Correlation of thyroid antibodies with TSH, T_3 and T_4 hormones in patients diagnosed with autoimmune thyroid disorders

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Abstract: The serum concentrations of anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies are directly correlate in the induction and diagnosis of autoimmune thyroid disorders (AITDs). Therefore, the evaluation of serum anti-TPO and anti-TG antibodies in relation to thyroid function test parameters including thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4). This evaluation would be helpful in early diagnosis of abnormal thyroid function and associated autoimmune thyroid diseases. In this cross-sectional study, the serum anti-TPO, anti-TG, T3, T4 and TSH levels of 311 suspected patients of autoimmune thyroid disorders and 40 control subjects were evaluated. The data were presented as mean, ± standard deviations of the mean. Pearson correlation and chi-square tests were used to assess the correlation coefficients and significance in the contingency tables. The thyroid function test parameters in normal and AITDs suspected patients were significantly different in correlation to elevated serum levels of anti-TPO antibody. A significant association was detected between female gender and elevated levels of anti-TPO (P value = 0.047). A higher percentage of women showed elevated levels of anti-TG, but it was not statistically significant (P value= 0.107). The findings of the study reveal a strong correlation between thyroid function test and thyroid antibodies levels, elaborating the clinical importance of thyroid antibodies in clinical examination and follow-up of patients with autoimmune thyroid disorders.

Keywords: Thyroid, Autoimmune, Antibodies, TSH, anti-TPO antibody, anti-TG antibody.

INTRODUCTION

Autoimmune thyroid disorders (AITDs) commonly affect adult and middle-aged women (Swain *et al*., 2005). The AITDs are multifactorial where genetic and environmental factors play a major role in the initiation process (Swain *et al*., 2005). Global prevalence of these autoimmune disorders reached 4% of females and 1% of males (Canaris *et al*., 2000). Thyroid per oxidase (TPO) has an essential role in the generation of thyroid hormones (Mclachlan &Rapoport, 1992). It is activating the iodination and coupling process for the synthesis of thyroid hormone. It was known as thyroid micro somal antigen. Studies found that anti-thyroid peroxidase antibody (anti-TPO antibody) is involved may acting through complement fixation and directly harm thyroid cells (Guo *et al*., 1997). In another hand, the excess amount of dietary iodine was found to increase in the antigenicity of thyroglobulin (Rose *et al*., 2002). Thyroglobulin autoantibodies (anti-TG antibodies) are found in about two-thirds of patients with lymphocytic thyroiditis and a third of Graves' disease. Anti-TPO antibody, in addition to the anti-thyroglobulin antibody, are usually used in the diagnosis and follow-up of patients with autoimmune thyroid diseases. The concentrations of anti-TPO and anti-TG were found to be correlated with the occurrence of autoimmune thyroid disorders (Ghoraishian *et al*., 2006, Ali *et al*., 2015). Thus, the assessment of serum concentrations of anti-TPO antibody and anti-TG antibody in comparison to serum levels of thyroid hormones could elaborate their role in hypo- or hyperthyroidism. Recently, there is evidenceof the association between thyroid antibodies and autoimmune thyroid diseases (Roti *et al*., 1992). Autoimmune hypothyroidism could affect a tenth of women at the middle or elderly age. Graves' disease (GD) usually affects fewer people and younger age subjects (Jameson & Weetman, 2001). The progression to hypothyroidism occurs spontaneously or due to iatrogenic causes after radiotherapy or surgical intervention. The elevation of thyroid antibodies is the main feature of autoimmune thyroid diseases (Braverman & Cooper, 2012). Furthermore, the immune-pathological findings showed a direct association with histological features in thyroiditis (Baker *etal*., 1983). Elevated levels of anti-TPO antibodies are found in the vast majority of patients with autoimmune thyroid disorders. It is known that thyroid damage is a result of complement fixation and antibody-dependentcell-mediated cytotoxicity exhibited by autoantibodies (Chiovato *et al*., 1993).

