Journal of Endocrinological Investigation (2018) 41:1457–1468
https://doi.org/10.1007/s40618-018-0945-6

ORIGINAL ARTICLE

Usefulness of TSH receptor antibodies as biomarkers for Graves' ophthalmopathy: a systematic review

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Received: 6 July 2018 / Accepted: 10 August 2018 / Published online: 7 September 2018

Abstract

Purpose Over the past several decades, many papers have been published about the usefulness of thyrotropin receptor antibodies (TRAbs) as biomarkers of Graves' ophthalmopathy (GO). However, results have been inconsistent. The purpose of this analysis is to determine a possible cause of these discrepancies and to examine the usefulness of TRAbs as biomarkers for GO, especially 'thyrotropin-binding inhibiting immunoglobulin (TBII)' and 'thyroid-stimulating antibody (TSAb)'.

Method 26 articles discussing the association between TRAbs and GO were selected which were then divided into three groups based on the study method and whether or not the patients had been treated for hyperthyroidism. From the results of the papers reviewed, a provisional conclusion was made and a theoretical model on the TBII–TSAb coordinate plane was developed to confirm that conclusion.

Results TSAb is reported to be significantly or strongly associated with GO in the studies of pre- and post-treated patients for hyperthyroidism. TBII is positively correlated, negatively correlated or uncorrelated with GO in studies of pre-treated patients. However, it is generally agreed upon that TBII and GO are closely correlated in studies of post-treated patients.

Conclusion We conclude that the level of TBII may not be a reliable indicator of the current state of GO in pre-treated patients. Whereas, in post-treated patients, due to changes in the correlation between TBII and TSAb due to the effect of hyperthyroidism treatment, the level of TBII can be a more reliable indicator of GO. Furthermore, the current level of TBII is closely associated with the onset and severity of GO in the future and it can be a valid predictor of GO. However, the TSAb level appears to be more reliable.

Keywords Graves' ophthalmopathy · TBII · TSAb · TRAb

Introduction

Elevated expression of thyroid-stimulating hormone (TSH) receptor in orbital tissues in patients in the active stage of Graves' ophthalmopathy (GO) seems to support the important role of TSH receptor antibodies (TRAbs) in the pathogenesis of GO [1–3]. TRAbs are subdivided into thyroid-stimulating antibody (TSAb), thyroid-blocking antibody (TBAb), and neutral antibody (Neutral Ab) according to their functional effects. Unknown antibodies (Unknown Abs) may also be included [4]. Of these TRAbs, TSAb is known to be a direct parameter in GO [5, 6] as well as in Graves' hyperthyroidism [7]. On the other hand, TBAb is responsible for hypothyroidism, by blocking the activity of TSAb or TSH [8–10] and it has been reported that it exhibits a blocking effect on the signals caused by TSAb in the orbital tissue [6]. Neutral Abs are known to have no functional influence when bound to the TSH receptor [11, 12]. However, it has recently been found to have a more significant role than was expected, such as regulating selective signaling cascades and inducing apoptosis in thyroid epithelial cells [13].

Currently, two different assays are used to detect TRAbs. The first is the thyrotropin-binding inhibitory immunoglobulin (TBII) assay, also called a 'ligand' or 'competition-based' assay. The TBII assay detects immunoglobulins that inhibit the binding of labeled TSH (1st and 2nd generation) or M22 (3rd generation, M22: monoclonal human TSHR-stimulating antibody) to the purified

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or recombinant TSH receptor, allowing quantification of TRAbs. This technique does not distinguish between stimulating, blocking or no functional effect on the thyroid gland [4]. It is believed that TRAbs assessed by the TBII assay are mostly TSAb and TBAb [14], although it is possible the other two types of TRAbs are also included. Despite being useful in the diagnosis of Graves' disease (GD), displaying a sensitivity of 90–99% and specificity of 90–100% [15, 16], there is no consensus on the relationship between TBII and GO in the articles reviewed.

The second assay is known as a 'biological' or 'cell-based' TRAb assay and it can distinguish between TSAb and TBAb through their effect on cAMP or luciferase production in a cell line transfected with the TSH receptor [4]. A close relationship between the TSAb levels and the prevalence, activity and severity of GO was reported in several papers among hyperthyroid [17–32], euthyroid [33, 34] and hypothyroid [35, 36] patients. These observations seem to suggest that TSAb can be considered as a functional biomarker for thyroid-associated ophthalmopathy regardless of the functional thyroid status. However, it should be noted that the TSAb bioassays are costlier, technically more demanding, and less accessible than the TBII assays [37].

It is more difficult to assess TBAb than TSAb, and its value can be altered by the presence of TSAb [9]. Regarding its relationship with GO, which has been less thoroughly investigated, there are indications that all patients with GO are negative for TBAb [24] and for patients with higher TSAb/TBAb ratio, their GO is more active [38]. One study obtained a conflicting result, stating that patients with GO had higher TBAb levels [39]. Therefore, more detailed studies are needed to clarify this relationship.

