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Thyroid Stimulating Hormone Suppression Post-Therapy in Patients with Graves' Disease: A Systematic Review of Pathophysiology and Clinical Data

Abstract

Background: Post-treatment hypothyroidism is common in Graves' disease, and clinical guidelines recommend monitoring for it; however, thyroid stimulating hormone (TSH) can remain suppressed in these patients following treatment. The objectives of this study were to explore the proposed pathophysiology behind the phenomenon of post-therapy TSH suppression and to systematically review existing clinical data on post-therapy TSH suppression in patients with Graves' disease.

Source: A systematic literature search was performed using EMBASE and PubMed databases, with several combinations of MeSH terms. Bibliography mining was also done on relevant articles to be as inclusive as possible.

Principal findings: A total of 18 articles described possible mechanisms for post-therapy TSH suppression. Several of the studies demonstrate evidence of thyrotroph atrophy and hypothesize that this contributes to the ongoing suppression. TSH receptors have been identified in folliculo-stellate cells of the pituitary as well as astroglial cells of the hypothalamus, mediating paracrine feedback. A few studies have demonstrated inverse correlation between autoantibody titres and TSH levels, suggestive of their role in mediating ongoing TSH suppression in patients with Graves' disease. In addition, five studies were identified that provided clinical data on the duration of TSH suppression. Combined data show that 45.5% of patients recover TSH by 3 months after treatment, increasing to 69.3% by 6 months, and plateauing to 73.8% by 12 months ($p < 0.0001$). Sub-analysis also shows that for patients who are TBII negative, 80.7% recover their TSH by 6 months compared with only 58.7% in those who are TBII positive ($p = 0.003$).

Conclusion: Clinical data suggests that TSH recovery is most likely to occur within the first 6 months after treatment, with recovery plateauing at approximately 70% of patients, suggesting that reliance on this assay for monitoring can be very misleading. Furthermore, TBII positivity is associated with lower likelihood of TSH recovery. Pathophysiology behind suppressed TSH involves not only anatomical but also autoimmune mechanisms.

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Hyperthyroidism is not uncommon in North America, with an estimated prevalence of 1.2% and with the most common causes being Graves' disease and toxic multinodular goitre [1]. Graves' disease is an autoimmune disorder characterized by hyperthyroidism caused by non-thyrotropin, thyroid-stimulating factors. First-line treatment usually involves anti-thyroid medications such as propylthiouracil (PTU) and methimazole (MMZ). If medication is inadequate or believed to be unlikely to induce remission, then radioactive iodine ablation is performed. Both treatment modalities can lead to a hypothyroid state.

Hypothyroidism occurs in 20% of patients treated with antithyroid medication [2]. Post-ablation, the rates are even higher; it has been cited as being as prevalent as 24% within the first year and as high as 82% by 25 years [3]. American Thyroid Association/American Association of Clinical Endocrinologists (ATA/AACE) guidelines recommend regular thyroid function tests to monitor for hypothyroidism [1]. Most primary care physicians monitor thyroid-stimulating hormone (TSH), both to diagnose and to titrate supplementation [4]; however, Ehrmann *et al.* showed that even with the new, sensitive TSH assay, up to 17% of the general population presenting with a suppressed TSH were actually hyperthyroid and the authors cautioned physicians to recognise the limitations of this test [5]. In post-treatment Graves' disease patients, TSH is well-recognised to remain suppressed even when the patient is clinically euthyroid [6].

By better understanding the pathophysiology and observed time-course of TSH recovery after treatment for Graves' disease, physicians can better assess the reliability of TSH levels to accurately reflect the thyroid function of their patients. The

first objective of this study was to review the literature behind the possible pathophysiology accounting for the prolonged TSH suppression. The second objective was to identify existing clinical data on the duration of suppression, in order to better predict when, or if, TSH levels can be expected to recover.

Materials and Methods

A systematic literature search was performed with EMBASE and Medline databases from 1946 to April 2014, using a variety of MeSH terms (Table 1). Keywords used in various combinations include hyperthyroidism, Graves', thyrotoxicosis, anti-thyroid drug, iodine radioisotopes, immunoglobulins, auto-antibodies, pituitary, thyrotroph, hypothalamus, hypophysis, adenohypophysis, hypothalamic-pituitary-thyroid axis, hypothyroidism, thyroid-stimulating hormone and thyrotrophin. The total number of articles obtained from various search combinations is listed under "Found" in Table 1. In reviewing titles and/or abstract, some articles were chosen for more detailed reading (listed under "Selected" in Table 1) based on the following inclusion criteria: English language, adult population, non-pregnant and non-malignancy related. For articles relating to pathophysiology, studies relating to hyperthyroidism and animal studies were included where applicable. For articles relating to TSH timeline, inclusion criteria was specific to Graves' disease.

All articles that were read in more detail were then further evaluated for inclusion into the study. For pathophysiology, articles were excluded if it discussed assays only, or did not relate back to TSH suppression. Articles relating to TSH Timeline were excluded if they did not provide specific time increments, did not specify how thyroid status was defined (i.e., by

TABLE 1. Various search combinations and the articles found and reviewed

	PUBMED		EMBASE	
	Found	Selected	Found	Selected
Antibodies, hyperthyroidism and treatment	169	10	378	10
Antibodies, hyperthyroidism and TSH	624	35	823	6
Hyperthyroidism, treatment outcome and hypothyroidism	30	1	101	3
Hypothalamic-pituitary-thyroid and hyperthyroidism	205	10	469	6
Suppressed TSH and hyperthyroidism	40	6	66	10
Hyperthyroidism and pituitary/hypothalamus	203	6	436	12
Total articles reviewed (mutually exclusive)	72			
Total articles included in study (mutually exclusive)	18			

TABLE 2. Pooled data of the five studies detailing time to TSH recovery.

