

## **Effects of thyroxine tablet combined with iodine supplementation and dietary therapy on serum Midkine and VEGF in patients with benign thyroid nodules.**

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### **Abstract**

**Objective:** To investigate the efficacy of thyroxine tablets combined with iodine supplementation and dietary therapy in the treatment of benign thyroid nodules and its effect on serum Midkine as well as Vascular Endothelial Growth Factor (VEGF).

**Method:** A total of 116 patients with benign thyroid nodules treated in our hospital were randomly divided into treatment group and control group with 58 cases in each group in which the control group were given thyroxine tablet treatment with non-iodized salt in daily diet while the treatment group were additionally given edible iodized salt and dietary intervention besides thyroxine treatment, the thyroid hormone level as well as serum Midkine and VEGF levels before and after the treatment and the incidence of adverse reactions were compared between the two groups.

**Results:** Before treatment, there was no statistically significant difference between the two groups in the levels of FT3, FT4 and TSH ( $P>0.05$ ); while after treatment, levels of FT3, FT4 and TSH were improved in both groups compared with before with the improvement in the treatment group more significant than in the control group ( $P<0.05$ ). Before treatment, there was no significant difference in serum Midkine and VEGF levels between the two groups ( $P>0.05$ ) while after treatment, the levels of Midkine and VEGF in the treatment group were significantly lower than those in the control group ( $P<0.05$ ). The total effective rate of the treatment group was 94.83%, higher than that of the control group, that was 84.48%, and the difference between the two groups was statistically significant ( $P<0.05$ ). There was no difference in the incidence of adverse reactions between the two groups ( $P>0.05$ ).

**Conclusion:** Compared with simple application of thyroxine tablet, thyroxine tablet combined with iodine supplement and dietary therapy is more effective in the treatment of benign thyroid nodules, which can effectively improve the level of thyroid hormone and reduce serum Midkine and VEGF levels with less adverse reactions, thus worthy of clinical promotion.

**Keywords:** Thyroid benign nodule, Thyroxine tablet, Iodine, Dietary therapy, Midkine, Vascular endothelial growth factor (VEGF).

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### **Introduction**

Thyroid nodules result from many factors including endemic goiter of iodine deficiency, hyperthyroidism, single thyroid nodules, multinodular goiter, and thyroiditis as well as thyroid cancer and are roughly divided as benign thyroid nodules as well as thyroid cancer in which thyroid nodules are mostly benign and approximately 5-15% of nodules are malignant [1]. In recent years, the incidence of thyroid nodules has showed an increasingly rising trend with no obvious clinical symptoms in the majority of patients with thyroid nodules and it is only when the further growth of the lesion compresses surrounding tissues that the patients suffer from such symptoms like dyspnoea and dysphagia [2]. Although deep researches have been carried out into this disease in modern medicine, there

remains a lack of effective and safe treatment plant. At present, suppressive therapy of levothyroxine is mainly used for benign multiple thyroid nodule inhibition in western medicine, but the long-term suppression treatment often has adverse effects on cardiovascular and skeletal system [3]. Surgical treatment is costly and gives rise to great trauma with some adverse reactions as well as certain recurrence rate, thus affecting the beauty of neck and difficult to be accepted by the patients [4]. In addition, thyroid benign nodules can be treated with other methods such as regular follow-up, iodine supplement therapy, thyroid hormone suppression therapy, radioiodine therapy and percutaneous ethanol injection [5,6]. But different treatments have varying effects and combination therapy is currently the main trend in the treatment of thyroid nodules. In recent years,

we have applied thyroxine tablet combined with iodine supplement and dietary therapy to thyroid nodules treatment in our hospital and achieved certain efficacy. The existing data have shown that [7,8] medium-term growth factor (Midkine) and Vascular Endothelial Growth Factor (VEGF) help to differentiate benign and malignant thyroid nodules but there is less research report on their combination application to evaluating treatment effect of thyroid nodule. The purpose of this study is to investigate the efficacy of thyroxine tablet combined with iodine supplement and dietary therapy in treatment of thyroid nodules as well as its effects on serum CK-19 and HBME-1 levels.

## Data and Methods

### General information

A total of 116 patients with benign thyroid nodules treated in our hospital were selected as the objects.

**Inclusion criteria:** The patients had no compression symptoms with normal or subnormal thyroid function.

**Exclusion criteria:** Patients with graves hyperthyroidism and thyroid nodules and not suitable for iodine treatment; patients with other diseases of important organs like heart and brain.