In Saudi Arabia, there was no previous study investigating the correlation between thyroid antibodies and thyroid hormones among patients with autoimmune diseases. This study aimed to detect the correlation between thyroid antibodies (anti-TPO and anti-TG) with pituitary and thyroid hormones (TSH, T3 and T4) in patients diagnosed with various thyroid diseases in Saudi Arabia.

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MATERIALS AND METHODS

Study design

This is a cross-sectional study included 311 subjects, of them 261 were patients diagnosed of having autoimmune thyroid diseases (AITD) referred by an endocrinologist to the laboratory of King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia. The study was conducted to establish a correlation between anti-TPO concentrations and the patient's specific thyroid hormone levels (e.g., T3, T4, TSH) diagnosed to AITD. The study was approved by the ethical review board of King Abdul-Aziz University Hospital with ethical approval No. (155-16). Informed verbal witnessed consents were obtained from illiterate study participants, while written consents were obtained from literate participants.

Study population

311 patients were selected to evaluate the serum anti-thyroid peroxidase antibodies and thyroid hormones concentrations in relation to autoimmune thyroid diseases. The patient ages were ranged between 30 and 50 years. Forty healthy individuals were selected from King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia as a control group. Their ages were ranged between 20 and 50 years. Both experimental and control groups were physically examined and their thyroid glands were checked by the medical doctor in charge. The questionnaire was completed for all subjects of the study. Patients with metabolic disorders, hypertension, and diabetes, were excluded, also subjects with malnourishment, with negative Rhesus factor or exposed to toxic substances were excluded from the study. Negative Rhesus factor and malnourishment were confirmed by testing the blood grouping and hemoglobin (Hb %) levels respectively.

Samples collection

5ml of venous blood samples were collected from selected patients attending King Abdul-Aziz University Hospital, Jeddah, Saudi Arabia. An equivalent volume of venous blood samples was collected from the control subjects. Each specimen of blood was allowed to clot, centrifuged for three minutes and then serum was separated, aliquot and stored at -80ºC till analyzed. Personal and clinical data were collected from patients and controls by a structured questionnaire.

The anti-TPO and anti-TG antibodies were assessed using the cobas® 6000 analyzer series (Roche Diagnostics, North America) according to the manufacturer's recommendations. Serum TSH, T3, and T4 were evaluated using electro-chemiluminescence immunoassay (ECLIA, Roche Diagnostics, Mannheim, Germany). Then, the samples assayed at room temperature and mixed by gentle swirling or inversion. To reduce analytical differences, the samples were randomly selected and assayed in a single analytical round using same reagents, calibrations and quality assurance materials. The following ranges were considered normal: anti-TPO <34 IU/mL, anti-TG <115IU/mL, TSH = 0.358-3.74ulU/mL, T4= 9.0-19.0pmol/L and T3=3.3-6.1 pmol/L. Study participants were excluded if they were currently receiving thyroid therapy, they were pregnant, underwent thyroid surgery, or they were unable to provide informed consent.

STATISTICAL ANALYSIS

Data were collected using data collection sheet and analyzed using Statistical Package for Social Sciences (SPSS), Version 20. Age and sex of participants were also included despite there was no clinical examination of the neck for goiter or thyroid size. The mean and the standard deviation were calculated for all parameters. Data of the two groups (study and control) were presented as mean ± standard deviations (SD) of the mean. One-sample Pearson correlation and chi-square tests were used to assess the correlation coefficients and significance in the contingency tables. P-values less than 0.05 were considered statistically significant.

