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Original Article

Thyroid cancer and Hashimoto's thyroiditis in AUS/FLUS nodules: is there a correlation? A retrospective study

Saad M. Alqahtani, MD [a,*], Hamed I. Albalawi, MD [b], Shehata F. Shehata, PhD [c,d], Yousef S. Alalawi, MD [e] and Saif S. Al-Sobhi, MD [f]

[a] *Department of Surgery, College of Medicine, Majmaah University, Riyadh-Qassim Road, Al-Majmaah, KSA*
[b] *Department of Surgery, King Fahad Specialist Hospital, King Khalid Road, Tabuk, KSA*
[c] *Department of Family and Community Medicine, King Khalid University, Al-Faraa Road, Abha, KSA*
[d] *Biostatistics Department, High Institute of Public Health, Alexandria University, Egypt*
[e] *Department of Surgery, King Salman Armed Forces Hospital Northwestern Region, King Abdul Aziz Road, Tabuk, KSA*
[f] *Department of Surgery, King Faisal Specialist Hospital & Research Center, Makkah Road, Riyadh, KSA*

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الملخص

أهداف البحث: يتزايد الانتشار العالمي لالتهاب الغدة الدرقية الهاشيموتو وسرطان الغدة الدرقية المتمايز، خاصة السرطان الحليمي، وتظهر الدراسات التي تقيم العلاقة بين هذه الأمراض نتائج متباينة. علاوة على ذلك، يظهر المرضى المصابون بالتهاب الغدة الدرقية الهاشيموتو معدل انتشار أعلى للخلايا غير محددة التشخيص مقارنة بغير المصابين. هدفت هذه الدراسة إلى تقييم التفاعل بين التهاب الغدة الدرقية الهاشيموتو وسرطان الغدة الدرقية المتمايز في المرضى الذين خضعوا لاستئصال الغدة الدرقية للعقد غير محددة التشخيص، وبحث دور تكرار الخزعة بالإبرة الدقيقة في العقد غير محددة التشخيص المصاحبة لالتهاب الهاشيموتو.

طرق البحث: شملت هذه الدراسة الاستعادية 111 مريضا متتاليا خضعوا لاستئصال الغدة الدرقية للعقد غير محددة التشخيص على مدى أربع سنوات. تضمنت مقاييس النتائج المعلومات الديموغرافية، وعدد وتشخيصات الخزعة بالإبرة الدقيقة، واحتمال الخباثة، ومستويات الهرمون المحفز للغدة الدرقية في الدم، وخصائص الموجات فوق الصوتية وعلامات العدوانية، بما في ذلك الغزو اللمفي الوعائي، وامتداد الورم خارج الغدة الدرقية، ونقائل العقد اللمفاوية.

النتائج: من بين المشاركين، كان 76.6% نساء و46.8% لديهم أمراض خبيثة. بشكل عام، لم يزد التهاب الغدة الدرقية الهاشيموتو من خطر الخباثة بناء على التشريح المرضي النهائي. ومع ذلك، زاد وجود التهاب الغدة الدرقية الهاشيموتو بشكل كبير من احتمال تشخيص السرطان الحليمي في الخزعة بالإبرة الدقيقة المتكررة (نسبة الأرجحية = 9.3؛ فترة الثقة 95%: 1.0-96.3). علاوة على ذلك، لوحظت علاقات مهمة بين العقد الخبيثة المصاحبة لالتهاب الهاشيموتو والعمر والجنس ونقائل العقد اللمفاوية والحواف الموجبة.

الاستنتاجات: بشكل عام، لم يزد التهاب الغدة الدرقية الهاشيموتو من خطر الخباثة في التشريح المرضي النهائي للعقد غير محددة التشخيص، رغم أنه زاد من خطر التشخيص الخلوي للسرطان الحليمي في الخزعة المتكررة. نظرا لأن الدراسة اعتمدت على المجتمع المحلي، هناك حاجة لدراسات كبيرة متعددة المراكز للتحقق من النتائج.

