Predicting the Response to Growth Hormone Treatment in Short Children with Chronic Kidney Disease

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Context: Short stature in children with chronic kidney disease (CKD) is due to various underlying congenital or acquired renal disorders resulting in variable impairment of renal function and variable response to GH treatment.

Objective: It was the aim to develop a mathematical model that allows the prediction of the individual growth response and to identify nonresponders.

Design: Data from 208 prepubertal children on conservative or dialysis treatment in a large pharmacoepidemiological survey, the KIGS (Pfizer International Growth Database), were used for the model and data from 67 similar CKD patients registered at the Dutch Growth Research Foundation for validation.

Results: Annualized height velocity (centimeters per year) during the first year of GH treatment was best predicted by age at start, weight SD score, underlying renal disorder (hereditary kidney disorder), glomerular filtration rate (at baseline), and GH dosage. Using these parameters, the final model explained 37% of the overall variability of growth response. Standard error of the estimates was 1.6 cm. Age was the most important predictor of growth response (20.3% of variability) followed by weight SD score at start, and 27.2% of the variability of the second-year response could be predicted by the first-year response and glomerular filtration rate. Nonresponders of the validation group could be correctly identified.

Conclusion: Based on simple clinical variables, a robust prediction model was developed that provides realistic expectations of individual growth response to GH in short children with CKD. The model will help in identifying nonresponders and to tailor treatment strategies. (***J Clin Endocrinol Metab*** **95: 686–692, 2010)**

Impairment of longitudinal growth is a clinical hallmark in children suffering from chronic kidney disease (CKD) (1, 2). At the start of renal replacement therapy, stunting is more expressed in children with congenital renal disorders than in children with acquired renal diseases (2, 3), especially in children with nephropathic cystinosis (4). Even after renal transplantation, final height is below the lower normal limit in about 50% of patients (1, 5).

GH treatment is able to increase height velocity and height SD score (SDS) (6–8) and to substantially improve final height (9–11) in CKD patients. However, using a prediction model for GH deficiency (GHD) the first-year response to GH was less than in short GHD (12).

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Abbreviations: CKD, Chronic kidney disease; GFR, glomerular filtration rate; GHD, GH deficiency; rhGH recombinant human GH; SDS, SD score.

The magnitude of response to GH treatment depends on the GH dosage. A dose of 0.35 mg/kg × wk seems to be optimal for short CKD patients, because half of this dose was less effective, whereas doubling of this did not significantly improve the response in double-blind studies (13, 14). In most trials on GH treatment in CKD patients, a standard dose of 0.33–0.35 mg/kg × wk was used. However, the response in the individual patients showed a wide variation from no response to excessive response. Age, glomerular filtration rate (GFR), need for dialysis treatment, target height, and pretreatment growth rate were identified as predictors of response to GH treatment in prepubertal children during the first and second treatment year (15). Although those predictive factors for response to GH could be identified, accurate predictions were not possible.

Prediction models for the response to GH have been developed in a variety of conditions resulting in short stature, *e.g.* in patients with GHD (16) and Turner's syndrome (17) or in patients born small for gestational age (18, 19). Those prediction models allow the calculation of the individual expected height velocity. The aim of this study was to develop and validate a similar model for short children with CKD.

Patients and Methods

Patients

The data analyzed for prediction are from patients treated with recombinant human GH (rhGH) (Genotropin; Pfizer Co., New York, NY) during follow-up in a large pharmaco-epidemiological survey, the KIGS (Pfizer International Growth Study) database. Diagnosis was made according to the KIGS Etiology Classification List. All patients with subcodes of 3.8.5. (renal disorders) were included into the study with the exception of patients with secondary glomerular disorders like lupus-glomerulonephritis (3.8.5.3.7.–3.8.5.3.9).

Analyzed patients had to be prepubertal defined by breast stage I (girls) or testicular volume less than 4 ml (boys) and by an age less than 12 yr in boys and less than 10 yr in girls at the onset of GH treatment and who remained prepubertal during the first treatment year. GFR at start had to be less than 90 ml/min × 1.73 m^2. Patients on conservative treatment and on dialysis treatment were included, whereas patients with functioning renal allografts or being transplanted during the study period were excluded. Patients were required to receive seven injections of GH per week for at least 1 yr. Those patients missing GH injections for a total of more than 14 d during the first year of treatment were excluded from the analysis. Only six patients had to be excluded because of too long breaks in GH treatment. To identify nonresponders by the prediction model, the measured height velocity SDS during the first treatment year had to be more than 0.0 SDS, and patients with a lower height velocity were excluded from analysis.

