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Observational Study**Analysis of the value and safety of thyroid-stimulating hormone in the clinical efficacy of patients with thyroid cancer**

Liang JJ *et al.* Clinical efficacy of TSH in TC patients

Jian-Jing Liang, Wen-Jing Feng, Ru Li, Run-Tao Xu, Yu-Long Liang

Abstract**BACKGROUND**

Thyroid cancer (TC) is a common malignant tumor in the endocrine system. In recent years, the incidence and recurrence rates of TC have been raising due to increasing work pressure and irregular lifestyles. Thyroid-stimulating hormone (TSH) is a specific parameter for thyroid function screening. This study aims to explore the clinical value of TSH in regulating the progression of TC, so as to find a breakthrough for the early diagnosis and treatment of TC.

AIM

To explore the value and safety of TSH in the clinical efficacy of patients with TC.

METHODS

75 patients with TC admitted to the Department of Thyroid and Breast Surgery of our hospital from September 2019 to September 2021 were selected as the observation group, and 50 healthy subjects were selected as the control group during the same period. The control group was treated with conventional thyroid replacement therapy,

and the observation group was treated with TSH suppression therapy. The sIL-2R, IL-17, IL-35 Levels, FT₃, FT₄, CD3⁺, CD4⁺, CD8⁺, CD44V6, and TSGF levels were observed in the two groups. The occurrence of adverse reactions was compared between the two groups.

RESULTS

After treatment with different therapies, the levels of FT₃, FT₄, CD3⁺, and CD4⁺ in the observation group and the control group were higher than those before treatment, while the levels of CD8⁺, CD44V6, and TSGF were lower than those before treatment, and the differences were statistically significant ($P < 0.05$). More importantly, the levels of sIL-2R and IL-17 in the observation group were lower than those in the control group after 4 wk of treatment, while the levels of IL-35 were higher than those in the control group, and the differences were statistically significant ($P < 0.05$). The levels of FT₃, FT₄, CD3⁺, and CD4⁺ in the observation group were higher than those in the control group, and the levels of CD8⁺, CD44V6, and TSGF were lower than those in the control group. There was no significant difference in the overall incidence rate of adverse reactions between the two groups ($P > 0.05$).

CONCLUSION

TSH suppression therapy can improve the immune function of patients with TC, lower the CD44V6 and TSGF levels, and improve serum FT₃ and FT₄ levels. It demonstrated excellent clinical efficacy and a good safety profile.

Key Words: Thyroid-stimulating hormone; Thyroid cancer; Clinical efficacy; Safety profile

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Core Tip: Thyroid carcinoma (TC) is the most common cancer in the endocrine system. It has been established that thyroid-stimulating hormone (TSH) stimulates the growth and development of thyroid malignancy, and a higher serum TSH level is associated with the incidence of thyroid cancer and an advanced tumor stage. This study aims to explore the clinical value of TSH in regulating the progress of TC, which can provide a new direction for thyroid therapy.

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INTRODUCTION

Thyroid cancer (TC) is the most common malignant tumor in the human endocrine system, accounting for 1%-5% of systemic malignant tumors^[1]. In recent years, the incidence of the disease has gradually increased due to people's increasing work pressure and irregular lifestyles^[2]. Therefore, it is of great importance to explore the methods for early diagnosis and treatment of TC. At present, the clinical treatment options for patients with TC mainly include initial thyroidectomy, radioiodine therapy, and long-term suppression of thyroid-stimulating hormone (TSH)^[3-5]. TSH is a glycoprotein hormone synthesized and secreted by thyroid cells in the anterior pituitary gland and plays a regulatory role by acting on the thyrotropin receptor (TSHR) on the cell surface. As a specific parameter for the primary screening of thyroid function, TSH has an important effect on the early detection of hypothalamic-pituitary-thyroid central regulation disorders and the identification of hypothyroidism^[6]. Studies have found that TSH levels were significantly increased in TC patients, and their invasiveness was associated with baseline serum TSH levels. The higher the TSH level, the greater the risk of TC. On the contrary, suppression of TSH decreased the expression of the TSHR gene in the thyroid tissue of patients, thereby slowing down tumor growth^[7,8]. At the same time, TSH suppression therapy has received increasing attention from clinical research scholars due to its effectiveness in reducing recurrence and mortality rates in patients with differentiated TC^[9].

