

Clinical Significance of Thyrotrophin Binding Inhibitor Immunoglobulins in Patients with Graves' Disease and Various Types of Thyroiditis

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It is well known that thyrotrophin receptor antibodies are present in the sera of patients with autoimmune thyroid disease.

There is now compelling evidence that the hyperthyroidism of Graves' disease is due to antibodies to the thyrotrophin (TSH) receptor. The measurement of these antibodies is valuable in the diagnosis and monitoring of Graves' disease and in predicting the outcome of treatment.

In the present study, thyrotrophin binding inhibitor immunoglobulin (TBII) activities were measured by radioreceptor assay, according to the method of Shewring and Smith¹⁾, in 30 patients with Graves' disease, 13 patients with Hashimoto's thyroiditis, 20 patients with lymphocytic thyroiditis with spontaneously resolving hyperthyroidism (LT-SRH), 5 patients with postpartum thyroiditis, and 7 patients with subacute thyroiditis.

The TBII activity results a mean of $3.0 \pm 3.0\%$ in normal controls, $44.8 \pm 8.7\%$ in Graves' disease, $8.69 \pm 8.06\%$ in Hashimoto's thyroiditis, $7.63 \pm 2.32\%$ in LT-SRH, $3.33 \pm 1.16\%$ in postpartum thyroiditis, and $2.67 \pm 2.33\%$ in subacute thyroiditis respectively.

These clinical and laboratory findings show that TBII also plays a role in the pathogenesis of Graves' disease.

The levels of the TBII activities in Hashimoto's thyroiditis and LT-SRH, suggest a pathognomic role similar to that of Graves' disease in above mentioned two disease, but that TBII activity is not significant in postpartum or subacute thyroiditis.

Key Words: *Thyrotrophin binding inhibitor immunoglobulins, Lymphocytic thyroiditis with spontaneously resolving hyperthyroidism*

INTRODUCTION

The recent development of a radioreceptor assay for thyrotrophin has made it possible to detect immunoglobulins that inhibit the binding of thyrotrophin to its receptor in some patients with autoimmune thyroid diseases²⁾.

Although these immunoglobulins have been detected primarily in patients with Graves' disease, in whom their relation with thyroid stimulating antibodies has been extensively studied³⁾, they have also been found in a small portion of hypothyroid patients with Hashimoto's thyroiditis²⁻¹⁰⁾. These immunoglobulins, originally called thyroid-stimulating immunoglobulins by Smith and Hall²⁾, are more appropriately termed thyrotrophin-binding inhibitor immunoglobulins⁴⁾, and they are now considered to be autoantibodies to portions of the thyroid plasma membrane, including the

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thyrotrophin receptor³¹). In the present study, we investigated the activity of thyrotrophin binding inhibitor immunoglobulins in Graves' disease and various types of thyroiditis, and analyzed the clinical and laboratory features of patients who have these inhibitors.

PATIENTS AND METHODS

Thirty patients with Graves' disease, 13 patients with Hashimoto's thyroiditis, 20 patients with LT-SRH, 5 patients with postpartum thyroiditis, and 7 patients with subacute thyroiditis (SAT) diagnosed inclusively between November, 1985 and October, 1986 have been studied (Table 6).

The diagnosis of Graves' disease was based on the following criteria: (1) Nervousness, profuse sweating, palpitation, fatigue and weakness, weight loss, increased appetite, thyroid enlargement and exophthalmos, (2) elevation of serum thyroxine (T4), and (3) increased radioactive iodine uptake.

The diagnosis of Hashimoto's thyroiditis was based on the following criteria: (1) hypothyroidism, enlarged, firm or hard thyroid gland, (2) decreased serum T4 and T3, (3) diffuse lymphocytic infiltration, often with a considerable admixture of plasma cells by the examination of fine needle aspiration cytology or biopsy, (4) decreased RAIU.

The clinical diagnosis of LT-SRH was based on the following criteria: (1) painless, non-tender goiter, (2) elevated serum T4, T3, and (3) decreased RAIU. The diagnosis of SAT was based on the following criteria: (1) painful, tender thyroid gland, (2) fever, (3) elevation of the erythrocyte sedimentation rate (ESR), (4) normal or elevated serum T4, T3, and (5) decreased RAIU.

