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Original Article

Coupling methimazole with L-thyroxine on bone of older patients with Graves' disease

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Abstract: Objective: To investigate the effect of methimazole (MMI) with L-thyroxine treatment on bone metabolism in older Graves' disease patients. Methods: Newly diagnosed older Graves' disease patients (n=109) were recruited and divided into control group (n=54) received treatment with MMI only, and treatment group (n=55) received MMI with L-thyroxine treatment. The clinical characteristics, blood serum examination of hyperthyroidism, biochemical indexes and bone mineral density (BMD) of the femoral neck, trochanter and Ward's triangle were analyzed. Results: Compared with control group, the levels of alkaline phosphatase (ALP) in treatment group were significantly increased by 30% andthe levels ofurine calcium (UCa), urine phosphorus (UP) were significantly decreased by 25% and 6% after 18 months of treatment, respectively (p<0.01). Meanwhile, BMD of the femoral neck, trochanter and Ward's triangle were significantly increased by 11%, 9% and 11% in treatment group than control group after 18 months of treatment, respectively (p<0.05). Conclusion: MMI with L-thyroxine treatment has a greater beneficial effect on bone metabolism in older Graves' disease patients than treatment with only MMI.

Keywords: Methimazole (MMI), L-thyroxine, hyperthyroidism, graves' disease, bone mineral density (BMD)

Introduction

It is reported that Graves' disease closely correlated with hyperthyroidism, which featured with osteoporosis and bone mineral metabolic abnormality [1, 2]. Hyperthyroidism has been considered to be a cause of secondary osteoporosis and excess thyroid hormone stimulates bone turnover in favor of bone resorption resulting a calcium balance and decreased BMD [3-5]. Anti-thyroid drugs (such as, MMI and L-thyroxine) have been used for treatment of hyperthyroidism, for example, Graves' disease [6]. It is reported that two thirds of the members of the European Thyroid Association choose anti-thyroid drugs as the first approach to the treatment of hyperthyroidism [7]. Long-term anti-thyroid drugs treatment was superior to radioiodine therapy [8] and could reduce the side effect of radioiodine therapy [9], which has been widely used for treatment of hyperthyroidism. Patients with Graves' disease have a 40-60% remission rate after anti-thyroid drugs treatment alone of [12-18] months. 10 Propylthiouracil plus L-thyroxine was effective to reduce general adverse features but didn't benefit on the psychomotor retardation in a patient with a mutation in monocarboxylate transporter 8 (MCT8) gene [11]. Compared with methimazole alone, a higher dose of methimazole plus L-thyroxine greatly reduced TSH receptor antibodies and relapse rates in patients with hypothyroidism [12]. L-thyroxine administration did not improve remission rate of Graves' disease during and after anti-thyroid drugs (propylthiouracil or MMI) withdrawal [6, 13]. Despite of intensive studies, it is still controversial to use anti-thyroid drugs alone or in combination with L-thyroxine in patients with Graves' disease.

To date, it is 20-70% in patients with relapse of hyperthyroidism following discontinuation of treatment [13]. For patients with Graves' disease, serum free triiodothyronine (FT3) and free thyroxine (FT4) levels were significantly higher than the normal, and thyrotropin (TSH) levels were significantly lower than the normal. It is safe for patients with Graves' disease to treat with MMI and has less complications [14]. Whereas, it is difficult to cure bone metabolism

disorders at the same time in controlling hyperthyreosis. Treatment with anti-thyroid drug alone for 12-18 months reduces serum concentrations of TSH receptor antibodies and usually results in remission of Graves' disease in 40-60% of patients [15]. Several studies have shown that 60%-70% of patients showed normal TSH levels, who received L-thyroxine instead of MMI [16]. Some study suggested that a moderate amount of thyroid hormones can increase the activity of bone cell, improve the circulation and metabolic disorders of bone [17].

The aim of this study was to further investigate the mechanism of bone metabolism and improving effect after treatment. In our study, we compared the effect of MMI with or without L-thyroxine on bone of older patients with Graves' disease.

