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ARTYKUŁ ORYGINALNY / ORIGINAL ARTICLE

Preoperative TSH and thyroglobulin levels: would it predict thyroid cancer?

Przedzabiegowe poziomy TSH i tyreoglobuliny: czy pozwalają na przewidywanie raka tarczycy?

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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ABSTRACT:

Objective: The goal of this study is to determine whether preoperative TSH and Tg levels can be used as predictors of thyroid cancer.

Study design: Retrospective chart review.

Methods: Charts of patients who had undergone thyroid surgery between 2006 and 2012 were subjected to review. Demographic data, preoperative TSH and Tg levels, and final histopathological results were recorded. Patients were divided depending on preoperative TSH and Tg levels. Group 1 consisted of patients with elevated TSH and Tg, Group 2 had elevated TSH only, Group 3 - elevated Tg only, and in Group 4 neither TSH nor Tg were elevated.

Results: 653 patient charts were reviewed and 386 patients were excluded due to incomplete information. 212 patients were female. Mean age was 50 years. Group 1 included 52 patients, 25 of them (48%) had well-differentiated thyroid cancer (WDTC). Relative risk was 1.59 and the odds ratio amounted to 1.79. Group 2 included 80 patients, 36 (45%) of whom had WDTC. Group 3 consisted of 58 patients, 23 (39.6%) of them with WDTC. Group 4 comprised 77 patients, where WDTC was present in 16 (20.8%) cases.

Conclusion: TSH and Tg levels can aid in preoperative assessment of a thyroid nodule.

KEY WORDS: TSH, thyroglobulin, thyroid cancer, thyroid nodule, thyroid neoplasms

STRESZCZENIE

Cel: Celem badania jest określenie, czy przedzabiegowe poziomy TSH i Tg mogą być stosowane jako czynnik przewidujący raka tarczycy.

Schemat badania: Retrospektywna analiza kart choroby.

Metody: Przeanalizowano karty pacjentów, u których przeprowadzono zabieg operacyjny na gruczole tarczowym w latach 2006–2012. Analizie poddano dane demograficzne, poziomy TSH i Tg przed zabiegiem, jak również ostateczne rozpoznanie histopatologiczne. Pacjentów podzielono na podstawie przedzabiegowych poziomów TSH i Tg. Grupa 1 składała się z pacjentów z podwyższonymi poziomami TSH i Tg, grupa 2 – z podwyższonymi poziomami jedynie TSH, grupa 3 – z podwyższonymi poziomami jedynie Tg, a grupa 4 – z niepodwyższonymi poziomami TSH i Tg.

Wyniki: Przeanalizowano karty 653 pacjentów. Z badań wyłączono 386 pacjentów ze względu na niekompletne dane. Wśród pacjentów 212 osób to kobiety. Średnia wieku wynosiła 50 lat. Grupa 1 obejmowała 52 pacjentów, u których w 25 (48%) przypadkach stwierdzono wysoko zróżnicowanego raka tarczycy (ang. well differentiated thyroid cancer; WDTC). Wartość ryzyka względnego wynosiła 1,59, a ilorazu szans 1,79. Grupa 2 obejmowała 80 pacjentów, u których w 36 przypadkach (45%) stwierdzono WDTC. Grupa 3 zawierała 58 pacjentów, u których w 23 przypadkach (39,6%) stwierdzono WDTC. Grupa 4 zawierała 77 pacjentów, u których w 16 przypadkach (20,8%) stwierdzono WDTC.

Wniosek: Poziomy TSH i Tg mogą pomóc w przedoperacyjnej ocenie guzka tarczycy.

SŁOWA KLUCZOWE: TSH, tyreoglobulina, rak tarczycy, guzek tarczycy, nowotwory tarczycy

INTRODUCTION

Thyroid nodules are common presenting complaints. It is estimated that 5% of the population have palpable nodules, with a reported prevalence of 35-67% in ultrasonographic studies in asymptomatic patients [1]. Although most of these nodules are benign, cancers can be found in 5-15% of them [2]. Among these malignant nodules differentiated thyroid cancers account for 90% of cases [3].