In selected 116 patients there 40 males and 76 females aged 23-69 with an average age of  $54.2 \pm 1.5$  y. The duration of 1 month 2 y,  $1.1 \pm 0.3$  years on the average; including 70 cases of nodular goiter who were diagnosed with goiter and multiple nodules by physical examination with such ultrasonography findings as thyroid nodules of varied size, smooth surface, clear boundary and no calcifications; 12 cases of thyroid adenoma (partial or complete nodular goiter, with the failure of pathological differentiation) who were diagnosed with solitary thyroid nodules by physical examination with such ultrasonography findings as thyroid nodules of smooth surface, clear boundary and no micro calcification and 34 cases of chronic lymphocytic thyroiditis who were diagnosed with nodular thyroid enlargement by physical examination with such ultrasonography findings as thyroid gland with diffuse lesion and significantly increased thyroglobulin antibody and microsomal antibody, Aspiration Cytologic Examination (ACE) showed follicular epithelial cells and lymphocytes with no atypical cells.

The involved 116 patients were randomly divided into treatment group and control group, 58 cases in each group. There were no statistically significant differences between the two groups in gender, age, course of disease and clinical manifestations in patients ( $P > 0.05$ ), suggestive of comparability.

### Treatment methods

The control group were given thyroxine tablet with the daily dose of 40-80 mg selected according to thyroid function, 1-2

times and with the diet of non-iodized salt in daily life (purchased from official sellers designated by Salt Company).

The treatment group, besides the treatment in the control group, were additionally given edible iodized salt (supplied by the market) and dietary intervention, which required eating light vegetables and fruit with high vitamin and nutritious meat, chicken, egg as well as fish with the avoidance of spicy food and stimulus like tobacco and alcohol.

The two groups were treated continuously for 3 months during which thyroid function was re-examined 1-2 times with the dose of thyroid hormone adjusted accordingly.

### Observation index

(1) Clinical curative effect was compared between the two groups. Standard of curative effect was classified as follow: Excellent effect: the symptoms were improved, thyroid volume reduced more than 1/2 or nodules were significantly narrowed. Effectiveness: the symptoms were alleviated, thyroid volume reduced less than 1/2 or nodules were partly narrowed. Ineffectiveness: there was no change in thyroid volume and nodule.

(2) The serum thyroid hormone levels, Free T3 (FT3), Free T4 (FT4) and Thyroid Stimulating Hormone (TSH) levels were compared between the two groups before and after treatment.

(3) The changes of serum medium growth factor (Midkine) and Vascular Endothelial Growth Factor (VEGF) levels were compared between the two groups before and after treatment. The serum levels of Midkine and VEGF were detected by using Antibody-Sandwich ELISA Method in two groups before and after treatment.

(4) The incidence of adverse reactions were observed and recorded in the two groups.

### Statistical processing

SPSS 21 statistical software was adopted for the analysis on data in which the measurement data were expressed by ( $\bar{x} \pm s$ ) and assessed by t-test. The enumeration data were expressed by (n (%)) and assessed by  $\chi^2$  test.

$P < 0.05$  suggested there was statistically significant difference in between.

## Results

### Comparison of thyroid hormone levels between the two groups

Before treatment, there was no statistically significant difference between the two groups in the levels of FT3, FT4 and TSH ( $P > 0.05$ ).

While after treatment, levels of FT3, FT4 and TSH were improved in both groups compared with before with the

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improvement in the treatment group more significant than in the control group ( $P < 0.05$ ) as shown in Table 1.

**Table 1.** Comparison of thyroid hormone levels between the two groups.

Group	n	FT3 (pmol/L)		FT4 (pmol/L)		TSH (mU/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	58	12.43 ± 1.46	7.68 ± 0.57	20.12 ± 1.35	14.6 ± 1.01	1.2 ± 0.13	2.48 ± 0.34
Treatment group	58	12.51 ± 1.65	5.92 ± 0.41	20.07 ± 1.28	10.2 ± 1.04	1.2 ± 0.12	2.81 ± 0.46
t		0.261	6.792	0.178	6.094	0.195	7.005
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

**Table 2.** Comparison of serum Midkine and VEGF levels between the two groups.

Group	n	Midkine (ng/ml)		VEGF (pg/ml)	
		Before treatment	After treatment	Before treatment	After treatment
Control group	58	7.43 ± 1.03	4.53 ± 0.93	43.98 ± 3.73	26.95 ± 2.05
Treatment group	58	7.45 ± 1.06	3.04 ± 0.57	44.12 ± 3.06	38.04 ± 1.76
t		0.149	7.038	0.135	6.793
P		>0.05	<0.05	>0.05	<0.05

**Table 3.** Comparison of clinical efficacy between the two groups.

Group	n	Excellent effect	Effectiveness	Ineffectiveness	Total effective rate (%)
Control group	58	14 (24.14)	35 (60.34)	9 (15.51)	84.48
Treatment group	58	35 (60.34)	20 (34.48)	3 (5.17)	94.83
$\chi^2$					8.936
P					<0.05

### Comparison of serum Midkine and VEGF levels between the two groups

Before treatment, there was no significant difference in serum Midkine and VEGF levels between the two groups ( $P > 0.05$ ) while after treatment, the levels of Midkine and VEGF in the treatment group were significantly lower than those in the control group ( $P < 0.05$ ), as shown in Table 2.

