

LONG-TERM OBSERVATION OF THYROID VOLUME CHANGES IN HASHIMOTO'S THYROIDITIS IN A SERIES OF WOMEN ON OR OFF LEVO-THYROXINE TREATMENT IN AN AREA OF MODERATE IODINE SUFFICIENCY

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Abstract

Context. Large variations in thyroid volume (TV) have been reported in Hashimoto's thyroiditis (HT). The need for long-term levo-thyroxine (L-T4) administration in order to control TV, as well as to normalise thyroid function, has not been well defined.

Subjects and Methods. Retrospective data on TV in 94 adult women with HT were analysed in an ambulatory setting in Liguria, an area of moderate iodine sufficiency. TV was evaluated by means of ultrasonography (US). Thyroid function, anthropometric data, smoking habits and pharmaceutical drugs were registered at each examination.

Results. At the baseline, an atrophic gland was noted in 16% of the women, and goitre in 13%. The women were evaluated 56 and 102 months after the baseline examination. At the time of each examination, 50%, 78% and 83% of women, respectively, were on L-T4 treatment. Baseline TV was not significantly different in women on/off L-T4 treatment. However, in those on L-T4, TV decreased significantly over the period of follow-up, while in those without L-T4 treatment, it did not change. By the end of the study, the percentage of L-T4-treated women with an atrophic gland had increased to 27%, and that of women with goitre had dropped to 6%; in untreated women, only minor changes were noted. There was a significant negative correlation between TV% change and baseline TSH levels in HT women on L-T4 treatment.

Conclusion. The majority of HT women living in an area of moderate iodine sufficiency have normal TV. Moreover, long-term L-T4 treatment can be used to control TV, as well as to maintain normal thyroid parameters.

Keywords: Hashimoto's thyroiditis, women, thyroid volume, levo-thyroxine treatment.

INTRODUCTION

Hashimoto's thyroiditis (HT) is an autoimmune disease; its incidence is estimated to be 0.8 per 1000 per year in men and 3.5 per 1000 per year in women (1). It is

now clear that HT is part of a spectrum of autoimmune diseases with variable histological, morphological and functional involvement of the gland (1). The prevalence of HT depends on age, gender and ethnicity (1). The pathology of the disease involves the formation of anti-thyroid antibodies that attack the thyroid tissue, causing progressive fibrosis (1). Apoptosis of thyroid follicular cells occurs in HT, probably as a result of its iodine-induced suppression of autophagy (2). HT is currently sub-classified as IgG4 thyroiditis and non-IgG4 thyroiditis (3). Younger patients and men have the highest prevalence of IgG4 thyroiditis, which is manifested on diagnosis as enlargement of the thyroid size and diffuse low sonographic echogenicity, and rapidly progresses to subclinical hypothyroidism (4). Painful HT is a rare variant of the disease and mostly affects women (5). In most HT patients, levo-thyroxine (L-T4) substitution is needed, owing to the impairment of thyroid function (1). In HT patients treated with L-T4, hypothyroidism rarely converts to hyperthyroidism (6). The diagnosis of HT is based on the presence of antibodies against thyroid peroxidase (TPOAb) and/or thyroglobulin (TgAb) and grey-scale ultrasonography (US) features (1); other, more sophisticated, imaging techniques do not seem to add anything to the diagnosis (7, 8).

Although thyroid volume (TV) is reported to be normal in about 50% of HT patients (7, 9), a greater dispersion of TV values is observed in HT patients than in controls (10-12). Indeed, TV is reduced (atrophic thyroiditis) in about 19-28% of subjects (7, 13) and increased (goitre) in 19-46% (7, 9, 12). Patients with smaller TV have more pronounced hypothyroidism (10, 12), whereas those with sub-clinical hypothyroidism (SCH) predominantly have goitre (11). During the course of HT disease, TV changes, and this may reflect changes in biologic function, stromal changes, lymphocytic infiltration, oedema, and vascularity (1, 10).

