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A CASE/CONTROL STUDY ON RAISED ANTI-THYROID PEROXIDASE ANTIBODY IN CASES OF HYPOTHYROIDISM AND EUTHYROIDS

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Abstract:
Objective: *To assess the raised level of anti-thyroid peroxidase antibody in patients of hypothyroidism and euthyroids.*
Material and methods: *This case/control study was conducted at Department of Biochemistry BUMHS, Bolan Medical Complex Hospital, Quetta from January 2018 to June 2018 over the period of 6 months. Total 69 patients of hypothyroidism (as per operational definition) having age 18-60 years either male or female were selected. Age and sex matched euthyroids (FT3, FT4 and TSH within normal range) as described in operational definition was served as controls. Anti-thyroid peroxidase antibody assessed between the cases of controls.*
Results: *A total of 138 cases fulfilling the inclusion/exclusion criteria were enrolled to compare the frequency of raised level of anti-thyroid peroxidase antibody in patients of hypothyroidism and euthyroids. Comparison of raised anti-thyroid peroxidase antibodies in both groups was done which reveals that Raised Anti-Thyroid Peroxidase Antibodies were recorded in 28.99%(n=20) in Group-A and 7.25%(n=5) in Group-B while 71.01%(n=49) in Group-A and 92.75%(n=64) in Group-B had no findings of Raised Anti-thyroid Peroxidase Antibodies, p value was calculated as 0.000 which shows a significant difference between the two groups.*
Conclusion: *We concluded positive relationship of the presence of TPOAbs with levels of TSH and showed that TPOAbs and TSH predict future development of hypothyroidism. These results are consistent with the presence of TPOAbs necessitating a compensatory increase in levels of TSH for maintenance of euthyroidism, even in the euthyroid range.*
Keywords: *Hypothyroidism, Euthyroids, Anti-thyroid peroxidase antibody.*

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INTRODUCTION:

Hypothyroidism is characterized by abnormally low serum T_4 and T_3 levels and high TSH level. The defect that predisposes an individual to develop autoimmune thyroid disease is still unknown. Proposed mechanisms include a tissue-specific defect in suppressor T-cell activity, a genetically programmed presentation of a thyroid-specific antigen, and an idiotype/anti-idiotype reaction. [1] There is a well-documented association between the presence of anti-thyroid peroxidase (anti-TPO) antibodies and the development of autoimmune hypothyroidism. [2] A survey by Amritha Institute, Cochin, in 2009 showed that thyroid function abnormalities were present in 19.6% of adult population and about 9.5% of the subjects had anti-TPO antibodies. [3]

Subclinical hypothyroidism is found in 6–8% of women (10% over the age of 60) and 3% of men. The annual risk of developing clinical hypothyroidism is about 4% when subclinical hypothyroidism is associated with positive TPO antibodies. [4]

A study conducted in Muzaffarabad also reported that positive anti-thyroid peroxidase antibodies were not age related, however they were found to be associated with elevated levels of thyroid stimulating hormone. [5]

Anti-TPO is also important in diagnosing autoimmune thyroid disease and for efficacy of treatment. In 2007 results of a study demonstrate that anti-TPO antibodies can damage cultured thyroid cells by mechanisms of antibody-dependent cell cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) by 11 to 74.5% and 56% respectively.[6] The monocytes, via their FcγRI, are important effector cells in antibody-dependent cell cytotoxicity (ADCC) mediated by anti-TPO antibodies and may contribute with T cells to the destruction of thyroid gland in autoimmune thyroid disease. [7] The clinical diagnosis of autoimmune thyroid disease is usually confirmed by the detection of various antibodies in the patient's blood sample. [8]

A study conducted by Elmugadam AA et al [9] showed that anti-thyroid peroxidase antibody of thyroid disease patients and control group was positive in 21.2% and 5% respectively.

As the presence of thyroid peroxidase antibodies may serve as a marker of future thyroid disease, we have planned this study to see raised anti-thyroid peroxidase antibody in patients of hypothyroidism and in euthyroids so that some practical recommendations could be made for preemptive prevention of developing hypothyroidism by early detection of anti-thyroid peroxidase antibody and subsequent early management by immunosuppressive drugs.

OPERATIONAL DEFINITIONS:

Hypothyroidism:

Patients of hypothyroidism was diagnosed by measuring FT3 and FT4 below the lower limit of normal range (normal range of FT3: 3.2-8.0 pmol/L and normal range of FT4: 10.3-34.7 pmol/L) and TSH above the higher limit of normal range (normal range of TSH: 0.4-4.2 mIU/L).

Euthyroids:

Euthyroids was labeled when the person has no signs and symptoms and FT3, FT4 and TSH was within normal range (normal range of FT3: 3.2-8.0 pmol/L, normal range of FT4: 10.3-34.7 pmol/L and normal range of TSH: 0.4-4.2 mIU/L).

