Thyroid function in children with growth hormone deficiency during long-term growth hormone replacement therapy

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Abstract

Aim of the study: The aim of this study was to investigate the effects of growth hormone (GH) therapy on thyroid function in a group of euthyroid children with isolated idiopathic growth hormone deficiency (GHD).

Material and methods: The study was retrospective and included 117 children treated with GH for 1-4 years. Anthropometric measurements and serum concentrations of insulin-like growth factor-1 (IGF-1), thyroid-stimulating hormone (TSH), and free thyroxine (fT4) were analysed at baseline and during GH therapy.

Results: TSH levels did not change significantly after the initiation of GH treatment, while fT4 levels decreased after the second year of GH treatment ($p < 0.01$) and remained lower than baseline until the end of observation ($p < 0.01$, after both the third and fourth year of therapy) in the whole group. Analysis according to baseline pubertal status revealed significant changes in TSH and fT4 levels during GH treatment, but only in the prepubertal children. Multiple regression analysis confirmed that mean GH doses administered in the first two years of GH therapy were independently ($R = 0.218$, $p < 0.05$) associated with changes in fT4 levels in this period ($\Delta fT4_{2\,years-baseline}$), even when taking into account changes in height SDS and bone age.

Conclusions: FT4 levels decreased during GH replacement therapy, while TSH levels appeared to be unaffected by GH therapy. Prepubertal children seem to be more predisposed to thyroid function alterations during such therapy in comparison to pubertal children. Changes in fT4 levels during GH replacement therapy are related to GH doses.

Key words: growth hormone/insulin-like growth factor-1 axis, thyroid function, growth hormone deficiency, growth hormone replacement therapy, children.

Introduction

Mutual associations between the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis and the hypothalamic-pituitary-thyroid (HPT) axis have been previously reported by several authors, but they were not fully explained [1-12]. The HPT axis affects the secretion and action of IGF-1, IGF binding protein-3 (IGFBP-3), and GH [2, 4, 9, 13, 14]. Untreated primary hypothyroidism usually coincides with a reduction in IGF-1 and IGFBP-3 serum concentrations, lower GH secretion rates, and deteriorated GH response to secretagogues [2, 4, 13]. Hyperthyroidism leads to an increase in mean 24-hour GH secretion accompanied by normal or high IGF-1 levels [2, 4, 9, 14-17]. On the other hand, the GH/IGF-1 axis could

alter the growth and function of the thyroid gland and lead to changes in thyroid hormone metabolism in peripheral tissues [2-4, 18]. The results of experimental and clinical studies evaluating the effects of GH administration are divergent [6, 19-23]. Some studies have revealed that GH treatment leads to a significant decrease in total thyroxine (T4) and free thyroxine (fT4) concentrations [5, 6, 19, 20, 24, 25] and to a significant increase in triiodothyronine (T3) levels [5, 20, 24], while others have reported that concentrations of thyroid hormones are unchanged during GH therapy [6, 21]. Secretion of thyroid-stimulating hormone (TSH) seems to be unaffected by GH and/or IGF-1 administration [6, 8, 20, 26] or decreases during such therapy [19]. The suggested mechanisms of those associations

included mainly alterations in serum binding proteins [27], increased peripheral deiodination of T4 to T3 [8, 28-30], and central inhibition of TSH release [2, 28]. The clinical significance of those changes is not clear. The study by Giavoli *et al.* [6] indicates that GH replacement therapy in GH-deficient children does not induce central hypothyroidism in patients with idiopathic isolated growth hormone deficiency (GHD), but in children with multiple pituitary hormone deficiencies (MPHD), especially due to organic lesions, this therapy usually unmasks the presence of clinical and biochemical central hypothyroidism. It is also emphasised that children with pre-existing central hypothyroidism, in contrast to initially euthyroid patients, require levothyroxine (LT4) replacement to achieve catch-up growth during GH treatment [6, 7, 30]. Agha *et al.* [31] recommend LT4 replacement prior to GH therapy also in hypopituitary adults with GHD and low normal serum T4 concentrations.

