CLINICAL STUDY

A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency

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Abstract

Objective: To identify parameters which predict individual growth response to recombinant human GH (rhGH) therapy and to combine these parameters in a prediction model.

Design: Fifty-eight prepubertal patients with GH deficiency (17 females) participated in this prospective multicenter trial with 1 year of follow-up.

Methods: Auxological measurements, parameters of GH status and markers of bone metabolism were measured at baseline and at 1, 3 and 6 months after the start of rhGH treatment. Correlations with height velocity during the first 12 months of treatment (HV + 12) were calculated. Prediction models were derived by multiple regression analysis.

Results: The model which best predicted HV + 12 combined the following parameters: pretreatment bone age retardation as a fraction of chronological age, pretreatment serum levels of IGF-I, urinary levels of deoxypyridinoline (a marker of bone resorption) after 1 month of treatment and height velocity after 3 months of treatment. This model explained 89% of the variation in HV + 12 with a standard deviation of the residuals of 0.93 cm/year. Defining successful rhGH therapy as a doubling of pretreatment height velocity, the model had a specificity of 90% and a sensitivity of 100% in predicting therapeutic success.

Conclusions: This model is an accurate and practicable tool to predict growth response in GH-deficient children. It may help to optimize rhGH therapy by individual dose adjustment and contribute to improved overall outcomes.

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Introduction

The growth response of short children to therapy with recombinant human growth hormone (rhGH) exhibits considerable interindividual variability (1). While this variability is particularly marked in non-endocrine growth disorders such as Turner syndrome, it is also noted in children who suffer from GH deficiency (GHD) (2). Obviously, sensitivity to rhGH differs between individuals even if they belong to the same diagnostic category.

rhGH therapy imposes a burden on treated children and their families and is costly for the health care system (1). It is therefore important to avoid futile treatment in non-responders and to direct resources to those children who are most likely to benefit from therapeutic intervention. Reliable prediction of an

individual's response to rhGH therapy may help to resolve this dilemma.

A variety of models have been proposed to this end. These models predict long-term response to rhGH therapy either on the basis of pretreatment characteristics or after a short period of rhGH therapy (2–11). Pretreatment parameters commonly used in such models include auxological criteria as well as indices of endogenous GH secretion, such as maximum GH serum levels (max-GH) in stimulation tests or serum levels of insulin-like growth factors (IGF) and their binding proteins (IGFBP). Parameters of bone and collagen metabolism have been proposed as growth predictors after a short 'trial' therapy (12–14). While all of these parameters show some correlation with growth response, the methods proposed so far do not appear to be sufficiently precise to base therapeutic

Table 1 Baseline characteristics of the study population. Results are given as mean (95% CI).

	Girls (n = 17)	Boys (n = 41)
Age (years)	7.7 (6.5 to 8.9)	7.9 (7.0 to 8.9)
Relative bone age retardation	-0.42 (-0.51 to -0.33)	-0.36 (-0.40 to -0.32)
Height (cm)	106.2 (99.3 to 113.0)	109.6 (104.8 to 114.5)
Height (SDS)	-4.4 (-5.1 to -3.8)	-3.7 (-4.1 to -3.2)
Midparental height (SDS)	-1.34 (-1.90 to -0.77)	-1.07 (-1.47 to -0.66)
HV (cm/year)	4.6 (3.6 to 5.2)	4.5 (4.0 to 4.9)
HV (SDS)	-1.8 (-3.0 to -0.7)	-1.8 (-2.8 to -0.7)
Birth weight (SDS)	-0.97 (-1.82 to -0.12)	-0.39 (-0.79 to 0.00)
Weight (SDS)	-2.83 (-3.58 to -2.09)	-3.14 (-3.74 to -2.53)
BMI (kg/m ²)	15.9 (14.8 to 17.0)	15.8 (14.9 to 16.6)
ln[max-GH (ng/ml)]	1.37 (0.77 to 1.97)	1.48 (1.16 to 1.79)

CI, confidence intervals; SDS, standard deviation score; HV, height velocity; BMI, body mass index.

decisions on the results. Thus, there is a need for more reliable prediction methods (1).

