Serum levels of anti-thyroid autoantibodies in different thyroid function status

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Background
Thyroid disorders are one of the most prevalent medical conditions, especially in women. Autoimmune thyroid diseases are the most common causes in which the patient's immune system attacks thyroid gland with generation of thyroid autoantibodies. However, antibody testing is not widely available for routine clinical practice.

Aim
This study was conducted to determine the level of autoantibodies against thyroid peroxidase (anti-TPO), thyroglobulin (anti-TG), and thyrotropin receptor (TRAB) in different status of thyroid function.

Patients and methods
Thyroid function tests included thyroid-stimulating hormone (TSH), Free T3 (FT3), and Free T4 (FT4) with anti-thyroid autoantibodies (anti-TG, anti-TPO, and TRAB).

Results
Anti-TG level was significantly increased in patients with hypothyroidism when compared with patients with normal thyroid function and control group. Anti-TPO level was significantly increased in patients with hypothyroidism when compared with those with normal thyroid function and control group, and it was significantly increased in patients with hyperthyroidism when compared with patients with normal thyroid function and control group. There was a nonstatistically significant increase in TRAB level in patients with hyperthyroidism when compared with patients with hypothyroidism, those with normal thyroid function, and control group. There was a significant moderate positive correlation between TRAB level and FT3 level and with FT4 level, and in the correlation study between thyroid autoantibodies with each other, there was a significant strong positive correlation between anti-TPO and anti-TG.

Conclusion
Anti-TPO and anti-TG have a role in the pathogenesis and diagnosis of autoimmune thyroid disorders, and their tests should be requested for patients with thyroid dysfunction.

Keywords:
anti-thyroglobulin, anti-thyroid peroxidase, autoimmune thyroid diseases, thyrotropin receptor

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Introduction

Thyroid disorders are one of the most prevalent medical conditions, especially in women. Disorders of the thyroid include both overt and subclinical hypothyroidism and hyperthyroidism [1]. Hypothyroidism means the thyroid gland is not making enough hormone. The most common cause of primary hypothyroidism is Hashimoto's thyroiditis [2]. Hyperthyroidism means the thyroid makes too much T4, T3, or both. The most common cause of hyperthyroidism is Graves' disease [3].

Autoimmune thyroid diseases are the most common causes of thyroid disorders in which the patient's immune system attacks and damages thyroid gland with generation of thyroid autoantibodies against thyroid antigens [4]. The etiology of autoimmune thyroid disorder (AITD) is multifactorial and the susceptibility to AITD including genetic predisposition and environmental factors [5].

Hashimoto thyroiditis is caused by interaction between thyroid cells, antigen-presenting cells (APCs), and T cells [6]. This is initiated by breakdown of the immune tolerance leading to accumulation of MHC class II-positive APC in the thyroid which invade thyroid as a consequence of inflammatory events in the gland [7]. APCs present autoantigens to T cells, leading to stimulation and clonal expansion of T cells followed by maturation of autoreactive T and B lymphocytes [8]. Thyroglobulin (TG) and thyroid peroxidase (TPO) are the most significant autoantigen in the thyroid of patients affected with Hashimoto thyroiditis resulting in the formation of anti-TG and anti-TPO [9].

Graves' disease is caused by the production of thyroid-stimulating hormone (TSH) receptor antibodies, which stimulate the TSH receptors, initiating unregulated synthesis of thyroid hormones [10]. The immunological events proceeds through T-cell receptor antigen recognition, followed by activation of the T-cell, leading to IL-2 secretion, which cause proliferation of the T-cell [11], leading to development of humoral autoimmune response. An increase in T-helper lymphocytes, especially in Th1 lymphocytes, results in activation of B lymphocytes and their conversion into plasma cells, which produce thyroid antibodies, primarily TRAB and also TPO Ab and TG Ab. The antibody deposits do not damage thyrocytes but augment their activity by activation of thyroid hormones receptors, leading to hyperthyroidism [12].