The clinical diagnosis of post-partum thyroiditis was based on (1) a non-tender diffuse enlarged thyroid gland, puffy face, (2) normal or decreased serum T4, (3) history of recent delivery, and (4) decreased RAIU.

Thyroid hormone concentrations were measured by radioimmunoassay (RIA) with commercially available kits and T4 by Tetrabead-¹²⁵ from Abbott.

The serum thyroid stimulating hormone (TSH) was measured by immunoradiometric assay with the TSH Riabead Kit. Thyrotrophin binding inhibitor immunoglobulins (TBII) was measured utilizing the radioreceptor assay method of Shewring and Smith¹¹. Radiiodine uptake was measured at

2 and 24 hours after oral administration of 50 μCi ¹³¹I.

RESULTS

Laboratory findings in 10 normal controls, 1 male and 9 females, show serum T4 10.1 ± 1.6 $\mu\text{g/dl}$, serum TSH 1.87 ± 0.94 $\mu\text{IU/ml}$, TBII $3.0 \pm 3.0\%$, and ¹³¹I uptake at 2 hours $8.0 \pm 3.0\%$ and at 24 hours $23.0 \pm 8.0\%$ respectively (Table 6).

In 30 patients with Graves' disease, 8 males and 22 females, serum T4, TSH, and TBII were 19.2 ± 1.8 $\mu\text{g/dl}$, 0.76 ± 0.06 $\mu\text{IU/mL}$, and $44.9 \pm 8.7\%$ respectively. ¹³¹I uptake at 2 hours was $44.7 \pm 7.36\%$ and at 24 hours $57.5 \pm 6.95\%$ (Table 1, 6). In 13 patients with Hashimoto's thyroiditis, 2 males and 11 females, serum T4, TSH, and TBII were 3.56 ± 4.37 $\mu\text{g/dl}$, 24.05 ± 14.20 $\mu\text{IU/mL}$, $8.69 \pm 8.06\%$ respectively. ¹³¹I uptake shows 2 hour levels of $9.9 \pm 7.2\%$ and 24 hour levels of $20.9 \pm 15.1\%$ (Table 2, 6) (Fig. 1, 2).

Laboratory data in 20 patients with LT-SRH, 1 male and 19 females, shows serum T4 10.57 ± 3.74 $\mu\text{g/dl}$, TSH 1.73 ± 0.95 $\mu\text{IU/mL}$, TBII $7.63 \pm 2.32\%$ respectively, and ¹³¹I uptake shows 2 hours levels of $4.7 \pm 2.9\%$, and 24 hours levels of $12.8 \pm 9.6\%$ (Table 3, 6). In postpartum thyroiditis, serum T4, TSH, and TBII were 7.18 ± 3.53 $\mu\text{g/dl}$, 1.74 ± 1.14 $\mu\text{IU/mL}$, $3.33 \pm 1.16\%$ respectively, while ¹³¹I uptake at 2 hours was $3.66 \pm 1.15\%$ and at 24 hours was $10.33 \pm 7.64\%$ (Table 4, 6).

In subacute thyroiditis, 7 patients all female, serum T4, TSH, and TBII were 10.47 ± 2.56 $\mu\text{g/dl}$, 1.46 ± 0.65 $\mu\text{IU/mL}$, $2.67 \pm 2.33\%$ respectively. ¹³¹I uptake levels at 2 hours were $6.86 \pm 3.13\%$ and at 24 hours $16.0 \pm 12.0\%$ respectively (Table 5, 6).

DISCUSSION

There is almost universal agreement that thyroid autoantibodies exist and belong to the IgG class of immunoglobulins. These are antibodies against components of the thyroid plasma membrane, possibly including the TSH receptor. These immunoglobulins are thought to bind to their complementary antigenic regions on the plasma membrane and activate adenylate cyclase, thereby initiating a chain of reactions that leads to thyroid growth, increased vascularity, and hypersecretion of hormone.

The recent development of a radioreceptor assay for thyrotrophin has made it possible to detect immunoglobulins that inhibit the binding of

thyrotropin to its receptor in patients with autoimmune thyroid disease²¹.