Previous studies have shown that serum-free triiodothyronine (FT₃) and free thyroxine (FT₄) are effective indicators of thyroid function. Serum triiodothyronine (T₃) is a hormone produced by the thyroid gland to maintain thyroid function, which is involved in the metabolism of the three major nutrients in the body. Thyroxine (T₄) is a hormone produced by thyroid follicular cells to promote cell metabolism and can stimulate tissue growth, differentiation, and maturation. Normally, the bound T₃ and T₄ have no physiological activity, while the free T₃ and T₄ can penetrate the blood-brain barrier and combine with target cells to play a role. Therefore, the levels of FT₃ and FT₄ can more accurately reflect thyroid function^[10,11]. T-lymphocytes are important indicators to measure the immune function of the body, mainly including CD3⁺, CD4⁺, CD8⁺, *etc*^[12,13]. The significance of TSH suppression therapy for TC has been elucidated by a number of studies. This study will further investigate the effects of TSH suppression therapy on FT₃ and FT₄ levels, peripheral T-lymphocyte subsets (CD3⁺, CD4⁺, CD8⁺), and the levels of regulators that can modulate the immune function of TC patients, such as sIL-2R, IL-17, IL-35, *etc.*, thereby exploring the specific efficacy of TSH suppression therapy. Based on this, this study investigated the effects and safety of TSH on the clinical treatment of TC patients by analyzing the clinical data of TC patients, hoping to provide more references for the early diagnosis and treatment of TC patients.

MATERIALS AND METHODS

General information

75 patients with TC admitted to the Department of Thyroid and Breast Surgery of our hospital from September 2019 to September 2021 were selected as the observation group, and 50 healthy subjects were selected as the control group during the same period. The clinical data were retrospectively analyzed. The study group consisted of patients aged 27-59 years, with an average age of (51.34 ± 7.56) years, of which 38 were males and 37 were females. The control group was aged 28-60 years, with an average age of (53.25 ± 4.67) years, of which 22 were males and 28 were females. All patients had voluntarily signed an informed consent form. There was no significant difference

between the two groups in terms of general information such as age and gender ($P > 0.05$), which was comparable, as shown in Table 1.

Inclusion and exclusion criteria

Inclusion criteria: (1) patients who were diagnosed by surgical pathology; (2) patients with no cervical lymph nodes or other metastases were observed; (3) patients who were compliant with treatment; (4) patients who signed informed consent and underwent thyroidectomy.

Exclusion criteria: (1) patients who were taking drugs observed by imaging tests such as diabetic corticosteroids or estrogen after surgery; (2) patients who had to discontinue the drug use due to hyperthyroidism; (3) patients with abnormal liver and kidney function; (4) patients with chronic diseases such as hypertension or diabetes that were not easily controlled; (5) patients with surgically injured parathyroid glands; (6) patients with a history of neck surgery or radiotherapy; (7) unconscious or psychotropic drug users^[14,15].

Methods

All patients underwent subtotal or total thyroidectomy and used iodine to remove residual thyroid tissue. The control group was given levothyroxine sodium tablets (approval number: registration certificate number H20100014, manufacturer: Laboratoire Aventis) (50 µg/time, 1 time/d in the first two weeks; 100 µg/time, 1 time/d in the latter two weeks) for conventional thyroid replacement therapy. The observation group was given levothyroxine sodium tablets (200 µg/time, 1 time/d) and treated with TSH suppression therapy. Both groups were administered continuously for 4 wk. The criteria for drug use were^[16]: plasma TSH concentration ≤ 0.1 -0.3 mU/L for patients in clinical stage I; ≤ 0.05 -0.5 mU/L for patients in stage III; and ≤ 0.05 mU/L for patients in stage IV. The thyroid function of patients was monitored regularly during drug administration.

