Association of High TPO Antibody Titer with Differentiated Thyroid Carcinoma: A Case-Control Study

[1]Umme Salma, [2]Faria Nasreen, [3]Prianka Jabin, [4]Sutanu Roy, [5]Mohammad Nurul Azam

[1]National Institute of Traumatology and Orthopedic Rehabilitation (NITOR)

[2]Bio-Science Division, Bangladesh Atomic Energy Commission, Dhaka

[3]National Institute of Nuclear Medicine & Allied sciences, BSMMU Campus, Dhaka

[4]Aliahat 20 Bed Hospital, Shibganj, Bogura

[5]Upazilla Health Complex, Chakaria, Cox's Bazar

Correspondence Address: Dr. Umme Salma, Resident Surgeon, NITOR, Sher-e- Bangla Nagar, Dhaka. Email: drummesalmaurmi@gmail.com

ABSTRACT

Background: The most common well-differentiated thyroid carcinomas are papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). PTC accounts for 80–90% of all thyroid cancers, and follicular carcinoma accounts for 10–15% of all thyroid cancers. Common established risk factors for thyroid carcinoma are head-neck irradiation, a positive family history, and a few genetic disorders. High anti-thyroglobulin antibodies (TgAb) have already been established as predictive markers for thyroid carcinoma, but anti-thyroid peroxidase antibodies (TPO Ab) have not been established as predictive markers till now.

Objective: To find out the association of high TPO Ab titer with differentiated thyroid carcinoma (DTC).

Patients and Methods: This case-control study was carried out at the National Institute of Nuclear Medicine & Allied Sciences (NINMAS), Dhaka, from September 2020 to November 2021. A total of 52 cytologically diagnosed DTC patients who underwent thyroidectomy were selected as cases. Another 52 age- and sex-matched healthy individuals who had sonographically normal thyroid glands and a biochemically euthyroid state were selected as controls. The total number of participants was 104. Written informed consent was obtained from each of the participants. A detailed history was taken, and a thorough clinical examination was carried out on each patient. High resolution ultrasonography (HRUS) of the thyroid gland, serum thyroid-stimulating hormone (TSH) level, and fine needle aspiration cytology (FNAC) report of the thyroid nodule of each participant were collected. Serum TPO antibody levels were measured in patients with DTC prior to thyroid surgery, as well as in the control group, in the NINMAS laboratory using the CLIA method. After the collection of all the required data, analysis was done by SPSS 24.0.

Results: The mean age of the cases was 35.8 ± 13.3 years and 34.6 ± 13.0 years in the control groups. Female patients were predominant in both the case and control groups (63.5% and 69.2%, respectively). Both groups were statistically almost similar in terms of age and sex. Around 46.2 % (n=24) patients in the case group had high serum TPO Ab levels and 15.4 % (n=8) of participants in the control group had high serum TPO Ab levels. The mean serum TPO Ab level in the case group was 306.77± 452.57 U/mL, and the mean serum TPO Ab level in the control group was 75.85±181.47 U/mL. Serum TPO antibody level was significantly higher in the case group compared to the control group (306.77±452.57 vs 75.85±181.47 U/mL, p = 0.001).

Conclusion: There was a significant association of high TPO Ab titer found with DTC

Keywords: Papillary thyroid carcinoma, Follicular thyroid carcinoma, anti-thyroid peroxidase antibody.

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INTRODUCTION

Thyroid cancer is the most frequent endocrine malignancy, accounting for around 1% of all malignancies and 90% of all endocrine tumors (1, 2). Thyroid carcinomas that are well-differentiated include papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). Papillary thyroid carcinoma accounts for 80–90% of all thyroid cancers, and follicular carcinoma accounts for 10%–15% of all thyroid cancers (3). Because of the biological nature of differentiated thyroid carcinoma (DTC) and the existing therapeutic options, roughly 85% of DTC has a favorable 10-year prognosis (4,5).

Thyroid nodules are the most common thyroid problem. More than 85% to 95% of these nodules are benign (6), and the remaining 5% to 15% are malignant (7). Thyroid cancer is becoming more prevalent around the world. It has been increasing at a rate of 1.9 percent in the United States in recent years, affecting 50,000 individuals and killing 2,000 people each year (8). The increased use of imaging modalities, which boosted the discovery of tiny and non-symptomatic tumors, can be attributed to the increase in the incidence of thyroid malignancy (9).