Materials and methods

Subjects

One hundred nine patients with active, previously untreated Graves' disease were recruited for the study from June 2012 to June 2013. Graves' disease was diagnosed by following criteria: 1) The diagnosis of Graves' disease was based on the symptoms of hyperthyroidism, biochemical evidence of thyroid functionand a thyroid ultrasound examination consistent with Graves' disease; 2) All individuals meet with Chineseguidelines of diagnosis and treatment for thyroid disease (version 2010); 3) All individuals showed clinical high metabolic symptoms and thyroid dysfunction; 4) All newly diagnosed patients were all with age ≥60 years old. Protruding eyes was measured by Hertel Exophthalmometry (BaoJia Electronics Co., Ltd., Guangzhou, China) and protruding eyes was diagnosed when the degree of exophthalmos >13.6 mm. Thyromegaly was measured by palpation though estimating the size of the thyroid and thyromegaly can be diagnosed if the size of one side lobe exceeds the width of subject's thumb tip. Exclusion criteria: 1) Individuals had viral hepatitis, cirrhosis, liver lesions, tumour of orbit, intracranialtumors, which may be easily confused with thyroid diseases; 2) Individuals had such hyperparathyroidism, osteoporosis, vitamin deficiency, or treated with long-term use of glucocorticoid therapy, which may lead to low bone mass; 3) Individuals taking drugs affecting calcium and phosphorus metabolism. The study was approved by the ethics committee of Sichuan Provincial People's Hospital, performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients before enrollment.

Grouping and sampling

According to random number table, total patients were randomly divided into two groups, including control group (n=54) and treatment group (n=55). Control group were treated with only MMI (Merck KGaA, Darmstadt, Germany). Treatment group were treated with MMI plus L-thyroxine (Merck KGaA, Darmstadt, Germany). Both groups were treated for 18 months. MMI was provided for all patients in two groups with the initial dosage of 15-30 mg/d, and adjusted appropriately according to thyroid function checked monthly. Besides, L-thyroxine was provided for treatment group with the dosage of 25 g/d. Any other drug was not used during treatment, which affected serum calcium and phosphorus metabolism.

Urine samples were collected at admission 24 h. Fasting blood of overnight about 14 h was collected. After centrifugation for 10 min at 4°C with 5,000 rpm, serum was placed in -70°C ultra-low temperature refrigerator (Model DW-86L626, Haier, Qingdao, China).

Data collection

Serum FT4 and FT3 were measured by saturation analysis and serum TSH, TRAb were analyzed by immunoradiometric assay using kits from (Abbott Ireland diagnostics Division, Ireland). PTH and CT were measured by the ELISA method using kits from (Siemens Healthcare Diagnostics Inc, Los Angeles, USA). The levels of blood calcium, serum phosphorus, ALP, 24 h UP and 24 h UCa were measured using kits (BIOSINO Biotechnology Company, Beijing, China). BMD was measured by dual-energy-X-ray absorptiometry (DEXA) with a Lunar DPX device (Madison, Wisconsin, USA). BMD was expressed in units as gram per cubic centimeter.

Therapeutic effect evaluation

The differences of the rate of protruding eyes and thyromegaly, the positive rate of thyrotrophin receptor antibody (TRAb), the contents

Table 1. Clinical characteristics analysis before treatment

Variable	Control group	Treatment group	*P* value
Age (years)	64.49±3.39	63.87±3.16	0.33
Sex (F/M)	38/16	38/17	0.88
Height (cm)	162.00±0.07	161.40±0.07	0.63
Weight (kg)	53.93±6.32	52.34±6.24	0.19
BMI	20.48±1.22	20.03±1.37	0.08
LDL (mmol/L)	2.01±0.74	1.95±0.73	0.66
Duration of symptoms (days)	3.78±1.67	3.778±1.82	0.99
Smoking history (years)	9.40±15.29	10.57±16.27	0.70
Drinking history (n, %)	8 (14.55%)	7 (12.96%)	0.81
Physical activity	Moderate	Moderate	--

Note: Body Mass Index (BMI), Low Density Lipoprotein (LDL).

of TSH, FT3, FT4, ALP, CT, 24 h UP, 24 h UCa, PTH, blood calcium, serum phosphorus and BMD were evaluated before and after treatment between control group and treatment group.