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For 30 years, it has been postulated that L-T4 can be used to reduce TV in HT patients. Indeed, in paediatric and adolescent HT patients, it has been observed that L-T4 treatment causes a reduction in TV (14-16). Moreover, in euthyroid (17, 18), hypothyroid (19) and SCH (19) adults with HT, short-term prophylactic L-T4 treatment has been shown to reduce both TV and markers of autoimmune thyroiditis. However, the available data are discordant. Padberg *et al.* (17) reported only a reduction in serological markers, but not in TV, in euthyroid HT patients after 1 year on L-T4. Conversely, in hypothyroid adults on L-T4 treatment for 2 years, Hegedus *et al.* (20) reported a reduction in large goitres in hypothyroid patients, but no changes in TPOAb levels. Furthermore, in a small group of euthyroid women with HT, Aksoy *et al.* (18) reported a reduction in TV and a concomitant decrease in TgAb after 2 years of L-T4 administration. More recently, Kawasaki *et al.* (9) observed that, in euthyroid HT subjects with large goitres, one year of L-T4 treatment did not change TV.

The recent literature contains few data on TV changes in HT patients, and, to our knowledge, no observational data covering a period as long as 9 years have been reported. The aim of our study was to observe changes in TV in a series of women with HT on or off L-T4 treatment. In an era in which the widespread use of suppressive L-T4 is not recommended in post-menopausal women (21), we believe that the effectiveness of chronic L-T4 administration on TV in HT women should be reassessed.

MATERIALS AND METHODS

Subjects

A total of 3552 outpatient medical files collected in the period 2008-2019 were retrospectively searched in order to anonymously pick out women with HT who had undergone long-term ultrasonography (US) follow-up. We based the diagnosis of HT on the documentation of TPOAb positivity and a heterogeneous hypoechoic pattern on US ultrasound examination. Exclusion criteria were: age <18 years; unavailable data on current pharmacological treatments; other chronic or serious diseases which tend to influence thyroid function tests; and pregnancy or lactation in the 12 months before examination. The study group comprised 94 women aged 49.8 ± 14.5 years (\pm SD; median 48.5 years, range 18-82 years) living in Savona (50%), Genoa (48%) and nearby districts (2%). All women were examined on inclusion and underwent 1 or 2 further examinations in the subsequent years (up to 10 years).

Methods

Body mass index (BMI) was calculated on the basis of the weight (kg) and height (m) reported in the medical files, according to the following formula: kg/m^2 . Body surface area (BSA: m^2) was calculated by means of the Du Bois and Du Bois formula. TV was calculated by means of US, as previously reported (22), by using the depth, width and length of each lobe, as reported in medical files. TV was obtained by combining the volumes of both lobes.

All US examinations were performed by the same experienced endocrinologist (MG); over the period considered, three different machines were used (MyLab 70-XV Esaote, Genoa, Italy; UF-850 XTD Fukuda Denshi, Tokyo, Japan; Logiq V2 General Electric, Milwaukee, WI, USA); these were equipped with linear probes working at 7.5 MHz. Intra-observer variability was 11.5%.

In our districts, normal TV in women is 8.0 mL (IQR 6.7–9.8 mL; range 3.2-19.8 mL) (23). Arbitrarily, thyroid atrophy and goitre were defined as TV <3rd (4.6 mL) and >97th percentile (14.2 mL), respectively (23).

Laboratory data

Free-T4 (f-T4) and TSH levels were sought in the medical files; the values recorded on the dates closest to that of TV evaluation were considered. In the districts where our population was living, the laboratories of the Public Health Service used the Cobas automated analytic platform (Roche Diagnostics, Mannheim, Germany). Normal ranges are 12.0 to 22.0 pmol/L for f-T4 and 0.3 to 4.2 mIU/L for TSH. The functional sensitivity of the TSH assay is 0.03 mIU/L, with intra- and inter-assay coefficients of variation of 3% and 7%, respectively. Several commercial methods were used for TPOAb evaluation during the study period, and judgements of negative TPOAb values were assigned according to the normal range reported by the manufacturers.