However, antibody testing is not widely available for routine clinical practice, and the utility of antibody testing in Egyptian patients with thyroid disease is unclear, so this study was designed to determine the levels of anti-TPO, anti-TG, and TRAB in different statuses of thyroid function to investigate their role in etiology and diagnosis of thyroid disorders.

Patients and methods

Patients were recruited from patients referred – for thyroid hormone testing – to the Hormones Laboratory of Clinical Pathology Department, Assiut University Hospital. Assiut, Egypt. The following exclusion criteria were applied: male patients, patients with thyroid malignancy, patients with previous thyroid surgery, patients with chronic liver disease, patients with chronic kidney disease, patients with positive antinuclear antibodies and/or positive rheumatoid factor, patients with diabetes mellitus, pregnancy, use of oral contraceptive, and patients on steroid therapy, amiodarone, nitroprusside, sulfonylureas, interleukin, lithium, interferon-α therapy, and iodide.

The study was conducted on 69 female patients. Their age ranged from 11 to 55 years. They included 30 patients with hyperthyroidism, 24 patients with hypothyroidism and 15 patients with normal thyroid function test. All patients were subjected to complete history taking. Moreover, 14 apparently healthy females were included in the study as a control group. Their age ranged from 16 to 54 years. The study was approved by the Ethical Committee of Faculty of Medicine, Assiut University. Patients were recruited into the study after giving informed consent either by patient herself or by her parent/guardian.

Collection of blood specimens

Four ml of venous blood was collected under complete aseptic conditions into Wasserman tube, allowed to clot for 15 min in water bath at 37°C, and then centrifuged at 3000 rpm for 10 min Sera were inspected to ensure it is clear and nonhemolyzed and evacuated in new tubes; part of collected serum was used immediately for thyroid function test, and the rest of serum was divided into aliquots and stored at −50°C for later use.

Laboratory investigations

(1) Serum TSH, free T4, and free T3 were measured in Hormones laboratory. These tests were performed on Immulite 1000 (Siemens Healthcare Diagnostics, Los Angeles, CA, USA) according to manufacturer's instructions.
(2) Thyroid autoantibody testing was done in Laboratory of Clinical Immunology. Anti-TG and anti-TPO were measured on Architect i1000 (Abbott, Illinois, USA) according to manufacturer's instructions. TRAB was tested using SinoGenClon Biotech ELISA kit (cat. no SG-90003; Sinogeneclon Biotech, Hangzhou, China) according to manufacturer's instructions. This SinoGenClon kit is for research use.

Statistical analysis

Data were collected and analyzed using IBM-SPSS 21 (IBM, Chicago, Illinois, U.S.A). Quantitative data were described by means, medians, SD, and range. Mann–Whitney *U*-test was calculated to test the differences between two groups for variables that do not follow normal distribution. For variables with more than two categories, independent sample Kruskal–Wallis test was used to compare the median difference, and if significant, *post-hoc* test was calculated using Bonferroni corrections. Pearson's correlation analysis was used to test the relation between variables. A *P* value equal to or less than 0.05 was considered significant.

Results

This study was conducted on 69 female patients with age ranged from 11 to 55 years (mean ± SD = 32.3 ± 10.3 years). In addition to the patient groups, 14 apparently healthy females were included in the study as a control group. Their age ranged from 16 to 54 years (mean ± SD = 26.5 ± 9.9). There was no statistically significant difference in age distribution between patients and control participants ($P = 0.165$). Study participants (patients and control) were classified into:

(1) Group I: twenty-four patients with hypothyroidism who were subclassified into the following:
   (a) Twelve newly diagnosed patients.
   (b) Twelve patients receiving hormonal replacement therapy.
(2) Group II: thirty patients with hyperthyroidism who were subclassified into the following:
   (a) Fifteen newly diagnosed patients.
   (b) Fifteen patients receiving carbimazole therapy.
(3) Group III: fifteen patients with euthyroid status; however, they have manifestations of thyroid disorders.
(4) Group IV (control group): fourteen apparently healthy females with normal serum TSH.