RESULTS

A total of 311 study participants were included, of them, 259 (83.3%) were females and 52 (16.7%) were males, and more than half of them were in 30-50 age group. The percentages of study participants who showed elevated levels of anti-TPO and anti-TG were 30.9% and 24.1% respectively. The distribution of the study participants according to levels of TSH, T_4 and $T_3$are demonstrated in table 1. The results showed a significant association between female gender and elevated levels of anti-TPO, where 32.2% of females showed elevated levels of anti-TPO in comparison with 19.2% of males (chi-square= 3.97, Pvalue =0.047). About 30% of females showed elevated levels of anti-TG in comparison to only 15.4% of males, but this difference was not statistically significant (chi-square=2.6, P value=0.107). In regards to age, the age group of 30-50 years old had the highest percentage of patients who had elevated anti-TPO levels, but this difference was not significant. In another hand, the same age group showed significantly the highest percentage of those who had elevated anti-TG (table 2).The mean and median of the anti-TPO level were (97.9 IU/mL and 10.3 IU/mL) and for the anti-TG level they were (165.6IU/mL and 19.4 IU/mL).Pearson's correlations showed many significant correlations between levels of anti-TPO and anti-TG in one side and levels of thyroid and pituitary hormones in another side. There was a significant positive correlation between the level of anti-TPO and the level of TSH (r =0.134, P value =0.036) (fig. 1). Similarly, there was a significant positive correlation between the level of anti-TG and the level of TSH (r =0.279, P value =0.000)

(figure 2). The results showed significant negative associations between the level of TSH and each of T_3 and T_4 hormones (r =- 0.289, P value =0.000 and r =-0.152, P value =0.009 respectively). Thyroid hormone T_3 showed significant correlations with each of anti-TPO and anti-TG (r =-0.192, P value=0.001 and r =-0.208, P value = 0.000 respectively).

