The Mathematical Model for Total Pubertal Growth in Idiopathic Growth Hormone (GH) Deficiency Suggests a Moderate Role of GH Dose

MICHAEL B. RANKE, ANDERS LINDBERG, DAVID D. MARTIN, BERT BAKKER, PATRICK WILTON, KERSTIN ALBERTSSON-WIKLAND, CHRIS T. COWELL, DAVID A. PRICE, AND EDWARD O. REITER, ON BEHALF OF THE KABI INTERNATIONAL GROWTH STUDY OF THE PFIZER INTERNATIONAL GROWTH DATABASE

Pediatric Endocrinology Section, University Children’s Hospital (M.B.R., D.D.M.), Tübingen D-72076 Germany; Pfizer (A.L., B.B., P.W.), Stockholm, Sweden; Pediatric Growth Research Center, University of Gothenburg (K.A.-W.), Gothenburg, Sweden; Institute of Endocrinology and Diabetes, The Children’s Hospital (C.T.C.), Westmead, Australia; Department of Child Health, Royal Manchester Children’s Hospital (D.A.P.), Manchester, United Kingdom; and Tufts University of Medicine (E.O.R.), Springfield, Massachusetts 01199

The role of GH treatment during total pubertal growth (TPG) is still unclear. We developed a prediction model for TPG (centimeters) through a multiple regression analysis of various prepubertal parameters in 303 adolescents with idiopathic GH deficiency from the KIGS database. Prepubertal catch-up growth and near-adult height were achieved, and GH dose was kept constant at approximately 30 μg/kg/d. The model was validated on a cohort of 36 patients from one center. Four TPG predictors explained 70% of the variability with an error SD of 4.2 cm: gender (TPG in males was >11.3 cm vs. that in females), age at onset of puberty (negative), height SD score minus midparental height SD score at puberty onset (negative), and mean GH dose during puberty (positive). Our analysis suggests that TPG in idiopathic GH deficiency is only moderately dependent on GH dose. The use of a higher GH dosage at the onset of puberty should thus depend on the individual’s height development. The TPG model aids in the planning of individually optimized and cost-effective GH treatment. (J Clin Endocrinol Metab 88: 4748–4753, 2003)

THE DYNAMICS OF pubertal growth are believed to involve the interplay between hormonal factors and cellular processes on the epiphyseal growth plate. The magnitude of growth during puberty accounts for approximately 25% of total postnatal height and is slightly higher in males. Although a continual rise in the concentrations of sex steroids occurs from the onset of puberty until adulthood is reached, the secretion of GH (1) and circulating levels of IGF-I tend to mimic the pattern of the pubertal growth spurt. These observations stimulated the hypothesis that a quantitative relationship exists between GH secretion and the magnitude of pubertal growth, a proposition that led to the deduction that it would be necessary to prescribe higher than prepubertal GH doses during puberty in GH-deficient (GHD) patients. Only a few studies have focused on the effect of GH dose in terms of total pubertal growth (TPG) in adolescents with GH deficiency (GHD), and their results are controversial (2, 3). The individualization and optimization of GH therapy during puberty are also particularly relevant to the aspect of safety and the costs involved. The aim of our study was to analyze the factors influencing TPG in a large cohort of adolescents with idiopathic GH deficiency from the Kabi International Growth Study of the Pfizer International Growth Database (KIGS) and to develop a mathematical model that would allow the prediction of TPG. We validated the model by applying it to an independent cohort of adolescents with idiopathic GHD.

Abbreviations: GHD, GH deficient, GH deficiency; MPH, midparental height; TPG, total pubertal growth.

Patients and Methods

The growth response expressed as TPG during GH therapy was determined in 303 patients with idiopathic GHD who were enrolled in the KIGS. Through a multiple regression analysis, these values were correlated with potential, relevant variables relating to the patients’ background characteristics, modalities of treatment, and physical status before and at the onset of puberty. A predictive growth model based on these variables was derived from this analysis. A comparison was then made between the predicted and observed growth responses in an independent cohort of children with idiopathic GHD who were treated in Tübingen, Germany. In addition, the model was applied to various other cohorts of patients with different causes of short stature who, within the framework of KIGS, also received GH treatment during the entire pubertal phase.

The height standards used for normal children were those reported by Tanner et al. (4, 5), and the weight standards were those described by Freeman et al. (6). Birth weight for gestational age was transformed into SD scores based on the standards presented by Niklasson et al. (7). The midparental height (MPH) SD score was calculated as follows: (father’s height SD score + mother’s height SD score) ÷ 1.61 (8), based on the standards described by Tanner et al. (4, 5). Bone age was determined according to the method of Greulich and Pyle (9), and the data we used were reported by the treating physicians.