Regarding TSAb and TBII, several studies mention the close association between TSAb and GO; however, few mention a close association between TBII and GO. This is likely due to the heterogeneity of TBII, as in the analytical result of the TBII assay blocking, neutral or unknown antibodies may be included alongside TSAb. These other antibodies do not appear to be positively or negatively correlated to GO. Furthermore, it is possible that there are similar cases because despite TSAb occupying a quantitatively a large part of TBII, it may fail to function due to its defects. However, some studies [23, 30, 40–42] suggest that TBII is an independent or powerful biomarker for GO. Therefore, the current review will focus on finding a possible cause of these discrepancies and will evaluate the usefulness of TBII as a biomarker for GO, which is currently widely used as a tool for diagnosis and monitoring of GD in many clinical laboratories.

Materials and methods

To collect published data related to GO and the above-mentioned biomarkers, we performed an initial search in the PubMed database using the following combination of words and logical operators:

(Graves' ophthalmopathy OR Graves' orbitopathy OR thyroid associated ophthalmopathy OR thyroid associated orbitopathy OR thyroid eye disease) AND (TRAb OR TSAb OR TBII OR Thyrotropin receptor OR TSH receptor OR thyroid stimulating OR thyrotropin binding)

The search was restricted to articles published from 1999 to the present (July, 2018) to obtain relatively recent articles. With this restriction we found 585 articles. Among these items only those who met the following criteria were included: (1) more than 20 patients who have hyperthyroidism or who previously had hyperthyroidism were included in the study; (2) analyzed the association between TSAb/TBII with prevalence, activity and severity of GO; (3) no children were included. As Shibayama et al. [43] suggested that the correlation between TSAb and TBII is different from adults to children pre-treated patients (as children have a stronger TBII–TSAb correlation than adults), the articles including children [43–45] were excluded; (4) patients treated with radioactive iodine were excluded [46, 47] (these papers are mentioned in the discussion).

After the exclusion criteria were applied, 26 core articles out of the 585 found in PubMed were selected. Within the selected articles, there was great heterogeneity regarding the type of study, selected patients, criteria for evaluation of activity and severity of GO, etc. However, they were then classified according to the type of study (non-follow-up and follow-up), and whether the studies were performed with pre-treated patients for hyperthyroidism or post-treated patients in the following manner:

Group 1: (7 articles) non-follow-up studies (cross-sectional) that were performed with pre-treated patients for hyperthyroidism or performed when the patients were diagnosed with hyperthyroidism

Group 2: (9 articles) non-follow-up studies (cross-sectional) that were performed with post-treated patients for hyperthyroidism (some studies involving both treated and untreated patients were included in this group)

Group 3: (10 articles) follow-up studies

One article [48] included both a cross-sectional study and a follow-up study, therefore it was included in groups

1 and 3. Article [32] was not included in any group as it was not specified whether the study involved pre- or post-treated patients. Once this was done, the analysis of the reported studies was carried out as follows. First, the conclusions of each article were reviewed, and the possible causes of discrepancies were analyzed. Second, to illustrate the discrepancies among the articles, a theoretical model on the TBII–TSAb coordinate plane based on the reported data was developed (these data included the changes in TBII and TSAb before and after hyperthyroidism treatment). Finally, the results of the reviewed articles were fed to the model and the outcome was presented. Figure 1 illustrates how this review was developed.

