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Influence of l-thyroxine Administration in Patients with Euthyroid Hashimoto's Thyroiditis

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Background: The present study aimed to evaluate the immune suppressive effect of l-thyroxine (LT4) on euthyroid Hashimoto's thyroiditis (HT). HT is the most common form of autoimmune thyroid disease and is characterized by lymphocytic infiltration of the thyroid gland, gradual destruction of the organ, and the production of thyroglobulin antibody (Tg-Ab) and thyroid peroxidase antibody (TPO-Ab). **Methods:** We examined the effect of 6-month LT4 administration in euthyroid HT patients. Twenty patients with euthyroid HT were enrolled. Ten patients were treated with 100 μg/day LT4 for 6 months. The other 10 were not treated with LT4. Thyroid function tests, thyroid volume, and autoantibody titers were measured before and after the 6-month study period. **Results:** There was significantly decreased serum TPO-Ab, Tg-Ab, thyroid-stimulating hormone, and increased free T_4 levels in the LT4-treated group (860±220 vs. 415±182 mIU/L, 168±61 vs. 71±43 mIU/L, 2.5±0.3 vs. 0.5±0.1 U/L, and 14.1±0.2 vs. 22.2±0.3 pmol/L, $p < 0.05$, respectively). In contrast, TPO-Ab and Tg-Ab levels did not change significantly; they were slightly increased in the LT4-untreated patients. Thyroid volume did not differ before and after therapy in both groups. **Conclusions:** Thus, early prophylactic LT4 treatment might be useful for ameliorating the progression of euthyroid HT autoimmunity. The long-term clinical benefit of LT4 therapy in euthyroid HT is yet to be clarified.

Key words: L-thyroxine, Hashimoto's thyroiditis, Euthyroid

INTRODUCTION

In 1912, Hashimoto first reported 4 women in whom the thyroid gland was enlarged and had been transformed into lymphoid tissue.[1] Over 40 years later, the manifestation of antithyroid antibodies was reported in patients with this disorder. Hashimoto's disease, or Hashimoto's thyroiditis, is now known as a form of chronic autoimmune thyroiditis.

HT, a common chronic autoimmune thyroiditis, presents histologically with diffuse lymphocytic infiltration, fibrosis, parenchymal atrophy, and eosinophilic change in acinar cells. Laboratory diagnosis is made by the detection of strongly positive titers of thyroglobulin antibody (Tg-Ab) and thyroid peroxidase antibody (TPO-Ab), and euthyroid or hypothyroid metabolic status.[2] The ultrasonographic parameters in patients with HT may be increased, normal, or decreased.[3] All patients with overt hypothyroidism should be treated with thyroxine (T_4), and the dose should be adjusted to normalize the serum thyroid-stimulating hormone (TSH) concentrations. The role of T_4 therapy in patients with subclinical hypothyroidism is more controversial.

In an animal model of spontaneous thyroiditis, early prophylactic L-thyroxine (LT4) treatment and the subsequent low TSH levels reduced the severity, incidence, and degree of lymphocytic infiltration and altered the time course in genetically predisposed animals.[4-6] In euthyroid patients with HT, 1-year LT4 treatment appeared to benefit the reduction of TPO-Ab titers and peripheral B lymphocytes.[7]

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The aim of the present study was to evaluate the effect of LT4 administration on the autoimmune response of patients with euthyroid HT.

MATERIALS AND METHODS

Patients

We recruited 20 patients with euthyroid HT (18 women and 2 men; age, 33-45 years; mean age, 41±5.1 years) from the outpatient clinics of Buddhist Tzu Chi General Hospital, Taipei Branch. We also recruited 10 patients with nontoxic goiter (7 women and 3 men; age, 36-47 years; mean age, 42±6.1 years) and 10 healthy controls (7 women and 3 men; age, 35-41 years; mean age, 36±4.1 years). All subjects provided written informed consent after the study was explained, and the local ethics committee approved the study. All subjects understood the study and accepted its conditions. The diagnosis of euthyroid HT was based on ultrasonography and laboratory criteria (normal levels of thyrotropin, free T_4 [FT_4], and elevated thyroid antibody titers: Tg-Ab and TPO-Ab). No participant had serious cardiovascular disease, liver disease, renal disease, or was pregnant. None had received LT4 therapy or other thyroid medication before.

Methods

The 20 euthyroid HT patients were randomly divided into 2 groups: one group (10 patients) took 100 μg/day LT4 (Eltroxin; Glaxo Operations Ltd., Greenford, England) for 6 months, while the other 10 did not. We conducted strict pill counts to ensure good patient compliance during the study period. Serum FT_4, TSH, TPO-Ab, and Tg-Ab levels were checked before and after the study. Thyroid ultrasonography was performed before and after the study. The therapeutic response was determined by thyroid function tests and levels of autoantibody titers before and at the end of the study.

