Association Between Thyroid Stimulating Hormone Levels and Thyroid Carcinoma Risk in Patients with Nodular Disease

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Abstract: Thyroid cancer (TC) is the most common type of endocrine cancer. Most thyroid cancers are of the well-differentiated type, such as papillary and follicular carcinoma. These types of carcinoma are the most treatable, and have a better prognosis. Thyroid stimulating hormone (TSH) is a thyroid growth factor that has been deemed important for the growth, development and also in the advancement of thyroid cancer. There is already a well-established association between TSH and the growth of thyroid nodules, and the association between TSH levels and thyroid carcinoma has also been demonstrated. This study is a retrospective chart review study of 107 patients with thyroid cancer. Thyroid stimulating hormone, thyroxine (T4) and triiodothyronine (T3) levels were measured at diagnosis of thyroid nodule and before surgery; demographic and clinical presentation were also documented. The results showed that most patients were female and most were aged 20-39 years. Binary logistic regression demonstrated that the risk factor TSH is segregated into five levels: <0.4 ulU/ml, 0.4-1.0 ulU/ml, 1.01-1.8 ulU/ml, 1.81-5.5 ulU/ml, and >5.5 ulU/ml. The risks for differentiated thyroid cancer were significantly increased in subjects with serum TSH levels ranging between 1.81-5.5 ulU/ml compared with other groups (p-value=.008). Binary logistic regression demonstrated that age and TSH levels ≥ 1.81 ulU/ml were independent risk factors for differentiated thyroid cancer (p<.05). Taken together, this study showed a positive association between elevated TSH levels and increased risk for thyroid cancer.

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Introduction

Thyroid cancer (TC) is the most common type of endocrine cancer, accounting for 87% of all cancers [1], [2]. Worldwide, its incidence has increased rapidly over the last thirty years [2]. In Saudi Arabia, thyroid cancers accounted for 7.0% of all newly diagnosed cases in 2010, and it is ranked second among the female population. It affected 149 (21.4%) males and 548 (78.6%) females, with a male to female ratio of 27:100[4].

Most thyroid cancers are of the well-differentiated type (papillary and follicular carcinoma), which are reportedly the most treatable and have a better prognosis [6]. In the Kingdom of Saudi Arabia, the incidence of well-differentiated carcinomas have increased at an alarming rate over the last few years; [7]. The presentation of thyroid tumours is a painless nodule in a typically euthyroid patient. The tumour can be a single nodule (SN) or multinodular goitre (MNG). The common mode of management for thyroid cancers include thyroidectomy, radioactive thyroid ablation, and thyroxine in an adequate dose to suppress the levels of thyroid stimulating hormone (TSH) [8].

A well-established association has already been described between thyroid-stimulating hormone (TSH) and the growth of thyroid nodules. Several studies have shown that high TSH levels were associated with an increased risk for differentiated thyroid carcinoma [9]–[11]. The mechanism behind this has remained largely unexplained. A possible mechanism is that TSH aids to increase the levels of adenylate cyclase which in turn results in elevated cyclic adenosine monophosphate levels, which further stimulates cell growth [9]. Conversely, some studies [12]–[14] refute this mechanism and suggest that TSH is not an independent predictor of thyroid carcinoma. However, the study by Boelaert et al. [15] did present that TSH can be an independent predictor for TC, but even so, the research that depicts this association needs to be explored further. The present study thereby aims to demonstrate the association between TSH and well-differentiated TC in patients with nodular thyroid disease.

Materials and methods

This study was a retrospective cohort conducted at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. A total of 107 medical records of patients who visited the medical clinics were examined. These records were selected because a diagnosis of differentiated thyroid carcinoma was documented in these cases. Among these, 88 had papillary thyroid

carcinoma (PTC) and 19 had follicular thyroid carcinoma (FTC).

Patients older than 15 years and with a proven histopathological diagnosis of TC and those who had surgery were included in this study. All cases of benign thyroid tumours and other types of malignancies such as lymphomas or sarcomas were excluded. Medullary and anaplastic thyroid cancers were also excluded.

Before reviewing patients' charts, an institutional ethics committee approval was obtained. As part of the screening process, patients' medical records were reviewed for age at the time of surgery, gender, nationality, and clinical presentation. The levels of TSH, thyroxine (T4), and triiodothyronine (T3) were measured at the time of diagnosis of nodular disease but before the histopathological findings that confirmed thyroid carcinoma.

