

## Original Research Article

# A correlative study of antithyroid antibodies level, thyroid functional status and histological evidence of thyroiditis in patients subjected to thyroidectomy

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### ABSTRACT

**Background:** There is inadequate data on relationship between histologic thyroiditis, thyroid functional status and antithyroid antibody levels. Aim of the study was to correlate prevalence of antithyroid antibody levels with thyroid functional status and histological evidence of thyroiditis in thyroidectomy specimen.

**Methods:** Thirty-two patients undergoing thyroidectomy were evaluated clinically and with thyroid function tests, preoperative TPOAb and TGOAb, ultrasound neck and FNAC. Histopathological examination to detect histological thyroiditis done. Patients with previous thyroid surgery or on thyroxine, antithyroid drugs, steroids, immune-suppressive drugs were excluded.

**Results:** Overall twenty-five out of thirty-two patients had elevation of one or other thyroid antibody levels (TPOAb- 22/32, TGOAb- 20/32). More than half of the patients with elevated antibodies were euthyroid biochemically, less than quarter each being hypothyroid and hyperthyroid. The incidence of hypothyroid increased in those with elevation of both antibody levels. FNAC reported four as Hashimoto's thyroiditis. Histology on the other hand showed a primary diagnosis of Hashimoto's thyroiditis in three, in one each as the secondary diagnosis with papillary carcinoma being the primary diagnosis in one and follicular adenoma in another. Histologic lymphocytic thyroiditis was seen in three cases and found to be always associated with a primary diagnosis such as colloid goitre. Thus, overall five patients had an additional primary diagnosis with thyroiditis being a secondary diagnosis. When histological thyroiditis was correlated with antibodies, it was seen that only seven out of eight with histological thyroiditis had elevated antibody levels. High titers in patients with histological thyroiditis were associated with euthyroid status in two patients and hyperthyroid status in the remaining three.

**Conclusions:** The study found no correlation between clinical and biochemical functional status with clinical examination under diagnosing both hypothyroidism and hyperthyroidism. No definite correlation was noted with mild increases in antithyroid antibody levels and histological thyroiditis, very high values and raises in both TPOAb and TGOAb may suggest histological thyroiditis.

**Keywords:** Histopathology, Thyroid antibody, Thyroid function, Thyroiditis, Thyroid surgery

### INTRODUCTION

Receiving a report of incidental thyroiditis existing along with another diagnosis on histopathology of an excised thyroid gland is not uncommon. Autoimmune thyroid

diseases affect about 2-4% of women and up to 1% of men worldwide.<sup>1</sup> Autoimmune thyroiditis may be associated with transient hyperthyroidism usually followed in the long duration by hypothyroidism, the exact relationship between the antibody levels,

histological thyroiditis and functional status of the thyroid remains unclear. Antithyroid antibodies have been traditionally used to make a diagnosis of thyroiditis.<sup>2</sup> The prevalence of thyroid auto-antibodies in the general population is reported to vary from 5-27%.<sup>3</sup> Thyroid auto antibodies are considered to be most sensitive in diagnosing autoimmune thyroid disease.<sup>4</sup> This study was carried out to study the prevalence of antithyroid antibody in patients undergoing thyroidectomy for varied indications, the incidence of histological thyroiditis in these patients and the correlation of these two with the functional status.

## METHODS

Thirty-two consecutive patients undergoing thyroidectomy for various indications were studied over a three-year period from May 2010. Data as per the prepared proforma was collected from these patients. Patients with previous thyroid surgery or on anti-thyroid medicine, thyroxine, steroids or any immunosuppressive therapy were excluded.

Informed consent was obtained from the patients and the project was cleared by the institute human ethics committee. All consecutive patients fulfilling the eligibility criteria were subjected to a detailed history, assessment of social status by Kuppuswamy's scale and a through physical examination. They were then subjected to the following:

- Thyroid function test (TFT) - FT3, FT4 and TSH
- Pre-operative antithyroid antibody levels viz. Thyroid anti-peroxidase antibody (TPOAb).
- Anti-thyroglobulin antibody (TGOAb) by chemiluminescence immunoassay
- Ultrasound neck

- Fine needle aspiration cytology of the thyroid (FNAC)
- Histopathological examination (HPE) of excised gland.

