

Papillary thyroid cancer and thyroid stimulating hormone: does sex matter?

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The relation between histopathological characteristics of papillary thyroid cancer (PTC) and thyroid functioning in patients of different sex was assessed. Levels of thyroid stimulating hormone (TSH) and thyroid hormones (fT3 and fT4) were measured in 576 patients (468 females and 108 males) with histologically confirmed PTC. Extrathyroid extension (ETE) of PTC, lymphovascular invasion (LVI) and lymph node metastasis (LNM) were assessed in patients of different sex. In addition, age, histological type and Hashimoto's thyroiditis (HT) were considered. We did not find sex differences in PTC staging. However, females demonstrated smaller tumor size and higher microcarcinoma rate, whereas PTC in men was related to a higher LNM incidence. Coexisting HT was found in 33.3% of the observed patients. HT rate was significantly higher in females than in males and was associated with elevated TSH, though, there was no statistically significant relationship between HT and thyroid hormone levels. Coexisting HT significantly decreased the risk of ETE (OR = 0.67; 95% CI 0.44–1.00; P = 0.05) and LNM (OR = 0.59; 95% CI 0.37–0.94; P = 0.028) among males with PTC. However, there was no significant impact of HT on ETE and LNM in females with PTC. The present study showed sex-related differences in TSH levels and microcarcinoma incidence associated with high rate of coexisting HT in females. Coexisting HT was associated with lower rate of LNM and ETE in males that could reflect a potentially protective role of HT in PTC progression.

Key words: papillary thyroid cancer, thyroid stimulating hormone, Hashimoto's thyroiditis, sex differences.

INTRODUCTION

Papillary thyroid cancer (PTC) accounts more than 80% of all thyroid malignancies, making it the most common type of endocrine cancers [1–3]. The incidence of PTC is about 3 times higher in females than in males [3–5]. Specific clinical and pathological differences between male and female PTC patients have been reported [5–8]. There are some data demonstrating that female patients with PTC had an earlier age of onset, whereas males tend to have a more aggressive disease with higher mortality [5, 8]. However, the reasons for these sex differences are unclear. As the peak incidence of PTC was established in females of 40–49 years of age, there were several studies defining the association of PTC with reproductive factors [3, 7]. By now there is no strong evidence for hormonal,

menstrual or reproductive factors impact on PTC in women [7]. On the other hand, thyroid stimulating hormone (TSH) is considered as an important additional risk factor in different types of thyroid pathology [9]. The TSH concentration is higher in women than in men and TSH secretion depends on age in women only [5]. In addition, it was shown that TSH plays a role in nodular thyroid disease and is a risk factor of thyroid cancer, including PTC [10]. However, the comprehensive evaluation of the TSH levels impact in PTC development and prognosis is controversial. A number of studies recorded an increased risk of thyroid cancer associated with elevated TSH levels [9, 11, 12]. However, there is an opposite point of view which is supported by many other studies, or not any relations between TSH and PTC are reported [10, 12,

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13]. Anyway, it is still unclear if there are any relations or causal effects of TSH levels with PTC progression in patients of different sex. In addition, assessment of hormone levels in PTC patients is important in terms of age and sex-associated differences in Hashimoto thyroiditis (HT) rate [14, 15]. The aim of this study was to compare TSH and thyroid hormone levels impact on PTC pathological features between the sexes.

METHODS

We conducted a retrospective one-center cohort study enrolling patients with PTC who were observed at Ukrainian Research and Practical Center for Endocrine Surgery. Enrolled cases met the following criteria: 1) primary diagnosed and histologically confirmed PTC in line with the updated WHO classification (2017) [16]; 2) measurements of TSH and thyroid hormone levels were done prior to surgery; 3) patients' age was 21 years or older at the time of hospital admission. Exclusion criteria were the following: 1) cases with any prior cancers recorded at the date of diagnosis of thyroid cancer; 2) patients who received hormonal replacement therapy prior to diagnostics and operation; 3) Graves' disease; 4) pregnancy. A total of 576 eligible cases of PTC were identified. In this study, PTC patients were sub-classified into male and female groups.

