

Original Article

Efficacy of low-dose levothyroxine combined with thiamazole for treatment of patients with hyperthyroidism

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Abstract: Objective: The current study aimed to explore the efficacy of low-dose levothyroxine combined with thiamazole (LL&T) for treatment of patients with hyperthyroidism, examining its effects on thyroid hormone, bone metabolism, and recurrence rates. Methods: A total of 86 patients with hyperthyroidism (PH), admitted from January 2016 to January 2017, were enrolled in this study. According to the random number table method, they were divided into the control group (CG) and study group (SG), with 43 cases in each group. The control group was given thiamazole, while the study group was given LL&T. Efficacy, thyroid hormone, bone metabolism, and 2-year recurrence rates were compared between the two groups. Results: The total effective rate of SG (88.37%) was higher than that of CG (69.77%) ($P<0.05$). After treatment, hormonal indexes of both groups were improved. Of these, SGTT3, TT4, FT3, and FT4 were lower, while TSH was higher, compared to those in CG ($P<0.05$). Bone metabolism outcomes were improved after treatment. SGCT, BGP, BALP, and PINP levels were lower in SG ($P<0.05$). There were no differences in incidence of adverse reactions between the two groups ($P>0.05$). Conclusion: LL&T has remarkable efficacy in the treatment of hyperthyroidism. It can improve levels of thyroid hormone and bone metabolism outcomes of PH. Moreover, it can reduce recurrence rates. Thus, it is worthy of promotion.

Keywords: Low-dose levothyroxine, thiamazole, hyperthyroidism, thyroid hormones, recurrence of bone metabolism

Introduction

Hyperthyroidism, a common endocrine system disease, is an autoimmune disease that is more common in women. It is a combination of a variety of factors caused by thyrotoxicosis [1-3], mainly characterized by an abnormal release of thyroid hormones and hypermetabolism [4]. In China, prevalence rates in females may reach 2%, with an annual incidence of about 0.2-0.3% [5]. Main clinical symptoms include thyroid hormones abnormalities, skin lesions, high metabolic groups, and eye signs [6]. In severe cases, calcium and phosphorus metabolism disorders, bone calcium loss, bone loss, and osteoporosis may occur [7]. Some patients even suffer from fractures, reducing quality of life levels. Commonly used treatments include surgery, anti-thyroid drugs, and radiation therapy. Of these, the application of anti-thyroid drugs is economical and simple. However, long-term

medication is needed, with many toxic and side effects. Thus, it is easy to relapse after drug withdrawal [8]. Therefore, controlling recurrence is of great significance to patients.

Thiamazole, an antithyroid drug that regulates thyroid hormones, can reduce levels of thyroid stimulating antibodies in the body's circulation and control symptoms of hyperthyroidism. Therefore, the application of thiamazole for treatment of hyperthyroidism can quickly control the disease, promoting the restoration of thyroidism [9, 10]. Levothyroxine, a synthetic sodium tetraiodothyronine salt, possesses the functions of promoting metabolism and enhancing the sensitivity of sympathetic-adrenal axis system. It may also inhibit the synthesis of thyroid hormones and thyroid enlargement. Previous studies have found that [11], if levothyroxine was given at the same time when thyroid function returned to normal, the thyroid

axis hormone could be stabilized. This is conducive to improving hyperthyroidism. However, in the process of clinical treatment, physicians often pay more attention to the control of hyperthyroidism, while neglecting treatment of bone metabolism disorders.

Therefore, the current study explored the effects on thyroid hormones, bone metabolic changes, and recurrence of PH after treatment with low doses of levothyroxine combined with thiamazole (LL&T).

Material and methods

General data

A total of 86 cases of PH, admitted from January 2016 to January 2017, were selected as observation subjects. Inclusion criteria: 1) Met diagnostic criteria for hyperthyroidism [12]; 2) Took no drugs that affected calcium and phosphorus metabolism in the past week; 3) Aged between 18 and 59 years; and 4) Provided informed consent. Exclusion criteria: (1) Patients with severe heart, liver, kidney, and pulmonary insufficiencies; (2) Patients with other bone metabolic diseases; (3) Patients with recurrence of thyroid surgery; and (4) Patients treated with radiotherapy. They were divided into the control group and study group using the random number table method, with 41 cases in each group.

