The Effect of Thyroid-Stimulating Hormone on Tumor Size in Differentiated Thyroid Carcinoma

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Abstract We evaluated the correlation between serum thyroid-stimulating hormone (TSH) levels and tumor size and other invasiveness parameters of tumor in patients with differentiated thyroid carcinoma (DTC). Several clinical studies have reported that TSH may also have a role as a regulator of the development and function of the thyroid gland. It is currently not clear whether TSH is involved in the existence of thyroid cancer or progression of thyroid cancer or both. Patients with DTC who underwent thyroid surgery between 2003 and 2008 were included this study. Preoperative serum T3, T4, and TSH levels were compared with the size and invasiveness of cancer, retrospectively. DTC was observed in 110 patients over the 5-year period. Seventy-seven (70 %) of them were euthyroid and classified as the “normal-TSH group” (NTG), and 33 (30 %) have an overt or subclinical hyperthyroidism, classified as the “low-TSH group” (LTG). The mean tumor diameter in the LTG was found to be 8.91 ± 8.03 mm; however, it was found to be 18.19 ± 16.24 mm in the NTG. There were significant differences among the groups related to the diameter of tumor ($p=0.001$). Microcarcinoma was determined in 36 patients (46.8 %) in the NTG and 23 patients (69.7 %) in the LTG ($p=0.027$). Although there were no significant differences, tumor capsule invasion (33.8 vs.

18.2 %, $p=0.099$) and lymphovascular invasion (16.9 vs. 6.1 %, $p=0.130$) rates were higher in the NTG. These findings suggest that TSH has effects on growing and proliferation of not only normal thyroid cells but also cancer cells in DTC. This study revealed that serum TSH level can be explored as an important factor that affects the size and invasiveness of tumor in DTC.

Keywords Differentiated thyroid cancer · Thyroid-stimulating hormone · Tumor size · Microcarcinoma

Introduction

Thyroid cancer is the most common cancer of the endocrine system [1]. The incidence of thyroid cancer is increasing more rapidly than any other cancers. The age-standardized incidence rate of thyroid cancer per 100,000 has increased from 1.1 in 1970–1972 to 6.1 in 2012 for males and from 3.3 to 22.2 in females during the same period [2]. Thyroid-stimulating hormone (TSH) is also a well-known thyrocyte growth factor [3]. It is a glycoprotein that is synthesized in the pituitary gland and consists of alpha and beta subunits. Several clinical studies have reported that TSH is the most important regulator of the development and functioning of the thyroid gland [4, 5]. Some authors have reported that higher levels of TSH are associated with an increased incidence of thyroid cancer in patients with nodular thyroid disease, but it is still unclear whether TSH is involved in the development of thyroid cancer or progression of thyroid cancer or both of them [6]. The present study was conducted to determine the association between preoperative serum TSH levels and tumor size and invasiveness in thyroid cancer patients.

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Materials and Methods

In the present study, 1,450 patients who underwent thyroidectomy for nodular goiters, multinodular goiters, drug-resistant toxic goiters, or thyroid carcinoma/suspected thyroid carcinoma were evaluated between 2003 and 2008. Of the total, 117 patients were diagnosed of having thyroid cancer, and 110 were diagnosed with differentiated thyroid carcinoma (DTC). Preoperative serum fT3, fT4, and TSH values of patients were determined, and their demographic data and pathology reports were documented retrospectively.

Patients with normal serum TSH levels (0.4–4.0 mU/L) were classified as “normal-TSH group” (NTG). Likewise, patients who have subclinical or overt hyperthyroidism and have lower serum TSH levels (<0.4 mU/L) were classified as “low-TSH group” (LTG). Patients in LTG were divided into two subgroups, named as “subclinical hyperthyroidism” and “overt hyperthyroidism.”

Tumor size was determined based on the largest diameter of tumor. The existence of multicentric tumor and lymphovascular and capsular invasion were investigated according to pathology reports, retrospectively. Tumor grading was performed according to WHO criteria. Tumors smaller than 1 cm in diameter were considered as microcarcinoma (MC). Chi-square test, Student's *t* test, and Mann–Whitney *U* test was used for statistically analysis.