Evaluation of a thyroid nodule begins with patient's history, including demographic data, past medical history and evaluation of risk factors for thyroid cancers, such as family history and history of radiation exposure followed by physical examination, imaging studies and cytological tests.

Thyroid functional status is determined by a serum assay for thyroid hormones and thyroid stimulating hormone (TSH) levels. Ultrasound (US) is used in many centers as a first-line examination for assessment of thyroid nodules, whereas CT scan can be helpful in selected cases, especially in cervical lymphadenopathy evaluation or when intrathoracic extension is suspected. Finally, a fine needle aspiration cytology or biopsy (FNA) specimen is obtained from the nodule to determine its nature. A recent study has reported that fine needle aspiration is a highly sensitive test for certain types of thyroid carcinomas, such as papillary thyroid cancers (PTC), medullary carcinomas, and poorly differentiated thyroid cancers. In another study, the sensitivity of FNA in detecting thyroid malignancy amounted to 84% with false negative rate of 9.1% and a significantly higher risk of cancer in nodules larger than 3 cm [4].

Addressing the appropriate management of thyroid nodules is based on cumulative data obtained from the above-mentioned investigations and patients' risk factors. Management becomes challenging when diagnosis cannot be established preoperatively, especially with inconclusive cytology results. These patients require further investigation and counseling in order to determine subsequent steps of management.

Causal factors behind the differentiated epithelial thyroid cancers (papillary, follicular, and Hurthle cell thyroid cancers) are poorly understood. The best recognized risk factors for papillary thyroid cancer are: age, gender, exposure to radiation, and family history of thyroid cancer. Recently, increasing body weight has also been linked with the development of papillary thyroid cancer [5]. Comprehensive risk assessment modalities, e.g. the McGill Thyroid Nodule Score (MTNS), have been used to help counsel such patients [6]. Nevertheless, development of further assessment tools is still required to improve accuracy of preoperative diagnostics in thyroid cancers.

Thyrotropin (TSH), a well-known thyroid growth factor, along with thyroglobulin (Tg), a large glycoprotein synthesized in relation to thyroid hormones, is used in preoperative assessment as well as in follow-up protocols to monitor thyroid cancer recurrence post treatment.

The aim of this study is to review the preoperative levels of TSH and Tg in patients with thyroid nodules and to study the correlation between these levels and the presence of thyroid cancer.

METHODS

This study comprises a retrospective review of charts of all patients who underwent total or subtotal thyroidectomy at The McGill Thyroid Cancer Centre from October 2006 to May 2012 performed by a single thyroid surgeon. Institutional Review Board (IRB) approval was obtained from the McGill University research ethics committee.

Patients demographics, serum TSH, T3, T4, thyroglobulin and thyroglobulin antibody levels, alongside the final pathology report were recorded. Details of the surgical specimen such as sample size, extracapsular, perineural, and lymphovascular invasions were documented. Normal ranges for serum TSH and Tg levels at our institution were 0.4-4.4 mIU/L and 1.6-55µg/L, respectively.

TSH and Tg levels were labeled either Elevated (E) or Not Elevated (NE) depending on their respective values. The cutoff value for TSH was 1.4 mIU/L, where all values below 1.4 mIU/L were considered NE and those equal to or higher than 1.4 mIU/L were labeled as E µg/L. Similarly, for Tg the cutoff

point was established at 75 µg/L, where values below 75 µg/L were considered NE and values equal to or higher than 75 µg/L were marked as E. Both TSH and Tg cutoff values (1.4 mIU/L and 75 µg/L, respectively) were based on a study previously published by the members of our institution [6]. The study population was divided into 4 groups based on TSH and Tg levels. Group 1 included patients with elevated preoperative serum levels of both TSH and Tg (E- TSH and E-Tg). Patients with E-TSH and NE-Tg levels were assigned to Group 2. Group 3 consisted of patients with NE-TSH and E-Tg levels, while group 4 included the remaining patients with NE-TSH and NE-Tg concentrations.

