Antithyroid Peroxidase Antibodies and Histopathological Outcomes in Egyptian Patients Subjected to Total Thyroidectomy for Nonmalignant Nodular Goiter

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Abstract

Objective: The study aimed to assess antithyroid antibodies in patients with benign thyroid masses and the effect of total thyroidectomy on the antibodies titers.

Patients and Methods: This is a retrospective work of 112 cases managed with total thyroidectomy who have positive antithyroid peroxidase antibodies (TPO-Ab), antithyroglobulin antibodies (Tg-Ab), or both. All patients were euthyroid before surgery. Thyroid function tests and thyroid antibodies levels were measured before and 6 and 12 months after surgery.

Results: Histopathological evaluation revealed Hashimoto thyroiditis (47.3%), colloid nodules (22.3%), and lymphocytic thyroiditis (30.4%). All patients were TPO-Ab positive, while 96 patients (85.7%) were Tg-Ab positive before surgery. There was no considerable change in TPO-Ab and Tg-Ab after surgery ($p = 0.817$, and $p=0.560$, respectively). Also, there was no significant difference between the three histopathological diagnoses in the levels of TPO-Ab ($p = 0.086$) or Tg-Ab ($p = 0.673$).

Conclusion: Antithyroid antibodies are not valuable markers for diagnosis or prognosis of benign thyroid diseases subjected to total thyroidectomy. We do not recommend their use beyond being a supportive evidence of the possibility of autoimmune nature of the disease if other criteria are confirmed.

Introduction:

Thyroid peroxidase (TPO) is the key thyroid enzyme for iodination and coupling of tyrosine residues in thyroglobulin for the synthesis of thyroid hormone [1]. Anti-TPO antibodies are found in 90–95% of autoimmune thyroid diseases (AITD) patients, and 10–15% of non-AITD patients [2]. Anti-TPO antibodies in euthyroid individuals has no blocking TPO activity or interferance with the blocking activity of anti-TPO antibodies from AITD patients [3], while anti-TPO antibodies from AITD patients can damage thyrocytes, and inhibit the enzymatic activity [4]. Thyroglobulin (Tg) is a large glycoprotein containing three molecules of T4 and only 0.3 molecules T3. Antibodies against Tg can be induced by major destruction of the thyroid gland [5]. Anti-TPO antibodies are more common than anti-Tg antibodies and more indicative of thyroid disease [6].

Anti-thyroid antibodies are considered a sensitive marker of autoimmune thyroid diseases [7]. However, these antibodies can be detected in 5 to 27% in the general population [8].

The study aimed to assess the relation between thyroid auto-antibodies and histopathological findings and the effect of total thyroidectomy on the auto-antibodies titers in patients with benign thyroid masses.

Patients And Methods:

This prospective study included 112 patients managed with total thyroidectomy in KasrAl-Aini hospital, Cairo University between May 2016 and 2018. All methods were carried out in accordance with relevant

guidelines and regulations. Study protocol was approved by the Institutional Review Board of Cairo University Hospitals. Informed consent was obtained from all subjects included in the study

All patients presented to the endocrine and metabolism outpatient clinic complaining of nodular thyroid swelling that was proved to be non-malignant. Patients who were thyrotoxic or on thyroxine, on anti-thyroid drugs, steroids, or immunosuppressive drugs were excluded.

All included patients have positive anti TPO ab with or without positive anti TG ab

All patients are euthyroid before surgery. In the department of surgery, all patients were subjected to total thyroidectomy after proper pre-operative preparation. Thyroidectomy was done for cosmetic purposes, to alleviate pressure symptoms, or for suspected malignancy. Operations were done using standard transverse neck incision. Dissection was done taking care not to injure parathyroid glands or recurrent laryngeal nerve. Suction drain insertion was performed when indicated.

Weight-based L-thyroxin(1.4–1.6 microgm/kg) is prescribed to all patients postoperatively with dose adjustment based on target TSH level.

All patients were subjected to throughout history taking, general and local examination. Laboratory assessment included TSH, freeT4,T3, antithyroid peroxidase(TPO-Ab), and antithyroglobulin (Tg-Ab). All patients were assessed with Ultrasonography of the neck region.

Anti TPO-Ab levels > 40 IU/mL were considered TPO-Ab-positive,andthose with Tg-Ab levels > 20 IU/mLwere considered Tg-Ab-positive [9]

Antibody negative patients were excluded from the study.

Some patients (n = 55) (solitary, ithmic or dominant nodules with suspicious criteria) had fine needle aspiration cytology (FNAC)of thyroid nodule.

Thyroidectomy specimens were subjected to histopathological examination using H and E stains. Both FNAC and postoperative specemins are examined at kasrelaini pathology departement.