Information on clinical and laboratory data as well as tumor histology were collected. The following characteristics were considered during grossing and histopathological examination: unifocal/multifocal growth, coexisting HT, extrathyroid extension (ETE), intrathyroid invasion (lymphovascular or in surrounding tissues), lymph nodes metastasis (LNM). Histological type of PTC was defined according to the WHO classification (2017) [16]. Pathological staging was performed in line with the American Joint Committee on Cancer TNM staging system (8th Edition; 2017) [17]. Diagnosis of HT was based on clinical and sonographic data, confirmed by serum autoantibodies to thyroglobulin and

TPO and by histological evaluation of slides. The following criteria for HT diagnostics were used: diffuse lymphocyte infiltration, lymphoid follicles with germinal centers and Hürthle cell changes [18]. To measure the serum concentrations of TSH and thyroid hormones levels Roche Cobas e411 automatic analyzer, the manufacturer's reagents and calibration kit were used. The normal ranges were considered as 0.04–4.0 μ U/ml for serum concentrations of TSH, 2.0–4.4 pg/ml for fT3 and 0.93–1.71 ng/dl for fT4. The predictive value of clinical features, laboratory data and histopathological findings in terms of PTC progression (ETE, LNM, stage) were explored and compared between male and female patients. Data assessment was conducted using MedCalc statistical software (MedCalc Software Inc, Belgium) and represented as $M \pm SEM$. The groups characteristics were compared using the chi-square test. To assess the association hormone levels and PTC characteristics the odds ratios (OR) with 95% confidence interval (95% CI) were calculated.

RESULTS AND DISCUSSION

There were 468 females (81.3%) and 108 males (18.7%) among observed patients with PTC aged 47.5 ± 0.65 (95% CI 46.2–48.7) and 45.05 ± 1.39 (95% CI 42.3–47.8) years old respectively. Most of the patients with PTC were euthyroid with fT3 and fT4 levels comprising 3.82 ± 0.14 pg/ml and 1.26 ± 0.05 ng/dl, respectively. Although TSH levels among enrolled cohort were within the normal range, the distribution of TSH variables was right-skewed, and more than 80% of observed patients had TSH level under 2.5 mkU/ml. We did not find statistical differences in fT3 and fT4 levels between sexes, but serum TSH concentration was significantly higher in females (Table 1). In addition, there were some peculiarities of age-related TSH dynamics in male and female patients with PTC. Moreover, we reported sex-related differences in PTC size (1.57 ± 0.06 vs 1.89 ± 0.13 cm in women and men, respectively, $P = 0.02$). However, we did

Clinical, laboratory and histopathological characteristics of PTC in patients of different sex

Characteristics	Overall		Females		Males		P
Number	576		468	81.2%	108	18.8%	
Age (years old)	47.1 ± 0.59 45.89–48.2		47.5 ± 0.64 46.23–48.77		45.1 ± 1.39 42.3–47.8		P = 0.104
Under 55 years old	414	71.9%	342	73.1%	72	66.7%	P = 0.224
Older 55 years old	162	28.1%	126	26.9%	36	33.3%	
Tumor characteristics							
Tumor size (in cm)	1.63 ± 0.06 1.52–1.74		1.57 ± 0.06 1.45–1.69		1.89 ± 0.13 1.61–2.15		P = 0.020
Multifocality							
Absent	433	75.2%	349	74.6%	84	77.8%	P = 0.568
Present	143	24.8%	119	25.4%	24	22.2%	
Histological type of PTC							
Papillary microcarcinoma	221	38.4%	193	41.2%	28	25.9%	P = 0.015
Conventional type	166	28.80%	122	26.1%	44	40.7%	
Tall cell variant	20	3.50%	17	3.6%	3	2.8%	
Sclerosing	10	1.70%	8	1.7%	2	1.9%	
Oncocytic	35	6.10%	32	6.8%	3	2.8%	
Solid	33	5.70%	26	5.6%	7	6.5%	
Follicular	91	15.80%	70	15.0%	21	19.4%	
Extrathyroidal extension							
Absent	414	71.9%	342	73.1%	72	66.6%	P = 0.223
Present	162	28.1%	126	26.9%	36	33.3%	
Lymph Node Metastasis							
Absent	462	80.2%	387	82.7%	75	69.4%	P = 0.003
Present	114	19.8%	81	17.3%	33	30.6%	
TNM stage							
I	474	82.3%	386	82.5%	88	81.5%	P = 0.925
II	94	16.3%	75	16.0%	19	17.6%	
III	8	1.4%	7	1.5%	1	0.9%	
Coexisting HT							
Absent	384	66.7%	293	28.4%	91	79%	P < 0.0001
Present	192	33.3%	175	41.6%	17	21%	
Hormone levels							
TSH (μIU/ml)	1.71 ± 0.05 1.62–1.80		1.75 ± 0.05 1.65–1.86		1.53 ± 0.08 1.36–1.69		P = 0.005
fT3 (pg/ml)	3.65 ± 0.09 3.44–3.84		3.61 ± 0.09 3.37–3.75		3.72 ± 0.37 3.29–4.91		P = 0.605
fT4 (ng/dl)	1.21 ± 0.02 1.17–1.25		1.20 ± 0.02 1.16–1.241		1.27±0.05 1.18 - 1.37		P = 0.127