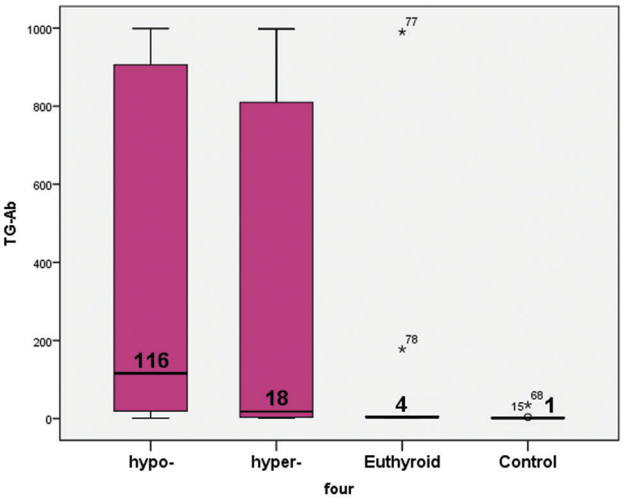
The results of thyroid autoantibodies showed statistically significant increase in anti-TG level in patients with hypothyroidism (mean ± SD = 349.1 ± 89.5 IU/ml) when compared with patients with normal thyroid function (mean ± SD = 81.1 ± 15.9 IU/ml) and control group (mean ± SD = 4.54 ± 1.8 IU/ml). Moreover, there was a statistically significant increase in anti-TG level in patients with hyperthyroidism (mean ± SD = 305.2 ± 82.5 IU/ml) when compared with control group. Anti-TG antibodies level was increased in patients with hyperthyroidism when compared with patients with normal thyroid function, but this did not reach level of statistical significance (P = 0.069; Table 1 and Fig. 1).

There was a statistically significant increase in anti-TPO level in patients with hypothyroidism (mean ± SD = 494.1 ± 94.5 IU/ml) when compared with patients with normal thyroid function (mean ± SD = 87.3 ± 18.3 IU/ml) and control group (mean ± SD = 2.26 ± 1.5 IU/ml). Moreover, there was a statistically significant increase in anti-TPO level in patients with hyperthyroidism (mean ± SD = 379.5 ± 82.3 IU/ml) when compared with patients with normal thyroid function and control groups (Table 1 and Fig. 2).

There was a nonstatistically significant increase in TRAB level in patients with hyperthyroidism (mean ± SD = 724.1 ± 53.8 μIU/l) when compared with patients with hypothyroidism (mean ± SD = 360.4 ± 24.5 μIU/l), those with normal thyroid function (mean ± SD = 451 ± 91.8 μIU/l), and control group (mean ± SD = 412 ± 121.5 μIU/l) (Table 1 and Fig. 3).

In the hypothyroid group, there was a statistically significant difference in serum anti-TG level between newly diagnosed patients (mean ± SD = 412.88 ± 142.5 IU/ml, median = 93 IU/ml) when compared with those receiving hormonal replacement therapy (mean ± SD = 290.5 ± 114.6 IU/ml, median = 121 IU/ml). There was a statistically significant increase in anti-TPO level in newly diagnosed patients (mean ± SD = 585.97 ± 132.5 IU/ml, median = 717 IU/ml) when compared with those receiving hormonal replacement therapy (mean ± SD = 443.9 ± 132.1 IU/ml, median = 247 IU/ml) (Table 2).

Figure 1



Anti-thyroglobulin level in different study groups.