Statistical Analysis

Frequency distribution was used to ascertain the demographic information of patients. A binary logistic regression model was used to identify independent risk factors for differentiated thyroid cancer. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS IBM Inc., New York, US), version 20.0 software. A p-value < 0.05 was considered statistically significant.

Results

Of the 107 patients included, 85 were females (47 Saudi and 38 non-Saudi). Most of the Saudi patients (n=15) were in the 20-29 year old group. Conversely, the majority of non-Saudi subjects (n=14) were aged between 30 and 39 years (Table 1).

Table 2 presents the association between predictors (sex, age, goiter, left thyroid nodule, right thyroid nodule and MNG) and 'differentiated thyroid cancer'. Thyroid stimulating hormone (TSH) was segregated as five levels viz., (i) <0.4 ulU/ml, (ii) 0.4-1.0 ulU/ml, (iii) 1.01-1.8 ulU/ml, (iv) 1.81-5.5 ulU/ml, and (v) >5.5 ulU/ml. Table 3 determines the association between differentiated thyroid cancer and TSH levels. The risk for differentiated thyroid cancer was significantly associated in pateints with serum TSH ranging from 1.81-5.5 ulU/ml level. As shown in Table 3, patients with TSH levels ranging from 1.81-5.5 ulU/ml had the higher risk to have differentiated thyroid cancer (OR, 43.000; CI, 2.647-698.59). Additionally, the combination of TSH level, left thyroid nodule presence and age group effect in the risk of differentiated thyroid cancer is shown in Table 4. Binary logistic regression showed that TSH (at levels > 1.81 ulU/ml) and age > 70 years significantly increased the risk of differentiated thyroid cancer ($p<.05$). In addition, the risk of differentiated thyroid cancer was significantly increased in patients with a left thyroid nodule and those with TSH levels ranging from 1.81-5.5 ulU/ml ($p=.006$) and age greater than 70 (Table 4).

Discussion

While several studies [10, 11, 15-17] have demonstrated the association between TSH and differentiated thyroid carcinoma, Boelaert [9] was the very first to demonstrate this association. He depicted that serum TSH concentration was an independent predictor for malignancy in existing thyroid nodules. The author examined a total of 1500 patients by means of fine needle aspiration and found that malignancy risk was increased in patients with high TSH concentrations. The study also illustrated that patients with subclinical hyperthyroidism showed a lower risk for malignancy and that those with subclinical hypothyroidism exhibited the highest risk for malignancy. Fighera et al. [16] in their study evaluated the same association and from their examination of 622 patients confirmed that an association between the two does exist. They found that the prevalence of thyroid cancer was higher in males and in patients presenting with a solitary nodule. Further, the investigators demonstrated that elevated TSH levels were associated with tumour size. A review by Fiore and Vitti [11] that examined the relation between TSH and thyroid cancer showed that the incidence of papillary thyroid cancer was reduced when the TSH levels were lower.

Zeng et al. [17], on the other hand, compared TSH levels in patients with malignant and benign tumours among 108 patients who underwent surgery for thyroid tumours. They analysed factors such as serum TSH levels, age, gender, number, and type of tumour and demonstrated an association between TSH and thyroid cancer. In their analysis, they found that patients with malignant tumours had higher serum TSH levels than those with benign tumours.

In the present study, differentiated thyroid cancer was more common in female patients as opposed to the findings of other authors who reported a higher prevalence in male patients [25].

Regarding the association between TSH levels and tumour size, it has been suggested that the levels not only increase the size but also play a role with respect to the expression of the thyroid gene and other growth factors [13] such as insulin-like growth factor 1, acid-labile subunit, and vascular endothelial growth factor [19].

Therefore, besides TSH, other factors have been known to contribute to thyroid cancers. Pellegriti et al. [2] measured the incidence and prevalence of thyroid cancers and also evaluated the factors that increased the risks for thyroid cancer. They found that amongst

other factors responsible for thyroid cancer risk, an increase in medical exposure to radiation was deemed the most likely. French investigators Cardis et al. [20] conducted a study for lessons learned after the Chernobyl incident and concluded that exposure to radiation increased the risk for thyroid cancer.

