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Correlation between Severity of Growth Hormone Deficiency and Thyroid Metabolism and Effects of Long-Term Growth Hormone Treatment on Thyroid Function in Children with Idiopathic Growth Hormone Deficiency

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Key Words
Growth hormone · Children · Thyroid · Growth hormone deficiency · Growth hormone treatment

Abstract
Background/Aim: The significance of changes in thyroid function in children during growth hormone (GH) treatment remains uncertain. We aimed to evaluate the impact of GH replacement on thyroid status in children with idiopathic GH deficiency (GHD). ***Methods:*** Data of 105 GHD children (82 M, 23 F; aged 11.13 years) during a 36-month follow-up were analyzed. At diagnosis the areas under the curve of GH (AUC_{GH}) were calculated during a GH-releasing hormone + arginine (GHRH-Arg) and insulin tolerance test. ***Results:*** A significant ΔfT_3 ($p < 0.001$) was documented at 12 months, without any further change at 24 and 36 months and without fT_4 and TSH modifications. Grouping patients according to ΔfT_3 at 12 months into those with lower (n = 80, 76%) or greater values than the 75th percentile (n = 25, 24%), the latter showed lower AUC_{GH} and GH peak during a GHRH-Arg ($p = 0.018$ and 0.014, respectively) and insulin tolerance test ($p = 0.023$ and 0.020, respectively) at diagnosis. In addition, children with lower GH at diagnosis showed a greater ΔfT_3 at 12 months ($p = 0.030$). ***Conclusions:*** In GHD children, GH treatment is associated with a significant increase in fT_3 in the first 12 months, more pronounced in patients with more severe GHD, highlighting the strong correlation between severity of GHD and thyroid metabolism.

Introduction

Normal thyroid hormone levels are necessary for the optimal effect of growth hormone (GH) on the growth rate and a complex interdependent relationship between GH-insulin growth factor-1 (IGF-1) and the hypothalamic-pituitary-thyroid (HPT) axis is well documented [1–4]. Alterations in the HPT axis have been reported following GH treatment both in adults and children affected by GH deficiency (GHD), but the mechanism of HPT changes during GH replacement are not fully understood. A decreased binding capacity of thyroxine-binding globulin (TBG) [5–7] and a central inhibitory effect on thyroid-stimulating hormone (TSH) release [8, 9] have been suggested. In addition, the hypothesis that GH alters the peripheral deiodination of thyroxine (T_4) to triiodo-

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Table 1. Pubertal status (Tanner) at baseline and after 12, 24 and 36 months of GH treatment in males and females

	Baseline, n (%) (n = 105; M/F = 82/23)	12 months, n (%) (n = 105; M/F = 82/23)	24 months, n (%) (n = 100; M/F = 79/21)	36 months, n (%) (n = 88; M/F = 70/18)
Pubic hair status				
1	82/23 (100/100)	82/23 (100/100)	76/20 (96/95)	64/16 (91/89)
2	–	–	3/1 (3.7/4.7)	5/2 (7.1/11)
3	–	–	–	1/– (1.4/–)
4	–	–	–	–
5	–	–	–	–
Genital status (for males)				
1	82 (100)	82 (100)	76 (96)	64 (91)
2	–	–	2 (2.5)	4 (5.7)
3	–	–	1 (1.2)	2 (2.8)
4	–	–	–	–
5	–	–	–	–
Breast status (for females)				
1	23 (100)	23 (100)	20 (95)	16 (89)
2	–	–	1 (4.7)	1 (5.5)
3	–	–	–	1 (5.5)
4	–	–	–	–
5	–	–	–	–

thyronine (T_3) is supported by the findings from most studies, but with controversial data [10–17]. Previous studies have been unable to demonstrate overt changes in the HPT [18, 19] or the clinical relevance of these changes during GH therapy [20, 21]. Conversely, a number of studies have shown changes in HPT in children to be transient [13, 16] or persistent up to 12 months [15]. If the mentioned data demonstrate some biochemical changes on thyroid function tests associated with GH treatment, the clinical significance of these changes remains uncertain and requires some scrutiny.

The aim of this study was to further elucidate the impact of GH replacement on thyroid status in a large selected cohort of prepubertal children affected by isolated idiopathic GHD during long-term therapy and to evaluate the correlation between thyroid function and biochemical-auxological data.