Statistical methods

Categorical variables were described as percentages, and continuous variables as mean, median and interquartile range (IQR) values. Continuous variables were compared by means of the two-tailed Kruskal-Wallis analysis of variance, Mann-Whitney test, and Wilcoxon test when applicable. For categorical variables, percentages were compared by means of the Fisher exact test. Relationships among variables were sought by applying the Spearman correlation coefficient (Sr). P values less than 0.05

were considered statistically significant. All statistical analyses were performed by means of GraphPad 8.4.0 software (San Diego, CA, USA). Data collection and subsequent analysis were performed in compliance with the Helsinki Declaration. As this evaluation was retrospective, no formal request was made to the Liguria Ethics Committee. All patients gave written consent for data collection.

RESULTS

Eighty-eight women were evaluated 56 ± 1 months (median 56 months; IQR 47-64 months) and 41 women 102 ± 3 months (100 months; 88-118 months) after the baseline examination. Six women missed the intermediate evaluation, but attended the final examination, and one woman was lost to the end-of-study examination. At the moment of data analysis, 52 women were still waiting for their 3rd scheduled examination. At the time of each examination (baseline, 56 months and 102 months), 50% (n=47), 78% (n=69) and 83% (n=34) of women, respectively, were on L-T4 treatment. Table 1 reports clinical data on all women at the baseline. For the purpose of comparison, the women were also subdivided into two groups: those on L-T4 (n=48) and those without L-T4 (n=19) treatment. Women who started L-T4 after the baseline examination were excluded from these two groups. None of the women who were on L-T4 at the

baseline, or who started L-T4 after this time-point, discontinued the drug during the follow-up period. The only significant difference between the two groups was in fT4 levels (P=0.01) (Table 1).

At the baseline, atrophic glands and goitres were noted in 16% and 13% of women, respectively. In the whole population, TV declined from 8.3 mL (5.6-11.1 mL) at the baseline to 7.3 mL (4.8-10.2 mL) at the intermediate examination and to 6.9 mL (5.2-10.2 mL) at the last examination (P=0.20). Baseline TV was not significantly different (P=0.19) in women on/off L-T4 treatment (Table 1). At the baseline, atrophic glands and goitres were recorded in 19% and 10%, respectively, of L-T4-treated women, and in 11% and 5% of those without L-T4 treatment.

In women on L-T4 for the entire study period, TV decreased from 7.1 mL (5.1-10.2 mL) at the baseline to 6.0 mL (4.4-9.6 mL) at the last examination (P=0.03), while in untreated women, it increased from 9.1 mL (6.2-12.3 mL) to 10.0 mL (6.6-12.2 mL) (P=0.99). TSH and f-T4 levels did not change from the baseline (Table 1) to the last examination in either L-T4-treated [TSH 1.97 mIU/L (0.92-3.50 mIU/L), P=0.37; f-T4 15.2 pmol/L (12.4-17.4 pmol/L), P=0.30] or L-T4-untreated women [TSH 2.39 mIU/L (1.93-4.68 mIU/L), P=0.11; f-T4 12.9 pg/mL (10.4-15.2 pmol/L), P=0.11].

By the end of the study, the percentage of L-T4-treated women with atrophic glands had increased to

Table 1. Some clinical data of patients at the baseline evaluation. Significance is reported between subjects with (on) L-T4 and without (off) L-T4 therapy for the entire period of TV evaluation. Significance values are: (a) P=0.10, (b) P=0.18, (c) P=0.19, (d) P=0.29, (e) P=0.01 on Mann-Whitney test; (f) P=0.36 on Fisher's test.