Methods

SG group: SG group was given thiamazole tablets orally (Merck Drugs & Biotechnology, BX-20000048) at 10 mg/time, 3 times per day. During treatment, the dose was reduced in combination with patient conditions and maintained at 5-15 mg/day. After 2 months of treatment, SG was added for oral administration of levothyroxine sodium tablets (Merck Drugs & Biotechnology, approval number: H20140052), at 25-50 µg/time, once daily. The current study was approved by the Ethics Committee of Geriatric Hospital of Zhejiang Province.

CG group: CG group was given thiamazole tablets orally (Merck Drugs & Biotechnology, BX-20000048) at 10 mg/time, 3 times per day. During treatment, the dose was reduced in combination with patient conditions and maintained at 5-15 mg/day. After 6 months of continuous treatment, efficacy rates of the two groups were observed. Thyroid hormone and

bone metabolism levels were also detected. Moreover, 1-year follow-ups were conducted, observing recurrence.

Evaluation criteria

(1) **Efficacy:** Healed indicates that the signs and symptoms of the symptoms disappeared, with levels of total triiodothyroid hormone (TT3), total tetraiodo thyroid hormone (TT4), free triiodothyroid hormone (FT3), free ioroid thyroid hormones (FT4), and thyroid stimulating hormones (TSH) returning to normal. Obvious effects: Clinical symptoms and signs basically disappeared, with TT3, TT4, FT3, FT4, and TSH returning to normal. Effective: Clinical symptoms and signs were significantly improved. TT3, TT4, FT3, FT4, and TSH were also improved. Ineffective: No improvement or aggravation of clinical symptoms and signs, including TT3, TT4, FT3, FT4, and TSH; (2) **Thyroxine:** Levels of TT3, TT4, FT3, FT4, and TSH were determined by immune-chemiluminescence before treatment and after treatment. Siemens automatic chemiluminescence immune-analyzer was used; (3) **Bone mineral density:** Bone mineral density levels of the tibia, hip, and lumbar vertebrae (L2-4) before and after therapy were measured by dual-energy X-ray absorptiometry (manufactured by GE, USA); (4) **Bone Metabolism Index:** Serum calcitonin (CT), osteocalcin (BGP), total type I procollagen N-terminal peptide (PINP), and bone alkaline phosphatase (BALP) were detected by enzyme-linked immunosorbent assay before and after treatment. The reagents were produced by Shanghai Jianglai Biotechnology Co., Ltd; (5) Two groups of adverse reactions were observed; (6) 1-year recurrence was followed-up.

Statistical analysis

Data analysis was performed using SPSS19.0 statistical software. Measurement data were analyzed by t-tests, while count data were analyzed by χ^2 tests. $P < 0.05$ indicates statistical significance.

Results

Clinical data of two groups of patients after admission

There were no differences in gender, age, course, BMI, cholesterol, triglycerides, and low-density lipoprotein between the two groups ($P > 0.05$), which were comparable (**Table 1**).

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Table 1. Comparison of two groups of general data ($\bar{x} \pm s$, n)

Group	n	Gender		Age (year)	Course (year)	BMI (kg/m ²)	Cholesterol (mmol/L)	Triglyceride (mmol/L)	Low density lipoprotein (mmol/L)
		Male	Female						
SG	43	11	32	39.1±6.4	4.9±1.3	23.7±3.1	3.79±0.82	1.41±0.75	2.76±0.77
CG	43	9	34	38.4±7.2	4.7±1.6	22.9±4.2	3.86±0.99	1.35±0.85	2.57±0.82
χ^2/t		0.261		0.476	0.636	0.518	0.164	0.155	0.480
P		0.610		0.653	0.526	0.607	0.870	0.878	0.633

Table 2. Comparison of clinical efficacy between the two groups [n (%)]

Group	n	Healed	Markedly effective	Effective	Ineffective	Total effective
SG	43	20 (46.51)	14 (32.56)	4 (9.30)	5 (11.11)	40 (93.02)
CG	43	14 (32.56)	13 (30.23)	3 (6.98)	13 (28.89)	32 (74.421)
χ^2			-	-	-	5.460
P			-	-	-	0.019