Results

There were 1,450 patients who underwent thyroidectomy during the 5-year period. Two hundred ninety-five (20.3 %) have overt hyperthyroidism, 138 (9.5 %) subclinical hyperthyroidism, and 1,004 (69.2 %) euthyroidism. DTC was detected in 33 (7.62 %) of 433 patients who had “low TSH level”, and 77 (7.66 %) of 1,004 patients had “normal TSH level” (Table 1). The data of 110 (7.6 %) cancer patients were analyzed.

DTC was diagnosed in 90 (81.8 %) females and 20 (18.2 %) males. The mean age was 45.10 ± 12 in NTG and

45.21 ± 17 in LTG. There was no significant difference among groups related to demographic parameters ($p > 0.05$).

Thirty-one patients (28.1 %) underwent bilateral subtotal thyroidectomy, and completion thyroidectomy is subsequently performed on all these patients. Bilateral near-total thyroidectomy and bilateral total thyroidectomy performed on 53 (48.2 %) and 26 (23.7 %) patients, respectively. Furthermore, nine patients (11.7 %) in NTG and one patient (3.1 %) in LTG underwent a modified radical neck dissection as a result of detection of metastatic lymph nodes in the cervical region.

The mean tumor diameter was 8.91 ± 8.03 mm in LTG and 18.19 ± 16.24 mm in NTG. There was a significant difference in tumor diameters among two groups ($p = 0.001$) (Table 2).

Histopathological evaluation revealed that 59 (53.6 %) of patients' had MC, 36 (46.8 %) of them were in NTG and 23 (69.7 %) in LTG. There was a significant difference in MC incidence of groups ($p = 0.027$). The presence of multicentric tumor was higher in LTG, whereas the incidence of tumor capsule invasion, thyroid capsule invasion, and lymphovascular invasion was higher in NTG, but there was no significant difference among groups (Table 2).

There was no significant difference in tumor size ($p = 0.927$), rates of MC ($p = 0.616$), and the presence of multicentric tumor ($p = 0.549$) among the subgroups of subclinical and overt hyperthyroidisms.

Discussion

Thyroid cancer accounts for 5–15 % of all thyroid nodules, and papillary carcinoma constitutes 80–90 % of all thyroid cancers [7]. Consistent with previous literature, papillary carcinoma was observed in 102 patients (92.7 %) in this study. TSH is known as the major stimulant in both the functioning and the development of the thyroid gland [4, 5], but there are insufficient data on TSH's direct mitogenic effect on the human thyroid gland. Existence of TSH receptors on thyroid cancer cells is known and also supports this effect [8]. Previous studies have shown that TSH has a mitogenic effect on the thyroid glands of animals [9]. A number of researchers have

Table 1 The distribution of hormonal spectra in patients diagnosed with cancer and who underwent thyroidectomy

Hormonal spectra of patients	Number of patients who underwent thyroidectomy ($n = 1,450$) n (%)	Number of patients who have thyroid carcinoma ($n = 110$) n (%)
Number of patients with normal TSH level (0.4–4.0 mU/L)	1,004 (69.2)	77 (70)
Number of patients with low TSH level (<0.4 mU/L)	433 (29.9)	33 (30)
Patients with overt hyperthyroidism	295 (20.4)	21 (19.1)
Patients with subclinical hyperthyroidism	138 (9.5)	12 (10.9)
Number of patients with high TSH level (>4.0 mU/L)	13 (0.9)	– (–)

Table 2 Evaluation of groups with respect to the tumor diameter, incidence of microcarcinoma, presence of multicentric tumor, capsular invasion of tumor, capsular invasion of thyroid gland and lymphovascular invasion

	NTG (n=77)	LTG (n=33)	Total (n=110)	Test	
				Z ^a (p)	χ ^{2b} (p)
Tumor diameter (mm, mean±S.D.)	18.19±16.24	8.91±8.03	15.40±13.77	−3.405 (0.001**)	
Microcarcinoma	36 (46.8)	23 (69.7)	59 (53.6)		4.89 (0.027*)
Presence of multicentric tumor	16 (20.8)	11 (33.3)	27 (24.5)		1.966 (0.161)
Invasion of tumor capsule	26 (33.8)	6 (18.2)	32 (29.1)		2.720 (0.099)
Invasion of thyroid capsule	7 (9.1)	2 (6.1)	9 (8.2)		0.282 (0.595)
Lymphovascular invasion	13 (16.9)	2 (6.1)	15 (13.6)		2.297 (0.130)