Materials

Serum FT_4 and TSH levels were measured by commercial kits (Immulite 2000 Diagnostic Products Corporation [DPC], Los Angeles, CA, USA). The normal ranges for FT_4 and TSH were 10.30-24.32 pmol/L and 0.4-4 mIU/L, respectively. The inter-assay and intra-assay coefficients of variation for each assay were 4.4% and 3.9% for the FT_4 assay and 5.4% and 3.5% for the TSH assay, respectively. TPO-Ab and Tg-Ab were measured by a commercial kit (Immulite 2000, anti-TPO Ab assay, and anti-Tg Ab assay; DPC). The normal ranges for TPO-Ab and Tg-Ab were 0–35 mIU/L and 0–40 mIU/L, respectively. The inter-assay and intra-assay coefficients of variation for each assay were 4.8% and 4.3% for the TPO-Ab assay and 5.1% and 2.8% for the Tg-Ab assay, respectively.

Thyroid size was determined by ultrasound before and at the end of the study using a Toshiba SAL 240 apparatus with a 7.5-MHz transductor.[8] The total thyroid gland volume (V) was calculated from the sum of the partial volumes: V = V right lobe + V left lobe + V isthmus. The volume of each part was calculated using the formula V = (length×width × thickness)×0.5.

Statistical analysis

Data were analyzed using the non-parametric and paired t-test; significance was defined as $p < 0.05$. The results were expressed as mean±SD.

RESULTS

In total, 20 patients with euthyroid HT were recruited and randomly divided into 2 groups: one group (10 patients) received 100 μg/day LT4 for 6 months while the other (10 patients) did not. Compliance was good: the subjects took 98.5% of the study pills over the study period. The baseline data of these patients are listed in Table 1.

There were no significant differences in sex, age, and percentage of elevated TPO-Ab and Tg-Ab levels between the 2 groups of euthyroid HT patients (100% and 80%, respectively). In contrast, the levels of both thyroid antibodies were not elevated in the patients with nontoxic goiter and in the healthy controls (Table 1).

Table 2 shows that there was significantly decreased serum TPO-Ab, Tg-Ab, TSH, and increased FT_4 levels in the LT4-treated group (860 ± 220 vs. 415±182 mIU/L, 168±61 vs. 71±43 mIU/L, 2.5±0.3 vs. 0.5±0.1 U/L, and 14.1±0.2 vs. 22.2±0.3 pmol/L, $p < 0.05$, respectively). In contrast, the serum concentrations of TSH and FT_4 in the LT4-untreated euthyroid HT patients did not change significantly, nor did the TPO-Ab and Tg-Ab levels; the levels of these antibodies even increased slightly.

DISCUSSION

In 1912, Hashimoto first reported 4 women in whom the thyroid gland was enlarged and had been transformed into lymphoid tissue[1]. The presence of anti-thyroid antibodies (TPO-Ab and Tg-Ab) as a major form of chronic autoimmune thyroiditis with this disorder has been re-

Table 1. Baseline characteristics of euthyroid HT patients and controls

Subjects	n	Age (years)	Elevated TPO-Ab	Elevated Tg-Ab
Euthyroid HT	20	41±5.1	20/20 (100%)	16/20 (80%)
LT4-treated	10	40±3.2	10/10 (100%)	8/10 (80%)
LT4-untreated	10	38±4.1	10/10 (100%)	8/10 (80%)
Nontoxic nodular goiter	10	42±6.1	0/10 (0%)	0/10 (0%)
Healthy controls	10	36±5.7	0/10 (0%)	0/10 (0%)

HT: Hashimoto's thyroiditis, TPO-Ab: thyroid peroxidase antibody, Tg-Ab: thyroglobulin antibody, LT4: L-thyroxine. Data are expressed as mean±SD. Normal ranges: TPO-Ab, 0-35 mIU/L; Tg-Ab, 0-40 mIU/L.

Table 2 Changes in thyroid hormone and autoantibody titers in patients with euthyroid HT before and after 6-month LT4 therapy

	Euthyroid HT with LT4 therapy (n = 10)		Euthyroid HT without LT4 therapy (n = 10)	
	Before	After	Before	After
TPO-Ab (0-35 mIU/L)	860±220	415±18.2*	1208±310	1482±362
Tg-Ab (0-40 mIU/L)	168±61	71±43*	232±93	285±87
TSH (0.4-4 mIU/L)	2.5±0.3	0.5±0.1*	2.3±0.3	2.2±0.3
FT4 (10.30-24.32 pmol/L)	14.1±0.2	22.2±0.3*	16.3±0.3	16.9±0.4
TRAb (10%)	23.1±8.2	25.6±7.9	32.6±10.1	36.1±9.9
Thyroid volume (mL)	21.2±4.2	19.6±3.8	22.5±7.1	20.6±5.8