A combination of parameters belonging to different diagnostic categories (indicators of GH secretion, biochemical bone and collagen markers, auxological measurements) might improve the accuracy of the prediction. This hypothesis was tested in the present prospective multicenter study.

Patients and methods

Patients

Fifty-eight prepubertal children with isolated GHD (17 girls aged 3–12 years; 41 boys aged 2–14 years) from 27 German centers of pediatric endocrinology participated in this prospective longitudinal trial (Table 1). In addition, the same study protocol was used to treat nine girls with Turner syndrome (aged 5–10 years).

The diagnosis of GHD was based upon a height velocity (HV) below the 25th percentile for age and a max-GH below 10 ng/ml in at least two provocative tests. Endocrinological testing and quantification of GH were performed locally using various immunoassays. The most commonly used provocative tests were the insulin tolerance test (73%) and the arginine test (97%).

None of the patients had received rhGH therapy before. To avoid interference with growth due to pubertal development, the study included only those patients whose bone age was below 10 years for boys and 9 years for girls, and who had no clinical signs of puberty (genital stage, breast development). Patients with a disorder of GH secretion secondary to chronic illness or malignancy were excluded from the study. Standard deviation scores (SDS) of height, weight and HV were calculated on the basis of German reference values as given by Brandt & Reinken (15). Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in m). Bone age was determined in each participating center according to the Greulich–Pyle standards (16). Relative bone age retardation was

calculated as bone age minus chronological age divided by chronological age. Midparental height-SDS was calculated as the sum of the father's and mother's height-SDS divided by 1.61 (3). Data were collected using specially designed case report forms. Data monitoring, including source data verification, was performed by trained personnel from Lilly Germany. The study was approved by all local ethics review boards of the participating centers and written informed consent was obtained from the patients' parents.

Therapy

rhGH replacement therapy was carried out with a standard dose of 0.07 IU/kg per day (0.023 mg/kg per day) (Humatrope, Lilly Deutschland GmbH, Bad Homburg, Germany). The dose remained unchanged in the first year of treatment. No other growth-promoting medications were administered during the study period. Seven patients received thyroid hormones, one hydrocortisone and one antidiuretic hormone.

Blood and urine collections

Serum and 24-h urine collections were obtained prior to therapy and after 1, 3 and 6 months of treatment with rhGH. Urine was collected at home just before the visit and samples were handed to the attending physician. Serum and urine samples were stored at -20 °C until analysis. Markers of bone and collagen metabolism were analyzed in the osteological laboratory of the University Children's Hospital, Cologne. IGF-I and IGFBP-3 were determined in the endocrinological laboratory of the University Children's Hospital, Gießen.

Analytical methods

The following parameters were determined in serum samples: alkaline phosphatase with a photometric method (optimierte Standard-Methode; Boehringer

Mannheim, Mannheim, Germany); bone-specific alkaline phosphatase by immunoradiometric assay (Tandem-R-Ostase; Hybritech Inc., San Diego, CA, USA); osteocalcin by chemiluminescence assay (Osteocalcin Chemiluminescence; Nichols Institute Diagnostics Inc., San Juan Capistrano, CA, USA); procollagen type 1 C-terminal propeptide (P1CP) by radioimmunoassay (PICP; Orion Diagnostica, Espoo, Finland); IGF-I was measured with an IGFBP-blocked radioimmunoassay in the presence of a large excess of IGF-II (Mediagnost, Tübingen, Germany), as described previously (17); IGFBP-3 was measured with a specific radioimmunoassay as described previously (18).

The following parameters were determined in urine samples: deoxypyridinoline (DPD) was measured by enzyme immunoassay (Pyrilinks-D; Metra Biosystems Inc., Mountain View, CA, USA); C-terminal telopeptide of collagen type 1 by enzyme immunoassay (Crosslaps; Osteometer Bio Tech Inc., Herlev, Denmark); N-terminal telopeptide of collagen type 1 by enzyme-linked immunosorbent assay (ELitestNTX; Osteomark Inc., Seattle, WA, USA); urinary creatinine was quantified by the Jaffé method.

