



## Effects of levothyroxine on growth hormone (gh) sensitivity in children with idiopathic short stature<sup>☆</sup>



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### ABSTRACT

**Background:** The possible relationship between the circulating concentrations of T4 and GH sensitivity has not been elucidated.

**Objective:** The aim of this study is to evaluate the effect of levothyroxine supplementation on GH sensitivity in prepubertal boys with idiopathic short stature (ISS).

**Methods:** We selected 28 prepubertal boys with ISS (mean age  $8.2 \pm 0.5$  years) and free T4 (Ft4) concentrations between the 3rd and the 25th percentiles (Ft4: 0.8–1.5 ng/dl). They were randomly divided into two groups: Group A received thyroid supplementation (1–3  $\mu\text{g}/\text{kg}/\text{day}$ ) for 120 days, and Group B received placebo for the same period. To evaluate GH sensitivity, an IGF-I generation test (GH: 33  $\mu\text{g}/\text{kg}/\text{day}$  sc for 3 days) was performed in both groups: under basal conditions, and after 120 days of levothyroxine supplementation (or placebo).

**Results:** After thyroid supplementation, Group A had higher Ft4 concentrations compared with Group B ( $2.14 \pm 0.06$  vs  $1.48 \pm 0.06$  ng/dl,  $p = 0.01$ ), their growth velocity was significantly higher ( $2.3 \pm 0.1$  vs  $1.5 \pm 0.2$  cm/4 months), and they exhibited a greater increase in IGF-I after GH administration (Group A:  $32.5 \pm 3.8\%$  vs Group B  $17.3 \pm 2.6\%$ ).

**Conclusion:** Supplementation with levothyroxine for 120 days promotes an increase in growth velocity, and a greater IGF-I response to short-term GH administration in prepubertal boys with ISS and low-normal thyroid hormone concentrations.

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## 1. Introduction

The importance of thyroid hormone on growth and development in children is well established. Linear growth is highly dependent on the response of peripheral tissues to GH [1], a process known as GH sensitivity [2]. A number of parameters such as nutritional status [3,4] as well as the circulating concentrations of sex steroids [5,6] may influence GH sensitivity, but little is known about the possible effects of levothyroxine on this process. Several papers have been published regarding the growth promoting effects of supplementing thyroid hormone in short children with free T4 levels in the low-normal range, but the mechanism leading to the improvement in growth velocity in these children during T4 therapy has not been clarified. Some studies have postulated that thyroid hormone stimulates the GH–IGF-I axis, in

part by increasing GH secretion by the pituitary [7,8]. However, relatively little is known about the relationship between the circulating concentrations of T4 and GH sensitivity. Thus, the purpose of the study was to assess the effects of levothyroxine supplementation on GH sensitivity in children with idiopathic short stature.

## 2. Methods

We studied 28 prepubertal boys between the ages of five to ten years, with short stature (stature below  $-2.0$  SDS in the NCHS CDC 2000 growth charts and/or  $-2$  SD below mid parental stature). These patients had ISS as defined by a normal phenotype associated with a normal complete blood count, serum biochemistry and lipid profile, urinalysis, intestinal absorption serum IGF-I, IGF-BP3, Ft4, TSH, a normal GH response to insulin or clonidine stimulation ( $>10$  ng/ml).

The 28 children had a baseline serum free T4 from the 3rd to the 25th percentile for age. The free T4 (Ft4) normal range for children of this age group was established in a previous study from our laboratory, as shown in Fig. 1. At our research center, Ft4 values between 0.8 and

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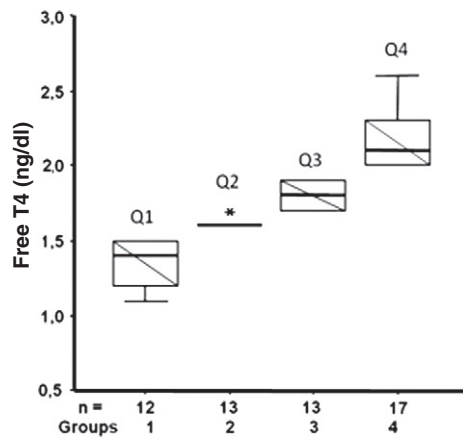


Fig. 1. Serum free T4 values in prepubertal healthy children classified by quartiles.