Antithyroid peroxidase antibody (TPO Ab) and antithyroglobulin antibody (TgAb) are common in patients

with autoimmune thyroid disease (10). Graves' disease and autoimmune hypothyroidism are the most common autoimmune thyroid diseases (11). Hashimoto's disease, on the other hand, is the most common autoimmune disease characterized by thyroid damage caused by lymphocyte infiltration, affecting 2 to 15% of the population (12). It has two different clinical variants, namely diffuse and nodular variants. Papillary thyroid cancer is the most common cause of the nodular type (13). Chronic inflammation is related to the formation of malignant tumors, as evidenced by several human tumors (14). Positive serum thyroid peroxidase antibody (TPO Ab) titers are associated with an increased risk of thyroid cancer in individuals suffering from chronic thyroid inflammatory disease (12). In the general population, however, one or both of these antibodies are often identified (15). The prevalence of serum positive for TPO Ab and TgAb was 13.1 percent and 13.0 percent, respectively, in a case-control study done in areas of iodine deficit in Denmark among adults with no present or recent thyroid illness (15).

There have been conflicting findings about the link between thyroid cancer and Hashimoto's thyroiditis. Dailey et al. were the first ones to discover a relationship between Hashimoto's thyroiditis (HT) and PTC in 1955. The purpose of this study was to see whether there is an association between a high TPO Ab titer and differentiated thyroid carcinoma.

MATERIALS AND METHODS

This case-control study was carried out at the Thyroid Division of NINMAS, the Department of Otolaryngology at BSMMU, the Department of Otolaryngology at DMC, and the National ENT Hospital, Tejgaon, Dhaka, from September 2020 to December 2021. A total of 52 patients with FNAC proven DTC who underwent thyroidectomy later on were selected as cases based on the inclusion and exclusion criteria. All cancer patients provided informed written consent, including personal information. Clinical history, physical examination findings, HRUS of the neck, serum TSH level, and FNAC reports of the thyroid gland were noted. Except for the FNAC report, similar clinical information was recorded for the control group also. However, if sonographic and laboratory investigations were within the normal limit, they were included in the control group. Patients with a history of head and neck irradiation, previous thyroid surgery, recurrence of thyroid carcinoma, or pregnancy were excluded from the study. After getting approval for his study from the Scientific Review Committee (SRC) and the Medical Research Ethics Committee (MREC), NINMAS obtained proper permission from the institutions and departments concerned for this study. Serum TPO antibody levels of both case and control groups were measured in the laboratory of NINMAS by the CLIA method. This is to mention that in the case group, serum TPO-Ab was collected prior to thyroidectomy. The participants did not gain financial benefits from this study. Confidentiality was strictly maintained, and participants had the freedom to withdraw themselves from the study at any time.

STATISTICAL ANALYSIS

The required collected data were checked, verified for consistency, and tabulated using the SPSS 24 software. Exploratory data analysis was carried out to describe the study population. Statistical significance was set at a 95% confidence level. Categorical variables were expressed by frequency and percentage. The mean and standard deviation were used to express continuous variables. A chi-square test was done to determine the association between categorical variables. To determine the difference between continuous variables, an independent sample t-test was used for normally distributed continuous variables. For skewed data, a non-parametric test (the Mann-Whitney U) was also used for analyzing continuous variables. For all statistical tests, a *p*-value less than 0.05 was considered statistically significant.

RESULTS

A total of 52 patients were in the case group, and the same number of patients were in the control group. The distribution of the study population by age is shown in Table 1. It was discovered that 32.7% of patients between the ages of 31 and 40 were in the case group, while 34.6% of individuals between the ages of 31 and 40 were in the control group. Furthermore, 30.8% of patients in the case group were between the ages of 21 and 30, while 34.6% of individuals in the control group were between the ages of 21 and 30. The mean age of the case group was 35.8 ±

13.3(SD) years, and the mean age of the control group was (34.6± 13.0) years. The independent student t-test resulted in a *p*-value of 0.64. The difference between the two groups was not statistically significant (P > 0.05).