Statistical analysis

Statistical analysis was performed using SPSS (version 21.0). Data were expressed as means ± standard deviation (SD). Comparisons between groups were conducted using x^2 tests or Student *t* test as appropriate. A *P* value, $P \leq 0.05$ or $P \leq 0.01$, was considered as statistically significant.

Results

Basic characteristics in older patients with Graves' disease

A total of 109 hospitalized patients (male/female=33/76) were recruited in the study. All patients were randomly divided into control group (n=54, male/female=16/38) and treatment group (n=55, male/female=17/38). To figure out the health status of older patients with Graves' disease, we analyzed clinical data of patients in two groups including age, sex, body mass index (BMI) and other related factors in the first 24 h of admission (**Table 1**). As shown, control group were with their mean age 64.49±3.39 years, and treatment group werewith their mean age 63.87±3.16 years. There were no significant differences among sex, age, height, weight, BMI and other clinical characteristics in two groups ($p>0.05$).

Hyperthyroidism biochemical data in older patients with Graves' disease

The rate of protruding eyes, and thyromegaly, the positive rate of TRAb, the contents of TSH, FT3 and FT4 in two groups were analyzed before and after treatment (**Table 2**). As shown, compared with control group, there were no significant differences in hyperthyroidism biochemical data in treatment group whether before or after treatment ($P>0.05$). For control group, after treatment with MMI, the rate of protruding eyes, and thyromegaly, the positive rate of TRAb, the contents of FT3 and FT4 were all significantly decreased ($P<0.05$) and the content of TSH were significantly increased ($P<0.01$). For treatment group after treatment with MMI plus L-thyroxine, the rate of protruding eyes and thyromegaly, the positive rate of TRAb, the contents of FT3, FT4 and TSH showed the similar changes with control group. The rate of protruding eyes decreased significantly ($P<0.05$). The rate of thyromegaly, the positive rate of TRAb and the contents of FT3 and FT4 were also significantly decreased ($P<0.01$). The content of TSH were significantly increased ($P<0.01$). Moreover, the variation after treatment between two groups showed no significant difference among the hyperthyroidism biochemical data ($P>0.05$). The contents of FT3, FT4 and TSH were back to the normal range after treatment, while all of them were abnormal with TSH content too low and the contents of FT3, FT4 too high before treatment.

Analysis of bone biochemical parameters in older patients with Graves' disease

To further figure out the effect of methimazole with L-thyroxine on bone of older patients with Graves' disease, bone biochemical parameters were analyzed (**Table 3**). As shown, the contents of ALP, 24 UCa and 24 UP were markedly improved, which were significantly decreased after treatment both in control group and treatment group ($P<0.01$). Compared with control group, the contents and the variation of ALP, 24 UCa and 24 UP in treatment were showed sig-

Table 2. Anlysis of hyperthyroidism biochemical data in elderly patients with Graves' disease

Variable	Normal range	Control group (n=54)			Treatment group (n=55)		
		Before treatment	After treatment	Variation	Before treatment	After treatment	Variation
Protruding eyes (n, %)	--	10 (18.52)	2 (3.70)*	8 (14.81)	9 (16.36)	2 (3.63)#	7 (12.72)
Thyromegaly (n, %)	--	9 (16.67)	1 (1.90)**	8 (14.81)	10 (18.18)	0 (0.00)##	10 (18.18)
TRAb-positive (n, %)	--	28 (51.85)	10 (18.52)**	18 (33.33)	29 (52.73)	11 (20.00)##	18 (32.73)
TSH (mIU/L)	0.34-4.94	0.02±0.03	3.14±0.96**	3.12±0.95	0.01±0.02	2.88±1.25##	2.87±1.25
FT3 (pmol/L)	2.63-15.70	15.98±3.04	3.96±1.61**	-12.02±3.01	16.91±2.89	3.85±1.32##	-13.06±2.95
FT4 (pmol/L)	9.01-19.05	58.49±10.89	14.55±2.90**	-43.94±10.53	54.77±10.74	13.78±2.76##	-41.00±10.02

