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Predicting growth response among Egyptian prepubertal idiopathic isolated growth hormone deficient children[1)]

Abstract

Objective: To determine the predictors of growth response to growth hormone treatment in a group of isolated idiopathic growth hormone (GH).

Patients and methods: 477 GH deficient (GHD) children with GH therapy were included in the study. Patients were followed up for a minimum of 1 year and up to 6 years. Multiple linear regressions were performed to identify predictors of growth response to rhGH in the first 4 years of treatment.

Results: In the first year, three significant predictors of growth were identified: GH peak [ln (ug/L)], age of onset of therapy and target height-height SDS. In the second and third years of therapy, growth velocity (GV) was both significantly and positively correlated to the GV (cm/year) of the previous year.

Conclusion: Prediction models offer a valuable tool for individualization and assuring adherence to rhGH and thus a cost effective treatment, which is the ultimate goal of GH therapy.

Keywords: growth hormone deficient (GHD) children; growth response; prediction.

[1)]All authors listed have contributed to the work, all authors have agreed to submit the manuscript for publication, and all human studies have been reviewed by the appropriate Ethics Committees.

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Introduction

The use of growth hormone (GH) in the treatment of growth hormone deficient (GHD) children has been proved to be effective and safe. The use of GH in the treatment of children with growth disturbance should be guided by four key goals:

1. Normal height should be reached as soon as possible.
2. The adult height attained should be within the normal range.
3. The risks of therapy should be minimized.
4. The aims of treatment should be attained for the minimum cost (1).

The development and application of growth prediction models represent an attempt to account for the definable variability of individuals so that clinicians can tailor initial GH treatment to each patient's needs. Such models also help patients and physicians to develop realistic expectations of therapy. In the latter case, physicians can compare predicted and actual growth throughout the growth process, and thus perhaps take corrective action as discrepancies occur (1).

Despite more than 50 years of experience of GH treatment in children of short stature, there is still some uncertainty about how best to describe and interpret a growth response numerically, particularly in the context of variations in prescribed dose. There is also limited information on how different causes of short stature determine the response of children to GH during the first year of treatment. Such information is a key because the outcome of the first year of GH therapy seems to be the most important in determining the overall success of treatment (2).

We aimed to determine the predictors of growth response to growth hormone treatment in a group of isolated idiopathic GH deficient prepubertal children treated with GH.

Patients and methods

Patients

This is a retrospective longitudinal observational study with a variable follow-up duration that ranged from 1 to 6 years. It was performed after obtaining approval by the Ethical Committee of the National

Research Centre. Written informed consent was obtained from all patients and their parents after full discussion about the aim of the study. A total number of 477 growth hormone (GH) deficient children (307 males, 170 females) were included in the study. All selected patients received GH therapy provided by the Egyptian GH National Committee of School Health Insurance. There, they were followed up in association with the unit of Diabetes Endocrine Metabolism Pediatric Unit (DEMPU), Children's Hospital, and Cairo University.

Inclusion criteria included:

1. Short stature more than 2 SD below the mean according to Tanner and Whitehouse (3).
2. A peak GH level of ≤10 ug/L by two provocative tests [Insulin Tolerance Test (ITT) and Clonidine].

Patients were subclassified into either isolated GHD or with multiple growth hormone deficiency (MPHD). Moreover, patients with isolated GHD were defined as being idiopathic GHD if they were lacking the criteria of familial GHD or any brain CT/MRI abnormalities. Only patients with idiopathic isolated GH deficiency were included in the prediction model. There were 310 patients in year 1, 268 in year 2, 193 in year 3, 72 in year 4, 33 in year 5 and only 16 in the sixth-year follow-up. We included the first four years follow-up only in the prediction model as the number of patients became small in the fifth- and sixth-year follow-up.

Exclusion criteria included: patients with short stature due to Turner Syndrome (TS), idiopathic short stature (ISS), chronic medical illness, malnutrition, psychological deprivation, small for gestational age (SGA) and bone dysplasia.

Methods

For all patients a detailed prenatal, natal and postnatal history was taken and the following were performed.