Observation index

Comparison of sIL-2R, IL-17, IL-35 levels: 4 wk before and after surgery, fasting venous blood was collected from the patients in the morning and centrifuged for 10 min at a rate of 3000 *r/min*. After serum separation, soluble interleukin (IL)-2 receptor (sIL-2R), IL-17, and IL-35 levels in the serum were measured by enzyme-linked immunosorbent assay using an FC automatic micro-plate reader produced by Thermo Fisher Scientific Inc. The kits were purchased from Thermo Fisher Scientific Inc., and the operating steps were performed in strict accordance with the relevant kit instructions.

FT₃, FT₄, CD3⁺, CD4⁺, CD8⁺ levels: 4 wk before and after surgery, fasting venous blood was collected from the patients in the morning and centrifuged for 20 min at a rate of 3000 *r/min*. The upper serum was collected and stored in a -20 °C environment. FT₃ and FT₄ levels were measured using an automatic biochemical analyzer (AU5800, Ailaibao Medical Technology Co., Ltd., approval number: Chuanxieguangshen No. 220601-00020), and CD3⁺, CD4⁺, CD8⁺ levels in peripheral blood were measured using a flow cytometer [CytoFLEX, Beckman Coulter International Trading Co., Ltd., approval number: SFDA (I) 2400332839 (2008)].

CD44V6, TSGF levels: 4 wk before and after surgery, fasting venous blood was collected from the patients in the morning and centrifuged for 10 min at a rate of 3000 *r/min*. The upper serum was collected and stored in a -20 °C environment. The levels of CD44V6 and TSGF were measured by double-antibody sandwich enzyme-linked immunosorbent assay. The kits were purchased from Shanghai Jianglai Technology Co., Ltd. The operation steps strictly followed the relevant kit instructions.

Adverse reactions: Patients with rash, osteoporosis, and postoperative recurrence were recorded.

Statistical analysis

SPSS 21.0 software was used to process and analyze the data of this study. The measurement data were demonstrated as ($\pm s$). The *t*-test was adopted for comparison between groups. The enumeration data were demonstrated as (*n*, %). The χ^2 test was adopted for comparison. The differences were statistically significant at $P < 0.05$.

RESULTS

Comparison of sIL-2R, IL-17 and IL-35 levels in patients in each group

SIL-2R and IL-17 have strong biological effects and can trigger inflammatory responses by inducing T-cell activation and stimulating endothelial cells, epithelial cells, and neutrophils to release large amounts of inflammatory cytokines, and their increased levels will further aggravate the condition of TC patients^[17,18]. In addition, IL-35 has a strong immunosuppressive effect and plays an important role in regulating inflammatory and immune disease conditions^[19]. Therefore, we compared the levels and performance of sIL-2R, IL-17, and IL-35 in the observation group and the control group, and found that there was no significant difference in the levels of sIL-2R, IL-17, and IL-35 between the two groups before treatment ($P > 0.05$). After 4 wk of treatment, the levels of sIL-2R and IL-17 in the observation group and the control group were lower than those before treatment, and the levels of IL-35 were higher than those before treatment. The levels of sIL-2R (359.56 ± 21.98 U/mL) and IL-17 (6.79 ± 2.78 pg/mL) in the observation group were significantly lower than those in the control group (10.27 ± 2.32 pg/mL), and levels of IL-35 (94.98 ± 6.78 pg/mL) were significantly higher than those in the control group (68.78 ± 6.34 pg/mL) after thyroid hormone suppression therapy. The differences were statistically significant ($P < 0.05$), which indicated that thyroid hormone suppression therapy significantly improved the immune function of patients with TC (Table 2).