Author	Year	Number of patients	3months*	6months*	12months*
Uy <i>et al.</i>	1995	21	8/21	21/21	
Chiovato <i>et al.</i>	1998	24	16/24	22/24	24/24
Brokken <i>et al.</i>	2003	45		22/45	
Chung <i>et al.</i>	2006	167	77/167	115/167	115/167
Woeber <i>et al.</i>	2011	23	6/23	14/23	19/23
			107/235	194/280	158/214
			(45.5%)	(69.3%)	(73.8%)

* Proportion of patients at each time point with recovery of TSH

free thyroxine, TSH, or clinical parameters), did not specify TSH values, or were related to thyroidectomy. For three studies where some of the needed information for inclusion was missing, attempts were made to contact the corresponding authors for clarification but no reply was received [7-9]. Bibliographies of relevant articles were also examined to ensure the maximum possible number of articles were included for consideration; these articles are included in the final count for total number of articles read and included in the study.

For the clinical data on TSH recovery, Chi square analysis for difference of proportion was utilized to assess for statistically significant change over time, as well as for correlation with TBII (thyroid binding inhibiting immunoglobulin) positivity. Clinical data was pooled in this study for sub-analysis of TSH recovery 6 months after medical therapy.

Results

Pathophysiology

In total, 18 articles specifically discussed mechanisms by which TSH may remain suppressed (see Appendix 1). These articles were grouped into three different categories: atrophy, regional mechanisms or immune-mediated suppression. Three studies showed evidence of pituitary atrophy as one of the possible mechanisms for TSH inhibition [10-12]. This was first proposed in a functional study in humans, but was subsequently seen in dogs, as well as post-mortem in patients with hyperthyroidism.

Six articles presented findings suggestive of regional control mechanism that mediates serum TSH levels, the majority of which alludes to a paracrine feedback [13-18]. The earliest studies were in rat models and this was then extended to hu-

mans, and two studies in patients with Graves' disease supported the initial findings. Nearly all of the studies focused on a local feedback system at the level of the pituitary gland, Motta *et al.* found that in rats, TRH secretion decreased in response to TSH, suggesting that a feedback loops exists in the hypothalamus as well [17].

A total of nine studies correlated TSH suppression with an immune-mediated process [19-27]. Of these, two were based in animal models, while the remainder were specific to Graves' patients. A variety of thyroid autoantibodies were studied, including anti-microsomal antibody, anti-thyroglobulin antibody, long-acting thyroid stimulator (LATS), thyroid stimulating immunoglobulin (TSI), and TBII; however, of these, only the thyroid stimulating hormone receptor antibody (TRAb) was hypothesized to be the culprit.

TSH Timeline

Five articles provided sufficiently detailed information to be included in the analysis of TSH recovery timeline [13,19, 20, 27, 28] (Appendix 2). Three of these studies included small samples, but were prospective cohort studies. The largest study found, with a population of 167, was a retrospective study from Korea [20]. A total of 235 patients were monitored after anti-thyroid medication, whereas the other 52 were monitored following radioactive iodine ablation. Of note, a separate study by Chiovato *et al.* clearly disclosed that the patients they studied after ablation had received a mean of 13 months' of antithyroid medication as well [28].

Clinical data from all five studies was pooled based on proportion of reported patients with evidence of TSH recovery at 3 months, 6 months and 12 months after treatment with

FIGURE 1. Proportion of Graves' patients with recovered TSH by months after medical therapy. Error bars represent the variance in the available data set. McNemar's test was used to analyse the change in proportion between 0 and 12 months after therapy ($p < 0.0001$). Sub-analysis of recovery from 0 to 3 months, and 3 to 6 months ($p < 0.0001$). However, sub-analysis between 6 and 12 months showed no statistically significant recovery ($p = 0.27$).

either radioactive iodine ablation or antithyroid medication (Table 2), then plotted in graphical form (Figure 1). The available data demonstrates an increase in the proportion with recovery of TSH levels over time with 45.5% patients recovering their TSH levels by 3 months, 69.3% of patients by 6 months, and 73.8% by 1 year after treatment ($p < 0.0001$). Sub-analysis of recovery between 0 and 3 months, as well as between 3 and 6 months both demonstrate statistical significance ($p < 0.0001$); however, in comparing the change in proportion that recovered their TSH between 6 and 12 months, no statistical significance was found ($p = 0.27$).

Two articles also reported TSH recovery relative to TBII positivity [19, 20]. Chung *et al.* [20] found that pre-treatment TBII titres predicted lower TSH levels at each of their follow-up intervals of 3 ($p < 0.05$), 6 ($p < 0.001$) and 12 ($p < 0.001$) months after completing a course of antithyroid medication, despite normal thyroid hormone levels [20]. On the other hand, Brokken *et al.* found a strong inverse correlation between

post-treatment TBII titres, measured at mean of 6.7 months after antithyroid medication, and suppressed TSH ($r = -0.423$, $p = 0.004$) [19]. The clinical data from these studies were pooled for sub-analysis (Table 3) and showed that 80.7% of patients with negative TBII titres had recovered TSH levels by 6 months after medical treatment, as compared with only 58.7% of patients with positive TBII ($p = 0.003$).

