

The association between serum thyroid-stimulating hormone concentration and development of differentiated thyroid cancers in nodular thyroid disease

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Objective

To evaluate the relation between serum thyroid-stimulating hormone (TSH) and development of differentiated thyroid cancers in nodular thyroid disease (NTD) in Egyptians.

Patients and methods

One hundred patients were included in this study at Al-Azhar University Hospitals from 2010 to 2013; all patients with NTD, who were fit for surgery, were selected for study. The preoperative TSH level was estimated and was compared with the final histopathological diagnosis for the presence of malignant thyroid lesions.

Results

A total of 100 patients were included in the study, with an average age of 46 years. The male to female ratio was 1 : 4.7. Seventy-five patients had multinodular goiter, whereas 25 patients had a solitary thyroid nodule. Eighty-six patients underwent total thyroidectomy, whereas 14 patients underwent near- total thyroidectomy. The final histopathological data showed no evidence of malignancy in 83 patients, 83% (benign group), whereas malignant lesions were present in 17 patients, 17% (malignant group). The preoperative mean TSH level in the benign group was 1.72 ± 1.4 mIU/L, whereas the mean TSH concentration in the malignant group was 2.61 ± 2.2 mIU/L.

Conclusion

There is a definite relation between serum TSH and development of differentiated thyroid cancers in NTD as the risk of thyroid malignancy increases with increased serum TSH concentrations.

Keywords:

nodular thyroid disease, thyroid cancer, thyroid-stimulating hormone

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Introduction

About 4–7% of the population has thyroid nodules [1]; this range depends on differences in iodine nutrition in different communities [2]. Thyroid nodules are mostly benign [3]. Almost thyroid cancers (TCs) are found as nodules. In the USA, TC accounts for about 1% of all new malignancies, but the annual incidence is reported to be increasing [4].

Risk factors associated with the development of TCs include a history of irradiation, a family history of medullary TC, and age less than 20 or more than 60 years [5]. Also the risk of development of malignancy is increased in solitary more than in multiple nodularity [6,7].

Fine-needle aspiration cytology (FNAC) has been proven to be an accurate method for differentiating benign from malignant thyroid nodules [8,9]. In some series, FNAC results were nondiagnostic in 20–25% of the patients, with false-positive and false-negative results up to 5% [10].

Thyroid-stimulating hormone (TSH) is the main regulator of thyroid cell differentiation and growth; this action of TSH is also retained in malignant cells of differentiated thyroid cancers (DTCs) [11]. There is an increased risk of thyroid malignancy with increased serum TSH concentrations in patients with nodular thyroid diseases (NTDs) [12–15]. Also, the stage of thyroid malignancy may be worse with higher TSH levels [16–18]. It is not clear whether TSH is involved in the pathogenesis of thyroid malignancy, or in the progression of established malignancy, or both [19].

Treatment of DTCs depends on total thyroidectomy (with cervical lymphadenectomy if lymph nodes were affected), radioactive iodine therapy for ablation of active thyroid remnants or metastases, and suppressive treatment with l-thyroxine [20]. A high dose of l-thyroxine to suppress the secretion of TSH (to maintain TSH level lower than 0.1 mIU/l) is associated with a lower recurrence rate and cancer-related death, and higher overall survival [21].

There is increasing evidence that the serum concentration of TSH is an independent predictor for the diagnosis of thyroid malignancy in patients with NTD. Furthermore, preoperative serum TSH concentrations are higher in patients with more aggressive tumors, suggesting a potential role for TSH in the progression of DTC. On the basis of these observations, patients with higher serum TSH concentrations and borderline cytological results of FNAC may require more aggressive investigation and treatment when compared with those with lower baseline TSH levels. The aim of the present study was to evaluate the relationship between elevated TSH and DTC in a sample of Egyptian patients with NTD.

Materials and methods

Population

This was a prospective, interventional study carried out at the Department of Surgery, Al-Azhar University Hospitals, in the period between September 2010 and March 2013. It was carried out on 100 patients (79 women and 21 men), with a mean age of 46.0 ± 12.7 years. They presented with NTD [75 patients had multinodular goiter (MNG) and 25 had a solitary thyroid nodule].