Although these immunoglobulins have been principally detected in patients with Graves' disease³, they have also been found in a small proportion of hypothyroid patients with Hashimoto's thyroiditis²⁻¹⁰. These immunoglobulins, originally called thyroid-stimulating immunoglobulins by Smith and Hall³, are more appropriately termed thyrotrophin-binding inhibitor immunoglobulins⁴ and are now considered to be antibodies to por-

tions of the thyroid plasma membranes, including the thyrotrophin receptor³.

Radioreceptor techniques are employed to demonstrate that IgG is capable of inhibiting the binding of ¹²⁵I-labeled bovine TSH to specific binding sites on the humane or porcine thyroid membrane.

The present study shows that thyrotrophin inhibitor immunoglobulin levels are significantly elevated in all 30 patients with untreated Graves' disease (Table 1, 6). TBII activity was detected in

Table 1. Clinical and Laboratory Findings in Patients with Graves' Disease

Patient No. (n=13)	Age/Sex	Serum thyroxine (μ g/dl)	Serum thyrotrophin (μ IU/ml)	TBII (%)	RAIU (%)	
					2hr	24hr
1	33/M	14.2	0.60	58	58	52
2	33/F	16.2	0.73	44	65	69
3	22/F	16.2	0.68	70	42	63
4	49/M	22.9	0.65	51	22	44
5	26/F	24.0	0.75	40	69	47
6	40/M	14.0	0.50	22	24	47
7	33/F	20.2	0.75	21	34	44
8	20/M	23.4	0.90	64	70	72
9	43/F	19.6	0.66	23	52	52
10	17/F	14.3	1.15	17	66	51
11	39/F	24.0	1.0	77	40	75
12	28/M	19.0	0.75	40	20	40
13	48/M	21.7	0.88	74	48	66
14	32/F	14.4	0.64	23	21	38
15	33/F	22.3	0.76	22	45	65
16	49/F	16.5	0.91	95	45	65
17	29/F	18.0	0.77	82	51	86
18	46/F	12.7	1.06	31	30	50
19	33/F	24.0	0.60	85	25	62
20	64/F	24.0	1.23	53	40	47
21	59/F	24.0	0.79	63	21	11
22	51/M	23.3	0.98	48	26	25
23	36/F	24.0	1.03	14	53	77
24	60/F	24.0	0.92	22	97	78
25	22/F	10.1	0.73	21	44	57
26	24/F	24.0	0.63	34	67	93
27	46/F	24.0	0.69	32	55	91
28	33/F	10.6	0.62	38	41	64
29	17/F	10.7	0.79	22	14	40
30	35/M	23.1	0.76	63	69	65
	Mean $\pm$ S.D.	19.2 $\pm$ 1.8	0.76 $\pm$ 0.06	44.9 $\pm$ 8.7	44.7 $\pm$ 7.36	57.5 $\pm$ 6.95

Table 2. Clinical and Laboratory Findings in Patients with Hashimoto's Thyroiditis

Patient No. (n=13)	Age/Sex	Serum thyroxine ($\mu\text{g/dl}$)	Serum thyrotrophin ($\mu\text{IU/ml}$)	TBII (%)	RAIU (%)	
					2hr	24hr
1	24/F	3.5	60.0	0	16	35
2	54/F	6.7	7.34	0	8	10
3	57/F	4.8	44.43	11	1.4	4
4	33/F	4.4	42.0	10	13	23
5	23/F	4.8	45.16	7	27	44
6	31/F	11.5	5.34	22	5	17
7	60/F	1.4	60.0	0	4	4
8	39/F	8.1	1.36	1	5	10
9	37/F	8.1	0.77	0	7	27
10	32/F	8.0	4.09	7	11	39
11	49/M	8.9	33.8	48	5	13
12	38/F	9.4	7.28	0	19	42
13	30/F	8.5	1.19	7	8	4
Mean		3.56	24.0	8.7	9.9	20.9
$\pm$ S. D.		± 4.37	± 23.7	± 13.5	± 7.2	± 15.1

Table 3. Clinical and Laboratory Findings in Patients with Lymphocytic Thyroiditis with Spontaneously Resolving Hyperthyroidism

