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Correlation Between the Responses to Growth Hormone (GH) Treatment During Childhood and Adulthood in a Monocentric Cohort of GH-Deficient Patients

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ABSTRACT

Our aim was to analyze a cohort of patients with childhood-onset growth hormone deficiency (GHD) to evaluate if there is some correlation between the response to GH treatment during childhood and adulthood, respectively. This was an observational retrospective monocentric cohort study of 47 patients treated with GH during childhood and adulthood. Changes in growth parameters during childhood were compared with the increase of IGF-I z-score and other indexes of GH response (body composition, lipid profile) after 1 year of treatment in adulthood. The only significant positive correlation was observed between final growth velocity during the last year of childhood GH treatment and increase in IGF-I z-score in GH-treated adults ($r = 0.592$, $p = < 0.01$). No correlation was observed between growth-promoting effects of GH as child and metabolic changes induced by GH as adult. We also observed a negative correlation between weight at the end of childhood GH treatment and the IGF-I response during first year of treatment in adults ($r = -0.335$, $p < 0.05$). No significant positive correlation could be observed between the main parameters that evaluate response to GH treatment in children and adults. However, the final growth velocity, which may be considered as one of the main criteria of end of GH treatment in children, was identified as parameter that could predict future response to GH treatment in adulthood.

Introduction

Growth hormone deficiency (GHD) in children is mainly characterized by a reduced growth rate and the objectives of GH replacement therapy are to promote linear growth and to achieve adult height within the target height range [1, 2]. In adults, GH deficiency is associated with abnormalities in body composition, metabolic alterations, and suboptimal physical performance [3]. Multiple studies have confirmed the beneficial anabolic effects of GH replacement therapy in both childhood onset (CO) and adulthood onset (AO) in GHD adult patients, [4–6].

Several models have been developed to predict linear growth response to GH treatment in children with GHD [7–12] and different predictive factors for estimation of final adult height have been proposed [11]. In contrast, in GHD adults, very few models have

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been found that can allow to predict good or poor responders [13, 14]. Furthermore, except for changes in serum insulin-like growth factor (IGF-I), the metabolic responses to GH in adults are less reliably quantified, being assessed by variable markers such as body composition, cardiovascular risk factors or quality of life (QoL) indicators [15]. Thus, identifying parameters that could predict response to treatment in adults is important for clinicians in order to better target patients for whom GH treatment would be the most beneficial.

In the current study, we aimed to evaluate whether there might be a correlation between the respective childhood and adulthood responses to GH in CO-GHD patients, and to eventually identify factors in childhood that could predict the response to treatment when it is resumed in adult life.

Patients and Methods

Patients

We retrospectively reviewed the medical charts of 54 patients with CO-GHD who had been treated with GH during both childhood and adulthood and who were regularly followed in our unit of adult endocrinology from January 1996 until December 2013. Patients were excluded from the study if they had received GH during adulthood for less than twelve months (n = 7).The final study group consisted of 47 well-characterized GHD adult patients (29 men and 18 women). The diagnosis of GHD had been established in childhood by observation of a maximum GH peak below 10 µg/l during two consecutive GH stimulation tests [insulin-induced hypoglycemia (ITT) and glucagon tests] and confirmed at adulthood in all patients by a maximum GH peak less than 3 µg/l at one of the above-mentioned provocative tests [2, 4, 16]. Patients still under treatment (n = 5) had to discontinue GH for at least 1 month before undergoing the test [17]. The mean time interval between the end of GH treatment at adolescence and restart in adulthood was 78 ± 65 months. The underlying diagnoses resulting in GHD were either congenital GHD [n = 27; 57.5 % (idiopathic, n = 24; genetic mutation, n = 3)], or acquired GHD [(n = 20; 42.5 % (craniopharyngioma, n = 10; treatment of malignant disease distant from pituitary-hypothalamic area, n = 9; and germinoma, n = 1)].

Methods

We collected pediatric data concerning clinical characteristics at diagnosis of GHD and childhood GH treatment. Mid-parental height (MPH) was calculated and expressed in term of SDS and in absolute value, as described by Tanner [18]. Height and weight SDS were calculated using the reference growth charts of Flanders published in 2004 [19]. Height, weight, and GH dose were recorded at baseline, after one year of treatment and at the end of GH treatment. Growth velocity (GV) was calculated during the first and last years of treatment. We chose height gain (SDS) and growth velocity (cm/year) during the first year of GH treatment as well as the difference between final adult height and MPH as the main parameters to evaluate response to treatment in children. More specifically, children were classified as good GH responders if height gain SDS after the first year of treatment was ≥ 0.5 and as poor responders if it was below 0.5. Final growth velocity (cm/year) was also calculated during the last year of GH treatment and may be considered as one of the main criteria of end of GH treatment in children. Final adult height was the height measured at the first visit in our unit of adult endocrinology.