الكلمات المفتاحية: علم الخلايا؛ التهاب الغدة الدرقية الهاشيموتو؛ العقد الدرقية غير محددة التشخيص؛ سرطان الغدة الدرقية الحليمي؛ خطر الخباثة

Abstract

Objectives: The global prevalence of Hashimoto's thyroiditis (HT) and differentiated thyroid cancer (DTC), particularly papillary thyroid cancer (PTC), is increasing. However, studies assessing correlations between these diseases have yielded inconsistent findings. Furthermore, patients diagnosed with HT show a higher prevalence of indeterminate cytology than those without HT. This study was aimed at assessing the interaction between HT and DTC in patients undergoing thyroidectomy for indeterminate thyroid nodules (ITNs), and investigating the role of repeated fine-needle aspiration cytology (FNAC) in ITNs with HT.

Methods: This retrospective study enrolled 111 consecutive patients who underwent thyroidectomy for ITNs over a 4-year period. The outcome measures included

* Corresponding address: Department of Surgery, College of Medicine, Majmaah University Riyadh-Qassim Road, Al-Majmaah 11952, KSA.
E-mail: sm.alqahtani@mu.edu.sa (S.M. Alqahtani)
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demographic information; numbers and diagnoses of FNAC; risk of malignancy; serum thyroid-stimulating hormone levels; ultrasound features; and features of aggressiveness, including lymphovascular invasion, extrathyroidal extension and lymph node metastasis.

Results: Among the participants, 76.6 % were women, and 46.8 % had malignant pathology. Overall, HT did not increase malignancy risk, according to the final histopathology. However, the presence of HT significantly increased the probability of a PTC diagnosis with repeated FNAC (odds ratio = 9.3; 95 % confidence interval: 1.0–96.3). Furthermore, significant correlations were observed between malignant nodules with HT and age, sex, lymph node metastasis and positive margins.

Conclusions: Overall, HT did not increase malignancy risk in the final pathology of ITNs but did increase the risk of a cytological PTC diagnosis with repeated FNAC. Because this study was based in a local community setting, large, collaborative, multicenter studies are required to validate our findings.

Keywords: Cytology; Hashimoto's thyroiditis; Indeterminate thyroid nodules; Papillary thyroid cancer; Risk of malignancy

Introduction

Thyroid nodules (TNs), the most prevalent endocrine disease, are found in 50 % of the adult population and are usually detected by neck ultrasound (US).[1] TN evaluation remains a major clinical challenge, and preoperative differentiation between benign and malignant TNs is particularly problematic.[2,3] Fine-needle aspiration cytology (FNAC) is the recommended technique for the diagnostic assessment of TNs.[4–6] Approximately 60–70 % of all thyroid FNACs are benign, whereas 5–10 % are malignant. Despite FNAC's high accuracy, 10–25 % of FNACs are categorized as indeterminate, and the estimated risk of malignancy (ROM) is 5–75 % (typically 15–30 %) based on the "indeterminate category".[3]

In the indeterminate category, atypia/follicular lesion of undetermined significance (AUS/FLUS) has the most problematic and challenging diagnosis, management and ROM estimation. Recommended management strategies vary from observation to repeated FNACs with molecular testing, surgical intervention or surveillance.[6] In the general population, the ROM in AUS/FLUS TNs ranges from 5 % to 15 %, although this rate is higher in surgically resected TNs (50–76 %).[7] Notably, in centers with a high ROM, Bethesda category III is a clear indication for surgical intervention. In contrast, in centers with a low ROM (<10 %), the choice between conservative management and surgical intervention when a repeat FNAC yields another category III diagnosis remains a subject of debate (because this scenario occurs in approximately one-third of cases).[2] This issue is particularly important in patients diagnosed with Hashimoto's thyroiditis (HT), because they exhibit a greater incidence of indeterminate cytology than individuals without HT.[2]

The rate of HT diagnosis has been increasing worldwide, and the global prevalence has been estimated to be 0.3–1.5 cases per 1000 individuals; thus as much as 2 % of the general population is affected. HT is among the most prevalent endocrine disorders[8] and is the most prevalent autoimmune disorder with a female predilection. This condition is defined by diffuse infiltration of lymphocytes, parenchymal atrophy and fibrosis leading to the gradual destruction of glandular tissue and the development of hypothyroidism.[9]