Table 1: Distribution of the study population by age (n=104)

Age (Years)	Case (n=52) n (%)	Control (n=52) n (%)	Total (n=104) n (%)	*p*-value
Age group				
10-20	6 (11.5)	4 (7.7)	10 (9.6)	0.505*
21-30	16 (30.8)	18 (34.6)	34 (32.7)	0.676*
31-40	17 (32.7)	18 (34.6)	35 (33.7)	0.836*
41-50	5 (9.6)	6 (11.5)	11 (10.6)	0.749*
51-60	6 (11.5)	3 (5.8)	9 (8.7)	0.295*
61-70	1 (1.9)	2 (3.8)	3 (2.9)	0.558*
71-80	1 (1.9)	1 (1.9)	2 (1.9)	1.000*
Total	52 (100)	52 (100)	104 (100)	
Mean ± SD	35.8 ± 13.3	34.6 ± 13.0		0.64**

Chi-square test* and Independent student t-test** were performed to compare between two groups.

The majority of the study populations were female in both case and control groups. In this study, 63.5 % (n=33) participants in the case group were female, and 69.2 % (n=36) participants in the control group were female (Figure 1). In terms of gender distribution, both groups were statistically similar (p >0.05).

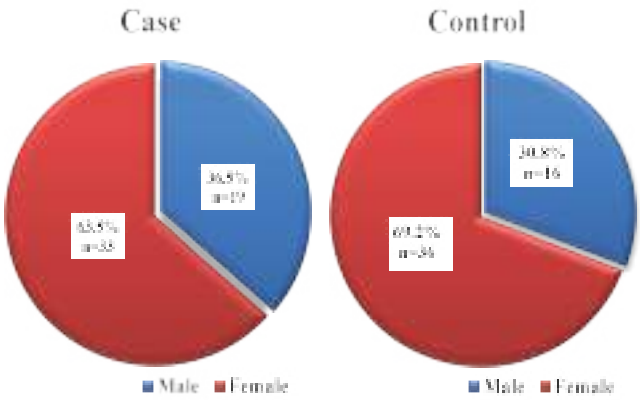

Figure-1: Pie diagram showing the gender distribution of the study subjects

*Data were analyzed using the Chi-square test to compare between two groups

Table 2 shows the distribution of study subjects according to normal or high serum TPO Ab levels. It was observed that 46.2% (n = 24) of the case group had a high TPO-Ab level. On the other hand, 15.4% (n = 8) of the control group had high TPO Ab levels. The mean serum TPO Ab level in the case group was 306.77±452.57(SD), whereas the mean serum TPO Ab level in the control group was 75.85±181.47(SD). High TPO Ab levels were significantly associated with the case group and were 4 times higher in the case group in comparison to the control group.

Table 2: Association of serum TPO antibody levels among the study population (n=104)

TPO Ab (U/mL)	Case (n=52)	Control (n=52)	OR (95%CI)	*p*-value*
Normal (<60)	28(53.8%)	44(84.6%)	4.71 (1.86-11.94)	0.001*
High (>60)	24(46.2%)	8(15.4%)		
Mean±SD	306.77±452.57	75.85±181.47		
Median	45.93	28		
Range	28-1300	28-1300		

Data were analyzed using **Chi-square test** to see the association between two groups,

Independent samples **Mann-Whitney U test** was performed to compare between two groups.

DISCUSSION

There is an association between chronic inflammation and the development of malignant tumors, which has already been proven in many human tumors such as colorectal cancer due to inflammatory bowel disease, hepatocellular carcinoma due to hepatitis B and C, and cervical cancer due to HPV infection. Hashimoto's thyroiditis is the most common chronic illness of the thyroid gland. It is thought that there may be an association between Hashimoto's thyroiditis and DTC, although there are many controversies regarding this issue.

In this study, the mean age of the case group was 35.8 ± 13.3 (SD) years, and the mean age of the control group was 34.6 ± 13.0 (SD) years. The mean age difference between the two groups was nearly similar, and there was no statistically significant (p > 0.05) difference between them.

A previous study conducted by Graceffa et al. found the mean age to be 47.5 years in patients with differentiated thyroid carcinoma, with a range of 13–82 years (13). Another study by SA Fish revealed that, of 2651 patients, the average age was 52.2 years in thyroid cancer patients (16). The findings of the above mentioned study are not similar to the findings of this study. The higher mean age and age range found by the studies of the above authors may be due to geographical variation, racial factors, and genetic factors that significantly influenced their study subjects.