The aim of this study was to evaluate the effects of GH replacement therapy on thyroid function in a group of initially euthyroid children with isolated idiopathic GHD taking into consideration baseline pubertal status.

Material and methods

The study was conducted in the Department of Paediatrics and Endocrinology of the Medical University of Warsaw, Poland after obtaining the approval from the Bioethics Committee at the Medical University of Warsaw, Poland in accordance with the Declaration of Helsinki. The study was designed as a retrospective collection of data of 117 children and adolescents (mean age 9.8 ±3.5 years) with idiopathic isolated GHD treated with recombinant human GH for 1 to 4 years, including 29 children treated for one year, 24 children – for two years, 20 children – for three years, and 44 children – for four years. All the recruited children were initially euthyroid without any thyroid disease diagnosed. Data were analysed in the whole group and also according to baseline pubertal status [32]. The diagnosis of GHD was based on auxological criteria (height < 3rd percentile for age and sex according to Polish growth charts, height velocity < –1 SD below mean for age- and sex-matched Polish population), delay in bone age, and biochemical criteria (decreased GH secretion in a spontaneous nocturnal test and GH peak levels < 10 ng/ml in two provocative tests with clonidine, insulin, glucagon, or arginine) after exclusion of other causes of short stature [33]. Bone age was evaluated before the initiation of GH treatment and after each full year of therapy using Greulich and Pyle standards [34]. Magnetic resonance imagining (MRI) of the hypothalamic-pituitary region was conducted in all the patients to exclude organic lesions. Recombinant human GH was administered once daily as a subcutaneous injection, at bedtime. Mean GH doses during therapy in the whole group are reported in Table 1 and in prepubertal and pubertal children in Table 2. Height and weight measurements and body mass index (BMI) are expressed as standard deviation scores (SDS) for chronological age (height measurements) or for height-age (weight measurements and BMI) [35]. Baseline height velocity (HV) was calculated using data from 6-12 months before GH replacement therapy was initiated. Anthropometric and biochemical measurements were taken at baseline, after six months of GH therapy, and after each full year of therapy.

Biochemical analyses

Serum GH and IGF-1 concentrations were measured by immunoassay using an IMMULITE 2000 Xpi analyser (Siemens). IGF-1 concentrations were normalised for

Table 1. Characteristics of the whole study group at baseline and during GH replacement therapy

Parameters	Baseline	6 months	1 year	2 years	3 years	4 years
Number of patients	117	117	117	88	64	44
GH doses (mg/kg/week)	–	0.183 ±0.01	0.183 ±0.01	0.185 ±0.02	0.193 ±0.02	0.194 ±0.02
Height SDS	–2.6 ±0.56	–2.24 ±0.54***	–1.97 ±0.58***	–1.59 ±0.62***	–1.43 ±0.64***	–1.28 ±0.61***
Weight SDS for height-age	–0.3 (–0.7-0.2)	–0.4 (–0.6-0.1)	–0.3 (–0.6-0.1)	–0.3 (–0.5-0.0)	–0.2 (–0.5-0.0)	–0.4 (–0.55-0.0)
BMI SDS for height-age	–0.4 (–0.8-0.3)	–0.5 (–0.8-0.1)	–0.3 (–0.8-0.2)	–0.4 (–0.6-0.1)*	–0.2 (–0.6-0.0)*	–0.4 (–0.7-0.1)*
HV (cm/year)	5.06 ±1.36	–	9.05 ±1.52***	7.57 ±1.47***	6.53 ±1.79***	6.31 ±1.43***
Bone age (years)	7.6 ±3.59	–	9.1 ±3.61***	9.9 ±3.3***	10.7 ±3.02***	10.9 ±2.44***
IGF-1 SDS for bone age	–0.3 (–0.93-0.34)	1.95 (0.73-4.13)**	1.69 (0.64-4.0)**	2.14 (0.6-4.24)**	1.96 (0.89-3.58)**	1.91 (0.52-3.62)**
TSH (µIU/ml)	1.76 (1.33-2.42)	1.87 (1.31-2.27)	1.94 (1.48-2.65)	1.69 (1.15-2.16)	1.55 (1.09-2.0)	2.15 (1.54-2.36)
fT4 (ng/dl)	1.03 (0.93-1.09)	0.96 (0.9-1.04)	0.97 (0.87-1.05)	0.92 (0.86-1.02)**	0.94 (0.88-1.05)**	0.93 (0.88-1.01)