FNAC in patients with HT frequently yields ambiguous outcomes, predominantly Bethesda category III.[2] Furthermore, HT can lead to an increase in cytological atypia on FNAC and consequently result in microscopic similarities to AUS/FLUS, including enlarged nuclei, lymphocyte and plasma cell infiltration, atrophic follicles containing numerous oncocytes and atypical epithelium.[1,7] This substantial overlap between the histological characteristics of AUS/FLUS and HT can complicate diagnosis based on cytopathology. Hence, the precise effects of HT on AUS/FLUS diagnosis remain uncertain.[1,7]

Differentiated thyroid carcinomas (DTCs) encompass papillary and follicular carcinomas. Papillary thyroid carcinoma (PTC), the predominant type, has a more favorable prognosis than other thyroid cancers (TCs).[8] Radiation exposure and various genetic alterations have been recognized as factors contributing to PTC development.[8] Despite a longstanding debate regarding the potential association between PTC and HT, the coexistence of DTC and HT has been reported to range from 0.5 % to 58 %, and the likelihood of having HT is 2.8 times greater in individuals diagnosed with PTC than in those with non-malignant thyroid conditions.[8] However, whether HT is a coincidental finding or an integral part of the host tumor response remains uncertain. Moreover, a consensus is lacking regarding the effects of HT on the clinical and pathological features of DTC, and on the progression and prognosis of PTC.[9]

However, some studies have shown a correlation between the presence of concurrent HT and less aggressive disease presentation, as well as a more favorable prognosis in individuals with DTC. Concomitant HT and PTC might potentially be associated with persistent stimulation of the thyroid tissue caused by increased levels of thyroid-stimulating hormone (TSH),[8,9] thereby triggering or facilitating TC development. An immunological association between HT and DTC, attributed to the involvement of thyroglobulin and thyroglobulin antibodies, has also been proposed. These substances are the primary target antigens for both cytotoxic cellular and humoral immune responses in HT and DTC.[8]

In contrast, HT has been reported to protect against tumor metastasis by restricting tumor growth; this effect has been ascribed to immunological, genetic and environmental factors, including the participation of regulatory, CD4+ and CD8+ T cells, as well as CD201+ and TH17 cells.[8] Although DTC and HT are immunologically linked, the precise cause and temporal relationship between these conditions remain

unclear. In addition, whether PTC develops as a result of an immune reaction or whether HT develops because of cross-reacting antitumor immunity is unclear.

Given the conflicting findings regarding the association between DTC and HT, this study was aimed at assessing whether HT might increase the probability of developing TC, as well as investigating the role of repeated FNAC in AUS/FLUS nodules with HT.

Materials and Methods

This retrospective observational analysis included patients with AUS/FLUS cytology, according to the Bethesda system for reporting thyroid cytopathology (TBSRTC),[4] who underwent thyroidectomy between January 2011 and December 2014 at a single tertiary center. A total of 111 patients included in our previous report[10] were also included in this study, whereas four were excluded: two with a final pathological diagnosis of lymphoma and two with missing data. HT diagnosis was based on the final pathological results.

The population was stratified into two groups according to the presence of HT: AUS/FLUS with HT, and AUS/FLUS without HT. Participants were also stratified by age at diagnosis (<55 years or ≥55 years) according to the eighth edition of the American Joint Committee on Cancer/TNM cancer staging system.[11]

Patients' electronic medical charts were reviewed to determine age, sex, nodule laterality and size, TSH level, extent of surgery and final pathological results. For malignant nodules, aggressiveness features including lymphovascular invasion, lymph node metastasis and extrathyroidal extension were also recorded.

The ROM was assessed on the basis of postoperative histopathological findings.

Ultrasound features

The sonographic features of indeterminate thyroid nodules were retrospectively re-evaluated by an expert radiologist and included the following: echogenicity, shape, content, echotexture, margins, calcification, vascularity, presence of lymphadenopathy and peripheral halo. The nodule size was categorized according to two schemes: (1) ≤10, 11–20, 21–40 and > 40 mm, according to the American staging system for TC[11] and (2) ≥4 or <4 cm.

TSH

Serum TSH levels were measured preoperatively with an electrochemiluminescence immunoassay; normal values ranged between 0.27 and 4.2 mIU/L.

Statistical analysis

Data were gathered and examined, and analysis was performed in the Statistical Package for Social Sciences (version 21; IBM Corp., Armonk, NY, USA). All statistical tests were two-tailed, with an alpha level of 0.05; a *p*-value ≤0.05 was considered significant. Descriptive analyses of study variables, including demographic data, thyroid data and HT frequency, consisted of frequency distributions and percentages. Cross-tabulation to demonstrate the differences between study groups was performed with the Pearson chi-square test and exact probability test for small frequency distributions.

