



Research Article

Adherence to Growth Hormone-Determined by a Consensual, Center-Based Supply-Associates with Height Outcomes in Youth

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Abstract

Objective: The efficacy of recombinant human growth hormone (rhGH) therapy in children and adolescents depends on underlying cause, younger age and height at therapy onset, expected height related to mid-parental height (MPH), duration of treatment and optimal adherence. Here, we investigated the association between adherences to rhGH-therapy with gain in height standard deviation (Δ HSD) in reference to mid-parental height (MPH), from treatment start to the most recent visit.

Methods: Single-center, retrospective data analysis in patients on rhGH between 2006-2020. Anthropometric data were normalized using national representative growth charts. Adherence was calculated as the ratio (%) of rhGH distributed / rhGH needed (reported by specialized nursing staff and treating endocrinologist). Linear interpolation was used to calculate annualized follow-up data. Multiple linear regression modelling was applied.

Results: A total of 125 patients received rhGH, of whom 102 had longitudinal data (>12 months) over a mean of 5.4 years (SD 2.9). In the first year after treatment start, the mean (SD) growth velocity (GV) was 9.4cm/y (2.5), followed by measures in the upper normal range in subsequent years. Adjusted for duration of treatment, sex and MPH, adherence (per 10% increment) was associated with Δ HSD (β -coefficient 0.36, 95% confidence interval 0.04-0.67, p-value 0.026).

Conclusion: In the setting of a centre-based distribution of rhGH, the assessment of adherence as the ratio of rhGH distributed/needed can help to identify those who respond poorly and may benefit from further support to optimize treatment efficacy.

Keywords: Adherence; Growth hormone; Short stature; Children

Introduction

Children with short stature due to various underlying causes including growth hormone deficiency, Turner syndrome and chronic renal failure are treated with recombinant human growth hormone (rhGH), aiming to achieve their genetically determined adult height and body composition. The largest published longitudinal study undertaken by the Safety and Appropriateness of Growth hormone treatments in Europe (SAGhE) consortium, including more than 400,000 patient-years of follow-up, has provided evidence that treatment with rhGH is safe and effective [1]. Efficacy of rhGH treatment for short stature depends on the underlying cause. In addition, younger age and lower height at therapy-onset, higher mid-parental height [2], appropriate rhGH dosing and better therapy adherence [3-6] have all been identified as factors contributing to efficacy. Adherence has previously been defined as “the extent to which a person’s behaviour, with regard to taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health-care provider” [7]. Challenges for optimal adherence to rhGH treatment include a requirement for daily, long-term subcutaneous injections, lower socio-economic status [8], adolescent age [9], and an inadequate understanding of the treatment goals [9]. Observational evidence has shown non-adherence to rhGH treatment in up to 82% of individuals [10]. Poor adherence to rhGH therapy is associated with reduced height velocity and ultimately with unsatisfactory final adult height [4,6]. From a public health perspective, poor adherence to rhGH treatment causes unnecessary costs [11]. Despite key for efficacy, methods to assess adherence are sparse. Here, we investigate adherence and efficacy of rhGH therapy in all children and adolescents treated with rhGH since 2006 in a Swiss tertiary centre. Our study aims were to i) assess efficacy of growth hormone treatment in our centre and ii) to investigate any association between adherence and height achievement, assessed by the increase in height SD from treatment start to the most recent visit (Δ HSD).

Methods

Design and Patients

This study is a single-centre, retrospective, observational

analysis of all patients who received rhGH treatment between January 2006 and October 2020 at the department of paediatric endocrinology at the Inselspital Berne, Switzerland. The study did not require approval by the ethics committee as it was subject to an internal audit. The study fully conforms to the World Medical Association Declaration of Helsinki. Patients were reviewed at the timepoint of diagnosis (baseline), 3 months after initiation of rhGH treatment and every 6 months thereafter.

Data collection

Participant’s data included sex, age (y), height (m), weight (in kg), BMI (determined by weight in kg divided by height in m²), sex-related mid-parental height expectation (MPH, calculated as half the combined parental heights minus 6.5 cm for females, plus 6.5 cm for males) and pubertal status according to Tanner [12,13]. Height was measured using a wall mounted Harpenden stadiometer (Ulmer Stadiometer 751.000, Busse Design+Engineering®, Elchingen, Germany). Growth velocity (GV) was calculated in centimetres per year with a minimum of 6 months interval between assessments. Height, weight, BMI, MPH and GV were given in absolute measures and in standard deviations (SD) based on national normative reference data [14]. Baseline and annualized data for height and GV since treatment start were estimated using linear interpolation of measures obtained at visits before and after each anniversary, as previously described [15]. Annualized growth rate and annualized height SD in relation to individual mid-parental height SD were determined for every patient for the number of treatment-years completed and used to assess efficacy. Annual bone age results were obtained by comparison of a left wrist X-ray compared with the Greulich and Pyle radiographic atlas [16] by trained paediatric endocrinologists. Growth hormone stimulation testing was performed according to site-specific protocols, using either Arginine or Insulin tolerance tests. Serum growth biomarkers IGF-1 and IGF-BP3 were measured using Chemiluminescent Immunoassay technology (Siemens, Immulite® 2000).