One small sample study by Woeber in 2011 examined TSH levels as they related to TSI levels. Twenty-seven Graves' patients, who were positive for TSI at time of diagnosis, were followed longitudinally for at least 24 months after initiation of antithyroid medication. Of the initial 23 patients, 12 patients became TSI negative at a mean of 15 months, which was later than the mean recovery time of 6 months for TSH. This was a statistically significant time difference ($p = 0.005$) [27]. Of the 11 patients who remained TSI positive throughout follow-up, TSH levels in all but one recovered within the first year. Due to the difference in the assay used to measure TSH

TABLE 3. TSH Recovery at 6 months Post-Treatment Based on TBII Positivity

Author	Year	Total N	TBII	
			+	-
Chung <i>et al.</i>	2006	167	84/133	31/34
Brokken <i>et al.</i>	2003	45	7/22	15/23
			91/155	46/57
			58.7%	80.7%*

* $p=0.003$ by Chi-square test comparing likelihood of TSH recovery between TBII positive and TBII negative individuals

levels, these data were not pooled for analysis of TSH recovery and autoantibodies in our study.

Discussion

Graves' disease has an annual incidence of 0.5 per 1000 person, with age of onset peaking between 20 and 40 years old [29]. Patients often undergo medical management with antithyroid medication or radioactive iodine ablation, or a combination of the two therapies. Hypothyroidism can occur in 20% of patients on medications² and as high as 82% of patients twenty-five years after ablation³. Monitoring for treatment complications, especially hypothyroidism, is important for patient well-being and quality of life. Serum TSH is often used as the test of choice by primary care physicians, since evidence suggests that a normal sensitive TSH level is usually sufficient to rule out thyroid disease [4]; however, TSH can remain suppressed after treatment for Graves' disease, even in the setting of biochemical and clinical euthyroidism [1]. Hypotheses regarding the mechanism behind this finding are heterogeneous and some are still under debate. A systematic review of existing literature has shown no consensus on the duration of suppression, which would be relevant for physicians monitoring Graves' patients post-treatment. With better understanding of the natural time-course and pathophysiology behind TSH suppression, physicians would be better equipped to predict when, or if, TSH would recover, avoiding delays in diagnosis and even treatment for post-therapy hypothyroidism.

For the organisation of the discussion, the theories have been broadly categorized as anatomical (relating to atrophy), local mechanisms (pituitary or hypothalamic) and immune-mediated. It is acknowledged in more than one article that likely more than one mechanism is at play; however, for the purposes of this review, studies have been organised under the category that is felt to be most strongly supported by the results.

Pituitary atrophy

Of the possible mechanisms to explain ongoing TSH suppression, perhaps the most logical is that of pituitary atrophy. Thyroid hormones, especially triiodothyronine, have the strongest suppressive effect on TSH levels. In rats, this effect is even more profound than up to 50 days after complete destruction of the paraventricular hypothalamus, where TRH is produced [30]. As early as 1982, a lag time was noted in TSH recovery in patients with hyperthyroidism, and it was theorized that this lag corresponded to the time needed for atrophied thyrotrophs to regain function [10]. Since then, animal models and post-mortem analysis of human pituitary glands have indicated both gross atrophy and morphologic evidence of inactivity at the cellular level [11, 12], confirming this theory. The changes are so distinct that pituitary glands from hyperthyroid patients could be easily distinguished from euthyroid patients [12].

Pituitary Control

In 1965, Solomon et al. examined rat pituitary glands and thyrotrophin release in vitro [16]. They quantified the TSH secreted by the isolated pituitary gland. Without thyroid hormone to provide negative feedback, higher TSH levels are expected with less frequent bath changes; however, Solomon et al. found that the TSH secreted per unit pituitary remained constant, suggesting that a feedback mechanism isolated to the pituitary must exist. In 1976, Buerklin et al. performed TRH stimulation tests in Graves' patients, as well as thyroid uptake scans after a supra-physiologic dose of levothyroxine. The latter assessed for thyroid autonomy suggestive of relapsed Graves' disease. Buerklin found that 25% of euthyroid Graves' patients demonstrated a blunted response to TRH stimulation even without evidence of thyroid autonomy, making subclinical Graves' as the sole cause for TSH suppression less likely [15]. Uyet al. also noted ongoing pituitary suppression in patients

who had undergone radioactive iodine ablation. Using serial TRH stimulation tests, they found that 90.5% of patients underwent an intervening period of subnormal TSH response [13], adding to the body of evidence suggesting a local mechanism by which thyrotrophs regulated their own TSH secretion.

A possible mediator was identified by Prummet *et al.*, who demonstrated that TSH receptor RNA sequences were not only translated, but functionally expressed on the surfaces of folliculo-stellate cells of the pituitary [14]. Theodoropoulou *et al.* independently arrived at the same results [31]. That TSH receptors exist on extra-thyroidal tissue is not surprising as it has been identified on various other tissues, including but not limited to cardiomyocytes [32], retro-orbital preadipocytoblasts [33], adipocytes [34], kidney [35], osteoclasts and osteoblasts [36], as well as porcine enterocytes [37]. To discover its presence and to hypothesise that it may have a functional role within the pituitary, is in keeping with what has already been identified about this receptor.

