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Zeena Nooreldin Abdulrhman
Department of Family and Community Medicine, Tikrit Medical College, Tikrit University, Iraq

Waleed Qahtan Rajab
Department of Surgery, Tikrit Medical College, Tikrit University, Iraq

Ghassan Faris Idan Al-Jumaily
Department of Anesthesia and Pain Management, Tikrit Teaching Hospital, Salahaddin, Iraq

Mohammed Adel Jasim
Department of Anesthesia and Pain Management, Tikrit Teaching Hospital, Salahaddin, Iraq

Corresponding Author:
Zeena Nooreldin Abdulrhman
Department of Family and Community Medicine, Tikrit Medical College, Tikrit University, Iraq

Significance of anti-TPO levels in autoimmune thyroiditis regarding development of papillary carcinoma

Zeena Nooreldin Abdulrhman, Waleed Qahtan Rajab, Ghassan Faris Idan Al-Jumaily and Mohammed Adel Jasim

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Abstract
Background: Thyroid peroxidase antibodies (Anti-TPO) are markers of autoimmune thyroiditis, a condition characterized by inflammation of the thyroid gland. Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, often occurring concurrently with autoimmune thyroiditis.
Aim: The study aims to assess the relationship between Anti-TPO levels and the development of papillary carcinoma in patients with autoimmune thyroiditis. Specifically, it seeks to determine the prevalence and significance of elevated Anti-TPO levels in patients with PTC compared to those with autoimmune thyroiditis.
Materials and Methods: This case-control study was conducted at Salah Al-Din General Hospital in Tikrit city between January 1st and April 10th, 2023. It included 32 preoperative papillary thyroid carcinoma patients and 32 autoimmune thyroiditis patients aged over 30 years and of both sexes. Various investigations, including imaging studies, thyroid function tests, fine-needle aspiration cytology (FNAC), and blood sample collection for Anti-TPO determination, were performed as preoperative examinations.
Results: The study revealed similar age distribution patterns between PTC and autoimmune thyroiditis patients, with the highest incidence in the 44-55 age group for both conditions. Females predominated in both groups, with urban-rural residence distribution differing between the two. Smoking, hypertension, and diabetes were more prevalent in PTC patients compared to autoimmune thyroiditis patients. However, radiation exposure showed no significant difference between the groups. Elevated Anti-TPO levels were more prevalent and had a higher mean value in autoimmune thyroiditis patients compared to PTC patients. Clinical features and prognostic factors varied based on tumor size in PTC patients.
Conclusions: The study suggests a significant association between elevated Anti-TPO levels and autoimmune thyroiditis, with implications for the development of papillary carcinoma.

Keywords: Autoimmune thyroiditis, papillary thyroid carcinoma, thyroid peroxidase antibodies, anti-TPO levels, case-control study

Introduction

Thyroid dysfunction, encompassing a wide range of disorders associated with the thyroid gland, significantly impacts human health. An estimated 20 million individuals in the United States are currently afflicted with some type of thyroid disorder [1]. The prevalence of thyroid dysfunction varies among different populations due to factors such as geography, environment, ethnicity, age, and sex. The classification of functional thyroid disorders primarily consists of hypothyroidism (Insufficient thyroid function) and hyperthyroidism (Excessive thyroid function), which can be further categorized as overt or subclinical conditions. Approximately 4.6% of the US population is estimated to have hypothyroidism, with 0.3% having clinical hypothyroidism and 4.3% having subclinical hypothyroidism. Additionally, 1.3% of the population has hyperthyroidism, with 0.5% having clinical hyperthyroidism and 0.7% having subclinical hyperthyroidism. A significant number of individuals with thyroid disease remain undiagnosed due to the gradual onset of symptoms and their lack of specificity. While it may seem reasonable to conduct screenings for thyroid disease, there is no unanimous endorsement for universal screening. This is primarily due to the absence of clinical trials that have established the advantages of subsequent therapy.

