Epidemiology of Thyroid-stimulating immunoglobulin in Recent Onset Symptomatic Thyroid Eye Disease

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Running Head: TSI in Thyroid eye disease

Abbreviations: EGO=Euthyroid Graves’ Ophthalmopathy, IRB= Institutional Review Board, IVMP=Intravenous methylprednisolone, TED= Thyroid Eye Disease, TSH=Thyroid stimulating hormone, TSI=Thyroid Stimulating immunoglobulin
Abstract:

Purpose:

This study aims to report correlations between thyroid-stimulating immunoglobulin (TSI) and both clinical and radiological parameters in recent-onset symptomatic thyroid eye disease (TED) patients.

Methods:

A prospective cohort study of TED patients managed at the Chinese University of Hong Kong from January 2014 to May 2022. Serum TSI levels were determined with the functional assay. Outcomes included the clinical activity score (CAS), marginal reflex distance1 (MRD1), extraocular muscle motility restriction (EOMy), exophthalmos, and diplopia. The radiological assessment included cross-sectional areas and signal of extraocular muscles on STIR-sequence MRI.

Results:

A total of 255 (197 female) treatment-naïve patients, with an average onset age of 50±14 years, were included. Elevated pre-treatment TSI level was observed in 223(88%) patients. There was a weak positive correlation between TSI and CAS (r=0.28, \( P=0.000031 \)), MRD1 (r=0.17, \( P=0.0080 \)), and the size of the levator palpebrae superioris/superior rectus complex (r=0.25, \( P=0.018 \)). No significant correlation existed between TSI and STIR signals. The AUC and optimal cut-off value for clinical active TED were 0.67(95% confidence interval:0.60-0.75) and 284% (specificity:50%, sensitivity:85%). 64 patients received intravenous methylprednisolone (IVMP) during the study interval, and they had a higher baseline TSI level than those who did not have IVMP(\( P=0.000044 \)). Serial post-IVMP TSI among the 62 patients showed a significant reduction compared to the baseline.
level \( (P<0.001) \). Both the baseline and post-IVMP TSI levels, and percentages of TSI changes were comparable between patients who responded and non-responded to the first course of IVMP.

Conclusion:

TSI can be a serum biomarker for the diagnosis, prognosis, and treatment response of TED. Further validation should be warranted.
Introduction:

Thyroid eye disease (TED), also known as thyroid-associated orbitopathy or Graves’ ophthalmopathy, is the most common extrathyroidal manifestation of Graves’ disease. It can also occur in euthyroid patients, known as euthyroid Graves’ ophthalmopathy (EGO). TED is an autoimmune inflammatory orbital disorder with a biphasic clinical course that begins with active inflammation followed by a chronic fibrotic phase. Prompt immunosuppressive treatment is recommended to suppress the inflammation during the inflammatory phase to reduce both the disease activity and severity. The pathogenesis involves orbital inflammatory infiltration, adipogenesis, and hyaluronan production. A presumed mechanism is the activation of orbital fibroblast by autoantibodies that results in tissue fibrosis.

Increased expression of thyroid stimulating hormone (TSH) receptors has been found in the orbital tissue of TED patients, and TSH receptor antibodies (TRAbs) are recognized to have a pivotal role in the pathogenesis. According to their properties, TRAbs can be subdivided into thyroid-stimulating antibodies, thyroid-blocking antibodies, and neutral antibodies. Thyrotropin binding inhibitor immunoglobulin (TBII) assay is the conventional method, and it does not differentiate between the TRAbs subtypes. TBII level is closely related to Graves’ disease, however, the relationship with TED is inconsistent. Another assay is the functional thyroid-stimulating immunoglobulin (TSI) bioassay which mainly detects the thyroid-stimulating antibody subtype. Despite TSI is more closely related to the disease activity and severity than TBII, the clinical implications and correlations are not fully understood.
This study correlates the TSI levels with both clinical and radiological parameters and determines their clinical values in the management of TED.