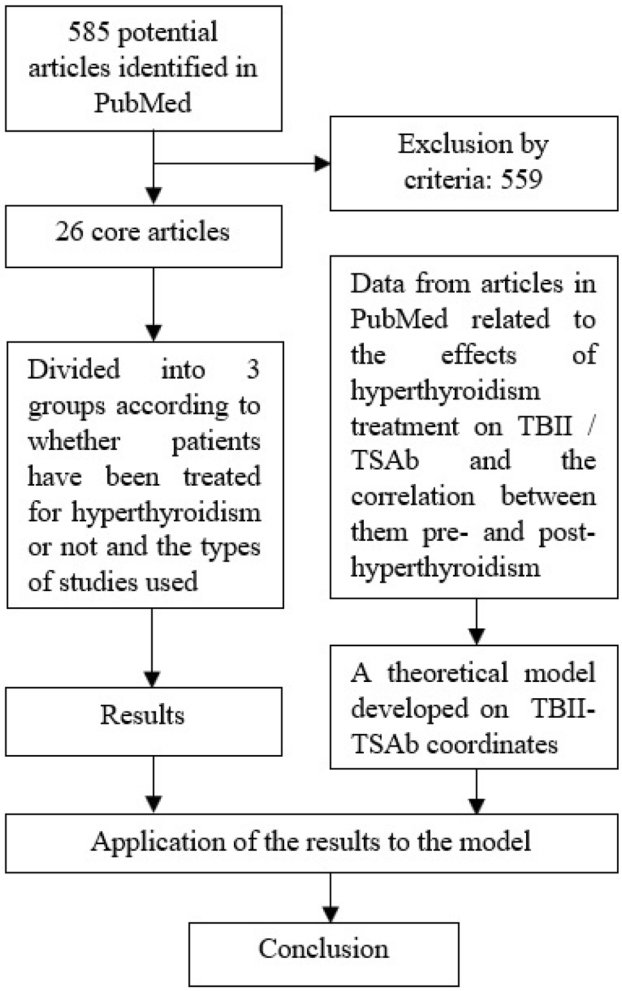


Fig. 1 Flow diagram of the method used to perform this review

Results

Table 1 shows the list of core articles found in the search and their characteristics, grouped as mentioned above. The main conclusions of the collected articles are the following.

First, all studies (Group 1, 2, 3) that used the TSAb assays [17–32] concluded that the TSAb level and the prevalence, severity or activity of GO are significantly or strongly associated.

Second, in pre-treated patients (Group 1), the TBII level is positively [48–50], negatively [17, 51] and not associated [18, 19] with GO.

Third, in post-treated patients in the cross-sectional studies (Group 2), TSAb and TBII are strongly positively correlated with each other [20, 23, 24, 26] and both TSAb and TBII levels are positively associated with GO, but TSAb is a better indicator [20–22, 25]. On the contrary, Woo et al. [28], state that TBII is not associated with GO; however, it should be noted that this is likely due to the small sample size (50).

And finally, in the follow-up studies (Group 3), both TSAb and TBII [30, 40–42, 48, 52, 53] are associated with GO onset and severity.

Utility of TSAb and TBII

TSAb, TBII and GO and provisional conclusion

In summary, according to the articles reviewed, TSAb is strongly or significantly associated with GO in pre- and post-treated patients (Group 1, 2, 3), whereas the association between TBII and GO is variable (positively, negatively or not associated) in pre-treated patients (Group 1). In treated patients (Group 2, 3), it is generally agreed upon that TBII and GO are closely correlated. Thus, the discrepancies in the association between TBII and GO may be attributed to differences in whether the studies were conducted on pre-treated or post-treated patients. It can also be deduced that the relationship between TBII and GO depends on the correlation between TBII and TSAb. That is, before hyperthyroidism treatment, there is no correlation or a weak correlation between TSAb and TBII, but after treatment, there is a stronger correlation. TBII may then be a more reliable indicator or predictor of GO than previously, although TSAb is more effective. To verify this idea, we have developed a theoretical model to explain the effect of hyperthyroidism treatment on the correlation between TBII, TSAb and GO.

Table 1 Comment or conclusion of the articles reviewed on TBII and TSAb

Article	Patients	Comment on TBII/TSAb
Group 1: studies with pre-treated patients for hyperthyroidism (cross-sectional)		
Tanda et al. [48]*	255 only with GD (no GO), 91 GO	With respect to patients with no GO**, serum TBII*** levels were significantly higher in patients with mild GO ($p=0.005$) or moderate-to-severe or sight-threatening GO ($p=0.02$), with no significant differences between the latter two groups
Vos et al. [49]	259 GD	Serum TBII was positively correlated to the prevalence of GO
Laurberg et al. [50]	208 GD	A positive but rather weak correlation was found between TBII in serum and the major clinical manifestation of Graves' disease (TBII correlated with the presence of eye signs and symptoms of GO ($r=0.15$, $p=0.036$))
Goh et al. [17]	31 GO 71 GD	TSAb emerged as the strongest independent predictor of GO, while TBII emerged as an independent negative predictor of EOM (extraocular myopathy) and lid retraction
Mukasa et al. [51]	238 GO	The TBII titers were significantly higher in the inactive-GO group than in the active-GO group
Khoo et al. [18]	57 only with GD 43 with GO + GD	TSAb is an independent biomarker of GO. Prevalence of GO appeared to be higher in those with the highest as well as lowest TBII values
Noh et al. [19]	115 GO	TSAb levels significantly correlated with GO severity score, while TBII is not correlated with GO
Group 2: studies with post-treated patients for hyperthyroidism (cross-sectional)		
Jang et al. [20]	317 GO (D****: 7 months)	GO is more active and severe in patients with predominant TSAb than in patients with predominant TBII. TBII and TSAb are strongly correlated. TBII is positively correlated with GO*****
Lytton et al. [21]	45 only with GD 155 with GO + GD (D: 8 months)	Strong positive correlations of TSAb with both CAS (clinical activity score) and CSS (clinical severity score) as well as weaker correlations of two independent TBII assays with CAS or CSS were noted
Ponto et al. [22]	108 GO (D: no present)	The ophthalmic parameters of GO correlated with both TSAb and TBII levels, but TSAb has a stronger correlation with GO
Gerding et al. [23]	63 with GO euthyroid post-treatment (D: 20 months)	TBII and TSAb titres were strongly related to each other. A striking and highly significant correlation between CAS and both TBII and TSAb
Kampmann et al. [24]	101 with GO euthyroid post-treatment (D: N)	TBII and TSAb are strongly correlated. TSAb is widely present in GO and closely correlate with disease severity.
Jang et al. [25]	155 GO (D: N)	Both TSAb and TBII yielded results that were significantly positively correlated with CAS, but the TSAb bioassay was superior
Eckstein et al. [26]	239 GO (D: N)	TBII and TSAb are strongly correlated. Even after anti-inflammatory therapy, TBII and TSAb levels and prevalence still correlate with the severity and activity of GO
Stein et al. [27]	536 GD (D: no present, but within 12 months)	Of the 261 individuals with undetectable TSAb levels, 19 (7.3%) manifested GO. Of the 275 individuals with greater than 130% detectable levels of TSAb, 50 (18.2%) developed GO ($p<0.001$)
Woo et al. [28]	50 GO euthyroid post-treatment (D: 52 months)	TSAb was significantly correlated with NOSPECS score. However, TBII was not associated
Group 3: follow-up studies		
Wiersinga et al. [40]	348 GD (D: 0–18 months)	TBII is one of the independent determinants as predictors of GO development
Tanda et al. [48]*	255 only with GD (not GO), 91 GO (D: 0–18 months)	Among patients with mild GO at baseline, serum TBII levels were significantly lower in those whose GO improved than in those whose GO did not improve after 18 months of treatment with ATD (antithyroid drug)