The majority of thyroid carcinomas originate from follicular epithelial cells. The two main types of well-differentiated thyroid cancer are typically classified as papillary thyroid carcinoma (80%) and follicular thyroid carcinoma. Medullary thyroid cancer, which makes up 3% of cases, and anaplastic thyroid carcinoma, accounting for 12% of cases, are the two most prevalent types of thyroid malignancies. Thyroid cancer is more likely to occur in females and individuals with a family history or genetic predisposition. Other risk factors include exposure to radiation, elevated levels of thyroid-stimulating hormone, iodine deficiency, autoimmune thyroid disease, and exposure to harmful chemicals [6]. The predominant form of thyroid dysfunction, referred to as autoimmune thyroid disease, can lead to either hypothyroidism (Hashimoto's thyroiditis) or hyperthyroidism (Graves' disease). Thyroid autoantibodies, specifically anti-TPO and anti-Tg, are a clear sign of thyroid autoimmunity. Autoantibodies have demonstrated their utility as early diagnostic markers in various conditions, such as cancer, rheumatoid arthritis, and celiac disease [5, 6]. The predominant form of thyroid dysfunction, referred to as autoimmune thyroid disease, can lead to either hypothyroidism (Hashimoto's thyroiditis) or hyperthyroidism (Graves' disease). Thyroid autoantibodies, specifically anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (Anti-Tg), are a clear sign of thyroid autoimmunity [7]. Regrettably, the evaluation of thyroid autoantibodies is commonly performed only when irregularities in thyroid hormones, specifically TSH and FT4, are detected. Nevertheless, their existence prior to the primary indicator, the TSH marker, has not been acknowledged [8]. The objective of this study was to examine the importance of thyroid peroxidase antibodies levels in autoimmune thyroiditis in relation to the occurrence of papillary carcinoma.

Patients and Methods: The case-control study was carried out in Tikrit city from January 1st to April 10th, 2023, at Salah Al-Din General Hospital. The study comprised 32 patients diagnosed with preoperative papillary thyroid carcinoma and 32 patients diagnosed with autoimmune thyroiditis (Hashimoto's thyroiditis), all of whom were over the age of 30 and represented both sexes.

The clinical manifestation of papillary thyroid carcinoma, encompassing the patient's medical history and physical examination. The symptoms encompass a neck mass, difficulty swallowing, difficulty breathing, voice changes, symptoms related to excessive thyroid hormone production, symptoms related to insufficient thyroid hormone production, and pain. Physical observations encompassing the examination of the thyroid, classification of goitre, assessment of cervical lymph nodes, and evaluation of vocal cord function.

The study utilized a standardized procedure to obtain blood samples from each participant, extracting a volume of five millilitres from each patient. Afterwards, the blood samples were subjected to a process of separating the serum in order to accurately measure specific parameters related to the thyroid, namely Triiodothyronine (T_3), Thyroxine (T_4), Thyroid-Stimulating Hormone (TSH), and anti-Thyroid Peroxidase Antibodies (Anti-TPO).

The serum separation procedure effectively isolated the serum component of the blood, which encompasses a variety of biologically significant substances, such as hormones and antibodies. Subsequently, this serum, which was kept separate from other substances, underwent additional examination to measure the quantities of T_3, T_4, TSH, and anti-TPO antibodies.

Statistical analysis

Statistical analysis was conducted using SPSS version 23.1 statistical software, employing various tests such as the Chi-square ($\chi 2$) and T-test, to calculate the probability (P) value. The interpretation of the P-value is straightforward: a P-value greater than 0.05 indicates a non-significant result, suggesting no statistically significant relationship or difference between variables. Conversely, a P-value of 0.05 or less signifies a significant result, indicating a statistically significant relationship or difference between variables.

Results

Table 1 displays a juxtaposition of demographic traits among individuals diagnosed with Papillary Thyroid Carcinoma and Autoimmune Thyroiditis. Both conditions exhibit a comparable distribution among different age groups, with the highest occurrence in the 44-55 age range for Papillary Thyroid Carcinoma (46.88%) and Autoimmune Thyroiditis (40.63%). There is a clear difference in gender representation in both conditions, with females making up the majority - 93.75% for Papillary Thyroid Carcinoma and 71.88% for Autoimmune Thyroiditis. For Papillary Thyroid Carcinoma, males make up only 6.25% of cases, while for Autoimmune Thyroiditis, males account for 28.13%. Furthermore, there is a disparity in the choice of residence: Papillary Thyroid Carcinoma cases are evenly distributed between urban and rural areas (53.13% urban), whereas Autoimmune Thyroiditis cases are more common in rural settings (71.88%).

Table 1: Demographic characteristics of Papillary Thyroid Carcinoma and Autoimmune Thyroiditis

Demographic characteristics	Papillary Thyroid Carcinoma		Autoimmune Thyroiditis	
Age groups	No.	%	No.	%
34-35	3	9.38	4	12.50
44-55	15	46.88	13	40.63
>55	14	43.75	15	46.88
Total	32	100	32	100
Sex				
Female	26	93.75	23	71.88
Male	6	6.25	9	28.13
Total	32	100	32	100
Residence				
Rural	15	46.88	23	71.88
Urban	17	53.13	9	28.13
Total	32	100	32	100

The study revealed a slightly higher prevalence of smoking among PTC patients (25%), a greater incidence of hypertension (65.63%), and a higher occurrence of diabetes (53.13%) in PTC patients. Nevertheless, there was no notable disparity in radiation exposure between the two groups, as it stood at 9.38% for PTC patients and 6.26% for Autoimmune Thyroiditis patients.