Results

We enrolled a cohort of 111 patients with AUS/FLUS nodules (demographic characteristics in Table 1). The patients' ages ranged from 15 to 71 years, and the mean (standard deviation [SD]) was 40.9 (11.5) years. When stratified by age (≥55 years or <55 years), most patients (n = 99, 89.2 %) were younger than 55 years. A total of 85 patients (76.6 %) were women. The average TSH level was 1.93 (range, 0.02–189) mIU/L, and 91 patients (82.0 %) had levels in the normal range. FNAC was repeated in 46 patients (41.4 %). Indications for thyroidectomy after a single FNAC (n = 65) included progressive nodule enlargement, presence of retrosternal extension, pressure symptoms, suspicious features on US, unresponsiveness to medical treatment for Graves' disease and patient preference.

Examination of nodule laterality and size indicated that most (54.1 %) nodules were located on the right side. The average (SD) size of the nodules was 3.4 (2.3) cm, and 66.7 % of participants had nodules <4 cm.

Analysis of nodule pathology indicated that 52 patients (46.8 %) had malignant pathology, predominantly PTC, which accounted for 94.2 % of cases. Among those cases, the

Table 1: Demographic characteristics of study participants (n = 111).

Demographic characteristics	N	%
Age (years)		
<55	99	89.2
≥55	12	10.8
Mean (SD)	40.9 (11.5)	
Sex		
Male	26	23.4
Female	85	76.6
TSH (mIU/L)		
<0.27	7	6.3
0.27–4.2	91	82.0
>4.2	13	11.7
Median (range)	1.93 (0.02–189)	
Pathology		
Benign	59	53.2
Malignant	52	46.8
Laterality		
Right	60	54.1
Left	47	42.3
Isthmus	4	3.6
Nodule size (cm)		
<4	74	66.7
≥4	37	33.3
Mean (SD)	3.4 (2.3)	
Hemithyroidectomy		
Right	44	39.6
Left	36	32.4
Total thyroidectomy	31	27.9

SD, standard deviation; TSH, thyroid-stimulating hormone.

distribution of pathological subtypes was as follows: 29 individuals (59.2 %) had the follicular variant, nine (18.4 %) had the classic type, four (8.2 %) had the oncocytic type, three (6.1 %) had the tall cell type, one (2 %) had the columnar cell type, and three (6.1 %) did not have a specific subtype. In contrast, follicular thyroid cancer occurred at a rate of 5.8 %: two of three cases (66.7 %) were classified as oncocytic, and one was classified as unspecified.

Regarding the scope of the surgical procedures performed, 80 patients (72 %) underwent hemithyroidectomy, whereas 31 (27.9 %) underwent total thyroidectomy. Twenty-eight patients who underwent hemithyroidectomy and were found to have malignant pathology required completion thyroidectomy.

Of the 111 participants, 37 (33.3 %) had HT. Factors associated with HT are shown in Table 2; of these, only TSH levels were significantly associated with HT. Notably, of the patients with HT, 91.9 % had TSH levels ≥1 mIU/L, whereas 8.1 % had TSH levels <1 mIU/L ($p = 0.001$).

A total of 22 (19.8 %) patients had malignant nodules with HT, whereas 30 (27 %) had malignant nodules without HT. Table 3 presents factors associated with malignant nodules in the presence or absence of HT. Among these factors, age showed a significant correlation: 46.8 % of patients were <55 years of age, and none were ≥55 years of age ($p = 0.04$). Significant differences were observed by sex: 23.5 % and 51.4 % of male and female participants, respectively, had malignant nodules with HT ($p = 0.05$). Moreover, 80 % of malignant nodules with HT had lymph node metastasis and positive margins, whereas only 38.3 % of nodules lacked these features ($p = 0.05$).

Table 4 presents the cytological results obtained from repeated FNAC among patients with or without HT.

Table 2: Factors associated with Hashimoto's thyroiditis (n = 111).

