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TSH levels are associated with increased risk of thyroid carcinoma in patients with nodular disease

Związek między stężeniem TSH a podwyższonym ryzykiem raka tarczycy u pacjentów z guzkami tarczycy

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Abstract

Introduction: Several studies have shown an increased risk of thyroid malignancies in patients with elevated TSH levels, even if these levels fell within the normal range. The aim of this study was to evaluate the relationship between TSH and risk of malignancy in patients with thyroid nodules.

Material and methods: We included 622 patients with thyroid nodules evaluated by fine needle aspiration and/or thyroidectomy and diagnosed by cytology or histology. Clinical and laboratory data, such as gender, weight, ultrasound findings, serum TSH, and free T4, were obtained from medical records or collected during each patient's first visit to our centre, prior to any intervention.

Results: Thyroid cancer was more prevalent in males ($p = 0.012$) and in patients with a solitary nodule ($p < 0.01$). Malignant tumours were predominantly solid, whereas benign tumours were solid or mixed ($p = 0.053$). The carcinoma risk in patients with thyroid nodules increased with increasing serum TSH concentration, with a significant elevation in patients with serum TSH levels above 1.64 mU/L ($p < 0.001$). This relationship persisted even when the subgroup of patients undergoing thyroidectomy was analysed separately. Patients with follicular lesions presented with significantly higher TSH levels compared to patients with benign cytology ($p < 0.001$). We also found correlation between elevated TSH and tumour size ($p = 0.005$).

Conclusions: Our results suggest that in patients with nodular thyroid disease the carcinoma risk rose in parallel with serum TSH concentration, with significant increases evident in patients with serum TSH greater than 1.64 mU/L. **(Endokrynol Pol 2015; 66 (6): 480–485)**

Key words: *TSH; malignancy; thyroid nodules*

Streszczenie

Wstęp: Niektóre badania wykazały zwiększone ryzyko wystąpienia guzów tarczycy u pacjentów z podwyższonym stężeniem TSH, nawet jeśli stężenie to nie przekracza zakresu wartości referencyjnych. Celem niniejszego badania była ocena związku pomiędzy TSH i ryzykiem nowotworu u pacjentów z guzkami tarczycy.

Materiał i metody: Badaniem objęto 622 pacjentów z guzkami tarczycy, którym wykonano biopsję aspiracyjną cienkoigłową i/Lub tyreoidektomię oraz zdiagnozowano cytologicznie lub histologicznie. Dane kliniczne i laboratoryjne, takie jak płeć, masa ciała, wyniki USG oraz stężenie TSH i fT4 w osoczu, pobrano przed jakąkolwiek ingerencją z dokumentacji medycznej lub zebrano podczas pierwszej wizyty każdego z pacjentów w centrum medycznym, w którym pracują autorzy artykułu.

Wyniki: Rak tarczycy występował częściej u mężczyzn ($p = 0{,}012$) oraz u pacjentów z pojedynczym guzkiem ($p < 0{,}01$). Guzy złośliwe były głównie struktury litej, podczas gdy guzy łagodne miały charakter lity lub mieszany ($p = 0{,}053$). Ryzyko raka u pacjentów z guzkami tarczycy wzrastało wraz ze wzrostem stężenia TSH w osoczu, wraz ze znacznym wzrostem tego ryzyka u pacjentów ze stężeniem TSH powyżej 1,64 mU/L ($p < 0{,}001$). Związek ten utrzymał się nawet, gdy podgrupę pacjentów poddanych tyreoidektomii zanalizowano osobno. U pacjentów ze zmianami pęcherzykowatymi stwierdzono znacznie wyższe stężenie TSH w porównaniu z pacjentami z obrazem cytologicznym ilustrującym łagodną zmianę ($p < 0{,}001$). Odnotowano również związek pomiędzy podwyższonym stężeniem TSH i rozmiarem guza ($p = 0{,}005$).