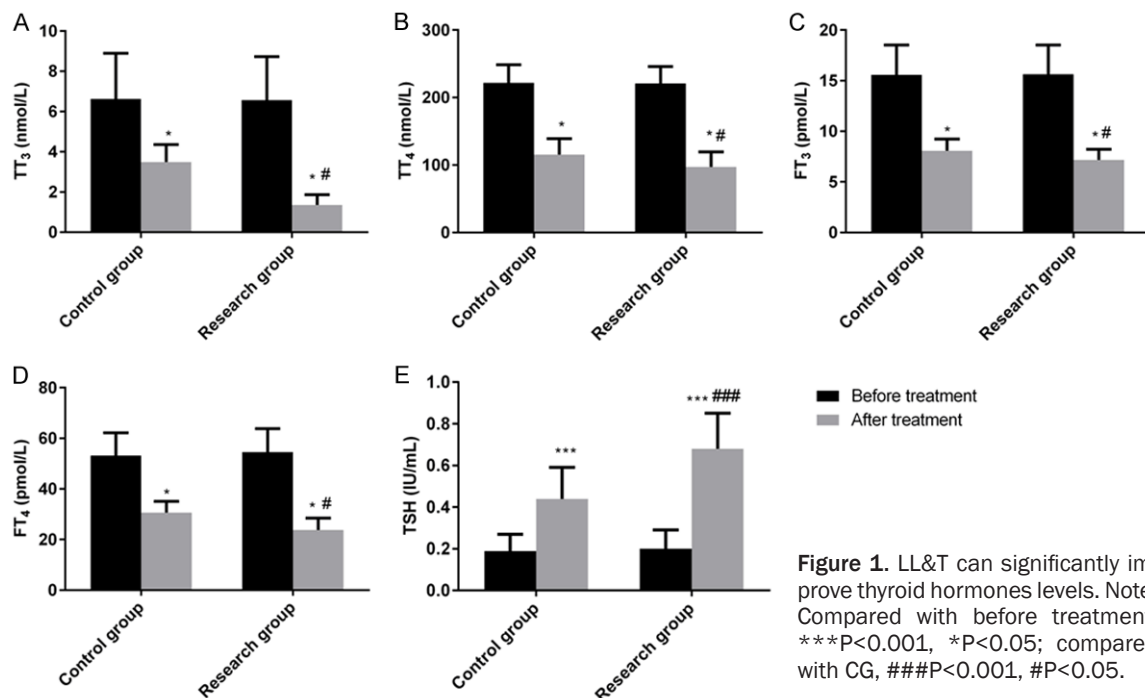


Figure 1. LL&T can significantly improve thyroid hormones levels. Note: Compared with before treatment, ***P<0.001, *P<0.05; compared with CG, ###P<0.001, #P<0.05.

LL&T can significantly improve clinical efficacy

The total effective rate of SG (88.89%) was higher than that of CG (71.11%) (P<0.05), suggesting that LL&T can significantly improve the clinical efficacy of PH. Thus, it is superior to thiamazole alone (Table 2).

LL&T can significantly improve levels of thyroid hormones

Differences in TT₃, TT₄, FT₃, FT₄, and TSH between the two groups were not significant

before treatment (P>0.05). They improved after treatment. SGTT₃, TT₄, FT₃, and FT₄ were lower than those in CG, while TSH was higher than that in CG (P<0.05). Results suggest that LL&T can significantly reduce levels of thyroid hormones, showing better effects than thiamazole alone (Figure 1).

LL&T can significantly increase bone mineral density

Before treatment, there were no differences in bone mineral density levels between the two