Existing literature suggests that folliculo-stellate cells may be integral in the short-loop feedback control of thyrotrophs. Folliculo-stellate cells are MHC-II-expressing dendritic cells that reside within the pituitary; in rat models, prevalence ranges from 5-10% [38]. These cells are interlinked and dispersed throughout the gland, carrying the capacity for organised and extensive cross-communication with each other and with endocrine cells as well [39]. Paracrine regulation by these cells on other anterior pituitary endocrine cells has been described. For example, pituitary folliculo-stellate cells in the rat tightly regulate the proliferative response of lactotrophs by controlling the amount of fibroblast growth factor released in response to estradiol [40]. These cells have even been shown to secrete IL-6 in response to bacterial lipopolysaccharide, acting as a potent stimulator for corticotrophs; this effect is not observed without the presence of serum [41].

Another study found an inverse correlation between the number of folliculo-stellate cells and the magnitude of GH response to GRH, as well as PRL to dopamine, respectively [42]. Interestingly, this effect was still observed when the cells were perfused, suggestive that communication does not require a direct cellular crosslink [42]. These results all support the hypothesis of an important regulatory role exerted by the folliculo-stellate cells over endocrine cells, and in particular, thyrotrophs. Although thyroid hormones provide the predominant feedback control, folliculo-stellate cells may act via paracrine mechanisms to fine-tune that response, avoiding drastic swings in TSH as thyroid function fluctuates [23].

Hypothalamic control

Within the brain, TSH receptors have also been identified in regions beyond the pituitary, including the hippocampus, post-cingulate gyrus, cortex, cerebellum and hypothalamus in sheep [43, 44] and rat models [44]. Motta *et al.* experimented with thyroidectomised rats, injecting them with TSH, and measuring hypothalamic TRH content [17]. They found a significant decrease in TRH, leading to the hypothesis that a local feedback mechanism exists above the pituitary. Dandona *et al.* made a contrasting but related finding in their study [22]. In thyroidectomised guinea pigs, exogenous TSH, at much lower doses than used by Motta *et al.*, resulted in a statistically significant increase in pituitary TSH content. Despite no significant increase in serum TSH, the authors postulated that a positive feedback mechanism exists in the hypothalamus, potentiating TSH production in the setting of hypothyroidism. Finally, a study by Rondeel *et al.* examined the effect of thyroid function status on TRH. Although rats induced to be hyperthyroid, showed a 30-40% increase in TRH secretion, rats treated with antithyroid medication unexpectedly showed no change in TRH, despite a significant 20-fold increase in serum TSH. Rondeel suggested that a feedback mechanism is at play within the hypothalamus, which modulates TRH and ultimately TSH secretion, preventing drastic swings in thyroid function. No other studies since then have examined the functional implications of TSH receptors within the hypothalamus on TSH. Nevertheless, these findings raise the possibility of a supra-pituitary mechanism for regulating TSH levels.

Autoimmunity Factors

Graves' disease is unique from other causes of hyperthyroidism in that it shows the presence of autoantibodies. With the discovery of TSH receptors within the brain, it has been proposed that TRAb acts on these receptors to provide negative feedback [19, 43]. The observation that something within the sera of Graves' patients contributes to TSH suppression was first described in guinea pigs [22]. When injected with IgG from patients with Graves' ophthalmopathy, Dandona *et al.* found that 50% of treated guinea pigs demonstrated lower TSH levels. Over a decade later, the first of several studies correlating autoantibodies with TSH level was published. In studying the utility of TSH measurement to accurately define thyroid status during Graves' therapy, Ng *et al.* found that TBII titres were significantly higher in patients with suppressed TSH²⁴. This finding was beyond the scope of the original study and no explanation was offered by the authors. Since then, three other studies have made similar findings [19, 21, 26]. In 2001, Brok-

ken *et al.* noted a dose-dependent relationship between TBII and TSH [21]. In euthyroid rat models, they injected control IgG and "high" strength TBII (512u/L) from Graves' patients. They found that "high" TBII doses resulted in TSH levels approximately 25% lower than controls ($p=0.009$). A similar, inverse relationship between TBII titres and TSH levels was observed in euthyroid humans with Graves' disease, suggesting an active role by autoantibodies in suppressing TSH [19, 20].

In their study, Dandona *et al.* examined the effects of LATS as well, one of only three studies demonstrating the effects of non-TBII TRAb. When injected with LATS, the pituitary glands showed a statistically significant drop in TSH content, although not as profound as the decrease seen when guinea pigs were injected with either TSH or thyroxine [22]. Because LATS was still detected in the serum, TSH could not be accurately measured. Based on these findings and limitations, the authors noted that it would be difficult to elucidate whether LATS inhibited the pituitary secretion (negative feedback) or increased the pituitary synthesis (positive feedback) of TSH.