These inclusion criteria resulted in an original cohort of 287 children. Because primary renal disease subgroups are predictive regarding loss of renal function per year (20) and might also be predictive for response to GH, the patients were subdivided into four groups, *i.e.* renal hypo/dysplasia (3.8.5.1.1–3.8.5.1.9), hereditary kidney disorders (3.8.5.2.1–3.8.5.2.9), glomerular disorders (3.8.5.3.1–3.8.5.3.6), and others (3.8.5.5.1–3.8.5.7.9). Height measurements recorded at intervals of 9–15 months during GH treatment were used to calculate height velocity (centimeters per year).

A complete data set was available for 208 patients (158 boys) treated for at least 1 yr. The mean age at start of GH treatment was 6.6 ± 2.7 yr, and mean height SDS amounted to −2.3 ± 1.0 according to Tanner's reference values (21). Additional demographic characteristics are given in supplemental Table 1 (published as supplemental data on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org). The underlying primary renal disease was renal hypo-/dysplasia in 126 patients (60.5%), hereditary kidney disorders in 53 (25.5%), glomerular diseases in 12 (5.8%), and other disorders in 17 (8.2%).

A total of 125 patients (96 boys) with complete data sets during 2 yr GH treatment were available for prediction analysis of the response to GH during the second treatment year. The mean age at start of GH treatment was 6.1 ± 2.6 yr. The detailed demographic data at time of start of second treatment year are given in supplemental Table 2.

The validation group was recruited from the registry of the Dutch Research Foundation (22). The patients were treated with Norditropin (Nordisk Co., Bagsvaerd, Denmark). For 67 (44 boys) of 114 patients, the data sets were complete. The inclusion criteria were the same as for the KIGS cohort. Sixty of these patients (40 boys) had a height velocity SDS greater than 0.0 during the first treatment year. These patients were used for validation; their mean age at start of treatment was 6.7 ± 3.0 yr, and mean height SDS was −1.8 ± 0.9 according to Tanner standards (21). The demographic characteristics are shown in supplemental Table 3. The primary renal disease was renal hypo-/dysplasia in 33 patients (55%), hereditary disorders in 12 (20%), glomerular diseases in five (8.3%), and other disorders in 10 (16.7%). The additional seven patients with a height velocity SDS less than or equal to 0.0 were defined as nonresponders and were used as a test for nonresponders.

To be consistent with previous prediction models (16–18, 23), the height standards used for the model were those of Tanner and Whitehouse (21), and the weight standards were those of Freeman *et al.* (24). The mid-parental height SDS was calculated according to Cole (25). Using these standards and not the actual national standards (26, 27), the height deficit of KIGS and Dutch patients is underscored (supplemental Tables 1–3), which, however, does not significantly influence the results of the prediction model.

Prediction model

Predictive models for growth response (annualized height velocity in centimeters per year) during the initial year of GH therapy were estimated using univariate and multiple regression analysis with potential relevant variables measured at the beginning of the point in time at which the growth response was tracked.

The variables taken from the visit at the start of GH treatment and tested were chronological age, gender, height (centimeters), height velocity (centimeters per year) during the year before start of GH treatment, weight (kilograms), height velocity (SDS), height SDS, weight SDS, BMI, mid-parental height (centimeters), height/mid-parental height SDS, duration of renal failure (years), GFR (ml/min × 1.73 m^2), primary renal disease group, dialysis treatment, and dose of GH (milligrams per kilogram per week)

TABLE 1. Univariate regression analysis

Variable	n	r	*P* value
Age at start (yr)	287	−0.422	<0.001
Height (cm)	287	−0.349	<0.001
Height velocity (cm/yr) before start	176	0.325	<0.001
Weight (kg)	287	−0.305	<0.001
Duration of renal failure	220	−0.214	0.001
Height velocity (SDS) before start	176	0.161	0.033
Dialysis	287	−0.154	0.009
Hypoplasia	287	0.138	0.020
Hereditary renal disorder	287	−0.125	0.034
GFR	211	0.124	0.073
GH dose (mg/kg · wk)	287	0.116	0.050
Weight (SDS)	287	0.105	NS
Height SDS (Tanner) (21)	287	0.096	NS
Glomerular diseases	287	−0.089	NS
BMI	287	0.081	NS
Mid-parental height	259	0.068	NS
Gender, boys	287	−0.059	NS
Height SDS − MPH SDS	259	0.011	NS

Regression variables are for predicting the first-year response to GH (centimeters per year). Data are for the total cohort from KIGS. NS, Not significant.