Comparison of FT₃ and FT₄ levels between the two groups

4 There was no significant difference in FT₃ and FT₄ levels between the two groups before treatment ($P > 0.05$). After treatment, the levels of FT₃ and FT₄ in the observation group and the control group were higher than those before treatment. More importantly, after treatment, the FT₃ level was (3.12 ± 1.65 ng/L) and the FT₄ level was (1.56 ± 1.48 ng/L) in the observation group, which were significantly higher than those in the control group [FT₃ level was (2.23 ± 1.62 ng/L) and FT₄ level was (0.89 ± 0.82 ng/L)], and the differences were statistically significant ($P < 0.05$). This indicated that TSH suppression therapy could better reflect the thyroid function of TC patients and provide a reference for further treatment (Table 3).

2 Comparison of CD3⁺, CD4⁺, and CD8⁺ between the two groups

2 There was no significant difference in CD3⁺, CD4⁺, and CD8⁺ levels before treatment between the two groups ($P > 0.05$). After treatment, the levels of CD3⁺ and CD4⁺ in the observation group and the control group were higher than those before treatment, and the level of CD8⁺ was lower than that before treatment. The difference was statistically significant ($P < 0.05$). More importantly, after treatment, CD3⁺ (64.98 ± 6.56) and CD4⁺ (49.78 ± 5.65) levels in the observation group were higher than those in the control group [CD3⁺ (61.21 ± 6.32) and CD4⁺ (46.87 ± 6.76)], CD8⁺ level (29.87 ± 9.87) was lower than the CD8⁺ (35.65 ± 9.67) in the control group as well. The differences were statistically significant ($P < 0.05$), which indicated that the use of TSH suppression therapy had a significant effect on regulating the normal flora of T-lymphocytes (Table 4).

3 Comparison of CD44V6 and TSGF levels in each group

3 There was no significant difference in CD44V6 and TSGF levels between the two groups before treatment ($P > 0.05$). After treatment, the levels of CD44V6 and TSGF in both groups were lower than those before treatment, and the differences were statistically significant ($P < 0.05$). More importantly, after treatment, the levels of CD44V6 (314.23 ± 20.12) ng/mL and TSGF (42.38 ± 5.21) ng/mL in the observation group were

significantly lower than those in the control group [CD44V6 (367.56 ± 24.67) ng/mL and TSGF (56.87 ± 5.76) ng/mL], and the differences were statistically significant ($P < 0.05$). The above results showed that TSH suppression therapy could reduce the tumor recurrence and metastasis rates of TC cells after surgery, which was conducive to improving the prognosis (Table 5).

Comparison of adverse reactions in each group

The overall incidence of adverse reactions in the two groups was observed, and the occurrence of osteoporosis, rash, and other subclinical symptoms were compared. There was no significant difference found in the overall incidence of adverse reactions between the two groups ($P > 0.05$), which indicated that TSH suppression therapy has no significant adverse reactions and is associated with high safety (Table 6).

DISCUSSION

TC is an endocrine malignant tumor derived from thyroid epithelial cells^[20-22]. Although the treatment of TC has been continuously advanced with the improvement of the diagnosis of TC, it is still a challenge to manage TC because it is sometimes difficult to differentiate between thyroid adenoma and nodular goiter in clinical practice. Moreover, although most patients with differentiated TC have a good prognosis, some advanced thyroid malignancies may also lead to systemic spread and death due to their high aggressiveness and metastasis, such as anaplastic TC and some phenotypes that progress to poor or undifferentiated. The treatment of TC is still difficult^[23,24]. Therefore, it is urgent to study timely therapies for the early identification and treatment of TC.