Table 2: Comparative analysis of smoking, hypertension, exposure to radiation and diabetes prevalence between PTC and autoimmune thyroiditis patients

Associated risk factors		Papillary thyroid carcinoma		Autoimmune thyroiditis		P-value
		No.	%	No.	%	
Smoking	Yes	8	25	6	18.75	0.28
	No	24	75	26	81.25	
	Total	32	100	32	100	
Hypertension	Yes	21	65.63	16	50	0.025
	No	11	34.38	16	50	
	Total	32	100	32	100	
Diabetes	Yes	17	53.13	11	34.38	0.007
	No	15	46.88	21	65.63	
Exposure to radiation	Yes	3	9.38	2	6.26	0.17
	No	15	90.62	31	93.75	

When comparing the levels of Anti-TPO between Papillary thyroid carcinoma (PTC) and autoimmune thyroiditis, it is noted that only 53.12% of PTC patients have normal Anti-TPO levels. In contrast, this percentage decreases to 3.13% in autoimmune thyroiditis, with a statistically significant P-value of 0.005. In Autoimmune thyroiditis, the occurrence of elevated Anti-TPO levels is significantly higher at 96.88% compared to 46.88% in PTC patients. In addition, the average Anti-TPO level in Autoimmune thyroiditis (79.9±2.69 IU/ml) is considerably greater than in the PTC group (55.7±1.61 IU/ml), as evidenced by a P-value of 0.001, despite the fact that the typical range for Anti-TPO is 0-34 IU/ml.

Table 3: Differential distribution of Anti-TPO levels between papillary thyroid carcinoma and autoimmune thyroiditis.

Anti- TPO (IU/ml)	Papillary thyroid carcinoma		Autoimmune thyroiditis		P-value
	No.	%	No.	%	
Normal level	17	53.12	1	3.13	0.005
Elevated	15	46.88	31	96.88	
Mean ± SD	55.7±1.61		79.9±2.69		0.001

Normal range of anti-TPO: 0 - 34 IU/ml.

Table 4 displays a juxtaposition of demographic variables among patients who have been diagnosed with Papillary Thyroid Carcinoma, classified according to the size of their tumours. The data provides a clear depiction of the distribution of age and gender across various tumour size categories. The average age for patients with tumour size less than or equal to 1 cm is 45.67 years, whereas for those with tumour size greater than 1 cm, it is 46.18 years. Despite a slight disparity, the p-value of 0.17 indicates that this distinction lacks statistical significance. Regarding gender, a greater proportion of females is found in both tumour size categories (76.47% in ≤ 1 cm and 86.67% in > 1 cm), with a p-value of 0.19, suggesting no significant gender-related difference.

Table 4: Comparison of demographic factors among patients diagnosed with Papillary Thyroid Carcinoma, categorized by tumor size

Demographic factors	Papillary thyroid carcinoma patients		p-value
	Tumor Size ≤ 1 cm	Tumor Size > 1 cm	
Age (years)	45.67 ± 7.28	46.18 ± 6.48	0.17
Sex			
Females	13 (76.47%)	13 (86.67%)	0.19
Males	4 (23.53%)	2 (13.33%)	
Total	17 (100%)	15 (100%)	

Table 5 illustrates the prevalence of symptoms observed in cases of Papillary Thyroid Carcinoma (PTC). The data is presented in terms of both numerical counts and corresponding percentages. Significant findings include a high occurrence of neck pain at 96.88%, the complete absence of neck mass in all cases, dysphagia in 37.50% of cases, dyspnea in 59.38% of cases, thyrotoxicity in 9.38% of cases, and hoarseness in 93.75% of cases.

