Dose-Dependent Effect of Growth Hormone on Final Height in Children with Short Stature without Growth Hormone Deficiency

Kerstin Albertsson-Wikland, A. Stefan Aronson, Jan Gustafsson, Lars Hagenäs, Sten A. Ivarsson, Björn Jonsson, Berit Kriström, Claude Marcus, Karl Olof Nilsson, E. Martin Ritzén, Torsten Tuvemo, Otto Westphal, and Jan Åman

Göteborg Pediatric Growth Research Center (K.A.-W., B.K., O.W.), Department of Pediatrics, Institute of Clinical Sciences, The Sahlgrenska Academy at University of Gothenburg, SE-41685 Gothenburg, Sweden; Department of Pediatrics (A.S.A.), The Central County Hospital of Halmstad, SE-30185 Halmstad, Sweden; Department of Women's and Children's Health (J.G., B.J., T.T.), Uppsala University, SE-75185 Uppsala, Sweden; Department of Woman and Child Health (L.H., E.M.R.), Karolinska Institutet, SE-17176 Stockholm, Sweden; Department of Clinical Sciences (S.A.I., K.O.N.), University Hospital Malmö, Lund University, SE-20502 Malmö, Sweden; Department of Clinical Science, Paediatrics (B.K.), Umeå University, SE-90185 Umeå, Sweden; Division of Pediatrics (C.M.), Department for Clinical Science, Intervention and Technology, Karolinska Institutet, SE-14186 Stockholm, Sweden; and Department of Pediatrics (J.A.), Örebro University, SE-70185 Örebro, Sweden

Context: The effect of GH therapy in short non-GH-deficient children, especially those with idiopathic short stature (ISS), has not been clearly established owing to the lack of controlled trials continuing until final height (FH).

Objective: The aim of the study was to investigate the effect on growth to FH of two GH doses given to short children, mainly with ISS, compared with untreated controls.

Design and Setting: A randomized, controlled, long-term multicenter trial was conducted in Sweden.

Intervention: Two doses of GH (Genotropin) were administered, 33 or 67 μg/kg·d; control subjects were untreated.

Subjects: A total of 177 subjects with short stature were enrolled. Of these, 151 were included in the intent to treat (All_{ITT}) population, and 108 in the per protocol (All_{PP}) population. Analysis of ISS subjects included 126 children in the ITT (ISS_{ITT}) population and 68 subjects in the PP (ISS_{PP}) population.

Main Outcome Measures: We measured FH SD score (SDS), difference in SDS to midparenteral height (diff MPH_{SDS}), and gain in $height_{SDS}$.

Results: After 5.9 $\pm$ 1.1 yr on GH therapy, the FH_{SDS} in the All_{PP} population treated with GH *vs.* controls was -1.5 ± 0.81 (33 μg/kg·d, -1.7 ± 0.70; and 67 μg/kg·d, -1.4 ± 0.86; $P < 0.032$), *vs.* -2.4 ± 0.85 ($P < 0.001$); the diff MPH_{SDS} was -0.2 ± 1.0 *vs.* -1.0 ± 0.74 ($P < 0.001$); and the gain in $height_{SDS}$ was 1.3 ± 0.78 *vs.* 0.2 ± 0.69 ($P < 0.001$). GH therapy was safe and had no impact on time to onset of puberty. A dose-response relationship identified after 1 yr remained to FH for all growth outcome variables in all four populations.

Conclusion: GH treatment significantly increased FH in ISS children in a dose-dependent manner, with a mean gain of 1.3 SDS (8 cm) and a broad range of response from no gain to 3 SDS compared to a mean gain of 0.2 SDS in the untreated controls. **(*J Clin Endocrinol Metab* 93: 4342–4350, 2008)**

0021-972X/08/$15.00/0

Printed in U.S.A.

doi: 10.1210/jc.2008-0707 Received March 31, 2008. Accepted August 15, 2008.

First Published Online August 26, 2008

Abbreviations: AGA, Appropriate for gestational age; diff MPH_{SDS}, difference in SDS to MPH; FH, final height; FSS, familial short stature; GHD, GH deficiency; IGFBP-3, IGF binding protein-3; ISS, idiopathic short stature; ITT, intent to treat; MPH, midparental height; PP, per protocol; SDS, SD score; SGA, small for gestational age.

GH has been used therapeutically in humans since the 1950s (1). Children with short stature of various etiologies were treated soon thereafter, but owing to a supply shortage, the use of GH was restricted to children with very low GH secretion (2, 3). When biosynthetic GH became available in the late 1980s (4), the cutoff level defining GH deficiency (GHD) changed (5–8). Databases were initiated to monitor the safety and efficacy of GH treatment in children, and these data support the good safety profile of biosynthetic GH that has been seen in clinical trials (9, 10). However, there was limited information on the effect of GH for non-GHD short children with idiopathic short stature (ISS) (11–13). Therefore, to investigate the GH effect in short non-GHD children especially, randomized, controlled trials were initiated in both the United States (14) and Sweden in children born either slightly small for gestational age (SGA) or appropriate for gestational age (AGA). The results of some of these trials have been published; however, some lack randomized control groups, whereas others have a limited number of subjects who were followed to final height (FH) (14–16).

The aim of the present study was to investigate in a long-term trial the effects of GH therapy on FH in short non-GHD children as compared with randomized, untreated controls. Secondary aims of the study were to determine whether there was a dose-response relationship, to evaluate whether GH therapy induced earlier onset of puberty, and to evaluate if and how the variation in FH could be explained.

Subjects and Methods

Ethics

The study was approved by the Ethical Committees of Sweden at Göteborg, Lund, Linköping, Uppsala, Huddinge, Umeå, and Karolinska Institutet. Informed consent was obtained from all the children and their parents.

Subjects

Inclusion

Short children, defined as height below −2 SD score (SDS) according to the Swedish population-based reference (17), whose chronological age was 8–13 yr for girls and 10–15 yr for boys, with a corresponding bone age no more than 11 yr in girls and no more than 13 yr in boys according to Tanner-Whitehouse, were included.

Exclusion

Children were excluded if they had GHD, defined as GH_{max} value at two GH stimulation tests below 10 μg/liter (20 mU/liter); had a bone age retardation of at least 3 yr; or had significant chronic diseases, skeletal dysplasia, or chromosome aberrations. Children born at a gestational age less than 35 wk or with extreme intrauterine growth retardation were also excluded.

