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Research Article

Utility of thyroid peroxidase autoantibodies levels in Type 2 Diabetes Mellitus

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Abstract

This study sought to define the prevalence of autoimmune thyroid disease by measuring thyroid peroxidase autoantibodies (ATPO) in Type 2 diabetes mellitus (T2DM) and to determine the prevalence of comorbidy. Adults (aged >18, n=184) with diagnosed with type 2 Diabetes were screened for Thyroid Stimulating Hormone (TSH) and ATPO. This study revealed that the prevalence of thyroid illness in T2DM patients by TSH was 21.7% and the prevalence increased to 23.9% on combining TSH with ATPO. The sensitivity and specificity of positive ATPO for the thyroid illness was 69.2% and 81.8% respectively. Female subjects had high frequency of thyroid illness and statistically higher ATPO values and particularly in hypothyroid group. ATPO had no correlation with other parameters namely fasting serum glucose (FSG), TSH and ATPO. Kruskal–Wallis one-way analysis of variance for ATPO and TSH values with the various groups showed a significant difference in means of ATPO between the TSH groups. Therefore, detection of these ATPO in T2DM may be of use in early diagnosis of thyroid illness and help in prevent complications associated with delayed diagnosis..

Keywords: thyroid peroxidase autoantibodies, Type 2 diabetes mellitus, Thyroid Stimulating Hormone.

Introduction

Type 2 Diabetes Mellitus (T2DM), the fastest growing public health problem has reached approximately 40 million in India. T2DM, on long term is associated with vascular complications that are responsible for increased morbidity and mortality. T2DM is also beginning to appear much earlier in life in India, because of which chronic long-term complications are becoming more common (Ramachandran and Snehalatha (2009). Recently, it has been found that T2DM subjects are at risk for thyroid dysfunctions also. Unrecognized thyroid dysfunction worsens the metabolic control and impedes the management of diabetes (Duntas et al., 2011). Studies have also suggested that T2DM patients with subclinical hypothyroidism are at risk of complications like nephropathy and cardiovascular event (Chen et al., 2007). Therefore, there is a need for an early marker for the thyroid illness in T2DM.

Anti-thyroid peroxidase (ATPO) is IgG class autoantibody formed against thyroid peroxidase (TPO), an enzyme that catalyses the synthesis of thyroid hormones. High titers of ATPO are found to be associated with hypothyroidism in non diabetics (Walsh et al., 2010). ATPO was found to be associated with auto immune disorders like Type1Diabetes mellitus (T1DM), rheumatoid arthritis etc. (Chang et al., 1998; Doullay et al., 1991). T2DM being associated with inflammation may be a risk factor for development of organ specific antibodies (Syed et al., 2002). With this rationale this study was undertaken to estimate the ATPO levels in T2DM patients. This study was also intended to find prevalence and predictive value of ATPO for thyroid illness in T2DM.

Materials and Methods

This cross sectional study was conducted in the M S Ramaiah Medical College, Bangalore. This study was carried out for a period of 3 months from May to July 2013 after obtaining the approval from the institutional ethics committee. The study population included the 184 T2DM patients who attended the out patient department for routine follow up. A written informed consent was obtained from the participants after explaining the objectives and procedures of the study. T2DM patients with past history of thyroid dysfunction, auto immune disorders and DM induced complications were excluded from the study. The blood sample was collected after an overnight fast of 8-12 hours. The blood samples were collected in *BD Vacutainer*® SST™ *GEL* Tubes. The sample was allowed to clot and centrifuged to separate the serum. Serum was divided into 2 parts. Part 1 was used to estimate fasting serum glucose (FSG) and part 2 was aliquoted into ependorff tubes and stored at -20°C for the estimation of Thyroid Stimulating Hormone (TSH) and ATPO. FSG was measured in *cobas*® *6000* analyser (Roche Diagnostics, Basel, Switzerland); TSH and ATPO were measured by ELISA kits (*calibiotech, Inc*®, California).

The results were analyzed by forming groups based on TSH and ATPO values. The patients were grouped as euthyroid, hypothyroid and hyperthyroid based on the TSH values; based on ATPO values, patients were grouped as negative, borderline positive and positive (Table 1). Study population was also grouped based on the gender and statistically analyzed to find the gender susceptibility.

Proportions in the groups were compared using a Fisher exact test. Descriptive statistics were reported as the mean ± SD. Results were considered statistically significant with $\alpha<0.05$. Kruskal–Wallis one-way analysis of variance was used to find the significant difference in ATPO values in TSH based groups and vice versa.