Note: Thyrotrophin receptor antibody (TRAb), Thyroid stimulating hormone (TSH), Freetriiodothyronine (FT3), Free thyroxine (FT4). *p<0.05 vs control group before treatment; **p<0.01 vs control group before treatment; #p<0.05 vs treatment group before treatment; ##p<0.01 vs treatment before treatment.

nificant differences after treatment (P<0.01). The contents and the variationof ALP in treatment group were significantly increased by 30% and 42% than control groupafter 18 months of treatment, respectively. The contents and the variation of ALP, 24 UCa and 24 UP were significantly decreased by 25%, 16% and 6%, 3% after 18 months of treatment, respectively (p<0.01). To be different, the contents of PTH, CT in two groups were slightly increased and showed no significant differences before and after treatment (P>0.05). For serum phosphorus and blood calcium, the contents of serum phosphorus and blood calcium in control group were both slightly increased, whereas, in treatment group were both slightly decreased after treatment. And there were no significant differences before and after treatment (P>0.05).

BMD analysis

BMD of the femoral neck, trochanter and Ward's triangle were analyzed (**Table 4**). Before treatment, there were no significant differences among BMD of the femoral neck, trochanter and Ward's triangle in two groups (P>0.05). After treatment, BMD of the femoral neck, trochanter and Ward's triangle were significantly increased compared with pretreatment values (P<0.01). Moreover, compared with control group after 18 months of treatment, BMD of the femoral neck, trochanter and Ward's triangle were significantly increased by 11%, 9% and 11% in treatment group, respectively. Even, the variation of BMD of the femoral neck, trochanter and Ward's triangle in treatment showed a significant difference with control group after treatment (P<0.01).

Discussion

In the present study, we focused on the potential benefit of MMI with L-thyroxine therapy on older patients with Graves' disease. Similar cure rates were observed after treated with MMI plus L-thyroxine or not, while a greater effect with MMI plus L-thyroxine therapy on bone of older patients with Graves' disease.

Studies showed that patients with Graves' disease always had osteoporosis and anti-thyroid drugs could alleviate symptoms [17]. In patients with Graves' disease, increasing TNF-α, interleukin-6 induced by thyroid hormone and thyroid stimulating hormone affected osteoclast activity and reduce the concentration of parathyroid hormone, resulting in bone metabolism abnormality and BMD decreased [18, 19]. Thyroid hormone acted on T3 receptor of osteoblast nuclear, which caused cycle time of bony remodeling shorten and BMD decreased [17]. Moreover, the absorption of calcium and phosphorus reduced and the excretion of calcium and phosphorus increased in patients with Graves' disease also resulted in BMD decreased [21]. As we previously described, long-term MMI treatment is safe for treat Graves' disease [14]. In our study, anti-thyroid drugs MMI and L-thyroxine were selected to improve BMD of older patients with Graves' disease.

Analysis of clinical characteristics indicated no significant differences before treatment. While the number of female patients recruited in our study was much more than male, and this may be explained by a higher disease incidence in older patients with Graves' disease in Chinese population. Further, we analyzed hyperthyroidism biochemical data in patients of two groups, which were all improved after treatment. The mean levels of TSH significantly increased to the normal range, and the mean levels of FT3 and FT4 significantly decreased to the normal range. All the above illustrated that MMI plus L-thyroxine or not was effective for hyperthyroidism treatment. Some study reported that

Table 3. Analysis of bone biochemical parameters in elderly patients with Graves' disease