Methods:

We conducted a prospective cohort study including 255 TED patients managed at the Thyroid Eye Clinic at The Chinese University of Hong Kong from 1 January 2014 to 31 May 2022. Written informed consent was obtained from all the patients in this study. This study followed the Declaration of Helsinki and ethical, and ethical approval was obtained from the Institutional Review Board: Kowloon Central /Kowloon East Cluster Research Ethics Committees (10-0218/ER-3 and 2010_594). We included patients who met the following inclusion criteria:

1) TED patients with pre-treatment TSI level.\textsuperscript{17}
2) No concurrent orbital disorders.
3) Patient age ranges from 18 to 75 years.
4) The venous blood sample was collected for a functional TSI bioassay.
5) Patients who were recruited in this study were followed up for at least 12 months.

Outcome measures:

Clinical Activity Score (CAS) was used to assess the disease activity clinically.\textsuperscript{18} Gorman diplopia score was used to score diplopia: (1) no diplopia, (2) gaze-evoked diplopia, (3) intermittent primary-gaze diplopia, and (4) constant primary-gaze (intractable) diplopia.\textsuperscript{19} Extraocular motility (EOMy) restriction was scored according to the position of the limbus in 9 cardinal gaze photos. We scored 0 for the full excursion and −5 for failure to reach the midline (−4 to −1 for an excursion in 25% increments).\textsuperscript{20} Exophthalmos was measured by the Hertel exophthalmometer.\textsuperscript{21}
Eyelid positions were documented using margin reflex distance (MRD): MRD1 - defined as the distance between the upper lid margin to the central corneal light reflex. Ophthalmic examination were performed by two ophthalmologists in every visit.

MRI was performed on a whole-body 3T magnet (Achieva TX, Philips Healthcare, Best, the Netherlands) using a standard 8-channel head coil covering both eyes for signal reception. The scanning sequence for the orbit consisted of coronal contrast enhanced STIR (TR/TE: 4800/80 ms; TI: 200 ms; NEX: 2; matrix 281 x 300) and coronal non-contrast T1-weighted (TR/TE: 641/13 ms; NEX: 1; matrix 239 x 300). All images were acquired using a slice thickness of 3 mm, a slice gap of 0.3 mm, and a field-of-view of 180 mm. Images were analyzed using a Philips DICOM Viewer (R3.0-SP13, Philips Medical Systems Nederland B.V.).

Two trained research assistants independently segmented the cross-sectional areas of both lacrimal glands and extraocular muscles on a T1-weighted image of the worse affected eye clinically. The average area from the 3 consecutive measurements was used for data analysis. The Short Tau Inversion Recovery (STIR) sequence signal, which provides useful measure of TED activity radiologically, was measured by comparing the signal intensity of individual EOM and lacrimal gland with the ipsilateral temporalis muscle of the worst affected eye clinically to give the signal intensity ratio (SIR). The highest SIR value among the 3 consecutive slices was used for data analysis.

Intravenous methylprednisolone (IVMP) was indicated in progressive moderate to severe TED with CAS greater than 3 or radiological evidence of active disease. The 12-weekly IVMP regimen treatment protocol was prescribed in patient with active TED.
disease clinically or radiologically: six weekly 500mg IVMP succinate diluted in 500ml normal saline for slow infusion over 2 hours, followed by 6-weekly infusions of 250mg IVMP succinate diluted in 250ml normal saline for slow infusion over 1 hour. Oral immunosuppressant (including methotrexate and mycophenolate mofetil) was optionally prescribed during the 12-weekly IVMP treatment to patients with moderate to severe disease. Patients were assessed every 4 weeks in those who received IVMP course, and repeated TSI assessment was arranged within the 12 weeks post first course of IVMP. In patients with mild inactive disease, we would follow up every 6 months.

The venous blood sample was collected at the Thyroid Eye Clinic. TSI level was measured using the TSI bioassay (Quest Diagnostic Hybrids, San Juan Capistrano, CA). According to the manufacturer’s instructions. The bioassay utilizes genetically engineered Chinese hamster ovary (CHO) cells expressing TSH receptors and a luciferase reporter gene induced by cAMP. If the TSH receptor is stimulated by TSI in patient serum, the TSH receptor signaling increases intracellular cAMP and induces luciferase enzyme activity which is measured by the luminescence. Results were considered positive if the specimen-to-reference ratio is greater or equal to 140%.