In this study, the majority of the study populations were female in both case and control groups. It was observed that 63.5 % (n = 33) of patients in the case group were female, with a male female ratio of 1:1.7, and 69.2 % (n = 36) of participants in the control group were female. In terms of gender distribution, the difference between both groups was not statistically significant (p >0.05). A previous study conducted by Graceffa et al, observed that 84.6% of the patients were female and 15.4% were male in the differentiated thyroid carcinoma group, resulting in a male to female ratio of 1:5 (13). Another prospective cohort study found that 83.9 percent of the population was female (16). A previous retrospective study conducted by Uhliarova et al, showed a total of 2117 patients underwent partial or total thyroidectomy for thyroid cancer, and there were 1738 (82%) female participants and 379 (18%) male participants in the study group (1). The above mentioned findings were similar to the findings of this study.

In this study, the mean serum TPO Ab level in the control group was four times higher in the case group in comparison to the control group, which is significant. A study by Larson et al. showed patients with Hashimoto's thyroiditis were three times more likely to have differentiated thyroid cancer in comparison to patients without Hashimoto's thyroiditis, suggesting a strong link between Hashimoto's thyroiditis and differentiated thyroid carcinoma (17). A previous study conducted by Graceffa et al discovered that the association between differentiated thyroid carcinoma and Hashimoto's thyroiditis was very significant (p 0.001) (13). According to a meta-analysis, the Hashimoto's thyroiditis incidence in patients with differentiated thyroid carcinoma is 2.77 times higher than in patients with benign thyroid diseases. Furthermore, the relationship of Hashimoto's thyroiditis with differentiated thyroid carcinoma is 1.99 times greater in patients with thyroid carcinoma than in individuals with other clinical forms of thyroid cancer (18). Kratky et al. discovered a significant association between the presence of both antithyroid antibodies (anti-TPO and anti-TG) and thyroid cancer (positivity of anti-TPO 44% in the thyroid carcinoma group vs. 27% in patients with benign nodules, positivity of anti-TG 35% in the thyroid carcinoma group vs. 21% in patients with benign nodules). When compared to the benign group, the thyroid cancer group had considerably higher serum TSH levels. When compared to anti-TPO-negative individuals, positive anti-TPO was found to be an independent predictor of thyroid nodule malignancy, increasing the risk 2.28 times. Indirectly, these findings may suggest that Hashimoto's thyroiditis patients are more likely to develop thyroid cancer (19). Another study by Mazokopakis et al. found there was no statistically significant relationship between the presence of Hashimoto's thyroiditis and the presence of thyroid carcinoma (20).

Although the findings of a few previous studies are not conclusive or supportive of establishing any relationship between high serum TPO Ab and differentiated thyroid carcinoma, the current study suggests an increased risk of differentiated thyroid carcinoma in a patient with high serum TPO Ab, which is also supported by a few other previous studies.

CONCLUSION

The findings of this study indicate that there is an association between elevated TPO antibodies and DTC, which may be beneficial for predicting the probability of developing DTC in patients with high serum TPO antibodies. Further multicenter studies with a larger sample size are recommended. Anti-TPO antibody estimation may be used as a predictive marker of developing DTC. A diagnosed case of Hashimoto’s thyroiditis needs more careful follow-up and close monitoring, especially those with nodular variants.

