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THYROTROPIN AND THYROID HORMONE ECONOMY IN EUTHYROID HASHIMOTO'S THYROIDITIS

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SUMMARY – Little is known about thyrotropin (TSH) and thyroid hormones in euthyroid Hashimoto's thyroiditis (HT), thus the aim was to investigate TSH and thyroid hormone economy in euthyroid HT and its relation to thyroid function. Ninety-five patients with euthyroid HT with normal TSH and thyroid hormones on the last follow up between 2009 and 2011 were investigated. Previous observation period ranged from 1.5 to 4.8 (mean 2.8) years, and they had never been treated with levothyroxine. The results of TSH and thyroid hormones were compared with 210 healthy subjects and expressed as median (25%-75%). According to TSH value, the subjects were divided into quartiles: TSH 0.4-0.99 (1q), 1.0-1.99 (2q), 2.0-2.99 (3q) and 3.0-4.0 mIU/L (4q). Euthyroid HT patients had higher TSH (2.53 [1.79-3.14] *vs.*1.95 [1.24-2.72], p<0.001). T4 and T3 were not different. The distribution of TSH in HT patients was significantly shifted to the right; 71% of patients were in the 3q and 4q groups. When HT patients with higher TSH (3q and 4q) were compared with those with lower TSH (1q and 2q), significant differences emerged in TSH (3.01 [2.48-3.48] *vs.*1.45 [1.07-1.71] mIU/L), T4 (99.0 [88.2-112.0] *vs.*112.0 [105.0-122.0] nmol/L) and T3 (1.78 [1.48-2.05] *vs.* 2.10 [1.85-2.21] nmol/L; p<0.01). TPO values were similar in both groups. A gradually increasing proportion of euthyroid HT patients with at least one supranormal TSH during the observation period were found: 0% in 1q, 10% in 2q, 15% in 3q and 44% in 4q TSH group. Euthyroid HT patients maintain euthyroidism only under strenuous TSH stimulation. The patients with high normal TSH are identified as those with a major risk of hypothyroidism in the near future.

Key words: *Hashimoto disease; Thyroid diseases; TSH; Thyroid hormones*

Introduction

Hashimoto's thyroiditis (HT), the most common cause of thyroid failure in the western world, is a slowly progressive disease, evolving from euthyroidism to subclinical and overt hypothyroidism[1]. When these patients should be treated is a matter of controversy. Little is known about thyrotropin (TSH) and thyroid hormone economy in euthyroid Hashimoto's thyroiditis, and the results in this study pointed to difference in TSH and thyroid hormones between these patients, particularly those with high normal TSH, and healthy subjects, suggesting that the disease is progressing even when TSH and thyroid hormones are still within the normal range.

Subjects and Methods

This study included 95 euthyroid patients with HT referred to Thyroid Center for regular follow up testing between January 2009 and December 2011. The last follow up analysis, which was taken into account, showed normal values of TSH and thyroid hormones. Previous observation period ranged between 1.5 and 4.8 (mean 2.8) years, and the patients had never been

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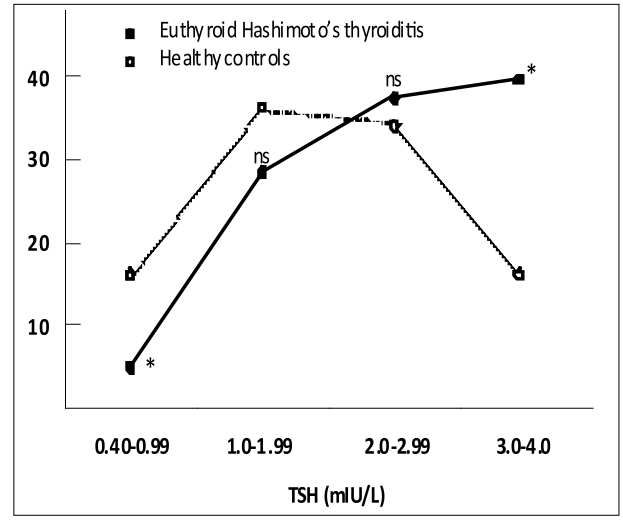
treated with levothyroxine. This group was selected from a total number of 616 HT patients followed up in that period, 521 being treated with replacement therapy. The diagnosis of HT was confirmed by ultrasound, positive TPO autoantibody titer (>50 IU/mL), and occasionally by fine-needle aspiration biopsy when hypertrophic thyroid nodules required morphological analysis.

According to their TSH values, euthyroid HT patients were divided into quartiles: TSH=0.4-0.99 (1 quartile [q]), TSH=1.0-1.99 (2q), TSH=2.0-2.99 (3q) and TSH=3.0-4.0 mIU (4q).