Data are presented as mean ± standard deviation (SD) or median with interquartile range as appropriate. *p < 0.05 vs. baseline value; **p < 0.01 vs. baseline value; ***p < 0.001 vs. baseline value; GH – growth hormone; SDS – standard deviation score; BMI – body mass index; HV – height velocity; IGF-1 – insulin-like growth factor-1; TSH – thyroid-stimulating hormone; fT4 – free thyroxine

Table 2. Comparison between prepubertal and pubertal children at baseline and within the first two years of GH treatment

Parameters	Prepubertal	Pubertal	*p*-value
At baseline:			
Number of patients	92	25	
Age (years)	8.7 ±3.0	13.8 ±1.8	< 0.001
GH max (ng/ml)	7.36 ±1.78	7.34 ±1.83	NS
Bone age (years)	6.3 ±2.84	12.3 ±1.66	< 0.001
Height SDS	−2.6 ±0.59	−2.4 ±0.41	NS
Weight SDS for height-age	−0.4 (−0.8-0.2)	0.0 (−0.5-0.5)	NS
BMI SDS for height-age	−0.45 (−1.0-0.3)	0.0 (−0.6-1.1)	< 0.05
HV (cm/year)	4.9 ±1.3	5.6 ±1.46	< 0.05
IGF-1 SDS for bone age	−0.27 (−0.76-0.47)	−0.39 (−1.25-0.04)	NS
TSH (μIU/ml)	1.8 (1.32-2.46)	1.71 (1.46-2.13)	NS
fT4 (ng/dl)	1.04 (0.97-1.12)	0.93 (0.87-1.02)	< 0.001
After 6 months:			
Number of patients	92	25	
Height SDS	−2.3 ±0.56[***]	−2.2 ±0.44	NS
Weight SDS for height-age	−0.4 (−0.6-0.0)	−0.2 (−0.5-0.7)	NS
BMI SDS for height-age	−0.5 (−0.8-0.0)	−0.2 (−0.6-1.0)	NS
IGF-1 SDS for bone age	2.1 (0.72-4.89)[**]	1.85 (1.09-3.03)[*]	NS
TSH (μIU/ml)	1.89 (1.34-2.33)	1.81 (1.31-1.95)	NS
fT4 (ng/dl)	0.99 (0.92-1.05)[**]	0.87 (0.84-0.92)	< 0.001
After first year:			
Number of patients	92	25	
Bone age (years)	7.9 ±3.1	13.5 ±1.21	< 0.001
Height SDS	−2.0 ±0.59[***]	−1.8 ±0.5[***]	NS
Weight SDS for height-age	−0.3 (−0.6-0.0)	−0.2 (−0.5-0.6)	NS
BMI SDS for height-age	−0.4 (−0.8-0.1)	−0.2 (−0.6-0.9)	NS
HV (cm/year)	9.0 ±1.4[***]	9.3 ±1.9[***]	NS
IGF-1 SDS for bone age	1.55 (0.82-2.89)[**]	3.26 (0.33-4.55)[**]	NS
TSH (μIU/ml)	2.01 (1.67-2.8)[**]	1.56 (1.19-2.01)	< 0.01
fT4 (ng/dl)	0.99 (0.9-1.07)[**]	0.87 (0.79-0.93)	< 0.001
Mean GH doses in the first year (mg/kg/week)	0.180 ±0.01	0.194 ±0.01	< 0.001
After second year:			
Number of patients	74	14	
Bone age (years)	9.1 ±2.9	14.5 ±0.64	< 0.001
Height SDS	−1.7 ±0.58[***]	−1.1 ±0.56[***]	< 0.001
Weight SDS for height-age	−0.3 (−0.5-0.0)	−0.2 (−0.5-0.2)	NS
BMI SDS for height-age	−0.4 (−0.7-0.1)	−0.25 (−0.6-0.4)	NS
HV (cm/year)	7.6 ±1.35[***]	7.5 ±2.06[*]	NS
IGF-1 SDS for bone age	2.13 (0.65-3.45)[**]	3.63 (−0.23-7.0)[**]	NS
TSH (μIU/ml)	1.79 (1.39-2.21)	1.18 (0.94-1.66)	< 0.05
fT4 (ng/dl)	0.94 (0.87-1.03)[**]	0.88 (0.82-0.97)	NS
Mean GH doses in the second year (mg/kg/week)	0.182 ±0.02	0.204 ±0.02	< 0.001
Mean GH doses in the first two years (mg/kg/week)	0.181 ±0.01	0.2 ±0.02	< 0.001