Studies have demonstrated that the development of TC is closely related to estrogen levels in the human body^[25,26]. It has been reported that TSH is one of the main regulatory hormones that regulate thyroid function. TSH is feedback inhibited by T₃ and T₄ while promoting thyroid follicular epithelial cell proliferation and thyroid hormone synthesis. Excessive secretion of TSH promotes epidermal growth factor-

mediated cell proliferation and reduces the production of $\beta 1$ transforming factor, thereby increasing the risk of TC^[27]. In addition, more and more studies have suggested that TSH is an independent risk factor for predicting TC in patients with nodular goiter. High levels of TSH are closely related to the high incidence of TC as well as advanced thyroid^[28]. Based on this, this study aims to find a breakthrough in inhibiting the malignant progression of TC from the interventional treatment of TSH, and to investigate the effect of TSH suppression therapy in the clinical treatment of TC and related adverse reactions, hoping to provide some help for the prevention and treatment of TC patients.

In this study, sIL-2R, IL-17, IL-35 Levels, FT₃, FT₄, CD3⁺, CD4⁺, CD8⁺, CD44V6, TSGF levels, and adverse drug reactions were compared between 75 TC patients and 50 healthy subjects. The differences in sIL-2R, FT₃, FT₄, CD3⁺, CD4⁺, and CD8⁺ levels between two different groups after TSH suppression therapy intervention were compared. The results showed that, after the intervention of TSH suppression therapy, the sIL-2R and IL-17 Levels were lower than those in the control group, and the IL-35, FT₃, and FT₄ levels were higher than those in the control group. All of these indicated that TSH suppression therapy was important for maintaining normal hormone levels and meeting normal physiological needs after surgery. This therapy could reduce the pituitary gland response to thyrotropin-releasing hormone in the blood, resulting in thyroxine feedback inhibition of TSH secretion from the pituitary gland, reducing TSH levels in the serum of patients with TC, and thus inhibiting tumor growth and recurrence of TC. In addition, the levels of CD3⁺ and CD4⁺ in the observation group were higher than those in the control group, and the levels of CD8⁺ were lower than those in the control group, which indicated that the levels of T-lymphocytes in patients after TC surgery could be regulated and improved by TSH suppression therapy. CD44 is a transmembrane glycoprotein that increases cell adhesion and prevents tumor cell invasion and metastasis. CD44V6 is a variant of CD44, which acts quite opposite to CD44. CD44V6 can reduce tumor cell adhesion, resulting in enhanced motility of tumor cells, which in turn increases tumor recurrence and metastasis rates^[29,30]. The results of

this study demonstrated that TSH suppression therapy could reduce the level of CD44V6 in serum, thus reducing the tumor recurrence and metastasis rates of TC cells after surgery, which was conducive to improving the prognosis. TSGF, also known as a malignant tumor-specific growth factor, is a novel tumor marker whose performance is closely associated with malignant tumor angiogenesis^[31,32]. In this study, we also found that TSGF levels were significantly lower in TC patients after TSH suppression therapy, which further proved the therapeutic effect of TSH suppression therapy. The above results indicated that TSH suppression therapy has the potential to delay the malignant biological behavior of TC. TSH suppression therapy can inhibit the malignant progression of TC by suppressing TSH levels through a cascade of negative feedback responses in thyroid hormone secretion^[33]. Bae *et al*^[34] performed thyroid function tests regularly in 369 patients who underwent thyroid lobectomy and ipsilateral central neck dissection for papillary TC and found that postoperative supplementation with TSH inhibitors significantly inhibited the recurrence rate of TC. The reports of Liu *et al*^[35] also showed that adjuvant treatment with recombinant human TSH was effective in reducing the possibility of postoperative hypothyroidism in patients with differentiated TC. However, hypothyroidism caused by hormone withdrawal can negatively affect the life quality of TC patients^[36]. Meanwhile, Liu *et al*^[37] performed endocrine therapy to inhibit TSH in 150 papillary TC patients and 21 patients with normal thyroid tissues, finding that TSH inhibition significantly promoted apoptosis and inhibited metastasis of TC cells. What's more, serum TSH levels can be used as a predictor of differentiated TC staging. To improve the outcome of thyroidectomy in patients with TC, long-term postoperative TSH suppression therapy can be used to reduce the risk of recurrence of differentiated TC and control disease progression^[38,39]. More importantly, the 2015 American Thyroid Association guidelines also recommend TSH suppression therapy for patients with low-risk well-differentiated TC, which is effective in slowing disease progression and reducing postoperative recurrence^[40]. Fortunately, our results were also consistent in this study. Our study found that TSH suppression therapy could