The results were expressed as mean ± standard deviation (SD). The baseline and post-treatment TSI levels were compared using paired T-test. The diagnostic performance of TSI for clinical active TED was evaluated using area under the curve (AUC) of receiver-operating characteristic (ROC) curve, and optimal clinical cut-off value was determined using maximization of Youden index. The correlation between TSI and both clinical and radiological parameters (worse affected eyes) was measured using Spearman correlation. Multiple testing corrections using the
Bonferroni algorithm were implemented to address the risk of type 1 errors. We set the significance threshold at 0.05. For example if 5 comparisons are made, we would adjust the threshold level to 0.05/5 = 0.01. All statistical analyses were performed using SPSS statistical software package (Windows version 24.0; IBM Corp., Armonk, NY).

Results:

A total of 255 (197 female) treatment naïve TED patients were included in this study. All patients were ethnically Han Chinese, average TED onset 50±14 years old (range, 29 to 90 years old). The average follow up was 32±2 months. The average presenting CAS was 1.5±1.4. Elevated pre-treatment TSI level was observed in 223 (88%) patients, and the average baseline TSI level was 301±131% among all patients. The background and initial clinical presentation information were summarized in Table 1.

There were weak positive correlated the baseline TSI level with the clinical parameters and found weak positive correlations with CAS (r=0.28, P=0.000031), and MRD1 (r=0.17, P=0.0080). (Figures 1 and 2) For exophthalmos (r=0.14, P=0.023), there was no significant correlations with TSI after Bonferroni correction. (Table2) The area under the curve (AUC) and optimal cut-off value for clinical active TED were 0.67 (95% confidence interval: 0.60 to 0.75) and 284% (Specificity: 50% and sensitivity: 85%).

Correlation between baseline TSI level and size of the of the levator palpebral superioris /superior rectus complex was 0.25 (P=0.018). No significant correlation between TSI and SIRs of other extraocular muscles. (Table 3)

In our cohort, 62 patients received 12-weekly intravenous methylprednisolone (IVMP) and 18 of them also received oral immunosuppressant. (Table 4) The post-
IVMP TSI levels assessed within 3 months after the first course of IVMP showed a significant reduction from 357±97% to 239±125% (P<0.001). The baseline TSI level among the 62 TED patients who received IVMP was higher than those who did not receive IVMP. (352 ±98 % versus 273±137%, P=0.000044). Both the baseline and post-treatment TSI levels (Baseline: 325±120% versus 359±87%, P=0.14, Post-IVMP: 232±141% versus 224±120% P=0.42), and percentage of TSI changes (-28±34% versus -29±58%, P=0.48) were similar between the 14 patients who required additional IVMP, and the 48 patients who didn’t require additional IVMP after the first course. Among the 193 patients who did not receive IVMP, only 12 had repeated TSI at 12±10 months, and the percentage of TSI change was -28±25%, which was similar to the 62 patients who received IVMP (-29±30%, P=0.49) (Figure3).

Discussion:
This cross-sectional follow-up study reports the TSI levels in 255 treatment naïve TED patients. Up to 88% of patients presented with an elevated baseline TSI level. Our results show a significant positive correlation between the baseline TSI and both disease activity (CAS) and severity (MRD1, exophthalmos, and size of the levator palpebrae superioris/superior rectus). However, the relationship is weak. In addition, patients who received IVMP were associated with a higher TSI level than those who did not require IVMP. The optimal cut-off value for clinical active TED was 284%. There was a reduction of TSI following the course of IVMP. Importantly, no difference in both baseline and post-treatment TSI levels, and percentage of TSI changes between those who responded and not responded to the first course of IVMP.
The pathogenesis of TED involved orbital inflammatory infiltration, de novo adipogenesis, and glycosaminoglycan synthesis. Both TSH receptors and insulin growth factor-1 (IGF-1) receptor overexpressed in the orbital tissue. The activation of TSH receptors can enhance the hyaluronic acid synthesis in orbital fibroblast and promote adipogenesis. TSH receptors expression was found higher during the active phase of the disease. TRAbs has been suggested as one of the key autoantigens in TED, as it was elevated in most of the TED patients, and those with EGO. An elevated TRAb level was found associated with TED after the diagnosis of Graves’ disease, and persistent high TRAb levels were associated with the severity of TED.

