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Research Article

Levothyroxine Effect on Thyroid Volume in Children with Autoimmune Hashimoto Thyroiditis (AHT) Presenting Subclinical (SH) or Overt (OH) Hypothyroidism

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Abstract

Purpose: The use of Levothyroxine (L-T4) to reduce thyroid size in pediatric patients with Autoimmune Hashimoto Thyroiditis (AHT) remains controversial. In this study we aimed to assess the thyroid volume and L-T4 needs in relation to TSH and FT4 at diagnosis of children with AHT and Subclinical (SH) or overt (OH) Hypothyroidism. Methods: Two hundred one children (155 girls) with AHT were divided according to TSH and FT4 levels at diagnosis of hypothyroidism [SH-FT4 >1.0 ng/dl: Group 1: TSH: 5-7.5 mIU/L, Group 2: TSH: >7.5 mIU/L, OH: Group 3: TSH>7.5 mIU/L and FT4 ≤1.0ng/dl]. All these children were treated with L-T4. Thyroid volume was defined as the sum of the volumes of both lobes (isthmus not included). Results: At diagnosis mean age was 9.6 years (SD, 2.6) and L-T4 dose and thyroid volume were significantly different ($p<0.001$) between SH (groups 1 and 2) as compared to OH (group 3). At 2.9 yrs of follow-up all patients were euthyroid and TSH and FT4 levels did not differ significantly between groups. L-T4 dose was significantly higher in OH as compared to group 1 ($p<0.001$) but not group 2 ($p=0.21$). Thyroid volume did not differ significantly among groups. Conclusion: At diagnosis, L-T4 needs and thyroid volume are significantly lower in SH patients as opposed to OH patients. At follow up, children with OH receive significantly higher LT-4 doses than those with SH and TSH < 7.5 mIU/L but similar with those of SH and TSH > 7.5 mU/l. All patients present similar thyroid volumes.

Keywords: Autoimmune Hashimoto Thyroiditis; Children; Thyroid volume; Levothyroxine Treatment

Abbreviations

AHT; Autoimmune Hashimoto Thyroiditis; SH; Subclinical Hypothyroidism; OH: Overt Hypothyroidism; L-T4: Levothyroxine; TSH: Thyrotropin Stimulating Hormone; T4: Thyroxine; T3: Triiodothyronine; Anti-Tg Ab: Thyroglobulin Autoantibodies; Anti -TPO Ab: Thyroid Peroxidase Autoantibodies; BMI: Body Mass Index

Introduction

Chronic autoimmune thyroiditis (Hashimoto Thyroiditis Or Chronic Lymphocytic Thyroiditis) (AHT) is the most common cause of thyroid dysfunction during childhood and adolescence, in the iodine sufficient population. It has been previously reported, that there has been a threefold increase in the prevalence of autoimmune thyroiditis, among Greek schoolchildren 7 years of age, following elimination of iodine deficiency [1]. AHT typically presents as a goiter during a routine clinical examination. Most of these children are asymptomatic euthyroid, however they may present with Subclinical Hypothyroidism (SH) or even symptoms and signs of Overt Hypothyroidism (OH). In adults with goiter due to AHT, a significant reduction of thyroid volume while on Levothyroxine (L-T4) Treatment, has been reported [2]. However, treatment with L-T4, in order to reduce thyroid size in children with AHT and goiter is still a matter of debate. Generally, management of children with goiter and subclinical hypothyroidism indicated by mildly elevated Thyrotropin Stimulating Hormone (TSH) and normal levels of Thyroxine (T4) And Triiodothyronine (T3), is still controversial. There are many prospective studies for the natural history of subclinical hypothyroidism in pediatric populations [3-10] and there are many concerns that if children with subclinical hypothyroidism are left untreated it may progress to overt hypothyroidism. Most experts treat patients with TSH levels higher than 10 mIU/L [11], independently of the T4 levels. On the other hand, in regards to patients with mild elevations (TSH 5-10 mIU/L), some experts elect to initiate L-T4 treatment while others monitor thyroid function test without intervention. Some studies have shown that TSH levels at the time of presentation are important in signaling the clinical course of the disease [12,13]. In our study we have looked retrospectively at the medical files of 201 children with AHT and recorded laboratory and echographic findings in those treated with L-T4 initiated when TSH levels were > 5 mIU/L, regardless of the T4 levels. There is a limited number of studies that investigate the effect of therapy on the clinical course of AHT in pediatric populations [7,14-17]. Additionally, when interpreting changes in thyroid volume in growing children, auxological parameters and chronological age need to be taken into account. Furthermore, although SH is quite common, there is restricted evidence regarding the age–appropriate dose recommendations for L-T4 supplementation of these patients [18,19]. In this retrospective analysis, we have investigated the influence of L-T4 treatment on thyroid size determined by ultrasonography, which is an objective