Data retrieved at adulthood included height, weight, BMI, blood pressure, waist-hip ratio (WHR), waist circumference, fasting glycemia, lipid levels, IGF-I concentration, and body composition assessment by bioimpedance analysis (BIA), both at baseline and after 1 year of GH treatment. As an index of GH responsiveness, we used the change (Δ) in IGF-I z-score divided by the dose of GH in mg/day after one year of treatment. We also analyzed the changes in the other above-mentioned parameters as possible indexes of GH response in adulthood.

All patients had been treated with recombinant human GH, except for 11 patients who had received pituitary-extracted human GH at the beginning of their childhood treatment (between1974 and1984) but were switched to recombinant GH thereafter.

Hormonal assays

Growth hormone during testing was measured by different methods over time: a radioimmunoassay (RIA) (GH standard WHO RP 80/505) until 09/1999, the Nichols Advantage® GH immunoassay until 04/2006, the Siemens DPC Immulite® assay between 04/2006 and 04/2008 and the Beckman DXI® GH assay using the RP WHO standard 98/574 from 04/2008 to the time of the study. The following assays were used for IGF-I: a RIA until 02/2000, the Nichols Advantage® IGF-I assay until 07/2006, the Siemens DPC Immulite® IGF-I assay between 08/2006, and 03/2009 and the Liaison Diasorin® IGF-I assay from 03/2009 to time of evaluation. The IGF-I values were expressed as z-scores related to specific reference intervals for age, as reported by Brabant et al. [20]. For IGF-I values determined by other assays, we used specific conversion formulas derived from comparisons between internal determinations carried out on large series of serum samples, as reported previously [21].

Statistical analysis

For normally distributed variables, differences between groups were analyzed using one way ANOVA test followed by Student–Newman–Keuls tests when $p < 0.05$, while Kruskal–Wallis tests were used for non-normally distributed continuous variables. To test for GH treatment effect on different parameters a Student t-paired test or a Wilcoxon signed rank test were used as indicated. Chi-square tests were used for comparisons between categorical parameters. Pearson and Spearman correlation coefficients were calculated to assess relationships between normally and non-normally distributed variables, respectively. All statistical analyses were performed with the SPSS 22.0 program (SPSS Inc., Chicago, IL, USA).

Results

Pediatric data

We included in our study 47 patients (18 women and 29 men). Thirty-nine out of the 47 patients (83 %) had multiple pituitary defi-

ciencies. Biological age and bone age at GHD diagnosis were 9.0 ± 4.2 years and 7.6 ± 4.8 years, respectively. The majority of patients had severe GHD defined in children as a peak GH concentration below 5 µg/l [22]. Mean GH peak value at provocative tests was 1.2 ± 1.0 µg/l. The GH treatment during childhood started at the age of 9.6 ± 4.4 years with a mean initial dose of 26.4 ± 6.6 µg/kg/day and ended at the age of 16.7 ± 1.9 years. As shown in ▶**Table 1**, the mean growth velocity after one year of treatment was 10.1 ± 6.2 cm with a gain of height of 0.8 ± 0.9 SDS (mean ± SD). The height gain SDS at the end of pediatric GH treatment [median duration: 75 (12–198) months] was 2.2 ± 1.7, leading to a height SDS at the end of GH treatment of − 1.3 ± 1.4 compared to the reference population. The mean final adult height was 169.4 ± 9.1 cm for men and 160.3 ± 9.5 cm for women and a difference of − 0.5 ± 1.3 SDS was observed between final adult height and MPH. There was a parallel increase of body weight from − 2.6 ± 2.1 SDS to − 1.2 ± 1.8 SDS at the end of GH treatment (▶**Table 1**). Overall, the GH dose remained stable over the treatment period (26.4 µg/kg/day at start vs 26.1 µg/kg/day at the end).

Adult data

GH peak, GH dose, and IGF-I z-score

The diagnosis of GHD was confirmed at adulthood in all patients (GH peak < 3 µg/l), by an ITT in 34 patients (72 %) and by a glucagon test (GT) in 11 (28 %). The mean GH peak was 0.71 ± 0.76 µg/l for ITT and 0.55 ± 0.37 µg/l for GT. The mean age at first visit in the adult department (corresponding to the age of the stimulation test) was 21.7 ± 6.3 years but GH treatment was started at a mean age of 24.0 ± 6.9 years. At initiation, mean GH dose was 0.58 ± 0.36 mg per day and increased to 0.67 ± 0.29 and 0.75 ± 0.28 mg per day after one and two years of treatment, respectively.