(Table 1). In patients on dialysis treatment, the GFR was set to 5 ml/min × 1.73 m^2.

Similarly, predictive variables for the second treatment year were tested. Variables considered for the second year were almost the same as for first year but taken from the 1-yr visit (including first-year height velocity in centimeters per year): age (years), gender, height SDS, body weight SDS, BMI SDS, mid-parental height (centimeters), mean log dose GH (milligrams per kilogram per week), height velocity (centimeters per year), GFR (milliliters per minute × 1.73 m^2), change in GFR, dialysis treatment, and primary renal disease group.

Statistical analysis

The prediction model was developed by means of multiple linear regression analysis fitted by least squares and the REG procedure in the SAS computer program (version 8.0; SAS Institute, Inc., Cary, NC). PRESS statistics were used to help assess model performance. The Cp statistic was used to help to choose an appropriate predictive model and to determine the approximate number of variables to include into the model. After the selection of predictors was determined (using an all possible regression approach), the rank of predictors (Table 2) represents the order they were added in a forward selection, and the partial R^2 represents the specific variables contribution to the overall R^2. Detailed descriptions of selecting model and performing diagnostic statistics was published earlier (16–18, 23). The square root of the estimated variance about the regression is the SE of the estimates. To be consistent with earlier publications, it is referred as the error SD of the prediction model.

Residual analysis was used to help to asses model adequacy. Differences between observed and predicted height velocity were expressed in terms of Studentized residuals. The residual is calculated as the difference of the observed height velocity minus the predicted height velocity for each observation, and the Studentized residual is the residual divided by its SE.

TABLE 2. Regression equation variables for predicting the first-year growth response (centimeters per year) to GH therapy in 208 children with CKD from KIGS

	Parameter estimate	Rank	Partial R^2	Variable significance
Intercept (constant)	13.3			
Age at start (yr)	−0.38	1	0.203	<0.001
Weight SDS at start	0.39	2	0.062	<0.001
Hereditary renal disorder	−1.16	3	0.039	0.0008
GFR (ml/min × 1.73 m^2)	0.023	4	0.039	0.0005
Log dose GH (mg/kg · wk)	1.04	5	0.022	0.0090

Nonparametric statistics (two-sided Wilcoxon's rank sum test) were used to test differences between groups in case of unknown or skewed distributions, otherwise Student's *t* test. $P < 0.05$ was considered as significant.

Validation of the model

For the group of patients from the Dutch Growth Research Foundation, the actual growth response over the first treatment year was calculated and then compared with the growth response predicted from the model. For this, the individual prediction values of growth responses of all patients of the Dutch cohort were added to the Studentized residuals calculated for the KIGS cohort. If the model fits the mean residual plot of the validation group should ideally be equal to 0, and the SD = 1. There should be a similar residual distribution as in the KIGS cohort, no correlation, no indication of nonlinearity, and a constant variance over predicted values.

Results

The demographic characteristics at the start of GH treatment for patients treated for at least 1 yr are given in supplemental Table 1. The children were typical for short children with CKD under conservative or dialysis treatment when compared with several intention-to-treat studies. Mean age was 6.6 ± 2.7 yr, and mean pretreatment height velocity was 5.0 ± 1.9 cm/yr. The height velocity during the first treatment year was 9.2 ± 2.0 cm corresponding to a height increment of 0.75 ± 0.38 SDS during the first treatment year. The absolute height velocity during the first treatment year was lowest in patients with glomerular and hereditary disorders (Fig. 1).