Wnioski: Wyniki badania sugerują, że u pacjentów z guzkami tarczycy, ryzyko raka wzrasta wraz ze wzrostem stężenia TSH w osoczu, ze znacznym wzrostem ryzyka u pacjentów ze stężeniem TSH w osoczu powyżej 1,64 mU/L. **(Endokrynol Pol 2015; 66 (6): 480–485)**

Słowa kluczowe: *TSH, nowotwór złośliwy, guzki tarczycy*

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Introduction

Thyroid nodules are a common problem. The prevalence of palpable nodules is 4–7% in adults [1, 2]. Nodules can be detected by ultrasound in 19–67% of the population, but they are more common in women and the elderly [3]. The Framingham study in the USA reported that 5–10% of individuals developed thyroid nodules, whereas the Whickham survey in the UK, which was conducted in an area of iodine deficiency, reported a 15% incidence of goitre or thyroid nodules [2, 4]. Thyroid cancer is the most common endocrine malignancy; approximately 37,000 new cases of thyroid cancer were diagnosed in the U.S. in 2009, and this disease accounted for 1,600 deaths [5]. This increased incidence has been observed in men and women of all ages but is particularly evident in women 55–64 years old. Currently, well-differentiated thyroid carcinoma is the fifth most common malignancy in women [6]. Although the causes of this increase in incidence are not fully understood, the use of ultrasound in cervical biopsies of thyroid nodules in recent decades has probably been the primary contributing factor in the increased detection of thyroid carcinoma [7]. Most patients with nodular thyroid disease can be managed conservatively because the probability of malignancy is low. The main clinical parameters associated with an increased risk of malignant disease are the following: age (< 20 years or > 70 years), male sex, presence of a solitary nodule, nodule size (> 4 cm), rapid nodular growth, and a history of radiation exposure [8]. Well-differentiated thyroid carcinomas express the TSH receptor [9], and although oncogenes and growth factors are involved in cancer development and growth, it is probable that TSH acts as a stimulus [10]. TSH induces the expression of factors that are essential for tumour growth [11], and low TSH levels in a hyperfunctioning nodule are rarely associated with malignancy [12]. Obesity, and more specifically body surface area, have been associated with an increased incidence of thyroid cancer [13]. The mechanism underlying this association has not been elucidated. Some authors have suggested that thyroid cancer is mediated by hormonal and inflammatory changes [14] caused by adiposity. Another hypothesis is that high levels of insulin, commonly found in overweight people, cause increased thyroid proliferation [15]. Typically, the physical examination findings have poor sensitivity and specificity and are not useful for differentiating between benign and malignant nodules. Fine-needle aspiration is the preferred method for diagnosing a lesion as benign or malignant [16]. The sensitivity of this method is 65% to 98%, the specificity is 72% to 100%, the false negative rate is 1% to 11%, and the false positive rate is 1% to 8% [16].

The objective of this study was to evaluate the relationship between various clinical and laboratory parameters, particularly serum TSH level, to identify potential predictors of thyroid cancer.

Material and methods

We retrospectively reviewed the medical records of 622 patients with uni- or multi-nodular goitre. Of these, 349 patients were selected from a review of all thyroidectomies analysed in the Department of Pathology between January 1999 and December 2008. Additionally, 273 patients submitted to fine-needle aspiration between May 1988 and December 2009 were selected directly from the Thyroid Outpatient Clinic from our hospital (Fig. 1). TSH and free T4 were performed on the first evaluation of each patient, before any procedure. We excluded patients without baseline thyroid function measurements and those who were receiving levothyroxine or antithyroid drugs. Age, weight, and BMI data were collected from all patients during the clinical evaluation. TSH was measured by chemiluminescence, with a coefficient of variation less than 10% (TSH Architect, Abbott Laboratories, Illinois, USA; reference range: 0.35–4.94 mU/L). Free T4 was also measured by chemiluminescence (Architect Free T4, Abbott Laboratories, Illinois, USA; reference range: 0.7–1.48 ng/dL). The patients were classified according to thyroid function as euthyroid, subclinical hypothyroidism, clinical hypothyroidism, subclinical hyperthyroidism, or clinical hyperthyroidism [17].

Ultrasound was performed when a nodule was detected on physical examination. The type of nodule (single or multinodular), the largest diameter, and the characteristics of the nodule (solid, cystic, or mixed) were recorded. Fine-needle aspiration biopsies were performed in dominant or suspicious nodules. They were first classified as benign or malignant and then further characterized cytologically by Bethesda System classifications. Patients with medullary and anaplastic carcinoma were excluded. The nodules from patients who underwent thyroidectomy were histologically classified as colloid goitre, lymphocytic thyroiditis, follicular adenoma, papillary carcinoma, Hürthle cell adenoma, Hürthle cell carcinoma, or follicular carcinoma.