Thyroidectomy specimens were sent for histopathological examination. Histopathological preparing of the slides was done as per standard methods using H and E stains by making thin sections from the tissue blocks (<3 mm) for examination. All slides were reported by a single pathologist for the presence of thyroiditis apart from the primary disease. The study was observational with no comparisons; statistical methods included percentage and ratio analysis.

## RESULTS

Patients ranged in age from 23-67 years (Mean 38.46) with a male: female ratio of 1:7. Duration of thyroid swelling varied. More than two-third of patients had the swelling for 1-3 years (68.8%). Minimum duration of the swelling among the 32 patients was eight months. Three patients had the swelling for less than three years, 22 for 1-3 years and seven for more than 3 years. Most common symptoms were pain in the swelling and rapid growth (40.6% each) followed by discomfort while swallowing (25%). Tachycardia was the most common sign followed by cardiac murmur and raised JVP. Clinically 23 patients had multi-nodular goiter, seven had solitary thyroid nodules and two had diffuse goiter.

Clinical assessment showed that 23 were euthyroid, five were hyperthyroid and four were hypothyroid. Assessment of function biochemically revealed different findings (Table 1). Only 46.9% were euthyroid biochemically as opposed to 71.9% clinically, the rest were almost equally hypothyroid and hyperthyroid.

**Table 1: Thyroid function tests at admission (N=32).**

FT3	N.	(%)	FT4	N.	(%)	TSH	N.	(%)	Thyroid status*
<2	12	37.5	<0.93	6	18.7	>4.2	9	28.1	Hypothyroid
2.0-4.4	14	43.8	0.93-1.7	11	34.4	0.27-4.2	15	46.9	Euthyroid
>4.4	06	18.7	>1.7	15	46.9	0.27	8	25.0	Hyperthyroid
Total	32	100		32	100		32	100	

\*Based on TSH value, normal values of lab: FT3: 2.0-4.4 pg/ml, FT4: 0.9-1.7 ng/dl, TSH: 0.27-4.2 IU/ml, Patients 'values: FT3: mean: 4.96, SD: ±6.95, median: 2.46, FT4: mean: 2.05, SD: ± 1.82, median: 1.33, TSH: mean: 3.68, SD: ±4.50, median: 2.15.

The levels of anti-thyroid antibodies are shown in Table 2. 22 patients (68.7%) had increased levels of TPOAb and 20 (62.5%) had increased levels of TGOAb. Overall 25 out of 32 patients had elevation of one or both antibodies.

Biochemical functional status of the patients who had either antibody level elevated is shown in Table 3. More

than two-third were euthyroid functionally (87.5%). None were hypothyroid and one was hyperthyroid indicating that elevation of one of the antibody levels can be associated with different functional status. The functional statuses of 17 patients with elevation of both antibody levels are shown in Table 3. When both the antibody titres are elevated, patients are more likely to be

hypothyroid (35.3%) than when one antibody alone is raised (00%).

There was no correlation of duration of thyroid swelling with antibody positivity or functional status. 65.7% of FNAC were reported as consistent with colloid goiter. Two had colloid goiter with lymphocytic infiltration. Five patients were reported as papillary cancer and four patients had Hashimoto's thyroiditis. Correlation between FNAC and histopathological reports is shown in Table 4.

**Table 2: Anti-thyroid antibody levels (N=32).**

Antibodies	Normal	(%)	Increased	(%)	Total
TPOAb	10	31.3	22	68.7	32
TGOAb	12	37.5	20	62.5	32

Lab. reference values: anti-thyroid peroxidase antibody (TPOAb): < 5.6 IU/ML, anti-thyroid globulin antibody (TGOAb): < 4.1 IU/ML, Patients' values: TPOAb: mean: 117.17, SD: ±248.0, median: 11.97, TGOAb: mean: 77.40, SD: ±183.5, median: 7.520.