Table 1 (continued)

Article	Patients	Comment on TBII/TSAb
Jarusaitiene et al. [52]	130 juveniles with GD (D: 0–72 months)	TBII concentrations at diagnosis were found to be significantly higher in the GO (+) compared to GO (−)
Takakura et al. [29]	33 GD (D: 0–20 months)	TSAb > 400 SRR % at diagnosis of GD is associated with an elevated risk of developing GO
Lantz et al. [53]	399 GD (D: 0–67 months)	TBII > 6.3 IU/L at diagnosis of GD is associated with an elevated risk of developing GO
Yoshioka et al. [54]	45 GD following total thyroidectomy (D: 0–12 months)	The presence of GO were significantly associated with prolonged half-lives of the serum TBII values
Orgiazzi et al. [41]	392 GD (D: 0–18 months)	Higher TBII is one of the independent initial factors of GO development
Eckstein et al. [42]	159 GO (D: 12–24 months)	Patients with mild GO had low level TBII, and patients with severe GO had high level TBII. TBII is an independent risk factors for GO
Jang et al. [30]	112 GO (D: 7–24 months)	The predictive power of the TBII assay was equivalent to that of the TSAb bioassay in predicting severe patient disease outcome
Dragan et al. [31]	23 GO (D: N)	A statistically significant correlation between the change in TSAb and change in TAOS (thyroid-associated orbitopathy scale) score
Ohtsuka et al. [32]	43 GO******	The serum levels of TSAb in the subgroup of patients with proptosis were significantly higher than those in the subgroup of patients without proptosis

* Two types of studies were carried out: a cross-sectional study at diagnosis of GD and a follow-up study; **since most of the above papers were for patients with Graves' disease, instead of TAO (thyroid-associated orbitopathy)/TED (thyroid eye disease) we use the term GO; ***in many papers TBII assay is called TRAb assay. However, TSAb and TBAb bioassays are also a kind of TRAb assays from a functional point of view, so in this review we refer to it as TBII assay rather than TRAb assay to eliminate the confusion of terms; ****mean or median duration of hyperthyroidism treatment/duration of GD after diagnosis/duration of follow-up; *****when calculated from the data shown on the paper, the groups (2, 4) with the higher TBII level had higher CAS, NOSPECT score and Active GO;******it was not included in any group since whether they performed with pre- or post-treated patients was not mentioned

A theoretical model developed

First, the difference in correlation between TBII and TSAb in pre-treated and in post-treated GD patients must be examined. An exhaustive search in PubMed was performed without any criteria of exclusion to find as many relevant correlations as possible.

Weak correlation has been reported in pre-treated adult GD patients, [18]: $r = 0.21$, [33]: 0.34 [55]:0.26, [56]:0.40, [57]:0.48, [58]:0.30, [59]:0.31, [60]:0.33, [61]:0.47, [62]: 0.52, [63]:0.58. A similar weak degree of correlation was observed in earlier experiments conducted using the porcine receptor and rat thyrocytes [11, 64]. However, Shibayama et al. [43] reported a strong correlation ($r = 0.80$, $p < 0.001$) in pre-treated children GD patients and mentioned that TBII was significantly correlated with ophthalmopathy. Whereas in the treated adult GD patients, stronger correlation has been reported, [20]: $r = 0.67$, [23]:0.62, [24]: 0.54, [26]: 0.65, [60]: 0.56 (6 months after therapy), [62]: 0.55 as well as in the relapse group: 0.70, [63]:0.62, [65]:0.88 (in hyperthyroidism patients several years after therapy).

