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Comparison between thyroid stimulating immunoglobulin and TSH-receptor antibodies in management of Graves' orbitopathy

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Introduction

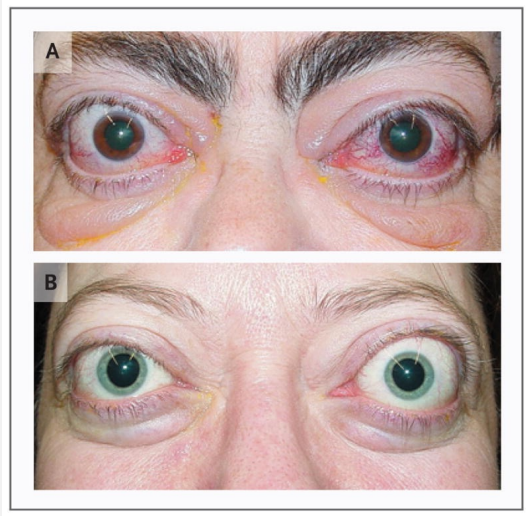
- Graves´ disease (GD) is an autoimmune disease caused by TSH-receptor antibodies (TRAb).
- TRAb bind to the TSH-receptor (TSH-R) and activate the cAMP signal transduction pathway.
- TSH-receptor stimulating immunoglobulin (TSI) is a subtype of TRAb which lead to stimulation of thyroid hormone production.
- Other types of antibodies block the action of TSH-R, TSH-R-binding inhibitory immunoglobulins (TBII), while others are neutral without any functional effect.

- Graves´ orbitopathy (GO) is clinically relevant in approximately 50% of patients with GD , with severe forms affecting 3–5% of patients.

- In patients without clinically apparent ophthalmopathy, radiological signs of muscle enlargement have been found in 40%.

- The risk of GO has been linked to TSH receptor stimulation, high TRAb levels, smoking, low levels of thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TgAb).

- Severe forms of GO may cause irreversible eye complications and in some severe cases can even threaten vision.



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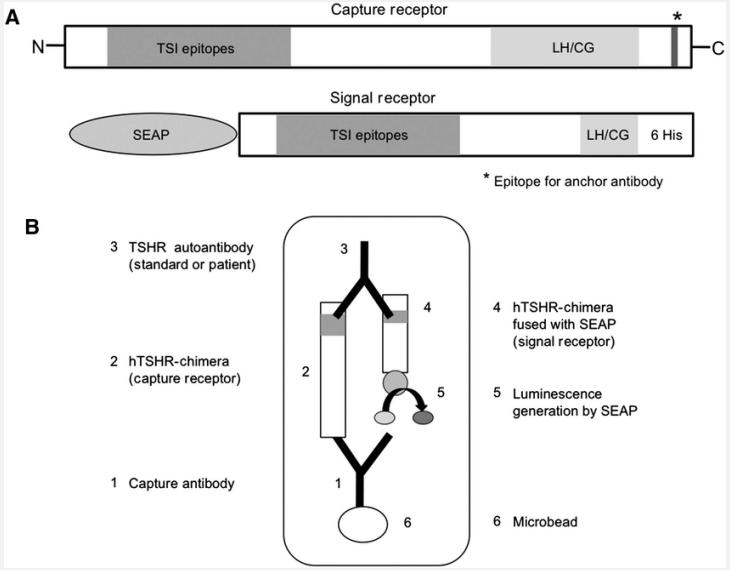
- Delay in the diagnosis is associated with worse prognosis of GO.
- Therefore, there is an increased need for a scoring system that includes different markers for prediction and assessment of GO.
- Measurement of TRAb is a standard method for confirmation of diagnosis, monitoring of therapy and prediction of remission or relapse in patients with GD.
- A potential pitfall of using TRAb is that the method measures all antibodies, including blocking and neutral antibodies.

The IMMULITE® 2000 TSI assay

- The IMMULITE® 2000 TSI assay utilizes two recombinant human TSH receptor (hTSHR) chimeras for the capture and detection of thyroid-stimulating autoantibodies.
- The capture receptor is constructed by replacing the major epitope for TBI binding with amino acid sequence from rat luteinizing hormone-choriogonadotropin (LH-CG) receptor.
- The signal chimera uses N-terminus amino acids of hTSHR conjugated to alkaline phosphatase (AP).
- The clinical sensitivity of IMMULITE TSI in a study was 96.8%, Anti-TSHR was 96.8%, and THYRETAIN 91.2%. The clinical specificity of the IMMULITE TSI was 98.6%, Anti-TSHR 97.3% and THYRETAIN 99.3%.