	All (n=94)	On L-T4 (n=48)	Off L-T4 (n=19)
Age (year); mean \pm SD	49.8 \pm 14.5	52.5 \pm 15.0	46.1 \pm 11.6 (a)
BMI (kg/m ²); median, IQR	23.4; 21.2-26.7	24.0; 22.3-27.9	23.5; 20.7-26.1 (b)
BSA (m ²); median, IQR	1.65; 1.57-1.72	1.67; 1.59-1.73	1.61; 1.53-1.72 (b)
Thyroid volume (mL), median, IQR	8.3; 5.6-11.1	7.1; 5.1-10.1	9.1; 6.2-12.3 (c)
Former/current smokers (%)	37 52%	15/40 (38%)	8/15 (53%) (f)
Non-smokers (%)	34 48%	25/40 (62%)	7/15 (47%)
TSH (mIU/L); median, IQR	3.23; 1.69-6.17	2.44; 1.42-4.02	1.61; 1.34-3.44 (d)
f-T4 (pmol/L); median, IQR	14.2; 11.7-16.2	15.2; 12.4-17.4	12.9; 10.4-15.2 (e)
L-T4 (μ g/kg bw/day); median, IQR	-	0.98; 0.88-1.43	n.e
Other ongoing drugs; %			
none	45%	42%	42%
hypotensive drugs	18%	23%	16%
psychotropic drugs	18%	17%	21%
anti-reabsorptive drugs/vitamin D/Ca	16%	21%	21%
hormonal contraceptive/HRT	12%	13%	16%
anti-secretory drugs	10%	8%	16%
statins	10%	4%	10%
steroids/NSAIDs	8%	10%	10%
HI-inhibitors	3%	6%	0%

NSAIDs =nonsteroidal anti-inflammatory drugs.

27%, while that of those with goitre had decreased to 6%; in the off-L-T4 group, minor changes were noted (atrophic gland 5%, goitre 5%). Figure 1 reports the percentage change from the baseline to the last examination in the two groups of women. There was a significant difference ($P=0.03$) in changes between the groups. Figure 2 reports the negative correlation between TV% change and baseline TSH levels in women on L-T4 treatment ($n=48$; $Sr -0.41$, $P=0.004$); no correlation between TSH and TV % change was noted in the 19 women without L-T4 treatment. No other correlation between TV % change and initial TV, age, BMI, BSA, smoking or f-T4 levels was noted in either group.

DISCUSSION

US is the imaging tool most commonly used to determine the volume and structure of the thyroid gland. It is non-invasive, relatively inexpensive and readily accessible. US evaluation is one of the examinations suggested in the diagnosis of HT (1, 7, 8).

Normative values of TV in Italy are lacking. The introduction of iodine supplementation in salt was regulated by Italian law in 2005 (24). Recently, we retrospectively searched for data on urinary iodine concentration (UIC) and TV in subjects living in Liguria in medical files recorded since 2010. Conte *et al.* (25) reported a median UIC of 113 $\mu\text{g/L}$ in 415 subjects living in Savona, Genoa and nearby districts. Several years since the introduction of iodine supplementation, about 50-60% of the Ligurian population now have an adequate iodine intake (25). In 382 selected women of

median age of 34 years living in the above-mentioned areas since 2008, and free from laboratory- and US-detected thyroid abnormalities, Giusti & Sidoti (23) reported a median TV of 8.0 mL. In this group of women, the 3rd and 97th percentiles of TV were set at 4.6 mL and 14.2 mL, respectively (23). While information is lacking as to whether a gland of below normal volume should be regarded as displaying hypoplasia, data from this study indicated goitre in <5% of subjects (23), as reported in several other similar evaluations (26, 27).

In the present study, median TV was 8.3 mL at the first examination, but a large variability in TV was noted, as already reported in HT (12). In our HT women, the cumulative frequency of goitre and thyroid atrophy was less than 30%. We were not able to diagnose women with IgG4 HT, a condition in which SCH and goitre are more frequent. In our opinion, however, given that our patients were middle-aged women and IgG4 thyroiditis has an overall low incidence in HT (3), it was not indispensable to know their IgG4 levels.