Raised anti-thyroid peroxidase antibody:

These are autoantibodies targeted against thyroid peroxidase (TPO) enzyme and serum value ≥10 IU/ml was labeled as raised anti-thyroid peroxidase antibody and <10 was labeled as normal.

MATERIAL AND METHODS:

This case/control study was conducted at Department of Biochemistry BUMHS, Bolan Medical Complex Hospital, Quetta from January 2018 to June 2018 over the period of 6 months. Total 69 patients of hypothyroidism (as per operational definition) having age 18-60 years either male or female were selected. Age and sex matched euthyroids (FT3, FT4 and TSH within normal range) as described in operational definition was served as controls.

Patients who received any medical or surgical treatment for any thyroid disorder, patients with hyperthyroidism, thyroiditis or thyroid malignancy, patients having other medical illness like renal diseases, cardiac diseases, hepatic diseases, pulmonary diseases or any neoplastic disease, patients having autoimmune diseases or on immunosuppressive therapy and pregnant patients were excluded from the study. This study was approved from hospital ethical committee and written informed consent was taken from every patient. Patients were recruited from medical OPD of Bolan Medical Complex Hospital, BUMHS Quetta. Patients presenting with hypothyroidism (FT3 and FT4 below the lower limit of normal range and TSH above the higher limit of normal range) were served as cases and placed in group-A. Age and sex-matched euthyroids (FT3, FT4 and TSH within normal range) were served

as control group and placed in group-B. Both in group-A and group-B, 5 ml blood was withdrawn from the vein of elbow or the back of hand. Blood was immediately collected and transferred to red-top or gel tubes. Samples were allowed to clot for one hour before centrifugation. Test serum was clear and non-hemolysed. Serum was analyzed through fully automated chemistry analyzer using enhanced chemiluminecence method to detect serum FT3, FT4 and TSH. Anti-thyroid peroxidase antibodies were measured by ELISA (Bio Rad Kallestad). A proforma was used to collect the pertinent information from every patient.

Data was entered and analyzed by SPSS version 14.0 software for health statistics. Mean and standard deviation was calculated for quantitative variables like age. Frequency and percentage were calculated for qualitative variable like sex and raised anti-thyroid peroxidase antibodies in each groups. Raised anti-thyroid peroxidase antibodies were compared in two groups by chi square test. P-value ≤0.05 was taken as significant. All the results were presented in the form of tables and charts. Stratification of data was done with regards to age and gender. Chi square test was used to see the effect of these on outcome variables. P-value ≤0.05 was taken as significant.

RESULTS:

A total of 138 cases fulfilling the inclusion/exclusion criteria were enrolled to compare the frequency of raised level of anti-thyroid peroxidase antibody in patients of hypothyroidism and euthyroids.

Raised Anti-Thyroid Peroxidase Antibodies were found in 20 (28.99%) cases and in 5 (7.25%) controls. After applying chi-square test, statistically significant (P = 0.00) difference of Raised Anti-Thyroid Peroxidase Antibodies between cases and controls was detected. (Table 1)

Age distribution of the selected patients was done and two groups were formed, age group 18-30 years and age group 31-60 years. In age group 18-30 years, total 37 (53.62%) were cases and 41 (59.42%) controls. Raised Anti-Thyroid Peroxidase Antibodies was noted in 9 (24.32%) cases and in 2 (4.88%) controls. Difference of Raised Anti-Thyroid Peroxidase Antibodies between the cases and controls was statistically significant with p value 0.02.

In age group 31-60 years, out of 32 (46.38%) cases, Raised Anti-Thyroid Peroxidase Antibodies were found in 11 (34.38%) cases while among the 28 (40.58%) controls Raised Anti-Thyroid Peroxidase Antibodies were detected in 3 (10.71%) controls. Significantly higher rate of Raised Anti-Thyroid Peroxidase Antibodies was noted in cases as compared to controls with p value 0.03 (Table 2)

Total 13 (18.84) cases were male and 11 (15.94) controls were male. Total 4 (30.77) male cases were found with Raised Anti-Thyroid Peroxidase Antibodies and no control found with Raised Anti-Thyroid Peroxidase Antibodies. Difference was not statistically significant (P 0.09) between male cases and male controls. In 56 (81.16) female cases, Anti-Thyroid Peroxidase Antibodies were found raised in 16 (28.57) female cases. Out of 58 (84.06) female controls, Anti-Thyroid Peroxidase Antibodies were found raised in 5 (8.62) female controls. Difference was statistically significant with p value 0.00. (Table 3)

TABLE No. 1
COMPARISON OF RAISED ANTI-THYROID PEROXIDASE ANTIBODIES IN BOTH GROUPS

Group	Raised Anti-Thyroid Peroxidase Antibodies		Total	P value
	Yes (%)	No (%)		
Cases	20 (28.99)	49 (71.01)	69	0.00
Controls	5 (7.25)	64 (92.75)	69	