Categorization of patients on rhGH treatment

Variability of indications for rhGH treatment affects anticipated efficacy. For descriptive purposes we therefore categorized patients according to a modified Säwendahl et al. risk group classification (1) (indications and baseline characteristics are described in Table 2).

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Characteristic	n (%)	Mean (SD)	Range (min - max)
Sex, males (%)	76 (61)		
Age (y)	125	6.04 ± 3.12	0.50 - 16.09
Weight (kg)	125	17.0 ± 7.6	5.3 - 46.0
Weight SD	125	-1.83 ± 1.38	-7.07 to 3.34
Height (m)	125	1.03 ± 0.19	0.54 - 1.50
Height SD	125	-2.40 ± 1.33	-8.78 to 1.16
BMI (kg/m ²)	125	15.4 ± 2.0	11.6 - 25.7
BMI SD	125	-0.39 ± 1.26	-3.72 to 4.73
Tanner stage	125 (100)		
n pre-pubertal	120 (96)		
n peri-pubertal	5 (4)		
n post-pubertal	0		
Difference in BA to CA (y)	118 (91)	-1.34 ± 1.26	-5.72 to 4.77
Category	125 (100)		
1a	60 (48)		
1b	22 (18)		
2a	18 (14)		
2b	13 (10)		
3	12 (10)		

Abbreviations: n, number of individuals; BA, Bone age; CA, chronologic age; y, years; BMI, body mass index.

Table 1: Patient characteristics.

Characteristic	1a (60)			1b (22)			2a (18)			2b (13)			3 (12)		
	n (%)	Mean (SD)	Range (min-max)	n (%)	Mean (SD)	Range (min-max)	n (%)	Mean (SD)	Range (min-max)	n (%)	Mean (SD)	Range (min-max)	n (%)	Mean (SD)	Range (min-max)
Sex, males (%)	41 (68)			16 (72)			10 (56)			5 (38)			4 (33)		
Age(y)	60	6.67 ± 3.12	1.29 - 16.09	22	5.91 ± 1.81	4.13 - 10.19	18	3.50 ± 2.36	0.50 - 7.93	13	4.68 ± 2.74	2.16 - 11.51	12	8.41 ± 3.30	3.14 - 13.30
Weight (kg)	60	17.5 ± 7.2	5.6 - 44.5	22	15.6 ± 4.2	9.8 - 26.2	18	12.7 ± 6.3	5.3 - 27.4	13	15.2 ± 5.7	8.0 - 27.0	12	25.3 ± 10.7	11.1 - 46.0
Weight SD	60	-2.04 ± 0.92	-5.65 to 0.18	22	-2.10 ± 1.01	-4.23 to 0.51	18	-1.89 ± 2.26	-7.07 to 1.90	13	-1.32 ± 2.10	-4.75 to 3.34	12	-0.88 ± 1.36	-2.55 to 2.10
Height (m)	60	1.05 ± 0.18	0.61 - 1.50	22	1.02 ± 0.12	0.84 - 1.27	18	0.86 ± 0.20	0.54 - 1.30	13	0.96 ± 0.14	0.78 - 1.30	12	1.20 ± 0.20	0.85 - 1.50
Height SD	60	-2.53 ± 0.98	-7.36 to -1.12	22	-2.56 ± 0.78	-4.44 to -0.71	18	-2.75 ± 2.46	-8.78 to 1.16	13	-2.00 ± 1.69	-4.08 to 1.12	12	-1.55 ± 1.10	-3.13 to 0.08
BMI (kg/m2)	60	15.1 ± 1.6	12.6 - 20.1	22	14.8 ± 1.5	11.6 - 17.9	18	16.1 ± 1.7	13.1 - 19.3	13	16.0 ± 2.4	13.1 - 23.4	12	16.8 ± 3.3	13.9 - 25.7
BMI SD	60	-0.64 ± 1.03	-3.07 to 1.54	22	-0.57 ± 1.22	-3.72 to 1.31	18	0.08 ± 1.25	-2.24 to 2.51	13	0.11 ± 1.60	-1.93 to 4.73	12	0.03 ± 1.59	-1.60 to 4.10
Tanner stage	60			22			18			13			12		
n pre-pubertal (%)	58 (97)			22 (100)			17 (94)			13 (100)			10 (83)		
n peri-pubertal (%)	2 (3)			0			1 (6)			0			2 (17)		
n post-pubertal	0			0			0			0			0		
Difference in BA to CA (y)	58	-1.62 ± 1.09	-5.72 to 0.76	22	-1.49 ± 1.07	-3.46 to 0.90	13	-0.74 ± 1.97	-3.59 to 4.77	11	-1.42 ± 0.99	-3.59 to 0.03	12	-0.84 ± 1.55	-4.63 to 1.40