Study populations

In total, 177 short children were enrolled into the study, of whom three did not participate; therefore, 174 children constituted the safety population. Of the patients enrolled, 26 were not included for the efficacy analysis, primarily owing to protocol inclusion/exclusion violations in the GH-treated group (n = 14) and the use of treatment regimens such as GH or testosterone that were violations of the protocol in the controls (n = 12). The remaining 151 children constituted the all subject intent to treat (All_{ITT}) population, of which 108 adhered to the protocol, the all subject per protocol (All_{PP}) population, the primary efficacy population for the analyses.

When the study was initiated, there was no distinction between children with ISS and those born SGA. As knowledge about differences between these two groups became known, we then classified children as ISS or SGA based on current clinical guidelines (18, 19). The growth responses of subjects with ISS were further evaluated. Thus, after exclusion of 48 subjects [45 with SGA (20, 21), three without available birth weight or length data], our analysis included 126 children with ISS in the ISS intent to treat (ISS_{ITT}) population and 68 subjects in the ISS per protocol (ISS_{PP}) population. The baseline characteristics of the various populations are described in Table 1.

Methods

Study design

Eligible children were enrolled into this randomized, controlled, dose-response study at seven university hospitals in Sweden between 1988 and 1999. Children were evaluated during a 12-month prestudy period, and those who remained prepubertal were randomized to no treatment (controls, n = 47) or to one of two doses of GH (Genotropin; Pfizer Inc., New York, NY): 33 μg/kg·d (0.1 U/kg·d), n = 49; or 67 μg/kg·d (0.2 U/kg·d), n = 50.

The 31 children who entered puberty during the prestudy year were randomized to either 67 μg/kg·d of GH (n = 16) or an untreated control group (n = 15).

Children were followed at least once a year at a university hospital for efficacy and safety measurements, which included bone age determination, lab tests, auxology, and puberty staging. Children were also clinically evaluated for dose adjustments every third month at their local children's hospital. They were followed until they reached FH, which was defined as the height when growth velocity was less than 1 cm/yr (the height end point value used for analyses of FH). However, according to this definition of FH, GH treatment was stopped prematurely in 64 children. All children had passed their peak height velocity; 34 had a growth rate between 1 and 2 cm/yr, 16 had a growth rate between 2 and 3 cm/yr, and 14 had a growth rate of more than 3 cm/yr at the time they stopped GH treatment.

Prestudy assessments

During the year before randomization, standing and sitting heights were measured using a stadiometer every third month, and the mean of three measurements was recorded. GH provocation tests and a spontaneous 24-h GH secretion profile were performed (22); methods for assaying GH and IGF-I concentrations were previously reported (6, 23, 24). Bone age was evaluated according to Tanner-Whitehouse by one radiologist in a blinded manner (Table 1).

Growth outcome variables

Three outcome variables were used for evaluation of response to GH treatment: 1) FH as measured in centimeters and SDS using the reference population born in 1974 (17); 2) gain in $height_{SDS}$, which was calculated using FH_{SDS} minus $height_{SDS}$ at baseline using the childhood component of the growth reference (25); and 3) FH_{SDS} minus midparental height (MPH) SDS, referred to as diff MPH_{SDS}. MPH_{SDS} was calculated as follows: (father's height SDS + mother's height SDS)/1.61 (26). Body mass index SDS was calculated *vs.* the new Swedish reference (27).

Statistical analyses

The statistical analyses were performed using the standard statistical package SPSS, version 15.0 (SPSS Inc., Chicago, IL). Results are expressed as mean ± SD unless otherwise specified. Analyses were performed using nonparametric tests of Wilcoxon type. Safety analyses included all 173 children in the safety population.

For analyses, the All_{PP} population of 108 children was used as the

TABLE 1. Subject characteristics at birth, at study start, and at FH of the all subjects and ISS populations

Population	All_{PP} (n = 108)				All_{ITT} (n = 151)				ISS_{PP} (n = 68)				ISS_{ITT} (n = 126)			
	Control		GH		Control		GH		Control		GH		Control		GH	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
At birth/early growth																
Gestational age (wk)	39.3	2.04	39.4	1.66	39.1	2.13	39.5	1.60	39.2	1.67	39.4	1.76	39.1	2.22	39.3	1.67
Birth length SDS	−1.25	0.96	−0.94	0.95	−1.18	1.02	−1.16	1.08	−0.62	0.56	−0.71	0.68	−0.71	0.60	−0.73	0.76
Birth weight SDS	−0.88	0.97	−0.67	0.95	−0.81	0.96	−0.83	1.08	−0.26	0.78	−0.33	0.70	−0.48	0.72	−0.39	0.72
MPH SDS	−1.41	0.88	−1.27	0.88	−1.35	0.81	−1.32	0.85	−1.30	0.64	−1.36	0.79	−1.07	0.70	−1.30	0.82
Mother's height SDS	−1.23	0.97	−1.02	0.95	−1.13	0.93	−1.11	0.90	−1.06	0.78	−1.10	0.92	−0.85	0.78	−1.08	0.91
Father's height SDS	−1.04	0.97	−1.02	0.96	−1.04	0.94	−1.02	0.97	−1.03	0.73	−1.09	0.74	−0.87	0.84	−1.01	0.83
Δ length, birth to 3 yr	−0.48	0.57	−0.63	0.41	−0.48	0.57	−0.60	0.42	−0.69	0.64	−0.73	0.38	−0.63	0.48	−0.70	0.38
At study start																
Pretreat yr growth, SDS	0.03	0.20	−0.02	0.27	−0.12	0.41	−0.09	0.33	−0.13	0.38	−0.08	0.29	−0.14	0.36	−0.08	0.30
Age (yr)	11.4	1.4	11.3	1.4	11.8	1.4	11.5	1.4	12.0	1.6	11.5	1.3	12.0	1.3	11.5	1.3
Height SDS, childhood	−2.57	0.34	−2.75	0.54	−2.69	0.46	−2.82	0.59	−2.76	0.39	−2.84	0.56	−2.67	0.42	−2.75	0.54
Body mass index SDS	−1.16	0.86	−1.48	0.96	−1.35	0.88	−1.50	0.94	−0.89	1.00	−0.84	1.07	−0.97	0.83	−0.81	1.05
Diff MPH SDS	−0.84	0.95	−0.91	1.05	−0.83	1.00	−0.87	1.02	−1.46	0.77	−1.48	0.91	−1.6	0.79	−1.45	0.91
GH_{max} AITT/24 h (mU/liter)	45.6	17.9	48.4	26.1	47.7	17.2	49.7	26.1	46.6	17.7	47.1	24.8	44.8	16.7	46.3	22.8
IGF-I SDS	−0.75	1.25	−0.83	1.22	−0.76	1.14	−0.80	1.16	−0.73	0.79	−0.92	1.15	−0.99	0.96	−0.83	1.14
Bone age delay (yr)	−1.63	0.92	−1.68	0.90	−1.54	0.94	−1.60	0.95	−1.80	0.69	−1.73	1.01	−1.56	0.87	−1.58	0.94
At FH																
Years on GH			5.94	1.12			5.26	1.67			5.64	1.37			5.38	1.54
Age (yr)	19.3	2.73	19.0	1.88	19.7	3.32	19.2	2.14	19.8	2.72	19.3	2.16	20.2	3.04	19.2	1.98