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method for estimation of thyroid volume in children with Hashimoto thyroiditis. In other words, in this study we aimed to bring in evidence first, sonographic changes and second, L-T4 needs in regard with initial TSH levels in patients with SH as opposed to OH.

Materials and Methods

The records of 201 children and adolescents (155 girls, 46 boys) younger than 16 years of age that were followed by the Pediatric Endocrinology Outpatient Clinic of Aglaia Kyriakou Children's Hospital in Athens, Greece, were evaluated retrospectively. The study protocol was approved by the institute's committee on human research, "P & A Kyriakou" Children's Hospital, Athens, Greece. Patients with AHT and treated with L-T4, were included in the analysis, according to the following inclusion criteria a) TSH levels at presentation above 5 mIU/L and b) positivity for at least one of either thyroglobulin autoantibodies (anti-Tg Ab) or thyroid peroxidase autoantibodies (anti–TPO Ab). Patients who had a history of a syndrome or chromosome abnormality or any chronic disease were excluded. Age and gender of the patients, family history of thyroid disease, birth weight and concomitant diseases were recorded. The thyroid sonograms were performed at baseline and at the end of the follow up period (mean 2.9 years). The patients had been treated with L-T4 in increasing dose until TSH levels have reached normal levels. For adjustment of L-T4 dosage children were examined 6 weeks after the start of therapy and every 3-6 months at the outpatient clinic. Age, height, Body Mass Index (BMI) standard deviation scores, pubertal stage and physical examination as well as FT4, TSH serum levels, anti TPO and anti-TG antibody levels were also monitored" Individuals were classified as: Group1: TSH 5-7.5 mIU/L, Group 2: TSH >7.5 mIU/L, (Group 1 and Group 2 were recorded as SH and had FT4 >1 ng/dl) and Group 3: TSH >7.5 mIU/L and FT4 <1 ng/dl (OH).

Thyroid Ultrasound

Thyroid ultrasound examinations were performed by an experienced radiologist of the hospital using high frequency US (Philips HDI 3000; ATL, Bothell, Wash USA equipped with a 5-to 10-MHz linear –array probe). Examinations were performed in a supine position with the neck hyperextended.

Thyroid volume was calculated according to the modified formula of the rotation ellipsoid, Vol (ml)= 0.479xdxwxl. The thyroid volume was defined as the sum of the volumes of both lobes (isthmus not included). The diagnosis of AHT was carried out by subjective measurements of thyroid hypogenecity or nodules.

We used the 97th percentile value as the upper thyroid volume limit according to the normal volume ranges with age described by Kaloumenou et al. in 2007 [20], who carried out a study in thyroid volume in schoolchildren living in an iodine-replete area, Athens, Greece.

Laboratory Methods

Thyroid function tests were determined in the fasting status (8:00-8:30am) and performed in the same laboratory for each subject. FT4 and TSH were measured by Electrochemiluminessence (ECLIA) immunoassay (TSH normal values: 0.5-5IU/lt, FT4 normal values: 0.9-1.9ng/dl). Auxological assessment was based on height measurement and BMI calculation. Standing height was measured with a Harpenden stadiometer. BMI was calculated as weight divided by squared height (kg/m2). Height z-score and BMI z- score were calculated according to the standards of the Center For Disease Control (CDC) growth charts

Statistics

Data are presented as mean (+/-) SD. Statistical analyses were performed using the SPSS 25 for Windows. One-Way Analysis of Variance (ANOVA), ($p<0.05$) (Tukey post-hoc analysis) was used to compare means among the three (3) groups or paired T-test to compare means in the same group at the beginning vs. the follow up period.