Category 1a: children with isolated growth hormone deficiency; 1b: children born small for gestational age; 2a: children with multiple pituitary hormone deficiencies and rare genetic syndromes; 2b: children with Turner syndrome and SHOX-gene deficiency; 3: children with short stature related to cancer treatment and chronic renal failure. Abbreviations: n, number of individuals; BA, Bone age; CA, chronologic age; y, years; BMI, body mass index.

Table 2: Patient characteristics by category.

Adherence analyses

The specialized endocrine nursing staff exclusively distribute rhGH to all patients, according to their reported remaining household stock from the previous visit, and the clinician's prescribed daily dose for the period until the next visit. Hence, adherence was calculated in retrospect at each visit, based on the ratio of rhGH distributed to the rhGH dose needed for the relevant interval. During follow-up visits, the rhGH dose was adjusted based on the patient's weight, growth velocity and IGF-1 result as per published recommendations for the underlying diagnosis [17-20]. For the analysis, the cumulative adherence over the whole duration of treatment was used until the most recent consultation. Adherence values above 100% for patients who received a higher amount of rhGH than needed at the start of the rhGH treatment to secure sufficient stock (in the magnitude of ~10-20% in case of postponed clinical follow-up visits) were set to 100% for the inferential analysis. Patients with less than 12 months of longitudinal data (i.e. two follow-up visits) were excluded from the adherence analyses.

Statistics

Descriptive statistics for patient characteristics were mean, SD and range (min-max) for continuous variables and proportions for categorical variables. Linear regression modelling was performed to examine any association between adherence to rhGH treatment (independent variable) and efficacy of GH treatment (dependent variable). Efficacy was calculated as the difference in baseline height SD to the most recent height SD (Δ HSD) in reference to individual MPH. The final model was adjusted for duration of treatment and sex.

Results

A total of 125 patients with an exposure of 578 patient-years to rhGH were included (see Table 1 and Table 2). Mean pre-treatment height SD varied from -2.56 SD in category 1b to -1.55 in category 3. A sex ratio of 3:1 in favour of the male sex was seen. Two patients presented a height SD >1 at the start of GH therapy: one diagnosed with late onset congenital adrenal hyperplasia had a bone age 4.8 years advanced above chronological age, the second patient was started on rhGH in the first year of life due to persistent hypoglycaemia in the context of septo-optic dysplasia and multiple pituitary hormone deficiencies.

Adherence

Data for adherence was available for a total of 102 patients covering 553 patient years. Cumulative adherence results were 100% in 51 patients (50%), between ≥ 90 -100% in 32 patients (31%), ≥ 80 -90% in 16 patients (16%) and <80% in 3 patients (3%). The results of the regression model to investigate any association between adherence to and efficacy of rhGH treatment, adjusted for sex, MPH and the duration of treatment are shown in Table 4. The β -coefficient (95% confidence interval, p-value) for a 10% increase in adherence was 0.37 SD (0.06-0.7, p=0.026) in Δ HSD.

Efficacy

A total of 107 patients had longitudinal data with a mean (SD) duration of treatment of 5.4 years (2.8). The largest increases in mean (SD) height and absolute measures of growth velocity (GV) were seen during the first year of treatment with 0.77 (0.55) and 9.4 cm/y (2.5), respectively. After the first year of treatment, mean GV remained within the upper normal range adjusted for age and sex. Figure 1 illustrates catch-up growth per year of treatment with rhGH for participants with longitudinal data. Figure 2 illustrates efficacy-trajectories of rhGH treatment per category. Relevant GV's and increases in height SD in relation to baseline height SD are summarized in Table 3.

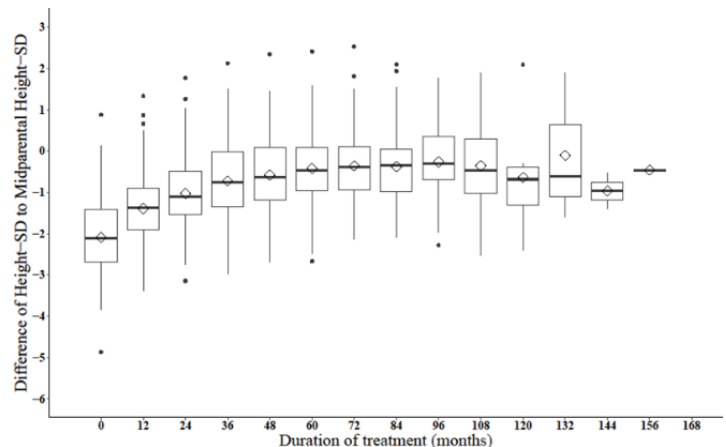


Figure 1: Box and whisker plot to indicate the difference between height SD at commencement of rhGH to individual MPH-SD over time. Bold line indicates median, rectangle indicates upper and lower quartile, diamond indicates mean value.