Conflict of interest: The authors have no conflicts of interest

REFERENCES

1. Uhliarova B, Hajtman A. Hashimoto's thyroiditis-an independent risk factor for papillary carcinoma. Brazilian journal of otorhinolaryngology. 2018;84:729-35.
2. Faugeras L, Pirson AS, Donckier J, Michel L, Lemaire J, Vandervorst S et.al. Refractory thyroid carcinoma: which systemic treatment to use?. Therapeutic Advances in Medical Oncology. 2018;10:1758834017752853.
3. Resende de Paiva C, Grønhøj C, Feldt-Rasmussen U, Von Buchwald C. Association between Hashimoto's thyroiditis and thyroid cancer in 64,628 patients. Frontiers in oncology. 2017; Apr 10;7:53.doi:10.3389/ fonc.2017.00053. eCollection 2017
4. Gilliland FD, Hunt WC, Morris DM, Key CR. Prognostic factors for thyroid carcinoma: A population-based study of 15,698 cases from the Surveillance, Epidemiology and End Results (SEER) Program 1973–1991. Cancer: Interdisciplinary International Journal of the American Cancer Society. 1997 ;79(3):564-73.
5. Brose MS, Smit J, Capdevila J, Elisei R, Nutting C, Pitoia F, Robinson B, Schlumberger M, Shong YK, Takami H. Regional approaches to the management of patients with advanced, radioactive iodine-refractory differentiated thyroid carcinoma. Expert Review of Anticancer Therapy. 2012;12(9):1137-47.
6. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Sherman SI, Tuttle RM. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Taskforce. Thyroid. 2006 ;16(2):109-42.
7. Xiao Y, Zhou Q, Xu Y, Yuan SL, Liu QA. Positive thyroid antibodies and risk of thyroid cancer: A systematic review and meta analysis. Molecular and clinical oncology. 2019; 11(3):234-42.
8. Anand D, Yashashwi K, Kumar N, Rane S, Gann PH, Sethi A. Weakly supervised learning on unannotated H&E-stained slides predicts BRAF mutation in thyroid cancer with high accuracy. J Pathol. 2021;255(3):232-42.
9. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States. JAMA 2006 May 10;295(18):2164-7. doi: 10.1001/jama.295.18.2164.
10. Bjoro T, Holmen J, Kruger O, Midthjell K, Hunstad K, Schreiner T, Sandnes L, Brochmann H. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). Eur J Endocrinol. 2000 Nov;143(5):639-47. doi: 10.1530/eje.0.1430639
11. Weetman AP. Autoimmune thyroid disease. Autoimmunity. 2004;37(4):337-40.
12. Silva de Morais N, Stuart J, Guan H, Wang Z, Cibas ES, Frates MC et. al. The impact of Hashimoto thyroiditis on thyroid nodule cytology and risk of thyroid cancer. Journal of the Endocrine Society. 2019;3(4):791-800.
13. Graceffa G, Patrone R, Vieni S, Campanella S, Calamia S, Laise I, Conzo G, Latteri M, Cipolla C. Association between Hashimoto's thyroiditis and papillary thyroid carcinoma: a retrospective analysis of 305 patients. BMC Endocrine Disorders. 2019;19:1-6.
14. Krátký J, Ježková J, Kosák M, Vítková H, Bartáková J, Mráz M, Lukáš J, Límanová Z, Jiskra J. Positive antithyroid antibodies and non suppressed TSH are associated with thyroid cancer: a retrospective cross-sectional study. Int J Endocrinol. 2018; 2018 Sep 6. doi: 10.1155/2018/9793850
15. Pedersen IB, Knudsen N, Jørgensen T, Perrild H, Ovesen L, Laurberg P. Thyroid peroxidase and thyroglobulin autoantibodies in a large survey of populations with mild and moderate iodine deficiency. Clinical endocrinology. 2003;58(1):36-42.
16. Fish SA. Hashimoto's thyroiditis is a risk factor for thyroid cancer. Clinical Thyroidology. 2019;31(8):333-5.
17. Larson SD, Jackson LN, Riall TS, Uchida T, Thomas RP, Qiu S et.al. Increased incidence of well-differentiated thyroid cancer associated with Hashimoto thyroiditis and the role of the PI3k/Akt pathway. Journal of the American College of Surgeons. 2007 1;204(5):764-73.
18. Singh B, Shaha AR, Trivedi H, Carew JF, Poluri A, Shah JP. Coexistent Hashimoto's thyroiditis with papillary thyroid carcinoma: impact on presentation, management, and outcome. Surgery. 1999 ;126(6):1070-7.
19. Hosseini S, Payne RJ, Zawawi F, Mlynarek A, Hier MP, Tamilia M et.al. Can preoperative thyroglobulin antibody levels be used as a marker for well-differentiated thyroid cancer?. Journal of Otolaryngology-Head & Neck Surgery. 2016 ;45:1-6.
20. Mazokopakis EE, Tzortzinis AA, Dalieraki-Ott EI, Tsartsalis AN, Syros PK, Karefilakis CM et al. Coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma. A retrospective study. Hormones. 2010 ;9:312-7.