Patient No. (n=20)	Age/Sex	Serum thyroxine ($\mu\text{g/dl}$)	Serum thyrotrophin ($\mu\text{IU/ml}$)	TBII (%)	RAIU (%)	
					2hr	24hr
1	52/F	2.9	2.2	0	4	8
2	45/F	11.2	2.28	6	3	6
3	60/F	10.5	1.16	8	3	6
4	53/F	3.5	0.78	0	7	14
5	26/F	6.9	0.91	0	3	33
6	24/F	9.3	1.81	9	6	22
7	63/F	10.5	1.12	7	4	10
8	22/F	9.1	1.52	5	5	9
9	45/F	12.5	1.78	8	5	19
10	26/F	10.0	0.82	10	3	1
11	36/F	14.0	4.77	2	8	26
12	24/F	7.5	1.63	6	4	11
13	53/F	9.4	1.8	12	9	22
14	33/F	13.1	0.71	8	1	1
15	29/F	8.6	1.97	5	2	6
16	32/F	17.7	1.43	10	1	1
17	32/F	15.8	0.87	9	1	1
18	42/F	8.6	1.34	2	4	8
19	26/F	11.6	2.22	7	4	12
20	32/F	8.2	1.73	8	12	23
Mean		10.0	1.73	7.63	4.7	12.8
$\pm$ S. D.		± 3.6	± 0.95	± 2.32	± 2.9	± 9.56

110 of 132 patients (83.3%) with untreated Graves' disease by Cho et al.¹¹⁾ In 9 cases of untreated Graves' disease, TBII activities ranged from 14-76 %, and were abnormally high in all cases when compared with 0.82% TBII activity in the normal controls by Kim et al.¹²⁾

In the present study, the mean serum TBII activities were $8.69 \pm 8.06\%$ in Hashimoto's thyroiditis and $7.63 \pm 2.32\%$ in lymphocytic thyroiditis with spontaneously resolving hyperthyroidism (LT-SRH) (Fig. 1, 2).

LT-SRH is characterized by a painless, non-

tender goiter, transient hyperthyroidism, decreased thyroid radioactive iodine uptake and focal or diffuse lymphocytic infiltration on biopsy (Table 3, 6).

LT-SRH has been classified as a variant of subacute thyroiditis (SAT), because the clinical course of each is so similar^{13,14)}. However, Dorfman et al.¹⁵⁾ and Nikolai et al.¹⁶⁾ have reported that LT-SRH was a similar form of the chronic lymphocytic thyroiditis (CLT), on the basis of the findings of positive thyroid auto-antibodies and lymphocytic infiltration on biopsy specimen. So far, LT-SRH

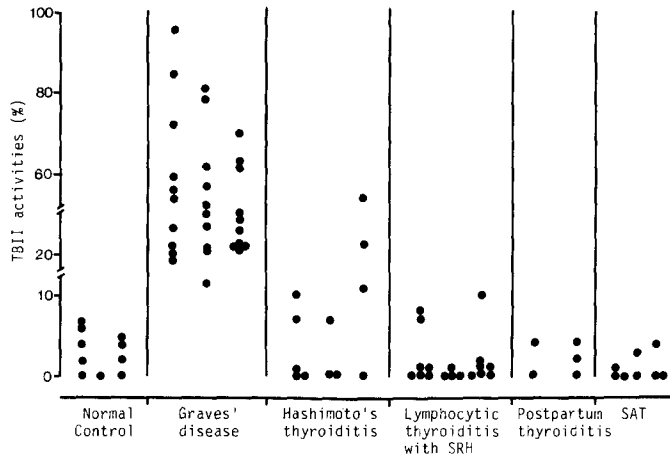


Fig. 1. TBII activities in the normal control and in patients with Graves' disease, Hashimoto's thyroiditis, lymphocytic thyroiditis with spontaneously resolving hyperthyroidism, postpartum thyroiditis and subacute thyroiditis.