Table 5: Symptoms presented in PTC

Presenting symptoms	No.	%
Neck pain		
Yes	31	96.88
No	1	3.13
Neck mass		
Yes	32	100
No	0	0
Dysphagia		
Yes	12	37.5
No	20	62.5
Dyspnea		
Yes	19	59.38
No	13	40.63
Thyrotoxic		
Yes	3	9.38
No	29	90.63
Hoarseness		
Yes	30	93.75
No	2	6.25

The table presented illustrates a comparative examination of Anti-TPO (IU/ml) levels among patients diagnosed with Papillary Thyroid Carcinoma (PTC), categorized by tumour size (≤ 1 cm and > 1 cm). The graph displays the distribution of patients with normal and elevated Anti-TPO levels, presented in both percentages and absolute numbers, categorized by tumour size. The average Anti-TPO levels, along with their standard deviations, indicate a significant distinction between the two groups (36.3±1.88 for ≤ 1 cm vs. 58.39±2.16 for > 1 cm). The P-value of 0.001 indicates a statistically significant difference, suggesting a potential correlation between tumour size and Anti-TPO levels in PTC patients.

Table 6: Comparison of Anti-TPO (IU/ml) Levels and Proportions in PTC Patients Based on Tumor Size, with Significance Analysis

Anti- TPO (IU/ml)	PTC patients				P-value
	tumor size ≤ 1 cm		tumor size > 1 cm		
	No.	%	No.	%	
Normal level	3	17.65	0	0	0.001
Elevated	14	82.35	16	100	
Total	17	100	15	100	
Mean ± SD	36.3±1.88		58.39±2.16		0.001

The study revealed notable variations in clinical characteristics and prognostic determinants among patients diagnosed with prostate cancer (PTC), depending on the size of the tumour. Central lymph node involvement was detected in 35.29% of patients with tumours measuring ≤ 1 cm, compared to 40% of those with tumours measuring > 1 cm. Nevertheless, the incidence of capsule invasion was higher in patients with tumours larger than 1 cm, with 26.67% exhibiting this phenomenon, in contrast to only 5.88% in those with tumours equal to or smaller than 1 cm. Patients with tumours larger than 1 cm had a higher prevalence of multifocality, with 29.41% exhibiting this characteristic. There was no notable disparity in lymphadenopathy between the two groups. Nevertheless, the incidence of surgical margin infiltration was higher in patients with tumours larger than 1 cm.

Table 7: Clinical features and prognostic factors PTC in relation to tumor size

Clinical features and prognostic factors	PTC patients				P-value
	Tumor size ≤ 1 cm		Tumor size > 1 cm		
	No	%	No	%	
Central lymph node positivity					
Yes	6	35.29	6	40	0.24
No	11	64.71	9	60	
Total	17	100	15	100	
Capsule invasion					
Yes	1	5.88	4	26.67	0.004
No	16	94.12	11	73.33	
Total	17	100	15	100	
Multifocality					
Yes	1	5.88	5	29.41	0.001
No	16	94.12	10	58.82	
Total	17	100	15	100	
Lymphadenopathy					
Yes	2	11.76	3	17.65	0.16
No	14	82.35	12	70.59	
Total	16	94	15	100	
Surgical border invasion					
Yes	0	0	4	23.53	0.017
No	16	94.12	13	76.47	

Discussion

Table 1 displays a juxtaposition of demographic traits between individuals who have been diagnosed with Papillary Thyroid Carcinoma and Autoimmune Thyroiditis. Both Papillary Thyroid Carcinoma and Autoimmune Thyroiditis show a comparable distribution among different age groups. The highest occurrence of Papillary Thyroid Carcinoma is observed in the 44-55 age range, accounting for 46.88% of cases, while Autoimmune Thyroiditis has its highest incidence in the same age range, with a prevalence of 40.63%. Both conditions exhibit a clear gender disparity, with females constituting the majority - 93.75% for Papillary Thyroid Carcinoma and 71.88% for Autoimmune Thyroiditis. The proportion of males is smaller, accounting for 6.25% in Papillary Thyroid Carcinoma and 28.13% in Autoimmune Thyroiditis. Furthermore, there is a disparity in the choice of residence: Papillary Thyroid Carcinoma cases are relatively evenly distributed between urban and rural areas, with 53.13% occurring in urban settings. On the other hand, Autoimmune Thyroiditis cases are more common in rural areas, accounting for 71.88% of the cases. Within the present investigation, females exhibit a prevailing presence in both scenarios, accounting for 93.75% of Papillary Thyroid Carcinoma cases and 71.88% of Autoimmune Thyroiditis cases. On the other hand, males make up a relatively small proportion-specifically, 6.25% for Papillary Thyroid Carcinoma and 28.13% for Autoimmune Thyroiditis. Consistent with these findings, Al-Katib *et al*. also observed a higher prevalence of PTC in women compared to men. Additional research has also discovered comparable results, demonstrating a higher incidence of PTC and autoimmune diseases, such as thyroiditis, in females [9-11]. The causes of this gender imbalance are not completely comprehended, but it could be ascribed to hormonal factors, such as the potential impact of oestrogen on the development of thyroid cancer. Furthermore, these differences may be influenced by genetic and environmental factors [9].