Table 1 Levels of thyroid autoantibodies in the study groups

	Hypothyroid (I) (n=24)	Hyperthyroid (II) (n=30)	Euthyroid (III) (n=15)	Control (IV) (n=14)	P[a]
Anti-thyroglobulin (IU/ml)					
Mean±SD	349.1±89.5	305.2±82.5	81.1±15.9	4.54±1.8	0.021
Median (range)	116 (1-999)	18 (1-998)	4 (2-990)	1.5 (1-35)	
P[b]	I vs. II=0.614	II vs. III=0.069	III vs. IV=0.592	**I vs. IV=0.010**	
	I vs. III=0.031	**II vs. IV=0.023**			
Anti-thyroid peroxidase (IU/ml)					
Mean±SD	494.1±94.5	379.5±82.3	87.3±18.3	2.26±1.5	<0.001
Median (range)	352 (1-998)	95 (1-997)	1.5 (1-623)	0.6 (0.3-32)	
P[b]	I vs. II=0.306	**II vs. III=0.008**	III vs. IV=0.548	**I vs. IV <0.001**	
	I vs. III=0.001	**II vs. IV=0.001**			
Thyrotropin receptor (μIU/l)					
Mean±SD	360.4±24.5	724.1±53.8	451.9±91.8	412±121.5	0.303
Median (range)	328 (229-612)	349 (131-9185)	351 (112-1819)	369 (190-608)	

[a]Kruskal-Wallis test. [b]*Post-hoc* analysis with Bonferroni corrections. Significance of the bold values in the table to easily visualize significant P values

In the hyperthyroid group, there was no statistical difference between newly diagnosed patients and those receiving carbimazole therapy regarding anti-TG (mean ± SD = 218.72 ± 104.7 and 369.99 ± 120.3 IU/ml, respectively), anti-TPO (mean ± SD = 405.31 ± 110.6 and 414.50 ± 119.2 IU/ml, respectively) and TRAB (mean ± SD = 1518.57 ± 781 and 448.23 ± 58.6 μIU/l, respectively) (Table 3).

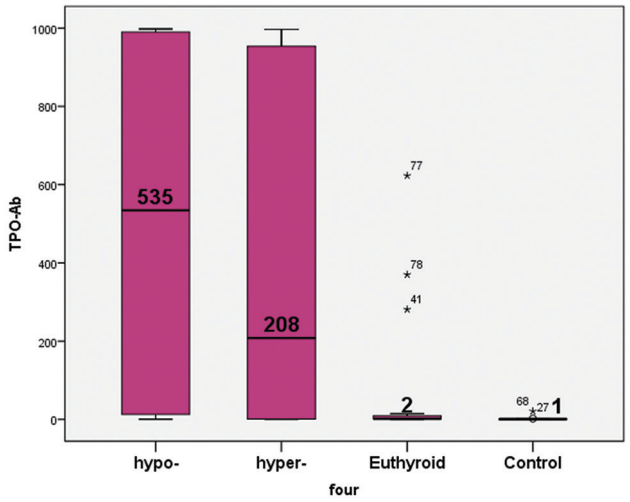
In the correlation study between thyroid autoantibodies and thyroid hormones levels, there was a significant moderate positive correlation between anti-TG level and TSH level (Table 4 and Fig. 4). There was a significant moderate positive correlation between anti-TPO level and TSH level (Table 4 and Fig. 4). There was a significant moderate positive correlation between TRAB level and each of FT3 and FT4 levels (Table 4 and Fig. 5).

In the correlation study between thyroid autoantibodies with each other, there was a significant strong positive correlation between anti-TPO and anti-TG (Table 5). There was a nonsignificant weak negative correlation between anti-TG and TRAB and between anti-TPO and TRAB (Table 5).

Discussion

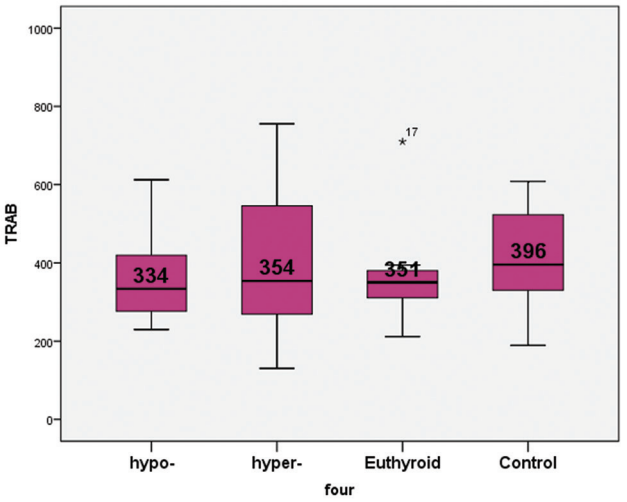
In this study, there was a statistically significant increase in anti-TG level in patients with hypothyroidism and patients with hyperthyroidism

Figure 2



Anti-thyroid peroxidase level in different study groups.