The remaining non-TBII TRAb studies examined the correlation of TSH with TSI [25, 27]. In their observational cohort study in 2007, Kabadi *et al.* collected thyroid function tests and TSI from 50 Graves' patients during routine follow-up. All patients were at various stages of therapy with antithyroid medication, RAI ablation, or both. Using linear regression, the authors found that TSI was inversely correlated with TSH, irrespective of thyroid hormone levels ($r = -0.45$, $P < 0.01$). The authors proposed that TSH in post-therapy Graves' disease was more reflective of autoantibody levels, with mechanisms for suppression likely through pituitary or hypothalamic TSHR. In a smaller study with a longer follow-up, no association was found between TSH recovery and TSI titres [27]. In his cohort, Woeber found that in the subgroup whose TSI changed from positive to negative, mean time to negativity was 15 months (range 11-20 months); however, TSH in this group recovered at a mean of 6 months (range 3-8 months), well before TSI conversion. Even in the group whose positive TSI levels remained unchanged during treatment, 10 of 11 patients recovered their TSH. Although the sample size is small, Woeber's results suggest that TSI may not be the autoantibody that exerts a direct suppressive effect on TSH levels.

TSH Timeline

Only five studies were identified in the literature as providing sufficient clinical data for further analysis of the duration of TSH suppression. Although the pooled sample population size is only 280, graphical analysis of the recovery timeline show a

statistically significant plateauing in the change over time (Figure 1). The analysis of existing clinical data suggests that 6 months after completing treatment with either antithyroid medication or radioactive iodine, 69.3% of patients would have recovered their TSH. By one year, the prevalence of recovery is 73.8%, a small and statistically insignificant increase ($p = 0.27$). Extrapolating on the trajectory of the graph, it would be expected that there would be no significant, further recovery of TSH beyond the first year. This seems to correspond with the limited long-term clinical data from the two retrospective studies. In his study, Woeber followed patients for a mean of 37 months [27]. By the end of his study, the number of patients with recovered TSH had increased minimally, from 19 after the first 12 months, to 21. The larger cohort study out of Korea retrospectively followed patients for as long as 30 months after normalisation of free T3 and T4 levels [20]. They found that 85.7% of the 35 patients still included in the study have recovered their TSH at 30 months; a significant loss-to-follow-up accounted for the substantial decrease in population size from 167 at onset, to 35 [20]. Nevertheless, it suggests a plateauing effect similar to that seen by the pooled data within this study.

Various pathophysiological mechanisms have been proposed to account for the ongoing TSH suppression, including that of atrophy; however, thyrotrophs have been shown to respond relatively quickly to changes to thyroid status. In dog models, Panciera *et al.* induced hyperthyroidism in 2 groups: one group was sacrificed after 9 weeks of supraphysiologic thyroxine therapy, the other was taken off of the supplement for 6 weeks before sacrifice. Histologically, the dogs in the latter group were found to have significantly higher volume density than even normal control thyrotrophs, but near-normal morphologically [11]. This suggests that atrophy recovers within the first two months of thyroid hormone normalisation, which would not account for the 6 months of TSH suppression seen in this study. This is in keeping with studies in Graves' patients, in whom no correlation is found between duration of pre-treatment thyrotoxicosis and TSH suppression [19].

With the discovery of TSH receptors in the brain, it raises the intriguing possibility that TRAb may act upon them to mediate a negative feedback [23]. Studies have shown that autoantibodies fluctuate with therapy. TSI for example, has been shown to rise within the first six months, both in the number of patients testing positive, and the titres [28, 45]. Usually, the titres peak at 6 months then slowly return to pre-treatment titres by one year, after which it progressively declines [46]. This is in contrast to the gradual decline in TSI after antithyroid medications [45]. It is believed that the dramatic rise in autoantibodies after radioactive iodine ablation is

in part due to the significant damage on the follicles, thereby releasing more antigens [28, 45]. However this observation is inconsistent, as others have shown TSI levels to show erratic and unpredictable changes [47]. It is not surprising, therefore, that attempts to correlate TSI levels with TSH have shown mixed results [25, 27]. In Woeber's retrospective cohort of 23 patients on antithyroid medication, he was able to demonstrate that TSH recovers at a mean of 6 months, well before the normalisation of TSI occurring at a mean of 15 months ($p=0.005$) [25]. Based on this finding, TSI is unlikely to mediate the suppression of TSH.

TBII has also been studied as a potential predictor of disease prognosis [48, 50], and in the course of doing so, its variability with different therapies have been described. In an earlier study by Bliddal *et al.*, TBII significantly decreased between three and six months before stabilising in patients receiving either antithyroid therapy or ablation [48]. Similar to TSI fluctuations, post-radioiodine ablation TBII also was found to increase within 3-5 months [26, 51], then decreasing back to pre-treatment levels [26, 52]. In a five year, prospective, randomised analysis of different treatment modalities in Graves' patients, Laurberg *et al.* found that post-surgery or with antithyroid medication, TBII fell toward normal levels within the first year [52]. In contrast, patients receiving radioiodine ablation demonstrated a sharp increase within the first six months before gradually falling, but remained above the average titres of the other two modalities. Interestingly, in their graphical presentation of the proportion of patients becoming TBII negative, a plateau is seen in those on medications after just one year, stabilising around 80-90% [52]; this is similar to the plateau observed in the clinical data for TSH suppression reported in this study. Although this study pooled the clinical data for both post-ablation and antithyroid therapies, the majority of the data on the patient population came from studies on oral therapies, comprising 235 of the total 280 patients. Admittedly, examining only the clinical data from the two studies on post-ablation patients, 100% recover their TSH by one year; however, the pooled sample size is only 45, making it difficult to know whether the recovery time course would be different if a larger sample size was used.