Data from euthyroid HT patients were compared with those obtained from 210 healthy control subjects recruited from persons admitted to our outpatient clinic for investigation of thyroid function. There was no history or signs of thyroid disease, TSH and thyroid hormones were normal, and TPO was negative (<50 IU/mL). Due to the small number of male subjects in both HT patient and control groups (N=6 and N=13, respectively), only females were included. The subjects from either HT or control group did not suffer from any (other) endocrine disease and were free from medication that could affect TSH-thyroid hormone secretion.

Blood samples were taken in fasting condition between 7.30 an 9.00 a.m., and TSH, thyroid hormones and TPO determined on Immulite 1000 analyzer. Normal values for TSH, T4, and T3 were 0.4-4.0 mIU/L, 65-165 nmol/L and 1.1-2.9 nmol/L, respectively.

Statistical analysis included Mann-Whitney rank sum test for nonparametric data and Fisher's exact test; $p<0.05$ was considered significant.



*p<0.001; nsnonsignificant; total number of HT patients was 3 in 1q, 24 in 2q, 31 in 3q and 37 in 4q TSH. In controls, total numbers were 31, 76, 72 and 31, respectively.

Fig. 1. Different TSH distribution in patients with euthyroid Hashimoto's thyroiditis (HT) and healthy control subjects.

Results

Figure 1 shows distribution of TSH values in euthyroid HT patients and healthy subjects. Unlike normal distribution in controls, results in euthyroid patients were markedly shifted toward higher values. Only 3% of patients had TSH <1.0 mIU/L (1q TSH group) in comparison with 16% of healthy subjects ($p<0.001$), while 35% of euthyroid HT patients and merely 16% of controls had TSH in the 4q group ($p<0.001$).

Table 1. Age, TSH, T4, T3 and T4/TSH ratio in euthyroid Hashimoto's thyroiditis patients and control subjects

	Euthyroid Hashimoto's thyroiditis (N=95)		Controls (N=210)	
	Median	25%-75%	Median	25%-75%
Age (years)	46.0*	35.0-60.0	41.0	29.0-58.7
TSH (mIU/L)	2.53**	1.79-3.14	1.95	1.24-2.72
T4 (nmol/L)	104.5ns	91.5-116.0	104.0	92.3-119.5
T3 (nmol/L)	1.98ns	1.68-2.13	1.82	1.24-2.72
T4/TSH	36.9**	29.4-61.4	54.8	37.5-99.0

*p<0.05; **p<0.001; nsnonsignificant

Table 2. Comparison of age, TSH, T4, T3, T4/TSH ratio and TPO-Ab between two groups of euthyroid Hashimoto's thyroiditis patients (with lower and higher normal serum TSH)

	TSH 0.4-1.99 mIU/L (N=28)		TSH 2.0-4.0 mIU/L (N=67)	
	Median	25%-75%	Median	25%-75%
Age (years)	46.0	16.0-37.0	48.0^{ns}	37.0-60.0
TSH (mIU/L)	1.45	1.075-1.71	3.015**	2.48-3.48
T4 (nmol/L)	112.0	105.0-122.0	99.0 **	88.2-112.0
T3 (nmol/L)	2.10	1.85-2.21	1.78*	1.48-2.05
T4/TSH ratio	78.2	72.4-103.4	33.2**	26.0-40.3
TPO-Ab (IU/mL)	226.5	125,0-600.0	285.0^{ns}	185.0-430.0

*p<0.01; **p<0.001; ^{ns}nonsignificant

Euthyroid HT patients were older, with a significantly higher serum TSH than controls. Serum T4 and T3 were not different (Table 1). When data from euthyroid HT patients with serum TSH >2.0 mIU/L (3q and 4q TSH groups) were compared with those with serum TSH <2.0 (1q and 2 q TSH groups), significant differences emerged in TSH, T4 and T3 values (Table 2). The values of TSH in 3q and 4q groups were significantly higher and those of T4 and T3 lower than in 1q and 2q TSH groups. The T4/TSH ratio in 3q and 4q TSH groups was also significantly lower than in HT patients with 1q and 2q TSH. The values of TPO antibody titer were similar in both groups.

During the observation period, some euthyroid HT patients showed at least one supranormal (4.1-6.5 mIU/L) TSH value. The percentage of these patients increased in relation to their TSH value on the last follow up: none in 1q, 10% in 2q, 15% in 3q and 44% in 4q TSH group.

Discussion

The distribution of TSH in euthyroid HT patients was shifted toward higher values. Only three patients had low normal (1q) TSH and more than 70% showed 3q and 4q TSH. In fact, the distribution curve in euthyroid HT patients was similar to that in properly treated (TSH=0.4-4.0 mIU/L)) hypothyroid patients (unpublished data). Age could influence TSH values, especially in the upper end of the normal range; however, although HT patients in general were older than controls, there was no difference between those with lower and higher normal TSH.