Variable	Normal range	Control group (n=54)			Treatment group (n=55)		
		Before treatment	After treatment	Variation	Before treatment	After treatment	Variation
PTH (pg/mL)	10.00-69.00	34.66±12.53	36.39±13.91	1.73±9.51	33.06±13.51	34.17 ±12.87	1.11±6.11
CT (ng/mL)	F<11.50 M<18.20	8.34±3.79	9.07±3.19	0.73±2.91	8.95±3.88	9.32±3.44	0.36±2.85
Blood calcium (pmol/L)	2.20-2.65	2.25±0.18	2.28±0.19	0.03± 0.19	2.31±0.25	2.26±0.20	-0.05±0.24
Serum phosphorus (pmol/L)	0.81-1.45	1.18±0.20	1.21±0.16	0.03±0.18	1.22±0.22	1.21±0.17	-0.014±0.15
ALP (IU/L)	45.00-125.00	132.70±22.12	67.30±12.03**	-65.39±14.74	126.40±21.03	88.30±7.21##,&&	-38.15±16.26&&
UCa (mg/24 h)	--	1173.97±45.89	437.49±33.33**	-736.48±38.41	1186.30±41.37	328.46±34.26##,&&	-857.86±27.30&&
UP (mg/24 h)	--	4951.857±58.04	1409.922±41.04**	-3541.94±27.95	4971.16±61.63	1324.87±46.02##,&&	-3646.30±49.39&&

Note: Parathyroid hormone (PTH), Calcitonin (CT), Alkaline phosphatase (ALP), Urine calcium (UCa), Urine phosphorus (UP). **p<0.01 vs control group before treatment; ##p<0.01 vs treatment group before treatment; &&p<0.01 vs control group after treatment.

Table 4. BMD analysis in elderly patients with Graves' disease (g/cm^3)

Variable	Control group (n=54)			Treatment group (n=55)		
	Before treatment	After treatment	Variation	Before treatment	After treatment	Variation
Femoral neck	0.81±0.21	0.89±0.23**	0.07±0.06	0.79±0.13	0.98±0.17##,&	0.20±0.08&&
Trochanter	0.77±0.18	0.78±0.19**	0.08±0.03	0.67±0.13	0.85±0.13##,&	0.18±0.04&&
Ward's triangle	0.73±0.20	0.80±0.20**	0.07±0.03	0.70±0.12	0.89±0.13##,&&	0.19±0.04&&

Note: **$p<0.01$ vs control group before treatment; ##$p<0.01$ vs treatment group before treatment; &$p<0.05$ vs control group after treatment; &&$p<0.01$ vs control group after treatment.

L-thyroxine treatment increased in serum TSH in patients with Graves' diseases [13]. Our results illustrated an increasing level of TSH, even in control group with a therapy of only MMI, which excluded the effect of L-thyroxine on TSH level.

We further analyzed bone biochemical parameters in older patients with Graves' diseases. After treatment, a significant difference was observed in ALP, UCa, UP between control group and treatment group. As we know, ALP is often used to evaluate the activity of osteoblasts in clinical practice, which mainly exists in the liver and bones and reflects osteoblasts metabolism when liver function is normal. Levels of ALP were both significantly decreased in two groups after treatment than before after treatment [21]. Besides, 24 h UCa, 24 h UP are often used to evaluate the activity of osteoclasts in clinical practice. The levels of ALP, 24 h UCa and 24 h UP were higher and recovered in line with the recovery of thyroid function in older patients with Graves' diseases in our study. After treatment, the levels of 24 h UCa and 24 h UP in treatment group decreased significantly than control group. Bone metabolism was improved significantly after treatment in patients, especially with the therapy of MMI plus L-thyroxine.

Furthermore, the results of BMD analysis indicated that mean BMD in patients with the therapy of MMI plus L-thyroxine was much higher than patients with only MMI whether femoral neck, trochanter or Ward's triangle. And the result was inconsistent with previous results, that no difference in remission rates showed in Graves' disease patients treated for 18 months with either MMI alone or a combination of MMI and L-thyroxine [23]. The inconsistencies may be explained by the different subjects and geographical restrictions. Patients in our study were elder with mean age over 60 years and all Chinese, and subjects in previous study were mainly Caucasian (144/149) with mean age 38 years.

In conclusion, MMI plus L-thyroxine treatment has a greater beneficial effect on bone metabolism than treatment with only MMI, especially in older patients with Graves' disease when the levels of ALP, 24 UCa and 24 UP are seriously high.

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Disclosure of conflict of interest

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