Patients

The data for patients with idiopathic GHD, who were enrolled in KIGS until October 24, 2002, were analyzed to construct the prediction model. At that point in time, the KIGS database included 303 children (180 males and 123 females) whose data were suitable for analysis, the inclusion criterion being a peak GH level of 10 μg/liter or less after 2 standard provocation tests (excluding testing with GHRH), as reported by the treating physician. The diagnosis was based on the KIGS Etiology Classification System Code 1 (10). The patients were treated exclusively with recombinant human GH (Genotropin, Pharmacia Corp., Stock-
holm, Sweden) and received six or seven injections of GH/wk. All patients had been treated with GH for at least 5 yr, including a minimum of 2 prepubertal yr and a minimum of 2 yr during puberty. The onset of puberty was defined as the first appearance of breast stage B2 (Tanner) in girls, and a mean testicular volume greater than 3 ml in boys, or the pharmacological induction of puberty. The time elapsed between the prepubertal status and the observed onset of puberty was less than 6 months. Age at puberty onset was limited to 10–17 yr of age in boys and 9–16 yr of age in girls. The end of pubertal growth was assumed if the height velocity during the previous years was less than 2 cm/yr and the growth curve showed an asymptotical pattern indicating the end of growth. Furthermore, the GH dose level was not an inclusion criterion, but was approximately constant over the total phase of pubertal growth. All patients analyzed had a normal birth size for gestational age, whereas patients who were born small for gestational age were excluded.

Statistical analysis

TPG is defined as the distance in centimeters between height at the onset of puberty and height at near-adult stature. TPG was correlated with the following variables by means of multiple regression analyses (results were calculated as the median and 10th to 90th percentiles): 1) status at birth: gender, weight sd score, length sd score, ponderal index, mode of delivery, and Apgar score; 2) genetic background: height sd score of the mother, height sd score of the father, MPH sd score, and ethnic origin (the ethnic background was analyzed by adding dummy variables, e.g. 0/1 Asian/not Asian, to allow a mathematical analysis using the multiple regression computer software); 3) treatment modality: mean GH dose at the beginning of and during puberty; and 4) variables at the onset of puberty: age, bone age, height sd score, weight sd score, height sd score minus MPH sd score, peak GH levels during initial provocative testing, and pituitary hormone deficiency status (i.e. isolated or multiple pituitary hormone deficiencies).

The prediction model was developed by means of multiple linear regression analysis fitted by least squares and the REG procedure in the SAS computer software (version 6.12, SAS Institute, Inc., Cary, NC). A hierarchy of prediction factors was derived for ordering predictive factors, as described by Weisberg (11, 12). Differences between observed and predicted TPG were expressed in terms of Studentized residuals. The residual is calculated as the observed TPG minus the predicted TPG for each observation, and the Studentized residual is the residual divided by its se.

Model validation

For validation of the prediction model, data from a cohort of patients (n = 36; 24 males and 12 females) from the University Children’s Hospital (Tubingen, Germany) were used. The inclusion criteria were identical to those in the cohort used to establish the prediction model, and all parameters required for the prediction model were available for these patients. These patients were treated with various brands of GH, as we assumed that the commercially available recombinant GH preparations have equal potency.

Results

Demographic characteristics of the cohort used for construction of the TPG prediction model

The characteristics at the start of GH treatment, onset of puberty, and near-adult height of the patients with idiopathic GHD treated longitudinally are listed in Table 1A. Equivalent characteristics of the patients from Tubingen, which were used for validation of the prediction model, are listed in Table 1B. The two cohorts showed very similar characteristics at the three time points documented. Patients from Tubingen were slightly younger at the onset of GH replacement and were older when near-adult height was documented. TPG was very similar in the male cohorts, whereas the observed TPG in females from the KIGS cohort was greater (P < 0.05).

Growth prediction model

The variables that were predictive of TPG, their rank order as predictors, the overall correlation coefficient of the prediction model, and the error sp of the prediction are listed in Table 2. All single predictors were found to be significant at a level of P < 0.0001.