To explain these different correlations before and after treatment and the relationship between the correlations and

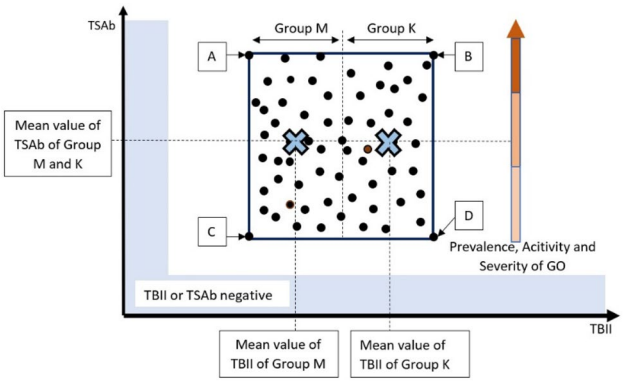


Fig. 2 Theoretical distribution of untreated GD patients. The black dots represent theoretical patients. We supposed that there is no correlation between TBII and TSAb, although some articles mention that they are weakly or quite correlated. Crosses represent the intersection points of the mean TBII and TSAb values of the group M and K, respectively. According to the articles reviewed, TSAb value is strongly or significantly correlated with the prevalence, activity and severity of GO

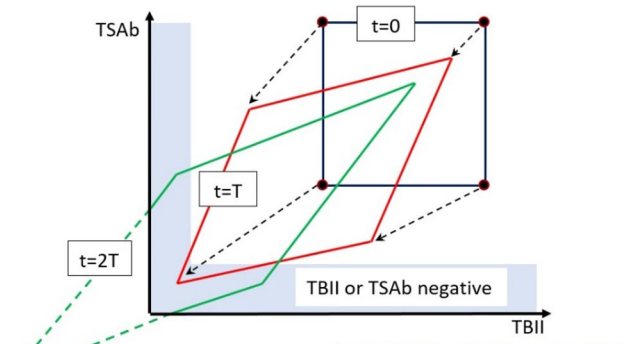
GO, we developed a theoretical model. We assumed that pre-treated adult patients are distributed on the TBII–TSAb coordinate plane with no correlation between TBII and TSAb, that is $r=0$, as shown in Fig. 2.

After starting hyperthyroidism treatment with ATDs (antithyroid drugs), radioactive iodine or thyroidectomy, TBII and TSAb decrease in different degrees depending on the initial levels of the antibodies. The following studies seem to support that concept.

Laurberg et al. [66] reported that with radioactive iodine therapy (I-131) the antibodies initially increased and then decreased, and after 18 months of hyperthyroidism treatment with ATDs or after radioactive iodine or thyroidectomy, TBII in serum disappeared in 70–80% of the patients. And all patients that had high levels of TBII before therapy showed no or little decrease in TBII levels during the period of therapy. Eckstein et al. [42] reported that patients who had a higher initial TBII level had a lower rate of reduction in their TBII level than those who had a lower initial TBII level. Similarly, in patients with a high initial TSAb level, TSAb decreased less than in patients with a low initial TSAb level after treatment [45]. Woeber et al. [67] observed that TSAb disappeared after 15 months of treatment in 52% of GD patients. However, in those with a high initial TSAb level, the percentage of patients in which this disappearance was observed was lower. Leschik et al. [68] observed that those patients with a high initial level of TBII and TSAb did not respond well to treatment and had less reduction in their antibodies after treatment. Additional studies show that patients with high initial levels of TBII or TSAb, or those with GO, have more difficulty in achieving remission of GD and have a higher rate of relapse. [61, 63, 69–74] (note that those observations are not always true but are likely. For example, some authors state that GO and relapse of hyperthyroidism are not related [75]). To summarize the above given data, there is a high possibility that in patients with a high level of both TBII and TSAb, (patient B in Fig. 2), the antibodies are less likely to decrease than in patients with low TBII and TSAb (patient C). In patients with a predominantly high level of either TBII or TSAb (patient A and D) there is likely to be an increased reduction in the antibody which has a higher level (this can be observed indirectly in [57]. Article [21] also reported that the patients with high TBII levels and low TSAb levels reached remission quickly).

Based on the above given data, due to differences in the degree of reduction of TBII/TSAb according to their initial levels, it is highly likely that a stronger correlation will be made than before treatment as shown in Fig. 3. This can be observed in figures shown in several reported studies.