**Table 3: Functional status (biochemical) of patients with elevation of either antibody or both antibody levels.**

TSH	Patients with one or both antibody level raised (n=25)		Patients with one antibody level raised (n=8)		Patients with both antibody levels raised (n=17)		Thyroid status
	Number	(%)	Number	(%)	Number	(%)	
>4.2	6	24.0	0	00.0	6	35.3	Hypothyroid
0.27-4.2	14	56.0	7	87.5	7	41.2	Euthyroid
<0.27	5	20.0	1	12.5	4	23.5	Hyperthyroid
Total	25	100.0	8	100.0	17	100.0	

**Table 4: correlation of FNAC with histo-pathological examination (n=32).**

FNAC diagnosis	N.	Histopathological diagnosis					Total
		Papillary carcinoma	Hashimoto's thyroiditis	Follicular adenoma	Colloid goitre	Lymphocytic thyroiditis	
Papillary carcinoma	5	5*	-	-	-	-	5
Hashimoto's thyroiditis	4	-	3	1#	-	-	4
Colloid goitre	21	2	-	2	16	1	21
Colloid goitre with lymphocytic infiltration	2	-	-	-	-	2	2
Total	32	7	3	3	16	3	32

\*One out of five had additional finding of Hashimoto's thyroiditis, #HPE diagnosis of follicular adenoma with Hashimoto's thyroiditis.

**Table 5: Functional status of the seven out of eight patients with histological thyroiditis who had raised antibody levels.**

HPE finding	Antibody status		Functional status
	TPOAb	TGOAb	
Papillary carcinoma	702.0	250.0	Euthyroid
Follicular adenoma	781.2	30.7	Euthyroid
Lymphocytic thyroiditis	2.9	3.4	Euthyroid
Hashimoto's thyroiditis	10.0	6.9	Euthyroid
Lymphocytic thyroiditis	348.8	124.3	Hyperthyroid
Lymphocytic thyroiditis	184.0	235.6	Hyperthyroid
Hashimoto's thyroiditis	1.3	39.7	Euthyroid
Hashimoto's thyroiditis	1000	1000	Hyperthyroid

On histology three patients were reported to have Hashimoto's thyroiditis as their primary diagnosis. Two additional patients one with papillary cancer and the other with follicular adenoma, showed evidence of Hashimoto's thyroiditis as second diagnosis. Three

patients had lymphocytic thyroiditis without sufficient evidence for calling it Hashimoto's thyroiditis. The functional status of seven out of eight patients who had both, thyroiditis and raised antibody levels is shown in Table 5. It is seen that the majority (five out of eight) were euthyroid. The rest were hyperthyroid.

## DISCUSSION

Autoimmune thyroid diseases affects about 2-4% of women and up to 1% of men worldwide.<sup>1</sup> Estimation of thyroid antibody levels for identifying autoimmune thyroiditis is in practice since 1953.<sup>2</sup> The prevalence of thyroid auto-antibodies in the general population is reported to vary from 5-27%.<sup>3</sup> Thyroid auto antibodies are considered to be most sensitive in diagnosing autoimmune thyroid diseases.<sup>4</sup> However, they can be present even in normal individuals without any apparent thyroid disorder.<sup>4,5</sup> The recent national health and nutrition examination survey- III from the United States of nearly 17,000 subjects without apparent thyroid diseases reported detectable TPOAb levels in 12 % of subjects using a competitive immunoassay method.<sup>5</sup> Besides, autoimmune thyroid disease may present with absent thyroid antibodies as was noted in one of our patients. Such a finding has also been documented in a study done by Feldt-Rasmussen et al, hence the use of thyroid auto-antibodies in diagnosis and/or monitoring the treatment for auto immune thyroid disorders requires a relook.<sup>6</sup>

There are very few studies which correlate antibody levels with histological evidence of thyroiditis. The present study was conducted to determine the efficacy of anti-thyroid antibodies in diagnosing thyroiditis and at correlating the thyroid functional status, histological thyroiditis and anti-thyroid antibody levels in patients undergoing thyroidectomy. In a developing country like ours the cost of anti-thyroid antibody titer estimation is prohibitive for large segments of the society, especially in a setting wherein the sensitivity and specificity of such estimation lacks conclusive proof. Hence this study will yield results which may rationalize selection of patients for evaluating antibody levels.