not find size-related differences of serum TSH, fT3 and fT4 levels in patients of different sex.

Among the entire cohort, the rate of LNM was 19.8% (114 of 576 patients). Risk of LNM was closely related to sex and was much higher in males ($P = 0.0014$). In addition, the frequency of LNM was closely associated with histological type of PTC ($P < 0.0001$). The most frequent LNM was found in patients with diffuse-sclerotic and tall cell variant of PTC (53%). The conventional type of PTC comprised 39% LNM, the follicular variant – about 11%, and the lowest incidence of LNM was found among patients with papillary microcarcinoma (8%). However, these differences were not related to TSH levels.

Assessing sex-related differences in histological types and size of PTC, we found that females demonstrated much higher incidence of the microcarcinoma compared to males (46% vs 34%, respectively; $P = 0.044$); though there were no sex-related peculiarities of histological pattern of PTC. In addition, hormone levels were similar in patients with papillary microcarcinoma and PTC sized more than 10 mm in both male and female patients. Moreover, TSH levels did not affect TNM stage of PTC (OR = 1.229; 95% CI 0.79–1.89; $P = 0.35$).

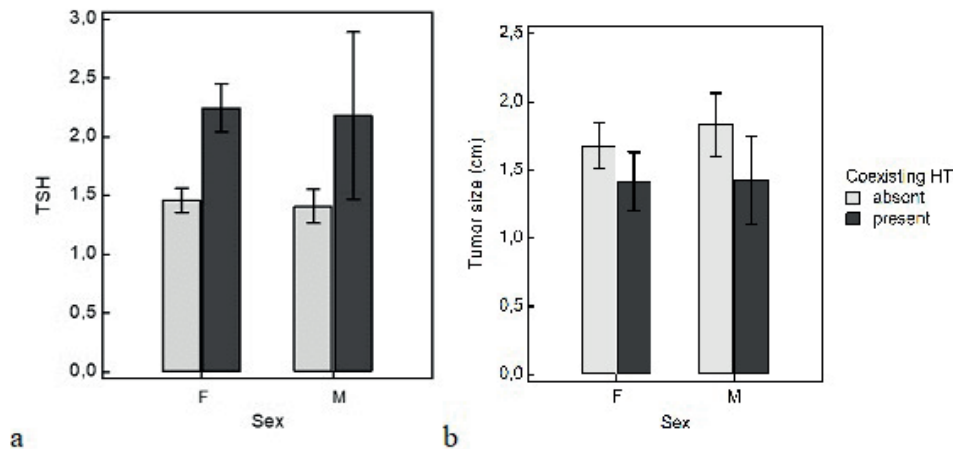
Although there were no significant differences in ranges of fT3 and fT4 in patients of different sex, it was found that high-normal (more than 2,5 $\mu\text{IU/ml}$) and high (more than 4,2 $\mu\text{IU/ml}$) levels of TSH were more frequent in females than that in males ($P = 0.03$). This was due to a higher rate of the PTC-HT coexistence in females. Coexisting HT was found in 33.3% of the observed cohort with PTC. HT rate was significantly higher ($P < 0.0001$) in females than in males (41.6% vs 21%). Assessing the impact of HT on PTC, we noticed that coexisting HT is associated with higher frequency of microcarcinoma ($P = 0.015$). Naturally, the size of PTC was lower in patients with coexisting HT ($P = 0.007$). In addition, coexisting HT affected TSH levels (Fig. 1); that was significantly higher in PTC patients with coexisting HT compared to patients with PTC alone ($P < 0.001$); though,

we did not find a statistically important relationship between HT and fT3/fT4 levels in patients with PTC.