The baseline demographic data of children who were treated for at least 2 yr did not differ significantly (two-sided Wilcoxon's rank sum test) from those who were treated for 1 yr (supplemental Table 2). Their mean height velocity during the first treatment year was 9.5 ± 2.2 cm, and the gain in height SDS was 0.73 ± 1.0. The height

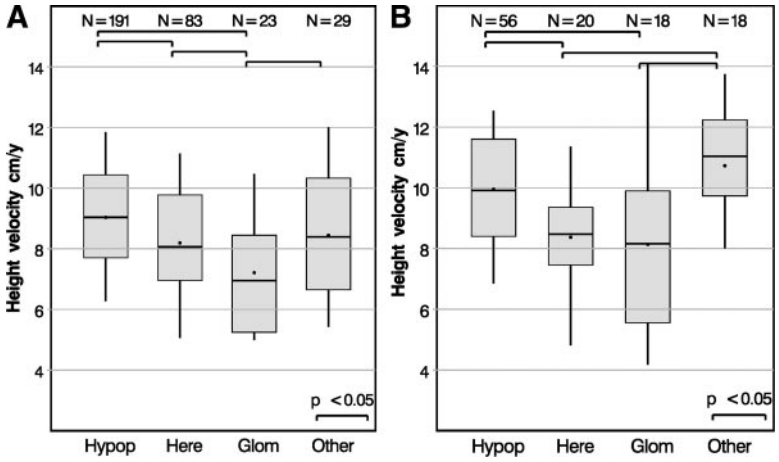

FIG. 1. Height velocity during the first treatment year according to subclassification of renal disorders. A, Height velocity (centimeters per year) for the KIGS cohort used to set up the prediction model; B, height velocity (centimeters per year) for the Dutch cohort used for validation.

velocity during the second year was 7.3 ± 1.7 cm, and the increase in height SDS was 0.3 ± 0.3.

The demographic characteristics at the start of GH therapy and the first year responses to GH treatment in the children of the Dutch validation group were comparable to those of the KIGS cohort. The mean age at baseline was 6.7 ± 3.0 yr, mean height velocity during the first treatment year amounted to 10.1 ± 2.1 cm, and the mean increase in height SDS was 0.9 ± 0.4 (supplemental Table 3).

Prediction model

The tested univariate analyses are listed in the order of the highest significance in Table 1. Height velocity during the first treatment year was strongest correlated with age (negatively), followed by height (negatively), weight (negatively), and height velocity (positively) at start of GH treatment.

The variables found by multiple linear regression analysis to be predictive of growth response over one year are given in Table 2. In addition, the rank of predictive variables (in the order they were added in a forward selection, see methods) and the contribution of each variable (partial R^2) to the cumulative coefficient of determination of the prediction model (R^2) are given. R^2 was 0.37.

The equation describing the predicted height velocity (PHV) for the first year of GH therapy is as follows: PHV (centimeters per year) = 13.3 − [age (years) × 0.38 + (weight SDS × 0.39)] − [hereditary renal disorder (0 when absent or 1 when present) × 1.16] + [Ln GH dose (milligrams per kilogram per week) × 1.04] + [GFR (milliliters per minute × 1.73 m^2) × 0.023]. This equation explains 37% of the overall variability of the growth response. The SE of the estimate or error SD of the prediction model was 1.6 cm.

Age and weight SDS were the most important predictors of the five identified in this model, accounting for 26% of the variability followed by the type of primary renal disease, dose of GH, and GFR. Height SDS was not included in the model because it was highly associated with weight SDS ($r = 0.65$; $P < 0.001$) and was the least predictive value. Weight, Ln dose of GH, and GFR were positively associated with growth response to GH, whereas age and the presence of a hereditary disorder as a primary renal disease were negatively associated.

Studentized residuals *vs.* the predicted response for the KIGS cohort is shown in Fig. 2A. The plot of residuals showed a symmetrical distribution.

The height velocity during the second treatment year was best predicted by a two-parameter model. The response was best predicted by the height velocity (centimeters per year) during the first treatment year (intercept 3.509; parameter estimate 0.350; $P < 0.001$) followed by GFR (parameter estimate 0.013; $P < 0.032$). Those two parameters explained 27.2% of the variation with an error SD of 1.46 cm.

Validation of prediction model

The KIGS model was validated using the independent Dutch cohort. The corresponding residual plot of the validation cohort is shown in Fig. 2B. Comparing Fig. 2, A and B, the residual plot of the Dutch cohort did not show any pattern that suggests a problem with the model. The mean of residuals of the validation group was nearly 0 and the SD nearly 1.

When the total Dutch cohort (n = 67 including the seven patients who were defined as nonresponders, see *Patients and Methods*) were tested by the model, the nonresponders could correctly be identified as those patients with residuals below −2.0 (Fig. 3).