1.5 ng/dl are considered between the 3rd and 25th percentiles for prepubertal children.

All 28 boys fulfilled the criteria regarding serum free T4 levels, so they underwent an IGF-I generation test. The test consisted in administering human GH at a dose of 33  $\mu\text{g}/\text{kg}/\text{day}$  sc for 3 days, at times 0, 24 and 48 h, with measurements of serum IGF-I at times 0 (prior to GH administration) and 72 h.

After completion of the initial IGF-I generation test, these boys were divided randomly into two groups: in Group A ( $n = 15$ ), the patients were supplemented with levothyroxine for 120 days at doses ranging between 1 and 3  $\mu\text{g}/\text{kg}/\text{day}$ , in order to increase their serum concentrations of free T4 to a range between the 75th and 97th percentiles (Fig. 1), whereas the patients in Group B ( $n = 13$ ) received placebo during the same period.

At the end of the study period, a second IGF-I generation test was performed in both groups of patients, by administering human GH at a dose of 33  $\mu\text{g}/\text{kg}/\text{day}$  sc for 3 days, with measurements of serum IGF-I levels at times 0 and 72 h. The IGF-I response to GH was determined by the percent increase in serum IGF-I after GH administration. The study was approved by the Ethics Committee of the San Borja Arriaran Hospital. Informed parental consent was obtained from the parents, and assent was obtained from the children who participated in this study.

#### 2.1. Parameters assessed during the course of the study

At the beginning and at the end of the study we evaluated the following parameters: height and weight, complete blood count and chemistry profile. In addition, as indicated before, we performed an IGF-I generation test at the beginning and the end of the study.

During the study we measured serum Ft4 on a monthly basis in both groups of patients. We did not measure serum T3 or ALS during this study. Whenever necessary, we modified the thyroid supplementation dose in order to maintain the Ft4 levels between 75th and 97th percentiles in Group A, without observing any adverse effect in these patients.

#### 2.2. Hormonal determinations

Serum IGF-I levels were determined using a locally developed RIA requiring sample extraction as a first step. The sensitivity of this assay is 5 ng/ml. Intra- and interassay CVs were 8.6% and 10.2%, respectively [9]. Serum GH and IGFBP-3 concentrations were determined using commercial IRMAs (Izotop, Hungary and DAsource Immuno Assays, Belgium, respectively). The sensitivity of each assay is 0.05 ng/ml and 0.1 mg/l, respectively. The intra-assay CVs were 4.0% and 1.1% respectively, and the inter-assay CVs were 5.8% and 1.8%, respectively. Serum free T4 concentrations were determined by RIA, and TSH was

determined by IRMA (Siemens Healthcare Diagnostics, USA). The intra-assay CVs were 4.0% and 3.5% respectively, and inter assay CVs were 6.6% and 5.1%, respectively.

#### 2.3. Calculations and statistical analysis

Continuous variables were expressed as the mean  $\pm$  SEM or median (interquartile range) and categorical variables as count and percentages. One-way analysis of variance or a Kruskal–Wallis test was used for parametric and nonparametric continuous variables respectively, and a Mantel–Haenszel  $\chi^2$  test was used for categorical variables. All statistics were run on SPSS 11.0 for Windows, and a  $p$  value  $< 0.05$  was considered significant. The sample size was calculated to allow documentation of a 20% difference between parameters with a power of 95%.

### 3. Results

The 28 recruited children participated in the protocol, but one patient from the placebo group exhibited evidence of poor compliance, so he was excluded from the study. In Table 1, we show the clinical and hormonal characteristics of the children from Group A (supplemented with T4) and Group B (placebo). In addition, we show the delta height (end – beginning stature) in our subjects during the study.