Materials and Methods

For the purpose of this study, we reviewed all files from consecutive children with isolated idiopathic GHD coming to the Units of Endocrinology of the University of Palermo from January 1, 2005 to December 31, 2010, treated with GH for at least 12 months. Of 145 patients newly diagnosed as affected by GHD, 105 children (82 boys and 23 girls; mean age 11.13 ± 2.61) were studied. Patients with already known thyroid dysfunction, with multiple pituitary hormone deficiency or receiving any other kind of hormonal replacement treatment or drug and with a follow-up of less than 12 months were excluded from this analysis. All children evaluated were in the first stage of sexual development according to the criteria of Marshall and Tanner [22] and maintained this status during the first 12 months of GH therapy. During the second and third year of follow-up, the first stages of puberty spontaneously began in 3 and 6 (3.7 and 8.5%, respectively) males and 1 and 2 (4.7 and 11.1%, respectively) females (table 1). The diagnosis of GHD was established by the clinical, auxological and biochemical criteria of the GH Research Society [23].

A sex hormone priming before GH stimulation tests was not performed in our cohort of children due to the absence of a consensus about this point and controversial data from the literature [24–27]. However, to reinforce the diagnosis of GHD, as auxological data we considered height (standard deviation, SD), height velocity (HV) 1 year before the diagnosis (SD) and height in comparison to the midparental height (SD). All patients underwent an insulin tolerance test (ITT) and a GH-releasing hormone + arginine (GHRH-Arg) test. GHD was demonstrated by failure of GH to respond to the two stimuli, with GH peaks <10 and <20 μg/l, respectively. During the tests, the areas under the curve of GH (AUC_{GH}) were calculated. At therapy onset, the euthyroid state for all patients was determined on the basis of normal baseline free T_3 (fT_3), free T_4 (fT_4) and TSH levels and negative anti-thyroperoxidase antibody (TPOAb) and anti-thyroglobulin antibody (TgAb). The patients received GH once daily at bedtime with a pen injection system. The initial daily dose was

Table 2. Baseline clinical and biochemical features of all patients at diagnosis

Parameter	Subjects (%)
Males	82 (78)
Females	23 (22)
Age, years	11.13±2.61
BMI	17.57±3.05
Height (SD)	−2.11±0.89
Height in comparison to the midparental height (SD)	−1.93±0.12
Height velocity 1 year before the diagnosis (SD)	−1.58±0.23
Bone age, years	9.04±2.67
Bone/chronological age ratio	0.79±0.09
IGF-1, μg/l	98.83±47.94
Basal GH, μg/l	0.47±0.64
AUC_{GH} during ITT	203.86±181.89
Peak GH during ITT, μg/l	2.71±2.18
AUC_{GH} during GHRH+Arg test	745.68±505.16
Peak GH during GHRH+Arg test, μg/l	9.32±6.08
fT_3, pg/ml	3.05±0.91
fT_4, ng/dl	1.25±0.24
TSH, μU/ml	1.98±0.84

0.025 mg/kg. 5 patients (3 males and 2 females) discontinued GH treatment at 12 months, 12 (9 males and 3 females) discontinued it at 24 months, and 88 patients continued the follow-up for at least 36 months.

During the study, the GH dose administered was adjusted in order to maintain serum IGF-1 levels within the normal range for sex and age. In all patients, at baseline and yearly up to 36 months for those who did not discontinue therapy, blood samples were taken and, according to our fixed internal protocol, we measured body height (SD), HV, body mass index (BMI), IGF-1, fT_3, fT_4 and TSH. Bone age was evaluated according to the Tanner and Whitehouse (TW2) method [28]. We calculated the ratio between the bone age and the chronological age (normal = 1) and showed the data as bone/chronological age ratio. The study outcome considered fT_3, fT_4 and TSH modifications (Δ) during treatment and their correlations with IGF-1 and biochemical and auxological data. The institutional ethics committee of the University of Palermo approved this study. At the time of hospitalization, an informed consent for the scientific use of the data was obtained from parents.