Figure 3



Thyrotropin receptor level in different study groups.

Table 2 Levels of anti-thyroglobulin and anti-thyroid peroxidase antibodies in hypothyroid group

	Newly diagnosed hypothyroidism (*n*=12)	Hypothyroidism on treatment (*n*=12)	*P*[a]
Anti-thyroglobulin (IU/ml)			
Mean±SD	412.88±142.5	290.5±114.6	0.002
Median (range)	93 (2-999)	121 (1-996)	
Anti-thyroid peroxidase (IU/ml)			
Mean±SD	585.97±132.5	443.9±132.1	0.001
Median (range)	717 (2-998)	247 (0.5-998)	

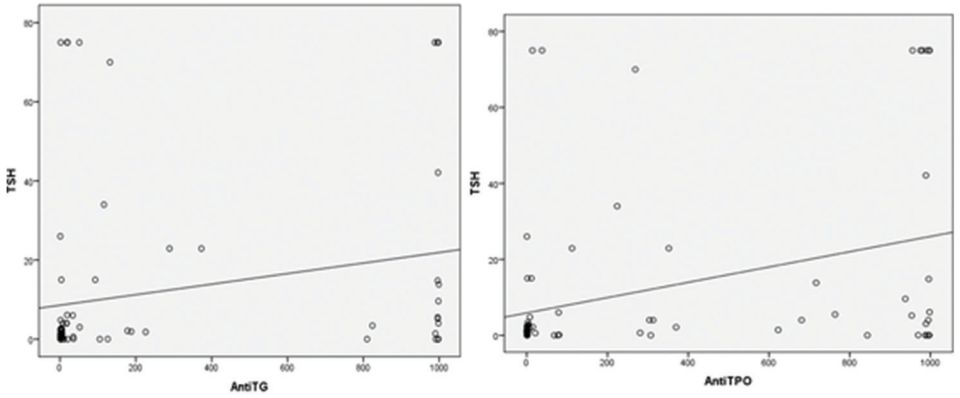
[a]Mann-Whitney test.

Table 3 Anti-thyroid autoantibodies levels in hyperthyroid group

	Hyperthyroid newly diagnosed (*n*=15)	Hyperthyroid with treatment (*n*=15)	*P*[a]
Anti-thyroglobulin (IU/ml)			
Mean±SD	218.72±104.7	369.99±120.3	0.624
Median (range)	17 (2-998)	34 (1-998)	
Anti-thyroid peroxidase (IU/ml)			
Mean±SD	405.31±110.6	414.50±119.2	0.995
Median (range)	77 (1-997)	112 (0.5-995)	
Thyrotropin receptor (μIU/l)			
Mean±SD	1518.57±781	448.23±58.6	0.624
Median (range)	281 (131-9185)	353 (257-1111)	

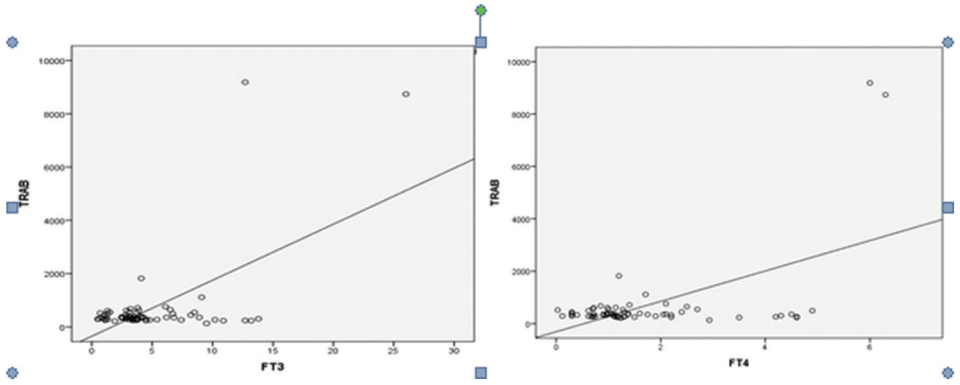
[a]Mann-Whitney test.