In the present study, both Papillary Thyroid Carcinoma and Autoimmune Thyroiditis were found to be more prevalent in elderly patients. Additional studies have also reported comparable results, demonstrating a higher prevalence of PTC and autoimmune diseases, such as thyroiditis, in the elderly population [11, 12].

Research has emphasised the potential similarities between hypertension and cancer, specifically thyroid cancer. Hypertension may suggest the presence of chronic inflammation and oxidative stress, both of which are contributing factors to the development of cancer. A study conducted by Paul and Nedelcu [12] revealed a significant prevalence of hypertension among patients diagnosed with thyroid cancer. Patients with hyperthyroidism display various cardiovascular alterations, such as elevated heart rate, amplified pulse amplitude, and a significant rise in cardiac output, frequently reaching levels of up to 300% [13]. This pattern exhibits resemblances to increased adrenergic activity [6, 19], regardless of the presence of either normal or decreased levels of catecholamines in the blood. Furthermore, the influence extends to multiple hormonal factors. Elevations in levels of atrial natriuretic peptide, brain natriuretic peptide, endothelin-1, and the vasodilating polypeptide adrenomedullin are observed in individuals with hyperthyroidism [14].

Comparatively, the occurrence of diabetes is notably greater in the PTC group (53.13%) in contrast to the autoimmune thyroiditis group (34.38%), with a P-value of 0.007, indicating a robust statistical significance. Multiple studies have demonstrated a higher incidence of both hypothyroidism and hyperthyroidism in individuals with Type 2 Diabetes Mellitus (T2DM) compared to those without diabetes [15, 16]. Thyroid hormones have a significant impact on glucose, lipid, and protein metabolism, potentially worsening the control of blood sugar levels in individuals with type 2 diabetes mellitus (T2DM). It is crucial to acknowledge that hyperthyroidism and thyrotoxicosis can worsen subclinical diabetes mellitus (DM) and contribute to high blood sugar levels in patients with type 2 diabetes mellitus (T2DM), thereby increasing the likelihood of diabetic complications [18, 19].

The occurrence of elevated Anti-TPO levels is significantly greater in autoimmune thyroiditis, reaching 96.88%, compared to 46.88% in PTC patients. In addition, the average Anti-TPO level in Autoimmune thyroiditis (79.9±2.69 IU/ml) is significantly greater than in the PTC group (55.7±1.61 IU/ml), as evidenced by a P-value of 0.001, despite the fact that the normal range for Anti-TPO is 0-34 IU/ml.

Chahardoli *et al*. [20] showed similar results, indicating a significantly higher prevalence of Anti-TPO in patients with autoimmune thyroiditis compared to the control group. Zaletel [21] discovered that anti-thyroperoxidase antibody (Anti-TPO Ab) is detected in over 90% of patients with autoimmune thyroiditis. The significant disparity in average Anti-TPO levels between the Autoimmune Thyroiditis and PTC groups, specifically 79.9±2.69 IU/ml versus 55.7±1.61 IU/ml, reinforces the connection between increased Anti-TPO levels and autoimmune thyroiditis. This inconsistency is consistent with research conducted by Effraimidis *et al*. [22], which demonstrated elevated average levels of Anti-TPO in individuals with autoimmune thyroid disorders. This discovery reinforces the clinical importance of elevated Anti-TPO levels as a diagnostic indicator for autoimmune thyroiditis. In a study conducted by Brix and Hegedüs [23], the significance of anti-TPO levels in forecasting thyroid dysfunction was emphasised.

Research has shown a significant rise in the occurrence of high levels of anti-TPO in the blood serum of people with Hashimoto's thyroiditis, Graves' disease, and subacute thyroiditis compared to other thyroid conditions [24]. Multiple studies have investigated the correlation between thyroid cancer and autoimmune thyroid disease [25-27]. For example, Fiore and colleagues. In contrast, other retrospective studies have examined the outcomes of patients with solitary thyroid nodules, specifically 197 patients with positive thyroid autoantibodies and 393 patients with negative autoantibodies. The results of the Fine Needle Aspiration Biopsy (FNAB) were classified into three groups: benign, intermediate risk, and suspicious. The group of patients with positive thyroid autoantibodies had a significantly higher percentage of malignant nodules compared to the group without these autoantibodies (18.8% vs. 9.2%, $p<0.001$). This study definitively demonstrated a substantial correlation between thyroid cancer and thyroid autoimmunity [28].

Conflict of Interest: Not available

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