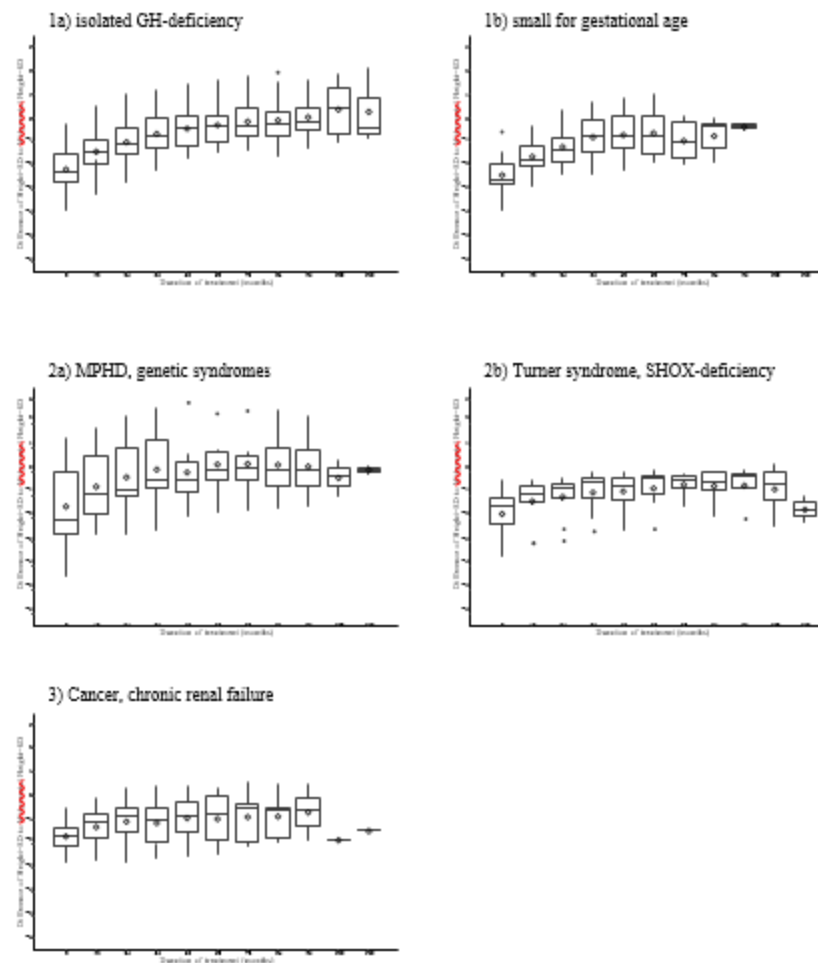


Figure 2: Box and whisker plot to indicate the difference between heights SD at rhGH-treatment start to individual MPH-SD over 10 years. Bold line indicates median, rectangle indicates upper and lower quartile, diamond indicates mean value. Number of participants for each category: 1a) 53; 1b) 20; 2a) 14; 2b) 11; 3) 9.