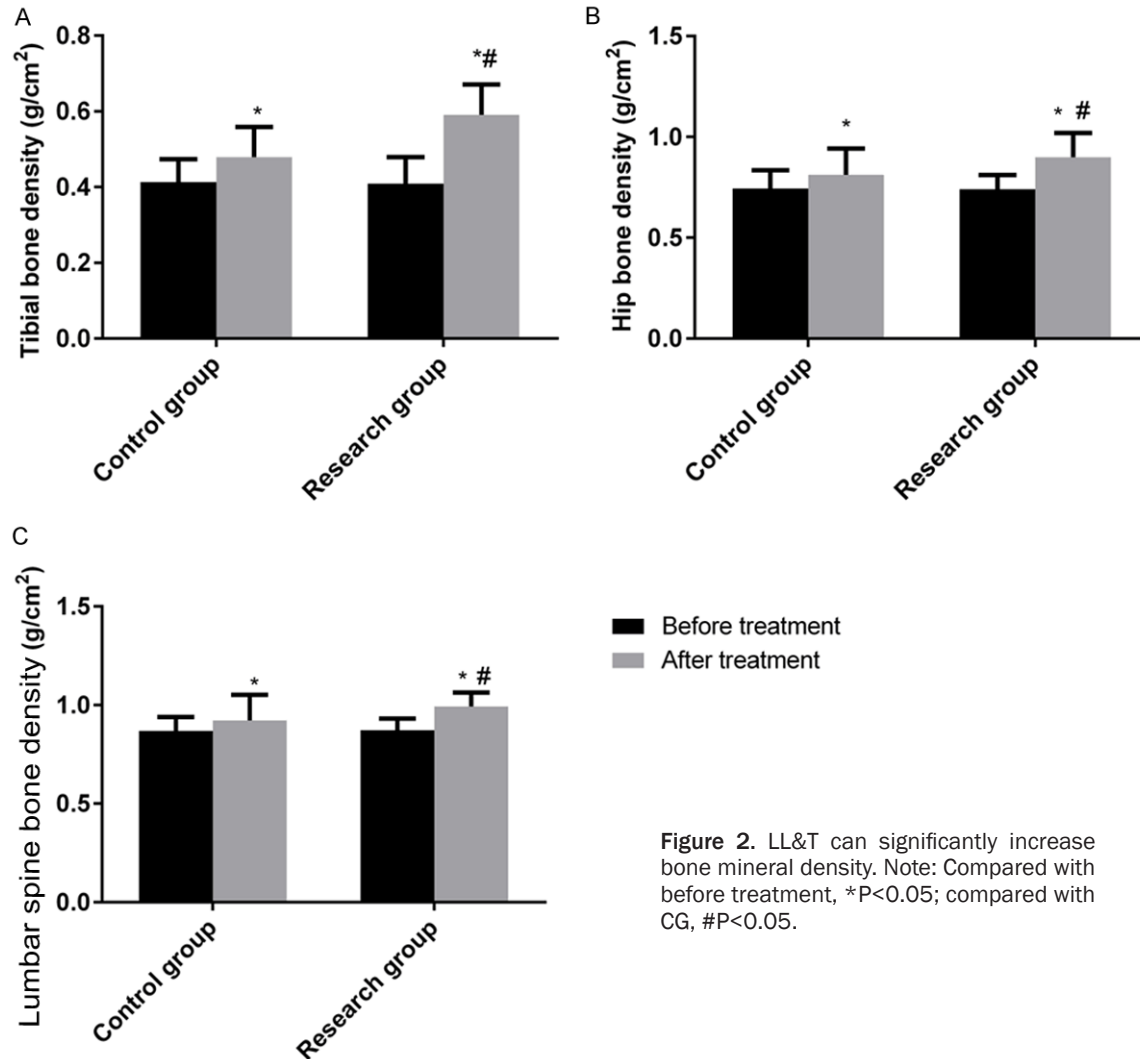


Figure 2. LL&T can significantly increase bone mineral density. Note: Compared with before treatment, * $P < 0.05$; compared with CG, # $P < 0.05$.

groups ($P > 0.05$). After treatment, both increased. SG was higher than CG ($P < 0.05$), suggesting that LL&T can significantly increase levels of bone mineral density, showing better effects than thiamazole alone (Figure 2).

LL&T can significantly improve levels of bone metabolism indicators

There were no differences in levels of CT, BGP, BALP, and PINP between the two groups before treatment ($P > 0.05$). After treatment, they all decreased. SG was lower than CG ($P < 0.05$), suggesting that LL&T can significantly reduce levels of bone metabolism indicators, showing better effects than thiamazole alone (Figure 3).

LL&T was safer

Incidence rates of adverse reactions in the two groups were not different ($P > 0.05$), suggesting

that LL&T provides less adverse clinical reactions and higher safety levels (Table 3).