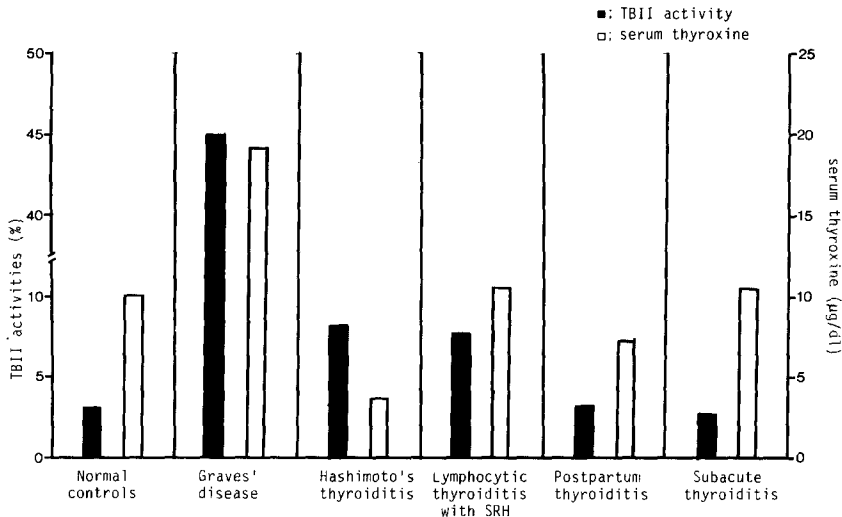


Fig. 2. TBII activities and serum T4 values (mean) in patients with Graves' disease, Hashimoto's thyroiditis, lymphocytic thyroiditis with spontaneously resolving hyperthyroidism, postpartum thyroiditis, subacute thyroiditis and normal controls.

has been known as an autoimmune thyroiditis. The TBII activity findings of our studies on Hashimoto's thyroiditis and LT-SRH, suggest that those diseases were a similar form of the disease from an immunological basis. The clinical course of LT-SRH has not been certain until now. Nikolai et al.¹⁶⁾

observed 54 patients with a history of LT-SRH over a 1 to 15 year period follow-up. 23 patients (42.6 %) were found to have a goiter after returning to normal thyroid hormone levels and persistent lymphocytic infiltration was noted on biopsy specimen. 5.6% of the patients showed permanent

Table 4. Clinical and Laboratory Findings in Patients with Postpartum Thyroiditis

Patient No. (n=5)	Age/Sex	Serum thyroxine (ug/dl)	Serum thyrotrophin (μ IU/ml)	TBII (%)	RAIU (%)	
					2hr	24hr
1	27/F	9.4	1.9	0	5	17
2	29/F	9.8	0.52	2	3	2
3	31/F	4.0	60.0	4	37	52
4	25/F	2.7	60.0	0	51	90
5	31/F	10.0	2.79	4	3	12
	Mean $\pm$ S. D.	7.18 $\pm$ 3.53	1.74 $\pm$ 1.14	3.33 $\pm$ 1.16	3.66 $\pm$ 1.15	10.33 $\pm$ 7.6

Table 5. Clinical and Laboratory Findings in Patients with Subacute Thyroiditis

Patient No. (n=7)	Age/Sex	Serum thyroxine (μ g/dl)	Serum thyrotrophin (μ IU/ml)	TBII (%)	RAIU (%)	
					2hr	24hr
1	44/F	8.9	1.4	0	8	19
2	35/F	9.3	1.68	0	7	19
3	48/F	7.4	1.49	1	10	15
4	26/F	10.8	1.44	3	9	35
5	43/F	13.4	2.68	4	9	22
6	61/F	14.4	0.89	0	3	1
7	31/F	9.1	0.68	0	2	1
	Mean $\pm$ S. D.	10.47 $\pm$ 2.56	1.46 $\pm$ 0.65	2.67 $\pm$ 2.33	6.86 $\pm$ 3.13	16.0 $\pm$ 12.0

Table 6. Clinical and Laboratory Data for Normal Control, Graves' Disease, and Various Types of Thyroiditis