Hormone and Biochemical Assays

All biochemical data were collected after overnight fasting. Thyroid hormone levels were measured in our centralized laboratory using standard methods. Serum fT_3, fT_4 and TSH concentrations were analyzed using enzyme immunoassay kits (BioCheck, Inc., Foster City, Calif., USA). Sensitivity values were 0.05 pg/ml for fT_3 and 0.05 ng/dl for fT_4. For TSH, at concentrations of 0.1 and 0.2 μU/ml, the interassay coefficients of variation (CVs) of sensitivity were determined to be 11.4 and 7.9%, respectively. The intra- and interassay CVs were 2.4–11.9 and 4.2–10.7% for fT_3, 4.5–9.8 and 3.7–11.5% for fT_4, and 2.5–5.7 and 5.7–8.9% for TSH. TPOAb and TgAb were determined by immunoenzymometric assay (Radim SpA, Pomezia/Rome, Italy). Reference ranges of serum parameters for euthyroid subjects were the following: fT_3 1.4–4.2 pg/ml, fT_4 0.8–2.0 ng/dl, TSH 0.4–4.2 μU/ml, TPOAb <100 IU/ml, and TgAb <100 IU/ml. During the entire study period the GH levels were assayed by two immunoradiometric assays in our laboratory (Radim, SpA) according to availability. The sensitivity of the assay changed accordingly: 0.2 μg/l for the first year (2005) or 0.05 μg/l thereafter, intraassay CVs were 2.4–4.5 and 2.5–3.9% and interassay CVs were 5.8–8.5 and 3.8–5.0%, respectively. Serum total IGF-1 was assayed in the same laboratory using the ELISA method (OCTEIA IGF-1 Kit; IDS Inc., Fountain Hills, Ariz., USA). The sensitivity of the method was 1.9 μg/l; inter- and intraassay CV values were 7–7.1 and 2.3–3.5% and IGF-1 levels were 90.7–186 and 66.7–120.9 μg/l, respectively. The normal ranges (males and females combined) of total IGF-1 levels (μg/l) were 12–108 (0–1 years), 13–100 (1–3 years), 26–280 (3–6 years), 85–230 (6–9 years), 98–404 (9–12 years), 142–525 (12–15 years), and 146–415 (15–20 years).

Statistical Analysis

SPSS version 17 was used for data analysis. Baseline characteristics were presented as mean ± SD for continuous variables, and rates and proportions were calculated for categorical data. Normality of distribution for quantitative variables was assessed with the Kolmogorov-Smirnov test. Differences between groups in univariate analysis were detected with the Mann-Whitney test. $p < 0.05$ was considered statistically significant.

Results

The baseline clinical and biochemical features of patients are shown in table 2. As expected, a significant increase in weight, height, BMI and bone age was documented annually during the entire follow-up (table 3). In all children, HV was 8.4, 6.9 and 6.5 cm at 12, 24 and 36 months of therapy, respectively (data not shown). IGF-1 levels showed a significant increase after 12 months (314.68 ± 193.25 vs. 98.83 ± 47.94; $p < 0.001$) and 36 months (349.90 ± 145.88 vs. 330.30 ± 172.95; $p = 0.012$) of GH treatment, while no significant difference was shown after 24 months (330.30 ± 172.95 vs. 314.68 ± 193.25; $p = 0.192$), although IGF-1 remained significantly higher than the pre-therapy levels ($p < 0.001$). A significant increase in fT_3 (ΔfT_3) (4.13 ± 0.53 vs. 3.10 ± 0.94 pg/ml; $p < 0.001$) was documented after 12 months of GH treatment, without any further change after 24 and 36 months, although it remained significantly higher than the pre-therapy values. ΔfT_3 did not show any correlation with the auxological and biochemical parameters during the entire follow-up, or with ΔfT_4 and ΔTSH. Similarly, no correlation between ΔfT_3 and ΔIGF-1 was shown

Table 3. Variation of clinical and biochemical parameters after 12, 24 and 36 months of GH treatment