Anthropometric and pubertal assessment

Height and sitting height were measured twice by the same observer at the same time during the day and rounded to the next millimeter using a Harpenden Stadiometer (Holtain Ltd., Crymmych, Wales, UK) and the mean of the two readings was taken. Patients' weight in decimal of kilograms using electronic balances was recorded. Target height and growth velocity in cm/year were expressed. Puberty was assessed by rating breast development in girls (4) and genital development in boys (5). The onset of puberty is defined in girls by stage 2 of breast development (breast bud) and in boys by a testicular volume more than 4 mL (6). Anthropometric and pubertal assessments were documented every 3 months. All auxological data, including that of the parents, were expressed in the standard deviation score (SDS) using Tanner and Whitehouse standards (3). The data were analyzed by the software program growth vision2 (Novo-Nordisk, Copenhagen, Denmark).

Radiological assessment

Bone age at the start and termination of treatment was determined from an x-ray of the left wrist and hand and interpreted using the Greulich and Pyle method (7). Cranial CT/MRI were done initially, and also at follow-up for patients with organic intracranial lesions.

Laboratory investigations

Routine blood work up was done to exclude chronic medical illness, e.g., CBC, alkaline phosphatase, calcium, liver and kidney functions. Thyroid profile (TSH and FT4) was performed basally to exclude hypothyroidism as a cause of SS. If hypothyroidism is evident, euthyroidism was achieved by L-thyroxine treatment before the performance of GH provocative tests. TSH was analyzed by the immunoradiometric assay, and radioimmunoassay kits from Diagnosis Product Corporation (Los Angeles, CA, USA) were used for FT4. The analysis of karyotyping was a rule for all short stature girls excluding TS.

GH assessment

Two GH provocative tests (Clonidine and ITT), separated by 1 week, were performed and samples were analyzed by a monoclonal antibody-based immunoradiometric (m-IRMA) (Pharmacia & Upjohn, Uppsala, Sweden), WHO International Reference Preparation (IRP) to the first biosynthetic GH standard was IRP 88/624. Females at 9 years or more and males at 10 years or more with no pubertal signs (prepubertal patients) were primed with sex hormones 3 days prior to GH testing. Ethinyl estradiol was given to girls at a dose of 20 μg three times/day for 3 days, and testosterone was given to boys at a single dose of 100 mg three days preceding the test.

Treatment protocol

All patients received biosynthetic GH therapy at a fixed dose of 20 IU/m^2/week (0.2 mg/kg/week). This weekly GH was divided into 6–7 daily doses and was given subcutaneously at night. Surface areas of patients were calculated annually and GH dose was revised accordingly. None of our patients received sex hormones to initiate pubertal development.

Follow up

Patients were followed up for a minimum of 1 year and up to 6 years with anthropometric assessment every 3 months. Thyroid profile was followed up every 6 months to detect central hypothyroidism. Side effects to GH were also documented and fundus examination was done for those complaining of recurrent headache. Compliance was observed and documented knowing the number of missed injections.

Statistical methods

Statistical analyses were performed with Statistical Package for Social Science (SPSS) for Windows (version 13.0; SPSS Inc., Chicago, IL, USA). Multiple linear regressions were performed to identify

predictors of growth response to rhGH in the first 4 years of treatment. Simultaneous entry of the variables was performed using the enter method (8). The annual growth velocity (GV) (cm/year) was treated as the dependant variable whereas the demographic, auxological and biological data were treated as independent variables. These variables included: distance to mid parental height (target height SDS-height SDS), demographic and auxological data at onset of therapy (age in years, body weight SDS and height SDS). GV of the previous year (cm/year) was added as a factor for years 2, 3, and 4, and lastly the mean peak of GH level (ug/L) from both tests ITT and clonidine was an added variable. The natural logarithm of GH peak [ln (ug/L)] was used in a separate model. The natural logarithm of a number was used for finding the relationship between two variables. The logarithm is a better way to find relationship, especially in the presence of several independent variables (9).