Figure 4



Scattered diagram of thyroid-stimulating hormone level with anti-thyroglobulin level (left) and with anti-thyroid peroxidase level (right).

Figure 5



Scattered diagram of thyrotropin receptor level with FT3 level (left) and with FT4 level (right).

Table 4 Correlation between each autoantibody and thyroid hormones levels

	Thyroid-stimulating hormone		FT3		FT4	
	r[a]	*P*[b]	*r*	*P*	*r*	*P*
Anti-thyroglobulin	**0.311**	**0.023**	0.102	>0.05	0.121	>0.05
Anti-thyroid peroxidase	**0.358**	**0.001**	0.171	>0.05	0.100	>0.05
Thyrotropin receptor	−0.088	>0.05	**0.594**	**<0.001**	**0.547**	**<0.001**

[a]Pearson's correlation coefficient. [b]Based on normal approximation. Significance of the bold values in the table to easily visualize significant *P* values

Table 5 Correlation between anti-thyroglobulin, anti-thyroid peroxidase, and thyrotropin receptor

	Anti-thyroglobulin		Thyrotropin receptor	
	r[a]	*P*[b]	*R*	*P*
Anti-thyroglobulin			−0.145	>0.05
Anti-thyroid peroxidase	**0.758**	**<0.001**	−0.191	>0.05

[a]Pearson's correlation coefficient. [b]Based on normal approximation. Significance of the bold values in the table to easily visualize significant *P* values

when compared with control group, and there was a statistically significant increase in anti-TG level in patients with hypothyroidism when compared with patients with normal thyroid function. Similarly, a study in Saudia Arabia reported statistically significant increase in anti-TG level in hypothyroid group and hyperthyroid group when compared with control group [13]. Another study in India reported statistically significant increase in anti-TG level in female patients with hypothyroidism when compared with control group [14].

In this study, there was a statistically significant increase in anti-TPO level in patients with hypothyroidism and patients with hyperthyroidism when compared with patients with normal thyroid function and control group. Moreover, a study in Saudia Arabia reported statistically significant increase in anti-TPO level in hypothyroid group and hyperthyroid group when compared with control group [13]. In another study in India, there was a statistically significant increase in anti-TPO level in female patients with hypothyroidism when compared with control group [14].

The presence of anti-TPO antibodies in patients with normal TSH level was also reported by Prummel and Wiersinga [15] who found increased level of TPO antibodies in euthyroid patients and suggested impending thyroid failure. Moreover, another study in USA detected anti-TPO antibodies in patients with normal TSH level and reported increased risk for them to develop AITD [16].

The presence of anti-thyroid autoantibodies in euthyroid patients/control participants reflects the importance of autoantibody test interpretation with respect to clinical data and that testing for autoantibodies should be done only when clinically indicated. Patients with anti-thyroid autoantibodies should be subjected to follow-up as they may develop AITD later. The importance of follow-up in patients with positive autoantibodies is supported by the finding that the presence of thyroid autoantibodies had higher risk of developing AITD after follow-up of 5 years [17]. This can be explained by the regenerative capacity of the thyroid gland under the influence of TSH, so anti-thyroid autoantibodies can exist for several years before clinical thyroid dysfunction [18].

In this study, there was nonstatistically significant increase in TRAB level in patients with hyperthyroidism when compared with patients with hypothyroidism, those with normal thyroid function, and control group. A study in Saudia Arabia reported that TRAB was significantly higher in patients with hyperthyroidism when compared with those with hypothyroidism and control groups [13]. The difference between studies may be owing differences in ethnicity, geographical distribution, environmental factors, genetic factors, or variations in techniques of TRAB detection. It should be mentioned that the method used in the current study is a research-use only ELISA kit.