Parameter	Baseline (n = 105)	12 months (n = 105)	24 months (n = 100)	36 months (n = 88)	p*	p**	p***
Weight, kg	30.76±10.88	34.77±12.05	37.34±13.17	39.57±12.63	<0.001	<0.001	<0.001
Height (SD)	−2.11±0.89	−1.73±0.75	−1.44±0.76	−1.03±0.85	<0.001	<0.001	<0.001
BMI	17.57±3.05	17.75±2.97	18.15±3.33	17.98±3.29	0.005	<0.001	0.049
Bone age, years	9.04±2.67	10.70±2.56	11.71±2.25	12.69±2.04	<0.001	<0.001	<0.001
Bone/chronological age ratio	0.79±0.09	0.88±0.06	0.94±0.05	0.96±0.04	<0.001	<0.001	<0.001
IGF-1, μg/l	98.83±47.94	314.6±193.2	330.3±172.9	349.9±145.8	<0.001	0.192	0.012
fT_3, pg/ml	3.10±0.94	4.13±0.53	4.12±0.53	4.21±0.53	<0.001	0.788	0.681
fT_4, ng/dl	1.25±0.24	1.25±0.28	1.19±0.25	1.19±0.23	0.982	0.236	0.981
TSH, μU/ml	1.98±0.84	1.92±0.97	1.95±1.03	1.51±0.54	0.254	0.847	0.250

Difference between * 12 months and baseline, ** 24 and 12 months, and *** 36 and 24 months.

Table 4. Differences of auxological and biochemical parameters between patients with an increase in fT_3 (ΔfT_3) at 12 months of GH treatment according to the ≤75th and >75th percentile

	ΔfT_3 at 12 months ≤75th percentile (n = 80; 76%)	ΔfT_3 at 12 months >75th percentile (n = 25; 24%)	p
AUC_{GH}-ITT	255.72±200.03	130.99±132.38	0.023
AUC_{GH}-GHRH-Arg	785.99±503.15	465.63±273.63	0.018
Peak GH during ITT, μg/l	3.30±2.31	1.70±1.76	0.020
Peak GH during GHRH+Arg test, μg/l	9.74±5.97	5.97±3.60	0.014
Baseline IGF-1, μg/l	98.53±48.13	99.40±60.49	0.953
Baseline fT_3, pg/ml	3.53±0.54	1.81±0.72	<0.001
HV at 12 months, cm	8.54±2.33	8.13±2.17	0.550
ΔIGF-1 at 12 months	222.48±175.47	224.32±231.30	0.973

(data not shown). No significant variation in fT_4 and TSH levels was observed during follow-up (table 3).

Arbitrarily grouping all patients according to the ΔfT_3 at 12 months into those with Δ lower (80 patients, 76%) or greater (25 patients, 24%) than the 75th percentile, the latter showed significantly lower AUC_{GH} during GHRH-Arg (465 ± 273 vs. 785 ± 503; p = 0.018) and ITT (130 ± 132 vs. 255 ± 200; p = 0.023). In addition, a lower GH peak during GHRH-Arg (p = 0.014) and ITT (p = 0.020) has been documented. These children also showed lower fT_3 levels at baseline (1.81 ± 0.72 vs. 3.53 ± 0.54 pg/ml; p < 0.001), without any difference in fT_4 and TSH levels. No significant differences in auxological parameters were detected between the two groups of patients (table 4).

To support these data, we evaluated fT_3 and its Δ grouping in all children according to the GH levels at diagnosis into those with GH peak after ITT lower (26 patients, 25%) or greater (79 patients, 75%) than the 25th percentile (identified in 1.30 μg/l) to highlight children with more severe GHD. These latter showed lower, although not statistically significant, baseline fT_3 levels (3.42 ± 1.79 vs. 3.57 ± 1.03 pg/ml; p = 0.099) and a significant greater ΔfT_3 (1.09 ± 1.74 vs. 0.96 ± 0.88; p = 0.030) than children with higher GH levels (table 5).

Discussion

This retrospective analysis of a large cohort of prepubertal children affected by idiopathic GHD demonstrated that children with more severe hormone deficiency show lower fT_3 levels at diagnosis and a significant increase in

Table 5. Baseline fT_3 and its increase (ΔfT_3) after 12 months of GH treatment in patients with GH peak after ITT according to the ≤25th and >25th percentile

	GH peak after ITT <25th percentile (n = 26; 25%)	GH peak after ITT ≥25th percentile (n = 79; 75%)	p
Baseline fT_3, pg/ml	3.42 ± 1.79	3.57 ± 1.03	0.099
ΔfT_3 at 12 months	1.09 ± 1.74	0.96 ± 0.88	0.030

fT_3 during the first 12 months of treatment, without significant changes in fT_4 and TSH levels and with no significant correlation with auxological data.