Data are presented as mean ±standard deviation (SD) or median with interquartile range as appropriate. NS – not significant; [*]p < 0.05 vs. baseline value; [**]p < 0.01 vs. baseline value; [***]p < 0.001 vs. baseline value; GH – growth hormone; GH max – maximum growth hormone release; SDS – standard deviation score; BMI – body mass index; HV – height velocity; IGF-1 – insulin-like growth factor-1; TSH – thyroid-stimulating hormone; fT4 – free thyroxine

sex and bone age and were expressed as SDS according to the normative data provided by the manufacturer (Siemens Healthcare Diagnostics Inc.). Serum concentrations of TSH, fT4, anti-thyroid peroxidase (anti-TPO) antibodies, and anti-thyroglobulin (anti-Tg) antibodies were measured by immunofluorescence assays using an Architect i1000SR (Abbott Diagnostics).

Statistical analysis

Statistical analysis was performed using Statistica 13.1. The Shapiro-Wilk normality test was used to determine data distribution. Data were presented as means with standard deviation, median, and interquartile ranges, or as percentages, as appropriate. Comparisons between baseline and treatment values of the same parameter were conducted using repeated measures ANOVA with Bonferroni post hoc test for normally distributed data, and using the Friedman test with post hoc comparisons for non-normally distributed data. Comparisons between prepubertal and pubertal children were conducted using the *t*-test for normally distributed data and the U-Mann-Whitney test for non-normally distributed data. Correlations between variables were examined using the Pearson correlation coefficient for normally distributed data and Spearman correlation analysis for non-normally distributed data. Multiple regression analysis was used to evaluate the associations between changes in fT4 concentrations in the first two years of GH therapy (as a dependent variable) and GH doses, changes in anthropometric and biochemical parameters and in bone age (as independent variables). A *p*-value < 0.05 was accepted as significant.

Results

The characteristics of the whole study group at baseline and during GH replacement therapy are shown in Table 1. As expected, after the initiation of GH treatment IGF-1 SDS for bone age, HV and height SDS increased significantly (Table 1). Weight SDS for height-age did not change significantly during GH treatment compared to baseline values, while BMI SDS for height-age fluctuated. TSH levels did not change significantly after the initiation of GH treatment, whereas fT4 levels decreased significantly after the second year of GH treatment ($p < 0.01$) and remained lower than baseline until the end of observation ($p < 0.01$, after both the third and fourth year of therapy).

