

## Levothyroxine use and thyroid gland volumes in children with autoimmune thyroiditis: a systematic review and meta-analysis

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### Abstract

**Background** Autoimmune thyroiditis may manifest as overt hypothyroidism, subclinical hypothyroidism, euthyroidism, or hyperthyroidism in children. Although there is no consensus on treating euthyroidism and autoimmune thyroiditis in children, some studies have demonstrated the efficacy of levothyroxine in reducing thyroid volume, improving thyroid function, and stabilizing the immunological process.

**Objective** To determine the effect of levothyroxine on thyroid gland volume changes, thyroid function, and thyroid antibodies in euthyroid children with autoimmune thyroiditis.

**Methods** We performed a literature search of electronic databases (the Cochrane Library, MEDLINE, EBSCO, ProQuest, clinicaltrials.gov, and other sources, as well as a non-electronic search (searching journals and conference proceedings by hand) to identify studies of euthyroid children with autoimmune thyroiditis published by August 2018. Only English-language articles were included in the search (electronic and non-electronic). Randomized controlled trials that compared levothyroxine with a control (placebo or no treatment) in euthyroid children with autoimmune thyroiditis were selected. The outcome measures were thyroid volume changes, thyroid function, and thyroid antibody levels in euthyroid children with autoimmune thyroiditis. Two authors independently extracted the data, assessed the risk of bias, and analyzed the pooled data from the included studies using a random effects model. The same authors performed a sensitivity analysis.

**Results** We identified 57 studies. Of these, three studies, involving 97 subjects (51 subjects in an intervention group and 46 subjects in the control group) were selected for inclusion in a systematic review/meta-analysis. The meta-analysis revealed a significant difference in mean thyroid volume changes between the two groups (-1.10 SDs; 95%CI -1.56 to -0.64;  $I^2=6\%$ ;  $P<0.0001$ ). The mean difference in the thyroid-stimulating hormone (TSH) change of the two groups was -1.82 mU/L (95%CI -3.52 to -0.11;  $I^2=87\%$ ;  $P=0.04$ ). The standard-

ized mean difference in free thyroxine (fT4) change of the two groups was 0.82 pmol/L (95%CI -1.14 to 2.78;  $I^2=89\%$ ;  $P=0.41$ ).

**Conclusion** In euthyroid children with autoimmune thyroiditis, levothyroxine treatment reduces the thyroid volume better. The TSH level change in the intervention group is better than those in the control group. Levothyroxine treatment did not significantly improve free T4. [Paediatr Indones. 2019;59:202-10; doi: <http://dx.doi.org/10.14238/pi59.4.2019.202-10>].

**Keywords:** autoimmune thyroiditis; euthyroid; levothyroxine; thyroid volume

Autoimmune thyroiditis is a thyroid disorder caused by an autoimmune process. The disease commonly occurs in adolescents, and it is more common in girls than boys

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(ratio: 2:1).<sup>1,2</sup> The incidence of autoimmune thyroiditis is increasing with the annual incidence worldwide is 0.3-1.5 cases per 1000 persons. Multifactorial causes, such as immunological mechanisms, genetics, and the environment are involved in autoimmune thyroiditis.<sup>3,4</sup>

Thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) are the main antibodies produced in autoimmune thyroiditis.<sup>3</sup> From the clinical history, TgAb are released during the early immune response, but TPOAb are released later.<sup>5</sup> After thyroid antibodies arise, the thyroid glands, maybe affected anatomically and histologically, as a goitrous form or an atrophic form.<sup>6</sup> Autoimmune thyroiditis clinically manifests as euthyroidism (52.1% of cases), overt hypothyroidism (22.2% of cases), subclinical hypothyroidism (19.2% of cases), and occasionally as hyperthyroidism (6.5% of cases).<sup>7,8</sup>

Thyroid function deteriorates along with the progressive increment in antibody levels, especially TPOAb as well as thyroid stimulating hormone (TSH), and enlargement of thyroid gland volume.<sup>2</sup> The aforementioned parameters serve as prognostic markers of the development of hypothyroidism.<sup>2</sup> In autoimmune thyroiditis, ultrasound can be used to measure thyroid volume enlargement and detect lymphocyte infiltration based on echogenicity.<sup>5</sup> An enlarged thyroid gland can persist for a long period in autoimmune thyroiditis. The enlarged thyroid gland commonly increases gradually, but in some cases, it can increase rapidly.<sup>9</sup>