Year	Characteristic	1a (53)			1b (20)			2a (14)			2b (11)			3 (9)			Total (107)		
		n	Mean (SD)	Range (min - max)	n	Mean (SD)	Range (min - max)	n	Mean (SD)	Range (min - max)	n	Mean (SD)	Range (min - max)	n	Mean (SD)	Range	n	Mean (SD)	Range
1	GV (cm/y)	53	9.4 ± 2.5	5.7 - 16.3	20	9.0 ± 2.1	4.7 - 13.3	14	10.9 ± 3.2	6.3 - 18.8	11	9.1 ± 1.7	5.9 - 11.7	9	8.4 ± 2.2	5.9 - 12.	107	9.4±2.5	4.7 - 18.8
	Δ Height SD*	53	0.84 ± 0.62	-0.05 to 3.30	18**	0.77 ± 0.41	-0.07 to 1.67	11**	0.82 ± 0.55	-0.01 to 2.18	11	0.53 ± 0.37	-0.25 to 1.00	9	0.39 ± 0.62	-0.84 to 1.29	102**	0.75±0.57	-0.84 to 3.30
2	GV (cm/y)	48	7.5 ± 1.4	4.6 - 11.0	18	7.3 ± 1.6	3.5 - 10.1	11	8.1 ± 1.3	6.7 - 11.4	10	7.4 ± 0.8	6.2 - 8.7	9	6.2 ± 2.1	3.4 - 9.2	96	7.4±1.5	3.4 - 11.4
	Δ Height SD*	48	1.25 ± 0.87	-0.30 to 4.54	18	1.13 ± 0.56	0.09 - 2.18	11	1.26 ± 0.80	0.14 - 3.32	10	0.75 ± 0.47	-0.20 to 1.40	9	0.62 ± 0.65	-0.29 to 1.72	96	1.12±0.78	-0.30 to 4.54
3	GV (cm/y)	42	6.9 ± 1.2	5.3 - 10.7	13	7.0 ± 1.5	4.9 - 10.7	11	7.6 ± 1.1	6.2 - 9.1	9	6.5 ± 0.8	5.0 - 8.2	8	5.6 ± 2.3	0.9 - 7.7	83	6.8±1.4	0.9 - 10.7
	Δ Height SD*	42	1.46 ± 0.81	0.28 - 4.28	13	1.50 ± 0.58	0.59 - 2.46	11	1.55 ± 0.92	0.54 - 3.94	9	1.09 ± 0.44	0.26 - 1.59	8	0.55 ± 0.81	-0.53 to 1.80	83	1.35±0.80	-0.53 to 4.28

4	GV (cm/y)	41	6.4 ± 1.4	3.1 - 10.1	10	6.3 ± 1.0	5.3 - 8.3	7	7.0 ± 1.5	4.8 - 8.6	8	5.9 ± 0.5	5.2 - 6.8	7	5.2 ± 2.1	2.0 - 7.6	73	6.3±1.4	2.0 - 10.1
	Δ Height SD*	41	1.64 ± 0.88	0.15 - 4.84	10	1.67 ± 0.66	0.63 - 2.66	7	2.06 ± 1.12	1.15 - 4.44	8	1.21 ± 0.56	0.32 - 2.21	7	0.64 ± 0.95	-0.82 to 1.77	73	1.54±0.91	-0.82 to 4.84
5	GV (cm/y)	38	6.5 ± 3.5	3.1 - 26.3	7	6.2 ± 0.7	5.4 - 7.4	7	7.5 ± 1.2	6.3 - 9.2	7	5.7 ± 0.7	4.9 - 6.8	5	4.5 ± 1.9	1.3 - 6.1	64	6.3±2.9	1.3 - 26.3
	Δ Height SD*	38	1.81 ± 0.88	0.75 - 4.76	7	1.70 ± 0.84	0.53 - 2.80	7	2.39 ± 1.24	1.29 - 5.01	7	1.11 ± 0.42	0.50 - 1.83	5	0.59 ± 1.07	-0.08 to 1.71	64	1.69±0.97	-0.77 to 5.01
6	GV (cm/y)	31	6.3 ± 1.5	2.9 - 11.1	6	5.6 ± 1.0	4.4 - 7.0	6	6.2 ± 0.8	5.3 - 7.2	6	4.8 ± 0.5	4.4 - 5.4	5	4.5 ± 3.4	0.5 - 8.0	54	5.9±1.7	0.5 - 11.1
	Δ Height SD*	31	1.97 ± 1.00	0.66 - 4.84	6	1.47 ± 0.72	0.51 - 2.63	6	2.68 ± 1.30	1.38 - 5.17	6	1.02 ± 0.46	0.34 - 1.78	5	0.68 ± 0.93	-0.42 to 1.93	54	1.77±1.08	-0.42 to 5.17
7	GV (cm/y)	20	6.7 ± 1.8	4.2 - 11.6	5	6.1 ± 1.3	5.0 - 8.2	4	5.0 ± 1.5	3.4 - 6.7	6	5.3 ± 1.1	3.8 - 6.6	5	3.3 ± 3.5	0.3 - 8.5	40	5.8±2.2	0.3 - 11.6
	Δ Height SD*	20	2.10 ± 1.23	0.70 - 5.36	5	1.60 ± 0.80	0.32 - 2.53	4	2.23 ± 0.65	1.47 - 2.95	6	0.95 ± 0.55	0.27 - 1.85	5	0.70 ± 0.77	-0.04 to 1.85	40	1.7±1.12	-0.04 to 5.36
8	GV (cm/y)	13	6.4 ± 2.1	3.5 - 10.4	3	4.3 ± 1.6	2.6 - 5.7	4	4.2 ± 2.3	0.8 - 5.5	5	5.7 ± 0.9	4.9 - 6.8	3	3.0 ± 2.0	0.6 - 4.2	28	5.4±2.2	0.6 - 10.4
	Δ Height SD*	13	2.44 ± 1.30	0.64 - 5.26	3	1.36 ± 1.16	0.06 - 2.28	4	2.16 ± 0.68	1.53 - 2.92	5	1.06 ± 0.56	0.35 - 1.87	3	0.80 ± 1.01	-0.19 to 1.83	28	1.86±1.21	-0.19 to
9	GV (cm/y)	7	7.4 ± 1.6	5.7 - 10.4				3	5.1 ± 3.1	1.6 - 7.5	4	5.6 ± 2.3	3.9 - 9.0				14	6.2±2.2	1.6 - 10.4
	Δ Height SD*	7	3.20 ± 1.44	1.50 - 5.48				3	2.54 ± 0.58	1.94 - 3.09	4	1.06 ± 0.95	0.11 - 2.37				14	2.27±1.55	0.15 to 5.48
10	GV (cm/y)	3	7.3 ± 2.1	5.1 - 9.2				2	3.1 ± 2.9	1.0 - 5.1	2	4.3 ± 0.5	3.9 - 4.7				7	5.2±2.4	1.0 - 9.2
	Δ Height SD*	3	2.88 ± 1.48	2.02 - 4.58				2	2.77 ± 0.61	2.34 - 3.20	2	0.40 ± 0.23	0.24 - 0.56				7	1.9±1.53	0.23 - 4.58