Inclusion criteria

Egyptian patients between 20 and 68 years of age with NTD (MNG or a solitary thyroid nodule) were included in the study.

Exclusion criteria

Patients with recurrent goiter, a history of malignancy in the head and neck, a history of irradiation to the neck, and patients declared unfit for general anesthesia or surgery because of other comorbid factors were excluded from the study.

Study protocol

All patients referred from outpatient clinics were admitted to the surgical department. The study was approved by the local ethics committee of the surgery department. All patients were interviewed using a standardized questionnaire and underwent a physical examination. The questionnaire inquired about the history in terms of onset, course, duration, previous malignancy, irradiation or surgery, and history of toxic, compression, or malignant manifestations.

A complete physical examination (general and local) was performed for all patients. Routine preoperative

investigations including complete laboratory tests, ECG, chest radiograph, preoperative serum calcium concentration (total and ionized), and laryngoscopic examination of the vocal cords were performed for all patients.

Ultrasound examination of the neck confirmed NTD in all patients. FNAC was performed for patients with solitary thyroid nodules (25 patients) and thyroid scanning was also performed in these 25 patients.

The TSH concentration was evaluated preoperatively and grouped into the following three ranges: Less than 0.5 mIU/l, 0.5–5 mIU/l (euthyroidism), and higher than 5 mIU/l according to the method of Haymart *et al.* [17].

Thyroidectomy was planned for all cases. Patients were completely counseled on the procedure, outcome, and possible complications. A written consent was obtained.

The procedure

Patients were admitted a day before surgery. Assessment for general anesthesia was performed. Preoperative preparations such as showering, sedation, and fasting 8 h before surgery were performed. An intravenous antibiotic (third-generation cephalosporin) was administered at the induction of anesthesia as prophylaxis. The operations were carried out under general anesthesia. The patients were placed on the operating table in the supine position with the neck extended and a pillow between the shoulders. Eighty-six patients underwent total thyroidectomy, whereas 14 patients underwent near-total thyroidectomy. During surgery, the procedure followed was meticulous and precise [22]. It was ensured that all the recommended precautions were taken (careful dissection, adequate hemostasis, and recurrent laryngeal nerves were identified routinely on both sides and every attempt was made to identify and preserve the parathyroid glands). Suction drain was inserted routinely in all cases.

Postoperatively, all thyroid specimens were sent for histopathological examination. Effective analgesia was ensured and all patients were subjected to close observations for early complications (e.g. wound hematoma, suffocation). After their discharge from hospital, patients were followed up on a weekly basis for 4 weeks. At follow-up, patients were interviewed using the same standardized questionnaire as before, which included additional items related to surgery complications and results of histopathology.

Results

A total of 100 patients were included in the present study. They were between 20 and 68 years of age with a mean age of 46.7 ± 12.7 years. The most common age group in this study ranged from 35 to 55 years, 66 patients (66%). Of these 100 patients, 21 (21%) were men and 79 (79%) were women, with a male to female ratio of approximately 1 : 4. The median duration of symptoms was 2.2 years. Compression manifestations were present in 74 patients (74%), 63 patients presented with neck swelling (63%), two patients showed change of voice (2%), two patients had referred pain to the ear (2%), and one patient had dysphagia (1%). Neck ultrasound confirmed NTD in all patients (100%), FNAC was performed in 25 patients (25%), and thyroid scanning was performed in 25 patients (25%). Total thyroidectomy was performed in 86 patients (86%), whereas near-total thyroidectomy was performed in 14 patients (14%) (Table 1). The mean hospital stay for both procedures was 2 days.

Histopathological examination was performed for all cases; the final data showed no evidence of malignancy in 83 patients (83%) (benign group), whereas malignant lesions were present in 17 patients (17%) (malignant group).

In the benign group, 67 patients were women (80.7%) and 16 patients were men (19.3%). The mean age was 49.7 ± 12.1 years. Sixty-five patients had MNG (78.3%) and 18 patients had a solitary thyroid nodule (21.7%). The preoperative mean TSH level was 1.72 ± 1.4 mIU/l (Table 2).