These predictors were ranked in order of importance. Ranking was performed by the SPSS software in terms of percentage variability and p-value: the more the percentage variable and the more significant the impact of the variable has on the model, the higher it is ranked (8).

Results

Growth response of all patients with GHD to rhGH is shown in Table 1. Only prepubertal patients with idiopathic isolated GH deficiency were included in the prediction model. There were 310 in the year 1, 268 in year 2, 193 in year 3, 72 in year 4, 33 in year 5 and only 16 in the sixth-year follow-up. We included the first four years follow-up only in the prediction model as the number of patients became small in the fifth- and sixth-year follow-up.

For the prediction of growth response in prepubertal isolated idiopathic GHD during the first 4 years of treatment, multiple linear regressions were done with the results presented in Tables 2 and 3.

Regarding the model with the natural logarithm of GH (Table 2), in the first year three significant predictors of growth were identified. Their ranking in order

Table 1 Growth response of all patients with GHD to rhGH.

Variables	Basal Mean±SD (n=477)	Year 1 Mean±SD (n=477)	Year 2 Mean±SD (n=414)	Year 3 Mean±SD (n=306)	Year 4 Mean±SD (n=132)	Year 5 Mean±SD (n=67)	Year 6 Mean±SD (n=33)
Height, cm	121.0±15.7 (71.5–156.1)	130.1±15.1 (90.5–163.7)	135.6±14.7 (99.7–171.0)	139±14.5 (104.0–168.5)	139.3±11.8 (110.0–169.0)	140.3±10.4 (115.0–164.3)	141.3±8.3 (120.0–161.0)
Height, SDS	−4.4±1.3 (−11.1 to −2.3)	−3.7±1.2 (−10.4 to −1.4)	−3.3±1.3 (−9.7 to −0.6)	−3.0±1.2 (−8.8 to −0.1)	−2.8±1.2 (−8.3 to −0.1)	−2.6±1.3 (−8.0 to −0.1)	−2.6±1.1 (−5.5 to −0.1)
Ht gain, SDS	–	0.7±0.5 (−0.4–3.2)	0.4±0.4 (−0.7–2.1)	0.3±0.4 (−1.0–1.7)	0.3±0.3 (−0.7–1.4)	0.1±0.3 (−0.7–0.8)	0.1±0.2 (−0.3 −0.5)
Target ht-ht, cm	43.2±17.0 (12.2–94.8)	34.3±16.2 (3.4–75.8)	27.9±16.1 (−5.1–64)	24.6±15.2 (−5.0–57)	25.1±13.5 (−3–52)	26.8±11.2 (5.3–44.8)	24.8±10.4 (3.8–41)
Target ht-ht, SDS	3.3±1.5 (0.2–9.9) (n=404)	2.6±1.4 (−0.2–9.2) (n=404)	2.2±1.5 (−1.0–8.5) (n=355)	1.9±1.4 (−0.9–7.6) (n=261)	1.8±1.5 (−0.8–7.1) (n=116)	1.8±1.7 (−0.8–6.8) (n=58)	1.8–1.6 (−0.8–5.1) (n=31)
GV, cm	–	9.0±2.5 (3.3–23.1)	6.7±2.0 (1.2–17.7)	5.4±2.1 (0.7–12.2)	5.2±1.7 (0.5–9.9)	4.5±1.5 (0.8–8.1)	4.4±1.4 1.5–6.7)
GV, SDS	–	4.7±4.0 (−2.7–24.0)	3.4±4.4 (−4.2–25.5)	2.2±3.8 (−5.8–19.7)	1.9±3.4 (−4.3–14.3)	1.0±2.9 (−4.3–9.9)	0.2±2.8 (−4.4–7.3)
US/LS	1.1± 0.1 (0.4–1.5)	1.0±0.2 (0.2–1.3) (n=31)	1.1±0.08 (1.0–1.2) (n=10)	1.1±0.1 (1.0–1.3) (n=4)	ND	ND	ND
US/LS, SDS	0.4±1.5 (−4.3–7.2)	0.2±1.7 (−2.7–3.0)	0.2±1.7 (−1.9–2.9)	0.5±1.9 (−1.3–2.9)	ND	ND	ND
Weight, kg	25.3±9.9 (8.0–69.0)	30.0±11.5 (10.9–83.3)	33.8±12.4 (12.5–94.0)	36.4±12.3 (2.5–100.5)	37.1±12.9 (13.9–106.1)	37.2±11.1 (18.7–67)	37.2±8.2 (21.3–59)
Weight, SDS	−2.3±0.9 (−4.6–2.7)	−2.0±1.0 (−5.0–2.8)	−1.8±1.1 (−5.6–3.8)	−1.7±1.3 (−11.8–4.5)	−1.5±1.3 (−5.3–5.1)	−1.4±1.3 (−5.2–2.3)	−1.3±1 (−3.0–1)
BMI, kg/m²	16.7±3.4 (7.3–35.2)	17.2±3.6 (9.6–35.6)	18.0±3.9 (2.8–40.2)	18.5±4.0 (10.6–40.9)	18.8.0 ±4.0 (12.6–42.2)	18.8±3.6 (13.5–32.2)	18.5±2.5 (14.5–25.8)
BMI, SDS	– 0.8±1.4 (−5.6–4.2)	−0.8±1.4 (−4.4–3.3)	−0.7±1.4 (−4.6–3.6)	−0.5±1.4 (−5.2–3.7)	−0.4±1.5 (−5.9–3.8)	– 0.3±1.4 (−5.5–3.1)	−0.2±1.0 (−3.0–2.2)