The equation describing the predicted TPG is as follows:

\[
\text{TPG} = 48.3 + [\text{gender (males} = 1; \text{females} = 0) \times 11.3] + [\text{age at puberty onset (yr)} \times -3.0] + [\text{height at onset of puberty} - \text{MPH (sd score)} \times -1.3] + [\text{mean GH dose (mg/kg/d)} \times 137]
\]

(refer to Table 2). This model explains 70% of the variability of TPG with a total error sp of 4.2 cm. TPG was 11.3 cm greater in males than in females. The most important predictor of TPG (apart from gender) was the age at the onset of puberty. The correlation between age at puberty onset and TPG in girls and boys is illustrated in Fig. 1. Thus, the younger the child, the higher the anticipated height increment during puberty. The distance of height to MPH at the onset of puberty correlated negatively with TPG. Finally, the mean GH dose given was a positive predictor of TPG.

Validation of prediction model

The plots of the Studentized residuals (see Patients and Methods) vs. the predicted response in the original KIGS cohort and the validation cohort are illustrated in Fig. 2, A and B. The Studentized residual plots are used to diagnose outliers, nonlinearity, and nonconstant error variance in prediction models and are a part of their mathematical validation. The fact that the observations are randomly clustered implies that there is no heterogeneity in the group with respect to the relative importance of the different predictors.

Discussion

GH secretion increases during puberty (1, 13), but it is still not clear whether the additional GH secreted is required to ensure adequate pubertal growth and/or the normal adolescent development of other bodily structures and functions (14) or whether it is merely an epiphenomenon. The answer to this question will influence the therapeutics of GH replacement in GHD children as well as the course of GH therapy in other growth disorders. The main objectives of our attempts to derive prediction models for GH-treated children are to optimize and individualize GH therapy in terms of efficacy, safety, and cost effectiveness (15). The latter is particularly relevant during adolescence, as weight increases. The present model is the first to predict TPG on the basis of an analysis of 303 adolescents with idiopathic GHD. The prediction equation is a linear regression equation involving four predictors that are available at the onset of puberty. The prediction model was validated on another cohort from a single center (Tubingen). The calculated TPG difference of 11.3 cm between males and females is almost identical to the difference observed in normal children (4, 5).

We anticipated that TPG would be inversely related to the age at the onset of puberty, and our findings confirmed those
of others (16, 17), as a younger child has, in principle, a greater growth potential than an older one. Although the diagnostic group we studied was highly heterogeneous, and the adolescents treated with GH had different disorders, it was remarkable that the correlation between age and TPG was so consistently high, and its variance so low. In previous reports it had been found that TPG in GHD is inversely related to bone age at the onset of puberty (18, 19). As the growth potential is related to bone maturity, it would be expected that bone age is the better predictor compared with chronological age. In our statistical analysis, however, chronological age was consistently selected over bone age, and bone age did not prove to be an independent predictor. This may be due to the fact that age is the more accurate parameter. As adult stature is a genetically determined process, it is evident that the distance to MPH (which is a surrogate for the height target of an individual) is also a predictor for remaining growth, including TPG at the onset of puberty, a finding that was established in studies of the prepubertal growth response to GH (15). If the present model is applied

### TABLE 1. Demographic characteristics in children with idiopathic GHD from the KIGS cohort used for analysis of predictors of TPG (A) and patients from Tubingen (B)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Dimension</th>
<th>Parameters</th>
<th>Rank estimate</th>
<th>Partial $r^2$</th>
<th>Model $r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>Constant</td>
<td>38.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female = 0, male = 1</td>
<td>11.3</td>
<td>1</td>
<td>0.313</td>
<td>0.313</td>
</tr>
<tr>
<td>Age at puberty onset</td>
<td>yr</td>
<td>-3.0</td>
<td>2</td>
<td>0.338</td>
<td>0.636</td>
</tr>
<tr>
<td>Height minus MPH</td>
<td>SDS</td>
<td>-1.3</td>
<td>3</td>
<td>0.043</td>
<td>0.678</td>
</tr>
<tr>
<td>Mean GH dose</td>
<td>mg/kg/d</td>
<td>137</td>
<td>4</td>
<td>0.022</td>
<td>0.701</td>
</tr>
<tr>
<td>$r^2 = 0.70$</td>
<td>Residual SD 4.2 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IGHD, Idiopathic GHD.
to a child with a greater height distance to MPH at the onset of puberty, a better outcome is likely as compared with a child whose height is close to MPH.