First of all, it is important to specify that the recruitment and inclusion criteria of children in this study was based on the diagnosis of overt GHD made by the unanimously recognized GH stimulation tests [23], without a sex hormone priming test. There is no consensus in the literature about the significance of the diagnosis of GHD in children in the absence of priming test. If some author considers that omission of priming during the preadolescent period decreases the specificity of GH stimulation tests and increases the percentage of false-positive diagnosis results [24], others believe that it leads only to a temporary augmentation of GH secretion and may lead to underdiagnosis of peripubertal children that could have benefited from GH treatment [26].

Recently, Lazar and Phillip [25] have reviewed the available published data and suggested that priming should be considered only in adolescents with pubertal delay, girls aged 11.5–12 years and boys aged 13–13.5 years, exhibiting no evidence of puberty or only initial signs. The children evaluated in our study showed a mean chronological age of 11.34 ± 2.99 years (boys) and 9.87 ± 2.14 years (girls). In line with these data, we thought that a priming test would probably not have been useful.

This aspect could represent a hypothetical bias of this study and could decrease the specificity of the results obtained, even if the sensitivity of the thyroid data demonstrated cannot be affected by this aspect.

The relationship between GH and thyroid function has been evaluated by numerous studies, but the clinical data about the effect of GH replacement on thyroid hormonal levels in patients with GHD are contradictory and no clear correlation has been observed between thyroid hormones and auxological and biochemical data.

In normal healthy adults, short-time GH administration resulted in a reduction in total T_4 and fT_4, an increase in total T_3 and a concomitant marked decrease in TSH [11]. Following GH administration, some studies have demonstrated different degrees of thyroid hormone level changes, such as a reduction in serum fT_4 [8, 29] or an increase in fT_3 [10, 11, 16, 30], while other studies have not confirmed these observations [18, 20, 21, 30–32]. It has been suggested that the incidence of both central and peripheral hypothyroidism should be taken into account during recombinant human GH administration, as hypothyroidism may worsen the response to therapy. Some authors have demonstrated that GH therapy can unmask central hypothyroidism, leading to an attenuation of the benefit of GH in adult GHD patients with organic pituitary disease or multiple pituitary hormone deficiencies [15, 17]. For these reasons, Behan et al. [33] recently recommended that patients starting GH should have their thyroid function monitored closely, particularly in the first 6 months, to identify those who will develop hypothyroidism.

Some researchers described the possibility of a decrease in TSH secretion, however within the normal range, in children after 6 and 12 months of GH therapy. This phenomenon is probably connected with a direct effect of administered GH on the release of somatostatin, a natural TSH inhibitor [34]. On the other hand, Smyczynska et al. [35] showed a significant decrease in fT_4 serum concentrations during the initial 3–6 months of GH administration, with a concomitant significant increase in IGF-1 levels in 75 children with various disorders of GH secretion, with a lower improvement of HV in those who revealed overt hypothyroidism. For these reasons, an earlier assessment of THS and fT_4 concentration after GH therapy onset or levothyroxine administration from the beginning of GH therapy has been proposed. Conversely, our data demonstrated that GH replacement therapy does not induce hypothyroidism in children with idiopathic GHD. In our study, no significant change in TSH levels was observed during a 36-month follow-up. These findings, in line with the data of Wyatt et al. [13], seem to be discordant with other studies, probably for many reasons. Important factors which may explain the lack of consistent results are the different hormone assay methods, the small sample size of many studies and the different criteria for selection of the populations studied. In addition, the majority of published data are limited to the first 6–12 months of follow-up. To avoid these biases, for this analysis we selected the study population excluding patients with multiple pituitary hormone deficiency or

receiving any kind of hormonal replacement treatment. In addition, we also excluded all patients with a follow-up of less than 12 months in order to have a homogeneous study population with a longer follow-up.

