

# Treatment with L-thyroxine in congenital hypothyroidism

## Abstract

**Introduction:** Thyroid hormone deficiency in embryonic development is associated with congenital hypothyroidism (CH). CH is the most common endocrine disease in newborns and the biggest preventable cause of mental retardation

**Objective:** Review recent medical evidence of the use of levothyroxine as a hormone replacement therapy for brain protection, improvement of growth and development and decrease cognitive deficits in CH.

**Materials and methods:** The systematic review of PubMed/Medline databases, Redalyc, EBSCO, Virtual Health Library, Google Scholar. During period 2012-2017. Full text all world.

**Results:** Most authors recommend an initial dose of 10-15µg / kg/day and adjustments according to the patient's age and weight. It must be administered 2 hours before another food to avoid malabsorption. The monitoring of serum values every six to eight weeks helps to decide dose readjustment. The use of higher doses (50 µg/kg/day) and liquid solutions of levothyroxine in cases of severe HC, show improvement in the growth and cognitive development.

**Conclusion:** The articles demonstrated medical evidence of improvement in somatometric and cognitive status in patients, causing an impact on symptom relief. The untreated CH causes alterations of the growth and mental retardation, its severity produces deep and irreversible neurological alterations, the reason why the opportune treatment after the birth is indispensable.

**Keywords:** congenital hypothyroidism, pediatric, pharmacological treatment, levothyroxine, using boolean operators AND and OR

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**Abbreviations:** CH, congenital hypothyroidism; RCT, randomized clinical trials; CCT, controlled clinical trials

## Introduction

Thyroid hormone deficiency during embryonic development is associated with congenital hypothyroidism (CH). HC is a syndrome that results from the biological hypoactivity of thyroid hormones during fetal life, either due to a deficit in their production, resistance to their action in the target tissues or alteration of their transport or metabolism; which mainly involves the central nervous system and the skeletal system.<sup>1</sup> The untreated HC leads to alterations of growth and mental retardation, with clinical data of macroglossia, hypotonia, severe constipation and the umbilical hernia that, in its most severe forms, produces profound and irreversible neurological alterations. The brain damage is usually postnatal, due to the protection offered by the maternal thyroid hormone. This is why early treatment after birth achieves good results.<sup>2,3</sup> The pharmacological treatment of primary congenital hypothyroidism is carried out through the use of substitution therapy. For this, Levothyroxine<sup>4-6</sup> is commonly used. Therefore, the present work seeks to review the most recent medical evidence about the use of levothyroxine in hormone replacement therapy in the pediatric patient, as a factor of cerebral protection, as well as its benefits in improving growth and reducing deficiencies. Cognitive effects of these patients.

## Methods

A systematic review of clinical trials, published between January

2012 and January 2017, that analyze patients with primary CH and are treated with hormone replacement therapies. Regarding the language of the publications, it was limited to Spanish and English, no geographic scope was specified. The studies that did not address primary HC or that did not use hormone replacement therapy to treat it, as well as those that did not conform to the type of study included.<sup>7-10</sup>

## The electronic databases used were

PubMed/Medline, Redalyc, EBSCO, Virtual Health Library, Google Scholar. The combination of keywords used was the same in the different databases and according to the characteristics and scope of coverage of these, the language of the keywords was adapted; in Spanish: Congenital hypothyroidism, Pediatric, Pharmacological treatment, as well as the term Levothyroxine, using the Boolean operator AND. In English Congenital Hypothyroidism, Pediatric, Drug Therapy, as well as the term L-Thyroxine, was introduced, using the Boolean operator AND.<sup>11-13</sup>

## Study selection process

After applying the primary screening, based on the date of publication of the article, main topic, and type of study. We proceeded to the evaluation of the quality of the works according to the suggestions of authors such as Pazzini et al.<sup>7</sup> who proposed a design of selection criteria for the evaluation of the quality of the works, this was taken up and modified to analyze exclusively clinical trials. These criteria can be seen below:

i. Study design: randomized clinical trials (RCT), controlled

- clinical trials (CCT): 3 points, clinical trials (TC): 1 point.
- ii. Appropriate sample size: 1 point.
  - iii. An appropriate description of the selection: 1 point.
  - iv. Valid measurement methods: 1 point.
  - v. Use of method error analysis: 1 point.
  - vi. Blinding in the measurements: 1 point.
  - vii. Appropriate statistical methods: 1 point.
  - viii. Confusion factors included in the analysis: 1 point.