Comparison between initially prepubertal and pubertal children within the first two years of GH treatment is presented in Table 2. Analysis considering baseline pubertal status revealed significant changes in TSH and fT4 levels after the initiation of GH treatment, but only in prepubertal children. TSH concentrations increased significantly after the first year of GH therapy compared to baseline values ($p < 0.01$), but after the second year of therapy they de-

creased and did not differ from baseline. FT4 concentrations decreased significantly as early as after the first six months ($p < 0.01$) of GH treatment and remained significantly lower than baseline after the first ($p < 0.01$) and the second year ($p < 0.01$) of therapy. We also found that in four (3.4%) out of 117 children included in this study LT4 replacement therapy was started during GH treatment. Three of these children (all prepubertal, two boys and one girl) were suspected for central hypothyroidism, and one pubertal girl developed hypothyroidism due to autoimmune thyroiditis with increased concentrations of anti-TPO and anti-Tg antibodies. HV in these children did not differ significantly from others either before or during LT4 therapy (data not shown).

In further correlation analysis we did not find any associations between baseline parameters, such as maximum GH release in a spontaneous nocturnal test and in two provocative tests (GH max), bone age, HV, height SDS, BMI SDS for height-age, IGF-1 SDS for bone age, and changes in fT4 concentrations within the first two years of GH treatment ($\Delta fT4_{2\,years-baseline}$), either in the whole study group or in the prepubertal or pubertal subgroups.

We also verified whether $\Delta fT4_{2\,years-baseline}$ was associated with changes in height deficit (height SDS), BMI SDS for height-age, HV, bone age, IGF-1 SDS, and with GH doses in the first two years of GH therapy. Spearman's correlation analysis revealed significant positive associations between $\Delta fT4_{2\,years-baseline}$ and both mean GH doses in the first year of GH treatment ($r = 0.25$, $p < 0.05$) and mean GH doses in the first two years of GH treatment ($r = 0.32$, $p < 0.05$), but only in the prepubertal children. Multiple regression analysis for the whole study group confirmed that mean GH doses administered in the first two years of GH therapy were independently ($R = 0.218$, $p < 0.05$) associated with $\Delta fT4_{2\,years-baseline}$ also after including changes in height SDS ($\Delta height\ SDS_{2\,years-baseline}$) and bone age ($\Delta bone\ age_{2\,years-baseline}$) in that period ($\Delta fT4_{2\,years-baseline} = [0.054 \pm 0.109]\ \Delta height\ SDS_{2\,years-baseline} + [0.0431 \pm 0.109]\ \Delta bone\ age_{2\,years-baseline} + [0.222 \pm 0.110]$ mean GH doses within the first two years of therapy).

Discussion

In this retrospective study we analysed the effects of long-term GH replacement therapy on thyroid function in initially euthyroid children with idiopathic isolated GHD. TSH and fT4 concentrations were evaluated before the initiation of GH therapy and during the first four years of treatment. After the second year of GH therapy we found a significant decrease in fT4 levels accompanied by unchanged TSH concentrations in the whole study group. In the analysis taking into account baseline pubertal status, including the first two years of GH therapy, significant decreases in fT4 concentrations were found earlier, after the first six months of therapy, and also remained significant