Statistics

Descriptive statistics are shown as means and 95% confidence intervals (CI). Changes in parameters after the start of rhGH treatment were tested for significance by Student's two-tailed paired *t*-test. In linear regression analysis, HV after 12 months of rhGH treatment was treated as a dependent variable, and auxologic parameters, IGF parameters, and biochemical bone and collagen parameters as independent variables. In the multiple linear regression models, we tried to minimize the residual variance and to keep the number of included parameters as small as possible. The variance inflation factor is defined as $1/(1 - r_i^2)$, where r_i^2 denotes the coefficient of determination for the regression of the *i*th independent variable on all other independent variables. To avoid multicollinearity the variance inflation factor should be small, at least smaller than $1/(1 - r^2)$, where r^2 denotes the coefficient of determination of the whole model. Predicted values of HV were calculated in order to assess the prognostic value of the selected model. All calculations

Figure 1 Changes in HV during rhGH treatment of girls (upper panel) and boys (lower panel).

were performed using SAS 6.12 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline data are given in Table 1. As expected, mean HV increased rapidly after the start of treatment, but individual HV varied over a large range (Fig. 1). After 12 months of treatment HV had doubled in 36 of the 58 children.

Results for biochemical indices of bone formation and bone resorption are shown in Tables 2 and 3 respectively. All of these parameters increased to a peak at 3 months after the start of treatment. Thereafter, they remained at about the same level or showed a tendency to decline. IGF-I and IGFBP-3 increased within 1 month and remained constant thereafter (Table 4).

In order to identify predictors of growth response, linear regression analyses were performed. The relationships

Table 2 Serum concentrations of biochemical markers of bone formation before and during rhGH therapy. Results are given as mean (95% CI).

	Alkaline phosphatase (U/l)	Bone alkaline phosphatase (μg/l)	Osteocalcin (μg/l)	P1CP (μg/l)
Baseline	244 (225–262)	52 (47–58)	15.4 (14.0–16.7)	318 (285–352)
1 month	293*** (273–312)	66*** (61–71)	18.9*** (17.9–19.9)	514*** (438–589)
3 months	356*** (335–377)	83*** (76–89)	21.9*** (20.6–23.3)	580*** (504–657)
6 months	348*** (322–374)	83*** (76–89)	21.5*** (20.0–22.9)	519*** (449–588)

*** *P* < 0.0001 compared with baseline (two-sided paired *t*-tests).

Table 3 Urinary concentrations of biochemical markers of bone resorption before and during rhGH therapy. All values are relative to urinary creatinine levels. Results are given as mean (95% CI).

	DPD (nmol/mmol)	N-telopeptide (nmol/mmol)	C-telopeptide (µg/mmol)
Baseline	17.3 (15.3–19.4)	576 (512–641)	1150 (1020–1270)
1 month	24.9*** (22.3–27.5)	631 (573–690)	1850*** (1690–2000)
3 months	26.9*** (24.0–29.8)	924*** (822–1026)	2040*** (1880–2190)
6 months	25.6*** (22.7–28.6)	766*** (683–850)	1770*** (1650–1880)

*** $P < 0.0001$ compared with baseline (two-tailed paired t -tests).

between HV at 12 months and anthropometric measures, biochemical parameters of GH function and markers of bone metabolism were tested and a selection of the results is given in Table 5. For each parameter, the result of the time-point yielding maximum r^2 is indicated. The closest correlations from each category were for HV after 3 months of treatment, relative bone age retardation prior to therapy, maximum GH response in functional testing, baseline IGFBP-3, and the absolute values of urinary DPD and C-telopeptide after 4 weeks of therapy.

Various growth prediction models, shown in Table 6, were tested by multiple regression analysis using HV at 12 months as the dependent variable. The first model contains only parameters that were available before therapy. Maximal GH response to functional testing was the only significant predictor in this model. The second model uses biochemical results after 1 month of treatment. The third and fourth models use parameters which were obtained at 3 and 6 months, respectively, after the start of treatment.

Combinations of parameters obtained at different time-points were also examined in multiple regression models. This approach revealed that a combination of parameters from the three categories – auxology, GH status and bone parameters – yielded the best results (model 5). The equation of this model was as follows: $HV(+12) [in\ cm/year] = 3.543 + 0.100 \cdot DPD(+1) [in\ nmol/mmol\ creatinine] + 0.299 \cdot HV(+3) [in\ cm/year] - 0.010 \cdot IGF-I(0) [in\ \mu g/l] - 2.377 \cdot (relative\ bone\ age\ retardation) [as\ a\ fraction\ of\ bone\ age]$.