In the majority of these adult patients (87 %), IGF-I z-score was less than − 2 SDS at the onset of GH treatment in adulthood (baseline). There was no significant difference in the maximum GH peak or in IGF-I z-score between acquired and congenital GHD (data not shown). Patients with isolated GHD had a higher baseline IGF-I z-score compared to patients with multiple pituitary deficiencies (− 2.0 ± 1.5 vs. − 4.6 ± 2.3; p < 0.01). As expected, IGF-I z-score increased significantly from baseline (− 4.2 ± 2.4) to one year (− 0.4 ± 2.3) and two years of GH treatment (− 0.3 ± 1.8; p < 0.001). Although we observed a more important increase of GH doses in women compared to men (delta GH dose in µg/kg/day: + 3.47 ± 3.33 vs. − 0.14 ± 2.97; p < 0.001), their Δ IGF-I z-score was lower after one year of treatment (+ 2.4 ± 2.3 vs. + 4.0 ± 2.0 in women and men, respectively; p < 0.05). On the other hand, the one year GH-induced changes in IGF-I z-score did not differ between patients with congenital and acquired GHD.

Anthropometry and body composition

At baseline, 33 % of patients were overweight and 13 % had obesity (mean BMI for the total cohort: 23.9 ± 4.8 kg/m²). The waist-hip ratio (WHR) was 0.99 ± 0.09 in men and 0.85 ± 0.06 in women. Both weight and BMI increased significantly after 1 year of treatment while WHR decreased significantly compared to baseline values (▶**Table 2**). We also noticed an improvement of body composition evaluated by BIA, as fat mass (FM) decreased significantly and free fat mass (FFM) increased, at one year of treatment (▶**Table 2**).

Lipid profile and carbohydrate metabolism

Adult GHD patients showed an unfavorable lipid profile. However, the HDL-cholesterol remained within the target value in both genders (60 ± 18 mg/dl in women and 47 ± 13 mg/dl in men). After one year of treatment, we observed a significant decrease of LDL levels (− 14.7 ± 25.9 mg/dl, p < 0.05). The other parameters of the lipid profile were not significantly affected. No significant changes were seen in fasting glucose (▶**Table 2**).

▶**Table 1** Height and weight parameters before, under, and at the end of GH treatment during childhood.

Variables	Before treatment	After one year	End of GH treatment
Height SDS	− 3.5 ± 1.8	− 2.8 ± 1.6	− 1.3 ± 1.4
Height velocity (cm/y)	3.3 ± 1.8 *	10.1 ± 6.2	2.8 ± 1.5$
Height gain SDS	NA	0.8 ± 0.9	2.2 ± 1.7
Weight SDS	− 2.6 ± 2.1	− 2.4 ± 2.1	− 1.2 ± 1.8
BMI SDS	− 0.2 ± 1.3	− 0.6 ± 1.4	− 0.3 ± 1.7
ΔBMI (SDS)	NA	− 0.3 ± 0.6	− 0.1 ± 1.2

The results are expressed as mean ± standard deviation.
SDS: Standard Deviation Score; BMI: Body Mass Index; NA: Not Available.
* Year before start of GH treatment; $ Last year of GH treatment in childhood.

▶**Table 2** Effects of one year of GH therapy on body composition, lipid parameters, and plasma glucose in adult GHD patients.

	Baseline	After one year
Weight (kg)	66.4 ± 15.8	67.7 ± 17.1 *
BMI (kg/m²)	23.7 ± 4.8	24.1 ± 5.1 *
WHR	0.92 ± 0.11	0.85 ± 0.08 *
Fat mass (%)	30.6 ± 6.4	28.6 ± 6.9 *
Fat-free mass (%)	69.4 ± 6.4	71.4 ± 6.8 *
IGF-I z-score	− 4.2 ± 2.4	− 0.4 ± 2.3 ***
Total cholesterol (mg/dl)	213 ± 47	209 ± 45
LDL cholesterol (mg/dl)	136 ± 42	121 ± 35 *
HDL cholesterol (mg/dl)	53 ± 18	56 ± 19
Glucose (mg/dl)	79 ± 10	82 ± 6

The results are expressed as mean ± standard deviation.
BMI: Body mass index. WHR: Waist-hip ratio.
* p < 0.05. *** p < 0.001.
Baseline corresponds to onset of GH treatment in adulthood

Bone mineral density

Bone densitometry was performed at baseline and after one year of GH treatment (GHT) in only 18 adult patients. As expected, there was no significant change in bone mineral density, t-score or z-score at the lumbar spine, total hip and femoral neck after one year of GH treatment.