Discussion

Using data from a large cohort of children registered in KIGS, we have developed the first model allowing the prediction of the individual response to GH in children suffering from uremic growth failure. Thirty-seven percent of the variation in the first-year growth response is explained by the presented model. The error SD of prediction model amounted to 1.6 cm. This level of accuracy was based on the variables chronological age, weight SDS, Ln dose of GH, GFR, and primary renal disease. Thus, the present investigations also give the new information that the type of primary renal disorder and GFR independently influence the response to GH.

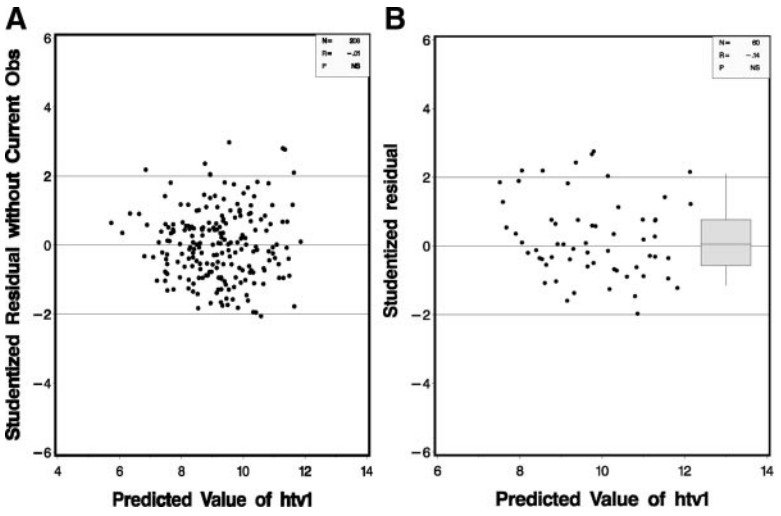

FIG. 2. Studentized residuals *vs.* predicted height velocity in the first year of GH treatment in children with CKD. A, Cohort used to develop the prediction model; B, cohort used for validation.

KIGS prediction models (16–18) describe the most likely response to GH considering the qualitative and quantitative variability of the predictors of the diagnostic group investigated with a certain degree of error. If this algorithm is applied to an individual, a difference between the predicted response and the observed response can be expressed in terms of a residual (observed minus predicted growth velocity/error SD of predicted). Depending on the predicted height response above or below the mean Studentized residual, it can be concluded that the individual shows a high or low response to GH.

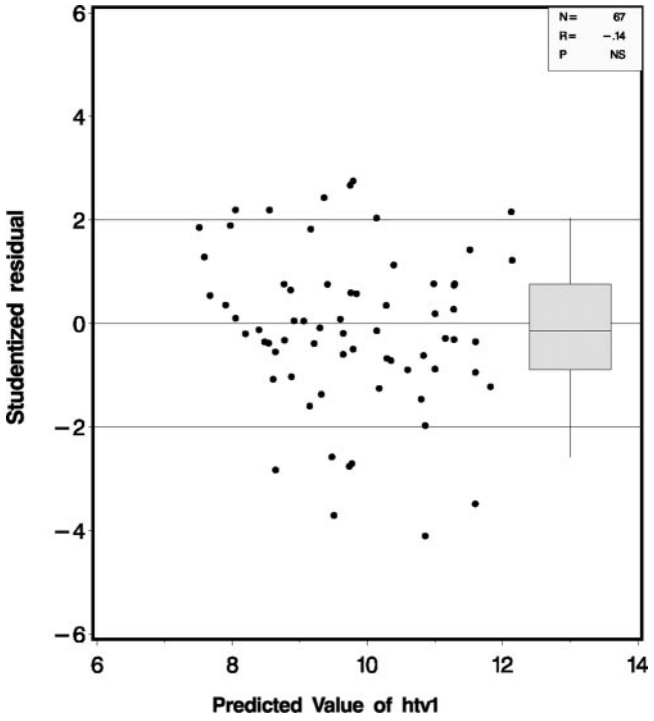

FIG. 3. Identification of nonresponders. Studentized residuals *vs.* predicted height velocity in the first year of GH treatment in children with CKD. The Studentized residuals are calculated from the patients of KIGS. All patients from the Dutch cohort including the seven patients who did not obtain a growth velocity of 0.0 SDS or greater were used for validation. The individual points per Dutch patient as well as the box plot for the entire Dutch cohort are indicated. All seven nonresponders are correctly identified by having values below −2 Studentized residuals.