BMI, body mass index; GHD, growth hormone deficiency; GV, growth velocity; US/LS, upper segment lower segment ratio; ht, height; height gain SDS, height SDS – previous year height SDS; ND, not done; rhGH, recombinant human growth hormone; SDS, standard deviation score.

Table 2 Multiple linear regression for prediction of growth response in prepubertal, isolated idiopathic growth hormone deficiency (GHD) regarding the model with the natural logarithm of GH.

	First year			Second year			Third year			Fourth year		
Model with GH ln, ug/L	**Parameter estimate**	**Percentage variable**	**Rank**	**Parameter estimate**	**Percentage variable**	**Rank**	**Parameter estimate**	**Percentage variable**	**Rank**	**Parameter estimate**	**Percentage variable**	**Rank**
Number of patients		115			96			72			26	
Intercept (constant)		10.9			3.5			4.1			3	
GV year 1, cm/year				0.5	0.72	1[a] (p=0.000)						
GV year 2, cm/year							0.4	0.44	1[a] (p=0.000)			
GV year 3, cm/year										0.9	0.94	1[a] (p=0.000)
Age at onset of therapy, years	−0.3	−0.27	2[a] (p=0.01)	−0.03	−0.05	2	−0.2	−0.03	3	−0.05	−0.13	5
BW basal, SDS	0.1	0.04	4	−0.09	−0.04	3	0.6	0.25	2	1	0.42	2[a] (p=0.002)
Target ht-ht basal, SDS	1.1	0.63	3[a] (p=0.04)	−0.1	−0.13	6	−0.4	−0.39	5	0.3	0.50	6
Ht basal SDS	0.5	0.68	5	0.2	0.15	5	−0.7	−0.61	6	0.2	0.33	4
GH peak ln, ug/L	−0.9	−0.38	1[a] (p=0.000)	−0.2	−0.07	4	−0.3	−0.16	4	0.2	0.11	3
R^2		0.32			0.52			0.34			0.8	
Error SD, cm		2.5			1.4			1.6			0.6	

[a]significant. ht, height; BW, body weight; GH, growth hormone; GV, growth velocity; SDS, standard deviation score.

Table 3 Multiple linear regression for prediction of growth response in prepubertal, isolated idiopathic growth hormone deficiency (GHD) regarding the model with GH level.