AITT, Arginine insulin tolerance test.

primary efficacy population. Analyses were also performed in subjects with ISS (ISS_{PP}, n = 68). Furthermore, growth response in children with MPH_{SDS} below −2 SDS, *i.e.* with familial short stature (FSS), was compared with growth in non-FSS children (18, 19). Stepwise multiple forward regression analyses were performed for the analysis of factors that significantly explained the variance in growth response and FH. In all analyses, low and high GH doses were included as dummy variables. Only variables entering the regressions at levels below the significance level 0.05 were used.

Results

FH outcome

All subject populations

In the All_{PP} population, GH-treated children (n = 77) reached a significantly taller FH compared with untreated controls (n = 31), for both males and females (Table 2). FH_{SDS}, gain in $height_{SDS}$ during treatment, and diff MPH_{SDS} also improved significantly in GH-treated subjects compared with untreated controls (Figs. 1 and 2). When the effects of GH treatment on growth outcomes in females and males were evaluated separately, the effects in females were less pronounced; the response in males was significant for all variables at the $P < 0.001$ level (FH_{SDS} −1.6, diff MPH_{SDS} −0.35, and gain in $height_{SDS}$ 1.0), whereas this was not the case for all comparisons in females [FH_{SDS} −2.1 ($P < 0.002$), diff MPH_{SDS} −0.45 ($P < 0.034$), and gain in $height_{SDS}$ 0.71 ($P < 0.001$)]. The results in the All_{ITT} population were similar to those found in the All_{PP} population (Table 2).

ISS populations

In the ISS_{PP} population (n = 68), GH treatment resulted in significant improvements in FH for both girls and boys compared with untreated control subjects, including FH_{SDS}, diff MPH_{SDS}, and gain in $height_{SDS}$ (Table 2). In fact, when growth parameters of the 24 SGA children in the All_{PP} population were compared with the ISS_{PP} population, there were no significant differences in growth responses (data not shown). A significant gain in height with GH therapy was also observed in the ISS_{ITT} population, which was similar to that seen in the ISS_{PP} population. The 45 SGA children (in the All_{ITT} population) exhibited a significant growth response to GH therapy similar to the children in the ISS_{ITT} population (data not shown).

Dose response

All subject populations

In the All_{PP} population, a dose-response relationship was evident when comparing the FH_{SDS} obtained in those receiving the higher dose (67 μg/kg·d) of GH *vs.* the lower dose (33 μg/kg·d): −1.4 ± 0.86 SDS *vs.* −1.7 ± 0.70 SDS; $P < 0.032$. A significant dose-response relationship was also observed in the All_{ITT} population for FH_{SDS} ($P < 0.008$), diff MPH_{SDS} ($P < 0.005$), and gain in $height_{SDS}$ ($P < 0.007$) (Table 2).

ISS populations

In both the ISS_{PP} and ISS_{ITT} populations, significant dose-response relationships were found for diff MPH_{SDS} ($P < 0.05$) (Table 2).

TABLE 2. Outcome results at FH of the four populations

		Controls			33 mg/kg·d			67 mg/kg·d			*P* <		
Population	**Outcome**	**Mean**	**n**	**SD**	**Mean**	**n**	**SD**	**Mean**	**n**	**SD**	**Control *vs.*33**	**Control *vs.*67**	**33 *vs.* 67**
All_{PP} (n = 108)	FH, cm boys	165	23	5.4	170	23	4.0	172	35	5.9	0.007	0.001	0.053
	FH, cm girls	150	8	4.8	155	9	5.2	157	10	4.0	0.059	0.001	NS
	FH, SDS	−2.4	31	0.85	−1.7	32	0.70	−1.4	45	0.86	0.001	0.001	0.032
	Gain height SDS	0.2	31	0.69	1.0	32	0.77	1.4	45	0.76	0.001	0.001	0.056
	Diff MPH SDS	−1.0	31	0.74	−0.1	32	0.99	0.4	45	1.04	0.009	0.001	0.057
All_{ITT} (n = 151)	FH, cm boys	165.5	32	5.83	168	33	6.3	171	47	6.1	NS	0.001	0.014
	FH, cm girls	151.8	14	5.64	155	10	5.1	157	15	4.8	NS	0.006	NS
	FH, SDS	−2.3	46	0.82	−2.0	43	0.85	−1.5	62	0.89	0.053	0.001	0.008
	Gain height SDS	0.4	46	0.85	0.9	43	0.81	1.3	62	0.82	0.005	0.001	0.007
	Diff MPH SDS	−1.0	46	0.83	−0.3	43	0.96	0.2	62	1.05	0.096	0.001	0.005
ISS_{PP} (n = 68)	FH, cm boys	166	14	4	169	14	4.4	171	24	5.8	0.062	0.001	NS
	FH, cm girls	151	5	3.9	159	4	4.8	157	7	3.9	0.063	0.018	NS
	FH, SDS	−2.2	19	0.75	−1.7	18	0.68	−1.5	31	0.84	0.004	0.001	NS
	Gain height SDS	0.4	19	0.62	1.2	18	0.82	1.3	31	0.73	0.004	0.001	NS
	Diff MPH SDS	−1.0	19	0.77	−0.1	18	0.64	0.4	31	1.03	0.057	0.001	0.042
ISS_{ITT} (n = 126)	FH, cm boys	166	36	7.38	169	26	5.2	172	39	5.7	0.042	0.001	0.059
	FH, cm girls	154	9	5.45	158	5	4.2	157	11	4.7	0.083	NS	NS
	FH SDS	−2.1	45	0.71	−1.7	31	0.77	−1.4	50	0.86	0.019	0.001	NS
	Gain height SDS	0.5	45	0.79	1.1	31	0.86	1.3	50	0.78	0.005	0.001	NS
	Diff MPH SDS	−0.6	45	0.8	−0.1	31	0.68	0.3	50	1.12	0.005	0.001	0.047
Non-FSS in All_{ITT} (n = 121)	FH, cm boys	167[a]	24	4.3	168	28	6.1	172[b]	36	5.3	NS	0.001	0.005
	FH, cm girls	153	12	4.6	156	9	5.1	158	12	4.9	NS	0.014	NS
	FH SDS	−2.1	36	0.71	−1.9	37	0.80	−1.3	48	0.81	NS	0.001	0.002
	Gain height SDS	0.5	36	0.78	0.9	37	0.80	1.4	48	0.79	0.019	0.001	0.007
	Diff MPH SDS	−0.7	36	0.79	−0.4	37	0.93	0.1	48	1.02	0.041	0.001	0.011
FSS in All_{ITT} (n = 30)	FH, cm boys	160	8	7.0	164	5	6.8	166	11	6.3	NS	0.062	NS
	FH, cm girls	145	2	7.6	150	1		153	3	2.5	NS	NS	NS
	FH SDS	−2.9[a]	10	0.94	−2.6	6	0.94	−2.2[b]	14	0.86	NS	0.064	NS
	Gain height SDS	−0.09[a]	10	0.97	0.5	6	0.77	0.9	14	0.83	NS	0.022	NS
	Diff MPH SDS	0.05[b]	10	0.71	0.4	6	0.86	0.8[a]	14	0.99	NS	NS	NS