Each group was further subdivided into 2 subgroups based on the final results of histopathological examination: well-differentiated thyroid cancer (WDTC) or benign lesion.

Patients in the WDTC subgroups presented with histological diagnoses of papillary thyroid cancer, follicular thyroid cancer or Hurthle cell cancer.

Inclusion and Exclusion Criteria

All patients who had undergone thyroid surgeries, in whom Tg and TSH levels had been determined preoperatively, were included in this study. Patients with a final histopathological diagnosis of medullary thyroid cancer or undifferentiated thyroid cancer were excluded from this study.

Statistical analysis

The collected data were analyzed statistically using IBM SPSS Statistics (v20.0.0) software. Odds ratio (OR) and relative risk (RR) were calculated. That was followed by analysis of variance (ANOVA) to detect significance.

RESULTS

A total number of 653 medical records were reviewed, but only 267 patients were included in this study based on the above-mentioned criteria. WDTC and micropapillary cancer were found in 100 and 63 patients respectively, whereas 104 patients had benign pathologies. Demographical analysis documented 212 females at a mean age of 50 years.

Group 1 (E- TSH & E-Tg) consisted of 52 patients; mean age of 54 years. Mean TSH was 2.60 mIU/L and mean Tg was 472.9 µg/L. As many as 25 patients (48%) were diagnosed with WDTC, 6 (12%) had micropapillary thyroid cancer, and 21 (40%) patients presented with benign thyroid pathology. For this group, OR for having WDTC was 1.79 with a relative risk of 1.59 (p = 0.06).

Group 2 (E-TSH & NE-Tg) included a total number of 80 patients, 64 of them were females at a mean age of 51 years. Mean TSH and Tg levels in this group were 4.02 mIU/L and 26.76 µg/L, respectively. 36 (45%) patients in group 2 had a diagnosis of WDTC, 18 (22.5%) subjects had micropapillary carcinoma and 26 (32.5%) harbored benign pathology. In this group OR was 1.56 with RR value of 1.35 (p = 0.09).

Group 3 (NE-TSH & E-Tg) comprised 58 patients. Of those, 47 patients were females at a mean age of 45.23 years. 23 patients (39.6%) had WDTC, micropapillary carcinoma was found in 15 (26%) patients and the remaining 20 (34.4%) cases had benign pathology. Mean value of TSH in this group was 0.79 mIU/L and 579.3 µg/L for Tg. Statistical analysis for this group revealed OR and RR of 1.3 and 1.09 (p = 0.39), respectively.

Group 4 (NE-TSH & NE-Tg) included 77 patients, 65 of them were females at a mean age of 47 years, mean TSH and Tg

Tabela 1. Związek średnich poziomów TSH i Tg z ostatecznie stwierdzaną zmianą

Grupa	N (n=267)	Mean age	Mean TSH mIU/l	Mean Tg microg/l	WDTC N (%)	Micropap N(%)	Bening	OR	RR	p
Group 1 Elevated TSH & Tg	52	54	2,6	472,9	25 (48)	6 (12)	21 (40)	1,7 (9)	1,5 (9)	0,06
Group 2 Elevated TSH, non-elevated Tg	80	51	4,02	26,76	36 (45)	18 (22,5)	26 (32,5)	1,5 (6)	1,3 (5)	0,09
Group 3 Non elevated TSH, elevated Tg	58	45	0,79	579,3	23 (39,6)	15 (26)	20 (34,4)	1,3	1,0 (9)	0,39
Group 4 Non elevated TSH & Tg	77	47	0,75	32,8	16(20,8)	24 (31,2)	37 (48)	0,3 (3)	0,4 (4)	0,000 (4)

of 0.75 mIU/L and 32.8 μg /L, respectively. 16 (20.8%) patients in this group had WDTC, 24 (31.2%) were diagnosed with micropapillary carcinoma and 37 (48%) - a benign pathology. Group 4 was characterized by OR of 0.33 and RR of 0.44 (p = 0.0004).