All patient data were voluntarily submitted to KIGS. Therefore, it has to be discussed whether or not patients documented within KIGS are representative. There is for instance no information about dropouts. However, when comparing the present KIGS cohort, the similarity to published pharmaco-epidemiological surveys (28) as well as to intention-to treat studies (29–31) is evident. In addition, the Dutch validation cohort shows a remarkably high level of concordance regarding age, height (timely national SDS) and response to GH (supplemental Tables 1 and 3).

The validation of the developed KIGS model was based on an analytical process that is part of the statistical analysis and on the application of a second cohort independent of KIGS. The mean of residuals ± SD of the validations group did not differ from those of KIGS patients (Fig. 2, A and B). Thus, the KIGS prediction model seems to be predictive not only for CKD patients registered in KIGS but also for CKD patients in general.

It is of note that the distribution of primary renal diseases was the same in the KIGS cohort as in the Dutch cohort. The subclassification of patients according to primary renal disorders has been used for the first time in a prospective controlled study on the progression of chronic renal failure in children with CKD (20). In this study, it has been shown that the yearly progression varied up to a factor of three within the subgroups being lowest in the patients with renal hypo-/dysplasia.

The present prediction model demonstrates that the primary renal disease is an independent predictor for the response to GH treatment. On the first view it looks like patients with renal hypodysplasia responded best (Fig. 1). However growth velocity is not corrected for age and other confounding factors. In addition, the number of patients with glomerular disorders is small. The statistical analysis identified hereditary renal disorders as an independent negative prediction factor of response to GH treatment.

One criticism might be that the present prediction model explains only 37% of the variation, whereas previous KIGS prediction models from KIGS for other short children explained 39–61% of the overall variability (16–

18). This may be related to two factors. First, short children with CKD are much more heterogeneous than short patients in the other patient groups. The factors leading to growth retardation are manifold and cover a wide spectrum including genetic (syndromal) disorders (32), acquired diseases, acidosis, malnutrition, metabolic bone disease, residual renal function, and treatment modalities (33). Second, in all of the other KIGS prediction models, the dose of GH was one of the strongest predictors, whereas in the present model, this was only the fifth strongest predictor. This discrepancy is most likely explained by the very narrow dose range used in renal patients, which makes this factor much weaker than in the case of a wide dose variation as in children born small for gestational age (18).

In consideration of these conditions, the predictive precision of the presented model in short children with CKD is remarkable. The error SD of the prediction model was within the range of the prediction models for other GH indications in which the SD varied between 1.3 and 1.7 cm/yr (16–18).

Certainly, the degree of explained variability needs to be increased by future studies. Parameters potentially improving the prediction such as biochemical parameters IGFs (19), GH-binding proteins (34), or calcitropic hormones as well as genetic factors leading to primary renal disorders (32) should be systematically collected. This has not been possible so far in a voluntary registry.

Nevertheless, the present model is robust and easily applicable and has clinical utility in a process aimed at optimizing and individualizing GH treatment in patients with CKD. Before treatment, a realistic expectation of the response to GH can be provided. In accordance with the targets of the prediction model, low and nonresponders to GH can easily be identified (Fig. 3). Those patients can then be discussed in detail. If clear reasons for nonresponse like temporary severe clinical conditions or noncompliance can be excluded, a decision to discontinue GH treatment in an individual patient might be made.

For discussions and development of treatment strategies, it is an important question whether the growth response to GH during the first treatment year is a predictor for the response during the following treatment years. Observational studies (15) seem to support this view. In accordance, in the present study, the response to GH treatment during the second year was primarily predicted by the obtained growth response during the first treatment year.

The present prediction model is valid only for prepubertal children. For pubertal children, the prediction needs to be analyzed separately. This will be much more difficult because of the well known methodological problems related to pubertal development including the fact that most children will be transplanted in this age group (35).

In conclusion, the presented prediction model for growth response in children with CKD is based on simple clinical information. It is easy to use, is robust, and gives important information that helps to individualize the GH treatment in short children with CKD. According to the model, it can be expected that the greatest first-year response occurs in younger children with no weight reduction, no hereditary renal disorder, and a high residual renal function. In addition, there is a small GH dose effect, at least during the first treatment year.