The study was approved by the Local Institutional Research and Ethics Committee, and written informed consent was obtaine7d from all the patients.

Statistical analysis

Categorical variables were presented as absolute frequency and relative frequency and compared using the chi-square test with or without Yates correction. Normally distributed quantitative variables were described

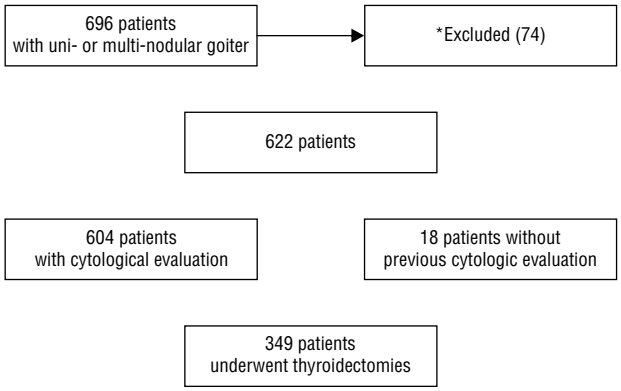

Figure 1. *Patient selection. *Excluded patients receiving levothyroxine and antithyroid drugs, patients without baseline thyroid function, and patients with medullary and anaplastic carcinoma*

Rycina 1. *Dobór pacjentów. *Z badania wyłączono pacjentów przyjmujących lewotyroksynę i leki przeciwtarczycowe, pacjentów bez pomiaru czynności tarczycy przed rozpoczęciem badania oraz pacjentów z rakiem rdzeniastym oraz anaplastycznym*

by their mean and standard deviation and compared using Student's t-test for independent samples. Quantitative variables with an asymmetric distribution were described by their median and interquartile range (25th and 75th percentiles) and were compared using the Mann-Whitney test. To establish the cutoff that provided the best sensitivity and specificity for the relationship between serum TSH and carcinoma risk, we performed ROC (receiver operating curve) analysis. To calculate the odds ratio (OR) we used logistic regression analysis. In multivariate analysis for association between TSH and malignancy, adjusting for each variable was performed by the Mantel-Haenzel test. Statistical analyses were performed using SPSS 18.0 statistics software (SPSS Inc., Chicago, IL, USA). A p value of less than 0.05 was considered statistically significant.

Results

The 622 enrolled patients included 110 patients with thyroid carcinoma (18%) and 512 patients with benign thyroid tumours (82%) (Table I). The majority of the patients were women (n = 567, 91.2%), but malignancy was more common in male patients (n = 17⁄55), 31%, than in female patients (n = 93⁄567), 16% (p = 0.012). There were no between-group differences in weight (p = 0.190) or BMI (p = 0.849). We detected a higher rate of malignant disease in patients with solitary nodules (54/197), 27.4%, compared with patients with multinodular goitre (55/421), 13% (p < 0.001). Malignant tumours were predominantly solid (58/110 malignancies were solid), 52.8%, whereas benign lesions were solid or mixed (255/512 solid benign lesions and 173/512 mixed benign lesions), 49.8% and 33.8%, respectively (p = 0.053). There were no significant differences in tumour diameter between benign and malignant tumours (p = 0.080). The median TSH level in the malign group was 2.6 mU/L (0.86–3.82), compared with 1.00 mU/L (0.42–2.10) in the benign group (p < 0.001). Analysing all patients, a ROC curve established the optimal TSH cutoff value, which had an area under the curve of 0.66. A cutoff value of 1.64 mU/L had the highest sensitivity and specificity for diagnosing malignant disease. Among the thyroid carcinoma patients, 62.7% presented with TSH > 1.64 mU/L, compared to only 32.6% in the benign group (p < 0.001) (Fig. 2). After adjusting for potential confounding factors (sex, age, BMI, nodule type, and thyroid function), we determined that patients with TSH > 1.64 mU/L had a 2.57-fold greater risk of cancer than a patient with TSH < 1.64 mU/L (OR 2.57, 95% CI 1.41–4.70) (p < 0.002). There were no statistically significant differences in fT4 values (p = 0.08). Most of the patients were euthyroid, regardless of the presence of benign or malignant nodules. In non-euthyroid patients hypothyroidism was more common in patients with malignant tumours (p < 0.001).