### Comparison of clinical efficacy between the two groups

The total effective rate of the treatment group was 94.83%, higher than that of the control group, that was 84.48% and the difference between the two groups was statistically significant ( $P < 0.05$ ), as shown in Table 3.

### Comparison of adverse reactions between the two groups

There was 1 case of rash and pruritus in the treatment group and the incidence rate of adverse reactions was 1.72% and in the control group there was 1 case of facial flushing and 1 case

of nausea and vomiting and the incidence of adverse reactions was 3.44%. The symptoms were alleviated after the reduction of drug dose and all patients completed the treatment without serious adverse effects. There was no significant difference in the incidence of adverse reactions between the two groups ( $P > 0.05$ ).

### Discussion

Thyroid nodules would frequently be benign and are often seen in nodular goiter, chronic lymphocytic thyroiditis and adenoma. There are many causes for benign thyroid nodules, including iodine deficiency or high iodine diet, environmental factors, smoking as well as goitrogen risk factors and it is associated with thyroid hormone level as well as cytokines level [9,10]. Thyroid hormone plays an important biological role in body growth, metabolism and action of target organs and its deficiency will cause great damages to normal physiological function in patients, requiring taking active treatment as a result. In clinical practices it is mainly treated by taking thyroid tablet in which with long cycle of using medicine and slow relief of symptoms, an overdose would lead

to abnormal skeleton metabolism or hyperthyroidism, thus causing poor compliance in patients with unfavorable effect [11,12]. Therefore, how to improve the thyroid function of patients with thyroid nodules is of important clinical significance. It has been reported that medication of anti-thyroid drugs with iodized salt is effective in controlling thyroid function in patients. The results of this study showed: Before treatment, there was no statistically significant difference between the two groups in the levels of FT3, FT4 and TSH ( $P>0.05$ ); while after treatment, levels of FT3, FT4 and TSH were improved in both groups compared with before with the improvement in the treatment group more significant than in the control group ( $P<0.05$ ); the total effective rate of the treatment group was 94.83%, higher than that of the control group, that was 84.48% and the difference between the two groups was statistically significant ( $P<0.05$ ) and there was no difference in the incidence of adverse reactions between the two groups ( $P>0.05$ ), all of which suggests that thyroxine tablets combined with iodine supplement and diet intervention has higher curative effects in treatment of thyroid benign nodules, compared with simple thyroxine tablet medication, which manages to improve thyroid hormone levels with less adverse reactions.

At present, specific mechanism for thyroxine tablets combined with iodine supplement and diet intervention in treatment of benign thyroid nodules is unclear. Midkine is a heparin binding growth factor and it was found almost no expression in normal thyroid tissues, but highly expressed in thyroid papillary carcinoma, whose malignant degree and BRAF mutation were also associated with Midkine [13,14]. Some scholars detected the serum level of Midkine in patients with 10 different types of cancers by ELISA method and found that the content of serum Midkine is limited in normal adults but moderately high in patients with cancer [15]. In recent years, it has been also demonstrated that Midkine has high concentrations in malignant thyroid nodules and low concentrations in blood of those with benign nodules and of normal people [16]. Meanwhile, the detection of MK concentration is of certain significance in the diagnosis of benign and malignant thyroid nodules. Serum VEGF can promote proliferation of vascular endothelial cells and increase permeability of blood vessels. Studies have shown that level of VEGF is moderately high in patients with thyroid nodules, suggesting that VEGF may be involved in the proliferation and angiogenesis of vascular endothelial cells in this case [17]. The results of this study also showed that before treatment, there was no significant difference in serum Midkine and VEGF levels between the two groups ( $P>0.05$ ) while after treatment, the levels of Midkine and VEGF in the treatment group were significantly lower than those in the control group ( $P<0.05$ ), suggesting that thyroxine tablets combined with iodine supplement and dietary therapy may reduce thyroid volume and nodule by decreasing the levels of Midkine and VEGF in patients with benign thyroid nodules.

In summary, thyroxine tablets combined with iodine supplement and dietary therapy can effectively improve the level of thyroid hormone and reduce Midkine as well as VEGF

levels with less adverse reaction, thus worthy of application and popularization as a useful attempt considering the absence of effective drugs in clinical trials. But for those with thyroid diseases or thyroid cancer of obvious compression symptoms, they are not recommended to take such a combination treatment so as not to delay the disease.

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