	First year			Second year			Third year			Fourth year		
Model with GH, ug/L	**Parameter estimate**	**Beta**	**Rank**	**Parameter estimate**	**Beta**	**Rank**	**Parameter estimate**	**Beta**	**Rank**	**Parameter estimate**	**Beta**	**Rank**
Number of patients		115			96			72			26	
Intercept (constant)		11.7			3.6			3.9			2.6	
GV year 1, cm/year				0.5	0.71	1[a] (p=0.000)						
GV year 2, cm/year							0.4	0.45	1[a] (p=0.000)			
GV year 3, cm/year										0.9	0.96	1[a] (p=0.000)
Age at onset of therapy, years	−0.2	−0.25	2[a] (p=0.002)	−0.03	−0.05	2	−0.2	−0.31	2[a] (p=0.001)	−0.04	−0.1	5
BW basal, SDS	0.1	0.04	4	−0.09	−0.04	3	0.6	0.25	3	1	0.42	2[a] (p=0.001)
Target ht-ht basal, SDS	0.9	0.24	3[a] (p=0.01)	−0.2	−0.16	6	−0.4	−0.4	5	0.3	0.54	6
Ht basal SDS	0.4	0.41	5	0.2	0.13	5	−0.7	−0.64	6	0.2	0.37	4
GH peak, ug/L	−0.4	−0.4	1[a] (p=0.000)	−0.06	−0.09	4	−0.07	−0.10	4	0.2	0.15	3
R^2		0.36			0.52			0.33			0.81	
Error SD, cm		2.4			1.4			1.6			0.6	

[a]significant; ht, height; BW, body weight; GH, growth hormone; GV, growth velocity; SDS, standard deviation score.

of importance was GH peak [ln (ug/L)], age at onset of therapy and target height-height SDS, where GV of the first year was negatively correlated to GH peak and age of therapy onset, while it was positively correlated to target ht-ht SDS. The first year model explained 36% of the variability with an error SD of 2.4 cm/year. In the second and third years of therapy, GV was both significantly and positively correlated to the GV (cm/year) of the previous year. These models explained 52% and 33% of the variability with an error SD of 1.4 and 1.6 cm/year, respectively. Regarding the fourth year of therapy, third year GV (cm/year), and body weight (SDS) were the significantly and positively correlated to GV. This model explained 81% of the variability with an error SD of 0.6.

For the model with GH level (ug/L) (Table 3), the same three significant predictors, and in the same order, were identified. This model explained 32%, 35%, 41% and 80% of the variability with an error SD of 2.5, 1.4, 1.6 and 0.6 cm/year for years 1, 2, 3 and 4, respectively.

The equation for prediction of growth velocity is presented as follows: GV (cm/year)=constant+(parameter estimate×variable)±error SD. For example the equation for year 1 (Table 1): GV (year1) =9.4+(−0.3×age)+(0.1× BWSDS)+[1.1×target ht-ht(SDS)]+(0.5×ht SDS)+(−0.9×ln GH peak)±[2.5].

Table 4 presents our data and previous KIGS models, predicting growth for prepubertal idiopathic GHD at the first-year follow-up, while Table 5 presents data from the second-, third- and fourth-year follow-ups.

Discussion

In the present work, some demographic, auxological and laboratory variables were tested as being predictors for growth velocity (cm/year) and being the response variable in a multiple regression analysis. The demographic variables were mainly represented by age at onset of GH treatment. Auxological variables included were: height and weight SDS and the degree of deviation from the genetic height (target height-height SDS) at onset of treatment, and the whole year GV (cm/year) of previous years (years 1, 2, 3 and 4). Laboratory variable was mainly represented by the mean peak GH value. The natural logarithm of GH peak (ln) was used in a separate model. In their model, Ranke et al. (11) used the natural logarithm (ln) of GH peak: this is because it was more significantly correlated to GV year 1 than the value of the test in ug/L. In statistics, the natural logarithm of a number is used for parameter estimates in finding the relationship between two variables. The logarithm is the best way to find this relationship, especially in the presence of several independent variables (9). Yet, there was no statistical difference between the two models we performed. Neither GH dose nor the frequency of injections was included as independent variables because they were standardized for all patients. Also, birth weight and pretreatment GV were excluded as they were missing variables.