Acknowledgments

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References

1. **Hokken-Koelega AC, van Zaal MA, van Bergen W, de Ridder MA, Stijnen T, Wolff ED, de Jong RC, Donckerwolcke RA, de Muinck Keizer-Schrama SM, Drop SL** 1994 Final height and its predictive factors after renal transplantation in childhood. Pediatr Res 36: 323–328
2. **Schaefer F, Wingen AM, Hennicke M, Rigden S, Mehls O** 1996 Growth charts for prepubertal children with chronic renal failure due to congenital renal disorders. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. Pediatr Nephrol 10:288–293
3. **Mehls O, Blum WF, Schaefer F, Tönshoff B, Schärer K** 1992 Growth failure in renal disease. Baillieres Clin Endocrinol Metab 6:665–685
4. **Wühl E, Haffner D, Offner G, Broyer M, van't Hoff W, Mehls O** 2001 European Study Group on Growth Hormone Treatment in Children with Nephropathic Cystinosis. Long-term treatment with growth hormone in short children with nephropathic cystinosis. J Pediatr 138:880–887
5. **Harmon WE, Jabs K** 1992 Factors affecting growth after renal transplantation. J Am Soc Nephrol 2(12 Suppl):S295–S303
6. **Hokken-Koelega AC, Stijnen T, de Muinck Keizer-Schrama SM, Wit JM, Wolff ED, de Jong MC, Donckerwolcke RA, Abbad NC, Bot A, Blum WF, Drop SL** 1991 Placebo-controlled, double-blind, cross-over trial of growth hormone treatment in pre-pubertal children with chronic renal failure. Lancet 338:585–590
7. **Fine RN, Kohaut EC, Brown D, Perlman AJ** 1994 Growth after recombinant human growth hormone treatment in children with chronic renal failure: report of a multicenter randomized double-blind placebo-controlled study. Genentech Cooperative Study Group. J Pediatr 124:374–382
8. **Tönshoff B, Mehls O, Heinrich U, Blum WF, Ranke MB, Schauer**