### *Significance of biochemical and clinical assessment of thyroid function*

Biochemical assessment of thyroid function is substantially different from clinical assessment of thyroid status. In present study, there was no correlation between the functional status as assessed by clinical and biochemical methods. Most of the patients were euthyroid based on clinical assessment (71.9%). Further 15.6% and 12.5% of the patients were hyperthyroid and hypothyroid respectively. However, on biochemical evaluation based on TSH values, 15 out of 32 were found to be euthyroid (46.9%). Also 8 out of 32 were found to be hyperthyroid (25%) and 9 out of 32 patients were hypothyroid (28.1%). Hence the percentage of patients found to be hypo or hyperthyroid increased on biochemical evaluation. This suggests the presence of subclinical hypothyroidism or hyperthyroidism may be missed on clinical examination alone and biochemical assessment of thyroid function rather than assessment based on clinical examination alone is required in every patient.

### *Correlation between antibody titres and biochemical functional status*

In current study, there were 25 patients who had elevations in thyroid antibody titres. Among these, 17 had elevations of both TPOAb and TGOAb while eight were found to have elevations of either TPOAb or TGOAb. Elevations in TPOAb (normal being less than 5.6 IU/ml) were found in 22 Patients (68.7%) and those elevated titres ranged from 10-1000 IU/ml. TGOAb titers were high (normal being less than 4.1 IU/ml) in 20 Patients (62.5%) and ranged from 5.66-1000 IU/ml when elevated.

Among patients with increased antibodies, 56% (14 out of 25) were found to be euthyroid, 20% (5 out of 25) were hyperthyroid and 24% (6 out of 25) were hypothyroid biochemically. In 17 patients who had elevations in both TPOAb and TGOAb, 41.2% (7 out of 17) patients were euthyroid, 23.5% (4 out of 17) were hyperthyroid and 35.3% (6 out of 17) were hypothyroid. In eight patients who had elevation in either TPOAb or TGOAb one was hyperthyroid (12.5%), the rest were euthyroid (87.5%). It appeared, therefore, that the number of patients who were hypothyroid increased when both the antibody titres were elevated rather than when single antibody titer was elevated (35.3% versus 00.0%). This difference was statistically significant with a p value of 0.05. Similarly, an increase in the rate of functional hyperthyroidism was also noted (23.5% versus 12.5%).

Therefore, an important correlation between antibody titres and functional status of thyroid was noted in the study wherein a simultaneous elevation in both antibody titres (TPOAb and TGOAb) was associated with an increased rate of hypothyroidism.

These results were also found by Anjali et al.<sup>7</sup> In their study, which included a hundred patients with autoimmune thyroiditis, it was shown that in patients with elevation of both the antibodies, 47% were euthyroid and 47 % of patients were hypothyroid. Raman et al, who studied the impact of two decades of universal salt iodization on the prevalence of goiter, thyroid autoimmunity and thyroid dysfunction in Indian adults, found that TPOAb was positive in 13.3% adults and it correlated positively with thyroid dysfunction.<sup>8</sup>

### *Histological findings and correlation with functional status and antibody titres*

Histopathological analysis of thyroidectomy specimens was done by making micro sections (less than 3 mm) and staining with hematoxylin and eosin. All slides were reported by a single pathologist. In present study 8 out of 32 patients (25%) were found to be having a histological diagnosis of thyroiditis. Three among these eight had a primary diagnosis of Hashimoto's thyroiditis; the other two cases of Hashimoto's thyroiditis were associated with a primary diagnosis of papillary carcinoma and

follicular adenoma in one each. Histological lymphocytic thyroiditis in present study was found to be always associated with a primary diagnosis such as colloid goiter.

Kollur et al, studied follicular thyroid lesions coexisting with Hashimoto's thyroiditis, Hashimoto's thyroiditis coexisted with follicular adenoma in six cases, follicular variant of papillary carcinoma in one case, and goitrous nodule in two cases.<sup>9</sup> The overall incidence rates of thyroid neoplasm and goitrous nodules coexistent with Hashimoto's thyroiditis were 15% and 3.5%, respectively.