For development of the model, we selected the group of prepubertal patients with idiopathic GHD. In the best example, data to be used in the model should be derived from large, well-defined cohorts of patients in whom there has been a reasonable degree of variation in the growth response over a defined period (11–13). Our sample included in the development of the prediction models was as follows: 115 patients in year 1, 96 in year 2, 72 in year 3 and 26 in year 4.

Looking at our results, three predictors were significantly correlated to the first year GV: namely GH peak, age at onset of GH therapy and degree of deviation of height SDS from target height SDS (target height-height SDS). The model explained 36% of the variability with an error SD of 2.4 cm. The GH peak by the stimulatory tests (or its natural logarithm) is the strongest predictor for growth response in the first year. It was negatively correlated to GV first year, the lower the growth hormone value, the higher the response. This result is in agreement with previous results (10–12). However, it is the most difficult parameter to measure accurately and consistently. There is inter-center and inter-individual variability. That is why the highest peak of the two stimulatory tests was taken by us and also by Ranke et al. (11). Added to this, in the model used by Ranke et al. (11), excluding ln GH peak in the first year, there was under prediction of children with severe GHD (GH peak <5ug/L). Yet, there was no statistical difference between the two models we performed. Age of onset of therapy had the second ranking order for prediction of growth response in the first year. It was negatively correlated to GV: the younger the age at onset of disease, the higher the GV. Distance to mid-parental height SDS was the third most important predictor of growth in the first year and it was positively correlated to GV: the more the distance to the target height, the more the GV of the first year will be. Distance to the midparental (target height) has been identified as a very powerful correlate to GV year 1 in the KIGS database (1, 11, 12).

Height velocity during the previous year is the most important predictor for growth in the years 2–4, confirming that the eventual height outcome is determined by the initial response to GH therapy and also agreeing with previous Egyptian studies (10) and international ones (12).

Table 4 Present study compared to others regarding predictive factors for growth derived by multiple linear regression for prepubertal patients with idiopathic growth hormone deficiency (GHD) in the first-year follow-up.

	Present study [model with GH, ln (ug/L)]	El Shaer, 2001 (10)	Ranke et al., 1999 (11)		Ranke et al. 2005 (12)	
Etiology of GHD	Idiopathic prepubertal	Idiopathic, prepubertal	Idiopathic, prepubertal		Idiopathic (0–3 years)	
Year 1	n=115	n=163	n=593	n=593	n=265	n=261
			Model a	Model b	Model a	Model b
Strongest predictor	GH peak ln (ug/L)	GH peak ln (ug/L)	GH peak ln (ug/L)	Ht-target ht SDS	GH peak ln (ug/L)	Age of onset year
Positive correlators (basal values)	BW SDS (N,4), height SDS (N,5), target ht-ht (SDS) [3]	BA delay (years)[4], Height SDS [2], triceps skin fold thickness [5]	BW SDS [4], birth wt SDS [6], GH dose IU/kg/wk [5]	BW SDS [5], birth wt SDS [3], GH dose IU/kg/wk [4]	Birth wt SDS [6], GH dose (IU/kg/week) [5], body wt [4]	Birth wt SDS [3], GH dose (IU/kg/w [2], body wt (N,5)
Negative correlators (basal values)	GH ln (ug/L) [1], age at onset [2]	GH peak ln (ug/L) [1], BW SDS [3]	GH peak ln (ug/L) [1], age at onset [2], ht-target ht (SDS)[3]	Age at onset [2], ht-target ht (SDS) [1]	GH peak ln (ug/L) [1], age at onset [2], ht-target ht (SDS)[3]	Age at onset [1], ht-target ht (N,4)
R^2	0.32	0.31	0.61	0.45	0.54	0.45
Error SD	2.5	2.8	1.46	1.72	2.12	2.3

GV, growth velocity (cm/year); BA, bone age; [number], the number indicates the rank of variable; N, non-significant; Model a, including GH peak level by stimulation test; Model b, excluding GH peak.