In addition, we found that presence of HT was associated with a dip in metastasis rate in patients with PTC ($P = 0.035$). The rate of LNM in patients with coexisting HT was almost twice lower than in those who had not any features of HT (14.6% vs 22.4%, respectively). Presence of HT significantly decreased risk of ETE (OR = 0.67; 95% CI 0.44–1.00; $P = 0.05$) and metastasis into LN (OR = 0.59; 95% CI 0.37–0.94; $P = 0.028$) among males with PTC. However, we did not find a significant impact of coexisting HT on the rate of both lymph node metastasis (OR = 0.81 (95% CI 0.48–1.34; $P = 0.407$) and extrathyroid expansion (OR = 2.0 (95% CI 0.69–5.72; $P = 0.19$) in females. This could be related to some sex-specific features of PTC progression and invasiveness and have to be clarified in future investigations.

This finding allows to suggest that elevation of serum TSH concentration is mostly the consequence of coexisting HT rather than the cause of thyroid dysfunction, malignant transformation and progression of PTC.

The sex disparity in incidence, aggressiveness and prognosis is well established for thyroid cancer but the mechanisms of these differences are not fully understood. Previous investigations showed that females with PTC had an earlier age of onset, but males tend to have a more aggressive disease with higher mortality [5, 6]. In contradiction with previous reports, the current study showed no significant difference in age of onset, multifocality, and stages between male and female groups. In addition, we did not find sex differences in fT3 and fT4 levels; though the serum concentration for TSH was statistically higher in females with PTC. This peculiarity was associated with a higher rate of coexisting HT. In fact, there have been numerous studies examined the relationship between serum TSH concentration and HT [17, 20]. Although there are some debates about the role of HT in PTC development, there is a strong evidence for the



Impact of coexisting Hashimoto's thyroiditis (HT) on thyroid stimulating hormone (TSH) levels and tumor size in patients of different sex.

a – relationship between patients' sex and TSH levels with regard to coexisting HT. b – relationship between patients' sex and tumor size with regard to coexisting HT

role of autoimmune inflammation in malignancy [19, 20]. In addition, we found a significant disparity in such PTC characteristics as size, ETE and LNM, and the relationship between these variables with coexisting HT. Interestingly, the higher rate of microcarcinoma and low frequency of LNM in females were associated with coexisting HT. This potentially demonstrates the reverse relationship between HT and PTC progression features. Partially, this observation could be related with immune cells infiltration of tumors [18, 20].

We found that a higher rate of LNM in males was associated with low coincidence of HT with PTC, this supports our concept of the relationship between HT and PTC. The protective effect of coexisting HT was demonstrated in terms of LNM and ETE risks. This allows us to suppose that HT attenuates PTC progression in males, that stimulates studying sex-related mechanisms of PTC development and progression. In fact, some authors postulate that lymphocytic infiltrate of HT may be an immunological response with a cancer-retarding effect, contributing to a favorable outcome of PTC [16, 20]. This concept could explain the negative feedback between PTC-HT coexistence and metastasis rate in males.

The present study showed sex-related differences in TSH levels and microcarcinoma incidence due to high HT rate in females. Coexisting HT was associated with a lower rate of LNM and ETE in males, this could reflect a potentially protective role of HT in PTC progression.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of coauthors of the article.