Conventionally, serum TRABs are detected using the TBII immunoassay which does not differentiate the TRAbs subtypes. The functional TSI bioassay can detect only the functional thyroid-stimulating antibody. Noh et al reported in a study of Japanese patients showed correlation of TED severity with TSI, and not with TBII. In an earlier study on Korea patients, there were more active and severe TED patients with predominant TSI than patients with predominant TBII. Ponto had previously reported in European patients that the correlation was stronger between TED parameters and TSI than with TBII. On the contrary, Khamisi et al did not show additional benefit of using TSI compared to the conventional TRAb assay in a Japanese study. A systematic review revealed that the discrepancies in the relationship between TBII and TSI could be due to ethnic differences. The relationship between TED and TBII seems to be stronger in Asian patients. Meanwhile, TSI was associated with both Asian and Caucasian TED patients.

STIR sequence suppresses the fat signal and becomes hyperintense with fluid-filled tissues. Hyperintensity on the STIR sequence gives an objective assessment of the
disease activity in TED patients. Mukasa et al studied the TRAb level using the third-generation assay and found no correlation with the STIR signals on MRI, which is comparable to our study that the TSI level does not correlate with radiological activity. Also in Japanese patients, an elevated TSI level was associated with proptosis but not extraocular muscle. Ko et al recently reported that TSI was significantly correlated with the NOSPECS score in a cohort of Korean patients. Jeon et al reported a cross-sectional study included 101 patients with TED and found the TSI level was higher among males patients and smokers, and the TSI level was inversely correlated with the duration of ocular symptoms. Ponto et al reported that TSI level can help to identify patients with DON of recent onset requiring urgent treatment. East Asian TED patients are associated with a lower presenting CAS, and less common eyelid involvement when compared to Caucasian patients. The predictive value of disease activity using CAS is unclear in the Asian population. This may explain the positive correlations between CAS and TSI was relatively weak from our study.

Serial measurements of TSI may help to evaluate the disease prognosis. There are some notable studies on Korean patients. Ko et al reported that the TSI level decreased at 1-year follow-up regardless of the treatment received. Lee et al reported that both TRAb and TSI levels dropped after receiving IVMP among 57 TED patients, and both antibodies correlated with restoration of chorioretinal capillary perfusion. Another recent Korean study reported a diminished decline of both TRAb and TSI levels in TED patients who are non-responsive to IVMP. On the contrary, our study did not show any difference in both the baseline and post-IVMP TSI levels between those IVMP responders and non-responders, which is comparable to the study reported by Bluszcz et al that no difference in both TRAbs
and TSI baseline levels between those IVMP responders or non-responders in Polish patients. The predictive value of TSI in the treatment response of TED patients is unclear, and the discrepancies in results among different groups may be due to the undersized studies. The clinical implications of TED should be further explored with a bigger sample size and in different ethnic groups.

Our data may serve as a reference for correlations between TSI and clinical and radiological parameters in ethnic Han Chinese TED patients. There are several limitations in the present study. Firstly, long-term changes in TSI levels in the TED patients are still to be assessed. Secondly, TSI was ordered in 255 patients among our TED cohort without 1500 patients, and further study with bigger sample size would be warrant to increase the power of the result. Thirdly, our study used the average STIR of both the extraocular muscles and lacrimal gland, hotpot was not applied. Fourthly, the correlation between disease parameters and other serological markers such as TBII was not reported.