Correlations between childhood and adulthood responses to GH treatment

As shown in ▶ **Table 3**, we did not find any significant correlation between most parameters of childhood response to GH treatment (height gain and growth velocity during the first year of treatment, difference between final height, and MPH) and parameters of adulthood response to GH administration (increase in IGF-I z-score and metabolic parameters). There was, however, a significant positive correlation between growth velocity measured during the last year of childhood GH treatment and the ΔIGF-I z-score/GH dose after one year of adulthood GH treatment ($r = 0.592$, $p = < 0.01$; ▶ **Fig. 1a**). Final growth velocity was also negatively correlated with the change in total cholesterol observed after one year of adult GH treatment ($r = -0.614$; $p < 0.01$). On the other hand, we observed a negative correlation between the gain of weight during the first year of childhood treatment and the increase of IGF-I z-score /GH dose after one year of adult treatment ($r = -0.658$, $p < 0.001$; ▶ **Table 3;** ▶ **Fig. 1b**), meaning that children gaining more weight at the onset of GH replacement therapy had a lesser IGF-I response to GH as adults. A similar, though less important, negative correlation was also observed between weight at the end of childhood GH treatment and the first year ΔIGF-I z-score/GH dose in adults ($r = -0.335$, $p < 0.05$). No significant correlation between changes in body composition in adulthood and pediatric parameters estimating GH response in childhood was observed, due probably to the small number of patients. Also, when we compared good and poor responders to GH treatment in childhood, no significant difference was observed in the parameters evaluating GH response in adulthood (data not shown).

These correlations were also analyzed after excluding patients with craniopharyngioma (n = 10), as this pathology might have influence some responses to GH, such as body weight gain. Data are shown in **Table 1S** . Importantly, the correlation between changes in IGF-1 z-score at adulthood and final growth velocity in children remains highly significant in this subgroup of patients. In contrast, other correlations were no longer significant, likely because of a lower number of data. Indeed, although the underlying pathology might influence weight gain over the first year of GH treatment, there was no significant difference in this parameter between patients with craniopharyngioma (+ 0.07 ± 1.11 SD) and the remaining children (+ 0.38 ± 0.67 SD; NS).

Discussion

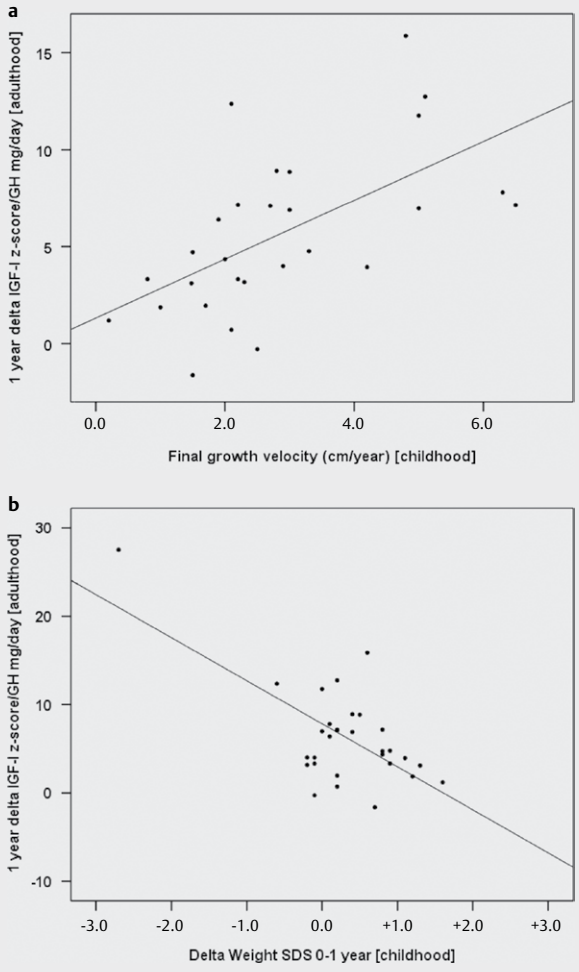
Although the benefits of GH treatment in GHD adults are now well established, individual effects are highly variable and predicting optimum response remains difficult. Clinical or biochemical predictors of GH response would clearly be of great interest for the clinicians and could help identifying individuals with high or low chance of gaining the most benefits from long-term GH treatment.

The response to GH varies considerably between individuals [23]. The reasons for such individual differences in GH responsiveness are not fully elucidated, but are probably influenced by factors acting at the level of the target tissue. Indeed, Hansen et al. [24] have demonstrated that body composition, IGFBP-1 and GH-binding protein (GHBP) affect the pharmacokinetics of GH in healthy adults independently of age. The role of the GH receptor (GHR) polymorphism has also been examined in both GHD children and adults with contradictory results [25, 26]. Recently, both GHR genotype and epigenetic variation in the CG methylation of the P2 promotor region of the IGF-I gene have been found to be major determinants of GH sensitivity in children with short stature [27].

▶ **Table 3** Correlations between pediatric estimates of GH response and adult Δ z-score IGF-I/GH dose, body composition, and lipid parameters after one year of GH treatment.