In the eight patients with histological thyroiditis seen by us, majority were found to be euthyroid functionally (62.5%), the rest were hyperthyroid. In the present study, it was found that 68.7% patients had elevated TPOAb, and 62.5% had elevated TGOAb. Of these, twenty-five patients with elevation of titre in single or both antithyroid antibodies levels, less than a third had thyroiditis on their final HPE diagnosis. Seventeen out of the twenty-five patients with positive antibody titres did not have any evidence of thyroiditis on histological evaluation. In those who had elevations of a single anti-thyroid antibody only (8 out of 32), none were diagnosed with thyroiditis on HPE. Of patients with elevated levels of both the antibodies (17 out of 32), seven were diagnosed to have histological thyroiditis.

Therefore, the elevation of single antithyroid antibody correlated poorly in predicting a diagnosis of thyroiditis. Elevations of both the antibodies (TPOAb and TGOAb) are more predictive in diagnosing thyroiditis than elevations in either TPOAb or TGOAb alone. However, the elevation of anti-thyroid antibody levels per se cannot be predictive of thyroiditis. There was one patient who was diagnosed to have histological thyroiditis and did not have an elevated antithyroid antibodies.

In patients with histological thyroiditis, the titer of antibodies was higher when compared to the rest suggesting that as the antibody titer rises, the possibility of thyroiditis increases. However, the titres above which such a possibility gains significance is yet to be determined and can be a case for further research.

In a study done by Shinto et al, in patients with histological diagnosis of autoimmune thyroiditis, majority were found to have raised levels of thyroid antibodies, TPOAb in 89% and TGOAb in 64% of the patients, which is like the antibody levels found in our patients with histological thyroiditis.<sup>10</sup> However, as shown in present study, an elevated antibody level does not necessarily imply a diagnosis of thyroiditis. In present study 25 patients had positive titres while only 8 cases of histological thyroiditis diagnosed; the rest 17 did not have histological thyroiditis despite high antibody titres). Hasanat et al, compared anti-thyroid antibody levels in patients with autoimmune thyroid disorder (AITD), non-

autoimmune thyroid disorder (NAITD) and indeterminate groups based on clinical and laboratory estimations, and found that a good number of those with clinically suspected AITD were negative for TPOAb (61.5%) and TGOAb (51.6%) antibodies.<sup>11</sup>

#### *Role of FNAC in diagnosing thyroiditis and correlation with histopathology*

Study found that FNAC underdiagnosed the prevalence of thyroiditis. Though it is highly specific for the diagnosis of Hashimoto's thyroiditis, as a tool for diagnosing lymphocytic thyroiditis it is unreliable. FNAC could diagnose thyroiditis in only four out of the 32 cases as opposed to eight cases which were diagnosed as thyroiditis on histopathology. In the four cases where FNAC diagnosed thyroiditis, the same was confirmed on HPE.

Parveen et al, studied the value of FNAC in diagnosis of different types of thyroiditis and its comparison with clinical and biochemical findings, it was found that FNAC is a safe, reliable, cost effective and time saving method in the diagnosis of thyroiditis which is in contradiction to present study where FNAC was diagnostic in only 50% of the cases.<sup>12</sup>

## CONCLUSION

Based on present study, the following conclusions were drawn.

- There was no correlation between clinical and biochemical thyroid functional status thus mandating need for routine biochemical assessment of thyroid function
- There was no correlation between antibody levels and functional status, with most patients having elevated antibodies being euthyroid. However, it was found that the incidence of hypothyroidism was more in patients with both antibody (TPOAb and TGOAb) titre positivity compared to either of them (TPOAb or TGOAb) alone
- There was no correlation between antibody levels and histological thyroiditis, with only eight patients showing histological thyroiditis among the twenty-five with positive antibody titres. However, it was found that in five out of eight patients with histological thyroiditis the titres were very high
- There was no correlation between FNAC and HPE in diagnosing thyroiditis. FNAC under diagnosed thyroiditis by diagnosing only four of the eight patients who had thyroiditis on HPE
- It was seen that histological diagnosis of Hashimoto's thyroiditis can be the sole pathology or can be secondarily be associated with a primary diagnosis such as papillary cancer or follicular adenoma
- Histological Lymphocytic thyroiditis in present study was found to be always associated with a primary



diagnosis such as colloid goiter. All procedures performed in studies involving human subjects were in accordance with the institute human ethical norms.

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