Factors		Hashimoto's thyroiditis				*p*-value
		Yes (n = 37; 33.3 %)		No (n = 74; 66.7 %)		
		N	%	N	%	
Age (years)	<55	33	33.3	66	66.7	0.99
	≥55	4	33.3	8	66.7	
Sex	Male	5	19.2	21	80.8	0.08
	Female	32	37.6	53	62.4	
TSH (mIU/L)	<1	3	9.4	29	90.6	0.001*
	≥1	34	43.0	45	57.0	
Pathology	Benign	15	25.4	44	74.6	0.06
	Malignant	22	42.3	30	57.7	
Nodule size (cm)	<4	29	39.2	45	60.8	0.06
	≥4	8	21.6	29	78.4	
Nodule size (cm)	≤1	2	16.7	10	83.3	0.13
	1.1–2	15	46.9	17	53.1	
	2.1–4	12	35.3	22	64.7	
	>4	8	24.2	25	75.8	
Ultrasound features						
Echogenicity	Hypoechoic	20	33.9	39	66.1	0.30
	Isoechoic	4	20.0	16	80.0	
	Hyperechoic	13	40.6	19	59.4	
Content	Solid	20	28.2	51	71.8	0.27
	Predominantly solid	13	40.6	19	59.4	
	Predominantly cyst-like	4	50.0	4	50.0	
Shape	Ovoid	21	29.6	50	70.4	0.26
	Irregular	16	40.0	24	60.0	
Echotexture	Homogeneous	17	36.2	30	63.8	0.59
	Heterogeneous	20	31.3	44	68.8	
Margin	Smooth	24	36.9	41	63.1	0.34
	Ill-defined	13	28.3	33	71.7	
Calcification	Yes	5	21.7	18	78.3	0.18
	No	32	36.4	56	63.6	
Vascularity	Hypervascular	20	32.8	41	67.2	0.89
	Hypovascular	17	34.0	33	66.0	
Lymphadenopathy	Yes	3	37.5	5	62.5	0.80[a]
	No	34	33.0	69	67.0	
Peripheral halo	Yes	22	36.1	39	63.9	0.50
	No	15	30.0	35	70.0	

p-values were calculated with the Pearson χ^2 test.
* denotes a significant association ($p < 0.05$).
TSH, thyroid-stimulating hormone.
[a] Analysis was performed with the exact probability test.[a]

Table 3: Factors associated with malignant nodules in the presence or absence of HT (n = 52).

Factors	Group				*p*-value
	Malignant nodules with HT (n = 22; 42.3 %)		Malignant nodules without HT (n = 30; 57.7 %)		
	N	%	N	%	
Age (years)					0.04*
<55	22	46.8	25	53.2	
≥55	0	0.0	5	100	
Sex					0.05*
Male	4	23.5	13	76.5	
Female	18	51.4	17	48.6	
Extrathyroidal extension					0.09
Yes	2	100.0	0	0.0	
No	20	40.0	30	60.0	
Lymphovasular invasion					0.65
Yes	4	36.4	7	63.6	
No	18	43.9	23	56.1	
LN metastasis					0.05*
Yes	4	80.0	1	20.0	
No	18	38.3	29	61.7	
Positive margins					0.05*
Yes	4	80.0	1	20.0	
No	18	38.3	29	61.7	
Nodule size (cm)					0.83
<4	16	43.2	21	56.8	
≥4	6	40.0	9	60.0	
Nodule size (cm)					0.20
≤1	0	0.0	5	100.0	
1.1–2	10	52.6	9	47.4	
2.1–4	6	46.2	7	53.8	
>4	6	40.0	9	60.0	

Analyses were performed with the exact probability test.
* denotes a significant association ($p < 0.05$).
HT, Hashimoto's thyroiditis; LN, lymph node.

Among patients diagnosed with Bethesda category III, the prevailing result of repeated FNAC in individuals with HT was a combination of AUS and FLUS, which occurred at a frequency of 75 %, as compared with 25 % in individuals without HT. Notably, 40 % and 25 % of patients diagnosed with HT received a cytological diagnosis of FLUS and suspicion of follicular neoplasm on repeated FNAC, respectively. Interestingly, HT was detected in all patients diagnosed with PTC on repeated FNAC, thus indicating that the presence of HT was associated with an approximately nine-fold increase in the likelihood of obtaining a cytological diagnosis of PTC with repeated FNAC (odds ratio [OR] = 9.3; 95 % confidence interval, 1.0–96.3).