Both models using alternatively absolute peak GH value or its natural logarithm provide high accuracy rate with p=0.0001 for all of the 4 years. To predict accurately the growth response in an individual patient on GH therapy, the model or the logarithm must describe a large proportion of variability in response (high R^2) with a low margin of error (low error SD). Despite the fact that our models had low predictive power in the first three years (R^2=0.36, 0.52, 0.33 for years 1–3, respectively), yet it has a relative low SD (2.5, 1.4 and 1.6 cm, respectively). Similarly, KIGS models have been criticized for explaining only 40–60% of the variability in response; this should be weighed against the low margin of error of the prediction (1).

The fourth year model is a highly accurate one with a high R^2 (0.84) and a very low margin of error with an error SD of 0.6 cm/year. However, we need to validate this model to ensure its applicability, and study larger number of patients in the future. The relative low predictive power of the model during the first three years may be explained by other variables that are missing from the models. Such parameters need to be identified in the future, but if they are to have practical utility it is mandatory that their measurements should be standardized and easily accessible, as in our present models. Parameters that might usefully be included in future models fall into a number of categories: anthropometrical, body composition, biochemical and genetic. Many anthropometrical parameters (e.g., height, weight) are already documented; additional parameters (e.g., head circumference, sitting height, leg length, limb length, fat folds) can be easily collected within a clinical setting and can probably be measured with a similar degree of accuracy (1). This does not apply to body composition parameters (e.g., fat and muscle mass, characteristics of bone structure), as sophisticated and expensive equipment (e.g., computed tomography scanners) is needed to collect these data, the processes are time-consuming and the standardization among them is probably inadequate for data from different sources to be pooled.

It is worth mentioning here that El Shaer, (10) included triceps skin fold thickness in their work. In 2001, Schonau et al. (2001) derived a prediction model for the first year GV for 58 prepubertal German patients with isolated GHD. The model was based on four predictors: pre-treatment bone age retardation and pretreatment serum levels of IGF-I, which were both negatively correlated to GV; also, urinary levels of deoxypyridinoline (urinary marker of bone turnover) after 1 month of treatment and GV after 3 months of treatment were included and both positively correlated. This model explained

Table 5 Our study compared to others regarding predictive factors for growth derived by multiple linear regression for prepubertal patients with idiopathic growth hormone deficiency (GHD) in the second-, third- and fourth-year follow-up.

	Our study	El Shaer 2001 (10)	Ranke et al. 1999 (11)
Year 2	n=96	n=114	n=573
Strongest predictors	GV year 1	GV year 1	GV year 1
Positive correlators	GV year 1 [1], ht SDS (N,5)	GV year 1 [1]	GV year 1 [1], BW SDS [2], GH dose [4]
Negative correlators	GH (N,4), target ht-ht SDS(N,6), BWSDS (N,3), age at onset (N,2)		Age at onset (3)
R^2	0.52	0.62	0.4
Error SD, cm	1.4	1.8	1.19
Year 3	n=72	n=63	n=335
Strongest predictor	GV year 2	GV year 2	GV year 2
Positive correlators	GV year 2 (1), BWSDS (N,2)	GV year 2 [1]	GV year 2 [1], body wt SDS [2], GH dose [4]
Negative correlators	Ht SDS (N,6), target ht-ht SDS (N,5), GH (N,4), age of onset (N,3)	Target ht-ht SDS [2]	Age at onset [3]
R^2	0.34	1	0.37
Error SD, cm	1.6	0.0	1.05
Year 4	n=26	n=49	n=180
Strongest predictor	GV year 3	Non-significant correlation	Body wt SDS
Positive correlators	GV year 3 [1], BW SDS [2],GH (N,3), target ht-ht SDS (N,6), ht SDS (N,4)		GV year 3 [2], body wt SDS [1], GH dose [3]
Negative correlators	Age of onset (5,N)		Age at onset [4]
R^2	0.8		0.3
Error SD, cm	0.6		0.95

GV, growth velocity (cm/year); GH, growth hormone; SD, standard deviation; [number], the number indicates the rank of variable; N, non-significant.