	ΔIGF-1 z-score/GH dose (mg/d)	ΔFM %	ΔFFM %	ΔWHR	ΔT-Chol	ΔLDL-Chol
Growth velocity first year R/GH (cm/year)	0.055	−0.080	0.088	0.471	0.040	0.144
Height Gain 0–1 year (SDS)	−0.050	−0.157	0.215	0.143	0.044	0.116
Difference (Adult Height – MPH) (SDS)	−0.237	0.122	−0.120	0.103	−0.018	0.312
Δ weight 0–1 year (SDS)	**−0.658****	−0.173	0.174	0.034	−0.360	−0.312
Final growth velocity (cm/year) (last year R/GH)	**0.592****	−0.414	0.411	−0.171	**−0.614****	−0.290

** $p < 0.01$, *** $p < 0.001$.
Δ 0–1 year: Difference between the parameter value after one year of GH treatment for pediatric period and its value at the initiation of therapy. R/GH: GH treatment; FM: Fat Mass; FFM: Fat-Free Mass; WHR: Waist-hip ratio; T-Chol: Total cholesterol; LDL-Chol: LDL-cholesterol; MPH: Mid-parental height.



▶ **Fig. 1** **a**: Positive correlation between final growth velocity during the last year of childhood GH treatment and the ΔIGF-I z-score/GH dose after one year of adulthood GH treatment ($r = 0.592$; $p < 0.01$). **b**: Negative correlation between Δ weight during the first year of childhood GH treatment and the ΔIGF-I z-score/GH dose after one year of adulthood GH treatment ($r = -0.658$; $p < 0.001$).

It is also known that IGF-I is not a reliable marker for the diagnosis of GHD in adults as a large overlap exists between GHD and normal subjects [28]. However, IGF-I is still the primary biochemical marker that is followed during GH replacement in adults and a dose titration regimen based on measurements of serum IGF-I is recommended [4, 29]. As the dose of GH depends on the baseline levels of IGF-I [30] and the IGF-I response is influenced by the GH dose, we decided to use as index of GH response in adults the ratio between the change in IGF-I z-score from baseline to year 1 and the daily GH dose at the end of this period. This approach has been used in previous studies [31], while Barbosa et al. [13] preferred to use the cumulative dose, as it would reflect the total dose exposure during the study period.

As recommended [4, 29], GH replacement therapy was commenced in our adult GHD patients by using a dose titration regimen based on measurements of serum IGF-I. The treatment allowed a significant increase of IGF-I z-score but the recommended target of reaching the upper half or quartile of the IGF-I normal range [4] was not achieved in most patients. This could be due to insufficient compliance of some patients or to some medical inertia in increasing GH doses in real life situation. However, despite that, we observed a significant improvement of body composition and lipid parameters after one and two years of treatment. We also observed expected significant correlations between the increase in IGF-I z-score and decreases in total cholesterol and LDL cholesterol (data not shown), suggesting that IGF-I levels may reflect a sufficient clinical response to treatment.

In previous studies [32, 33], a positive correlation between increases in IGF-I and FFM has been shown while other effects of GH replacement on quality of life or on dyslipidemia did not correlate with modifications of circulating IGF-I concentrations [33]. In the current study we could not identify a significant correlation between changes in IGF-I and body composition parameters. The small number of patients has probably attenuated the effects of GH treatment due to possible influence of different confounders. Interestingly, in a recent observational study including a much larger number of patients, Feldt–Rasmussen et al. [14] showed that the increase in IGF-I-SDS was associated with some but not with all parameters of the phenotypic response to GH treatment.

Our data confirm that adult men and women with GHD display marked differences in their responsiveness to GH replacement therapy, as the IGF-I response was much lower in women, despite a higher GH dose. This is in accordance with previous studies showing men to be more sensitive to GH than women [13, 23, 29, 34, 35]. Interestingly, such a gender difference does not seem to exist in children, suggesting that different factors must be involved in the mediation of growth and metabolic responses to GH. Besides, Drake et al. [29] have shown that the time taken to achieve an efficient maintenance dose of GH was significantly longer in female patients.

The response to GH therapy in children has been traditionally expressed in terms of growth velocity (GV) measured as cm/year. In our cohort of patients, after one year of treatment, the average GV was 9.4 ± 3.5 cm, similar to that reported in larger studies [22, 36]. The difference between near-adult height SDS and mid-parental target height SDS is, however, considered as the best indicator of whether an individual has achieved his/her height potential [10]. This difference was -0.5 ± 1.3 SDS in our patients suggesting that they indeed achieved a height close to their genetic potential, similar to results reported in other studies [10, 37–39]. Therefore, we can assume that our patients had efficient GH therapy during childhood as far as longitudinal growth is concerned.

The prediction of the response to GH in GHD children has been widely examined in several studies including very large numbers of patients [9, 22, 40, 41] and mathematical algorithms have been proposed to predict the individual response to GH therapy [7, 9, 11, 42]. On the other hand, very few prediction models exist to predict achievement of the main clinical end points with adult GH replacement therapy [13, 14, 35].