We performed a separate analysis of the subgroup of patients who underwent thyroidectomy (n = 349). In this

Table I. *Characteristics of patients included in the study (n = 622)*

Tabela I. *Charakterystyka pacjentów zakwalifikowanych do badania (n = 622)*

	Malign Group (n = 110)	Benign Group (n = 512)	p value
Age (years)	45.8 ± 13	50 ± 14	0.004
Weight (kg)	70 ± 15	69 ± 13	0.190
BMI [kg/ m²]	27.9 ± 5.5	28 ± 53	0.849
Larger diameter [cm]	3.5 ± 2.2	3.2 ± 1.7	0.080
TSH (mU/L)	2.6 (0.86–3.82)	1.00 (0.42–2.10)	< 0.001
Gender			
Male	17	38	0.012
Female	93	474	
Nodule type			
Solitary	54	143	< 0.001
Multinodular	55	366	
Characteristics of the nodule			
Solid*	58	255	0.053
Cystic	5	15	
Mixed	22	173	

*Solid: reference

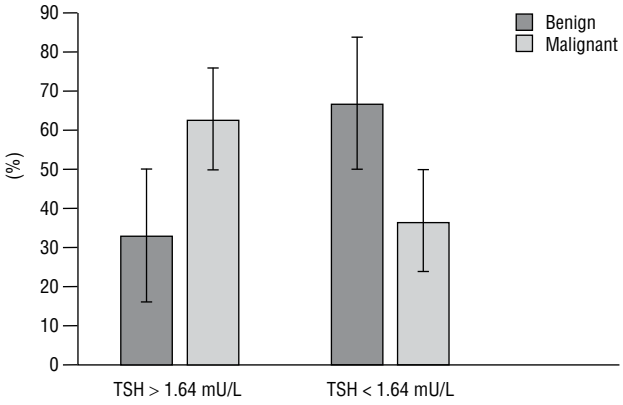

Figure 2. *Proportion of patients (622 total) with benign or malignant lesions with TSH above and below the cutoff of 1.64 mU/L (*p < 0.001)*

Rycina 2. *Proporcja pacjentów (622 ogółem) ze zmianami łagodnymi lub złośliwymi do stężenia TSH powyżej i poniżej wartości granicznej 1,64 mU/l (*p < 0,001)*

Table II. ***Logistic regression analysing the relationship between the associated factors and final diagnosis of malignancy***

Tabela II. ***Regresja logistyczna analizująca związek pomiędzy powiązanymi czynnikami i ostateczną diagnozą guza***

Variable	p-value	Adjusted OR (95% CI)
Age	0.013	194 (1.15–3.27)
Gender	0.136	1.79 (0.83–3.SS)
TSH	< 0.001	338 (2.05–5.59)
Nodule type	0.002	2.21 (1.33–3.68)
Characteristic of the nodule		
Solid*		
Cystic	0.500	0.68 (0.22–2.11)
Mixed	0.053	1.73 (0.99–3.02)

*Solid: reference

cohort, the incidence of malignancy remained higher in males (48.6% of men and 29.3% of women) (p = 0.032), in patients with a single nodule (45.2% of patients with a single nodule and 23.8% of patients with multinodular goitre) (p < 0.001), and in patients with hypothyroidism (p = 0.031). Although most of the patients were euthyroid, hypothyroidism was the most common abnormality, and it predominated in the malignant cases. There were no statistically significant between-group differences in nodule characteristics (solid, cystic, or mixed) (p = 0.217) or nodule diameter (p = 0.425). Furthermore, there were no between-group differences in weight (p = 0.334), BMI (p = 0.941), or age (p = 0.694). The median TSH level was 2.6 mU/L (0.84–3.83) in patients with thyroid carcinoma and 1.07 mU/L (0.39–2.36) in the benign group (p < 0.001). In this subgroup of patients, after adjusting for potential confounding factors (sex, nodule type, and thyroid function), we found that a patient with TSH > 1.64 mU/L had a 2.45-fold higher risk of cancer than patients with TSH < 1.64 mU/L (OR 2.45, 95% CI 1.33–4.48) (p = 0.004).