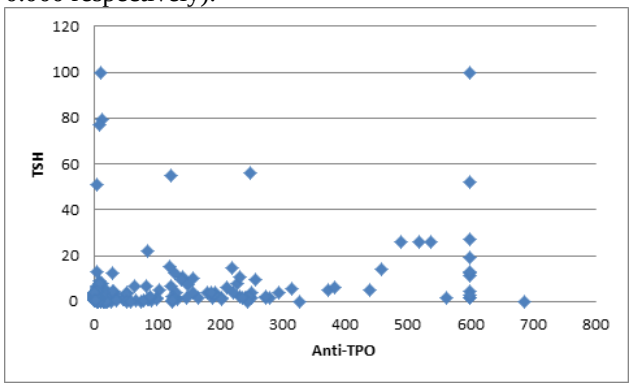

Fig. 1: Correlation between TSH and Anti-TPO levels

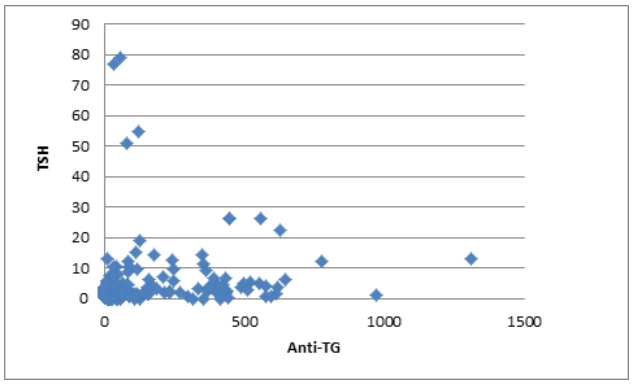

Fig. 2: Correlation between TSH and anti-TG levels

DISCUSSION

Autoimmune thyroid diseases (AITD) represent a group of pathologies related to thyroid dysfunction and an autoimmune response against this particular endocrine gland (Eschler *et al*., 2011). To reveal the important role of hormonal disturbances in thyroid diseases, the investigators have attempted to study correlation between thyroid antibodies (anti-TPO and anti-TG) with pituitary and thyroid hormones (TSH, T3, and T4) in patients diagnosed with various thyroid autoimmune diseases (How This paper author is interlinking, As if you are coping sentences from different paper at least write them properly) (Tomer *et al*., 2001). Although the prevalence of such pathologies varies in populations of different countries, the females are more prone to such diseases as compared to the male gender (5-15% vs. 1-5%) (Chan *etal*., 2001).Similarly, Helvaci *et al*. described that this frequency is increasing with the passage of time afflicting around 2-4% of women and up to 1% of men worldwide (Helvaci *etal*., 2014).Such pathologies are considered organ specific (e.g., rheumatoid arthritis, systemic lupus erythematosus) mostly seen in women 30-50 years old and are characterized by the presence of autoantibodies against thyroid specific components including thyroglobulin (TG), thyroid peroxidase (TPO), and thyroid stimulating hormone (TSH) receptor which may escalate or decrease the receptor activity (Pyne *et al*., 2002; Perez *et al*., 1995).Anti-thyroid peroxidase antibody (anti-TPO antibodies) and anti-thyroglobulin antibodies (anti-TGab) are vital in the diagnosis of AITD and judging treatment efficacy (Gordon *et al*., 1981). However, interestingly anti-TG antibodies and anti-TPO antibodies specific to AITD have been reported to non-thyroidal diseases and even in normal individuals (El-Gayyer *et al*., 2011). The presence of anti-TPO varies in the sera of normal adults and older age from 10% up to 30% respectively (Dayan *et al*., 1996). Anti-TPO antibodies detection is of prime significance in certain pathological states because of their tendency to fix complement and directly damage thyroid cells than any other antibodies (Helvaci *et al*., 2014). Higher serum concentrations of anti-TPO antibody demonstrate a positive correlation with the activity of chronic autoimmune thyroiditis (Porkodi *et al*., 2004). It was found that patients with thyroiditis had higher serum concentration of anti-TPO antibodies than anti-TG antibodies (Zakeri *et al*., 2010). Being cytotoxic in nature as *in vitro* studies reported, anti-TPO antibodies was considered to be involved in the development of hypothyroidism (Eschler *et al*., 2011). Anti-TPO antibodies may exacerbate thyroid injury but not involve initiating it (Zakeri *et al*., 2010). Therefore, the determination of anti-TPO antibodies levels in patient's serum in correlation to thyroid hormones (e.g., T3, T4, TSH) would be helpful in elucidating its pathologic role autoimmune thyroid diseases (Mousa *et al*., 2012).

In parallel to that, autoantibodies directed against nonthyroid-specific antigens are also reported in patients with autoimmune thyroid disorders (Shin *et al*., 2009). It might be suggested that organ-specific autoimmune diseases are polyclonal organs and immune reactions in such patients are due to non-organ-specific autoantigens (Perez *etal*., 1995). Hollowell *et al*. demonstrated that 13% anti-TPO and 11% anti-TG persist in the general population and the prevalence rises spontaneously in hypothyroid patients (Hollowell *et al*., 2002). One study described that positive thyroid autoantibodieswere found in 17% systemic lupus erythematosus patients without any thyroid disease (Assal *et al*., 2009). However, in contrast, Mousa *et al*. reported that anti-TPO were found in 19.7% SLE and 10.1% of the RA patients while anti-TG were found in 8.3% of the SLE and 6% of RA patients (Mousa *etal*., 2012).The presented study was aimed to correlate serum anti-TPO concentrations with thyroid hormones in patient's serum infected with certain diagnosed autoimmune thyroid diseases. The findings of the study showed a significant association between female gender and elevated levels of anti-TPO, where 32.2% of females showed elevated levels of anti-TPO in

Table 1: The distribution of the study participants according to demographic factors and levels of thyroid antibodies and hormones

Demographic variable		Frequency	Percent
Gender	Male	52	16.7%
	Female	259	83.3%
Nationality	Saudi	155	49.8%
	non Saudi	156	50.2%
Level of Anti-TG	Elevated	75	24.1%
	normal	236	75.9%
Level of Anti-TPO	Elevated	96	30.9%
	normal	215	69.1%
Age group	> 30	72	23.2%
	30-50	160	51.4%
	>50	79	25.4%
TSH (n=297)	Low	28	9.4%
	Normal	194	65.3%
	Elevated	75	25.3%
T_3 (n=295)	Low	37	12.5%
	Normal	238	80.7%
	Elevated	20	6.8%
T_4 (n=297)	Normal	267	89.9%
	Elevated	30	10.1%

Table 2: Associations between levels of anti-TPO, anti-TG, TSH, T3, and T4 in relation to some demographical factors