NS, Not significant.

[a] $P < 0.05$; [b] $P < 0.01$, FSS *vs.* non-FSS within same treatment group.

Prepubertal growth

Sixty-two children from the All_{PP} population were in the study for at least 1 yr before the onset of puberty. The mean gain in Δ $height_{SDS}$ after 1 yr on treatment compared with baseline was 0.53 ± 0.20 in the 33 μg/kg·d group (n = 17), 0.76 ± 0.22 SDS in the 67 μg/kg·d group (n = 27), and −0.01 ± 0.27 in the untreated controls (n = 18). Children in both GH-treated groups had significantly greater prepubertal growth than the untreated controls ($P < 0.001$), and there was a significant difference between the two GH dose groups ($P < 0.001$). During the pretreatment year, the change in $height_{SDS}$ was 0.01 SDS in the low dose, −0.01 in the high dose, and 0.07 in the untreated controls. If the same growth velocity was assumed when evaluating the changes in $height_{SDS}$ during the first year of treatment with GH (0.52 in the low dose, 0.77 in the high dose, and −0.076 in the controls), the changes remained significant within the treated group ($P < 0.001$). A GH dose-dependent growth response was found ($P < 0.004$).

Time from study start to onset of puberty

In the All_{PP} population, GH treatment had no effect on time until puberty onset, which started 22.6 ± 9.81 months after the study start in the GH-treated children and 22.2 ± 8.3 months in the untreated controls. Gain in height from onset of puberty to FH was significantly greater in both the 33 and 67 μg/kg·d GH-treated groups (0.95 ± 0.79 SDS and 1.10 ± 0.94 SDS, respectively) *vs.* the untreated controls (0.48 ± 0.70 SDS; $P < 0.02$ and $P < 0.006$, respectively). There was no significant difference between the two GH-treated groups.

FSS vs. non-FSS

Of the 108 children in the All_{PP} population, there were 21 with FSS of whom 13 were GH-treated. The non-FSS individuals grew significantly better than those with FSS; the difference between FSS and non-FSS in FH_{SDS} was 1.0 in the untreated controls ($P < 0.019$) and 0.7 ($P < 0.011$) in the GH-treated individuals; the difference in gain in $height_{SDS}$ was 0.7 ($P < 0.034$) in the controls and 0.4 ($P < 0.041$) in the GH group; and the difference in diff MPH_{SDS} was 0.7 ($P < 0.020$) in controls and 1.0 ($P < 0.001$) in GH-treated children. The FH of FSS children was closer to their parents' height than non-FSS children. The 36 non-FSS children treated with high-dose GH showed the highest growth response: the FH_{SDS} was −1.18, gain in $height_{SDS}$ was 1.53, and diff MPH_{SDS} was −0.20. The corresponding values of the All_{ITT} population are presented in Table 2.

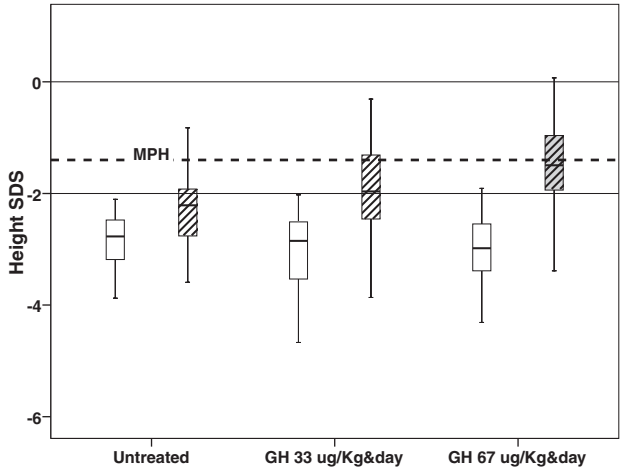

FIG. 1. Primary outcome. FH_{SDS} of the All_{PP} population (n = 108) of the three randomized groups: untreated (n = 31), GH 33 μg/kg·d (n = 32), and GH 67 μg/kg·d (n = 45). Box and whisker plot shows median, interquartile range (IRQ), and values within ± 1.5 IRQ of baseline and FH_{SDS}. The *dotted line* represents the mean MPH_{SDS} of the study population. *Open boxes*, Height at study start; *filled boxes*, FH.

Multivariate analyses

With the use of multivariate analyses in the All_{PP} population, the factors explaining the variance in growth outcomes were: 1) at birth and infancy—length at birth, height difference to the parents, infancy growth, high/low GH dose; and 2) at baseline—bone age delay, $height_{SDS}$, and $IGF\text{-}I_{SDS}$. These variables explained 58% of the variation in FH_{SDS}, 47% of the variation in gain in $height_{SDS}$, and 50% of the variation in diff MPH_{SDS}. Table 3 illustrates the order of entrance and the regression coefficients for the predictors of growth response. The high dose always entered the regression before the low dose independent of the study population, indicating a dose-dependent growth response.

In the All_{ITT} population relative to the All_{PP} population, the variables explained approximately 10% more of the variability in FH_{SDS}, gain in $height_{SDS}$, and diff MPH_{SDS} being 60, 68, and 61%, respectively (Table 3). The corresponding figures of the ISS_{PP} and ISS_{ITT} populations are presented in Table 3.