The use of levothyroxine as a treatment for autoimmune thyroiditis in children with hypothyroidism is well established, as is treatment for subclinical hypothyroidism.<sup>2,10,11</sup> However, there is no consensus on the treatment of euthyroid children.<sup>2,5</sup> Some studies reported that levothyroxine treatment in euthyroid individuals with autoimmune thyroiditis reduced thyroid volume changes, as well as TSH and thyroid antibody levels in children with or without goiters.<sup>2,12-19</sup>

## Methods

A systematic review of the literature and a meta-analysis were conducted to determine the effect of levothyroxine treatment on thyroid volume

changes, thyroid function, and thyroid antibodies in euthyroid children with autoimmune thyroiditis. The inclusion criteria were published and unpublished studies designed as randomized control trials. Children aged 0-18 years with positive thyroid antibodies (antithyroid peroxidase and antibody antithyroglobulin) and normal thyroid function (euthyroid), with or without goiters were included in the study. Patients with other concurrent diseases who met the above inclusion criteria were included. The control (comparison) groups consisted of euthyroid children with autoimmune thyroiditis who received a placebo or no treatment.

The intervention consisted of levothyroxine administration for at least 24 months in euthyroid children with autoimmune thyroiditis. No restrictions were placed on the levothyroxine dose in this study. The outcomes assessed were changes of thyroid volume and changes in the levels of TSH (mU/L), free thyroxine (pmol/L), thyroid peroxidase antibody (TPOAb, U/mL), and thyroglobulin antibody (TgAb, U/mL).

A systematic literature search was conducted in August 2018 to identify studies that met the inclusion criteria. We retrieved only English-language publications and placed no limitation on the year of publication before the time of searching. The following databases were searched: MEDLINE (PubMed), the Cochrane Library, EBSCO, ProQuest, and registered clinical trials (clinicaltrials.gov). In cases where more data from the study of interest was required, an electronic mail was sent to the authors. The potential studies were searched from the citations of clinical trial reports, reviews, meta-analyses, guidelines, and health technology assessments. A non-electronic search (by hand) of abstracts from the *American Thyroid Association and European Thyroid Association* conferences was also performed. The *World Health Organization's* international clinical trial registry platform (<http://www.who.int/ictrp/en/>) and clinicaltrials.gov were also searched to identify ongoing clinical trials.