TABLE No. 2
STRATIFICATION FOR RAISED ANTI-THYROID PEROXIDASE ANTIBODIES IN BOTH GROUPS WITH REGARDS TO AGE

Group	Raised Anti-Thyroid Peroxidase Antibodies		Total	P value
	Yes (%)	No (%)		
Age group 18-30 years				
Cases	9 (24.32)	28 (75.68)	37 (53.62)	0.02
Controls	2 (4.88)	39 (95.12)	41 (59.42)	
Age group 31-60 years				
Cases	11 (34.38)	21 (65.63)	32 (46.38)	0.03
Controls	3 (10.71)	25 (89.86)	28 (40.58)	

TABLE No. 3
STRATIFICATION FOR RAISED ANTI-THYROID PEROXIDASE ANTIBODIES IN BOTH GROUPS WITH REGARDS TO GENDER

Group	Raised Anti-Thyroid Peroxidase Antibodies		Total	P value
	Yes (%)	No (%)		
Male patients				
Cases	4 (30.77)	9 (69.23)	13 (18.84)	0.09
Controls	0	11 (100)	11 (15.94)	
Female patients				
Cases	16 (28.57)	40 (71.43)	56 (81.16)	0.00
Controls	5 (8.62)	53 (91.38)	58 (84.06)	

DISCUSSION:

Physicians in primary care settings need to be aware of a potentially high-risk population that should be identified and more closely followed. Patients with high normal TSH and positive anti TPOAbs are at potentially greater risk of developing true hypothyroidism over time. [10]

We hypothesized in this trial that the presence of thyroid peroxidase antibodies may serve as a marker of future thyroid disease, however, we planned this study to see raised anti-thyroid peroxidase antibody in patients of hypothyroidism and in euthyroids so that some practical recommendations could be made for preemptive prevention of developing hypothyroidism by early detection of anti-thyroid peroxidase antibody and subsequent early management by immunosuppressive drugs.

In our study, 53.62%(n=37) in Group-A and 59.42%(n=41) in Group-B were between 18-30 years, while 46.38%(n=32) in Group-A and 40.58%(n=28) in Group-B were between 31-60 years, mean+sd was calculated as 32.42±10.09 in Group-A and 32.45±10.12 in Group-B, 18.84%(n=13) in Group-A and 15.94%(n=11) in Group-B were male and 81.16%(n=56) in Group-A and 84.06%(n=58) in Group-B were females, comparison of raised anti-thyroid peroxidase antibodies in both groups was done

which reveals that Raised Anti-Thyroid Peroxidase Antibodies were recorded in 28.99%(n=20) in Group-A and 7.25%(n=5) in Group-B while 71.01%(n=49) in Group-A and 92.75%(n=64) in Group-B had no findings of Raised Anti-thyroid Peroxidase Antibodies, p value was calculated as 0.000 which shows a significant difference between the two groups.

Our findings are in agreement with a study conducted by Elmugadam AA et al[9] showed that anti-thyroid peroxidase antibody of thyroid disease patients and control group was positive in 21.2% and 5% respectively.

Our findings confirm the importance of TPOAbs as a marker for future thyroid disease and extends it to the general population. To the best of our knowledge, limited earlier prospective studies investigated the value of TSH and TPOAb titers in subjects with normal levels of TSH.

In the Whickham and Busselton studies it was found that increasing values of serum TSH at first survey increased the probability of developing hypothyroidism, and that this probability was further increased when TPOAbs were present. [11-12] In these studies, however, subjects with elevated levels of TSH at baseline were not excluded.

The pathophysiologic process behind the relationship of TPOAbs prevalence and future thyroid disease is complex and not completely understood. [13] Thyroid peroxidase (TPO) is not only known to be the primary enzyme in the synthesis of thyroid hormone, it also serves as a major autoantigen. [14] Moreover, it has been hypothesized that TPOAbs should not be viewed as one entity since their pathogenic potential might be influenced depending on which epitope of TPO they are binding to. [15] The presence of TPOAbs is characteristic for autoimmune thyroid disease, [16] both in hypothyroidism(Hashimoto's thyroiditis) and (Graves') hyperthyroidism. The cause of Hashimoto's thyroiditis is thought to be a combination of genetic susceptibility and environmental factors. The antibodies are mainly produced by a lymphocytic infiltrate in the thyroid gland, [17] with a significant correlation between the degree of this lymphocytic infiltration and the titer of microsomal antibodies. [18] In combination with the demonstrated higher prevalence of positive TPOAbs with increasing TSG concentrations, even in euthyroidism, the presence of TPOAbs can thus be regarded as a marker for increased risk of future thyroid failure.

CONCLUSION:

We concluded positive relationship of the presence of TPOAbs with levels of TSH and showed that TPOAbs and TSH predict future development of hypothyroidism. These results are consistent with the presence of TPOAbs necessitating a compensatory increase in levels of TSH for maintenance of euthyroidism, even in the euthyroid range.

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