

A Study of the Relationship between Preoperative Serum Thyrotropin Level and Thyroid Nodules*

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ABSTRACT Objective: To investigate the relationship between preoperative serum thyroid stimulating hormone (TSH) levels and the benign or malignant thyroid nodules. **Methods:** The serum TSH level, thyroid B-Doppler ultrasound reports, surgical records, pathological diagnosis reports of 1499 thyroid nodules selected patients were retrospectively analyzed. According to pathology reports to determine the benign or malignant thyroid nodules, the different distribution between benign and malignant thyroid nodules in preoperative serum TSH levels was analyzed. **Results:** The preoperative serum TSH levels in patients of differentiated thyroid carcinoma (DTC) were significantly higher than those in benign thyroid nodules group (2.179 ± 2.017 vs 1.259 ± 0.884 μ IU / ml), $P < 0.001$; In DTC patients, lymph node metastasis than those without lymph node metastasis, TNM stage III, IV longer than I, II stage, and tumor diameter ≥ 1 cm more < 1 cm in patients with preoperative serum TSH was significantly higher (all $P < 0.001$). **Conclusion:** Preoperative serum TSH levels is an important indicator to whether thyroid nodules benign or malignant.

Key words: Thyroid cancer; Differentiated thyroid carcinoma; Thyroid stimulating hormone

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Introduction

Thyroid nodule is a normal symptom for endocrine diseases. Bibliographical information reports that its morbidity is 5%~10%. Although the rate of canceration is less than 5%^[1], thyroid cancer morbidity is increasing annually^[2]. Based on histological characters, it is distinct for differentiated thyroid cancer (DTC) and Undifferentiated thyroid carcinoma. The former includes papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC). PTC takes about 59.9%~89.0% among thyroid cancer^[3,4]. In prevention research, thyroid cancer relates to heredity, hormones, environment, etc^[5], but the specific pathogen is obscure and it could be a result from a variety of causes. Thyroid stimulating hormone (TSH) is a hormone that adenohypophysis secretes to promote thyroid gland tissue and hyper function. Its connection with thyroid gland has been focused on experts from home and abroad, but the popular research result is also a controversial issue. This study retrospectively analysed the thyroid nodules in patients with preoperative serum TSH levels and relationship between benign and malignant nodules, further discusses the preoperative serum TSH levels and tumor size, lymph node metastasis and TNM staging of tumor relationship, to provide the basis for clinical prevention, diagnosis and treatment of thyroid cancer.

1 Material and Methods

1.1 Objects

1.1.1 Including objects ① Qingdao University Medical College subsidiary hospital department of general surgery, 2003.1-2011.6, the patients for thyroid nodule surgery; ② All patients to be hospital have serum TSH type-B ultrasonic for thyroid gland in the last week before they got surgery and clear diagnosis result for tissue pathology.

1.1.2 Excluding objects ① The patients who took medicine for thyroid gland or thyroid gland hormone in the last three months before surgery; ② having the record of radioactive iodine for cure; ③ pathological reporting to indistinctive thyroid cancer; ④ having the record of irradiation on head and neck or surgery for thyroid gland diseases.

1.1.3 Material content ① basic information for patients (age, sex, family history, etc); ② thyroid gland type-B ultrasonic report (the number of nodule, calcifying or not, border, blood stream, etc); ③ pathological reporting after surgery (size of nodule, pathological diagnosis), pathological reporting comes from Qingdao University medical college subsidiary hospital pathological department. The standard of the size of thyroid nodule in this paper based on the pathological reporting; ④ the record after surgery (having lymph node or not, moving further or not, saturation among the tissue around).

1.1.4 Lab checking Serum TSH, FT3, FT4, TgAb before surgery, coming from Qingdao University medical college subsidiary hospital endocrine department checking by Luo company's Electro-chemiluminescence Immunoassay Determination Kit. Nor-

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mal reference value: TSH (0.274~4.20 μ IU/mL), FT3 (3.10 ~ 6.80pmol/L), FT4 (12.0~22.0pmol/l), TPOAb (0~34IU/mL), TgAb (0~115IU/mL. This research makes TPOAb>34 IU/mL, TgAb>115 IU/mL as positive result.

1.2 Method

1.2.1 Statistic Method Analysis by SPSS17.0 system software, comparison among the average taking the "t" checking logarithmic transformation, comparison of rate taking chi-square to check, ver-

satile factors anglicizing taking logistic regression analysis $P<0.05$ as difference with statistic meaning.

2 Result

2.1 The connection of serum TSH level and the belong of thyroid nodule

The DTC group serum TSH level is obvious higher than that in the group of thyroid benign nodule ($P<0.001$)(Table 1).