Jang et al. [20] (Fig. 4) show a strong correlation between TBII and TSAb ($r=0.67$, $p<0.001$) in 317 post-treated GO patients (patients were a combination of hyper (58.7%), hypo and euthyroid).



	t=0	t=T	t=2T	t=∞
Correlation coefficient between TBII and TSAb	0	++	+	0
C. coefficient between TBII and TSAB in the positive TBII and TSAb region	0	++	+++	0

Fig. 3 Theorical change in the distribution of patients after hyperthyroidism treatment over time. Black dots represent theoretical pre-treated patients in Fig. 2. The dotted arrows represent the direction of descent of TSAb and TBII after treatment. In patients with high initial TSAb or TBII, there is a high probability that the antibodies will decrease less, and achieving remission will be more difficult. The table shows the presumed values of the correlation coefficient between TBII and TSAb over time. (t = time elapsed after starting the hyperthyroidism treatment)

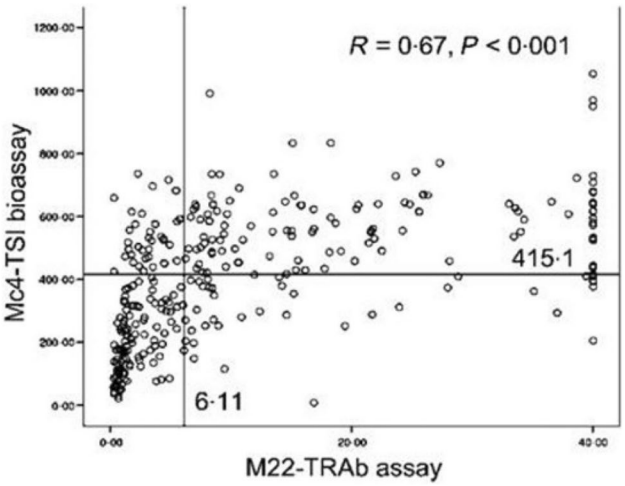


Fig. 4 Correlation between TRAb (TBII) and TSI (TSAb) post-treated patients with antithyroid drugs. Mean duration of the treatment was 7 months, Jang et al. [20]

Kampmann et al. [24] (Fig. 5) report a Spearman's rho = 0.538 ($p<0.001$) between TBII and TSAb. Although it is not mentioned how much time had elapsed since the initiation of hyperthyroidism treatment, it is possible that the mean duration of treatment was significantly longer than that of the patients in Jang et al. [20] (7 months) as all patients were in the state of euthyroid.

These changes in the correlation after hyperthyroidism treatment can also be seen in the following papers directly

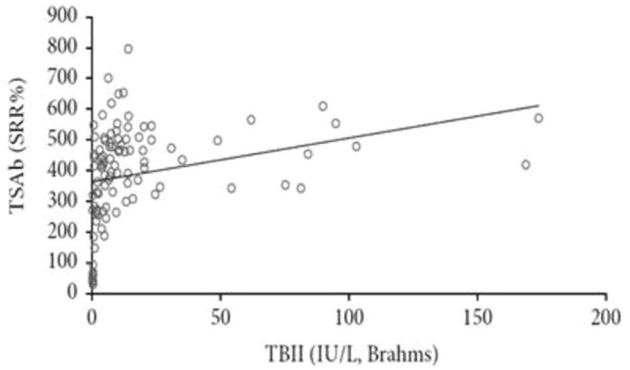


Fig. 5 Correlation between TBII and TSAb in euthyroid patients with ophthalmopathy after hyperthyroidism treatment, Kampmann et al. [24]

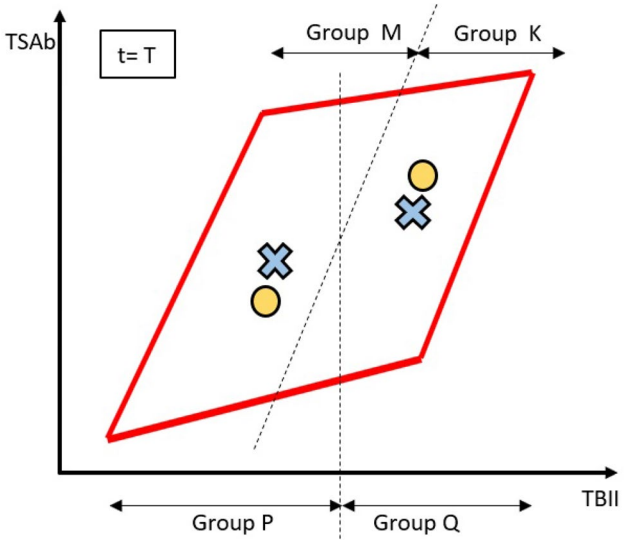


Fig. 6 Theoretical distribution of treated GD patients ($t=T$ in Fig. 3); crosses represent the intersection points of the mean TBII and TSAb values of the Group M and K, respectively, and circles represent intersection points of the mean TBII and TSAb values of the Group P and Q, respectively

compared before and after treatment, [63]: before therapy, $r=0.58$ ($p<0.0001$); 18 months after therapy, $r=0.62$ ($p<0.0001$), [62]: before therapy, $r=0.52$ ($p<0.0001$); 18 months after therapy, $r=0.55$ ($p<0.0001$) and for the patients in relapse, $r=0.70$ ($p<0.0001$), [60]: before therapy, $r=0.33$ ($p<0.05$); 6 months, $r=0.56$ (<0.001).