Results

This study revealed the sensitivity and specificity of positive ATPO for the thyroid illness as 69.2% and 81.8% respectively. Other results are shown in tables 1-6. Table 1 shows the distribution of the diabetic patients among the various groups. It is shown that, the prevalence of thyroid illness in T2DM patients by TSH alone was 21.7% (hyperthyroidism: 11.9%, hypothyroidism: 9.7%). High ATPO (>75 IU/ml) was present in 5.9% of the study population. The prevalence of thyroid illness increased to 23.9% on combining TSH with ATPO. Table 2 shows the gender differences in distribution of thyroid illness based on TSH and ATPO in the study population. It is shown that there is significantly high proportion of female patients had thyroid illness defined by both TSH and ATPO. Table 3 shows the mean ± SD of the various parameters in the total study population and the statistical difference in the values between the genders. It is shown that female patients had statistically higher ATPO values. Table 4 shows the comparison of TSH and ATPO values between the genders in each study group. It is shown that female patients had higher ATPO values only in the hypothyroid group. Table 5 shows the Pearson's correlation between the parameters namely FSG, TSH and ATPO. It is shown that there is no significant correlation between the parameters. Table 6 shows the Kruskal–Wallis one-way analysis of variance for ATPO and TSH values with the various groups. It is shown that there is significant

Table 1. Shows the distribution of the study population (N=184) among the various groups

GROUPS		GROUPS BASED ON ATPO			
		NEGATIVE (< 50 IU/ml) N=168 (91.3%)	**BORDERLINE POSITIVE (50 – 75 IU/ml) N=5 (2.7%)**	**POSITIVE (> 75 IU/ml) N=11 (5.9%)**	**p value***
GROUPS BASED ON TSH	EUTHYROID (0.4 – 4.2 µIU/ ml) N=144 (78.2%)	137 (72.8%)	3 (1.6%)	4(2.1%)	**0.01**
	HYPOTHYROID (< 0.4 µIU/ ml) N=18 (9.7%)	13 (7.1%)	1(0.5%)	4(2.1%)	
	HYPERTHYROID (> 4.2 µIU/ ml) N=22 (11.9%)	18 (9.7%)	1(0.5%)	3 (1.6%)	

*Fisher's Exact Test for Count Data

Table 2. Shows the gender differences in distribution of thyroid illness based on TSH and ATPO in the study population

Parameters	**Groups**	**Males N=100**	**Females N=84**	**p value***
TSH	EUTHYROID	78 (78%)	66 (78%)	**0.05**
	HYPOTHYROID	6 (6%)	12 (14%)	
	HYPERTHYROID	16 (16%)	6 (7%)	
ATPO	NEGATIVE	96 (96%)	72 (85%)	**0.03**
	BORDERLINE POSITIVE	2 (2%)	3 (3.5%)	
	POSITIVE	2 (2%)	9 (10.7%)	

* Fisher's Exact Test for Count Data

Table 3. Shows the Mean ± SD of the various parameters in the study population and comparison between the genders

Parameters	**Total**	**Males mean ± SD**	**Females mean± SD**	**p value***
Age (years)	55.8 ± 12.3	55.8 ± 12.9	55.8 ± 11.6	0.99
FSG (mg/dl)	163.3 ± 67.3	165.6 ± 71.9	160.5 ± 61.5	0.60
TSH (µIU/ ml)	3.2 ± 14.1	1.7 ± 1.6	4.9 ± 20.7	0.16
ATPO (IU/ml)	22.3 ± 21.5	18.0 ± 14.9	27.5 ± 26.5	**<0.01**

*student 't' test

Table 4. Shows the comparison of TSH and ATPO values between the genders in each group

	TSH			ATPO		
Groups	**Males mean ± SD**	**Females mean± SD**	**p value***	**Males mean± SD**	**Females mean± SD**	**p value***
NEGATIVE	1.8 ± 1.6	4.6 ± 21.6	0.28	15.6 ± 8.9	17.7 ± 10.1	0.18
BORDERLINE POSITIVE	0.4 ± 0.4	4.3 ± 2.3	0.09	60.4 ± 5.8	65.1 ± 5.9	0.46
POSITIVE	0.7 ± 0.8	8.1 ± 16.8	0.22	90.2 ± 22.4	93.4 ± 9.6	0.36
EUTHYROID	1.74 ± 1.04	1.63 ± 0.93	0.51	17.5 ± 13.2	21.8 ± 19.6	0.13
HYPOHYROID	6.57 ± 1.15	25.81 ± 51.79	0.22	19.2 ± 14.3	47.6 ± 37.6	**0.04**
HYPERHYROID	0.21 ± 0.09	0.22 ± 0.08	0.79	20.3 ± 22.4	49.3 ± 39.7	0.14

*student‘t’ test

Table 5. Show the Pearson’s correlation between the parameters

	FSG	**TSH**	**ATPO**
FSG	-	r value = -0.06 p value = 0.41	r value = -0.06 p value = 0.41
TSH	r value = -0.06 p value = 0.41	-	r value = 0.07 p value =0.34
ATPO	r value = -0.06 p value = 0.41	r value = 0.07 p value =0.34	-

r= Pearson’s correlation co-efficient

Table 6. Shows the Kruskal–Wallis one-way analysis of variance

		ATPO	**TSH**
Kruskal-Wallis rank sum test	χ^2 value	7.56 (ATPO values by TSH groups)	0.35 (TSH values by ATPO groups)
	p value	0.02	0.83