The logistic regression was performed using the diagnosis of thyroid carcinoma and the following variables: gender, age, BMI, larger diameter of the nodule, TSH levels, nodule type, and characteristics of the nodule. We observed that in the univariate analysis the variables associated with thyroid cancer were age (less than 50 years), gender, TSH, nodule type (single), and characteristics of the nodule (solid). Considering the variables that were significant in the univariate analysis, we used a logistic regression model associating these variables with TSH (≤ 1.64 mU/L or > 1.64 mU/L), and the response to malignancy as variable analysed (Table II). It was observed that TSH > 1.64 mU/L persists as a risk factor for malignancy independently of other variables.

Patients with follicular lesion had higher TSH levels compared with patients with benign cytological diagnosis. In the 40 patients with follicular lesion, the mean TSH was 2.29 mU/L (1.39–3.48), compared to 1.12 mU/L (0.48–2.25) in the other patients (p < 0.001). Considering the cutoff previously used, 72% of patients with follicular lesion showed TSH > 1.64 mU/L, while only 35% of patients with benign cytology were above this cutoff (p < 0.001).

We found a statistically significant correlation between TSH levels and tumour size (r = 0:28, p = 0.005). However, no association between TSH and number of lymph nodes affected by carcinoma (p = 0.613) or presence of metastases (p = 0.947) was observed. A possible explanation was the small number of patients with lymph node (n = 16) or distant (n = 6) metastasis. Finally, we classified the patients with final diagnosis of malignancy in stages I, II, III, and IV (TNM classification system) and found no association between TSH levels and thyroid cancer staging (p = 0.530).

Discussion

Several factors have been associated with thyroid carcinogenesis. Boelaert et al. were the first to report that the serum concentration of TSH is an independent predictor of malignancy in thyroid nodules, along with age, sex, and type of goitre. This study examined 1500 patients who underwent fine needle aspiration. The risk of malignancy rose in parallel with the serum TSH at presentation with a significant elevation above 0.9 mU/L [18]. The lowest risk of malignancy was evident in patients with subclinical hyperthyroidism (TSH < 0.4 mU/L), and the prevalence of thyroid cancer

was highest in those with subclinical hypothyroidism (TSH > 5.5 mU/L) [19]. However, this paper included different thyroid malignancies such as medullary, anaplastic cancers, and thyroid lymphomas, which have never been reported to be TSH dependent [20]. Haymart et al. [21] preoperatively evaluated TSH levels in 843 patients scheduled for surgery. The risk of malignancy was 16% for patients with TSH < 0.06 mU/L, 25% for patients with TSH between 0.40 and 1.39 mU/mL, 35% for patients with TSH between 1.40 and 4.99 mU/mL, and 52% for patients with TSH > 5 mU/L. Polyzos et al. [22] studied 565 patients with euthyroid nodular thyroid disease, who underwent fine-needle aspiration. These authors observed an increased risk of malignancy in patients with TSH levels between 1.5 and 4.0 mU/mL compared with those with TSH < 1.5 mU/L. More recent studies have shown conflicting results. Fiore et al. [20] published a review regarding the association between TSH and differentiated thyroid carcinoma. Based on the evidence showing this association, the authors suggest that the use of levothyroxine treatment in patients with thyroid nodule should be considered to reduce the risk of malignancy. McLeod et al. published a meta-analysis that included 28 studies to evaluate systematically the association between TSH and thyroid cancer. The authors analyzed 5786 cases of thyroid cancer in more than 42,000 patients and found a positive association between TSH levels and final diagnosis of malignancy [23]. Another meta-analysis published by Negro et al. [24] evaluated approximately 3000 patients with nodular thyroid disease, including 1964 who underwent thyroidectomy. The results found no difference in the risk of thyroid cancer associated with TSH levels.