Application of the results to the model

Let us consider the usefulness of TBII as a biomarker of ophthalmopathy in two aspects.

1. Does the level of TBII reflect well the current state of ophthalmopathy, as an indicator of GO? or Is the level of TBII associated with the current state of ophthalmopathy?

   In Fig. 2, if we divide the patients into two groups, M and K, according to their TBII level, the two groups have the same TSAb level and they are likely to have the same degree of GO. In other words, the TBII level may not correlate with the GO and TBII will not be a valid indicator of GO. Although most studies reported a weak correlation between TBII and TSAb in untreated patients, there may be a weak negative correlation in some cases. If we compare the distributions of pre-treated patients in some studies, we can observe that patients are randomly distributed without any uniform pattern ([55]: most patients are located near the TSAb axis, [57]: near the TBII axis, [33]: without bias to either side). Depending on which patients were chosen, the result could be completely different. Thus, it is possible that Group 1 papers concluded that TBII and GO are positively, negatively or not correlated. After hyperthyroidism treatment, no matter the initial form of distribution of untreated patients, the distribution is likely to change and show an increasing positive correlation between TBII and TSAb. If we investigate patients who have been undergoing hyperthyroidism treatment for a significant amount of time ($t=T$ in Fig. 6), the patients with a higher level of TBII (Group Q) will also have a higher level of TSAb too. Furthermore, these patients are more likely to have more severe or active GO. Therefore, the usefulness of TBII as an indicator of GO is likely to be more valid following hyperthyroidism treatment than prior to treatment, but TSAb remains a better indicator. This seems to coincide with the results of most of the studies from Group 2.
2. Does the current level of TBII indicate the onset and severity of ophthalmopathy in the future, as a predictor of GO?

   It is likely that patients with a higher level of TBII (patients in Group K in Fig. 2, $t=0$) will have been exposed to a higher level of TSAb over time ($t=T$, Fig. 6), and patients in group K will be more likely to have more severe and more frequent onsets of GO. Thus, the initial level of TBII can be a useful predictor of GO, which seems to coincide with the results of the Group 3 studies. If the level of TBII before treatment is high ($t=0$), there is *a possibility* that a new-onset GO will develop or that the existing GO will become worse in the future. If the level of TBII is high under or after the treatment ($t=T$), there is *a high possibility* that a new-onset GO will develop or that the existing GO will become worse in the future. In the latter case, it is likely that the simultaneous level of TSAb is also high. Thus,

TBII as a predictor may be more reliable after the initiation of the treatment.

Conclusion

At the time of hyperthyroidism diagnosis or before hyperthyroidism treatment, TBII may not be a reliable indicator of the current state of GO. However, after treatment, due to changes in the correlation between TBII and TSAb, TBII may be a more reliable indicator of GO than prior to treatment. Furthermore, the current level of TBII can be closely associated with the onset and severity of GO in the future and it can be a valid predictor of GO. However, TSAb seems to be a better indicator or predictor than TBII.

Discussion

In Fig. 3, if more time is allowed to pass ($t > T$), the number of patients in hyperthyroidism remission will increase and they will stay near the TSAb or TBII axis (TSAb or TBII negative). (Note that it seems that more patients will stay close to the TSAb axis than to the TBII axis as it has been reported that the disappearance of hyperthyroidism occurs prior to the disappearance of TSAb [67]). Therefore, due to these patients being close to the axes, the correlation coefficient between TBII and TSAB in all patients will decrease. This change is observed in article [60]: before therapy, $r = 0.33$ ($p < 0.05$); 1 month after therapy, 0.41 (< 0.02); 3 months, 0.51 (< 0.01); 6 months, 0.56 (< 0. 001); 9 months, 0.11 (ns); 12 months, 0.32 (< 0.05). The point at which the correlation starts to decrease is likely to depend on the distribution of patients before treatment, i.e., how far they are from the two axes. However, the correlation in patients who have positive TBII and TSAb continues to increase ($t = 2T$). This idea can be observed indirectly in Yoshida et al. [65], who showed that among patients treated with radioactive iodine years later, in those who still had hyperthyroidism (patients refractory to treatment, many of them still had positive TBII and TSAb), the correlation coefficient between TBII and TSAb was very strong ($r = 0.88$, $p < 0.01$). However, in euthyroid patients, sub-clinically hypothyroid patients and in patients with overt hypothyroidism, most of whom were close to the TSAb axis, the correlations were weaker ($r = 0.49$ ($p < 0.01$), $r = 0.34$ ($p < 0.05$), $r = 0.12$ ($p > 0.05$), respectively). Thus, despite a weaker correlation in all patients overall, TBII can remain useful as a biomarker to a certain extent due to such a stronger correlation in patients with positive TBII and TSAb.