89% of the variability with an error SD of 0.93 cm/year (14). Although there has been reports of significant association ($p<0.001$) between the urinary excretion of deoxypyridinoline after 4 weeks of GH therapy with the GV in prepubertal GH deficient children during the first treatment year (15). Yet, the model offered by Schonau et al. (14) was criticized – the high degree of explained variability could be partly due to the small size of the group and the central determination of biochemical parameters, thus avoiding standardization issues. The principal methodological defect, however, is the appearance of GV during GH treatment on both sides of the equation. Thus, much of the predicted 12 months' height velocity is already explained by the first 3 months of growth. Thus, there is doubt that such a model, although giving information about potential predictors, has clinical utility in a process aimed at optimizing and individualizing GH treatment in a worldwide setting (1). Yet in 2010 (16) this model was able to accurately predict height in 22 Italian prepubertal GH deficient children with $R^2=0.94$, but the reliability of this result is limited by the small sample size and the heterogeneity of patients with the age group 0.5–12.2 years compared to 6.5–8.9 years in the study done by Schonau et al. (14).

We conclude that prediction models offer a valuable tool for individualization and assuring adherence to rhGH and thus a cost-effective treatment, which is the ultimate goal of GH therapy.

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Conflict of interest statement

The authors declare that there are no financial or personal relationships with other people or organizations that could inappropriately influence (bias) the present work.

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References

1. Ranke MB, Lindberg A. Predicting growth in response to growth hormone treatment. Growth Horm IGF Res 2009; 19:1–11.
2. Ranke MB, Lindberg A. Observed and Predicted Growth Responses in Prepubertal Children with Growth Disorders: Guidance of Growth Hormone Treatment by Empirical Variables. J Clin Endocrinol Metab 2010;95:1229–37.
3. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 1976;51:170–9.
4. Marshall WA, Tanner JM. Variations in patterns of pubertal changes in girls. Arch Dis Child 1969;44:291–303.
5. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970;45:13–23.
6. Maghnie M, Ambrosini L, Cappa M, Pozzobon G, Ghizzoni L, et al. Adult Height in Patients with Permanent Growth Hormone Deficiency with and without Multiple Pituitary Hormone Deficiencies. J Clin Endocrinol Metabol 2006;91: 2900–5.
7. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist, 2nd ed. Stanford, CA: Stanford University Press, 1959.
8. Brace, N, Kemp R, Snelgar R. SPSS for psychologists, 4th ed. New York: Palgrave Macmillan, 2009, Ch 7.
9. Collin R, Murray D. Mathematical statistics with mathematica, Ch 11, New York: Springer-Verlag, 2002.
10. El Shaer T. Assessment of growth hormone therapeutic response in growth hormone deficient children and adolescents. MD thesis, Faculty of Medicine, Cairo University, Egypt; 2001.
11. Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield, W et al. 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;84:1174–83.
12. Ranke MB, Lindberg A, Albertsson-Wikland K, Wilton P, Price DA, et al. 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;90:1966–71.
13. Blethen SL, Compton P, Lippe BM, Rosenfeld G, August GP, Johanson A. Factors predicting the response to growth hormone (GH) therapy in prepubertal children with GH deficiency. Clin Endocrinol Metab 1993;76:574–9.
14. Schonau E, Westermann F, Rauch F, Stabrey A, Wassmer1 G, et al. A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency Europ J Endocr 2001;144:13–20.
15. Rauch F, George M, Stabrey A, Neu C, Werner F, et al. Collagen Markers Deoxypyridinoline and Hydroxylysine Glycosides: Pediatric Reference Data and Use for Growth Prediction in Growth Hormone-deficient Children. Clin Chem 2002;48: 315–22.
16. Valle D, Bartolotta E, Caruso M, De Sanctis C, Falorni A, et al. Prediction of Response to Growth Hormone Treatment in prepubertal Children with Growth Hormone Deficiency. J Endocrinol Invest 2010;10:3275–322.