Growth Hormone & IGF Research 24 (2014) 119–122

Contents lists available at ScienceDirect

Growth Hormone & IGF Research

journal homepage: www.elsevier.com/locate/ghir

Effects of levothyroxine on growth hormone (gh) sensitivity in children with idiopathic short stature☆

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ARTICLE INFO

Article history:
Received 10 January 2014
Received in revised form 10 March 2014
Accepted 1 April 2014
Available online 9 May 2014

Keywords:
Growth hormone
Levothyroxine
IGF-I
Growth hormone sensitivity
Idiopathic short stature

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 ± 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 μg/kg/day) for 120 days, and Group B received placebo for the same period. To evaluate GH sensitivity, an IGF-I generation test (GH: 33 μg/kg/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 ± 0.06 vs 1.48 ± 0.06 ng/dl, $p = 0.01$), their growth velocity was significantly higher (2.3 ± 0.1 vs 1.5 ± 0.2 cm/4 months), and they exhibited a greater increase in IGF-I after GH administration (Group A: 32.5 ± 3.8% vs Group B 17.3 ± 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.

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

☆ Supported in part by Merck-Serono.
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http://dx.doi.org/10.1016/j.ghir.2014.04.004
1096-6374/

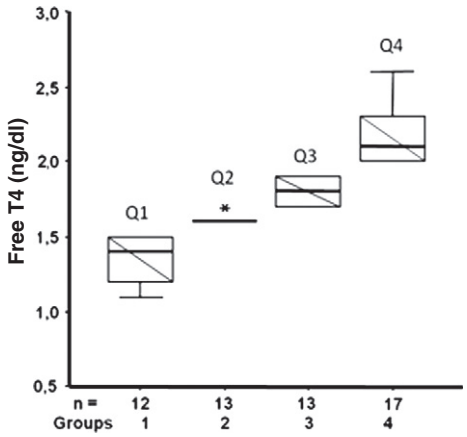

Fig. 1. Serum free T4 values in prepubertal healthy children classified by quartiles.

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 μg/kg/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 μg/kg/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 μg/kg/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 DIAsource 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 ± 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 X^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 ± 0.03 ng/dl at the beginning and 2.14 ± 0.06 ng/dl at the end of the study ($p < 0.05$), whereas in Group B Ft4 serum concentrations were 1.30 ± 0.04 ng/dl, at the beginning and 1.48 ± 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 ± 0.1 cm/4 months vs Group B 1.5 ± 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 ± 3.8%, whereas in Group B it was 17.3 ± 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 ± 0.4	8.5 ± 0.6
TSH (mUI/ml)	2.3 ± 0.4	2.1 ± 0.4
fT4 (ng/dl)	1.37 ± 0.03	1.30 ± 0.04
z IGF-I (SDS)	−0.72 ± 0.14	−0.65 ± 0.32
Initial height (cm)	115.4 ± 2.1	118.9 ± 2.7
Initial BMI kg/m2)	16.5 ± 0.3	16.8 ± 0.2
Final height (cm)	117.6 ± 2.2	120.4 ± 2.6
Final BMI (kg/m^2)	16.1 ± 0.3*	17.2 ± 0.3
Delta height (cm)	2.3 ± 0.1*	1.5 ± 0.2

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