This model combines parameters which are available before and during 3 months of treatment, and explains 89% of the variance in HV after 12 months of rhGH therapy. The accuracy of this model is demonstrated in Fig. 2, which compares predicted and observed HV at

12 months. The residuals (=prediction error) ranged from $-1.72\ cm$ to $+2.26\ cm$. There was no systematic trend to under- or overestimate the actual HV in the low or high HV range.

In comparison, Fig. 3 shows analogous results obtained with a model recently published by Ranke *et al.* (3). In contrast to that study, rhGH dosage could not be used as a predictor in our analysis, because we applied a standardized treatment regimen with a fixed dosage. Therefore, the results displayed in Fig. 3 are based on the remaining parameters of that model: $\ln[\max-GH]$, chronological age, birth weight, difference between height and midparental height, and weight (3). The scatter of residuals was larger and there was a trend to under-estimate HV when growth rates are low.

In order to subject our model 5 to a first test of its

Table 5 Linear correlations with HV during 12 months of rhGH treatment. The numbers in parentheses indicate the time-point when the parameter was examined (0, baseline; +1, 1 month after start of rhGH treatment; +3, 3 months after start of treatment). Parameter terms followed by 'SDS' indicate the standard deviation score of a result and other parameters are absolute values. The squares of correlation coefficients of the different parameters are shown only for the time-points at which r^2 values were maximal.

Parameter	P	r ²
Auxology		
Age (0)	0.005	0.13
Height-SDS (0)	0.05	0.06
BMI (0)	0.2	0.02
HV (0)	0.1	0.03
HV-SDS (0)	0.005	0.13
HV (+3)	<0.001	0.64
Relative bone age retardation (0)	0.002	0.16
Birth weight-SDS	0.03	0.11
Height-SDS – midparental height-SDS	0.006	0.14
Growth factors		
IGF-I (0)	<0.001	0.35
IGFBP-3 (0)	<0.001	0.38
Max-GH (0)	0.001	0.16
$\ln(\max-GH)$ (0)	<0.001	0.41
Bone formation markers		
Alkaline phosphatase (+3)	0.004	0.14
Bone alkaline phosphatase (+3)	0.02	0.09
Osteocalcin (+3)	0.008	0.13
P1CP (+1)	<0.001	0.23
Bone resorption markers		
DPD (+1)	<0.001	0.56
C-telopeptide (+1)	<0.001	0.48
N-telopeptide (+3)	0.002	0.16

Table 4 Biochemical markers GH status before and during GH therapy. Results are given as mean (95% CI).

	IGF-I (µg/l)	IGFBP-3 (mg/l)
Baseline	47 (34–60)	1.74 (1.45–2.02)
1 month	104*** (85–123)	2.79*** (2.54–3.05)
3 months	104*** (87–120)	2.75*** (2.52–2.98)
6 months	115*** (95–134)	2.98*** (2.71–3.24)

*** $P < 0.0001$ compared with baseline (two-tailed paired t -tests).

Table 6 Multiple regression models to predict HV at 12 months after the start of treatment. The numbers in parentheses indicate the time-point when the parameter was examined (baseline, 1, 3 or 6 months after start of treatment). Parameters not followed by (SDS) represent absolute values.