In this study, hypothyroid group showed statistically significant increase in anti-TG level in patients receiving hormonal replacement therapy when compared with newly diagnosed patients. This in agreement with Dörr *et al*. [19] who reported that the serum anti-TG levels were higher in hypothyroid patients on treatment than those without treatment. However, Tang *et al*. [20] and Özen *et al*. [21] reported that hormonal replacement therapy affects the level of anti-TG level, as there was a statistically significant increase in anti-TG level in newly diagnosed patients when compared with patients on treatment.

In this study, hypothyroid group showed statistically significant increase in anti-TPO level in newly diagnosed patients when compared with those on hormonal replacement therapy. This is in agreement with Tang *et al*. [20] who reported statistically significant decrease in anti-TPO levels in patients with hypothyroidism after hormonal replacement therapy. Similarly, in the retrospective study by Schmidt *et al*. [22], anti-TPO concentrations decreased by 8% after 3 months of hormonal replacement therapy, 45% after 1 year, and reached 70% decrease after 5 years of hormonal replacement therapy. Moreover, another study reported that there was a statistically significant increase of anti-TPO level in patients with Hashimoto's disease with high TSH values when compared with those with normal TSH and those with low TSH values [23]. This decrease in anti-TPO level after hormonal replacement therapy may be owing to a reduced thyroid antigen availability to the immune system and decreased disease activity after long-term treatment [22].

In this study, hyperthyroid group showed no statistical difference in anti-TG, anti-TPO, and TRAB between newly diagnosed patients and those with carbimazole therapy. This is in agreement with Siddiqui *et al*. [24] who found no significant difference between medicated and nonmedicated hyperthyroid groups in anti-TPO and anti-TG level, which may indicate the effectiveness of carbimazole to maintain euthyroidism, but it is not effective to eradicate the pathological problem of the disease. However, other studies by Laurberg *et al*. [25] and Aleksić *et al*. [26] reported significant decrease in level of TRAB at the end of carbimazole treatment when compared with beginning of carbimazole treatment, which indicate the good response to therapy and remission, whereas increased level of TRAB is a risk factor to relapse. They explained this finding by the immunosuppressive effect of carbimazole. The difference in TRAB results between studies may be owing to the difference in duration of carbimazole therapy as duration of carbimazole therapy was not specified in this study. However, other studies stated that decrease in TRAB level occurred after long carbimazole therapy.

In this study, there was a significant moderate positive correlation between anti-TG level and TSH level and between anti-TPO level and TSH level. These positive correlations were also reported in previous studies [13,27–29]. The finding of a significant positive correlation between anti-TPO and anti-TG with TSH reflects the autoimmune mechanism in development of hypothyroidism. In this study, TRAB showed a significant moderate positive correlation with FT3 and FT4. These correlations are in agreement with those reported in other studies by Laurberg *et al*. [25] and Elfadil *et al*. [30] who showed a significant moderate positive correlation between TRAB level with serum FT3 and serum FT4. This correlation could be

explained by the action of TRAB on TSH receptors with subsequent stimulation of the thyroid cell to produce excessive amount of thyroid hormones, resulting in hyperthyroidism. In this study, there was a significant strong positive correlation between anti-TPO and anti-TG. Moreover, other studies, such as Ali *et al*. [27] and Sultana *et al*. [28], reported the same correlation between anti-TPO and anti-TG. This indicates the role of both anti-TPO and anti-TG in the development of AITD.

Conclusion

Thyroid autoantibodies have a documented role in the pathogenesis of thyroid disorders. Thyroid autoantibodies testing should be requested for patients with thyroid dysfunction. Patients with positive anti-thyroid autoantibody test result and normal thyroid function should be subjected to follow-up as they may develop overt disease later. It would be more conclusive to re-evaluate the value of TRAB testing using test method approved for *in-vitro* diagnosis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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