Demographical factors		Participants with elevated anti-TPO (%)	Chi-square	P value
Age groups	< 30	21 (29.2%)	0.817	0.665
	30 - 50	53 (33.1%)		
	>50	22 (27.8%)		
Gender	Male	10 (19.2%)	3.97	0.045
	Female	86 (33.2%)		
Demographical factors		Participants with elevated anti-TG (%)	Chi-square	P value
Age groups	< 30	18 (25.0%)	6.39	0.041
	30 - 50	46 (28.8%)		
	>50	11 (13.9%)		
Gender	Male	8 (15.4%)	2.60	0.107
	Female	67 (25.9%)		

comparison with 19.2% of males. Ghoraishian *et al*. found higher elevated anti-TPO antibody levels among females (36.2%) than among males (32.5%) (Ghoraishian *et al*., 2006). Swain *et al*. study found 95% of the patients with autoimmune thyroid disease were women (Swain *etal*., 2005). Canaris *et al*. found that autoimmune thyroid diseases occur in females 2 to 4 times more than males (Canaris *et al*., 2000). Similar findings of a survey study in Norway, in which the percentage of elevated anti-TPO antibody was 13.9% in women and 2.8% in men (Bjoro *et al*., 2000). These lower percentages of elevated anti-TPO in Norwegian study could be attributed to the high cut-off point for anti-TPO antibody at 200 IU/mL compared with 34 IU/mL in the current study.

In regards to age, the current study found that age group of 30-50 years old had the highest percentage of patients who had elevated anti-TPO levels but this difference was not significant. According to Swain *et al*. study, the patients with autoimmune diseases were mainly in 30-50 years old (Swain *et al*., 2005). This reflected the well-established association between autoimmune thyroid diseases and Anti-TPO (Carta *et al*., 2004). Ghoraishian *et al*. found significant differences between various age groups in regards to anti-TPO level (Ghoraishian *et al*., 2006). They found more than half of patients with high anti-TPO antibody were 20-39 years. The findings of this study found that age group of 30-50 years old had significantly the highest percentage of patients who had elevated anti-TG.

The mean and median of anti-TPO level among patient with autoimmune thyroid disorders were (116.6 IU/mL and 13.1IU/mL respectively) and for the anti-TG level they were (197.0IU/mL and 25.7IU/mL respectively). These wide differences between mean and median values reflected the non-parametric distribution of the antibodies levels among patients group. In control group, the mean and median of the anti-TPO level were (0.51 IU/mL and 0.39 IU/mL respectively) and for anti-TG were (1.7 IU/mL and 1.8 IU/mL respectively). This reflected a parametric distribution of the antibodies levels among the control group. Similar results were found in a study aimed to assess the variability of antibodies levels. Thus, the variation around the mean and the median were high which indicated wide reference ranges for these thyroid autoantibodies (González *et al*., 2002).

This study found a significant positive correlation between the level of anti-TPO and the level of TSH (r = 0.134). It is consistent with the findings of Ghoraishian *et al*., where a positive correlation was detected between TSH and high anti-TPO antibody values (r=0.107) (Ghoraishian *et al*., 2006). The present study found a significant positive correlation between the level of anti-TG and the level of TSH (r =0.28), while Lin *et al*. found a higher positive correlation (r = 0.51) between the TSH level and anti-TG antibodies (Lin *et al*., 2014).The results of this study showed significant negative associations between the level of TSH and each of T_3 and T_4 hormones (r = - 0.289 and r = - 0.152 respectively). Legakis *et al*. found similar results with T_4 and TSH had a weak but significant negative correlation (Spearman's rho= - 0.205) (Legakis *et al*., 2013). In this study, thyroid hormone T_3 showed significant correlations with each of anti-TPO and anti-TG, which emphasizing the role of thyroid antibodies in thyroid diseases. The results showed the investigational importance of anti-thyroid auto antibodies in relation to the presence of high levels of TSH and thyroid hormones. The limitation of this study was the number of thecontrol group subjects which was little less than the study group with autoimmune diseases. It may decrease the statistical power to detect significant differences in the current study.

CONCLUSION

In conclusion, the findings of this study, confirm the correlation between thyroid function test and thyroid antibodies levels, elaborating the clinical importance of thyroid antibodies in clinical examination and follow-up of patients with autoimmune thyroid disorders.

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