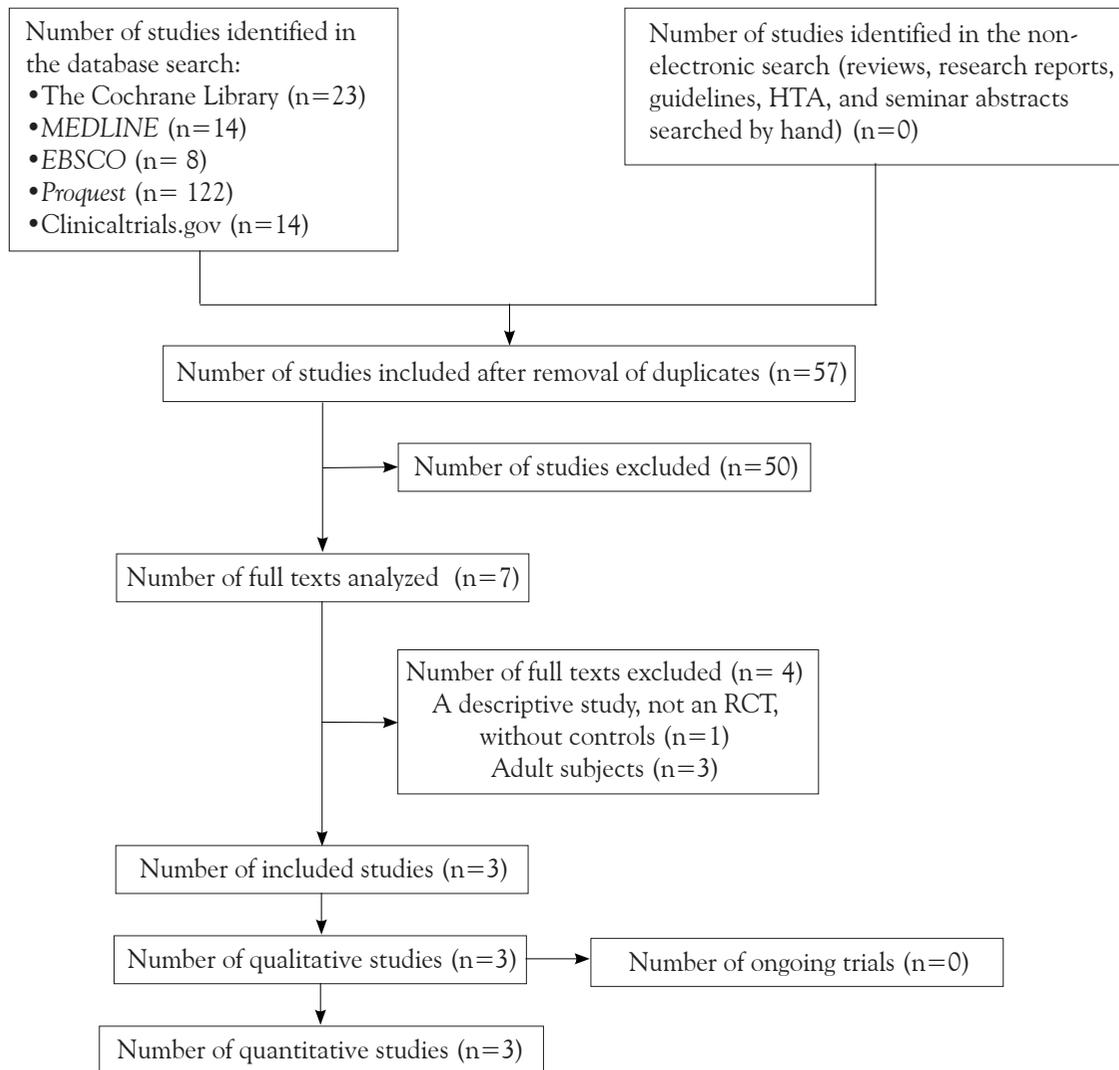
The keywords used were in accordance with medical subject heading (MeSH) terms. Combinations of the following keywords were used: "thyroiditis, autoimmune" "Hashimoto disease," "thyroxine," "euthyroid goiter," (supplementary concept), "euthyroid," "thyroid volume," and "thyroid gland."

Authors independently assessed titles and abstracts to identify potentially relevant articles, taking into account the restriction criteria of this study. The full texts of research articles considered potentially relevant to this systematic review were then appraised to assess their relevance. Any disagreement between the two researchers was resolved by discussion until a consensus was reached. A modified version of PRISMA (preferred reporting items for systematic reviews and meta-analyses) was used for the study selection.<sup>20</sup> A flow chart of the study selection process is presented in **Figure 1**.

The following data were extracted: type of study, study subjects, intervention, and outcomes.

Authors also independently assessed the risk of bias in each study based on the Cochrane Collaboration's tool for assessing the risk of bias.<sup>21</sup> The risk of bias consisted of assessment of randomization, allocation concealment, blinding, completeness of the outcome assessment, selective reporting, and other sources of bias.<sup>21</sup> Any disagreement between the two researchers was discussed until a consensus was reached.

The primary outcome in this study was the mean difference in thyroid volume changes, with a 95% confidence interval (CI). The data are presented as standard deviations (SDs). The secondary outcomes were changes in thyroid function and thyroid antibody



**Figure 1.** The study flow diagram

levels. Any missing data in the studies were reviewed, and the authors of the studies were contacted. The incidence of drop-outs, lost to follow-up, and withdrawal were reviewed. The missing data were appraised after receipt.