Table 1 The comparison preoperative serum TSH levels between DTC and benign nodules in patients

Group	DTC	Thyroid benign nodules	P*
Cases(n)	472	1027	
Sex			
Male	110	217	
Female	362	810	
Male/Female	1/3.3	1/3.7	
The mean age	49.3 $\pm$ 13.6	50.4 $\pm$ 12.8	
TSH(μ IU/ml)	2.2 $\pm$ 2.0	1.3 $\pm$ 0.9	
logTSH	0.3 $\pm$ 0.5	-0.8 $\pm$ 0.5	0.000

Note: *means logarithmic transformed P value.

2.2 The proportional numbers and proportion diversity TSH level group DTC and thyroid benign nodule patients

Based on Luo company's TSH normal value range (0.27 ~ 4.20 μ IU/mL), the patients were divided into 5 groups: (0,0.27]

μ IU/mL,(0.27,1.58] μ IU/L,(1.58,2.88] μ IU/mL,(2.88,4.2] μ IU/mL, >4.20 μ IU/mL, with the increasing of TSH level, the proportion of DTC patients is increasing gradually ($\chi^2=339.065$, $P=0.000$) Table 2.

Table 2 In different groups of TSH levels,the cases and its proportion in DTC and benign thyroid nodules patients

TSH(μ IU/ml)	Cases(n)	DTC (n/%)	Thyroid benign nodules (n/%)	χ^2	P
≤ 0.27	157	19(12.1)	138(87.9)	339.1	0.000
$>0.27\leq 1.58$	719	125(17.4)	594(82.6)		
$>1.58\leq 2.88$	393	154(39.2)	239(60.8)		
$>2.88\leq 4.2$	136	85(62.5)	51(37.5)		
>4.2	94	89(94.7)	5(5.3)		

2.3 The connection of serum TSH level and the size of DTC nodule

The patients were divided into two groups by the size of nod-

ule <1 cm and ≥ 1 cm, the size diameter ≥ 1 cm's DTC patients' serum TSH level before surgery is obviously higher than those <1 cm($P=0.000$) Table 3.

Table 3 The Comparison of preoperative serum TSH level in different tumor diameter of DTC patients

Group	Cases(n)	TSH(μ IU/mL)	logTSH	P*
<1 cm	198	1.8 $\pm$ 1.2	0.1 $\pm$ 0.5	0.000
≥ 1 cm	274	3.4 $\pm$ 2.2	0.4 $\pm$ 0.4	

Note: *means logarithmic transformed P value.

2.4 The connection of serum TSH level and DTC patients with lymph node metastasis

The patients were divided into lymph node metastasis and

lymph node unmoving group, the former preoperation serum TSH level is obviously higher than latter($P=0.000$) Table4.

Table 4 The comparison of preoperative serum TSH levels between DTC patients with lymph node metastasis and without metastasis

Lymph node metastasis	Cases(n)	TSH(μ IU/mL)	logTSH	P*
With	118	4.4 $\pm$ 2.5	0.5 $\pm$ 0.4	0.000
Without	354	2.2 $\pm$ 1.5	0.2 $\pm$ 0.5	

Note: *means logarithmic transformed P value.

2.5 The connection of serum TSH level and DTC patient's TNM terms

Based on malignancy (TNM)term , the DTC patients were divided into I II terms (n=332) and III IV terms (n=140) two groups, III IV terms patients TSH level was obviously higher than that in I II terms(4.132 $\pm$ 2.52vs2.543 $\pm$ 1.875) μ IU/mL, (P<0.001).

Table 5 The comparison of calcium degree in ultrasonography reports between DTC and benign thyroid nodules in patients

Group	Patchy calcification (n/%)	Sand-like calcification (n/%)	No calcification (n/%)	Cases (n)	x ²	P
DTC	116(24.6)	196(41.5)	160(33.9)	472	487.4	0.000
Thyroid benign nodules	96(9.4)	4(0.4)	927(90.3)	1027		

2.7 The connection of thyroid gland antibody (TPOAb and TgAb) and the belonging of thyroid nodules

In 472 cases for DTC patients, there were 398 cases check TPOAb and TgAb. In 1027 cases thyroid benign nodules patients, there were 827 cases check ,1027 TPOAb and TgAb.The rates

2.6 The connection of thyroid nodules calcify types and DTC

Thyroid gland ultrasonichecking seperates the thyroid nodules calcify as patchy calcification, sand-like calcification and uncalcify three types. The DTC patients of sand-like calcification is obvious increasing(P=0.000) Table5.

were 84.32% and 80.53%, and the same. On DTC and benign thyroid nodules in patients with TPOAb or TgAb positive rates were compared, it was found that patients DTC TPOAb or TgAb positive rate was significantly higher in patients with than benign thyroid nodules (P=0.000) Table6.