Significant difference in TSH value was found not only between euthyroid HT patients and controls, but also between patients with lower (1q and 2q) and higher (3q and 4q) normal TSH. Higher TSH, lower T4 and T3 and low T4/TSH ratio reflected borderline thyroid function with diminished TSH suppressibility in the latter group. There was no difference in TPO between these two groups, and probably the duration of the disease is the clue for these changes. Unfortunately, patients are seen relatively late due to some nonspecific symptoms, or are detected accidentally, and the beginning of the disease is hidden in patient history.

These patients manage to maintain euthyroidism under strenuous TSH stimulation, but in many of them, thyroid functions actually balance between euthyroid and subclinically hypothyroid, with occasional mildly elevated TSH.

Many euthyroid HT patients have 4q TSH. This implies that the other way around is also plausible; subjects with TSH close to the upper normal limit are probably not healthy and have euthyroid HT. TSH upper reference limit may be skewed by the occult thyroid dysfunction[2] and determination of TPO is mandatory.

Whether euthyroid HT patients should be treated is controversial. The situation is complicated by the proposal of a narrower normal TSH range with the upper limit of 2.5 mIU/L[3], supported by some[4,5] and

opposed by others[6,7]. A meta-analysis provided no convincing evidence that the treatment of subclinical hypothyroidism is generally justified[8]. On the other hand, it has been reported recently that patients with subclinical hypothyroidism improved their quality of life following levothyroxine administration[9]. However, many subclinically hypothyroid patients are not treated with replacement therapy[6], let alone should be those with upper normal TSH. The goal of treatment of euthyroid HT patients should be different, aimed at slowing down the autoimmune destructive process. A short-term levothyroxine treatment has been proposed to postpone hypothyroidism[10-12], and levothyroxine decreased TPO antibodies in euthyroid HT patients[13] and lowered the chance for miscarriage and premature delivery in pregnant women with euthyroid HT[14]. Or euthyroid HT patients could be the best candidates for selenium administration trial[15] to diminish the autoimmune/inflammatory damages to thyrocytes *via* glutathione peroxidase. In addition, either or both compounds are found to improve hemostatic disturbances in euthyroid HT patients[16].

In any case, euthyroid HT patients with high normal TSH (especially 4q group) are identified as those with a major risk of developing hypothyroidism in the near future and even if not treated, they should be carefully observed.

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Sažetak

TIREOTROPIN I HORMONI ŠTITNJAČE U EUTIREOIDNOM HASHIMOTOVU TIREOIDITISU

D. Solter i *M. Solter*

Malo je poznato o vrijednostima tireoptropina (TSH) i hormona štitnjače u eutireoidnom Hashimotovu tireoiditisu (HT) te je cilj bio istražiti razinu TSH i hormona štitnjače u HT i njihov odnos prema funkciji štitnjače. Ispitano je 95 bolesnika s eutireoidnim HT s normalnim TSH i hormonima štitnjače na posljednjoj kontroli između 2009. i 2011. godine. Prethodno razdoblje promatranja variralo je od 1,5 do 4,8 (u prosjeku 2,8) godina, bolesnici nisu nikada liječeni levotiroksinom. Rezultati TSH i hormona štitnjače uspoređeni su s onima u 210 zdravih osoba i prikazani kao medijan (25%-75%). Prema vrijednosti TSH ispitanici su podijeljeni u kvartile: TSH 0,4-0,99 (1q), 1,0-1,99 (2q), 2,0-2,99 (3q) i 3,0-4,0 mIU/L (4q). Eutireoidni bolesnici s HT imali su viši TSH (2,53 [1,79-3,14] prema 1,95 [1,24-2,72], p<0,001). T4 i T3 se nisu razlikovali. Raspodjela TSH u HT izrazito je pomaknuta udesno. Ukupno je 71% bolesnika bilo u skupini 3q i 4q. Kada se usporede HT bolesnici s višim (3q i 4q) i nižim TSH (1q i 2q) nalaze se značajne razlike u TSH (3,01 [2,48-3,48] prema 1,45 [1,07-1,71] mIU/L), T4 (99,0 [88,2-112,0] prema 112,0 [105,0-122,0] nmol/L) i T3 (1,78 [1,48-2,05] prema 2,10 [1,85-2,21] nmol/L; p<0,01). Vrijednosti TPO bile su slične u obje skupine HT bolesnika. Opažen je postupni porast postotka eutireoidnih HT bolesnika s najmanje jednom povišenom vrijednošću TSH tijekom razdoblja promatranja: 0% u skupini 1q, 10% u 2q, 15% in 3q i 44% u skupini 4q. Eutireoidni bolesnici s HT održavaju eutireozu jedino uz povećanu stimulaciju pomoću TSH. Bolesnici s visoko normalnim TSH imaju najveći rizik nastupa hipotireoze u bliskoj budućnosti.

Ključne riječi: *Hashimotova bolest; Štitnjača, bolesti; TSH; Hormoni štitnjače*