Two of the studies providing clinical data also examined the correlation of recovery with autoimmunity, as measured by TBII titres. Of note, patients in the study authored by Chung *et al.* were categorized based on pre-treatment TBII positivity; although TBII titres were assessed at each time interval, it did not appear that the authors re-categorized patients based on post-treatment titres [20]. Brokken *et al.*, on the other hand, found a strong negative correlation between TBII positivity at

end of study (mean 6.7 ± 1.5 months after treatment) and TSH recovery [19]. Both studies involved Graves' patients treated with antithyroid medications. Sub-analysis demonstrated that those with TBII positivity had a lower likelihood of recovering their TSH levels by six months. Although interpretation of this data should proceed with caution, given the fluctuations in TBII post therapy, this is consistent with existing data in the literature that is suggestive of a correlation between TBII titres and TSH suppression.

TBII is a purely structural assay, and does not detect any functionality in terms of the classic cAMP activation pathway [50, 53]. If autoantibodies exert an inhibitory effect through the TSHR found in the pituitary gland and hypothalamus, functional activation of these receptors would be expected. Interestingly, it has been demonstrated that in rat models, activation of the TSHR found on astroglial cells of the paraventricular nuclei of the hypothalamus has no cAMP activity⁵³. Further research has shown that TSHR upregulates the activity of type II iodothyronine deiodinase, the enzyme that converts thyroxine to the biologically active triiodothyronine in the brain [54]. From a physiological perspective, it is conceivable that TBII may exert feedback control of TSH secretion.

The primary limitation of this study is the low number of studies found in the literature delineating clinical data for TSH suppression. As a result, data had to be pooled for patients on both antithyroid medications and radioactive iodine ablation to allow for a meaningful analysis. It is possible that with larger, prospective and longer-term follow-up studies, the time line observed may be different. In the future, analysing data from multi-centred databases would be helpful in determining a better estimate for the pattern of TSH recovery. Heterogeneity also exists in the pooled data correlating TBII positivity and TSH recovery. Further testing would be required to validate TBII as a useful test for predicting the timeline of TSH recovery. Finally, for this to be useful in clinical application, a cost-effective analysis would need to be performed for this assay.

In conclusion, a systematic review of the literature has revealed various pathophysiological mechanisms, ranging from anatomical atrophy and regional feedback control in the pituitary and hypothalamus, as well as possible autoimmune mechanisms. This study is the first to systematically delineate the duration of TSH recovery, with the unexpected finding of a plateau seen after six months. There was also an increased prevalence in TSH recovery seen in patients who are TBII negative, although the authors recognise that some heterogeneity exists in the pooled data. The results of this study suggest that for Graves' patients after non-surgical therapy, TSH may not accurately reflect thyroid status. If TSH is found to remain

suppressed or inappropriately normal at 12 or even six months, the plateau observed here would suggest a low chance of recovery in the future. Selected TBII assessment may also be helpful in assessing the likelihood of recovery. If the chance of recovery is low, monitoring thyroid hormone levels rather than relying solely on TSH levels, may prevent delayed or even missed diagnosis of post-therapy hypothyroidism. With these patients, less frequent TSH tests would not only decrease healthcare costs, but more importantly, avoid confounding results as well.

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APPENDIX 1. Articles describing possible mechanisms for ongoing suppression of TSH in Graves' patients after medical management.

Author	Population	Study Design	Year	N	Country	Parameter	Relevant Findings	Interpretation
Atrophy								
Fischer <i>et al.</i> [10]	Human	Prospective	1982	23	Single centre, Rotterdam (Netherlands)	Thyrotoxic patients (15 MNG, 5 TN, 3 Graves') on stable-dose antithyroid medication were followed with TRH stimulation and thyroid function tests.	Found that TSH response (defined by positive TRH stimulation) lagged behind subnormal FTI (fT4 surrogate) by average 34 ± 10 days.	Lag time was hypothesized to be the period needed for atrophied thyrotrophs to resume TSH production and secretion.
Pancieret <i>et al.</i> [11]	Dogs	Experimental	1990	14	Single centre, Madison (USA)	Histomorphometric analysis of pituitary glands from dogs that were given excess exogenous thyroid hormone.	Evidence of atrophy and morphologic features of inactivity were seen in dogs with induced hyperthyroidism.	Evidence of thyrotroph atrophy in hyperthyroid dogs.
Scheithauer <i>et al.</i> [12]	Human	Retrospective Cohort	1992	33	N/A (Mayo Clinic Tissue Registry)	Pituitary glands from patients who died in a thyrotoxic state (18 with Graves', 15 toxic MNG) were examined post mortem.	Patients with untreated hyperthyroidism demonstrated significant atrophy. Degree of regression correlates well with severity of hyperthyroidism. Thyrotrophs of those with treated hyperthyroidism resemble normal controls.	Supports theory of pituitary atrophy seen in patients with severe hyperthyroidism.
Regional Mechanisms								
Solomon <i>et al.</i> [16]	Rats	Experimental	1965	N/A	Single centre, Montreal (Canada)	Pituitary glands from rats previously maintained on low-iodine diets were incubated, and total thyrotropin released was measured.	Length of incubation did not influence the rate of thyrotropin released per unit pituitary per unit time.	Supports existence of paracrine control for TSH release at the level of the pituitary gland.
Motta <i>et al.</i> [17]	Rats	Summary	1969	N/A	Single centre, Milan (Italy)	Thyroidectomized rats were injected with free thyroxine, TSH or saline (control). Hypothalamic TSH-RF, pituitary TSH, and plasma TSH contents were measured in response.	When rats were injected with TSH, hypothalamic TSH-RF and pituitary TSH content decreased, but plasma TSH level increased.	A short feedback control mechanism was hypothesized, although findings were suggestive of a positive feedback.
Buerklin <i>et al.</i> [15]	Human	Prospective	1976	20	Single centre, Philadelphia (USA)	Euthyroid Graves' patients off antithyroid medications. Used Δ TSH in TRH stimulation test to assess for intrinsic function, and suppressed thyroid uptake scan with high-dose L-thyroxine to assess for thyroid autonomy.	Found a variety of responses post therapy, but 25% of study population demonstrated blunted TRH stimulation response while maintaining TSH suppressibility.	This subset may point to suppressed TSH secretion at the level of the pituitary.