Postoperatively, laboratory assessment was repeated after 6 and 12 months. This included TSH,freeT4,T3, TPO-Ab, and Tg-Ab.Patients with TPO-Ab levels > 40 IU/mL were considered TPO-Ab-positive,andthose with Tg-Ab levels > 20 IU/mLwere considered Tg-Ab-positive [9].

Statistical Methods:

Statistical analysis was done using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relationship between qualitative variables.For quantitative data, a comparison between two groups was

made using independent sample t-test or Mann-Whitney test. Comparison between 3 groups was made using ANOVA test, or Kruskal-Wallis test followed by the appropriate post-hoc test. Comparison of repeated measures was made using Friedman test followed by Wilcoxon signed-ranks test. A p-value < 0.05 was considered significant.

Results:

The age of the patients ranged from 24 to 52 years with a mean of 37.2 ± 6.8 years. The male to female ratio was 1:3.7. The results of FNAC and postoperative histopathological examination are shown in Table 1. FNAC was acellular in 5 cases. In the remaining 50 patients, FNAC completely agreed with surgical specimen examination in the diagnosis of colloid nodules. The main difference was in the detection of lymphocytic infiltration in 40% of patients with colloid nodules (Table 2). Ultrasound examination revealed solitary thyroid nodule (STN) in 48 patients (42.85%), multinodular goiters (MNG) in 64 (57.15%).

Table 1
Histopathological findings of FNAC and examination of surgical specimens

Histopathology	FNAC (n = 50)	Surgical specimen (n = 112)
Nodular Hashimoto thyroiditis	23 (46.0%)	53 (47.3%)
Colloid nodules	18 (36.0%)	25 (22.3%)
Colloid nodules with lymphocytic infiltration	9 (18.0%)	34 (30.4%)

Table 2
Relation between FNAC diagnosis and surgical specimen examination in 50 patients

	Surgical specimen		
	Hashimoto thyroiditis	Colloid nodules	Lymphocytic Thyroiditis
FNAC			
Nodular Hashimoto Thyroiditis	23 (95.8%)	0 (0.0%)	0 (0.0%)
Colloid Nodules	1 (4.2%)	11 (100.0%)	6 (40.0%)
LymphocyticThyroiditis	0 (0.0%)	0 (0.0%)	9 (60.0%)

Table 3 shows the baseline thyroid function tests and antithyroid antibodies. All patients were TPO-Ab positive, while 96 patients were Tg-Ab positive (85.7%). Compared to baseline readings, there was no

significant change of TSH after surgery. On the other hand, free T4 increased significantly 12 months after surgery compared to baseline ($p < 0.001$). There was no significant change in T4 after six months compared to baseline ($p = 0.145$).Free T3 increased significantly six months after surgery compared to baseline ($p = 0.009$). By 12 months after surgery free T3 returned near the baseline reading ($p = 1.000$).There was no significant change in the two autoantibodies after surgery (Table 4).

Table 3
Baseline thyroid function tests and levels of antithyroid antibodies

	value
Thyroid-Stimulating Hormone (IU/mL)	2.36 ± 0.93
Free Thyroxine (ng/dL)	1.12 ± 0.19
Free Triiodothyronine (pg/mL)	2.84 ± 0.37
TPO-Ab (IU/mL)	512.5 (39.0-1300.0)
Tg-Ab (IU/mL)	256.0 (5.0-1300.0)
Data are presented as mean ± SD or median (range)	
TPO: antithyroid peroxidase, TGO: anti-thyroglobulin	
Table of postoperative histopathology(n = 112)	

Table 4
Baseline thyroid function tests and levels of antithyroid antibodies

	Baseline	**6 months**	**12 months**	**p value**
TSH (mIU/mL)	2.36 ± 0.93	2.51 ± 1.48	2.18 ± 0.90	0.112
Free T4 (ng/dL)	1.12 ± 0.19	1.19 ± 0.29	1.24 ± 0.30	0.001
Free T3 (pg/mL)	2.84 ± 0.37	3.05 ± 0.68	2.89 ± 0.47	0.010
TPO-Ab (IU/mL)	513 (39-1300)	505 (5-1300)	495 (5-1300)	0.817
Tg-Ab (IU/mL)	256 (5-1300)	256 (5-1300)	231 (5-1300)	0.560
Data are presented as mean ± SD or median (range)				
TSH: Thyroid-Stimulating Hormone, T4: Thyroxine, T3: Triiodothyronine, TPO-Ab: antithyroid peroxidase, Tg-Ab: anti-thyroglobulin				

As shown in Table 5, there was no significant difference between the three histopathological diagnoses in the levels of TPO ($p = 0.086$) or TGO ($p = 0.673$).Postoperative hypocalcemia was observed in 3 patients

while unilateral recurrent laryngeal nerve injury occurred in 2 patients.