In a small group of women, younger than ours, with HT and SCH, Gonzalez-Aguilera *et al.* (6) reported a median TV of 7.4 mL, without significant changes after spontaneous variation of thyroid function. Kawasaki *et al.* (9) reported that TV was normal in 54% of subjects with HT, but found a slight, moderate or severe goitre in 39%, 5% and 2%, respectively, of the remaining subjects. On the other hand, in HT women living in an iodine-sufficient area, Höfling *et al.* (7) reported normal (10.7 mL) TV in 62% of subjects and similar numbers of cases of goitre and thyroid atrophy in the remaining subjects. In a group of 144 adult patients with newly diagnosed HT and with normal

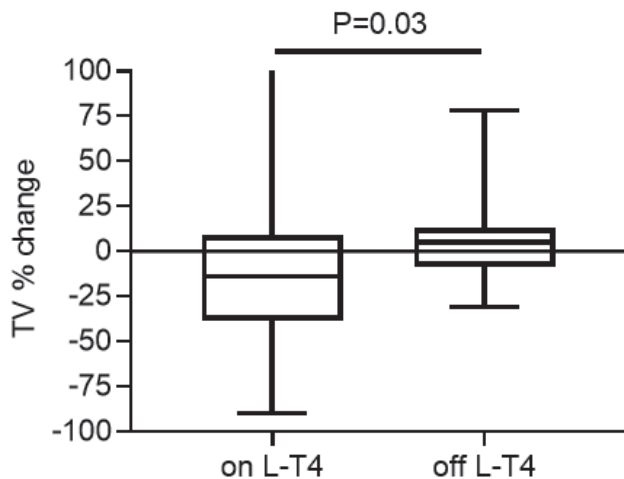


Figure 1. Median, IQR (box) and range (whiskers) of the percentage changes from baseline to last examination in women on or off LT4 treatment for the entire study period.

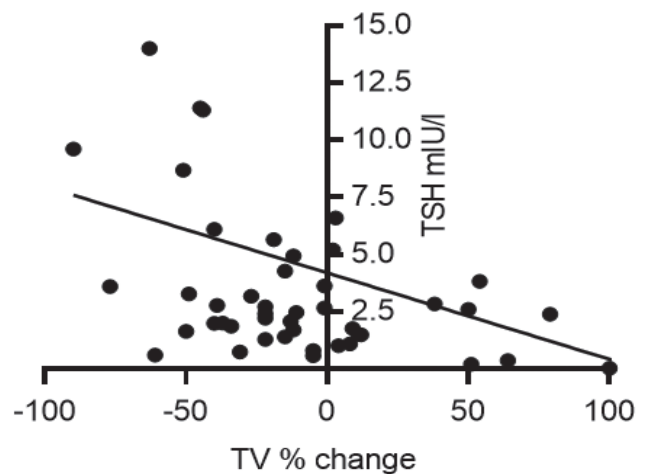


Figure 2. Correlation between baseline TSH levels and TV change observed from baseline to last examination in HT women on L-T4 treatment for the entire study period ($n=48$; $Sr -0.41$, $P=0.004$).

thyroid function or subclinical/overt hypothyroidism, Carle *et al.* (12) judged that goitre and thyroid atrophy constituted extremes within a normal range of TV.

In the long interval between one examination and the next, we observed an increasing trend in the need to begin L-T4 administration and a slight reduction in TV only in women on long-term L-T4 therapy. A reduced percentage of goitre and an increased percentage of thyroid atrophy seem to be favoured by L-T4 administration, as well as by the natural history of HT (10, 13). The median and IQR TSH levels that we recorded were always in the normal ranges and no deleterious events occurred, as has been observed during L-T4 therapy in a range of clinical hyperthyroxinaemia (21).