Ft4 serum concentrations in Group A were  $1.37 \pm 0.03$  ng/dl at the beginning and  $2.14 \pm 0.06$  ng/dl at the end of the study ( $p < 0.05$ ), whereas in Group B Ft4 serum concentrations were  $1.30 \pm 0.04$  ng/dl, at the beginning and  $1.48 \pm 0.06$  ng/dl at the end of the study (Fig. 2). As expected, Ft4 serum concentrations were higher in Group A compared to Group B ( $p < 0.01$ ). In addition, the growth velocity of the children who were supplemented with levothyroxine was significantly higher compared with the children who received placebo (Group A  $2.3 \pm 0.1$  cm/4 months vs Group B  $1.5 \pm 0.2$  cm/4 months). These children also exhibited a greater increase in IGF-I after short-term GH administration. In Group A the IGF-I percent increase was  $32.5 \pm 3.8\%$ , whereas in Group B it was  $17.3 \pm 2.6\%$ , as shown in Fig. 3.

The placebo and the thyroid supplementation subjects did not experience any clinical or laboratory adverse effects during the study.

### 4. Discussion

Very limited information is available regarding the possible effects of T4 on GH sensitivity. There is clear evidence however, that hypothyroidism hampers growth, whereas hyperthyroidism may enhance growth. Thus, thyroid hormones have a significant effect on linear growth during childhood and adolescence, but the potential mechanisms underlying this relationship have not been clarified. In vitro studies have demonstrated that thyroid hormone stimulates GH secretion by the pituitary [7,8]. In addition, data has been published regarding the effects

Table 1

Characteristics of the patients. Initial height = height prior to treatment. Final height = height at end of the study. Delta height = height at the end – height at the beginning of the study.

	Group A ( $n = 15$ )	Group B ( $n = 12$ )
Age (years)	$8.0 \pm 0.4$	$8.5 \pm 0.6$
TSH (mIU/ml)	$2.3 \pm 0.4$	$2.1 \pm 0.4$
Ft4 (ng/dl)	$1.37 \pm 0.03$	$1.30 \pm 0.04$
z IGF-I (SDS)	$-0.72 \pm 0.14$	$-0.65 \pm 0.32$
Initial height (cm)	$115.4 \pm 2.1$	$118.9 \pm 2.7$
Initial BMI ( $\text{kg}/\text{m}^2$ )	$16.5 \pm 0.3$	$16.8 \pm 0.2$
Final height (cm)	$117.6 \pm 2.2$	$120.4 \pm 2.6$
Final BMI ( $\text{kg}/\text{m}^2$ )	$16.1 \pm 0.3^*$	$17.2 \pm 0.3$
Delta height (cm)	$2.3 \pm 0.1^*$	$1.5 \pm 0.2$

\*  $p < 0.05$ ; Group A vs Group B.

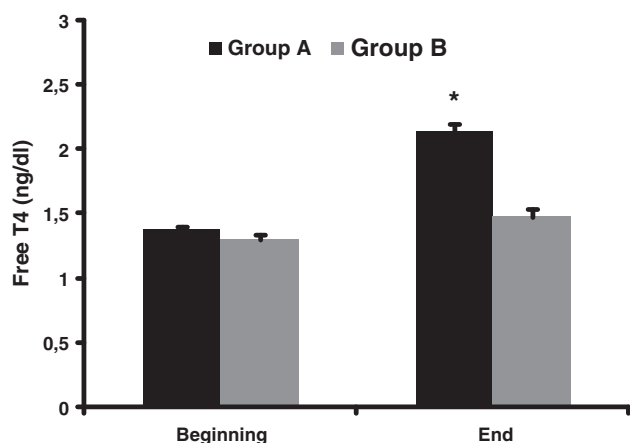


Fig. 2. Serum FT4 levels at the beginning and the end of the study. \* $p < 0.05$ ; beginning vs end.

of T4 on transcription of the GH gene [10]. Ramos et al. [11] have shown that hepatic IGF-expression increases with thyroid supplementation in thyroidectomized rats, suggesting that thyroid hormone may increase GH sensitivity. Our group has also shown that T4 stimulates GH signal transduction in fibroblasts from children with idiopathic short stature [12]. In addition, Xing et al. have demonstrated that thyroid hormone plays a significant role in regulating IGF-1 expression and bone acquisition in mice [13]. Unfortunately, in this study we did not measure serum markers of bone formation such as osteocalcin.