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ПАПИЛЛЯРНЫЙ РАК ЩИТОВИДНОЙ ЖЕЛЕЗЫ И ТИРЕОТРОПНЫЙ ГОРМОН: ПОЛОВЫЕ РАЗЛИЧИЯ

Проанализирована взаимосвязь патогистологических характеристик папиллярного рака щитовидной железы (ПРЩЖ) и показателей функциональной активности этого органа у пациентов разного пола (468 женщин и 108 мужчин). Исследовали содержание тиреотропного гормона (ТТГ), свободного трийодтиронина и тироксина (fT3 и fT4) в сыворотке крови. Оценивали стадию, частоту экстракапсулярной и лимфоваскулярной инвазии, а также метастазирования в лимфатические узлы. Кроме того, при анализе половых различий учитывали возраст, гистологический тип ПРЩЖ и наличие аутоиммунного

тиреозита (АИТ). В роботі не обнаружено статистически значимых различий стадии ПРЩЖ у пациентов разного пола. У женщин были зарегистрированы меньший размер опухоли и более высокая частота микрокарцином, в то время как у мужчин зафиксирована более высокая частота МЛУ. Сопутствующий АИТ был обнаружен у 33,3% пациентов, его частота была значительно выше у женщин, что сопровождалось повышением содержания ТТГ, хотя статистически значимой взаимосвязи между АИТ и содержанием тиреоидных гормонов не выявлено. Сопутствующий АИТ значительно снижал риск экстраклеточной инвазии (OR = 0,67; 95% ДИ 0,44-1,00; P = 0,05) и МЛУ (OR = 0,59; 95% ДИ 0,37-0,94; P = 0,028) у пациентов мужского пола с ПРЩЖ, но не оказывал влияние на показатели инвазивности у женщин. Таким образом, выявлены половые различия сывороточного содержания ТТГ и частоты микрокарциномы, что ассоциировано с высокой частотой сопутствующего АИТ у женщин. Сопутствующий АИТ у мужчин был сопряжен со снижением риска экстраклеточной инвазии и МЛУ, что может отражать защитную роль АИТ в прогрессировании заболевания.

Ключевые слова: папиллярный рак щитовидной железы, тиреотропный гормон, аутоиммунный тиреоидит, половые различия.

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ПАПИЛЯРНИЙ РАК ЩИТОПОДІБНОЇ ЗАЛОЗИ І ТИРЕОТРОПНИЙ ГОРМОН: СТАТЕВІ РОЗБІЖНОСТІ

Проаналізовано взаємозв'язок патогістологічних характеристик папілярного раку щитоподібної залози (ПРЩЗ) і показників функціональної активності цього органа у пацієнтів різної статі (468 жінок і 108 чоловіків). Досліджували вміст тиреотропного гормону (ТТГ), вільного трийодтироніну і тироксину (fT3 і fT4) у сироватці крові. Оцінювали стадію, частоту екстраклеточного поширення (ЕТП) та лімфоваскулярної інвазії (ЛВІ), частоту метастазування у лімфатичні вузли (МЛУ). Крім того, при аналізі статевих відмінностей враховували вік, гістологічний тип ПРЩЗ і наявність аутоімунного тиреоїдиту (АИТ). Не було виявлено статистично значущих відмін стадії ПРЩЖ у пацієнтів різної статі. У жінок були зареєстровані менший розмір пухлини і більш висока частота мікрокарцином, в той час як у чоловіків – більш висока частота МЛУ. Супутній АИТ був виявлений у 33,3% пацієнтів, його частота була значно вищою у жінок, що супроводжувалося зростанням вмісту ТТГ, хоча при цьому зв'язку між АИТ і концентрацією тиреоїдних гормонів не було виявлено. Супутній АИТ значно знижував ризик екстраклеточного поширення (OR = 0,67; 95% ДІ 0,44–1,00; P = 0,05) і МЛУ (OR = 0,59; 95% ДІ 0,37–0,94; P = 0,028) у пацієнтів чоловічої статі, проте не впливав на показники інвазивності у жінок. Таким чином, виявлено статеві відмінності сироваткового вмісту ТТГ і частоти

мікрокарцином, які були асоційовані з високою частотою супутнього АИТ у жінок. Супутній АИТ у чоловіків з ПРЩЖ був асоційований зі зниженням ризику екстраклеточного поширення і МЛУ, що може відображати захисну роль АИТ в прогресуванні захворювання.

Ключові слова: папілярний рак щитоподібної залози; тиреотропний гормон; аутоімунний тиреоїдит; статеві розбіжності.

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