Abbreviations: GV, growth velocity; SD, standard deviation. *Δ Height SD represents the difference of annualized height SD to height SD at rhGH start with reference to the MPH. ** MPH missing

Table 3: Efficacy of GH treatment.

SD Height-increase from baseline to most recent visit (ΔHSD)			
Predictor	Estimate	95%CI	p
(Intercept)	-1.96	-4.16 – 0.24	0.080
Adherence of GH therapy (per 10%)	0.36	0.04 – 0.67	0.026
Sex (male)	0.39	-0.01– 0.67	0.05
Duration of treatment (years)	0.16	0.08 – 0.23	<0.001
Observations	102		

Abbreviations: 95%CI, 95 % confidence interval; p, p-value; The measure of ΔHSD is in reference to individual midparental height expectancy.

Table 4: Regression model coefficients to predict height increase (SD) since start of GH therapy.

Discussion

In this single-center, retrospective cohort study of children and adolescents on rhGH treatment, adherence to rhGH therapy was positively associated with height gain over a mean duration of 5.4 years (SD 2.9). Besides adherence, duration of treatment and male sex was positively associated with height gain. Poor adherence to rhGH treatment is associated with impaired growth [4-6,21,22] and consequently, with unnecessary costs due to possible poorer final height outcomes [11]. The largest study on adherence investigated the connected easypod electronic drug delivery device with automated transmission of adherence data over 48 months. In a total of 13,553 children, a majority of 71% maintained an adherence rate $\geq 85\%$ during the study period [23]. Using the same device in the French Easypod Connect Observational Study in 220 children (122 with growth hormone deficiency, 79 born SGA and 19 with TS), a mean daily dose $< 30 \mu\text{g}/\text{kg}$ per day given on at least 3 days a week was associated with a 20% higher mean yearly height gain compared to when less than 3 injections per week were received [22]. Van Dommelen et.al. Recently showed that missing one injection per week (adherence rate of 86%) was associated with 0.11 SD decrease in height gain per treatment year [24]. Several previous studies have reported a positive association between medication adherence and treatment efficacy, when followed-up between 1 and 3.2 years [4,22,25,26]. Adherence rate declines with treatment duration as previously reported [27], and recently confirmed by Koledova E et al. [28], using the connected easypod electronic drug delivery device in 1190 pediatric patients (75% with growth hormone deficiency): adherence rate dropped from 87.2% after 3 years to 75.5% after 4 years and 70.2% after 5 years of rhGH treatment. In the same study, Koledova E et al. [28] also showed that the adherence rate after one year of treatment was not associated with the rhGH treatment indication (i.e, irrespective of whether the indication was growth hormone deficiency, SGA, Turner syndrome). Similarly, Cutfield et. al. [6] did not find an association between treatment indication and rhGH adherence in a complete national cohort of New Zealand children and adolescents. Our study was not sufficiently powered to test for effects of treatment indication on adherence. Sex has been investigated as a covariate for adherence/compliance, revealing inconsistent results. In our study, we found a trend for male sex towards better ΔHSD (β -coefficient of 0.39, 95%CI -0.01 to 0.78, p-value 0.053). Most of the recent literature on adherence to rhGH stems from investigations using electronic drug delivery devices, their main aim being improvement in medication adherence [29]. Whereas these devices allow an objective assessment of adherence, not all patients are willing to use such a device, and usage of an electronic device per se does not improve adherence. Besides factors related to patient attributes and the health care system, interaction and communication skills of the care giver (such as to enhance patient motivation, to provide emotional support or to build

