the TSI assay, is less expensive, and if interpreted within the clinical context, has excellent correlation with the TSI assay. Specific detection of TSI is accomplished by this second-order bioassay.

Reference Values

< or =1.3 TSI index
Reference values apply to all ages.

Interpretation

The sensitivity and specificity of an elevated thyroid-stimulating immunoglobulins (TSI) index for Graves disease diagnosis depends on whether patients have clinically active, untreated disease or disease treated with antithyroid drugs. Using a TSI index of 1.3 as the cutoff level in newly diagnosed, untreated patients, the sensitivity and specificity are higher than 90%. For a higher cutoff of 1.8, specificity approaches 100%, but sensitivity decreases somewhat. In patients with inactive or treated Graves disease the specificity is similar, while sensitivity is lower, ranging from 50% to 80%.

Significant neonatal thyrotoxicosis is likely if a pregnant woman with a history of Graves disease has a TSI index above 3.9 during the last trimester, regardless of her remission status. Lesser elevations are only occasionally associated with neonatal thyrotoxicosis. This is particularly relevant for women who have previously undergone thyroid-ablative therapy or are on active antithyroid drug treatment and therefore, no longer display biochemical or clinical evidence of thyrotoxicosis.

Gestational thyrotoxicosis, which is believed to be due to a combination of human chorionic gonadotropin cross-reactivity on the thyrotropin receptor (TSHR) and transient changes in thyroid hormone protein binding, is not associated with an elevated TSI index. Finding an elevated TSI index in this setting suggests underlying Graves disease.

An elevated TSI index at the conclusion of a course of anti-thyroid drug treatment is highly predictive of relapse of Graves disease. However, the converse, a normal TSI index, is not predictive of prolonged remission.

In patients with thyroid function tests that fluctuate between hypo- and hyperthyroidism or vice versa, a clearly elevated TSHR-antibody level (>25%) and a simultaneous TSI index that is normal or only minimally elevated (1.3-1.8) suggest a diagnosis of possible Hashitoxicosis.

Cautions

Positive results are strongly indicative of Graves disease but do not always correlate with the presence and severity of hyperthyroidism.

Patients with Hashimoto disease may have an elevated thyroid-stimulating immunoglobulins (TSI) index, which can be

above 1.8. A TSI index of above 1.3 and less than or equal to 1.8 also is occasionally observed in various other thyroid disorders, including nodular goiter, and subacute thyroiditis.

Supportive Data

Pediatric data is based on a Mayo study of 50 male and 50 female children between the ages of 10 days and 18 years.

Clinical Reference

1. Grebe SKG. Thyroid disease. In: King RA, Rotter JI, Motulsky AG, eds. The Genetic Basis of Common Diseases. 2nd ed. Oxford University Press; 2002:397-430
2. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26(10):1343-1421. doi:10.1089/thy.2016.0229
3. Kahaly GJ, Bartalena L, Hegedus L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018;7(4):167-186
4. Lytton SD, Schluter A, Banga PJ. Functional diagnostics for thyrotropin hormone receptor autoantibodies: bioassays prevail over binding assays. Front Biosci (Landmark Ed). 2018;23(11):2028-2043
5. De Leo S, Pearce EN. Autoimmune thyroid disease during pregnancy. Lancet Diabetes Endocrinol. 2018;6(7):575-586
6. Stan MN, Algeciras-Schimnich A, Murthy V, Thapa P, Araki N. Diagnostic utility of a new assay for thyroid stimulating immunoglobulins in Graves' disease and thyroid eye disease. Thyroid. 2022;32(2):170-176. doi:10.1089/thy.2021.0299

Performance

Method Description

This bioassay compares the cyclic adenosine monophosphate (cAMP) production of thyrotropin (TSH)-responsive cells upon exposure to patient serum with that obtained in the same cells after exposure to normal control serum.

The assay uses Chinese hamster ovary cells that have been permanently transfected with the human TSH receptor (TSHR) and a luciferase expression construct under the control of a cAMP responsive promoter. Luciferase transcription in these cells is proportional to the concentration of intracellular cAMP.

The cells are grown to near confluence. An aliquot of cells is then incubated with each diluted patient serum. Cells are lysed at the end of incubation, luciferase substrate is added, and chemiluminescence is measured in a luminometer. The ratio of the light-units produced in the cell-lysate exposed to patient serum divided by a control cell-lysate light-signal is the TSI index.(Preissner CM, Wolhuter PJ, Sistrunk JW, Homburger HA, Morris JC III. Comparison of thyrotropin-receptor antibodies measured by four commercially available methods with a bioassay that uses Fisher-rat thyroid cells. Clin Chem. 2003;49(8):1402-1404; package insert: Thyroid Stimulating Immunoglobulin Assay. Diagnostic Hybrids; PI4035011EN00, 10/2020)

PDF Report

No

Day(s) Performed

Monday through Friday

Report Available

2 to 6 days

Specimen Retention Time

3 months

Performing Laboratory Location

Mayo Clinic Laboratories - Rochester Superior Drive

Fees & Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

This test has been cleared, approved, or is exempt by the US Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

CPT Code Information

84445

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
TSI	Thyroid-Stimulating Immunoglob, S	30567-2

Result ID	Test Result Name	Result LOINC® Value
8634	Thyroid-Stimulating Immunoglob, S	30567-2