Kitahara et al. [22] demonstrated a correlation between obesity and thyroid cancer as well as elevated TSH levels by including a pooled analysis of some prospective studies of obesity on thyroid cancer. The investigators examined a total of 434,953 men and 412,979 women. Of these, 388 men and 768 women were diagnosed with thyroid cancer. The data revealed a positive correlation between thyroid cancer and body mass index (BMI). In a retrospective analysis of 2057 patients with papillary thyroid carcinoma, Kim et al.[23] demonstrated that for every 5 Kg/m^2 increase in the BMI an association with tumours > 1 cm was elucidated. Not only did they demonstrate that obesity was a risk factor for thyroid carcinogenesis, but they also found an association between obesity and tumour size. Furthermore, it was demonstrated that the aggressiveness of the tumour was also dependent on body weight. Pazaitou-Panayiotou [24] reported that the main causative factor for a rise in TSH levels was insulin like growth factor-1 which in turn maybe a causative agent of thyroid cancer. However, the author also states that while a strong association between obesity and insulin resistance does exist, the association with thyroid cancer is not fully supported. Even so, the study makes recommendation to the fact that if obesity shows causal relation then aiming to reduce obesity may prove to be beneficial in reducing cancer.

Conclusion

Taken together, a positive association exists between elevated TSH levels and thyroid carcinogenesis. This association was found in patients who had undergone surgical treatment for nodular disease. Furthermore, the prevalence of thyroid cancer was higher in women and younger patients (aged 20-39 years). The implication of the study findings is that monitoring TSH levels clinically can aid as an adjunct to other laboratory tests and consequently help clinicians to determine whether an individual is at an increased risk for thyroid cancer. Therefore, more prospective as well as retrospective researches should be conducted to determine the actual relationship between TSH levels and thyroid cancer.

Tables

Table 1: Demographic information of the patients[1]

Demographic details	**Nationality**	
	Saudi	**Non-Saudi**
Gender		
Male	15 (24.0)	7 (15.6)
Female	47 (76.0)	38 (84.4)
Total	62 (100.0)	45(100.0)
Age group		
< 20	5 (8.1)	2 (4.4)
20-29	15 (24.0)	13 (29.2)
30-39	13 (21.1)	14 (31.0)
40-49	9 (14.5)	10 (22.2)
50-59	9 (14.5)	2 (4.4)
60-69	8 (13.0)	2 (4.4)
70-79	2 (3.2)	2 (4.4)
≥ 80	1 (1.6)	0 (0.0)
Total	62 (100.0)	45 (100.0)

[1] The data are presented as frequency (percent).

Table 2: Binary logistic regression model of independent predictors of thyroid cancer diagnosis by gender, age, goitre, and nodule type

Variables	**p-value**	**Odds ratio**	**95% CI**
Male	0.285	2.928	0.408-20.993
Age 40-69 years	0.034*	0.087	0.009-0.836
Age > 70 years	0.012*	0.028	0.002-0.449
Presence of goitre	0.999	65800924	0.000
Presence of left thyroid nodule	0.469	0.148	0.001-26.087
Presence of right thyroid nodule	0.677	0.334	0.002-58.319
Presence of MNG	0.186	0.132	0.007-2.653
Constant	0.064	229.959	

Abbreviations: CI, confidence interval; MNG, multinodular goitre.

Table 3: Binary logistic regression model of independent predictors of thyroid cancer diagnosis by thyroid-stimulating hormone levels

Variables	p-value	Odds ratio	95% CI
TSH (ulU/ml)	.128		
TSH (0.40-1.0)	.097	11.000	0.646-187.17
TSH (1.01-1.80)	.998	3230949728.633	-
TSH (1.81-5.5)	.008**	43.000	2.647-698.59
TSH (>5.5)	.067	14.000	0.834-235.08
Constant	.571	.500	

Abbreviations: CI, confidence interval; TSH, thyroid-stimulating hormone.
[1] Significant at the .01 alpha level.

Table 4: Binary logistic regression model of independent predictors of thyroid cancer diagnosis by age and thyroid-stimulating hormone levels simultaneously

Variables	p-value	Odds ratio	95% CI
Age 40-69 years	0.070	0.053	0.002-1.267
Age > 70 years	0.014*	0.006	0.000-0.361
TSH (0.40-1.0)	0.082	17.120	0.697-420.619
TSH (1.01-1.80)	0.997	30889952823	0.000
TSH (1.81-5.5)	0.004**	251.909	5.947-10671.005
TSH (>5.5)	0.029*	42.730	1.471-1241.587
Left thyroid nodule	0.023*	0.060	0.005-0.678
Constant	0.213	9.075	

Abbreviations: CI, confidence interval; TSH, thyroid-stimulating hormone.
[1] Significant at the .01 alpha level.

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