Tozzoli R, D'Aurizio F, Villalta D, Giovanella L. Evaluation of the first fully automated immunoassay method for the measurement of stimulating TSH receptor autoantibodies in Graves' disease. Clin Chem Lab Med. 2017 Jan 1;55(1):58-64. doi: 10.1515/cclm-2016-0197. PMID: 27331310.

J Appl Lab Med. 2017 Nov 1;2(3):345-355. doi: 10.1373/jalm.2017.024067.

Analytical and Clinical Validation of Two Commercially Available Immunoassays Used in the Detection of TSHR Antibodies

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Affiliations + expand

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- Thyretain thyroid-stimulating immunoglobulin (TSI) Bioassay by Diagnostic Hybrids and 2 commercially available immunoassays: the TSI Bridge immunoassay by Siemens and the thyroid-stimulating hormone receptor antibody (TRAb) immunoassay by Roche.

- Results: equivalent performance in patients with untreated Graves disease.

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ORIGINAL PAPER

Diagnostic accuracy of Immulite® TSI immunoassay for thyroid-associated orbitopathy in patients with recently diagnosed Graves' hyperthyroidism

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- 140 participants recruited, 75 (53.6%) had TAO.
- The Immulite® TSI levels were higher among those with than those without TAO
- There was no correlation between TSI level and inflammatory index score (ρ = 0.14, 95% CI - 0.03, 0.30) or clinical severity (p = 0.527) among those with TAO.
- TSI level showed poor diagnostic accuracy for TAO (area under the receiver operating characteristic curve 0.60, 95% CI 0.51, 0.70).
- Although Immulite® TSI level was higher in the presence of TAO, it showed poor diagnostic accuracy and no correlation with clinical markers of TAO severity or activity.

Materials and Methods

- Thirty patients with *de novo* GD were recruited at the Uppsala University Hospital.

- GD diagnosis was based on decreased levels of TSH and sero-positivity for TRAbs. In one patient, the TRAb levels were below the reference range (1.7 IE/L, reference <1.75). This patient otherwise had symptoms, laboratory findings and homogenously increased uptake on thyroid scintigraphy in line with GD.

- Median age of the study cohort was 55 years (range 35-72 years). Two were smokers, 29 were women.

- The study consisted of 6 visits at baseline, 6 weeks, 12 weeks, 6 months, 12 months and 24 months from diagnosis.
- At each visit, blood was sampled to measure TSH, fT4, fT3, TRAb and TSI. All 30 patients received conventional block and replace treatment.
- 3 patients underwent total thyroidectomy (2 neutropenia and 1 pregnancy wish) and five patients received RAI during the study period. These patients were not included in the longitudinal analyses.
- All other patients (n=22), except 1 patient with spontaneous recovery received ATD for 18 months.

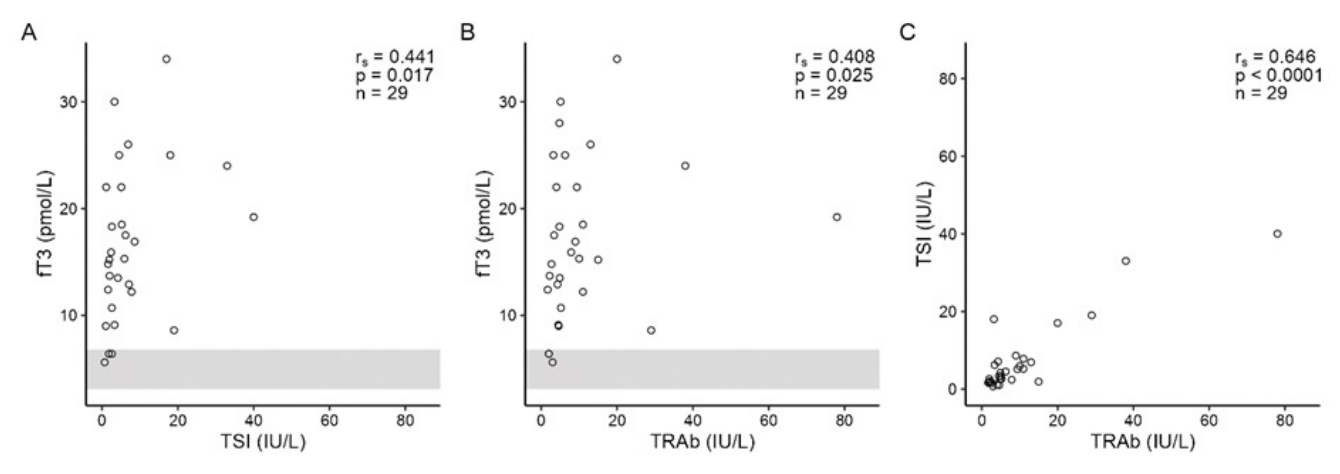
GO was identified by clinical signs and symptoms according to EUGOGO guidelines