The analysis of the results was carried out on the basis of the following:

Preoperative thyroid-stimulating hormone level: The preoperative mean TSH level in the benign group was 1.72 ± 1.4 mIU /l, whereas the mean TSH concentration in the malignant group was 2.61 ± 2.2 mIU/l. Thus, the TSH levels were higher in patients with a final diagnosis of DTC.

Patients with TSH level < 0.5 mIU/L were 13; one of them only was malignant (7.6%), patients with TSH level 0.5–5 mIU/L (euthyroidism) were 82; 14 of them were malignant (17%), while patients with TSH level > 5 mIU/L were 5; two of them were malignant (40%) (Fig. 1).

Findings of histopathological examination: In the malignant group, 12 patients were women (70.5%) and five patients were men (29.5%). The mean age was 45.2 ± 13.2 years. There were 10 patients with

MNG (58.8%) and seven patients with a solitary thyroid nodule (41.2%). Papillary thyroid carcinoma (PTC) was found in 15 patients (88.2%), whereas follicular TC was found in two patients (11.8%). The preoperative mean TSH level was 2.61 ± 2.2 mIU/l (Table 3).

Table 1 Characteristics of the patients

Parameters	Number of patients (%)
Sex	
Females	79 (79)
Males	21 (21)
Mean age	46.7 ± 12.7 years
Median duration of symptoms	2.2 years
Pressure manifestations	74 (74)
Neck swelling	63 (63)
Change of voice	2 (2)
Referred pain to the ear	2 (2)
Dysphagia	1 (1)
Neck ultrasound	100 (100)
FNAC	25 (25)
Thyroid scanning	25 (25)
Total thyroidectomy	86 (86)
Near-total thyroidectomy	14 (14)
Final pathology data	
Benign	83 (83)
Malignant	17 (17)

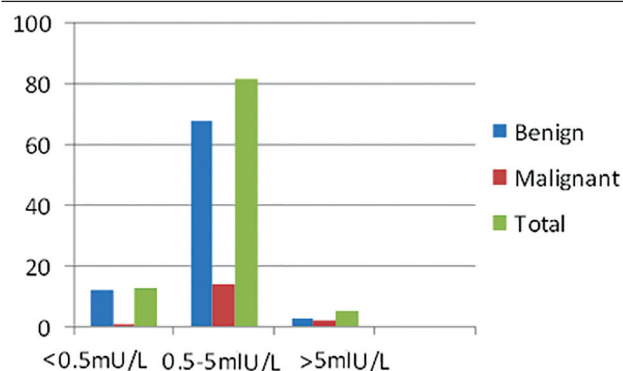
FNAC, fine-needle aspiration cytology.

Table 2 Characteristics of the benign group

Parameters	Number of patients (%)
Sex	
Females	67 (80.7)
Males	16 (19.3)
Mean age	49.7 ± 12.1 years
Patients with MNG	65 (78.3)
Patients with STN	18 (21.7)
Preoperative mean TSH level	1.72 ± 1.4 mIU/l

MNG, multinodular goiter; STN, solitary thyroid nodule; TSH, thyroid-stimulating hormone.

Figure 1



Incidence of benign and malignant goiters according to the level of thyroid-stimulating hormone.

Table 3 Characteristics of the malignant group

Parameters	Number of patients (%)
Sex	
Females	12 (70.5)
Males	5 (29.5)
Mean age	45.2 ± 13.2 years
Patients with MNG	10 (58.8)
Patients with STN	7 (41.2)
Papillary carcinoma	15 (88.2)
Follicular carcinoma	2 (11.8)
Preoperative mean TSH	2.61 ± 2.2 mIU/l

MNG, multinodular goiter; STN, solitary thyroid nodule; TSH, thyroid-stimulating hormone.

Discussion

NTD is a risk factor for epidemiologically ascertained TC. TC was found in mice following a diet lacking in iodine; a reduction in the mortality rate for TC registered in Switzerland following supplementation of iodine in table salt has confirmed this. Studies have shown that patients with NTD have a higher incidence of carcinoma than the general population [23].