Table 5
Baseline levels of antithyroid antibodies in different histopathological diagnoses

	TPO-Ab	Tg-Ab
Nodular Hashimoto thyroiditis	550 (39-1300)	265 (8-1300)
Colloid nodules	545 (110–1300)	160 (5-1250)
Lymphocytic Thyroiditis	460 (70-1300)	328 (5-1300)
p value	0.086	0.673
Data are presented as median (range)		
TPO-Ab: antithyroid peroxidase, Tg-Ab: anti-thyroglobulin		

Discussion:

The results of this study demonstrated that the levels of TPO-Ab and Tg-Ab were rather high in the majority of the studied group with no significant differences between the three diagnoses (Nodular Hashimoto thyroiditis, colloid nodules, and lymphocytic thyroiditis). One year after total thyroidectomy, there was no significant change in the levels of both TPO-Ab and Tg-Ab. Therefore, the two autoantibodies did not have a diagnostic or prognostic significance in the current series of benign nodular thyroid diseases.

Increased levels of anti-thyroid antibodies were linked to the diagnosis of autoimmune thyroid diseases (AITD) [1]. It is also detected in 10–15% of non-AITD patients [2]. Hashimoto thyroiditis is usually defined as the presence of serum thyroid autoantibodies which is correlated with intraglandular lymphocytic infiltrate [3]. The presence of thyroid antibodies in serum was found to be correlated well with lymphocytic infiltration [4, 5]. Also, a good correlation was found between the level of antibodies and the severity of thyroiditis histologically [6].

However, thyroid antibodies have been detected in population surveys and patients with extrathyroid diseases. TPO-Abs were detected in 6.8% and Tg-Ab in 2% of a sample of 2799 people in the Whickham study in the UK [7]. Data from the National Health and Nutrition Examination Survey from the USA showed TPO-Ab in 13% and Tg-Ab in 11.5% of the examined sample of 17,353 people [8]. A more recent population study in Tehran, reported TPOAb positivity in 12.8% of their sample, with a higher prevalence among women [9]. This variation may be contributed to genetic and environmental factors as iodine intake or the type of antibody assays used in different studies [10]. TPO-Abs are frequently detected in pregnant women [11, 12]. TPO-Ab positivity has been shown to be related to adverse pregnancy outcome as miscarriage, premature delivery and low birth weight [13–16].

In patients with autoimmune thyroid disease, Tg-Ab and TPO-Abs appear to increase due to thyroid inflammation. Thisis evidenced by their polyclonality and their failure to induce disease when transferred to animal models [3]. In animal models, thyroid antibodies develop spontaneously without a definite stimulus [17]. In humans, it is not clear how these antibodies are induced. However, epidemiological studies revealed valuable observations. Previous studies demonstrated that thyroid antibodies are not common in children. Female gender and puberty are strongly associated with thyroid antibody development [18, 19]. The autoantibodies showed a tendency to increase with age [20]. It was shown that 21% of women of the Whickham cohort coveted to thyroid antibody positivity around the age of menopause [21]. Increased titers were associated with increasing age [22].

The two important findings of the current study were increased antithyroid antibodies irrespective of the nature of the disease and non-significant effect of surgery on the antibody levels. These results indicate a lack of diagnostic value of TPO-Ab and Tg-Ab for differentiating AITD and non-AITD in this series. Colloid nodule with no evidence of thyroid inflammation was the diagnosis of 38% of cases in this series. In these patients, TPO-Ab and Tg-Ab were as high as in cases of Hashimoto and lymphocytic thyroiditis. The two antibodies were not valid as markers of the effect of surgery, as no significant change was associated with surgery.

Based on these findings and the literature evidence of the presence of antithyroid antibodies in healthy people, we can conclude that antithyroid antibodies are not valuable markers for diagnosis or prognosis of benign nodular thyroid diseases subjected to total thyroidectomy. We do not recommend their use in nodular goitre beyond being and supportive evidence of the possibility of autoimmune nature of the disease if other criteria are confirmed.

Conclusions:

The study aimed to assess antithyroid antibodies in patients with benign thyroid masses and the effect of total thyroidectomy on the antibodies titers.

Antithyroid antibodies are not valuable markers for diagnosis or prognosis of benign thyroid diseases subjected to total thyroidectomy. We do not recommend their use beyond being a supportive evidence of the possibility of autoimmune nature of the disease if other criteria are confirmed.

Abbreviations:

antithyroid peroxidase antibodies (TPO-Ab),

antithyroglobulin antibodies (Tg-Ab)

Declarations:

There is no financial interest to report. We have no conflict of interest and the article does not violate the policies and/or procedures established by the journal

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done

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Mohamed AbdAlla Salman (Corresponding Author)

Role: Takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process, general idea of work, planning the work.

Ahmed Rabiee

Role: Work idea , Data collection ,making modifications as appropriate as the work progresses

Tarek Elsayed Ftohy

Revision of data critically, General design of work with gathering of preliminary important information

Ahmed Salman

Role: Putting steps the work, making modifications as appropriate as the work progresses

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