Safety

The safety population consisted of 112 subjects treated with GH and 61 controls. No serious adverse events were attributed to GH therapy. Six children were withdrawn from the study owing to adverse events: four in the low-dose GH-treated group, and two controls. Dissociative identity disorder, pituitary cyst, mood swings, and irritability were the adverse events leading to discontinuation of GH therapy in the treated groups; in the untreated control group, discontinuations were due to a road traffic accident and a brain tumor. There was no effect found on thyroid or liver function during this long-term study. Fasting glucose and insulin levels increased in a dose-dependent fashion; however, no individual had persistently elevated glucose and insulin levels. During GH treatment, 29 subjects had an elevated glucose and insulin level that was subsequently normal on the following assessment.

IGF-I levels remained within ± 3 SDS throughout the study in

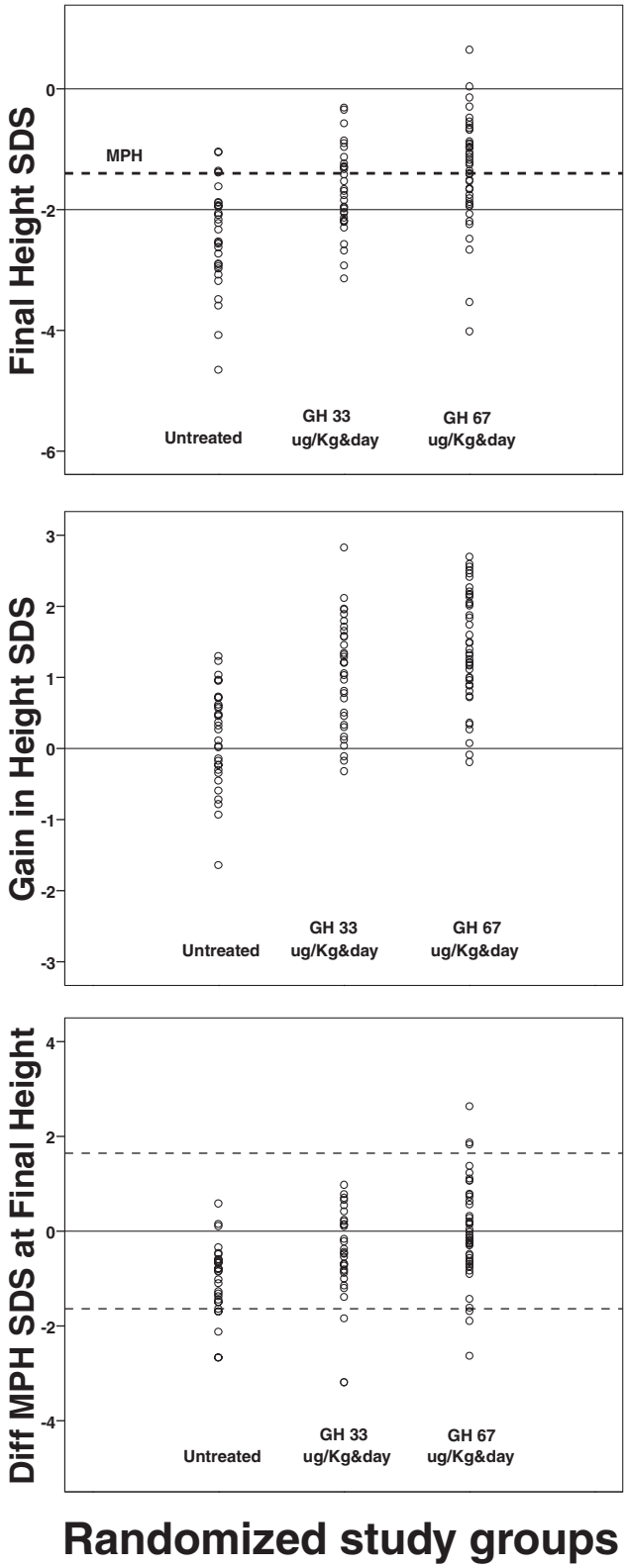

FIG. 2. Final outcome of the individuals of the All_{PP} population, expressed as FH_{SDS} (*top panel*), diff MPH_{SDS} (*middle panel*), and gain in $height_{SDS}$ from study start to FH (*bottom panel*). *Dotted lines* represent MPH_{SDS} of the entire population in *top panel* and 95% confidence interval for MPH, *i.e.* ± 1.64 SD, in *bottom panel*.

TABLE 3. Regression coefficients, adjusted R^2 signs, and order of entrance of the significant predictors in the multiple forward regression analyses are given for all four populations

		GH dose		At birth			At baseline			
At baseline	Rsq Adj (%)	High	Low	Length SDS	Diff MPH	Growth 0–3 yr	Height SDS	BA delay	Diff MPH	IGF SDS
All_{PP} (n = 108)										
FH SDS	50	0.95^2	0.34^7	0.40^1		0.52^6	0.71^3	-0.25^4	-0.25^5	
Gain SDS	47	0.74^2			0.23^4			-0.27^1	-0.48^3	
Diff MPH SDS	58	0.77^2			0.34^1	0.39^5		-0.26^4	-0.41^3	
All_{ITT} (n = 151)										
FH SDS	61	1.17^2	0.70^5	0.55^1	-0.17^4	0.49^3	0.69^6	-0.27^7	-0.17^4	-0.12^8
Gain SDS	59	1.17^1	0.72^3	0.19^5				-0.30^2	-0.18^6	-0.13^4
Diff MPH SDS	68	1.14^2	0.71^4		0.19^1			-0.27^5	0.67^3	-0.14^6
ISS_{PP} (n = 68)										
FH SDS	40	1.02^1	0.62^4	0.98^2	-0.29^5	0.83^3				
Gain SDS	41	0.95^2	0.62^4		0.34^3				-0.61^1	
Diff MPH SDS	58	0.96^2	0.62^4		0.35^3				0.40^1	
ISS_{ITT} (n = 126)										
FH SDS	40	0.82^1	0.44^5		0.22^7		1.04^2	-0.20^3	-0.44^6	-0.14^4
Gain SDS	40	0.85^2	0.45^5		0.24^4			-0.25^1	-0.45^3	
Diff MPH SDS	59	0.83^2	0.45^5		0.34^3	0.43^7		-0.19^4	0.46^1	-0.14^6

Superscripts represent order of entrance of the significant predictors in the multiple forward regression analyses. RsqAdj, Adjusted R^2; BA, bone age.

all but 21 children (20 on GH and one untreated control). During the first year of GH treatment, 14 children (seven on each GH dose) had one instance of an IGF-I level between 3 and 3.5 SDS. In six children (five high-dose GH and 1 low-dose GH), two to four subsequent IGF-I levels were above +3 SDS during the first and second years of GH therapy, whereas it remained high in only one child during the third year. Thereafter, all levels were below +3 SDS in all children while on GH treatment. Figure 3 illustrates the mean levels of IGF_{SDS} and ratio IGF-I/$IGFBP_3$ binding protein-3 (IGF-I/$IGFBP_3$) SDS for the three groups.