^a Mann–Whitney *U* test^b Chi-square test**p*<0.05; ***p*<0.01

demonstrated that TSH requires IGF-I or high-dose insulin for its mitogenic effect in vitro [10], although the correlation between high levels of TSH secretion and thyroid cancers remains unclear [11]. Similarly, Hancock et al. [12] demonstrated that prolonged TSH stimulation by the goitrogens leads to hyperplasia and, subsequently, to neoplasia in the thyroid gland. Boelaert et al. [13] suggested that an increased concentration of TSH could be an independent predictor of thyroid malignancy. Franco et al. [14] demonstrated that TSH plays a key role in Braf-induced PTC initiation in a mouse model. There have been only two studies that analyzed the association of TSH concentration with PTC. While the study of Haymart et al. revealed an escalating risk of malignancy with higher TSH concentration [15], the other study indicated that TSH was not involved in the oncogenesis of these cancers [16]. Various studies have reported that incidences of PMC range between 9 and 47 % [5, 6, 17]. Nowadays, increased rates of papillary MC have been identified as a result of technological advances in the imaging of thyroid diseases [18, 19]. MC usually have a good prognosis, and 10-year mortality rates range between 0 and 1 % [1, 20–22]. We determined MC at 59 (53.6 %) of 110 patients, with a statistically significant difference noted in the incidence of MC between the NTG (46.8 %) and the LTG (69.7 %).

Recently, Fiore et al. [23, 24] reported that higher TSH levels are not only associated with prevalence of DTC but also with the aggressive characteristics of DTC. Likewise, our study revealed that cancer course is more aggressive in NTG. Gerschpacher et al. [16] demonstrated that TSH is not likely involved in the de novo oncogenesis of DTC. Therefore, there is still no consensus in this matter. Jin et al. [25] reported that patients with serum TSH level of <0.9 have a malignancy probability of about 10 %, whereas cancer rate was 65 % in those patients with a serum TSH level of >5.5. We detected the DTC rates as 7.62 and 7.66 %, respectively, when we compared patients with low and normal TSH levels.

Shi et al. [4] reported that TSH level may be related to advanced stage, that is, progression of thyroid cancer, but not with the development of thyroid cancer; higher TSH level was also associated with lymph node metastasis and advanced disease (stages III and IV), related to this study. Consistent with this study, our study revealed that nine (11.7 %) patients in NTG and one (3.1 %) patient in LTG underwent neck dissection due to lymph node metastasis. Although the role of TSH levels in the development or progression of thyroid cancer remains controversial, their results support the hypothesis that TSH levels may play a role in the progression at the size of an existing DTC [4]. In our study, incidence of MC was statistically higher, and the tumor diameter was statistically lesser in the LTG when compared to the NTG. The mean tumor diameter was 8.91±8.03 and 18.19±16.24 mm, respectively (*p*=0.001). The relationship between tumor size and TSH levels is evaluated with correlation test and revealed a very strong positive linear correlation between them (*r*=0.658) (Fig. 1).

Fig. 1 Relationship between tumor size and TSH levels

Some of the studies revealed that the prevalence of multicentric tumors of patients with papillary thyroid carcinoma is approximately 25–88 %. In this study, multicentric tumors were observed in 27 patients (24.5 %), 11 (33.3 %) in the LTG and 16 (20.8 %) in the NTG. Although there was no significant difference among the groups related to the incidence of multicentric tumor, incidence ratio was higher in LTG, whereas poor prognosis criteria such as tumor capsule invasion and lymphovascular invasion were higher in the NTG with no significant difference.

Conclusion

Despite the incidence that DTC is similar in both groups, patients in LTG have lesser tumor diameters and higher incidence of MC. These findings suggest that TSH is played a role in the progression of preexisting cancerous foci in the thyroid gland. Because patients with hyperthyroidism were operated earlier due to the thyrotoxicosis symptoms, therefore, this can be the reason of detecting the tumor in smaller size. Nevertheless, we thought that the major reason on increased rates of MC in LTG is the lower levels of TSH. Higher probability of detection of MC in patients with low TSH levels must be remembered.

Conflict of Interest İbrahim Ali Özemer, MD and other coauthors declare no conflict of interest.

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