A few years ago, Jorgensen et al. [9] showed that GH administration stimulated peripheral T_4 to T_3 conversion in a dose-dependent manner in GHD adults, and Rezvani et al. [21] observed the same data in GHD children. These findings are partially concordant with our study. Indeed, our data demonstrated that the change in TSH and fT_4 secretion during GH substitution is less significant than fluctuations in fT_3 concentrations. In our patients, a significant increase in fT_3 at 12 months of therapy is documented in the majority of cases, in line with the data of Seminara et al. [16], without a significant relationship with IGF-1 and without any impact on catch-up growth. These changes, independently of TSH levels, might be an expression of the metabolic status of patients at that moment and could be explained by an increased GH-induced T_4 to T_3 deiodination, as previously reported [12, 14, 36]. The evidence that GHD reduces T_4 to T_3 conversion and GH improves T_4 to T_3 conversion through iodothyronine deiodinase activity is well known in animal models [37–39]. In our patients, fT_3 increase does not occur during long-term follow-up (24 and 36 months), when fT_3 does not change any further. To support this hypothesis, we grouped the children according to the degree of fT_3 increase at 12 months of therapy and analyzed the difference in auxological and biochemical parameters between the children with a more pronounced increase and those with a slight increase in fT_3. Subsequently, we evaluated fT_3 and its Δ grouping in all children according to the GH levels at diagnosis to highlight children with more severe GHD. Our data demonstrated that the increase in fT_3 levels after 12 months of treatment appears to be more pronounced in children with a more severe GHD at diagnosis, documented by GH levels during the stimulation tests performed at diagnosis. We speculate that a possible explanation of these data could be that children with lower GH levels at diagnosis, in terms of both peak and AUC during the test, also have a decreased T_4 to T_3 conversion due to more severe GHD. Therefore, at therapy onset these subjects seem to restore normal fT_3 levels, with an obvious greater increase than children with less severe GHD. It is probably for this reason that the higher ΔfT_3 does not correlate with the auxological data in terms of height, weight, bone age and HV.

A limit of this study could be represented by the lack of information about the total T_3 and T_4, reverse T_3 and TBG levels, probably useful to better understand these interesting mechanisms. In fact, the role of a decreased binding capacity of TBG or a reduction in reverse T_3 cannot be ruled out as additional mechanisms. However, this is a retrospective study and our internal protocol of management of GHD children does not include these evaluations.

In conclusion, in this study we demonstrated that GHD in children seems to reduce T_4 to T_3 conversion and the onset of GH treatment is associated with a significant increase in fT_3 levels in the first 12 months of therapy. The more pronounced increase in fT_3 after 12 months of treatment happens in children affected by more severe GHD, although without significant correlation of these changes with the auxological parameters. These data, partially confirming previous studies, for the first time highlight the strong correlation between the severity of GHD and the thyroid metabolism. Further studies carried out on a broad unselected group of children on GH therapy (i.e. organic GHD, Turner syndrome, small for gestational age) and a stratification of them according to the severity of GHD or the GH dose, could give more information about the real impact of GH therapy on thyroid function and could be useful to understand the utility of the routine monitoring of thyroid function in children during GH treatment.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1 Laron Z: Interactions between the thyroid hormones and the hormones of the growth hormone axis. Pediatr Endocrinol Rev 2003; 2:244–249.

2 Wolf M, Ingbar SH, Moses AC: Thyroid hormone and growth hormone interact to regulate insulin-like growth factor-1 messenger ribonucleic acid and circulating levels in the rat. Endocrinology 1989;125:2905–2914.

3 Miyakawa M, Saji M, Tsushima T, Wakai K, Shizume K: Thyroid volume and serum thyroglobulin levels in patients with acromegaly: correlation with plasma insulin-like growth factor-1 levels. J Clin Endocrinol Metab 1988; 67:1127–1132.

4 Akin F, Yaylali GF, Turgut S, Kaptanoglu B: Growth hormone/insulin like growth factor axis in patients with subclinical thyroid dysfunction. Growth Horm IGF Res 2009;19: 252–255.

5 Oliner L, Ballantine JJ: Effect of human growth hormone on thyroidal secretion, radiothyroxine turnover and transport in man. J Clin Endocrinol Metab 1968;28:603–607.