	Regression coefficient	95% CI	P	r ²
Model 1				
Intercept	13.5736	(10.4245; 16.7228)	<0.001	0.70
ln (max-GH)	-1.0930	(-1.6903; -0.4957)	<0.001	
Age (0)	-0.0373	(-0.2383; 0.1638)	0.71	
Birth weight (SDS)	0.0736	(-0.3232; 0.4705)	0.71	
Height (SDS-midparental height (SDS)	0.0445	(-0.4640; 0.3751)	0.83	
Weight (0) (SDS)	0.0746	(-0.2963; 0.4455)	0.69	
IGF-I (0)	-0.0159	(-0.0424; 0.0105)	0.23	
IGFBP-3 (0)	-0.0005	(-0.0018; 0.0009)	0.48	
Relative bone age retardation (0)	-1.0827	(-5.7991; 3.6337)	0.64	
Model 2				
Intercept	5.0492	(3.7236; 6.3748)	<0.001	0.59
DPD (+1)	0.1658	(0.1125; 0.2192)	<0.001	
P1CP (+1)	0.0017	(-0.0002; 0.0035)	0.07	
Model 3				
Intercept	1.8223	(-0.1987; 3.8434)	0.07	0.74
HV (+3)	0.4351	(0.3278; 0.5424)	<0.001	
Alkaline phosphatase (+3)	0.0040	(-0.0015; 0.0095)	0.10	
P1CP (+3)	0.0014	(-0.0001; 0.0029)	0.06	
DPD (+3)	0.0237	(-0.0156; 0.0629)	0.20	
Model 4				
Intercept	1.6598	(0.1673; 3.1524)	0.03	0.82
HV (+6)	0.6852	(0.5700; 0.8003)	<0.001	
DPD (+6)	0.0228	(-0.0069; 0.0525)	0.10	
Alkaline phosphatase (+6)	-0.0024	(-0.0061; 0.0012)	0.10	
P1CP (+6)	0.0015	(0.0003; 0.0028)	0.01	
Model 5				
Intercept	3.543	(1.868; 5.219)	<0.001	0.89
DPD (+1)	0.100	(0.062; 0.138)	<0.001	
HV (+3)	0.299	(0.213; 0.385)	<0.001	
IGF-I (0)	-0.010	(-0.018; -0.002)	0.01	
Relative bone age retardation	-2.377	(-4.777; 0.103)	0.06

Figure 2 Relationship between the predicted first year HV and the residuals (observed minus predicted value) using model 5. Open circles represent results in patients with GHD, solid triangles in patients with Turner syndrome. SDS of the residuals for patients with GHD, 0.93 cm/year; for patients with Turner syndrome, 0.77 cm/year.

Figure 3 Relationship between the predicted first year HV and the residuals (observed minus predicted value) using a previously published model (3) in patients with GHD. SDS of the residuals, 1.85 cm/year.

validity in disorders other than GHD, it was applied to a group of nine girls with Turner syndrome. These girls had undergone the same study protocol as the GHD patients, even though the dose was higher (0.15 IU/kg per day = 0.05 mg/kg per day). As can be seen in Fig. 2, the prediction was similarly accurate in girls with Turner syndrome. The distribution of residuals was comparable to that in GHD.

We then determined the ability of this growth prediction model to distinguish between responders and non-responders. As there are no agreed criteria to define acceptable response to rhGH therapy, we arbitrarily defined 'response' as a doubling of HV after 12 months of treatment. Using this definition of a positive growth response, the diagnostic sensitivity of model 5 (detection of 'responders') was 100%, while its specificity (detection of 'non-responders') was 90%.

Discussion

The aim of this study was to develop a new model to predict the growth response to treatment with rhGH. Three different types of parameters were tested, auxological measurements, indicators of GH secretion and biochemical markers of bone metabolism. These parameters have been shown to be individually associated with HV (2–10), but the accuracy of the prediction is not sufficient for clinical purposes. Growth, however, is a complex process that may be described better by a multidimensional approach. Parameters from different categories (dimensions) provide complementary information and, therefore, a combination of such parameters should be expected to yield a more precise prediction. This assumption, indeed, proved to be correct.

'Classical' pretreatment auxologic measures such as height-SDS, HV or HV-SDS were poorly associated with HV during the first year of treatment. However, there was a significant correlation between the relative bone age retardation at the start of treatment and subsequent growth. This may reflect the fact that bone age retardation indicates the long-term history of growth disturbance. If ossification is markedly delayed, a more pronounced catch-up growth is to be expected.

A close correlation was found between the calculated HV after 3 months and the observed HV after 12 months. In the light of the rather controversial debate on the value of short-term measurements of height, this parameter had been more or less ignored in the past (19). The calculation of short-term HV certainly carries some measurement error. Yet our results also show that growth in the first 3 months of therapy is very fast. This effect reduces the relative error in HV determination.