APPENDIX 1. Articles describing possible mechanisms for ongoing suppression of TSH in Graves' patients after medical management. (cont'd.)

Author	Population	Study Design	Year	N	Country	Parameter	Relevant Findings	Interpretation
Regional Mechanisms (cont'd.)								
Rondelet <i>et al.</i> [18]	Rats	Experimental	1990	N/A	Single centre, Rotterdam (Netherlands)	Rats were induced to be hypothyroid with use of MMI or hyperthyroid with T4 intra-peritoneal injections. Peripheral thyroid function tests, hypophyseal stalk blood samples, and hypothalami were retrieved.	In hyperthyroid rats, TRH secretion increased by 40%. In hypothyroid rats, TRH release was not increased despite a significant increase in TSH levels, even after 3 weeks.	Suggestive of a local negative feedback mechanism at the level of the hypothalamus.
Uyet <i>et al.</i> [13]	Human	Prospective	1995	21	Single centre, Texas (US)	Graves' patients were followed with serial TRH stimulation tests for 6 months following RAI ablation.	19/21 patients developed central hypothyroidism, with a significantly blunted TRH stimulation response.	Feedback suppression of TSH levels occurs primarily at level of pituitary thyrotrophes.
Prummet <i>et al.</i> [14]	Human	Experimental	2000	18	Amsterdam (Netherlands)	Examined pooled anterior pituitary samples of 18 humans. Used PCR and immuno-histochemistry to look for TSHR in human pituitary gland.	Presence of TSHR RNA as well as expressed surface TSHR were found on folliculo-stellate cells of human pituitary gland.	TSHR on folliculo-stellate cells may be mechanism for paracrine control to TSH levels.
Immune-Mediated								
Dandona <i>et al.</i> [22]	Guinea Pigs	Experimental	1978	90	Single centre, Oxford (England)	Exogenous LATS, TSH, and IgG from Graves' patients were each injected into intact as well as thyroidectomised guinea pigs.	(1) In thyroidectomised guinea pigs, exogenous TSH increased pituitary TSH content. (2) With LATS, pituitary TSH decreased. (3) With IgG from Graves', intact pigs showed increased pituitary TSH content; in thyroidectomised pigs, pituitary TSH increased with concomitant drop in serum levels.	(1) Possible positive feedback between hypothalamus and anterior pituitary. (2) A "component" of IgG from Graves' patient that exhibit a negative feedback from the pituitary.
Ng <i>et al.</i> [24]	Human	Retrospective Cohort	1993	106	Single centre, Selangor (Malaysia)	Measured TBII and other thyroid autoantibodies were correlated with thyroid function tests. A subset was analysed for change at 6-12 weeks after initiation of medical treatment.	TSH remained suppressed 6-12 weeks after treatment in at least 74.1%. TBII positivity was significantly higher in the hyperthyroid group (by fT3/FT4) than in the euthyroid. Furthermore, TBII positivity is higher in overt hyperthyroidism than in subclinical.	N/A
Aizawa <i>et al.</i> [26]	Human	Retrospective Cohort	1995	225	Single centre, Sendai (Japan)	Thyroid function tests and autoantibodies were examined in Graves' patients who had received a single dose of 131I. Primary aim was to describe the change in TBII and TSAb titres.	TBII positivity was strongly correlated with overt and subclinical hypothyroidism.	Not discussed.

APPENDIX 1. Articles describing possible mechanisms for ongoing suppression of TSH in Graves' patients after medical management. (cont'd.)