The physiological effects of TSH on thyroid cells are both early (increased iodine uptake, increased hormone synthesis and release) and late (cell proliferation). It is therefore not surprising that we found a reduction in TSH-related growth of the thyroid gland, which is in line with the negative correlation that we observed between TSH levels and TV changes. Indeed, a negative correlation between TSH and TV has already been reported by some authors in young (14) and adult (28) HT subjects. No other significant correlation was noted in our study of HT women. Smoking is reported not to be associated to an increased incidence of HT in an area of mild iodine deficiency (29). In accordance with that observation, we did not find any correlation between TV changes and smoking. In addition, like us, Kawasaki *et al.* (9) did not report correlation with BMI and age in HT. Finally, in our small cohort of women, BSA was unrelated to long-term TV changes.

The effectiveness of L-T4 treatment on TV in HT has been a matter of debate, and one problem is that some patients receive L-T4 replacement therapy before the evaluation of TV. This phenomenon was observed in our study, and this previous treatment could influence the US pattern, antibody levels, and subsequent TV changes.

Several years ago, in 90 HT subjects with a median age of 12 years at the beginning of L-T4 administration, Svensson *et al.* (15) reported a significantly larger reduction in TV after 2.8 years among patients with SCH and overt hypothyroidism than among euthyroid patients, irrespective of whether goitre was present or not at the baseline. In a randomized study involving subjects aged <18 years, Dörr *et al.* (16) reported a decline in mean TV after 30 months in the L-T4-treated group but not in the control group. However, only few subjects were evaluated and, at the

end of the study (36 months), mean TV was almost identical in both groups (16). In a small group of 21 adult HT subjects randomized to L-T4 or not, TV was found not to have changed after 12 months of therapy (17). In another group of 33 HT subjects, almost all adult women with normal thyroid function, who were randomised to L-T4 or observation for 15 months, a reduction in TV was noted only in the L-T4-treated group (18). These and our data suggest that L-T4 treatment is beneficial, a conviction that is also supported by the fact that the age-related progression of thyroid hypofunction is the most common consequence of HT.

Recently, Brčić *et al.* (30) conducted a genome-wide association study in HT in order to verify the hypothesis that TV in this condition is genetically determined. In 370 HT subjects, unselected for gender, some of whom were on L-T4 treatment, these authors reported that TV was lower in L-T4-treated subjects (mean 8.7 mL) than in L-T4-untreated subjects (10.6 mL). However, it was not clear from this study whether the lower TV was linked only to a greater expression of the genetic loci involved in apoptosis in the treated group than in the untreated group. Moreover, the study was not randomized, L-T4 was started because of progression of hypothyroidism, and the time from the beginning of L-T4 treatment to data analysis was not reported (30).

Our study has several limitations: a) it must be considered that the ellipsoid formula per se cannot provide an adequate mathematical description of TV; b) our cohort of subjects was small, which might have limited the statistical power of the analysis; c) as the study was performed at a single out-patient clinic with a specific population, the results may not be representative of the entire extra-regional area; d) neither UIC nor selenium levels were available; e) the COVID-19 pandemic prevented us from extending our follow-up data. The strengths of our study were the availability of a detailed clinical history comprising pharmacological anamnesis, and the absence of inter-observer variability.

In conclusion, our data indicated that the majority of women with HT living in an area of moderate iodine sufficiency had normal TV. Moreover, in these subjects, long-term L-T4 treatment can be undertaken in order to control TV, as well as to maintain normal thyroid function parameters.

Conflict of interest

The authors declare that they have no conflict of interest.

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Statement of Ethics

All procedures performed were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Owing to the retrospective nature of the study, no formal request was made to our regional ethics committee. All patients provided written informed consent for medical file data collection.

Author contributions

MG conceived the study, carried out US evaluations, conducted data collection and statistical analysis, and drafted the manuscript. MS participated in the conception of the study and data collection. The authors have read and approved the final manuscript.

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