Classification	Features
Mild GO	Patients whose features of GO have only a minor impact on daily life that have insufficient impact to justify immunomodulation or surgical treatment. They usually have one or more of the following: • minor lid retraction (<2 mm) • mild soft-tissue involvement • exophthalmos • <3 mm above normal for race and gender • no or intermittent diplopia and corneal exposure responsive to lubricants
Moderate-to-severe GO	Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have two or more of the following: • lid retraction ≥ 2 mm • moderate or severe soft-tissue involvement • exophthalmos ≥ 3 mm above normal for race and gender • inconstant or constant diplopia
Sight-threatening (very severe) GO	Patients with dysthyroid optic neuropathy and/or corneal breakdown

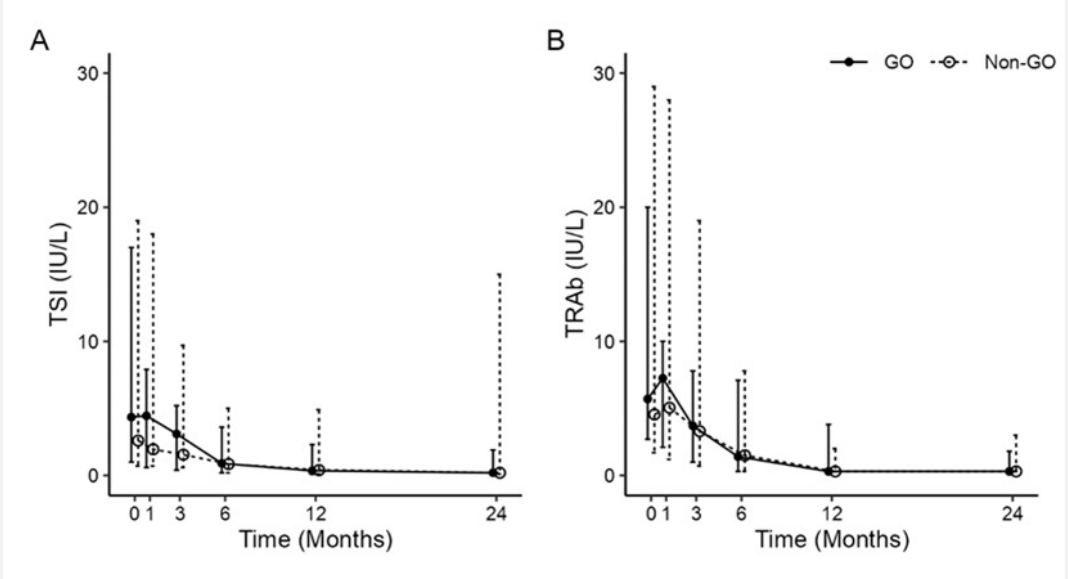
Results

- For all subjects, fT3 correlated to both TSI (r_s=0.44, p= 0.01) and TRAb (r_s=0.4 p= 0.02) at baseline (n=30).

- TSI was highly correlated with TRAb at baseline (r_s=0.64, p<0.001)



- 17 patients were diagnosed with GO at baseline (n=11) or during the study follow-up period (n=6).
- TSI and TRAb did not differ significantly at baseline between GO and non-GO patients (GO:non-GO=17:13)
- Both TRAb and TSI did not differ significantly at follow-up (n=22, GO:non-GO=12:10) and were similarly reduced and normalized in both groups during follow-up.



Conclusion

TSI levels were not different in subjects with GO. This study does not support any added benefit of TSI compared to TRAb for prediction and management of GO.