In summary, up to 88% of patients exhibited elevated pre-treatment levels of TSI. There was weak positive correlation between TSI and both disease activity and severity. Our data suggest that TSI may serve as a useful biomarker for diagnosis, monitoring treatment response, and guiding the management of TED. Further research is needed to validate these findings.
References:


31) Lantz M, Planck T, Asman P, Hallengren B. Increased TRAb and/or low anti-TPO titers at diagnosis of graves' disease are associated with an increased


Legends:

Figure 1: Correlation between thyroid stimulating immunoglobulin and presenting clinical activity score.

Figure 2: Correlation between thyroid stimulating immunoglobulin and presenting marginal reflex distance 1.

Figure 3: The change of thyroid stimulating immunoglobulin in patients who received/did not receive intravenous methylprednisolone.
Figure 1: Correlation between thyroid stimulating immunoglobulin and presenting clinical activity score.

136x88mm (144 x 144 DPI)
Figure 2: Correlation between thyroid stimulating immunoglobulin and presenting marginal reflex distance 1:

Legend: Marginal reflex distance 1: the distance between the upper lid margin to the central corneal light reflex
Figure 3: The change of thyroid stimulating immunoglobulin in patients who received/did not receive intravenous methylprednisolone.

Legend: IVMP = intravenous methylprednisolone.
Table 1: Demographic and background information of the thyroid eye disease patients. Data are presented as \( n \), \( n \) (%) or mean ±S.D.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>255</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50±14</td>
</tr>
<tr>
<td>Female</td>
<td>195 (76%)</td>
</tr>
<tr>
<td>Ex/chronic smoker</td>
<td>43 (17%)</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>6±3</td>
</tr>
<tr>
<td>EGO</td>
<td>7(3%)</td>
</tr>
<tr>
<td>Antithyroid treatment†</td>
<td>248</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>30</td>
</tr>
<tr>
<td>Radioactive iodine</td>
<td>21</td>
</tr>
<tr>
<td>Clinically active: Clinically inactive</td>
<td>53:202</td>
</tr>
<tr>
<td>TSI (%)* #</td>
<td>301±131</td>
</tr>
<tr>
<td>Free T4 (pmol/L)** #</td>
<td>22±29</td>
</tr>
<tr>
<td>Free T3(pmol/L)**#</td>
<td>7.6±9.5</td>
</tr>
<tr>
<td>TSH(mIU/L)#</td>
<td>0.6±0.8</td>
</tr>
<tr>
<td>CAS</td>
<td>1.5±1.4</td>
</tr>
<tr>
<td>MRD1 (mm)</td>
<td>5.3±1.7</td>
</tr>
<tr>
<td>EOMy</td>
<td>1.8±1.0</td>
</tr>
<tr>
<td>Diplopia</td>
<td>0.7±0.8</td>
</tr>
<tr>
<td>Exophthalmos(mm)</td>
<td>19±3</td>
</tr>
<tr>
<td>Mild^</td>
<td>88</td>
</tr>
<tr>
<td>Moderate to severe^</td>
<td>157</td>
</tr>
<tr>
<td>DON</td>
<td>10 (4%)</td>
</tr>
</tbody>
</table>

Legends: Age= Age of TED onset, CAS= Clinical activity score, Diplopia= Gorman diplopia scale, DON= Dysthyroid optic neuropathy, Duration= Duration from ocular symptom to consultation, EGO=Euthyroid Graves’ Ophthalmopathy, EOMy=Extraocular motility restriction, F=female, GD= Graves’ disease, MRD1=Marginal reflex distance 1, No.=Number, Proptosis= Exophthalmometer reading of the most protruding eye, TED=Thyroid eye disease, TSI=Thyroid Stimulating immunoglobulin, TSH=Thyroid stimulating hormone

*Reference range of TSH=0.27 to 4.20 mIU/L, **Reference range of Free T4=7.9-14.4 pmol/L, ***Reference range of Free T3=3.8-6.0 pmol/L