A pooled effect estimation was not obtained for any heterogeneity related to clinical substances, methodology, or statistics. The eyeball test was used to assess heterogeneity in a forest plot, and the Chi<sup>2</sup> test with  $\alpha=0.1$  was used to assess significance. The inter-study variation and degree of inconsistency ( $I^2$ ) in this review were assessed. The degree of inconsistency was categorized in accordance to the Cochrane Systematic Review guidance.<sup>22</sup> A random-effects model was applied if the synthesized studies were heterogeneous, and a fixed-effects model was applied in cases of a low degree of heterogeneity. Due to limited data in the included studies, we did not conduct subgroup analyses.

## Results

Fifty-seven studies were identified by the search methods. Of these, 50 studies were excluded based

on screening of the abstracts. Following full-text screening of the seven studies, four studies were excluded because they did not meet the inclusion criteria (adult subjects,  $n=3$ ; not a clinical trial,  $n=1$ ). The final result included three studies that could be analyzed quantitatively (Figure 1). The characteristics of the studies included in this systematic review are shown in Table 1a and Table 1b.

The quality of the research methods in this systematic review is illustrated in Figure 2. There was a low risk of selection bias, detection bias, and reporting bias. All the studies had a randomized control design. The mean difference (SD) in thyroid volume changes was calculated and plotted according to age and sex. However, there was a high risk of performance bias as none of the studies were blinded and none of the controls in the included studies received any treatment (observation only).

The primary outcome of this systematic review was the mean difference (SD) in the thyroid volume change. There was a significant difference in thyroid volume changes in the quantitative analysis (-1.10 SD; 95%CI -1.56 to -0.64;  $P<0.00001$ ). The meta-analysis indicated that the inconsistency was likely unimportant ( $I^2=6\%$ ;  $P=0.35$ ) (Figure 3). The

**Table 1a.** The basic characteristics of the studies

Study	Study design (n)	Intervention and control (n)	Intervention duration and dose
Karges <i>et al.</i> (2007) <sup>23</sup>	Randomized, open, controlled clinical trial (30)	Levothyroxine (16) vs. no treatment (14)	24 months + 6 months observation; 1.3 µg/kg/day
Dörr <i>et al.</i> (2015) <sup>24</sup>	Multicenter, randomized, controlled clinical trial (20)	Levothyroxine (10) vs. no treatment (10)	36 months; 1.6 ± 0.8 µg/kg/day
Scarpa <i>et al.</i> (2010) <sup>25</sup>	Randomized, controlled clinical trial (47)	Levothyroxine (25) vs. no treatment (22)	24 months; 1.44 ± 0.5 µg/kg/day

**Table 1b.** The basic characteristic of the studies

Study	Study population	Study period	Country	Setting	Mean age in the intervention vs. control groups (SD), years
Karges <i>et al.</i> (2007) <sup>23</sup>	Children with type 1 diabetes mellitus and euthyroid autoimmune thyroiditis	1 September 2002 to 30 December 2003	Germany	Outpatient tertiary care center	12.7 (2.0) vs. 13.9 (2.1)
Dörr <i>et al.</i> (2015) <sup>24</sup>	Euthyroid children with (goitrous and non-goitrous) autoimmune thyroiditis	January 2002 to December 2009	Germany	Six tertiary care centers	10.5 (2.50) vs. 13.4 (1.58)
Scarpa <i>et al.</i> (2010) <sup>25</sup>	Euthyroid children with non-goitrous autoimmune thyroiditis	January 2001 to October 2005	Greece	Outpatient of pediatric endocrinology clinic in children hospital	12.1 (11.1-13.4) vs. 12.2 (11.1-13.0)*

\*standard deviation data was not mentioned. Authors used range data.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participant and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Dorr, 2015	+	+	-	+	-	+	+
Karges, 2007	+	?	-	+	+	+	+
Scarpa, 2010	+	?	-	+	-	+	+