Table 4: Cytological results of repeated FNAC in patients with or without HT (n = 46).

Repeated FNAC	Total		Hashimoto's thyroiditis				*p*-value	OR (95 % CI)
			Yes		No			
	N	%	N	%	N	%		
Benign	10	21.7	3	30.0	7	70.0	0.03*	1
AUS	11	23.9	2	18.2	9	81.8		0.51 (0.06–4.1)
FLUS	5	10.9	2	40.0	3	60.0		1.6 (0.17–14.61)
AUS/FLUS	4	8.7	3	75.0	1	25.0		7.0 (0.51–97.7)
Suspicion of follicular neoplasm	4	8.7	1	25.0	3	75.0		0.77 (0.06–10.9)
Suspicion of papillary thyroid carcinoma	7	15.2	2	28.6	5	71.4		1.1 (0.11–7.81)
Papillary thyroid carcinoma	5	10.9	5	100.0	0	0.0		9.3 (1.0–96.3)*

* denotes a significant association ($p < 0.05$).
AUS, atypia of undetermined significance; CI, 95 % confidence interval; FLUS, follicular lesion of undetermined significance; FNAC, fine-needle aspiration cytology; HT, Hashimoto's thyroiditis; OR, odds ratio.

Table 5: Reported risk of malignancy in indeterminate nodules with or without HT.

Authors	Year	Risk of malignancy	
		With HT	Without HT
Suh et al.[22]	2020	36 %	46.6 %
Mulder et al.[7]	2020	44 %	60 %
Rotondi et al.[24]	2021	11 %	13.4 %
Cho et al.[1]	2021	48 %	48 %
Present study	2023	42.3 %	57.7 %

Studies in which the reported risk of HT did not increase PTC risk.
HT, Hashimoto's thyroiditis; PTC, papillary thyroid carcinoma.

Discussion

TBSRTC[4–6] is the universal standard for interpreting thyroid FNAC results. Although FNAC is recommended for the evaluation of TNs, it sometimes presents ambiguous microscopic results, namely Bethesda category III,[2] a heterogeneous group characterized by diverse cytological features. Notably, patients with HT have elevated likelihood of receiving a Bethesda category III or AUS/FLUS diagnosis, because HT can lead to an increase in cytological atypia.[1,7] Moreover, the most common cancer in indeterminate TNs is the follicular variant of PTC,[12] in accordance with our findings.

A correlation between PTC and HT was initially proposed by Dailey et al., in 1955. The association between these conditions is intriguing, because of the well-established understanding that chronic inflammation contributes to the development of neoplastic conditions in various tissues.[13] Additionally, the cytological and histopathological findings show a range of pathological alterations as HT progresses.[1]

Although clinical evaluation and antibody measurement play valuable roles in the diagnostic process, the primary method for diagnosing HT is histological examination. Furthermore, US features such as decreased echogenicity, hypervascularity, heterogeneity and hypoechoic micronodules with an echogenic rim are indicative of HT.[14] However, our findings showed no significant correlations in the US features between patients with versus without HT.

Interestingly, most individuals (>90 %) diagnosed with HT exhibit elevated levels of certain antibodies, including anti-thyroid peroxidase and anti-thyroglobulin antibodies. A recent nested case–control study has confirmed that the presence of thyroid antibodies 3–10 years before the clinical diagnosis of PTC correlates with elevated likelihood of PTC development.[13] Although the rise in cases is partially attributable to increased autoimmunity, this finding suggests that serum thyroid antibodies might have an overall negative effect. In contrast, that study also indicated that in cases identified to have thyroid autoimmunity, PTC exhibited diminished tumor sizes and a lymph node metastasis risk.[13]

In contrast, in a recent retrospective cohort study, individuals with HT have been found to have a four-fold greater risk of PTC metastasis to central lymph nodes than those without HT.[15] Similarly, in our study, lymph node metastasis and positive margins were significantly more frequent in individuals with rather than without HT. Most nodules in individuals with HT were 1.1–2 cm (46.9 %), whereas most nodules in patients without HT were >4 cm, in line with findings from prior studies.[9]