after the first and the second year of GH therapy, but only in prepubertal children. These changes in fT4 concentrations were accompanied by a significant increase in TSH levels at six months of therapy, which was then followed by a decrease in TSH levels to baseline values in further observation. In pubertal children fT4 and TSH levels were unchanged in the first two years of GH treatment. The main limitation of our study was its retrospective design, which resulted in a lack of measurements of other markers of thyroid function, such as free T3 (fT3) or reverse T3 (rT3) concentrations. On the other hand, the advantages of this study were the large number of enrolled children and adolescents, a long period of observation, and taking into consideration baseline pubertal status. The majority of clinical studies presented by several authors evaluated only the first year of GH treatment and included a small number of GH-deficient patients, limiting the value of the results reported. The most frequently postulated mechanisms of the influence of the GH/IGF-1 system on the HPT axis are an increase in peripheral conversion of T4 to T3 and the unmasking of previously unrecognised central hypothyroidism [2, 8, 28-30]. Giavoli *et al.* [6] compared the effects of one-year GH replacement therapy on the HPT axis in euthyroid GH-deficient children and in children with MPHD due to organic lesions, and they found significant reductions in fT4 concentrations, which occurred during GH therapy in both groups. Simultaneously, the authors noticed that in all the initially euthyroid patients fT4 values remained normal, while in four out of six children with MPHD, fT4 levels fell below the reference values. Serum fT3 and TSH concentrations did not change significantly during GH therapy in either subgroup. The authors also stated that in the patients with MPHD, who became hypothyroid during GH treatment, height velocity was below the 25th percentile until they achieved euthyroidism through appropriate LT4 substitution. They concluded that decreased HV, despite adequate GH substitution and normal IGF-1 levels, could be considered as a valuable clinical marker of central hypothyroidism in this group of patients. In our analysis, we found that LT4 replacement was started during GH therapy in four out of 117 initially euthyroid children included in the study. Three of these children (all prepubertal) were suspected for central hypothyroidism, and one pubertal girl developed hypothyroidism due to autoimmune thyroiditis. Simultaneously, we found that all of those children had HV adequate to GH doses and pubertal status, both before the initiation of and during LT4 therapy. Keskin *et al.* [25], in a one-year follow-up study including GH-deficient children and adolescents, evaluated not only thyroid function, but also its volume during GH therapy and reported significant decreases in fT4 and TSH levels in that period without any changes in thyroid volume. The value of their results is limited due to the small size of the study group. Portes *et al.* [8], who evaluated long-term effects of GH replacement therapy on thyroid function in GH-deficient children, found significant decreases in serum fT4 and rT3 levels and a significant increase in serum T3 levels after the initiation of GH treatment. The authors speculated that these changes were independent of TSH concentrations and resulted from increased conversion of T4 to T3 in peripheral tissues. The authors also stated that GH replacement therapy in GH-deficient children did not induce hypothyroidism, but only revealed previously unrecognised cases in which serum fT4 values decreased during GH replacement therapy. Seminara *et al.* [26] also confirmed significant changes in thyroid function during long-term GH therapy and postulated that the significant decreases in total and free T4 concentrations and the significant increases in total and free T3 concentrations observed in the first year of therapy resulted from an increase in thyroid hormone peripheral metabolism. However, they conclude that these changes seem to be transitory and disappear during further observation. Losa *et al.* [36], who estimated the incidence of clinically relevant hypothyroidism during long-term GH replacement therapy in adults with GHD, also confirmed a significant decrease in fT4 levels after the initiation of GH therapy, although they remained within the normal range. The authors reported that the largest decrease in fT4 was observed in the first six months of GH replacement therapy. They estimated the incidence of hypothyroidism at 6.7 events per 100 patient-years in initially euthyroid patients and at 1.2 events per 100 patient-years in patients on stable levothyroxine (LT4) replacement therapy [36]. Several authors recommended monitoring thyroid function during GH replacement therapy, especially in the first year of therapy, when the largest decrease in fT4 concentrations occurs in both GH-deficient children and adults [27, 36]. Apart from changes in thyroid function after the initiation of GH therapy our analysis also revealed a significant positive relationship between mean GH doses administered within the first two years of GH treatment and changes in fT4 concentrations in that period. These results confirmed the previous observation of Jørgensen *et al.* [28], who reported that significant increases in both T3 and fT3 concentrations and the T3/T4 ratio in GH-deficient adults were dose-dependent.

The results of the above-mentioned studies as well as our results reveal that monitoring thyroid function should be an important part of GH treatment. Some GH-deficient children, especially those with MPHD, could require LT4 replacement to achieve adequate HV and catch-up growth during GH treatment, but indications for such therapy should be strictly defined.

Conclusions

FT4 levels decrease significantly after the initiation of GH replacement therapy, while TSH levels appeared to be unaffected by GH therapy. Prepubertal children seem to

be more predisposed to thyroid function alterations during such therapy in comparison to pubertal children. Changes in fT4 levels during GH replacement therapy are related to GH doses.

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The authors declare no conflict of interest.

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