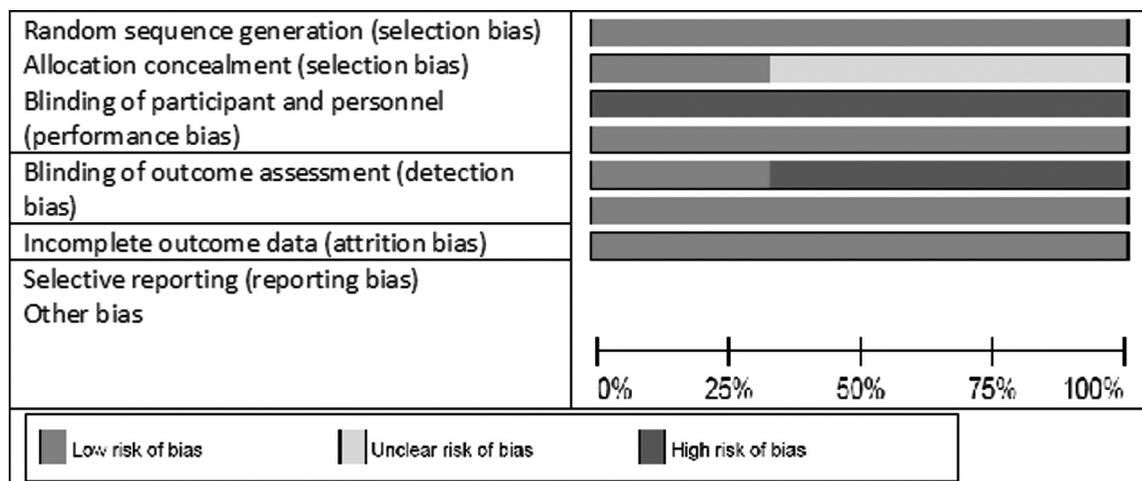


Figure 2. Assessment summary of the risk of bias in the three studies

populations in the studies by Karges *et al.*<sup>23</sup> and Dörr *et al.*<sup>24</sup> included subjects with goiters. In the subgroup analysis of the Karges *et al.*,<sup>23</sup> levothyroxine reduced thyroid volume in the treatment group as compared with that in the controls with goiters (-0.91 SD vs. +1.33 SD, P=0.0266). In subjects without goiters, the thyroid volume increased in both groups (intervention vs. control, 0.79 vs. 0.83, respectively; but statistically not significant P=0.7922).<sup>23</sup>

The pattern of thyroid volume changes observed differed between groups (Figure 3). Dörr *et al.* reported that although thyroid volume changes between the two groups were significantly different during 12-30 months of the study, the mean thyroid volume at the end of the study (36 months) was almost identical in both groups.<sup>24</sup> This observation was due to a tendency toward thyroid volume reductions in the follow-up period (30-36 months)

Study	Experimental			Control			Weight	Mean difference, fixed (95%CI), SDs	Mean difference, fixed (95%CI) (SDs)*
	Mean, SDs	SD, SDs	Total	Mean, SDs	SD, SDs	Total			
Dorr, 2015	-0.89	2.66	10	-0.98	1.63	10	5.7%	0.09 (-1.84, 2.02)	
Karges, 2007	-0.60	2.20	16	1.11	1.90	14	9.8%	-1.71 (-3.18, -0.24)	
Scarpa, 2010	-0.50	0.65	25	0.62	1.03	22	84.5%	-1.11 (-1.61, -0.61)	
Total (95%CI)			51			46	100.0%	-1.10 (-1.56, -0.64)	
Heterogeneity: Chi <sup>2</sup> =2.12, df=2, I <sup>2</sup> =6% (P=0.35)									
Test for overall effect: Z=4.70 (P<0.00001)									

SDs=the thyroid volume; SDs=(measured volume - mean predicted volume for age and sex)/SD; \*fixed=fixed effect model

**Figure 3.** The effect of levothyroxine on thyroid volume changes (SD) in euthyroid children with autoimmune thyroiditis.

in the control group. Karges *et al.*<sup>23</sup> noted that the thyroid volumes in subjects with goiters decreased in the intervention group and increased in the control group. But in subjects without goiters, the thyroid volumes increased in both groups. Furthermore, Scarpa *et al.*<sup>25</sup> reported that the thyroid volumes were similar in both groups at the 1-year follow-up, but significantly different at the 2-year follow-up. The thyroid volume declined in the intervention group during the 2-year follow-up period, but increased in the control group.<sup>23-25</sup>