To the best of our knowledge, our study is the first to investigate possible associations between the response to GH treatment in the same individuals treated during childhood and adulthood. We found no significant correlation between the main parameters, which evaluate response to GH treatment in children (height gain,

growth velocity during the first year of GH treatment and difference between adult height and MPH) on one hand, and the increase of IGF-I z-score or the changes in other metabolic parameters during the first year of adult GH treatment on the other hand. This again suggests that different mechanisms operate to mediate the pediatric linear growth-promoting effects of GH and its IGF-I generating and metabolic effects in adults. Alternatively, it is also possible that factors determining GH response are not genetically determined but may evolve in a positive or negative way during transition from adolescence to adulthood. We observed, however, a highly significant positive correlation between growth velocity during the last year of childhood GH treatment and changes in IGF-I z-score and total cholesterol after one year of GH treatment in adulthood. Thus, the final growth velocity, which may be considered as one of the main criteria of end of GH treatment in children, could serve to predict response to GH treatment in adult.

We also found a negative correlation between body weight achieved at the end of childhood GH treatment and the ΔIGF-I z-score at one year of treatment at adult life, suggesting that weight gain during childhood treatment is a negative predictor of subsequent response to GH in adult life. Barbosa et al. [13] found that adult patients with a higher BMI are more likely to be poor responders to GH in terms of body composition. Similarly, they showed that an increase in fat mass decreases the probability of good response to GH therapy. In a randomized double-blind placebo study, Ezzat et al. [33] demonstrated that having a higher BMI is a predictor for less significant improvements in fat mass and lean mass and that changes in lean body mass are associated with those of IGF-I. Bengtsson et al. [43] reported a lower increase of IGF-I with increase of baseline body weight. Accordingly, we found at adult life a negative correlation between BMI at baseline and ΔIGF-I z-score after one year of treatment. Taking into account that the BMI in adulthood was strongly correlated with the BMI at the end of pediatric treatment, one can speculate that children that took more weight during GH treatment remained overweight and thus were less good responders to GH in adulthood.

Some limitations of our study must be acknowledged. First, there were only a limited number of patients with a sufficient amount of available data to be included. Thus, the power of our statistical analyses was reduced and some significant associations might have been underestimated. Also, our analysis of the data was retrospective and could not take into account important factors such as patient compliance to treatment or the influence of other factors that might have interfered with the response to GH. Nevertheless, we believe that these limitations do not introduce major bias in our main conclusions.

In summary, the only positive pediatric clinical predictor of GH response in adults was the final growth velocity during the last year of childhood GH treatment. Furthermore, we identified a negative association between body weight increase during first year of childhood GH treatment, BMI at the end of pediatric treatment and BMI at the onset of adult treatment on one hand, and the IGF-I increase during first year of adult GH treatment on the other hand, thus suggesting that excessive weight gain during GH treatment in childhood could predict a less good response to GH treatment in adult life.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

[1] Wilson TA, Rose SR, Cohen P, Rogol AD, Backeljauw P, Brown R, Hardin DS, Kemp SF, Lawson M, Radovick S, Rosenthal SM, Silverman L, Speiser P. Update of guidelines for the use of growth hormone in children: The Lawson Wilkins Pediatric Endocrinology Society Drug and Therapeutics Committee. J Pediatr 2003; 143: 415–421

[2] Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: Summary statement of the research society. J Clin Endocrinol Metab 2000; 85: 3990–3993

[3] De Boer H, Blok GJ, Van der Veen EA. Clinical aspects of growth hormone deficiency in adults. Endocrine Reviews 1995; 16: 63–86

[4] Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and treatment of adult growth hormone deficiency: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1587–1609

[5] Carroll PV, Christ ER, the members of growth hormone research society scientific committee.Bengtsson BA, Carlsson L, Christiansen JS, Clemmons D, Hintz R, Ho K, Laron Z, Sizonenko P, Sönksen PH, Tanaka T, Thorner M. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: A review. J Clin Endocrinol Metab 1998; 83: 382–395

[6] Appelman-Dijkstra N, Claessen K, Roelfsema F, Pereira A, Biermasz N. Long-term effects of recombinant human GH replacement in adults with GH deficiency: A systematic review. Eur J Endocrinol 2013; 169: R1–R14

[7] Schonau E, Westermann F, Rauch F, Stabrey A, Wassmer G, Keller E, Bramswig J, Blum WF. A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency. Eur J Endocrinol 2001; 144: 13–20

[8] Albertsson-Wikland K, Kristrom B, Rosberg S, Svensson B, Nierop AFM. Validated multivariate models predicting the growth response to GH treatment in individual short children with a broad range in GH secretion capacities. Pediatr Res 2000; 48: 475–484

[9] Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W, Albertsson-Wikland K, Price DA. Derivation and validation of a mathematical model for predicting the response to exogenous recombinant human growth hormone (GH) in prepubertal children with idiopathic GH deficiency. KIGS International Board. Kabi Pharmacia International Growth Study. J Clin Endocrinol Metab 1999; 84: 1174–1183