significantly improve the immune function of patients, but also increase the levels of FT₃ and FT₄ in patients, which is of high clinical value.

In addition, in order to further analyze the safety of TSH suppression therapy in the clinical treatment of patients with TC, we compared the incidence of rash, osteoporosis, menstrual disorders, and other adverse reactions in patients before and after TSH suppression therapy intervention. There was no significant difference when compared with the control group and the overall incidence of adverse reactions was also not statistically significant when compared with the control group ($P > 0.05$). This suggests that TSH suppression therapy has a good safety value in the clinical treatment of TC. Of course, according to the specific clinical efficacy of the two groups at present, more research, evaluation, and monitoring are needed in the future to reduce the impact of TSH suppression therapy on the subclinical symptoms of patients in order to improve the clinical management and the life quality of patients.

CONCLUSION

In summary, TSH suppression therapy has a positive effect on the immune function of patients with TC. It can increase the levels of FT₃ and FT₄, and reduce tumor recurrence and metastasis rates. Meanwhile, it is of good safety profile and high clinical value, which provides great significance for early clinical treatment. However, this study also has some shortcomings, such as the small number of study comparison parameters and clinical studies. Subsequently, we will consider increasing the number of participants for multi-dimensional and multi-index comparisons and conduct an in-depth discussion on this.

ARTICLE HIGHLIGHTS

Research background

The incidence of thyroid cancer has increased worldwide over the past four decades, and thyroid cancer is the most common endocrine cancer. The discovery of new biomarkers for thyroid cancer has significantly improved the understanding of the

molecular pathogenesis of thyroid cancer, thus allowing more personalized treatments for patients with thyroid cancer.

Research motivation

Thyroid-stimulating hormone is the major regulator and growth factor of the thyroid. However, the role of thyroid-stimulating hormones in thyroid cancer still needs further exploration.

Research objectives

The aim of this study is to examine the relationship between thyroid-stimulating hormone and thyroid cancer.

Research methods

75 patients with thyroid cancer were collected as the observation group and 50 healthy people as the control group. The control group was treated with thyroid replacement and the observation group was treated with thyroid-stimulating hormone inhibition. The levels of sIL-2R, IL-17, IL-35, FT3, FT4, CD3+, CD4+, CD8+, CD44V6, and TSGF were observed in the two groups.

Research results

After 4 wk of treatment, the levels of sIL-2R and IL-17 in the observation group were lower than those in the control group, while the levels of IL-35 were higher than those in the control group, with a statistically significant difference ($P < 0.05$). The levels of FT3, FT4, CD3+ and CD4+ in the observation group were higher than those in the control group, and the levels of CD8+, CD44V6, and TSGF in the observation group were lower than those in the control group.

Research conclusions

Thyroid-stimulating hormone inhibition therapy, as the best treatment method for thyroid cancer, can slow down the condition of patients and is worthy of clinical promotion.

Research perspectives

Thyroid-stimulating hormone is considered a risk factor for thyroid cancer, and thyroid hormone suppression therapy can reduce and control the progression of thyroid cancer. However, ⁸ the effect of serum thyroid stimulating hormone may depend on the histological type of thyroid cancer. Therefore, in future research, we should focus on exploring the relationship between thyroid-stimulating hormones and different histological types of thyroid cancer.

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