Discussion

This randomized, controlled trial in non-GHD children with short stature and ISS demonstrated that GH treatment for a mean

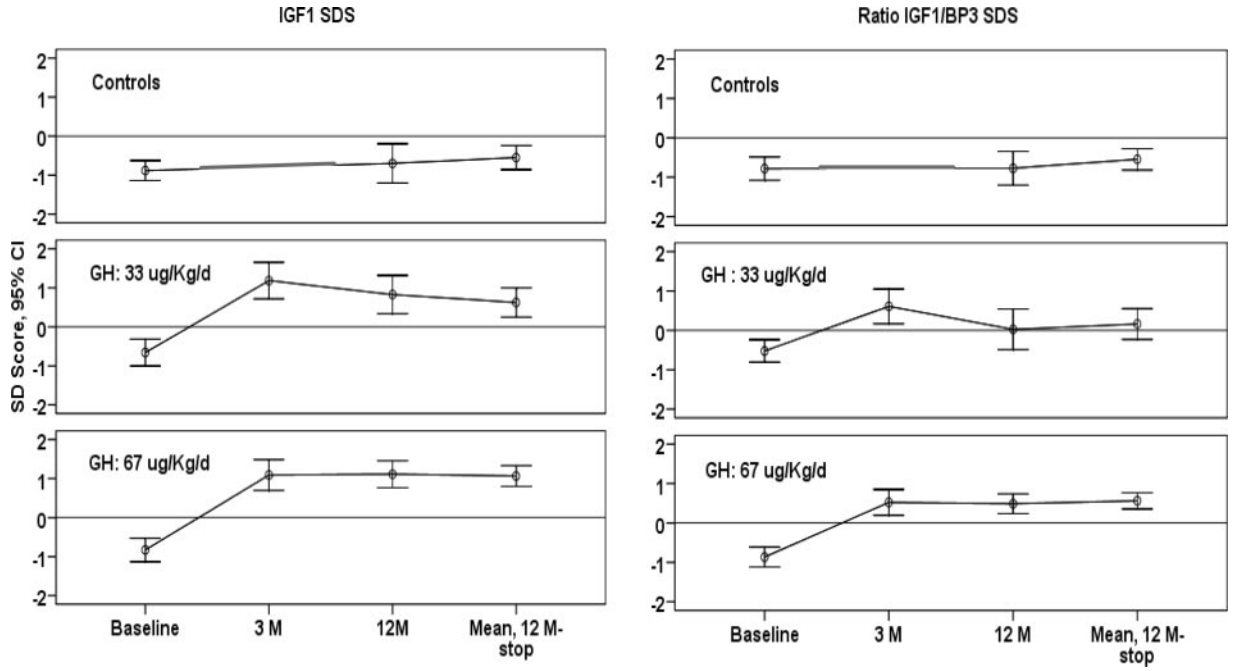

FIG. 3. Mean levels and 95% confidence intervals of All_{ITT} population for IGF_{SDS} (*left*) and ratio IGF-I/BP3 SDS (*right*) at baseline, 3 months, 1 yr, and the mean value of the individual mean between 1 yr and GH stop for the three different randomization groups. On GH 33 μg/kg·d, the ratio IGF/BP3 increased from -0.52 ± 0.93 to a mean level of 0.01 ± 1.5, whereas on GH 67 μg/kg·d the corresponding figures were from -0.99 ± 0.94 to 0.57 ± 0.8. IGF-I levels in the low-dose GH group increased from -0.66 ± 1.11 to 0.63 ± 1.10, and for the high-dose GH group, levels increased from -0.94 ± 1.2 to 1.11 ± 1.08. In the untreated controls, the corresponding data for IGF/BP3 SDS ratio was from -0.88 ± 0.83 to -0.70 ± 1.24, and for IGF-I SDS from -0.78 ± 0.96 to -0.77 ± 1.06.

of 5.9 ± 1.1 yr, given from near start of puberty, significantly increased the FH of subjects to a height close to that of their parents. The GH effect was dose-dependent, and the children with parents of normal heights responded best, their mean FH being −1.2 SDS and only 0.2 SDS below MPH after a gain of 1.5 SDS (approximately 9 cm). The FH in untreated controls was −2.4 SDS, and −1.0 SDS from their parents after a gain of only 0.2 SDS from the start of the study. Notably, one third of individuals receiving the high GH dose and one fifth of those receiving the low dose reached a FH above −1 SDS compared with none of the controls.

Since the study commenced in 1988, other long-term studies evaluating the growth effect of GH treatment in children with ISS have been reported (14–16). However, our study provides more conclusive results in that it is the only randomized, controlled study using two doses of daily GH with a start in prepubertal children who were followed to FH. Importantly, 88% of the prepubertal children enrolled in the study were part of the primary PP population of this study; 65% of children receiving the low dose, 90% of children receiving the high dose, and 66% of untreated control children were followed to the study endpoint of FH. It can be argued that those with the lowest growth response were those who decided to stop prematurely. If so, the dose effect may be somewhat overestimated. Placebo-controlled studies would have been superior to the present design with an untreated control group. However, placebo-treated subjects tend to show an even higher dropout rate; the only such GH trial reports as much as 90% dropouts (14).

In agreement with previous studies in GHD (28) and in ISS (16), we found that the higher the daily GH dose, the better the growth response, corresponding to the correlation between height and GH secretion in healthy children (22). In addition, a daily injection compared with a three times weekly administration schedule affects outcomes (29), although the spontaneous GH secretion is blunted owing to a negative feedback mechanism after each GH injection (30). Both the doses and the frequency of injections used contribute to the better growth in the present study compared with previous studies (14–16).

During puberty, the GH secretion rate more than doubles in boys and quadruples in girls compared with before puberty (22, 31). Consequently, giving boys and girls the same numerical GH dose during puberty will lead to a biologically lower dose in girls. In fact, the boys in the present study grew more than girls during puberty on GH treatment, although both girls and boys significantly responded to GH therapy.