In published reports, the incidence of carcinoma in MNG is reported at a percentage that varies from 7 to 17% [24]. Furthermore, it seems that there is no statistically significant difference between the incidence of TC in patients with a solitary nodule as shown in the postoperative histopathologic examination and those with MNG [23]. Thus, multinodularity does not seem to be a certain indicative factor of benign disease [24].

The present study found DTC in 17 patients out of 100 (17%) treated with thyroidectomy for NTD, which is in agreement with similar studies in the literature, with an increase in the incidence of DTC in patients with a solitary thyroid nodule (seven patients out of 25, 28%) than in patients with MNG (10 patients out of 75, 13.33%).

During the last few years, a number of studies have confirmed that the incidence of DTCs has increased worldwide [25,26]. In 2006, Boelaert *et al.* [12], in their study on 1500 patients, found that the incidence of TCs increases with higher TSH levels. These results were also confirmed by Polyzos *et al.* [16] in their study on 565 patients who had palpable thyroid nodules.

Haymart *et al.* [17] in a series of 843 patients subjected to thyroid surgery, reported a frequency of DTC of 16% when TSH was less than 0.06 mIU/l and 52% when TSH was higher than 5.00 mIU/l.

The relationship between serum TSH levels and the risk of PTC was analyzed by Fiore *et al.* [7] in 10 178 patients with a clinical diagnosis of nodular

goiter and with a cytological diagnosis of PTC ($n = 497$) and benign NTD ($n = 9681$). Serum TSH was significantly higher in PTC (median, 1.10 mIU/l) than in patients with benign NTD (median, 0.70 mIU/l), whereas serum concentrations of both free T3 and free T4 were not significantly different. The frequency of PTC was directly related to serum TSH, being the lowest in patients with subnormal TSH values (51 of 2024; 2.5%) and the highest in patients with TSH values between 1.6 and 3.4 mIU/l (152 of 1665; 9.1%).

Gul *et al.* [27], in a series of 441 patients, reported that serum T3 and T4 were lower, whereas serum TSH was higher in the patients with TC compared with patients with benign thyroid lesions. The same result was obtained by Hands *et al.* [28] in a series of 269 patients. Fiore *et al.* [29] suggested that the probability of PTC increases about 11% for each 1 mIU/l increase in TSH above the normal value.

Zafon *et al.* [30] reported that the TSH concentration was significantly higher in patients with DTC (2.08–2.1 mIU/l) than in benign thyroid disease (1.36–1.62 mIU/l). Moreover, he subdivided the malignant group into patients with papillary thyroid microcarcinomas and TC of larger size; he found a direct relationship between increase in tumor size and increase in the TSH level. Fiore *et al.* [7] and Haymart *et al.* [17] found that there was also a relation between a higher TSH concentration and advanced stage of malignancy, not only the risk to develop malignancy.

In the present study, the preoperative TSH level for the malignant patients showed that one patient (out of 13) had a TSH level less than 0.5 mIU/l (7.6%), 14 patients (out of 82) had a TSH level 0.5–5 mIU/l (17%), and two patients (out of five) had a TSH level higher than 5 mIU/l (40%). These figures are comparable with similar studies in the literature.

Gandolfi *et al.* [23] reported that in 13.7% of the patients operated for MNG, during the definitive histopathological examination, a pattern of MNG associated with carcinoma was observed. The histopathological type of carcinoma associated more frequently with MNG was shown to be the papillary (62.5%). Follicular carcinoma was found in 37.5%.

In the present study, 17 out of 100 patients (17%) operated for NTD were found, after histopathological examination, to harbor malignant lesions. PTC was found in 15 patients (88.2%), whereas follicular TC was found in two patients (11.8%).

Conclusion

There is a relation between the serum TSH and development of DTCs in NTD as the risk of thyroid malignancy increases with high serum TSH concentrations and, even within normal ranges (0.5–5 mIU/l), higher TSH values are associated with a higher frequency and more advanced stage of TC.

Acknowledgements

Conflicts of interest

None declared.

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