a partnership with a family) are key determinants of adherence and subsequent patient health outcomes [30]. Our simple and quick clinical method of assessing adherence offers an improved calculation of supplies remaining at home, and an opportunity to assess and directly address poor adherence when height gain is below expectations. Concerning treatment efficacy, our results are concordant with the literature. Maximum growth velocity and catch-up growth was seen during the first two years of treatment as shown in Figures 1 and 2. Patients treated for isolated growth hormone deficiency (group 1a) responded best to rhGH therapy. Patients born small for gestational age (SGA) nearly reached their target height SDS after 8 years of rhGH therapy as shown in Figure 2 [31-33]. There was a male preponderance in our study cohort of 61%, which may be a consequence of factors previously identified to contribute to sex disparity in rhGH treatment such as: screening bias by primary care physician, referral bias to pediatric endocrinologists for evaluation, bias of acceptable height cut-offs and interpretation of GH testing results, as well as bias related to prescribing and starting GH treatment [34]. Strengths of this study include duration, completeness and comprehensiveness of individual follow-up data. Limitations include the inability to identify modifiable determinants for adherence (such as lack of knowledge about consequences of missing injections; discomfort with injections; dissatisfaction with treatment results [9,35]. Accordingly, further studies to generate more appropriate measures are needed [36]. Our approach to assess adherence is based on a strictly centre-based distribution of rhGH. Insufficient data prevented a subanalysis of adherence based on our patient categorization.

Conclusion

Our approach to estimate adherence provides an easy and assessable method to identify patients who need further support to optimize treatment outcome. Any measure of adherence would be improved by methods that identify determinants for poor adherence.

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Author Contributions: CEF and CS conceptualized the study; AM, CEF and CS collected and prepared data for analysis; AM and CS performed the statistical analyses; AM prepared the manuscript draft; MZ, CS and CEF provided significant intellectual input and revised the manuscript draft. All authors revised and approved the manuscript.

Data Availability Statement: Data analyzed during the current study are not publicly available but are available in anonymised

form from the corresponding author on reasonable request.