Results

The study included 201 subjects (155 girls, 46 boys). The mean age of the study population was 9.6 years (range 2.7-15.5). More specifically, the mean age at baseline was 10.4 years (3-15.5), 8.9 years (3-14.9) and 9.6 years (2.7-14) for group 1, group 2 and group 3 respectively. The mean duration of L-T4 treatment was 2.9 (range 0.3 -7.8) years from baseline to final examination. Main characteristics are shown in table 1.

At diagnosis, TSH, FT4 levels, L-T4 dose and thyroid volume were significantly different ($p < 0.001$) between SH (Groups 1 and 2) as compared to OH (Group 3). Age, height z-score, BMI z-score were similar between the groups at the initiation of therapy and at follow up. At follow up all patients were euthyroid and TSH, FT4 and thyroid volume didn't differ significantly among groups.

Interestingly, during the treatment period there was a significant reduction in thyroid volume in group 3 (overt hypothyroidism) at

Table 1: Clinical, laboratory characteristics and L-T4 dose of AHT children population at diagnosis and at end of follow-up.

	Group 1 9(n=70)	Group2 (n=72)	Group 3 (n=59)	*p
AT DIAGNOSIS				
Age (yrs)	10.4 (2.6)	8.9 (2.6)	9.6 (2.4)	NS
Height z-score	0.55 (0.9)	0.52 (1.0)	0.43 (0.9)	NS
BMI z-score	0.87 (0.9)	0.93 (0.9)	0.92 (1.1)	NS
TSH (mIU/L)	6.1 (0.7)	10.9 (5.6)	47.9 (74.2)	*
FT4 (ng/dl)	1.2 (0.2)	1.3 (0.51)	0.85 (0.1)	*
L-T4 (μg/Kg/day)	1.1 (0.39)	1.3 (0.51)	1.5 (0.6)	*
Thyroid volume (ml)	8.0 (4.3) (<P97)#	6.3 (3.7) (<P97)#	10.1 (6.3) (>P97)#	*
AT FOLLOW UP (yrs)	2.8 (1.4)	3.16 (1.6)	2.98 (1.6)	
Age (yrs)	13.2 (2.4)	12.1 (2.7)	12.6 (2.4)	NS
Height z-score	0.56 (1.0)	0.59 (0.9)	0.43 (0.8)	NS
BMI z-score	0.82 (0.8)	0.76 (0.9)	0.92 (0.9)	NS
TSH (mIU/L)	2.2 (1.2)	2.6 (1.2)	2.2 (1.1)	NS
7FT4 (ng/dl)	1.4 (0.2)	1.4 (0.4)	1.3 (0.2)	NS
L-T4 (μg/Kg/day)	1.1 (0.3)	1.4 (0.4)	1.6 (0.7)	*
Thyroid volume (ml)	7.7 (4.1) (<P97)#	6.7 (3.9) (<P97)#	8.4 (3.5) (<P97)#	NS

Data are shown as means (SD).

* $p<0.001$

#The 97th Percentiles (P97) for thyroid volume measured by ultrasound according to age in apparently healthy school children living in the Athens area, Greece [20]

follow up, as compared to the beginning of treatment (p=0.022). In group 1 a reduction of thyroid volume during treatment was observed but with no statistical significance (p=0.35).

Required Levothyroxine Dose

In the beginning of the study the L-T4 dose which was required in order to maintain TSH within the normal range was 1.1 μg/kg/day for group 1, 1.3 μg/kg/day for group 2 and 1.5 μg/kg/day for group 3. At the end of the follow up when TSH was within the desired range, the mean required T4 dose was 1.1 μg/kg/ day for group 1, 1.4 μg/kg/day for group 2 and 1.6 μg/kg/day for group 3. Analyzing the different requirements for L-T4 by the disease severity (on the basis of the initial TSH) at 2.9 years of treatment, children with OH received significantly higher L-T4 doses, than those with SH and TSH <7.5 mIU/L (p<0.001) but similar with those of SH and TSH>7.5 mIU/L (p=0.21).