Several studies have been published regarding the effects of thyroid hormone supplementation in children with subclinical hypothyroidism, and/or short children with free T4 levels in the low-normal range. Some of these studies have demonstrated that thyroid hormone supplementation may increase growth velocity in short children with borderline thyroid function. Valcavi et al. [14] performed a study in children with and without hypothyroidism by investigating the relationship between serum thyroid hormone and IGF-I concentrations. This study showed a positive correlation between free T3 and IGF-1 levels after treatment with levothyroxine ( $r = 0.37$ ,  $p < 0.05$ ), which was associated with an improved growth velocity in both groups of subjects. In addition, Cetinkaya et al. [15] performed a study in prepubertal and pubertal children with subclinical hypothyroidism. They supplemented both groups of patients with thyroid hormone, and observed that both groups of children increased their growth velocity after 6 to 12 months of supplementation with thyroid hormone ( $p < 0.05$ ). As expected, TSH levels decreased during T4 administration in both groups of patients.

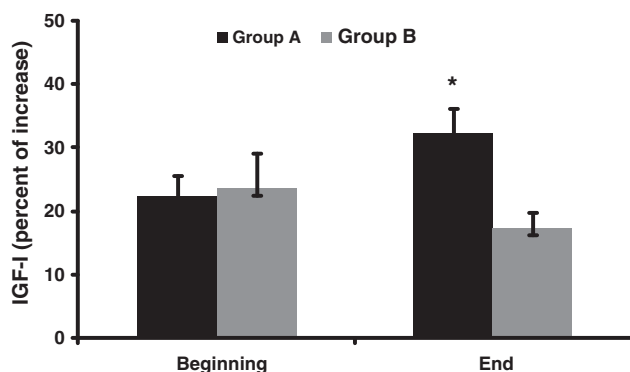


Fig. 3. IGF-I generation test (percent increase) at the beginning and the end of the study. \* $p < 0.05$ ; Group A vs Group B.

These results are similar to those published by Rose et al. [16] in a group of children with idiopathic short stature, who observed an improved growth velocity when they were supplemented with thyroid hormone. Subsequently, Eyal et al. [17] performed a similar study in children with Fanconi anemia and borderline thyroid function, and showed that they increased their growth velocity when they were supplemented with thyroid hormone. Thus, several authors have documented that thyroid hormone supplementation may increase growth velocity in children with low normal thyroid function tests, but the potential mechanisms underlying this effect have not been elucidated.

In our study, we investigated the effects of a shift in serum thyroid hormone concentrations from the low-normal to the high-normal range on the GH-induced IGF-1 generation test in children with idiopathic short stature. The IGF-1 generation test is a useful marker of GH sensitivity, so we investigated whether circulating thyroid hormone concentrations might modulate this parameter. The results of our study showed a greater increase in serum IGF-1 after short-term GH administration in the children who received thyroid supplementation, compared with those who received placebo. In addition, we observed a significantly increased growth velocity in the children who were supplemented with thyroid hormone, suggesting that a relatively short period of T4 supplementation may enhance linear growth.

We conclude that supplementation with levothyroxine for 120 days, leading to a shift in the serum thyroxine concentrations from the low-normal to the high-normal range, results in a greater increase in the IGF-1 response to short-term GH administration. These findings suggest that levothyroxine may enhance GH sensitivity in prepubertal boys with idiopathic short stature and low-normal thyroid function.

#### Conflict of interest

None.

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