Author	Population	Study Design	Year	N	Country	Parameter	Relevant Findings	Interpretation
Immune-Mediated (cont'd.)								
Brokken <i>et al.</i> [24]	Rats	Experimental	2001	24	Amsterdam (Netherlands)	Euthyroid rats (on MMZ and LT4) were injected with IgG of control humans (euthyroid), or Graves' humans in two different concentrations.	High-concentration Graves' IgG showed significantly lower 48h mean TSH levels relative to control and lower concentration ($p < 0.01$).	TBII of Graves' patients act on follicular-stellate cells with TSHR in the pituitary. Use of MMZ makes it unlikely that suppressed TSH is due to stimulated thyroid gland.
Brokken <i>et al.</i> [[19]	Human	Prospective Cohort	2003	45	Single centre, Amsterdam (Netherlands)	Graves' patients on anti-thyroid medications were followed until they achieved euthyroidism (by fT4 and fT3) for at least 3 months, at which time TSH and TBII titres were measured.	By mean time of follow-up (6.7 ± 1.5 months), 56% still had suppressed TSH. Strong negative correlation between TBII titres and TSH level ($p = 0.004$, $r = -0.424$).	Findings are supportive of the functionality of an ultra-short feedback via TSHR on folliculo-stellate cells.
Prummet <i>et al.</i> [23]	N/A	Review	2004	N/A	N/A	N/A	N/A	Ultra-short feedback via TSHR on folliculo-stellate cells allow for fine-tuning of TSH, preventing drastic swings in response to changes to serum thyroxine levels.
Chung <i>et al.</i> [20]	Human	Retrospective Cohort	2006	167	Single centre, Seoul (Korea)	Graves' patients on anti-thyroid medications, with biochemical euthyroidism (by fT4 and fT3) were followed until TSH recovered.	Mean time to TSH recovery was 8.7 ± 5.9 months after biochemical euthyroidism. Pre-treatment TBII activity was inversely correlated with serum TSH recovery at 3, 6, and 12 months ($p < 0.001$).	Continued TSH suppression is likely related to TRAb activity given the inverse correlation seen, with mean duration of suppression being 8.7 months.
Kabadiet <i>et al.</i> [25]	Human	Case Series	2007	50	Single centre, (USA)	Identified Graves' patients during a routine follow-up visit. Includes those on antithyroid medication or within 1 year after RAI ablation. Measured TSI concentration, TSH, fT3 and fT4.	Highest concentration of TSI corresponded with undetectable TSH; did not correlate with fT3/fT4. Lowest TSI levels with supranormal TSH levels.	TSI binds to TSHR on TRH-producing hypothalamic cells to provide negative feedback, upstream of pituitary gland, in addition to previously described ultra-short feedback loop in pituitary.
Woeber [27]	Human	Retrospective, Cohort	2011	23	Single centre, San Francisco (USA)	Data from TSI-positive Graves' patients on anti-thyroid medications were examined from initiation of treatment for 24 months or longer.	Mean time to TSH recovery was 6 months (range 3-8 months) in the group that converted from TSI positive to negative. In this same group, TSI became negative at a mean of 15 months (11-20 months). Where TSI remained positive, 10 ultimately had normal TSH despite high TSI titres.	Does not support direct suppressive effects on TSH by TSI. Questions whether a transient reduction in thyroidal responsiveness to TSI.

TSH: thyroid stimulating hormone; TSHR: thyroid stimulating hormone receptor; MMZ: methimazole; PTU: propylthiouracil; TBII: thyroid binding inhibitory immunoglobulins; TRH: thyrotropin-releasing hormone; MNG: multinodular goitre; TN: toxic nodule; FTI: free thyroxine index; LATS: long-acting thyroid stimulator

APPENDIX 2: Articles with clinical data on TSH recovery after medical management for Graves' disease.

Author	Study Design	Year	N	Population	Study Centre	End-Point	Therapy	Results	TBII-specific
Brokken <i>et al.</i> [19]	Prospective, Cohort	2003	45	Graves', mean age 38±12 years	Single centre, Amsterdam (Netherlands)	Euthyroid (by fT4 and fT3) for at least 3 months	Antithyroid medication only	Mean time to TSH recovery was 6.7±1.5 months	Strong negative correlation between TBII titres and TSH level (p = 0.004, r = -0.424)
Chiovato <i>et al.</i> [28]	Prospective, Cohort	1998	31	Graves', mean age 43.3±12.2 years	Single centre, Pisa (Italy)	Monitored at 1, 3, 6, and 12 months	Antithyroid medication for mean 13±9 months, followed by RAI ablation	At 1 year post-RAI, 24/31 (77.4%) were hypothyroid, as defined by persistently elevated TSH	N/A
Chung <i>et al.</i> [20]	Retrospective Cohort	2006	167	Graves', average age 40 years	Single centre, Seoul (Korea)	Data from 1995-2002; euthyroid (by fT4 and fT3) for a period of 12 or more months	Antithyroid medication (137 MMZ, 30 PTU)	Mean time to TSH recovery was 8.7±5.9 months	TBII activity is inversely correlated with serum TSH at 3, 6, and 12 months after recovery of TSH (p<0.001)
Uy et al. [23]	Prospective, Cohort	1995	21	Graves', mean age 34.8±2.3 years	Single centre, Texas (US)	Followed until hypothyroid (elevated TSH), euthyroid, or persistently hyperthyroid for 6 months post treatment	RAI ablation only	90% developed transient central hypothyroidism at a mean of 62.8±5.1 days post RAI	N/A
Woeber [27]	Retrospective, Cohort	2011	12	Graves', mean age not reported	Single centre, San Francisco (USA)	Followed after medication initiation at least 4 times within first 12 months, then ongoing follow-up at varied interval for at least 24 months or more. No end-point described	Antithyroid medication only	In this subgroup, mean time to TSH recovery was 6 months (range 3-8 months)	Did not examine TBII. However, found that in this subgroup, TSI disappeared by 15 months (range 11-20 months), whereas TSH recovery preceded this (p = 0.005).

TSH: thyroid stimulating hormone; RAI: radioactive iodine ablation; MMZ: methimazole; PTU: propylthiouracil; TBII: thyrotropin-binding inhibitory immunoglobulin