6 Porretti S, Giavoli C, Ronchi C, Lombardi G, Zaccaria M, Valle D, Arosio M, Beck-Peccoz P: Recombinant human GH replacement therapy and thyroid function in a large group of adult GH-deficient patients: when does L-T_4 replacement become mandatory? J Clin Endocrinol Metab 2002;87:2042–2045.
7 Jorgensen JO, Pedersen SA, Laurberg P, Weeke J, Skakkebaek NE, Christiansen JS: Effects of growth hormone therapy on thyroid function of growth hormone-deficient adults with and without concomitant thyroxine substituted central hypothyroidism. J Clin Endocrinol Metab 1989;69:1127–1132.
8 Lippe BM, Van Herle AJ, La Franchi SH, Uller RP, Lavin N, Kaplan SA: Reversible hypothyroidism in growth hormone-deficient children treated with human growth hormone. J Clin Endocrinol Metab 1975;40:612–618.
9 Jorgensen JO, Moller J, Laursen T, Orskov H, Christiansen JS, Weeke J: Growth Hormone administration stimulates energy expenditure and extrathyroidal conversion of thyroxine to triiodothyronine in a dose-dependent manner and suppresses circadian thyrotrophin levels: studies in GH-deficient adults. Clin Endocrinol (Oxf) 1994;41:609–614.
10 Sato T, Suzuki Y, Taketani T, Ishiguro K, Masuyama T: Enhanced peripheral conversion of thyroxine to triiodothyronine during hGH therapy in GH-deficient children. J Clin Endocrinol Metab 1977;45:324–329.
11 Grunfeld C, Sherman BM, Cavalieri RR: The acute effects of human growth hormone administration on thyroid function in normal men. J Clin Endocrinol Metab 1988;67:1111–1114.
12 Pirazzoli P, Cacciari E, Mandini M, Sganga T, Capelli M, Cicognani A, Gualandi S: Growth and thyroid function in children treated with growth hormone. J Pediatr 1992;121:210–213.
13 Wyatt DT, Gesundheit N, Sherman B: Changes in thyroid hormone levels during growth hormone therapy in initially euthyroid patients: lack of need for thyroid supplementation. J Clin Endocrinol Metab 1998;83:3493–3497.
14 Portes ES, Oliveira JH, MacCagnan P, Abucham J: Changes in serum thyroid hormone levels and their mechanisms during long term growth hormone replacement therapy in growth hormone-deficient children. Clin Endocrinol (Oxf) 2000;53:183–189.
15 Giavoli C, Porretti S, Ferrante E, Cappiello V, Ronchi CL, Travaglini P, Epaminonda P, Arosio M, Beck-Peccoz P: Recombinant hGH replacement therapy and the hypothalamus-pituitary-thyroid axis in children with GH deficiency: when should we be concerned about the occurrence of central hypothyroidism? Clin Endocrinol 2003;59:806–810.
16 Seminara S, Stagi S, Candura L, Scrivano M, Lenzi L, Nanni L, Pagliai F, Chiarelli F: Changes of thyroid function during long-term hGH therapy in GHD children. A possible relationship with catch-up growth? Horm Metab Res 2005;37:751–756.
17 Agha A, Walker D, Perry L, Drake WM, Chew SL, Jenkins PJ, Grossman AB, Monson JP: Unmasking of central hypothyroidism following growth hormone replacement in adult hypopituitary patients. Clin Endocrinol 2007;66:72–77.
18 Rubio GR, Mellinger RC, Zafar MS, Wolf CB: Evaluation of thyroid function during growth hormone therapy. Metabolism 1976;25:15–21.
19 Rose SR, Leong GM, Yanovski JA, Blum D, Heavner G, Barnes KM, Chipman JJ, Dichek HL, Jacobsen J, Klein KE: Thyroid function in non-growth hormone-deficient short children during a placebo-controlled double-blind trial of recombinant growth hormone therapy. J Clin Endocrinol Metab 1995;80:320–324.
20 Cacciari E, Cicognani A, Pirazzoli P, Bernardi F, Zappulla F, Salardi S, Mazzanti L, Biasini A, Valenti E: Effect of long-term GH administration on pituitary-thyroid function in idiopathic hypopituitarism. Acta Paediatr Scand 1979;68:405–409.