The secondary outcomes of this study are described in **Figures 4** and **Figure 5**. The mean difference in TSH levels between the two groups was -1.82 mU/L (95%CI -3.52 to -0.11; I<sup>2</sup>=87%; P=0.004). There was a statistically significant difference of TSH changes between two groups. The standardized mean difference in free T4 levels between the two groups was an increase of 0.82 (95%CI -1.14 to 2.78; I<sup>2</sup>=89%; P=0.41). The mean differences in TPOAb and TgAb levels between the two groups were: 193.53 U/ml (95%CI -201.31 to

Study	Experimental			Control			Weight	Mean difference, random (95%CI), mU/L	Mean difference, fixed (95%CI), mU/L*
	Mean, mU/L	SD, mU/L	Total	Mean, mU/L	SD, mU/L	Total			
Dorr, 2015	-1.81	1.28	10	-0.26	1.73	10	31.5%	-1.55 (-2.88, -0.22)	
Karges, 2007	0.14	1.80	16	0.56	2.40	14	29.7%	-0.42 (-1.96, 1.12)	
Scarpa, 2010	-1.80	0.37	25	1.30	0.49	22	38.8%	-3.10 (-3.35, 2.85)	
Total (95%CI)			51			46	100.0%	-1.82 (-3.52, -0.11)	
Heterogeneity: Tau <sup>2</sup> =1.93, Chi <sup>2</sup> =15.97, df=2, I <sup>2</sup> =87% (P=0.0003)									
Test for overall effect: Z=2.09 (P=0.04)									

\*random=random effect model

**Figure 4.** The effect of levothyroxine on the changes in the level of TSH in euthyroid children with autoimmune thyroiditis

Study	Experimental			Control			Weight	Mean difference, random (95%CI), pmol/L	Mean difference, fixed (95%CI), pmol/L*
	Mean, pmol/L	SD, pmol/L	Total	Mean, pmol/L	SD, pmol/L	Total			
Dorr, 2015	3.80	2.34	10	-0.50	2.07	10	47.85	1.86 90.78, 2.95)	
Karges, 2007	0.07	2.80	16	0.83	7.20	14	52.2%	-0.14 (-0.86, 0.58)	
Total (95%CI)			26			24	100.0%	0.82 (-1.14, 2.78)	

Heterogeneity: Tau<sup>2</sup>=1.79, Chi<sup>2</sup>=9.07, df=1, I<sup>2</sup>=89%(P=0.003)  
 Test for overall: effect Z=0.82 (P=0.41)  
 \*random=random effect model

**Figure 5.** The effect of levothyroxine on the changes in the level of free T4 in euthyroid children with autoimmune thyroiditis

592.36; I<sup>2</sup>=0%; P=0.34) and -93.9 U/mL; (95%CI -265.96 to 78.17; I<sup>2</sup>=0%; P=0.28), respectively. There were no significantly different between two groups in free T4 changes, TPOAb changes and TgAb changes.

The side effects reported in the studies are shown in **Table 3**. The incidence of goiter was lower in the intervention group than in the control group (3/25 vs. 17/25, respectively) [odds ratio (OR) 0.06; 95%CI 0.01 to 0.28]. Large goiters and goiters with nodules were found only in the control group.<sup>25</sup> Levothyroxine administration for 2 years reduced the incidence of hypothyroidism in euthyroid children with autoimmune thyroiditis as compared to controls (3/56 vs. 17/53; OR 0.12; 95%CI 0.03 to 0.44).

## Discussion

In this systematic review, levothyroxine administration reduced thyroid volume as compared to controls. In all the included studies, levothyroxine treatment for at least 24 months reduced thyroid volume, but thyroid volume increased in the control group.<sup>23-25</sup>

Studies on the natural history of untreated autoimmune thyroiditis reported that thyroid function did not deteriorate in most cases.<sup>7,26,27</sup> In previous studies, the incidence of overt or subclinical hypothyroidism varied (25-43%) in euthyroid subjects.<sup>7,26,27</sup> At present, the use of levothyroxine treatment in euthyroid children remains debatable