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References

1. Savendahl L, Cooke R, Tidblad A, Beckers D, Butler G, et al (2020) Long-term mortality after childhood growth hormone treatment: the SAGhE cohort study. *The Lancet Diabetes & endocrinology*. 8: 683-692.
2. Ranke MB, Lindberg A, Price DA, Darendeliler F, Albertsson-Wikland K, et al (2007) Age at growth hormone therapy start and first-year responsiveness to growth hormone are major determinants of height outcome in idiopathic short stature. *Hormone research*. 68: 53-62.
3. Root AW, Kemp SF, Rundle AC, Dana K, Attie KM (1998) Effect of long-term recombinant growth hormone therapy in children--the National Cooperative Growth Study, USA, 1985-1994. *Journal of pediatric endocrinology & metabolism* : JPEM. 11: 403-416.
4. Kapoor RR, Burke SA, Sparrow SE, Hughes IA, Dunger DB, et al (2008) Monitoring of concordance in growth hormone therapy. *Archives of disease in childhood*. 93: 147-148.
5. Desrosiers P, O'Brien F, Blethen S (2005) Patient outcomes in the GHMonitor: the effect of delivery device on compliance and growth. *Pediatr Endocrinol Rev*. 2: 327-331.
6. Cutfield WS, Derraik JG, Gunn AJ, Reid K, Delany T, et al (2011) Non-compliance with growth hormone treatment in children is common and impairs linear growth. 6: e16223.
7. Organization World Health. Adherence to Long-term Therapies - Adherence for Action.
8. Gacs G, Hosszu E (1991) The effect of socio-economic conditions on the time of diagnosis and compliance during treatment in growth hormone deficiency. *Acta paediatrica Hungarica*. 31: 215-221.
9. Rosenfeld R, G, Bakker B (2008) Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. *Endocr Pract*. 14: 143-154.
10. Fisher BG, Acerini CL (2013) Understanding the growth hormone therapy adherence paradigm: a systematic review. *Hormone research in paediatrics*. 79: 189-196.
11. Haverkamp F, Johansson L, Dumas H, Langham S, Tauber M, et al (2008) Observations of nonadherence to recombinant human growth hormone therapy in clinical practice. *Clin Ther*. 30: 307-316.
12. Marshall WA, Tanner JM (1970) Variations in the pattern of pubertal changes in boys. *Archives of disease in childhood*. 45: 13-23.
13. Marshall WA, Tanner JM (1969) Variations in pattern of pubertal changes in girls. *Archives 240 of disease in childhood*. 44: 291-303.
14. Christian Braegger Oskar Jenni, Daniel Konrad und Luciano Molinari (2011) Neue Wachstumskurven für die Schweiz. *Paediatrica*. 22: 9-11.
15. Kemp SF, Kuntze J, Attie KM, Maneatis T, Butler S, et al (2005) Efficacy and safety results of long-term growth hormone treatment of idiopathic short stature. *The Journal of clinical endocrinology and metabolism*. 90: 5247-5253.
16. Greulich WW, Pyle SI (1959) *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Stanford, CA: Stanford University Press.
17. Grimberg A, DiVall S, A, Polychronakos C, Allen D, B, Cohen L, E, Quintos J, B, et al (2016) Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. *Horm Res Paediatr*. 86: 361-397.
18. Clayton P, E, Cianfarani S, Czernichow P, Johannsson G, Rapaport R, et al (2007) Management of the child born small for gestational age through to adulthood: a consensus statement of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society. *J Clin Endocrinol Metab*. 92: 804-810.
19. Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, et al (2017) Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *Eur J 259 Endocrinol*. 177: G1-G70.
20. Drube J, Wan M, Bonthuis M, Wuhl E, Bacchetta J, et al (2019) Clinical practice recommendations for growth hormone treatment in children with chronic kidney disease. *Nat 262 Rev Nephrol*. 15: 577-589.
21. Lustig RH (2004) Optimizing growth hormone efficacy: an evidence-based analysis. *Hormone research*. 62: 93-97.
22. Coutant R, Nicolino M, Cammas B, de Buyst V, Tauber M, et al (2021) Yearly Height Gain Is Dependent on the Truly Received Dose of Growth Hormone and the Duration of Periods of Poor Adherence: Practical Lessons From the French Easypod Connect Multicenter Observational Study. *Front Endocrinol (Lausanne)*. 12: 790169.
23. Koledova E, Tornincasa V, van Dommelen P (2020) Analysis of real-world data on growth hormone therapy adherence using a connected injection device. *BMC Med Inform Decis Mak*. 20: 176.
24. van Dommelen P, Koledova E, Wit J, M (2018) Effect of adherence to growth hormone treatment on 0-2 year catch-up growth in children with growth hormone deficiency. *PLoS One*. 13: e0206009.
25. de Arriba Munoz A, Muniz VC, Saez JJA, Beisti A, Llovet E, et al (2021) Impact of adherence on growth response during the first 2 years of growth hormone treatment. 277 *Endocrine*. 72: 513-523.
26. Aydin BK, Aycan Z, Siklar Z, Berberoglu M, Ocal G, et al (2014) Adherence to growth hormone therapy: results of a multicenter study. *Endocrine practice* : official journal of the American College of Endocrinology and the American Association of Clinical 281 *Endocrinologists*. 20: 46-51.
27. Urakami T (2021) Effectiveness of a smartphone application on medication adherence in children with short stature receiving GH therapy: A multicenter prospective cohort study (GTL- App). *Clin Pediatr Endocrinol*. 30: 85-92.
28. Koledova E, Stoyanov G, Ovbude L, Davies PSW (2018) Adherence and long-term growth outcomes: results from the easypod() connect observational study (ECOS) in paediatric patients with growth disorders. *Endocr Connect*. 7: 914-923.
29. Vadlapatla R, Wong EY, Gayakwad SG (2017) Electronic drug delivery systems: An overview.
30. Sabaté World Health Organization / edited by Eduardo. Adherence to long-term therapies: evidence for action.
31. Chatelain P, Carrascosa A, Bona G, Ferrandez-Longas A, Sippell W (2007) Growth hormone therapy for short children born small for gestational age. *Hormone research*. 68: 300-309.
32. Hokken-Koelega AC, van Pareren Y, Sas T, Arends N (2003) Final height data, body composition and glucose metabolism in growth hormone-treated short children born small for gestational age. *Hormone research*. 60: 113-114.

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33. Thomas M, Beckers D, Brachet C, Dotremont H, Lebrethon M. C, et al (2018) Adult Height after Growth Hormone Treatment at Pubertal Onset in Short Adolescents Born Small for Gestational Age: Results from a Belgian Registry-Based Study. *Int J Endocrinol*. 2018: 6421243.
34. Kamoun C, Hawkes C. P, Gunturi H, Dauber A, Hirschhorn J. N, et al (2021) Growth Hormone Stimulation Testing Patterns Contribute to Sex Differences in Pediatric Growth Hormone Treatment. *Horm Res Paediatr*. 94: 353-363.
35. Oyarzabal M, Aliaga M, Chueca M, Echarte G, Ulled A (1998) Multicentre survey on compliance with growth hormone therapy: what can be improved? *Acta Paediatr*. 87: 387-391.
36. Garfield S, Clifford S, Eliasson L, Barber N, Willson A (2011) Suitability of measures of self-reported medication adherence for routine clinical use: a systematic review. *BMC Med Res* 11: 149.