However, if even more time is allowed to pass, firstly, an increasing number of patients will stay near the TSAb axis and few will remain in the TBII/TSAb positive region ($t \gg 2T$). Therefore, as time passes, theoretically, this correlation will disappear (t = infinite). Secondly, over time, it may be possible that in the orbital tissue, the expression of TSH receptor decreases [1, 2], the TBAb level increases [76, 77], and the affinity of TSAb for TSH receptor decreases [9, 78]. Therefore, the correlation between TSAb and GO may not be as strong as before. So, for patients who have been diagnosed with hyperthyroidism a very long time ago, the utility of TBII as a biomarker of GO may disappear again, i.e., the level of TBII may not be closely associated with GO.

Regarding the discrepancies in the relationship between TBII and GO, some authors [24, 28, 79] claim that the cause of the discrepancies may come from ethnic differences. Chng et al. [79] explain their conclusion as follows:

'TSAb is associated with GO in both Caucasian and Asian patients. In the studies conducted with Caucasian patients [23, 42], both TSAb and TBII are associated with GO. While in studies with Asian patients [17, 18, 20, 80, 81], only TSAb is associated with GO. Therefore, the reason for the discrepancies in the relationship between TBII and GO is probably due to ethnic differences.'

However, Caucasian studies mentioned in the article [79] were conducted with treated patients, [23]: the median duration of GD after diagnosis was 20 months and [42]: the duration of follow-up was 12–24 months. However, Asian studies were performed with pre-treated patients, except for Kung et al. [81]. As mentioned by the authors, if only TSAb is valid for Asian patients and for Caucasian patients both TBII and TSAb are valid for GO, it is difficult to explain some of the articles reviewed. For example, Jang et al. [30] performed the study with Asian patients and it shows that the predictive power of the TBII assay and TSAb bioassay are similarly strong. The Caucasian study, Laurberg et al. [50], showed that TBII was not as closely associated with the presence of eye signs and symptoms of GO ($r = 0.15$, $p = 0.036$). However, this review maintains that ethnic differences may affect the association between TBII and GO for the following reasons.

First, it has been reported that TBAb is rarely detected in Caucasian hyperthyroid patients [58, 82]. If TBII is mainly composed of TSAb and TBAb, and Caucasian patients have less TBAb than Asian patients, there is a high probability that Caucasians will have stronger TBII–TSAb correlation than the Asian patients. Indeed, it has been observed that most of the studies that reported a stronger correlation between TBII and TSAb in untreated patients were for Caucasian patients [61–63]. Note that some studies report that these correlations are weak in Caucasians [58–60]. Therefore, it may be possible that in untreated Caucasian patients, TBII is more closely associated with GO than in Asian untreated patients. However, reports that post-treated patients have a stronger TBII–TSAb correlation than pre-treatment patients regardless of ethnicity, and the papers reviewed in Groups 2 and 3, generally that TBII and GO

are correlated after treatment, regardless of ethnicity. Therefore, it can be concluded that agree: although in Caucasian patients TBII seems to be more associated with GO than in Asians, after treatment for hyperthyroidism, TBII is more closely associated with GO than before regardless of ethnicity.

We can also consider that the cause of discrepancies is probably due to the use of different assays. However, for example, in the studies that used TBII 1st generation assays [17–19, 25] or 3rd generation assays [25, 30, 51], the correlation between TBII and GO depends on whether the studies were conducted with pre-treated or post-treated patients, not on the different assays used. Thus, the difference in assay types is not likely to be a major cause of the TBII discrepancies in GO.

Interestingly, it seems that the baseline level of TBII prior to therapy cannot be used as a predictor of GO in patients treated with *radioactive iodine* [46, 47, 81] ([46]: 65%; [47, 81]:100% of patients treated with radioactive iodine. These studies are the only exceptions to the follow-up study group). This is likely due to the increase in antibodies to different degrees following therapy, regardless of the baseline level of TBII and TSAb.

Limitations of this review:

1. There is great heterogeneity in the studies reviewed. Therefore, it was difficult to analyze statistically the relationship between the level of TSAb/TBII and GO prevalence, activity and severity. We did not consider the type of hyperthyroidism treatment; however, we note that most of the patients in the papers reviewed were treated with ATDs.

2. We did not consider other factors that may be associated with GO such as TPO-Ab/TG-Ab, IGF-1, environment and genetics. Furthermore, we did not provide a precise physiological mechanism for why the correlation between TBII and TSAb might increase after hyperthyroidism treatment.

In this review, however, based on the given data published we have developed a theoretical model to explain how the effect of hyperthyroidism treatment can affect the correlation between TBII and TSAb. We have obtained as a result that the changes in TBII and TSAb caused by treatment can affect the usefulness of TBII as an indicator or predictor of GO. In addition, these changes can be a possible cause of the discrepancies regarding the usefulness of TBII as a biomarker of GO. However, it seems that to obtain a firmer conclusion, more studies on this subject are necessary.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and or animals Not applicable.

Informed consent Not applicable.

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