Table 6 In TPOAb or TgAb-positive and negative groups ,the cases and percentage of patients with DTC and benign thyroid nodules

Group		DTC (n/%)	Thyroid benign nodules (n/%)	x ²	P
TPOAb	Positive	93(55.0)	76(45.0)	44.8	0.000
	Negative	305(28.9)	751(71.1)		
TgAb	Positive	72(65.5)	38(34.5)	61.4	0.000
	Negative	326(29.2)	789(70.8)		

2.8 The DTC and thyroid benign nodules's proportion in thyroid gland antibody feminine patients who have a variety of TSH level

For exclude the thyroid antibody positive's influence to serum TSH level, we renew to separate patients of antibody feminine by a variety serum TSH level. Comparing the proporations of DTC and thyroid benign nodules patiens, the result is the same as including antibody positive. With the increasing of serum TSH level before surgery, DTC patients'proporation is increasing gradually (P<0.001) Fig. 1.

2.9 The connection of age and thyroid nodules

For observation of the connection of age and DTC, patiens were separated into four groups, analysising the four groups' DTC and thyroid benign nodule patiens' proporations and DTC proporational numbers. The 20-30 age group gets the higher proporation of DTC and the tendency of DTC is enhanced for the over 60 group, Table 7.

2.10 Versatile regression analysis

(1)Independent variable: TSH, FT3, FT4, TgAb, TPOAb, calcify or not, age, sex, diameter of nodules.

(2)Dependent variable:the belonging of nodules(DTC=1, be-

nign nodules =0).

Versatile regression analysis's result expresses:sand-like calcification, TSH, TgAb are the unique dangerous factors for the predictor differentiated thyroid cancer Table 8.

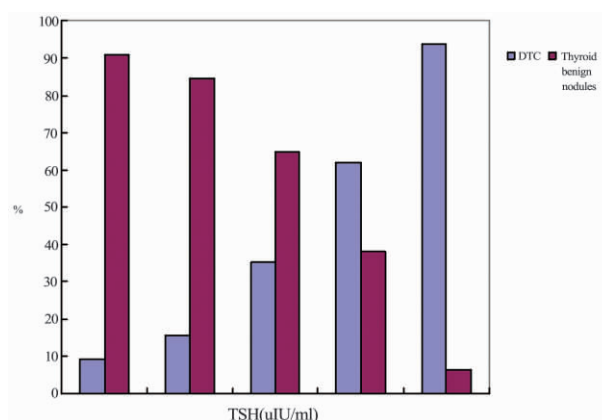


Fig.1 The proportion of DTC and benign thyroid nodules in different group of TSH level of TPOAb and TgAb negative patients(%)

Note:%means in TSH level, the proportion of DTC and benign thyroid nodules

Table 7 The number and percentage of patients in DTC and benign thyroid nodules in different age groups

Group	DTC(n%)	Thyroid benign nodules (n%)	Cases (n)
<20	3(27.3)	8(72.7)	11
20-39	125(36.9)	214(63.1)	339
40-59	228(29.4)	547(70.6)	775
≥ 60	116(31.0)	258(69.0)	374

Table 8 The independent risk factors of affect the DTC, P value, OR value 95% CI value

Factors	P	OR and 95%CI
Sand-like calcification	0.000	5.7(3.6-8.8)
TSH	0.000	1.5 (1.3-1.8)
TgAb	0.000	1.0 (1.0-1.1)

3 Discussion

Thyroid cancer is a usual endocrine system malignancy, DTC takes most about over 90%. The occurrence and development of thyroid cancer are versatile, but its pathogenetic mechanism is obscure. In recent years, the connection between TSH level and thyroid cancer is focused on experts. The abroad research reports, that the DTC morbidity is increasing with the increase of TSH level^[6]. Now the relative research reports in domestic is few, and the conclusion is controversial. Some experts consider high level TSH enhancing the danger of DTC^[7], but there also is also research pointing that there is no connection between thyroid nodules belong and TSH^[8]. Although TSH's function is obscure for the occurrence and development during the thyroid process, a variety of animals experiments expressing, TSH is not only promoting the growth and development^[9], but also could inhibit the malign cells' perishment^[10]. Thyroid gland is commanded exactly by hypothalamus-hypophysis-thyroid gland axis system, in this system, TSH's chronic stimulation could make follicular thyroid upper cell active and development, strength active^[11]. TSH exerts biological effect by corporating with TSH thyroid-stimulating hormone receptor (TSHR). When canceration of thyroid gland happens, part of follicular cells still keep the usual receptor system, tumor cell differentiate the better, TSHR expressing is higher. TSH is the promoting factor for the DTC cells, TSH level is connecting closely with DTC patients after prediction. High TSH level closely enhance thyroid cancer's recurrence rate and death rate. Decreasing the TSH concentration in blood, could prohibit the growth of DTC^[12]. In clinical work, DTC patients are always accepting levothyroxine prohibitive cure and the theory is that it is not only providing the thyroxine's psychological dose, but also prohibits the TSH's function, then stops the growth of DTC patients' cancer cell, decreasing the recurrence and death rate^[13]. The view points above express that serum TSH level takes the essential position in thyroid cancer happening, TSH joins the DTC happening.