Our model also proves that the GH dose is of relevance for TPG in idiopathic GHD. The dose effect, however, is evidently rather minor. It has been shown in patients with GHD (17, 19) and Turner syndrome (20) who were treated with prepubertal GH doses that the final height SD score corre-
lated highly with the height SD score at the onset of puberty. In our model the doubling of the GH dose over the prepubertal dose during puberty would basically result in a 3- to 4-cm increase in the predicted TPG. This is of the same order of magnitude as observed in dose-finding studies of adolescents with GHD (3) and also of the order of the error SD for TPG. Our model supports the concept that the basic biological circumstances (e.g. age and epiphysial maturity) and factors other than GH (e.g. sex steroids) are the major determinants of pubertal growth, whereas the childhood growth phase is chiefly the phase of higher GH sensitivity (21).

Although growth during puberty is an essential component of the growth process, it is difficult to define the term TPG. Different results are obtained depending on whether the onset of puberty is established by clinical observations (22, 23) or whether the nadir of prepubertal height velocity can be calculated on the basis of extensive longitudinal growth data documented on frequent visits (24). TPG is lower if it rests on clinical signs, particularly in girls, thus indicating that a part of pubertal growth occurs before pubertal signs are actually visible. The results presented by Marshall and Tanner (22, 23), based on pubertal signs, showed mean TPGs of 30.2 and 19.2 cm in normal boys and girls, respectively, whereas the corresponding values from the growth analysis by Gasser et al. (24) were 33.9 and 28.6 cm. In a pharmaco-epidemiological survey such as KIGS, however, data on growth during GH treatment is not documented as frequently as in longitudinal growth studies of normal children, which explains why the TPG in our present study is slightly lower. Similarly, the end of growth is not as accurately documented as is the case in growth studies of normal children. Nevertheless, despite these drawbacks, the determination of TPG according to clinical criteria is certainly the only practical and relatively robust approach that can be taken during standard GH treatment.

The prediction model for TPG in idiopathic GHD together with the published prediction models for the prepubertal growth phase (15) allows the calculation of predicted growth in a given individual from the time GH replacement starts until adulthood is achieved. This gives the physician the means to offer realistic expectations of GH therapy to the patient and other parties involved. It would also enable GH treatment to be designed according to the individual responsiveness to GH. As the sensitivity to GH is higher during childhood compared with adolescence and young children are lighter in weight, it is evident that the efforts to normalize height should begin during the first years of GH treatment. Even though it may be possible to achieve a positive effect on height outcome in individual adolescents by modifying the GH dosage and/or through pharmacological modulation of the onset and duration of puberty (25), our findings clearly indicate that the correction of the height deficit should begin well before puberty. This would not only be particularly beneficial from a psychological point of view, but would also improve the cost effectiveness of GH therapy. A patient with GHD who has an average sensitivity to GH and a normal predicted adult height at the onset of puberty will probably reach a height within the normal range on a prepubertal replacement dose of GH. In other groups of patients and in those with a poor prognosis and/or low GH sensitivity, the GH dose may have to be adapted. These concepts of dosing during puberty need to be validated, and further studies are required to ascertain whether an increase in the GH dose is necessary for the entire pubertal phase or whether the increase should occur during another phase, such as, for instance, during the ascending segment of the growth curve. Another issue that needs further analysis is the question of whether higher pubertal GH doses are required to normalize body composition in adult life, as some investigators have demonstrated that it is abnormal in childhood-onset GHD in adults (14).

Acknowledgments

Received April 7, 2003. Accepted July 11, 2003.
Address all correspondence and requests for reprints to: Dr. Michael B. Ranke, Pediatric Endocrinology Section, University Children’s Hospital, Eberhard Karls University Hoppe-Seyler, Strasse 1, Hoppe Seyler Strasse 1, Tubingen D-72076, Germany. E-mail: michael.ranke@med.uni-tuebingen.de.

References


---

**IOF-SERVIER YOUNG INVESTIGATOR RESEARCH FELLOWSHIP**

**For young scientists**

(up to 40 years of age)

The IOF-Servier Research Fellowship is a grant of 40,000 euros awarded every 2 years to a project within the field of osteoporosis. An international and independent jury selects the best candidate according to the originality of the project, its scientific value, and its international relevance.

The 3rd IOF-Servier Young Investigator Research Fellowship will be presented during the IOF World Congress on Osteoporosis in Rio de Janeiro in 2004.

Application forms are available at the IOF office and on the IOF Web site:

**IOF Office**
71, cours Albert Thomas
69447 Lyon Cedex 03-France
Fax: 33 4 72 36 90 52
IOF Web site: www.osteofound.org
Servier Web site: www.servier.com

Deadline for submission for next fellowship: December 1, 2003.