Figure 1. Shows the plot of ATPO values in the TSH groups

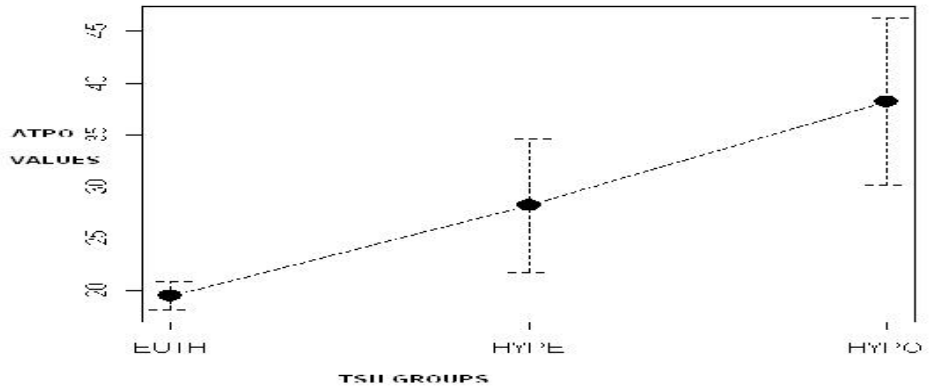
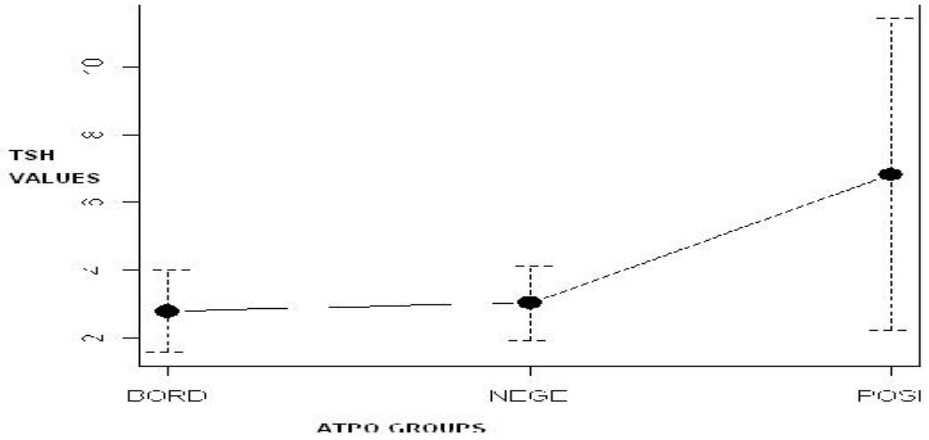


Figure 2. Shows the plot of TSH values in the ATPO groups



difference in means of ATPO between the TSH groups; it is also depicted in the plot of means shown in figure 1. But, similar significance was not found in the means of TSH between the ATPO groups, also shown in figure 2.

Discussion

T2DM is known to be associated with various complications. Its association with thyroid disorders has been the recent findings but the pathophysiology is still not established. Autoantibodies are one of the reasons that are suspected and hence this study was undertaken to find the ATPO levels in T2DM.

The prevalence of positive ATPO in this T2DM population was found to be 5.9%. Afkhami-Ardekani M et al, in their diabetic population showed the prevalence of ATPO as 36.9 % (Afkhami-Ardekani et al., 2009). Akbar et al. (2006) found the prevalence of positive ATPO as 10% in the Saudi diabetic population. This study showed lesser prevalence of raised ATPO in Indian diabetic population. Thus the susceptibility for the development of auto antibodies against thyroid gland varies with the population. Gender differences in distribution of thyroid illness were observed. Females showed high frequency of hypothyroidism and positive ATPO levels, where as in males hyperthyroidism was the commonest thyroid disorder.

The descriptive statistics also showed that female patients had statistically higher ATPO values in age matched diabetic subjects, though there was no significant difference in TSH values between the genders. Among the euthyroid, hypothyroid and hyperthyroid groups, females showed the higher Anti TPO values in hypothyroid groups which was statistically significant. This suggests that female patients are at risk for the development of auto antibodies against the thyroid gland and may be the cause for the hypothyroidism. This type of gender suseptibility for the development of ATPO had been observed in non diabetic subjects also (Feldt-Rasmussen et al., 1991).

Kruskal–Wallis one-way analysis of variance for ATPO and TSH values with the various groups showed significant difference in means of ATPO between euthyroid, hypothyroid and hyperthyroid groups. But, similar significance was not found in the means of TSH in the negative, borderline positive and positive ATPO groups. From this it can be inferred that TSH values don't denote the presence or the absence of autoantibodies, whereas ATPO values can predict thyroid status. This suggests the need for the inclusion of ATPO in the thyroid profile panel for the screening of thyroid illness in diabetes mellitus patients. Pearson's correlation between the parameters did not show any correlation, indicating that ATPO can be utilized as an independent marker for the thyroid illness. Small sample size and cross section type are the major limitations of this study to validate the findings.

Conclusion

This study concludes that T2DM patients are at increased risk for thyroid disorders for which autoantibodies against the thyroid gland may be one of the reasons. Between the genders, females are at the risk for thyroid dysfunction in particular for hypothyroidism. Hence this study emphasizes the need for estimating ATPO during the monitoring of diabetics with thyroid profile.

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