In this study we evaluated 622 patients who underwent fine-needle aspiration and/or thyroidectomy and correlated the cytological and histological results with the clinical and laboratory parameters. We confirmed an association between TSH levels and malignancy; patients with TSH levels above 1.64 mU/L exhibited a significantly increased risk of malignant disease, even after correcting for other variables. This risk increased proportionally with TSH levels, even for concentrations within the reference range. Patients with follicular lesions also had higher TSH compared to patients with benign diagnosis on cytology.

We found a positive association between TSH levels and increased tumour size. Therefore, it is possible that chronic TSH stimulation enhances the pathogenesis or proliferation of thyroid cancer. TSH is directly involved in the regulation of thyroid gene expression and is indirectly involved in regulating the expression of growth factors and their receptors [25], such as insulin-like growth factor type 1 [26], epidermal growth factor [27], and vascular endothelial growth factor [28]. However, it is unlikely that TSH acts alone; thyroid carcinoma has been found in patients with a wide range of TSH levels.

Other clinical and ultrasonographic parameters have been evaluated to assess the risk of malignant thyroid nodules. Kumar et al. [21] studied 1005 patients with goitre, who underwent fine-needle aspiration. Malignant disease was more prevalent in men with an enlarged thyroid than in women, and the presence of a solitary nodule, compared with diffuse or multinodular goitre, was associated with malignancy. Rio et al. [29] evaluated 741 nodules in 407 patients and observed an increased risk of cancer associated with male sex, the presence of microcalcifications, and ultrasound hypoechogenicity. There were no significant differences in the sizes of the benign and the malignant nodules. In our cohort, we identified a higher incidence of cancer in males and in patients with a single nodule, but there were no significant differences in the diameter of the benign and malignant lesions. We observed that the patients with carcinoma were younger than those in the control group (mean age 45.8 years and 50 years, respectively), but this association is controversial in the literature, with contradictory findings in several studies [30–32].

For differentiated thyroid cancer, exposure to ionising radiation and dietary deficiency of iodine are established environmental risk factors for tumour development. Animal experiments have demonstrated a clear increase in the incidence of thyroid epithelial cell carcinomas after prolonged iodine deficiency leading to a situation of the thyroid gland by thyrotropin and possibly other growth factors [33]. Obesity has also been reported to be associated with an increased incidence of thyroid cancer in some cohorts. Engeland et al. [34] demonstrated an increased relative risk of thyroid cancer in women above 50 years of age with a BMI greater than 30 kg/m2 (relative risk of 1.31 [1.09–1.57]). Rezzonico et al. [15] evaluated the relationship between obesity and thyroid volume in 111 women. The results showed a significant increase in the prevalence of thyroid nodules, as well as an increase in thyroid volume, in obese patients with insulin resistance. In a French Polynesian cohort, being overweight or obese at age 18 years was associated with an increased incidence of thyroid cancer later in life, particularly in women [35]. Conversely, Paes et al. [36] studied 259 patients with thyroid cancer and found no relationship between BMI and tumour aggressiveness or a greater risk of recurrence. Clero et al. [37] examined 554 thyroid cancer cases and 776 controls and found an increased risk of malignancy associated with increased weight, height, BMI, body fat percentage, and body surface area. However, this correlation was not confirmed after adjusting the parameters for body surface area. Here, we did not identify a significant association between weight or

BMI and the risk of malignant disease. Thus, although obesity is associated with an increased risk of several types of cancer, such as oesophageal, colon, kidney, endometrial, and malignant melanoma [38], its association with thyroid carcinoma remains controversial.

Conclusions

Our findings suggest an association between elevated TSH levels and an increased risk of malignant disease, even for TSH levels within the reference range. The same association between serum TSH and malignancy risk was observed in subgroup analyses of thyroidectomy patients. These results were consistent with recent data in the literature [39]. TSH is a known thyroid growth factor and may play an important role in the development and progression of thyroid cancer. Our findings suggest that TSH levels may be considered as an adjunct to cytological results to identify patients who are at increased risk of malignancy, requiring further investigation of thyroid nodules or careful clinical monitoring. The possibility of an association between elevated TSH and malignancy, even within the normal range, suggests that perhaps patients with thyroid nodules have an indication of low levels of TSH as well as other groups, such as pregnant women. Prospective studies are needed to confirm and define the role of TSH as a predictor of thyroid carcinoma.

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