DISCUSSION

This study demonstrates an association between higher preoperative thyroglobulin (Tg) levels and the diagnosis of well-differentiated thyroid cancer in the final histopathological diagnosis. It stands in contradiction to the study of Insoo Suh et al. [7], which has shown no differences in Tg levels between benign and malignant neoplasms. However, our results corroborate the findings of Eun Kyung Lee et al. for undetermined thyroid nodules, where increased preoperative Tg level was reported as a significant independent risk factor for follicular thyroid carcinoma in thyroid nodules with indeterminate fine needle aspiration (FNA) results [8]. Similarly, Rok Petric [10] reported a median preoperative Tg level of 407 ng/ml in patients with thyroid carcinoma compared to 172 ng/ml in lesions with benign histology and multivariate logistic regression analysis revealed that serum Tg concentration is an independent risk factor for malignancy.

Elevated TSH is a well-established independent risk factor for WDTC [10-14]. In addition to predicting the diagnosis of thyroid cancer, high TSH values are also associated with higher risk of extrathyroidal extension and more advanced tumor stage, as reported by Haymart et al. [13,14].

The proposed theory behind this observation is such that serum TSH is a well-established growth factor for thyroid nodules that exerts its effects through TSH receptors. This growth factor effect may be attenuated by suppressing serum TSH concentrations through administration of exogenous thyroxine, which may interfere with the growth of the already existing nodules, as well as formation of new thyroid nodules [10]. On the other hand, Boelaert reported other factors that contribute to the development of thyroid cancer, such as TSH receptor mutations, and other growth factors, such as insulin-like growth factor-I (IGF-I), that were shown to be more potent with regard to stimulating thyroid cancer growth [15]. It was also reported that TSH needs to act together with IGF-1 in order to exert its proliferative effects. The same study also established that thyroid cancer occurs in subjects with a broad range of TSH concentrations, including a suppressed state when the contralateral lobe harbors hyperfunctioning nodules. Finally, a recent genome-wide association study indicated that serum TSH concentrations are lower in patients carrying one of the two alleles associated with an increased risk of both papillary and follicular thyroid cancers [15].

Another important finding in our study is that patients in Group 4 (NE-TSH & NE- Tg) were characterized by reduced incidence of WDTC compared to the rest of the studied population. These results showed statistical significance.

However, to date, serum thyroglobulin level has been used for postoperative follow-up and for monitoring of recurrent and persistent thyroid cancer, but the significance of preoperative Tg level in the diagnostic evaluation of thyroid nodules is controversial.

Increasing incidence of thyroid cancer mandates us to improve our understanding of preoperative risk factors and to look for tumor markers that might help guide preoperative patient counseling. To our knowledge, this is the first study looking into the association between both Tg as well as TSH levels, and the final pathology of WDTC. Although the results of this study do not unequivocally indicate that Tg and TSH levels can jointly predict the presence of malignancy, they do aid in selection of a subgroup of patients at lesser risk risk of a malignant nodule (NE-TSH & NE-Tg). This is an important finding that could increase in clinical significance when addressed in future research. Furthermore, the study demonstrates an interesting trend toward higher incidence of WDTC without reaching statistical significance.

There are few limitations to this study, the first being the study design. A prospective study is necessary to confirm or dismiss the findings of this study. Another limitation is the potential bias. All patients were treated by a single thyroid surgeon. A more comprehensive review with patients treated by different surgeons is warranted. These limitations will be addressed in our future study.

CONCLUSION

Tg and TSH levels are markers important for monitoring patients with thyroids cancer post treatment, but they may also play a role in preoperative evaluation of thyroid nodules. This study demonstrated that patients with NE-Tg and NE-TSH were characterized by reduced incidence of WDTC. Further research is required to support the findings of this study. Future research should continue to focus on better understanding of preoperative risk factors and cancer markers, which will help guide patient management and counseling.

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