Discussion

In this retrospective analysis we investigated the L-T4 treatment effect on thyroid volume as well as the L-T4 needs in children and adolescents with AHT presenting with either SH or OH.

The study is of special interest due to the high prevalence of AHT (0.3-1.5 cases per 1000 persons) [21] as well as the high variability of the clinical course of the disease along with the uncertainties regarding L-T4 treatment effect on thyroid volume of hypoclinic as opposed to OH children with AHT [22]. In our study, at diagnosis TSH, FT4 levels and thyroid volume were significantly different between SH (groups 1 and 2) as compared to OH (group 3). Following 2.9 years of treatment at average, the children with OH had significantly smaller thyroid volume as compared with the one at the beginning of the treatment while the children with SH (group 1 and 2) showed non-significantly decreased thyroid volume between the start and the end of follow up, suggesting that L-T4 reduces thyroid size only in children with AHT and OH. During follow up TSH levels were within normal range, suggesting that TSH decrease may have a causal effect on the decrease of thyroid volume. In the present study all patients remained autoantibody positive throughout the investigation period. Our findings are generally in agreement with several other studies [23]. Svensson et al. [23], in their retrospective study, analyzed data of 90 children with (AHT) who were treated with L-T4 for 2.8 years. Using thyroid ultrasonography, they observed that thyroxine reduces thyroid volume in children and adolescents treated with L-T4 with the reduction in thyroid volume being significantly larger among the subclinically and overtly hypothyroid patients when compared with euthyroid patients. The retrospective study by Rother et al. [24] reported the effectiveness of thyroxine treatment in 65 goitrous children on reducing thyroid volume suffering from Hashimoto thyroiditis during a treatment period of 3.5 (+/-) 2.5 yrs. They concluded that a clear decrease of thyroid size after L-T4 treatment was obvious only among children with overt hypothyroidism whereas thyroid size remained unchanged among patients with normal plasma thyroxine levels prior to therapy regardless of TSH levels. A limitation of the study was that they used palpation for estimating thyroid size while we used thyroid ultrasound which is the preferred technique for estimating thyroid size.

Jaruratanasirikul et al. [9] followed up 28 euthyroid, 8 children who had normal FT4 and elevated TSH consistent with compensated hypothyroidism and 10 patients with OH for 5.9 (+/-) 0.3 years and found that thyroid volume was unchanged without L-T4 in the majority of these patients and that no spontaneous decrease in thyroid size took place. In the same study, the effect of L-T4 treatment among 14 patients with OH (4 patients with compensated hypothyroidism developed OH during the study) 9 patients had a significant reduction effect in thyroid size. However, Scarpa et al. [25] investigated prospectively 50 euthyroid non-goitrous children and adolescents with AHT for 2 years. Half of the patients received thyroxine treatment while the other half did not. At follow up the treatment group had lower thyroid volume compared to controls. Using thyroid ultrasonography they suggested that by treating euthyroid children with AHT the development of goiter may be prevented and they concluded that thyroxine treatment is beneficial for euthyroid children with AHT even in the absence of goiter. Dorr et al. [26] in a multicenter, randomized, controlled trial investigated 59 euthyroid children with AHT and 25 patients received L-T4 at a mean dose 1.6 μg/kg daily and 34 were not treated. Patients who developed subclinical hypothyroidism during the study were treated with L-T4. Thyroid gland volume in the treated group significantly decreased from the beginning of the study until the end of the follow up, but the effect was limited to a definite time period.

The mechanism of reducing thyromegaly after treatment with L-T4 is still uncertain. The cause may be the reduced TSH levels after therapy which lead to a decrease the B-lymphocyte infiltration and atrophy of hyperplastic thyroid follicular cells [27].

On the other hand changes in thyroid size have been studied in subclinical AHT hypothyroid patients without L-T4 treatment. Maenpa et al. [17] followed 46 children and adolescents with AHT for an average of 6.5 years. At the end of the observation period they reported increased, decreased and unchanged thyroid volume in subclinically hypothyroid and euthyroid patients, suggesting a variable course regarding the thyroid size in children with AHT.