We observed that 43.4 % of nodules consistently presented a cytological diagnosis of AUS/FLUS with repeated FNAC, a percentage within the 10–50 % range observed in previous studies.[2,16–18] In addition, the overall ROM was 46.8 %, a value comparable to those reported in the current literature.[19] Notably, the influence of HT on the ROM in AUS/FLUS nodules can be explained by two distinct mechanisms. First, HT can introduce complexities in the accurate diagnosis of TNs; second, HT can manifest in a premalignant state, thus significantly increasing the likelihood of developing malignancy.[1]

The question of whether the correlation between HT and PTC indicates the concurrent presence of two distinct yet prevalent illnesses, which are observed together as a result of increased use of neck ultrasonography and FNAC, or whether it indicates a genuine cause-and-effect connection, has been extensively debated. Several studies have proposed that thyroiditis might mitigate PTC severity, whereas others have suggested that thyroiditis facilitates the advancement of PTC.[13] The development of cancerous changes might be caused by immune cells producing cellular mediators during chronic inflammation or by elevated levels of TSH, which induce the growth of follicular epithelial cells. High TSH levels correlate with enhanced risk of TC and more advanced stages of TC (i.e., PTC).[20]

Several reports have shown that individuals with rather than without HT are more likely to develop PTC; however, other findings have indicated no heightened risk.[13] A meta-analysis of 27 studies has determined that individuals with HT are twice as likely to develop PTC than individuals with TNs and without HT.[21] Biomolecular markers, including PI3K/Akt expression, BRAF mutations, RET/PTC rearrangements and p63 protein expression, have been implicated in the neoplastic transformation from HT to TC. For example, the expression of p63 is frequently observed in HT and PTC, whereas normal thyroid tissue does not exhibit such expression.[20] Unfortunately, one limitation of our study is that molecular testing was not performed in our series. Interestingly, a prior study has reported significantly greater risk of PTC development in individuals with HT in Asia rather than in Europe or the USA,[21] thus suggesting that race might be a contributing factor.

Mulder et al. have reported that AUS/FLUS nodules coexisting with HT have a lower ROM than AUS/FLUS nodules without HT.[7] The authors have proposed that the presence of atypia caused by HT might potentially lead to an erroneous elevation in AUS/FLUS diagnosis. Consequently, AUS/FLUS cytology samples with an HT background exhibited a diminished incidence of TC.[7] In contrast, a study of 357 surgically resected TNs with AUS/FLUS cytology has concluded that the presence of HT does not affect the ROM in AUS/FLUS nodules,[1] in agreement with the findings of other studies (Table 5).[22–24] In addition, a recent study has concluded that the ROM in AUS/FLUS TNs is not influenced by the coexistence of HT,[2] in agreement with our findings.

The strengths of our study are that we investigated the association between HT and DTC in only AUS/FLUS

nodules and that, unlike other studies using FNAC to diagnose PTC, the diagnoses in our study were based on histopathological findings. However, this study also has several limitations. First, data on antithyroid antibodies and molecular testing were lacking. Second, this study was performed at a single institution and included a small sample size. Finally, overestimation of the ROM might have occurred because of selection bias, given that only resected TNs were included in the analysis.

Conclusions

Our study indicated that the presence of HT did not increase the ROM, according to the final pathology after thyroidectomy for AUS/FLUS nodules; however, it increased the probability of achieving a cytological diagnosis of PTC with repeated FNAC. Moreover, age, sex, positive surgical margins and lymph node metastasis were significantly associated with malignant TNs in patients with HT. However, because this study was based in our local community, a comprehensive, well-designed, multicenter study is required to validate these findings.

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Ethical approval

The Office of Research Affairs at King Faisal Specialist Hospital & Research Centre, Riyadh, KSA, approved the study protocol (protocol code 2235539, date of approval December 7, 2023). The requirement for informed consent was waived because the study involved no direct patient communication.

Conflicts of interest

None declared.

Authors contributions

Saad M. Alqahtani: Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing; Hamed I. Albalawi: Methodology, Investigation; Shehata F. Shehata: Methodology, Formal Analysis; Yousef S. Alalawi: Methodology, Investigation; Saif S. Al-Sobhi: Methodology, Investigation, Writing – Review & Editing. All authors have read and agreed to the published version of the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Disclosure

We analyzed data from the same study population in our previous study (https://doi.org/10.5005/jp-journals-10002-1220). However, the focus of the current study, the association between HT and DTC, was not considered in our previous publication.

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