FT4: free thyroxine, TPO-Ab: thyroid peroxidase antibody, Tg-Ab: thyroglobulin antibody, TRAb: thyroid-stimulating hormone receptor antibody. Values are expressed as mean±SD. Values in parentheses denote normal ranges. * $p < 0.05$, compared with before therapy.

ported.[9] The pathologic hallmark of HT is the lymphocytic infiltration of the thyroid gland.[10] Activated CD4 T cells recruit cytotoxic (CD8) T cells as well as B cells into the thyroid. The resulting migration of these cells into the thyroid gland and secretion of antibodies against thyroid-specific antigens is believed to be the main mechanism responsible for hypothyroidism.[11] An increase in thyroid-derived T-helper cells was demonstrated in euthyroid HT patients. This could prove that in euthyroid HT, an active inflammatory process also takes place in the thyroid gland[6]. Meanwhile, TPO-Ab has been postulated as a correlation of lymphocytic infiltration and activity of the disease process.[12] Schmidt et al. studied the long-term course of TPO-Ab in 38 patients with HT who received LT4 treatment and reported that although TPO-Ab levels decreased in most patients, only 16% of patients achieved normal TPO-Ab values despite the years of LT4 treatment.[13] In contrast, it has been suggested that Tg-Ab is the crucial pathogenetic event.[14] However, it remains unclear whether TPO-Ab or Tg-Ab are a serological feature of the intrathyroidal autoimmune process or whether they are able to induce functional changes.[1,15]

It was recommended that hormone replacement therapy with LT4 should be administered to all patients with overt hypothyroidism.[16] Thyroid hormone therapy was associated with a significant reduction of TPO-Ab levels in patients with euthyroid HT and idiopathic myxedema.[6] However, determining whether therapy is appropriate for patients with subclinical hypothyroidism or euthyroid sick syndrome still requires clinical judgment.[1] Studies on animal models of spontaneous HT have demonstrated that prophylactic treatment with LT4 can reduce the incidence and degree of lymphocytic infiltration in HT.[3-5] In models of spontaneous thyroiditis, early prophylactic LT4 treatment and the subsequent low thyrotropin levels decreased the severity and altered the time course in genetically predisposed animals such as cats, BB/Wor rats, and OS chickens.[3] Although LT4 treatment has been shown to inhibit the autoimmune process in animal models, its use in euthyroid HT patients, in whom the thyroid gland destruction is not sufficient to cause hypothyroidism, remains controversial. In 2001, Padberg demonstrated that LT4 was effective in reducing the TPO-Ab titers in patients with euthyroid HT after a 12-month 50 μg/day LT4 treatment. Aksoy et al. also reported significantly decreased TPO-Ab and Tg-Ab levels after 15 months of 50 μg/day LT4 treatment.[17] It is possible that a low initial antibody titer is the key point to this insignificance.[6]

In our study, both TPO-Ab and Tg-Ab were significantly suppressed in patients with euthyroid HT after the 6-month 100 μg/day LT4 treatment. The thyroid function tests also revealed a significant change in the serum TSH and FT_4 levels in the LT4-treated group. This could be explained by the reduced antigen availability of the immune system due to lower thyroid stimulation following the decrease in TSH levels.[18] Our study also dem-

onstrated that TPO-Ab is a better predictor for thyroid autoimmune disease than Tg-Ab because it is detected more frequently and in higher titers. It is not yet clear whether TPO-Ab or Tg-Ab is a serological feature of the intrathyroidal autoimmune process or whether they are able to induce functional changes.[19] However, it has been postulated that TPO-Ab is a correlation of lymphocytic infiltration and disease activity during disease progression.[12] In contrast, it has been suggested that Tg-Ab is the crucial pathogenetic event.[12] In summary, a clinically significant reduction in TPO-Ab can be achieved during LT4 treatment of euthyroid HT. It clearly inhibits the autoimmune process and the development of hypothyroidism.

It was reported that thyroid size diminished over the range of disease, from euthyroid to overtly hypothyroid, with LT4 treatment.[20] In our study, there was a slight decrease in goiter size after LT4 therapy.

This study had a limitation. As the small study population was our primary concern, the long-term beneficial effect of prophylactic LT4 treatment is still unknown.

In conclusion, the autoimmune process is ongoing in the early stages of euthyroid HT. Treating euthyroid HT patients with prophylactic LT4 for 6 months reduced both TPO-Ab and Tg-Ab titers significantly. However, the long-term beneficial effect of prophylactic LT4 treatment should be further clarified.

DISCLOSURE

The authors declare no conflicts of interest.

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