IGF-I and IGFBP-3, two markers of GH secretion, were highly interrelated at baseline (data not shown) and therefore yield redundant information in this particular situation. The negative correlations with

HV response found in this study are in agreement with previous reports (6–8). Baseline IGF-I (or IGFBP-3) provides information about the severity of GHD. The lower the GH secretion prior to therapy, the more likely is a good response. This concept is also supported by the finding that the maximal GH response in stimulation tests showed a strong negative correlation to HV response in the first year. In simple linear regression analyses the association between max-GH and HV response was actually slightly better than between IGF-I or IGFBP-3 and HV response. However, in the multiple regression model 5, IGF-I levels before therapy had a higher predictive power than max-GH.

The strong association between max-GH and HV was the reason for the predictive power of model 1. Compared with the model published by Ranke *et al.* (3) this model includes pretreatment IGF-I and IGFBP-3 levels as additional variables. In our group of GHD patients, model 1 explained 70% of the variability in HV at 12 months, which is comparable with results reported previously (3). However, using the model proposed by Ranke *et al.* (3), the prediction was rather inaccurate for individual patients (Fig. 3). The residuals of the prediction ranged from –2.21 cm/year to +7.46 cm/year and the SDS of the residuals was 1.85 cm/year. However, the advantage of this prediction model is that it is based on data which are already known before the start of treatment. Thus, this model might serve as an approximation to provide a first idea of the expected therapeutic success. If adequately precise, such a model might even be used to decide whether or not treatment should be started.

In the present study, we investigated the value of adding markers of bone metabolism to growth prediction models. In growing children bone metabolism consists mainly of two different processes, modeling and remodeling. Modeling is responsible for rapid changes in external bone size and shape (20). Remodeling converts 'young' spongiosa near the growth plate into mature secondary spongiosa and is responsible for the continuous turnover of bone tissue at all sites of the skeleton. Biochemical markers of bone metabolism provide information on the integrated activity of these processes. Therefore, these parameters can be expected to reflect the sensitivity of the skeleton to GH. The associations between most of these markers and HV at 12 months was similar to results reported by others (5, 13, 14, 21, 22). The best correlation with 1-year HV was found for urinary DPD at 4 weeks after the start of treatment. DPD is a crosslinking compound which arises during the maturation of collagen in the extracellular space. It is released into the circulation and excreted via the kidneys when bone collagen is degraded during bone resorption. Therefore, urinary DPD reflects the activity of bone resorption in the entire skeletal system. DPD at 4 weeks also proved to be the bone parameter which most consistently improved the accuracy of the prediction in multiple regression models.

Multiple regression model 5 explained 89% of the variation in HV in the first year of treatment. This model uses a combination of four parameters which are available at 3 months after the start of treatment. The prediction error of this model had a standard deviation below 1 cm/year, and in no case was the error larger than 2.26 cm/year. In addition, this model had a sensitivity of 100% in detecting 'responders' and a specificity of 90% in detecting 'non-responders'. Thus, the 1-year success of rhGH therapy can be predicted with sufficient precision based on this model.

Whether the predictive value also holds for HV in the second and following years remains to be established. However, given the close correlation between the first year HV and longer-term growth rates (23, 24), one may be confident that this important aspect will be met. In addition, the preliminary results in patients with Turner syndrome suggest that this model will also be useful in non-GHD patients. This finding may be surprising at first glance because of the well-known different responsiveness to rhGH treatment in both patient groups, children with GHD and girls with Turner syndrome, and because of the different rhGH doses used. However, it should be kept in mind that our prediction model 5 includes two parameters (dimensions) of GH efficacy, bone markers after 4 weeks of rhGH treatment and 3-month HV, which probably reflect implicitly individual GH responsiveness and GH dose. This may be considered a special strength of the model.

In summary, we have devised a growth prediction model which is sufficiently precise to be of clinical use. This model uses information which is obtained before the start of therapy or becomes available during the first 3 months of treatment. We are currently testing this model in an independent and larger cohort of children with GHD and in children with short stature due to other etiologies. Further controlled studies will have to address the question of whether rhGH dose adjustments based on the predictions of such a model lead to increased growth, since ultimately a prediction is only useful if it demonstrably improves patient care.

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