21 Rezvani I, DiGeorge AM, Dowshen SA, Bourdony CJ: Action of human growth hormone on extrathyroidal conversion of thyroxine to triiodothyronine in children with hypopituitarism. Pediatr Res 1981;15:6–9.
22 Marshall WA, Tanner JM: Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44:291–303.
23 Growth Hormone Research Society: Consensus guidelines for the diagnosis and treatment of growth hormone deficiency in childhood and adolescence: summary statement of the Growth Hormone Research Society. J Clin Endocrinol Metab 2000;85:3990–3993.
24 Marin G, Domené HM, Barnes KM, Blackwell BJ, Cassorla FG, Cutler GB Jr: The effects of estrogen priming and puberty on the growth hormone response to standardized treadmill exercise and arginine-insulin in normal girls and boys. J Clin Endocrinol Metab 1994;79:537–541.
25 Lazar L, Phillip M: Is sex hormone priming in peripubertal children prior to growth hormone stimulation tests still appropriate? Horm Res Paediatr 2010;73:299–302.
26 Collett-Solberg PF: Update in growth hormone therapy of children. J Clin Endocrinol Metab 2011;96:573–579.
27 Rosenbloom AL: Sex hormone priming for growth hormone stimulation testing in pre- and early adolescent children is evidence based. Horm Res Paediatr 2011;75:78–80.
28 Tanner JM, Whitehouse RH, Cameron N, Marshall WA, Healy MJR, Goldstein H: Assessment of Skeletal Maturity and Prediction of Adult Height, ed 2. London, Academic Press, 1983.
29 Losa M, Scavini M, Gatti E, Rossini A, Madaschi S, Formenti I, Caumo A, Stidley CA, Lanzi R: Long-term effects of growth hormone replacement therapy on thyroid function in adults with growth hormone deficiency. Thyroid 2008;19:1249–1254.
30 Moller J, Jorgensen JO, Moller N, Christiansen JS, Weeke J: Effects of growth hormone administration on fuel oxidation and thyroid function in normal man. Metabolism 1992;41:728–731.
31 Amato G, Izzo G, Salzano I, Bellastella A: Recombinant human growth hormone treatment at low doses does not significantly change thyroid function in growth hormone-deficient adults. J Endocrinol Invest 1996;19:563–566.
32 Saggese G, Cesaretti G, Di Spigno G, Cinquanta L, Giannessi N, Cioni C, Bracaloni C: Thyroid and thyrotropin functions in subjects with pituitary nanism treated with growth hormone. Pediatr Med Chir 1990;12:483–488.
33 Behan LA, Monson JP, Agha A: The interaction between growth hormone and the thyroid axis in hypopituitary patients. Clin Endocrinol (Oxf) 2011;74:281–288.
34 Kalina-Faska B, Kalina M, Koehler B: Assessment of thyrotropin concentrations in children with somatotropic deficiency treated with growth hormone. Endokrynol Diabetol Chor Przemiany Materii Wieku Rozw 2002;8:17–21.
35 Smyczynska J, Hilczer M, Stawerska R, Lewinski A: Thyroid function in children with growth hormone deficiency during the initial phase of growth hormone replacement therapy-clinical implications. Thyroid Res 2010;3:2.
36 Jorgensen JO, Moller J, Skakkebaek NE, Weeke J, Christiansen JS: Thyroid function during growth hormone therapy. Horm Res 1992;38:63–67.
37 Gøtzsche LS, Flyvbjerg A, Marshall S, Jørgensen KD, Weeke J: The influence of growth hormone and thyroxine on iodothyronine deiodinase activity in the liver, kidney and brown adipose tissue in hypophysectomized rats. Acta Endocrinol (Copenh) 1991;125:219–226.
38 Van der Geyten S, Buys N, Sanders JP, Decuypere E, Visser TJ, Kühn ER, Darras VM: Acute pretranslational regulation of type III iodothyronine deiodinase by growth hormone and dexamethasone in chicken embryos. Mol Cell Endocrinol 1999;147:49–56.
39 Silva JE, Larsen PR: Interrelationships among thyroxine, growth hormone, and the sympathetic nervous system in the regulation of 5-iodothyronine deiodinase in rat brown adipose tissue. J Clin Invest 1986;77:1214–1223.