**Table 3.** Side effects of levothyroxine

Study	Intervention (I) and control (C)	Randomized, n	Number of participants upon study completion, n	All side effects, n(%)	Serious/severe side effects, n(%)
Karges <i>et al.</i> (2007) <sup>23</sup>	I: levothyroxine	16	16	3 (19)*	0 (0)
	C: no treatment	14	14	4 (29)*	0 (0)
	Total	30	30	7 (23)*	0 (0)
Dörr <i>et al.</i> (2015) <sup>24</sup>	I: levothyroxine	40	10	0 (0)	0 (0)
	C: no treatment	39	10	13 (33)*	0 (0)
	Total	79	20	13 (16)	0 (0)
Scarpa <i>et al.</i> (2010) <sup>25</sup>	I: levothyroxine	25	25	3 (12)** 2 (8) <sup>@</sup> 0 (0) <sup>&amp;</sup>	0 (0)
	C: no treatment	25	22	17 (68)** 2 (8) <sup>@</sup> 2 (8) <sup>&amp;</sup>	1 (0.04) <sup>#</sup> 1 (0.04) <sup>\$</sup>
	Total	50	20 (4)**	4 (8) <sup>@</sup> 2 (4) <sup>&amp;</sup>	1 (0.04) <sup>#</sup> 1 (0.04) <sup>\$</sup>

\*hypothyroidism; \*\*goiter; @nodule; &subclinical hypothyroidism; #large goiter; \$a goiter and nodule of > 1 cm

due to the potential risk of developing hypothyroidism or goiters.

The mechanism of reducing thyroid volume by levothyroxine treatment is still unclear. According to one theory, it may be due to reduced TSH levels, which decrease antigen expression.<sup>17</sup> This results in decreased lymphocyte infiltration and atrophy of hyperplastic thyroid follicular cells.<sup>17</sup> The mean change in TSH levels in this study supports this theory. Comparing the TSH levels in the treatment and control groups, levothyroxine was beneficial in preventing increments in TSH levels. However, further study is needed to confirm the effect of levothyroxine in individuals with and without goiters.

Quality of life may be impaired in children with autoimmune thyroiditis and goiters. A previous systematic review of untreated autoimmune thyroiditis subjects with thyroid enlargement reported a decrease in overall quality of life (62%), obstacles in daily activities (22-35%), social problems (21%), anxiety disorders (13-60%), and cosmetic complaints (28-36%).<sup>28</sup> This study did not mention the age of the subjects. A study in Italy also reported quality of life impairment (mood disorders, fatigue, and sleep disorders) in euthyroid adults with goiters.<sup>29</sup> To our knowledge, no studies have examined the benefit of thyroid volume improvements in terms of quality of life, especially in children/adolescents.

The TPOAb is an important marker of thyroid function deterioration, as the levels are increased in 95% of autoimmune thyroiditis cases.<sup>2,5</sup> The risk of hypothyroidism increases in accordance with TPOAb level, with higher levels associated with a higher risk.<sup>30</sup> In this study, the changes in TPOAb levels were not different between levothyroxine treatment and control groups. This result was in agreement with other observational studies, but contrary to a study by Korzeniowska et al. who concluded that levothyroxine stabilized TPOAb levels as compared to controls.<sup>15,16,26</sup>

The small number of included studies and subjects were limitations of this meta-analysis. All the included studies also had a high risk of performance bias because of the absence of blinding methods. Another limitation was the composition of the study populations. One study included subjects with and without goiters,<sup>24</sup> and two other studies included only subjects without goiters.<sup>23,25</sup> Furthermore,

the duration of the treatment was limited to 24-36 months. Thus, the effect of levothyroxine beyond this period is unknown.

The clinical applicability of this review in non-goiter subjects without any disease or family history of autoimmune thyroiditis was difficult to determine. To date, there are no screening guidelines for healthy individuals with those conditions. The treatment of asymptomatic cases with positive thyroid antibodies needs to be carefully considered, taking into account cost-benefits, psychological aspects of chronic treatment in children, and the natural history of the disease.

In conclusion, there is a significant decrease in thyroid volume in euthyroid children with autoimmune thyroiditis who receive levothyroxine compared to controls. Studies containing larger sample sizes and a double-blinded design are needed to confirm these results.

## Conflict of Interest

None declared.

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