Comparison of recurrence rates between the two groups

During the 1 year of follow-up, there were 4 cases of recurrences (9.30%) in SG. There were 13 cases of recurrences in CG (30.23%). Thus, SG exhibited lower recurrence rates than CG ($\chi^2 = 5.939$, $P = 0.015$) (Table 4).

Discussion

Hyperthyroidism patients are often accompanied by abnormal bone mineral metabolism, reducing bone mass in severe cases [4, 13]. At present, clinical practice pays more attention to the control of hyperthyroidism symptoms and less attention to bone metabolism disorders. Treatment of hyperthyroidism with thiam-

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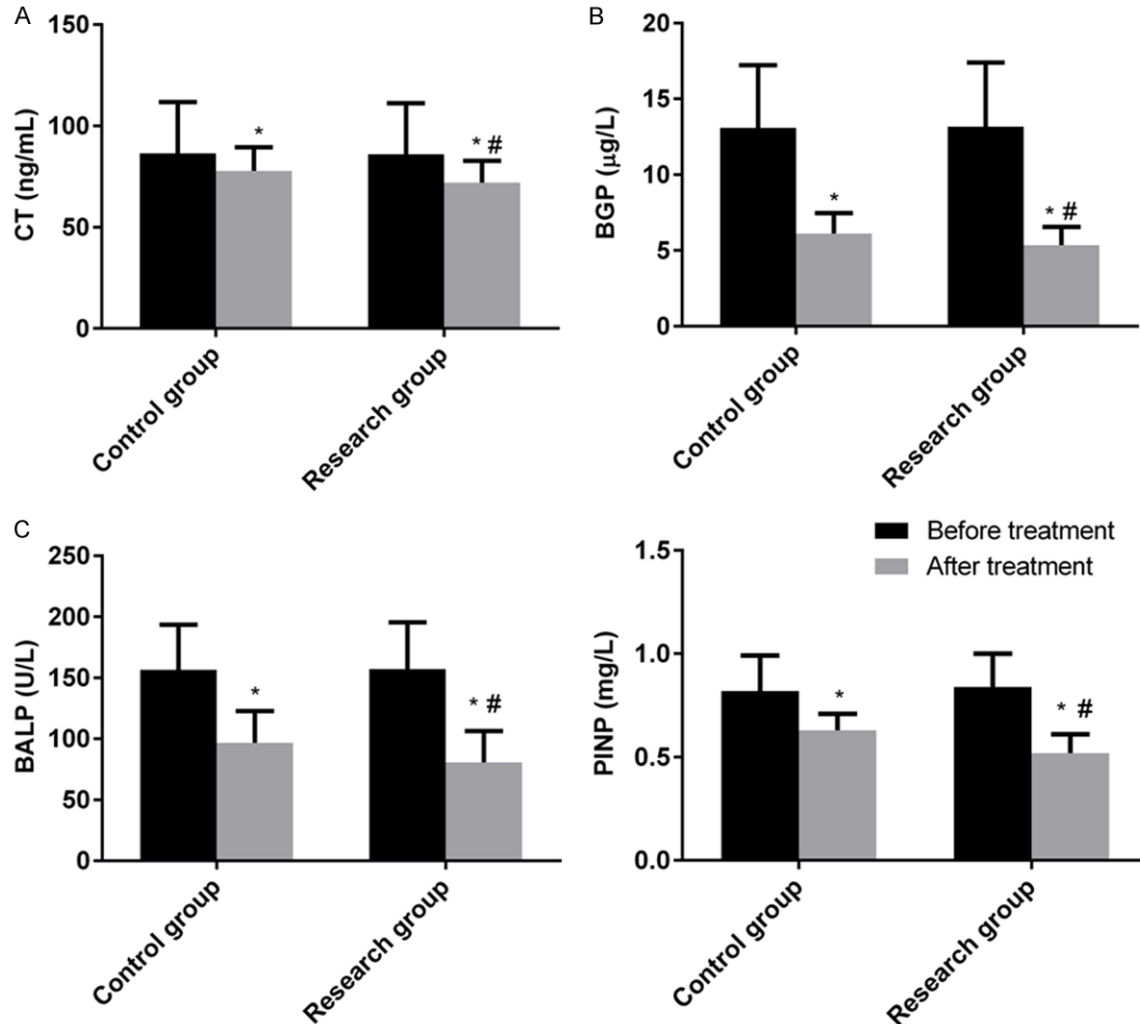


Figure 3. LL&T can significantly improve levels of bone metabolism indicators. Note: *P<0.05 compared with before treatment; Compared with CG, #P<0.05.