The natural course of AHT in children is highly variable and several studies have been performed to investigate it. OH is a condition which must clearly be treated with L-T4. SH is defined biochemically as a serum TSH concentration above the upper limit of the reference range and a serum FT4 concentration within is reference range [28]. However the use of L-T4 to manage SH is controversial and it is important to know how this condition will probably evolve and when it should be treated [29].

Gopalakrishnan et al [6] followed up 98 children and adolescents (aged 8-18 years) with a diagnosis of AHT and diffuse goiter for 2 years. At the beginning of the study 24 subjects were euthyroid, 32 had subclinical hypothyroidism and 42 subjects had hypothyroidism. Hypothyroidism developed in 3 of 24 children with euthyroidism and in 4 of 32 patients with subclinical hypothyroidism.

Lazar et al. [5] in their retrospective multicenter study analyzed a database of 121,052 children and adolescents who had a TSH determination in 2002 and follow up in 2007, while patients with overt hypothyroidism or hyperthyroidism were excluded. At the beginning of the study 2.9% patients had elevated TSH. During follow up of the patients with TSH >5.5-10 mIU/L 73.6% normalized

TSH, 25% maintained TSH between 5.5 - 10 mIU/L and 2% had TSH above 10 mIU/L with FT4 within the normal range and only 0.03% of the patients developed overt hypothyroidism. Of the patients with TSH >10 mIU/L, 40% reduced their TSH within the normal range, 33% reduced their TSH to a value between 5.5 and 10 mIU/L, 25% maintained their TSH >10mIU/L and only 0.2% developed overt hypothyroidism. Patients with initial levels of TSH greater than 7.5 mIU/L, particularly girls were at a greater risk of sustained abnormal TSH levels.

We also analyzed the different L-T4 requirements between children with AHT and SH or OH hypothyroidism. We found that children with OH receive significantly higher L-T4 doses than those with SH and TSH <7.5 mIU/L but similar with those of SH and TSH>7.5 miu/L. Patients with SH and TSH: 5-7.5 mIU/L were initially treated with a mean L-T4 dose of 1.2 μg/kg/day, patients with SH and TSH>7.5mIU/L with L-T4 dose of 1.3 μg/kg/day and patients with OH with L-T4 dose of 1.5 μg/kg/ day. During the follow up visit children and adolescents with SH and TSH: 5-7.5 mIU/L received 1.1 μg/kg/day, patients with TSH >7.5miu/L received 1.4 μg/kg/day while children with OH received 1.6μg/kg/day. This corresponds to the recommended dose of Victoria Ellerbroek et al. [30] where patients with AHT and mean elevated TSH in the beginning of the study, required at follow up a dose of L-T4 of 1.5±0.5 μg/kg/day.

De Vries et al. [31] in a retrospective chart review, found out that a mean L-T4 dose of 1.5 μg/kg per day was necessary to normalize the serum TSH concentration in 105 children with AHT and goiter or subclinical hypothyroidism or overt hypothyroidism which was similar with our study. There were no significant differences in dose during follow up by thyroid status or reason for referral.

Finally, in our study the mean L-T4 dose requirements for AHT patients were significantly lower than the recommended dose of Brown et al. [15] who advised the following L-T4 doses for school age children with AHT: 3-4μg/kg daily for 6-10 years old and 2-3μg/kg daily for older than 11 years. Similar recommended doses were given by Latrofa et al. [32] for L-T4 4 μg/kg daily for 6-12 years old children , 3μg/kg daily for adolescents with AHT. In conclusion, L-T4 treatment is effective in reducing thyroid volume in pediatric patients with AHT in cases with overt hypothyroidism as compared to those with subclinical hypothyroidism. However, the decrease in thyroid volume found in our study could be an effect of the natural course of the disease as well as the result of the L-T4 treatment. The mechanism of reducing thyroid volume by L-T4 treatment is still unclear [21]. According to one theory, it may be due to reduced TSH levels, which decrease antigen expression and results in decreased lymphocyte infiltration and atrophy of hyperplastic thyroid follicular cells [27]. Whether L-T4 therapy can prevent development of goiter in SH is a subject for future investigation. Studies with larger sample sizes and a double-blinded design are needed to confirm these results.

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