**The methodological quality of the studies evaluated was divided into three categories:** From 0 to 5 points were considered of low methodological quality; those works evaluated from 6 to 8 points were considered of medium quality, and finally, those evaluated from 9 to 10 points as high quality.<sup>14-16</sup>

## Results

The strategy used in the bibliographic search produced a total of 29 potential references. After the selection and application of the eligibility criteria in the evaluation of the quality of the recovered works, only 3 publications qualified for the final analysis (Table 1).<sup>17-19</sup>

**Table 1** Papers

Authors	Study groups	Sample	Year	Methods/ measurements	Findings
Cassio A et al. <sup>12</sup>	Forty-two consecutive infants with HC were subdivided into 2 groups composed of infants with the severe or moderate/mild form. For each form, newborns with HC were randomly assigned to receive liquid formulation (group 1) or tablet (group 2).	42	2013	SPSS (SPSS Inc., Chicago, Illinois)	The changes between the presentation of the drug were not statistically significant, however, it is said that the use in the liquid formula of Levothyroxine is much more adequate in changes of TSH and its normalization as well as in its reflection at T4 and T3. The changes seen in the doses were not statistically significant.
				Mann-Whitney U test	
Kurtoğlu Set al.	51 newborns, 26 who was diagnosed with congenital hypothyroidism due to iodine deficiency were treated with L-T4.	51	2014	SPSS 15.0 SPSS Inc., Chicago, Ill., USA) statistical package program.	The values of the first and third months of fT3, fT4, TSH, TG and thyroid volume for both groups were statistically similar. There were no significant differences between the two groups with respect to decreasing levels of fT3 and TSH, the rate of increase in fT4 levels or the rate of thyroid volume contraction
				parametric Student-Newman-Keuls and nonparametric Tukey tests	
				Mann-Whitney U test	
	Children who had plasma TSH concentrations <10µU / mL and thyroxine-free concentration (FT4)<0.8 ng / dL between 2 and 4 weeks of age. They were randomly assigned to the	70	2015	The quotient (DQ) using the Kyoto Scale for Psychological Development (KSPD)	There were no significant differences in growth,
Uchiyama A et al.	Treated (n=25) or group without treatment (n=45).				the incidences of developmental delay, cerebral palsy,
				Mann-Whitney U test	Visual and auditory impairments in the two groups.

## Quality of the works

The quality of the research and the methodology applied to the development of the reviewed clinical trials gave us as a result: 1 articles of low quality, 2 articles of medium quality and no article of high quality was obtained (Table 2) 3 articles were considered; 2 of medium quality and 1 of low quality, for purposes of the purpose of the work, the publication dates of the works ranged between 2012 and 2017, focused on patients with HC treated with hormone replacement therapy. All the articles found clinically significant medical evidence

**Table 2** Evaluation of quality in the recovered works

Authors	study design	Sample	Selection description	Validated measurements and methods	Method error analysis	Blind level	Confounding factors considered
Cassio A et al. <sup>12</sup>	CCT	Suitable	Suitable	yes	yes	yes	not specified
Kurtoğlu Set al.	CCT	Inadequate	Inadequate	yes			not specified
Uchiyama A et al.	CCT	Inadequate	Inadequate	yes	not specified	not specified	not specified

that showed an improvement in the somatometric and cognitive status of the patients who were treated with levothyroxine in hormone replacement therapies, for periods longer than 2 years of treatment, causing a positive impact on the improvement of the symptoms of p, for periods longer than 2 years of treatment, causing a positive impact on the improvement of patient symptoms. The groups/individual of study, the size of the population sample, year of publication of the work, methods, and measurements applied in the realization of the work and the relevant findings are described.<sup>20-23</sup>

## Discussion

The presentations found in the studies were limited to liquid formula and tablets.<sup>7</sup> Replacement therapy leads to an improvement in cognitive function.<sup>8</sup> In the review of the literature, an important reduction in intellectual deterioration and growth was found.<sup>9</sup> DOSE. Ahmad<sup>10</sup> recorded important measures to consider regarding TSH values and the amount of recommended dose to administer, with the initial recommendation standing out from the total revision of 10-15 µg/kg/day. The treatment with liquid formula compared to the usual treatments of tablets reflects a difference<sup>24</sup> not statistically significant, which nevertheless showed some increased improvement in the application of liquid solutions with the normalization of TSH and T4 levels. Regarding the recommended doses, it was possible to determine the levels of FT4, being less than 5 pmol/L. In the clinical practice guide the initial dose of 10-15 µg/kg/ day and adjustments according to the patient's age administration of said medication in a minimum interval of two hours before the food, as it decreases its absorption. Follow-up by measuring the serum values of this every six to eight weeks to decide if the dose should be readjusted. The use of these higher doses in cases of severe HC and, if possible, the availability of liquid levothyroxine solutions, demonstrated data that, although they were not statistically significant, that there was a better improvement of patients in the areas of growth and development cognitive.<sup>25-29</sup>

## Conclusion

The articles demonstrated medical evidence of improvement in somatometric and cognitive status in patients, causing an impact on symptom relief. The untreated CH causes alterations of the growth and mental retardation, its severity produces deep and irreversible neurological alterations, the reason why the opportune treatment after the birth is indispensable.

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## Conflict of interest

The author declares there is no conflict of interest.

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