[10] Reiter EO, Price DA, Wilton P, Albertsson-Wikland K, Ranke MB. Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: Analysis of a large international database. J Clin Endocrinol Metab 2006; 91: 2047–2054

[11] De Ridder MA, Stijnen T, Hokken-Koelega AC. Prediction of adult height in growth-hormone-treated children with growth hormone deficiency. J Clin Endocrinol Metab 2007; 92: 925–931

[12] Straetemans S, Roelants M, Thomas M, Rooman R, De Schepper J. Reference curve for the first-year growth response to growth hormone treatment in prepubertal children with idiopathic growth hormone deficiency: Validation of the KIGS first-year growth response curve using the Belgian Register for the Study of Growth and Puberty Problems. Horm Res Paediatr 2014; 81: 343–349

[13] Barbosa EJ, Koranyi J, Filipsson H, Bengtsson BA, Boguszewski CL, Johannsson G. Models to predict changes in serum IGF1 and body composition in response to GH replacement therapy in GH-deficient adults. Eur J Endocrinol 2010; 162: 869–878

[14] Feldt-Rasmussen U, Brabant G, Maiter D, Jonsson B, Toogood A, Koltowska-Haggstrom M, Krogh Rasmussen A, Buchfleder M, Saller B, Biller MK. Response to GH treatment in adult GH deficiency is predicted by gender, age, and IGF1 SDS but not by stimulated GH-peak. Eur J Endocrinol 2013; 168: 733–743

[15] Monson JP. Long-term experience with GH replacement therapy: Efficacy and safety. Eur J Endocrinol 2003; 148: 9–14

[16] Cook D, Rose S. A review of guidelines for use of growth hormone in pediatric and transition patients. Pituitary 2012; 15: 301–310

[17] Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. Eur J Endocrinol 2005; 152: 165–170

[18] Tanner JM. Standards for children's height at ages 2-9 years allowing for height of parents. Arch Dis Child 1970; 45: 755–762

[19] http://www.vub.ac.be/groeicurven website accessed 18/10/2017

[20] Brabant G, Von zur Mühlen A, Wüster C, Ranke MB, Kratzsch J, Kiess W, Ketelslegers JM, Wilhelmsen L, Hulthén L, Saller B, Mattsson A, Wilde J, Schemer R, Kann P. Serum Insulin-Like Growth Factor I Reference Values for an Automated Chemiluminescence Immunoassay System: Results from a Multicenter Study. Horm Res 2003; 60: 53–60

[21] Alexopoulou O, Bex M, Kamenicky P, Bessomo Mvoula A, Chanson P, Maiter D. Prevalence and risk factors of impaired glucose tolerance and diabetes mellitus at diagnosis of acromegaly: A study in 148 patients. Pituitary 2014; 17: 81–89

[22] Ranke MB, Lindberg A. KIGS International Board. Observed and predicted growth responses in prepubertal children with growth disorders: Guidance of growth hormone treatment by empirical variables. J Clin Endocrinol Metab 2010; 95: 1229–1237

[23] Johannsson G, Bjarnason R, Bramnert M, Carlsson LMS, Degerlad M, Manhem P, Rosen T, Thoren M, Bengtsson BA. The Individual Responsiveness to Growth Hormone (GH) Treatment in GH-Deficient Adults Is Dependent on the Level of GH-Binding Protein, Body Mass Index, Age, and Gender. J Clin Endocrinol Metab 1996; 81: 1575–1581

[24] Hansen TK, Jørgensen JO, Christiansen JS. Body composition and circulating levels of insulin, insulin-like growth factor-binding protein-1 and growth hormone (GH)-binding protein affect the pharmacokinetics of GH in adults independently of age. J Clin Endocrinol Metab 2002; 87: 2185–2193

[25] Van der Klaauw AA, Van der Straaten T, Baak-Pablo R, Biermasz NR, Guchelaar HJ, Pereira AM, Smit JWA, Romijn JA. Influence of the d3-Growth Hormone (GH) Receptor Isoform on Short-Term and Long-Term Treatment Response to GH Replacement in GH-Deficient Adults. J Clin Endocrinol Metab 2008; 93: 2828–2834

[26] Barbosa EJ, Palming J, Glad CAM, Filipsson H, Koranyi J, Bengtsson BA, Carlsson LMS, Boguszewski CL, Johannsson G. Influence of the Exon 3-Deleted/Full-Length Growth Hormone (GH) Receptor Polymorphism on the Response to GH Replacement Therapy in Adults with Severe GH Deficiency. J Clin Endocrinol Metab 2009; 94: 639–644

[27] Ouni M, Castell AL, Linglart A, Bougnères P. Genetic and epigenetic modulation of growth hormone sensitivity studied with the IGF-1 generation test. J Clin Endocrinol Metab 2015; 100: 919–925