Table 3. Comparison of adverse reactions between the two groups [n (%)]

Group	n	Rash	Abnormal liver function	Drug-induced hypothyroidism	Leukopenia	Total incidence
SG	43	5 (11.63)	2 (4.65)	1 (2.33)	4 (9.30)	12 (27.91)
CG	43	4 (9.30)	0 (0.00)	0 (0.00)	4 (9.30)	8 (18.60)
χ^2		-	-	-	-	1.042
P		-	-	-	-	0.307

azole can quickly control the disease, promoting the restoration of thyroidism.

Combined treatment of levothyroxine stabilizes the disease and provides synergistic effects [14, 15]. However, there are few studies concerning the effects of both on bone metabolism. Results of the current study showed that LL&T can significantly reduce levels of bone

metabolism indicators, showing better effects than treatment with thiamazole alone. Levothyroxine, a synthetic thyroid hormone, can be converted into a more active sodium triiodothyronine

salt after ingestion, thereby increasing the heat production, accelerating metabolism, and stimulating sympathetic-adrenal systemic susceptibility. Moreover, it plays a role in regulating thyroid hormones and reducing the volume of the thyroid gland [16, 17].

Thiamazole regulates hormone levels by inhibiting thyroid peroxidase, reducing the synthesis

Table 4. Comparison of recurrence between the two groups [n (%)]

Group	n	Recurrences	χ^2	P
SG	43	4 (9.30)	5.939	0.015
CG	43	13 (30.23)		

and release of T3 and T4. In PH treated with thiamazole, a small dose of levothyroxine can be used synergistically. In the current study, SG had a higher total effective rate and a lower recurrence rate than CG. Adverse reactions in the two groups were comparable. Results suggest that LL&T can improve the efficacy of hyperthyroidism and prevent recurrence, without increasing adverse reactions. The reason may be that LL&T can regulate the pituitary-thyroid axis function, inhibit TSH levels, and regulate levels of thyroglobulin and thyrotropin receptor antibodies, thus playing an anti-thyroid role and reducing the volume of hyperthyroidism [18-20]. Present results showed that the hormonal index of SG improved after treatment, superior to CG. Compared with CG, SG had lower TT3, TT4, FT3, and FT4, along with higher TSH. Results suggest that a combination of the two drugs can better regulate levels of thyroid hormones. This is basically consistent with previous reports [11]. In PH, abnormal levels of thyroid hormones can stimulate osteoclasts, causing disturbances in calcium-calcium metabolism, increased bone turnover, loss of bone mass, and decreased bone density. These can cause osteoporosis as the disease progresses [12]. Therefore, it is of great significance to improve bone metabolism levels of hyperthyroidism patients. The current study showed that, after treatment, bone metabolism indexes, including SG, CT, BGP, BALP, and PINP, decreased. Moreover, the decline was better. This suggests that LL&T can better improve bone metabolism in PH and correct abnormal bone metabolism, in accord with previous studies [4, 13, 14]. Long-term use of LL&T will inevitably produce various adverse reactions [21]. Present results showed no significant differences in adverse reactions between the two groups, suggesting that the use of thiamazole in hyperthyroidism patients and an increased use of low-dose levothyroxine do not lead to increased drug adverse reactions, with better safety. There were some shortcomings to the current study. These included a small sample size, short follow-up period, and no conclusion

concerning whether LL&T is suitable for special patients, such as elderly patients and adolescents. Thus, it will be necessary to expand the sample size for future studies.

In summary, LL&T provides remarkable efficacy in the treatment of hyperthyroidism. It can improve levels of thyroid hormones and bone metabolism outcomes of PH. Moreover, it can reduce recurrence rates. Therefore, it is worthy of promotion.

Disclosure of conflict of interest

None.

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