Children with short stature are diagnosed with ISS when all known causes of short stature are excluded (18, 19). It is presumed that within subgroups of children with ISS, there are different causes for their short stature including genetic disorders of the GH axis (32). Until more knowledge is gained on GH responsiveness, prediction models for growth response, based on estimations of the heterogeneity in GH sensitivity, can be clinically used to assess the individual responsiveness to GH therapy (33–36). The dose of GH in our study was chosen for each child based only on a strict randomization procedure and not on his or her own responsiveness to GH, which may account for the broad variation in the response to GH therapy, *i.e.* from no gain up to 3 SDS (18 cm), similar to findings in other studies (14–16). This variation may have been less if a dose estimated from the best available prediction model had been applied, rather than a fixed dose per kilogram of body weight (34). We recently demonstrated a reduction in the growth response variation using a prediction model for selection of the individual GH dose (33, 37).

There are many variables known to affect the growth response to GH treatment. In the present study, the results of the multivariate analyses showed that already at an early age, low and/or high GH dose, birth length, diff MPH_{SDS}, and early growth during the first years of life (38) were significantly correlated to growth response, confirming the results of other studies (14–16). The greater the height difference between the child and his or her parent, the better the response will be to GH (14, 15). In other words, children from parents of normal height (non-FSS) respond better than those from short parents (FSS). Similarly, bone age delay has been shown to be an important predictor of response to GH treatment (14, 16). In our study, there were no entry criteria regarding diff MPH_{SDS}; therefore, the genetic potential of the child's predicted height was not accounted for. Relative to other studies, the children of our study were taller. They were below −2 SDS *vs.* the population born in the mid-1970s, but in other trials, the height criteria for study entry were shorter and related to older reference values. Despite these variables, there was an even better growth outcomes in the individuals of our study relative to those of other studies (14–16).

Children born SGA were not excluded from the GH trials in children with ISS initiated in the 1980s (12, 14, 15), as was the case for the present study. In a population of short prepubertal children, approximately 30% of children would have been born SGA (20). We found that size at birth, as a continuum, is an important predictor of the variation in response. However, children born SGA responded at the same magnitude as those born AGA, suggesting a low value of the arbitrarily chosen statistical cutoff level of −2 SDS for the definition of SGA as an indicator of different GH responsiveness (20, 34).

In conclusion, GH treatment that commenced as late as near the start of puberty in children with short stature and with ISS resulted in a dose-dependent increase in FH of approximately 1 SDS more than the control group randomized to no treatment. GH therapy was safe and had no impact on the time until onset of puberty. This long-term, randomized, controlled trial is unique in that so many individuals were followed to FH. Although there was variation in the growth response owing to individual GH responsiveness, most individuals receiving the high-dose GH regimen reached normal adult height. However, the demonstration of a significant height gain in the GH-treated individuals compared with the nontreated group does not mean that such treatment is recommended for all children with ISS. On the contrary, it should be recommended to those predicted to have a good growth response (33, 34), and only after thorough discussions with the subjects and parents to determine, on a case-by-case basis,

those who suffer substantially from their short stature, thus justifying this long-term therapy.

Acknowledgments

The authors are thankful for the participation of all the children and their families, for great care of the study population over the years by our Swedish pediatric colleagues, for our own excellent pediatric nurses, and for the staff members at Göteborg Pediatric Growth Research Center for their long-term commitment to the study, not least of all Carola Pfeiffer Mosesson and Eva Mölleborn. The authors also thank Susan Sutch (Envision Pharma) for valuable editing of the manuscript.

Address all correspondence and requests for reprints to: Kerstin Albertsson-Wikland, Göteborg Pediatric Growth Research Center/ Växthuset, The Queen Silvia Children's Hospital, SE-416 85 Göteborg, Sweden. E-mail: kerstin.albertsson-wikland@pediat.gu.se.

This study was initiated in 1988 as a Kabi-sponsored study but was changed to an investigator-sponsored study in the 1990s. An unrestricted research grant as well as a free supply of drug was kindly provided by Pharmacia/Pfizer. The study was also supported by grants from Swedish Research Council (7905) the Swedish Foundation for Pediatric GH Research, and the Foundation Växthuset for Children.

Pfizer had no influence on the collection, analysis, and interpretation of the data or in the writing of this manuscript.

Disclosure Information: Research grants were received by K.A.-W., J.G., E.M.R., T.T., and O.W. Stock options were held by A.S.A., J.G., and J.Å. Consulting fees were obtained by J.G., L.H., B.J., B.K., E.M.R., T.T., and J.Å. Lecture fees were received by J.G., L.H., E.M.R., T.T., O.W., and J.Å. S.A.I., C.M., and K.O.N. have nothing to declare.