This research uses regression analysis to 472 case DTC and 1027 cases thyroid benign nodules patients and finds that DTC patients serum TSH level is obviously higher than thyroid benign nodules patients before surgery, in the normal value(0.27-4.20uIU/mL,

the prevalence rate of DTC is increasing obviously with the increase of concentration of serum TSH. For excluding thyroid gland antibody positive influence to serum TSH level, we renew to separate the patients with antibody positive into a variety of groups, by the serum TSH level, comparing the proportion of DTC and thyroid benign nodules patients, still expressing the DTC's proportion increasing with the TSH level increasing before surgery. The result is the same as unexcluding antibody positive result. Boelaere etc, reported firstly that serum TSH concentration could be independent predicting factor for thyroid cancer before surgery, with the serum TSH level increasing, the prevalence rate of DTC is increasing^[14]. Our research result is the same as that. When serum TSH level exceeds the normal range, the possible system which TSH works in DTC is that the corporation between TSH and its receptor cell could stimulus indirectly thyroid cells secrete growth factor, vascular endothelial growth factor and insulin like growth factor(IGF-1)etc, however, all these factors could function essentially in DTC^[15].

The research expresses that the high level TSH relates to malignant degree and the prognosis^[16]. We analyzed 472 cases DTC patients and found that TNM terms , terms patients serum TSH level is obvious higher than , terms patients; the DTC patients who have the lymph node metastasis serum TSH level are obviously higher than those who have not before surgery. At the same time, DTC patients' serum TSH level relates to the size of nodule more or less. The patients whose nodule diameter ≥ 1cm serum TSH level are obviously higher than those <1cm before surgery, which means serum TSH joins in the morbidity process and promotes it more or less. So we support the prognosis of the view of high level TSH and DTC malignant degree having relation.

And another research expresses that Hashimoto thyroiditis (HT) is the highest morbidity group for thyroid cancer and its morbidity is about 12%~53%^[17,18], especially having positive correlation with differentiated thyroid cancer^[19]. Our research expresses that, in TPOAb or TgAb positive patients, DTC's proportion is increasing obviously. The cause that makes HT patients getting DTC relates to HT patients' gene which exists in thyroid tissue and relates to DTC's ontogeny mutation possibly such as RET/PTC gene, it is a unique mutant gene for causing DTC^[20].

Age relates to thyroid cancer morbidity. In this research, the patients who are thyroid nodule and easy to get DTC during 20~39 and this tendency is increasing 60.

Moreover, versatile relative analysis expressing, pebble calci-fy, TSH, TgAb, are unique dangerous factors for predicting DTC.

In conclusion, serum TSH level before surgery is the unique index for predicting DTC; and TSH level relates to degree of malignant tumor, size, and lymph node metastasis and tumor terms more or less. Decreasing serum TSH level would improve to decrease thyroid morbidity, slow development, and meliorate prognosis.

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术前血清促甲状腺激素水平与甲状腺结节相关性的研究 *

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摘要 目的 探讨术前血清促甲状腺激素(TSH)水平与甲状腺结节良恶性的关系。方法 回顾性分析了 1499 例甲状腺结节手术切除患者术前血清 TSH、甲状腺 B 超、手术记录、术后病理诊断报告。根据术后病理报告判定甲状腺结节良恶性,分析术前血清 TSH 水平在甲状腺良恶性结节中的不同分布。结果:分化型甲状腺癌(DTC)患者术前血清 TSH 水平明显高于甲状腺良性结节组(2.179 ± 2.017 vs $1.259 \pm 0.884 \mu\text{IU/mL}$) $P < 0.001$;在 DTC 患者中,有淋巴结转移较无淋巴结转移、TNM 分期 III、IV 期较 I、II 期以及肿瘤直径 $\geq 1\text{cm}$ 较 $< 1\text{cm}$ 的患者术前血清 TSH 明显升高(均 $P < 0.001$)。结论 术前血清 TSH 水平是预测甲状腺结节良恶性的重要指标。

关键词 甲状腺癌;促甲状腺激素;分化型甲状腺癌

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