[28] Mukherjee A, Monson JP, Jönsson PJ, Trainer PJ, Shalet SM. Seeking the optimal target range for insulin-like growth factor I during the treatment of adult growth hormone disorders. J Clin Endocrinol Metab 2003; 88: 5865–5870

[29] Drake WM, Coyte D, Camacho-Hübner C, Jivanji NM, Kaltsas G, Wood DF, Trainer PJ, Grossman AB, Besser GM, Monson JP. Optimizing growth hormone replacement therapy by dose titration in hypopituitary adults. J Clin Endocrinol Metab 1998; 83: 3913–3919

[30] Murray RD, Howell SJ, Lissett CA, Shalet SM. Pre-treatment IGF-I level is the major determinant of GH dosage in adult GH deficiency. Clin Endocrinol 2000; 52: 537–542

[31] Meyer S, Haist M, Schaefer S, Ivan D, Ittner JR, Nawroth PP, Plöckinger U, Stalla GK, Tuschy U, Weber MM, Weise A, Pfützner A, Habbe N, Kann PH. Association of COLIA1 Sp1 polymorphism with the effect of subcutaneously injected recombinant hGH in GH-deficient adults. Pharmacogenomics 2008; 9: 1017–1026

[32] Thorén M, Hilding A, Baxter RC, Degerblad M, Wivall-Helleryd IL, Hall K. Serum insulin-like growth factor I (IGF-I), IGF-binding protein-1 and -3, and the acid-labile subunit as serum markers of body composition during growth hormone (GH) therapy in adults with GH deficiency. J Clin Endocrinol Metab 1997; 82: 223–228

[33] Ezzat S, Fear S, Gaillard RC, Gayle C, Marcovitz S, Mattioni T, Nussey S, Rees A, Svanberg E. Circulating IGF-I levels in monitoring and predicting efficacy during long-term GH treatment of GH-deficient adults. Eur J Endocrinol 2003; 149: 499–509

[34] Burman P, Johansson AG, Siegbahn A, Vessby B, Karlsson FA. Growth hormone (GH)-deficient men are more responsive to GH replacement therapy than women. J Clin Endocrinol Metab 1997; 82: 550–555

[35] Columb B, Smethurst LE, Mukherjee A, Jostel A, Shalet SM, Murray RD. GH sensitivity of GH-deficient adults is dependent on gender but not timing of onset. Clin Endocrinol (Oxf) 2009; 70: 281–286

[36] Straetemans S, De Schepper J, Thomas M, Verlinde F, Rooman R. and the members of BESPEED. Validation of prediction models for near adult height in children with idiopathic growth hormone deficiency treated with growth hormone: A Belgian Registry Study. Horm Res Paediatr 2016; 86: 161–168

[37] Thomas M, Massa G, Bourguignon JP, Craen M, De Schepper J, de Zegher F, Dooms L, Du Caju M, François I, Heinrichs C, Malvaux P, Rooman R, Thiry-Counson G, Vandeweghe M, Maes M. Final height in children with idiopathic growth hormone deficiency treated with recombinant human growth hormone: The Belgian experience. Horm Res 2001; 55: 88–94

[38] Darendeliler F, Lindberg A, Wilton P. Response to Growth Hormone Treatment in Isolated Growth Hormone Deficiency versus Multiple Pituitary Hormone Deficiency. Horm Res Paediatric 2011; 76: (Suppl 1): 42–46

[39] Cutfield W, Lindberg A, Albertsson Wikland K, Chatelain P, Ranke MB, Wilton P. Final height in idiopathic growth hormone deficiency: The KIGS experience. KIGS International Board. Acta Paediatr Suppl 1999; 88: 72–75

[40] Ranke MB, Lindberg A, Chatelain P, Wilton P, Price DA, Albertsson-Wikland K. The potential of prediction models based on data from KIGS as tools to measure responsiveness to growth hormone. Hormone Research 2001; 55: (Suppl 2): 44–48

[41] Blethen SL, Baptista J, Kuntze J, Foley T, Lafranchi S, Johanson A. Adult Height in Growth Hormone (GH)-Deficient Children Treated with Biosynthetic GH. J Clin Endocrinol Metab 1997; 82: 418–420

[42] Ranke MB, Lindberg A, Albertsson-Wikland K, Wilton P, Price DA, Reiter EO. Increased Response, But Lower Responsiveness, to Growth Hormone (GH) in Very Young Children (Aged 0–3 Years) with Idiopathic GH Deficiency: Analysis of Data from KIGS. J Clin Endocrinol Metab 2005; 90: 1966–1971

[43] Bengtsson BA, Abs R, Bennmarker H, Monson JP, Feldt-Rasmussen U, Hernberg-Stahl E, Westberg B, Wilton P, Wüster C. The effects of treatment and the individual responsiveness to growth hormone (GH) replacement therapy in 665 GH-deficient adults. KIMS Study Group and the KIMS International Board. J Clin Endocrinol Metab 1999; 84: 3929–3935