†Carbimazole/PTU/methimazole; # Tested in the first ophthalmic consultation (Only 31% of the patients in euthyroid state on presentation); ^ according to the EUGOGO criteria
Table 2: The correlations between clinical parameters and TSI in n=255 patients/eye.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Correlation with TSI (r)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS</td>
<td>0.26</td>
<td>0.000031**</td>
</tr>
<tr>
<td>MRD1</td>
<td>0.17</td>
<td>0.0080**</td>
</tr>
<tr>
<td>EOMy</td>
<td>0.11</td>
<td>0.082</td>
</tr>
<tr>
<td>Diplopia</td>
<td>0.034</td>
<td>0.63</td>
</tr>
<tr>
<td>Proptosis</td>
<td>0.14</td>
<td>0.023</td>
</tr>
</tbody>
</table>

**Legends:** CAS= Clinical activity score, Diplopia= Gorman diplopia scale, EOMy=Extraocular motility restriction, MRD1=Marginal reflex distance Proptosis= Exophthalmometer reading of the most protruding eye, TED=Thyroid eye disease, TSI=Thyroid Stimulating immunoglobulin

**=Statistically significant with P<0.01 after Bonferroni correction.
Table 3: The correlations between radiological parameters and TSI in n=90 patients/eyes.

<table>
<thead>
<tr>
<th>Radiological parameters</th>
<th>Correlation with TSI (r)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR SIR</td>
<td>0.18</td>
<td>0.088</td>
</tr>
<tr>
<td>MR SIR</td>
<td>0.17</td>
<td>0.10</td>
</tr>
<tr>
<td>IR SIR</td>
<td>0.15</td>
<td>0.16</td>
</tr>
<tr>
<td>LR SIR</td>
<td>0.12</td>
<td>0.25</td>
</tr>
<tr>
<td>LG SIR</td>
<td>-0.028</td>
<td>0.79</td>
</tr>
<tr>
<td>SR Size</td>
<td>0.25</td>
<td>0.018**</td>
</tr>
<tr>
<td>MR Size</td>
<td>0.036</td>
<td>0.74</td>
</tr>
<tr>
<td>IR Size</td>
<td>0.20</td>
<td>0.061</td>
</tr>
<tr>
<td>LR Size</td>
<td>-0.084</td>
<td>0.43</td>
</tr>
<tr>
<td>LG Size</td>
<td>0.025</td>
<td>0.82</td>
</tr>
</tbody>
</table>

**Legends:** IR=Inferior rectus, LG=Lacrimal gland, LPS=Levator Palpebrae superioris, LR=Lateral rectus, MR=Medial rectus, SR=Superior Rectus, SIR=Signal intensity ratio

**=Statistically significant with P<0.005 after Bonferroni correction.
**Table 4:** Background information of the thyroid eye disease patients who did and did not receive intravenous methylprednisolone.

<table>
<thead>
<tr>
<th></th>
<th>IVMP</th>
<th>Without IVMP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>62</td>
<td>193</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53±12</td>
<td>44±14</td>
</tr>
<tr>
<td>Female</td>
<td>41</td>
<td>154</td>
</tr>
<tr>
<td>Ex/chronic smoker</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>5±3</td>
<td>6±3</td>
</tr>
<tr>
<td>EGO</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>CAS</td>
<td>1.9±1.2</td>
<td>1.0±1.2</td>
</tr>
<tr>
<td>MRD1 (mm)</td>
<td>5.6±1.7</td>
<td>5.2±1.6</td>
</tr>
<tr>
<td>EOMy</td>
<td>1.6±1.3</td>
<td>1.3±0.9</td>
</tr>
<tr>
<td>Diplopia</td>
<td>1.3±1.1</td>
<td>0.5±0.7</td>
</tr>
<tr>
<td>Exophthalmos (mm)</td>
<td>19.6±1.8</td>
<td>19.0±1.6</td>
</tr>
</tbody>
</table>

**Legends:** Age = Age of TED onset, CAS = Clinical activity score, Diplopia = Gorman diplopia scale, Duration = Duration from ocular symptom to consultation, EGO = Euthyroid Graves’ Ophthalmopathy, EOMy = Extraocular motility restriction, F = female, GD = Graves’ disease, MRD1 = Marginal reflex distance 1, No. = Number, Proptosis = Exophthalmometer reading of the most protruding eye, TED = Thyroid eye disease.