Group	No. of patients	Sex		Age (yrs)	Total T4 (μ g/dl)	TSH (μ IU/ml)	TBII (%)	RAIU (%)	
		M	F					2hrs	24hrs
Normal control	10	1	9	28 $\pm$ 17	10.1 $\pm$ 1.6	1.87 $\pm$ 0.94	3.0 $\pm$ 3.0	8.0 $\pm$ 3.0	23.0 $\pm$ 8.0
Graves' disease	30	8	22	38 $\pm$ 12	19.2 $\pm$ 1.8	0.76 $\pm$ 0.06	44.9 $\pm$ 8.7	44.7 $\pm$ 7.36	57.5 $\pm$ 6.95
Hashimoto's thyroiditis	13	2	11	37 $\pm$ 11	3.56 $\pm$ 4.37	24.05 $\pm$ 14.20	8.69 $\pm$ 8.06	9.9 $\pm$ 7.2	20.9 $\pm$ 15.1
LT with SRH	20	1	19	38 $\pm$ 13	10.57 $\pm$ 3.74	1.73 $\pm$ 0.95	7.63 $\pm$ 2.32	4.7 $\pm$ 2.9	12.8 $\pm$ 9.6
Postpartum thyroiditis	5	(—)	5	29 $\pm$ 3	7.18 $\pm$ 3.53	1.74 $\pm$ 1.14	3.33 $\pm$ 1.16	3.66 $\pm$ 1.15	10.33 $\pm$ 7.64
Subacute thyroiditis	7	(—)	7	41 $\pm$ 12	10.47 $\pm$ 2.56	1.46 $\pm$ 0.65	2.67 $\pm$ 2.33	6.86 $\pm$ 3.13	16.0 $\pm$ 12.0

Mean $\pm$ S.D.

hypothyroidism while 32% of them had persistent antithyroid antibodies and 11% of the patients experienced recurrence. These findings suggest that LT-SRH may be as a persistent and progressive disease as CLT with recurrent episodes. Thus the development of goiter and thyroid failure may be a eventual progression. Gorman et al.¹⁷⁾ pointed out the lack of oxyphilic change, as a suggestive histologic difference from CLT, but Nikolai et al.¹⁸⁾ were against this finding by the observation of focal oxyphilic changes in the biopsy specimens of LT-SRH. One can not conclusively confirm a diagnosis of LT-SRH by only fine needle aspiration cytology of the thyroid gland^{19,20)} but we noted numerous lymphocytes in 20 patients of the LT-SRH group.

The TBII activities in subacute thyroiditis (SAT) were $2.67 \pm 2.33\%$, and were very low when compared with $3.0 \pm 3.0\%$ in the normal control values in this study (Table 5, 6).

These findings suggested that the etiology of SAT is rather than a classical autoimmune thyroiditis but of viral origin.

Volpé et al.²¹⁾ have described four functional stages of SAT. In the first stage, acute inflammation causes the release of preformed stores of thyroid hormones to the inflamed thyroid gland. The patients show signs of clinical hyperthyroidism, and thyroid RAIU is absent or quite low.

In the second stage, over a period of a few weeks, serum levels of thyroid hormones decline to normal and clinical evidence of hyperthyroidism ceases. In the third stage, serum thyroid hormone values decline to the hypothyroid level, serum TSH rises above normal levels, RAIU rises to normal or increased levels, and the patients may be clinically hypothyroid. The fourth stage is characterized by a return of all thyroid functions to normal.

The TBII activities in postpartum thyroiditis of this study were $3.33 \pm 1.16\%$, and were similar values compared with $3.0 \pm 3.0\%$ or normal control (Table 4, 6). Even though the TBII activities were almost equal between postpartum and subacute thyroiditis, but disease entity of these is quite different on the aspect of autoimmune basis.

Amino and co-workers^{22,23)} reported cases of transient postpartum hypothyroidism with positive antithyroid antibodies. Nikolai et al.^{24,25)} as well as Hamburger²⁶⁾ report an unusually high frequency of postpartum silent thyroiditis patients in the population. About half of the Amino group women with silent thyroiditis had episodes within 6 months of pregnancy. Fine needle biopsy in the thyrotoxic

phase showed lymphocytic thyroiditis²⁷⁾ and needle biopsy showed focal involution of epithelium without pseudogranulomas^{28,32)}. The occurrence of silent thyroiditis in the postpartum period indirectly suggests an autoimmune process. Moreover, antithyroid antibody titers fall during pregnancy and rebound at postpartum³³⁾. A reduction of goitrous hypothyroidism during pregnancy has been reported³⁴⁾. Patients with autoimmune thyroiditis, K-cells, and antithyroid antibodies increased after delivery³⁵⁾. These findings indirectly support a possible autoimmune etiology for silent postpartum thyroiditis, involving on antibody-dependent cell mediated cytotoxic process.

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