References

1. **Raben MS** 1958 Treatment of a pituitary dwarf with human growth hormone. J Clin Endocrinol Metab 18:901–903
2. **Lenko HL, Leisti S, Perheentupa J** 1982 The efficacy of growth hormone in different types of growth failure. An analysis of 101 cases. Eur J Pediatr 138: 241–249
3. **Tanner JM, Whitehouse RH, Hughes PC, Vince FP** 1971 Effect of human growth hormone treatment for 1 to 7 years on growth of 100 children, with growth hormone deficiency, low birthweight, inherited smallness, Turner's syndrome, and other complaints. Arch Dis Child 46:745–782
4. **Albertsson-Wikland K** 1987 Clinical trial with authentic recombinant somatropin in Sweden and Finland. Acta Paediatr Scand Suppl 331:28–34
5. **Attie K, Bengtsson B-Å, Blethen S, Blum W, Cameron F, Carel J, Carlsson L, Chipman J, Sandahl Christiansen J, Clayton P, Clemmons D, Cohen P, Drop S, Fujieda K, Ghingo E, Hintz R, Ho K, Ilondo M, Jasper H, Jesussek B, Kappelgaard A, Laron Z, Lippe B, Malozowski S, Mullis P, de Muinck-Keizer-Schrama S, Nishi Y, Parks J, Phelps C, Ranke M, Robinson I, Rosenfeld R, Rose S, Saenger P, Saggese G, Savage M, Shalet S, Sizonenko P, Strasburger C, Tachibana K, Tanaka T, Thorner M, Albertsson-Wikland K, Zadik Z** 2000 Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. J Clin Endocrinol Metab 85:3990–3993
6. **Jansson C, Boguszewski C, Rosberg S, Carlsson L, Albertsson-Wikland K** 1997 Growth hormone (GH) assays: influence of standard preparations, GH isoforms, assay characteristics, and GH-binding protein. Clin Chem 43:950–956
7. **Kristrom B, Karlberg J, Albertsson-Wikland K** 1995 Prediction of the growth response of short prepubertal children treated with growth hormone. Swedish Paediatric Study Group for GH treatment. Acta Paediatr 84:51–57
8. **Rosenfeld RG, Albertsson-Wikland K, Cassorla F, Frasier SD, Hasegawa Y, Hintz RL, Lafranchi S, Lippe B, Loriaux L, Melmed S, Preece MA, Ranke MB, Reiter EO, Rogol AD, Underwood LE, Werther GA** 1995 Diagnostic controversy: the diagnosis of childhood growth hormone deficiency revisited. J Clin Endocrinol Metab 80:1532–1540
9. **Maneatis T, Baptista J, Connelly K, Blethen S** 2000 Growth hormone safety update from the National Cooperative Growth Study. J Pediatr Endocrinol Metab 13(Suppl 2):1035–1044
10. **Wilton P** 2001 Safety in growth hormone replacement therapy: a matter of varied responsiveness? Horm Res 55(Suppl 2):61–64
11. **Albertsson-Wikland K** 1988 Growth hormone treatment in short children—short-term and long-term effects on growth. Acta Paediatr Scand Suppl 343: 77–84
12. **Ritzen M, Albertsson-Wikland K** 1989 GH of short stature. State-of-the-art 1989. Acta Paediatr Scand Suppl 362:1–89
13. **Underwood LE** 1984 Report of the conference on uses and possible abuses of biosynthetic human growth hormone. N Engl J Med 311:606–608
14. **Leschek EW, Rose SR, Yanovski JA, Troendle JF, Quigley CA, Chipman JJ, Crowe BJ, Ross JL, Cassorla FG, Blum WF, Cutler Jr GB, Baron J** 2004 Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 89:3140–3148
15. **Hintz RL, Attie KM, Baptista J, Roche A** 1999 Effect of growth hormone treatment on adult height of children with idiopathic short stature. Genentech Collaborative Group. N Engl J Med 340:502–507
16. **Wit JM, Rekers-Mombarg LT, Cutler GB, Crowe B, Beck TJ, Roberts K, Gill A, Chaussain JL, Frisch H, Yturriaga R, Attanasio AF** 2005 Growth hormone (GH) treatment to final height in children with idiopathic short stature: evidence for a dose effect. J Pediatr 146:45–53
17. **Albertsson-Wikland K, Luo ZC, Niklasson A, Karlberg J** 2002 Swedish population-based longitudinal reference values from birth to 18 years of age for height, weight and head circumference. Acta Paediatr 91:739–754
18. **Ranke MB** 1996 Towards a consensus on the definition of idiopathic short stature. Horm Res 45(Suppl 2):64–66
19. **Wit JM, Clayton PE, Rogol AD, Savage MO, Saenger PH, Cohen P** 2008 Idiopathic short stature: definition, epidemiology, and diagnostic evaluation. Growth Horm IGF Res 18:89–110
20. **Karlberg J, Albertsson-Wikland K** 1995 Growth in full-term small-for-gestational-age infants: from birth to final height. Pediatr Res 38:733–739
21. **Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P** 1991 An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977–1981). Acta Paediatr Scand 80:756–762
22. **Albertsson-Wikland K, Rosberg S, Libre E, Lundberg LO, Groth T** 1989 Growth hormone secretory rates in children as estimated by deconvolution analysis of 24-h plasma concentration profiles. Am J Physiol 257:E809–E814
23. **Löfqvist C, Andersson E, Gelander L, Rosberg S, Blum WF, Albertsson Wikland K** 2001 Reference values for IGF-I throughout childhood and adolescence: a model that accounts simultaneously for the effect of gender, age, and puberty. J Clin Endocrinol Metab 86:5870–5876
24. **Löfqvist C, Andersson E, Gelander L, Rosberg S, Hulthen L, Blum WF, Albertsson-Wikland K** 2005 Reference values for insulin-like growth factor-binding protein-3 (IGFBP-3) and the ratio of insulin-like growth factor-I to IGFBP-3 throughout childhood and adolescence. J Clin Endocrinol Metab 90:1420–1427
25. **Karlberg J** 1989 On the construction of the infancy-childhood-puberty growth standard. Acta Paediatr Scand Suppl 356:26–37
26. **Luo ZC, Albertsson-Wikland K, Karlberg J** 1998 Target height as predicted by parental heights in a population-based study. Pediatr Res 44:563–571
27. **Karlberg J, Luo ZC, Albertsson-Wikland K** 2001 Body mass index reference values (mean and SD) for Swedish children. Acta Paediatr 90:1427–1434
28. **Frasier SD, Costin G, Lippe BM, Aceto Jr T, Bunger PF** 1981 A dose-response curve for human growth hormone. J Clin Endocrinol Metab 53: 1213–1217
29. **Albertsson-Wikland K, Westphal O, Westgren U** 1986 Daily subcutaneous administration of human growth hormone in growth hormone deficient children. Acta Paediatr Scand 75:89–97
30. **Rose SR, Baron J, Bernstein D, Yanovski J, Troendle JF, Leschek E, Chipman J, Cutler Jr GB** 2000 Suppression and recovery of GH secretion after GH injection in non-GH deficient short children. J Pediatr Endocrinol Metab 13: 281–288
31. **Albertsson-Wikland K, Rosberg S, Karlberg J, Groth T** 1994 Analysis of 24-hour growth hormone profiles in healthy boys and girls of normal stature: relation to puberty. J Clin Endocrinol Metab 78:1195–1201
32. **Rosenfeld RG** 2005 The molecular basis of idiopathic short stature. Growth Horm IGF Res 15(Suppl A):S3–S5
33. **Albertsson Wikland K, Kristrom B, Rosberg S, Svensson B, Nierop AF** 2000 Validated multivariate models predicting the growth response to GH treatment in individual short children with a broad range in GH secretion capacities. Pediatr Res 48:475–484
34. **Dahlgren J, Kristrom B, Niklasson A, Nierop AF, Rosberg S, Albertsson-**

Wikland K 2007 Models predicting the growth response to growth hormone treatment in short children independent of GH status, birth size and gestational age. BMC Med Inform Decis Mak 7:40

35. **Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W, Albertsson-Wikland K, Price DA** 1999 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 84:1174–1183
36. **Schonau E, Westermann F, Rauch F, Stabrey A, Wassmer G, Keller E, Bramswig J, Blum WF** 2001 A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency. Eur J Endocrinol 144:13–20
37. **Kristrom B, Dahlgren J, Aronson S, Gustafsson J, Halldin M, Ivarsson S, Nilsson NO, Svensson J, Tuvemo T, Albertsson Wikland K** 2006 Individualized growth hormone (GH) dosing brings children closer to their target height after 2 years of treatment—a randomized study including prepubertal IGHD and ISS children. Horm Res 65:P159 (Abstract P101-553)
38. **Hochberg Z, Albertsson-Wikland K** 2008 Evo-devo of infantile and childhood growth. Pediatr Res 64:2–7