A 1990 Growth-stimulating effects of recombinant human growth hormone in children with end-stage renal disease. J Pediatr 116: 561–566
9. **Fine RN, Stablein D** 2005 Long-term use of recombinant human growth hormone in pediatric allograft recipients: a report of the NAPRTCS Transplant Registry. Pediatr Nephrol 20:404–408
10. **Haffner D, Schaefer F, Nissel R, Wühl E, Tönshoff B, Mehls O** 2000 Effect of growth hormone treatment on the adult height of children with chronic renal failure. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. N Engl J Med 343: 923–930
11. **Hokken-Koelega A, Mulder P, De Jong R, Lilien M, Donckerwolcke R, Groothof J** 2000 Long-term effects of growth hormone treatment on growth and puberty in patients with chronic renal insufficiency. Pediatr Nephrol 14:701–706
12. **Mehls O** 1996 Treatment with growth hormone for growth impairment in renal disorders. In: Ranke MB, Gunnarsson R, eds. Progress in growth hormone therapy: 5 years of KIGS. Mannheim, Germany: J & J Verlag; 267–277
13. **Hokken-Koelega AC, Stijnen T, De Jong MC, Donckerwolcke RA, De Muinck Keizer-Schrama SM, Blum WF, Drop SL** 1994 Double blind trial comparing the effects of two doses of growth hormone in prepubertal patients with chronic renal insufficiency. J Clin Endocrinol Metab 79:1185–1890
14. **Hokken-Koelega AC, Stijnen T, de Ridder MA, de Muinck Keizer-Schrama SM, Wolff ED, de Jong MC, Donckerwolcke RA, Groothoff JW, Blum WF, Drop SL** 1994 Growth hormone treatment in growth-retarded adolescents after renal transplant. Lancet 343:1313–1317
15. **Haffner D, Wühl E, Schaefer F, Nissel R, Tönshoff B, Mehls O** 1998 Factors predictive of the short- and long-term efficacy of growth hormone treatment in prepubertal children with chronic renal failure. The German Study Group for Growth Hormone Treatment in Chronic Renal Failure. J Am Soc Nephrol 9:1899–1907
16. **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
17. **Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W, Albertsson-Wikland K, Price DA; KIGS International Board. Kabi International Growth Study** 2000 Prediction of long-term response to recombinant human growth hormone in Turner syndrome: development and validation of mathematical models. KIGS International Board. Kabi International Growth Study. J Clin Endocrinol Metab 85:4212–4218
18. **Ranke MB, Lindberg A, Cowell CT, Wikland KA, Reiter EO, Wilton P, Price DA; KIGS International Board** 2003 Prediction of response to growth hormone treatment in short children born small for gestational age: analysis of data from KIGS (Pharmacia International Growth Database). J Clin Endocrinol Metab 88:125–131
19. **de Ridder MA, Stijnen T, Hokken-Koelega AC** 2008 Prediction model for adult height of small for gestational age children at the start of growth hormone treatment. J Clin Endocrinol Metab 93: 477–483
20. **Wingen AM, Fabian-Bach C, Schaefer F, Mehls O** 1997 Randomised multicentre study of a low-protein diet on the progression of chronic renal failure in children. European Study Group of Nutritional Treatment of Chronic Renal Failure in Childhood. Lancet 349:1117–1123
21. **Tanner JM, Whitehouse RH** 1976 Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. Arch Dis Child 51:170–179
22. **de Ridder MA, Stijnen T, Hokken-Koelega AC** 2003 Validation and calibration of the KIGS prediction model for children with idiopathic growth hormone deficiency. J Clin Endocrinol Metab 88: 1223–1227
23. **Ranke MB, Lindberg A** 2007 Predicting growth in response to growth hormone treatment: the KIGS approach. In: Ranke MB, Price DA, Reiter EO, eds. Growth hormone therapy in pediatrics: 20 years of KIGS. Basel: S. Karger AG; 389–399
24. **Freeman JV, Cole TJ, Chinn S, Jones PR, White EM, Preece MA** 1995 Cross sectional stature and weight reference curves for the UK, 1990.Arch Dis Child 73:17–24
25. **Cole TJ** 2000 A simple chart to identify non-familial short stature. Arch Dis Child 82:173–176
26. **Prader A, Largo RH, Molinari L, Issler C** 1989 Physical growth of Swiss children from birth to 20 years of age. First Zurich longitudinal study of growth and development. Helv Paediatr Acta Suppl 52:1–125
27. **van Wieringen JC, Roede MJ, Wit JM** 1985 Growth diagrams for patient care. Tijdschr Kindergeneeskd 53:147–152
28. **Seikaly MG, Salhab N, Warady BA, Stablein D** 2007 Use of rhGH in children with chronic kidney disease: lessons from NAPRTCS. Pediatr Nephrol 22:1195–1204
29. **Koch VH, Lippe BM, Nelson PA, Boechat MI, Sherman BM, Fine RN** 1989 Accelerated growth after recombinant human growth hormone treatment of children with chronic renal failure. J Pediatr 115:365–371
30. **Johansson G, Sietnieks A, Janssens F, Proesmans W, Vanderschueren-Lodeweyckx M, Holmberg C, Sipilä I, Broyer M, Rappaport R, Albertsson-Wikland K, Berg U, Jodal U, Rees L, Rigden SP, Preece MA** 1990 Recombinant human growth hormone treatment in short children with chronic renal disease, before transplantation or with functioning renal transplants: an interim report on five European studies. Acta Paediatr Scand 370(Suppl):36–42
31. **Mehls O, Broyer M** 1994 Growth response to recombinant human growth hormone in short prepubertal children with chronic renal failure with or without dialysis. The European/ Australian Study Group. Acta Paediatr 399(Suppl):81–87
32. **Weber S, Moriniere V, Knüppel T, Charbit M, Dusek J, Ghiggeri GM, Jankauskiené A, Mir S, Montini G, Peco-Antic A, Wühl E, Zurowska AM, Mehls O, Antignac C, Schaefer F, Salomon R** 2006 Prevalence of mutations in renal developmental genes in children with renal hypodysplasia: results of the ESCAPE study. J Am Soc Nephrol 17:2864–2870
33. **Wühl E, Haffner D, Nissel R, Schaefer F, Mehls O** 1996 Short dialyzed children respond less to growth hormone than patients prior to dialysis. German Study Group for Growth Hormone Treatment in Chronic Renal Failure. Pediatr Nephrol 10:294–298
34. **Tönshoff B, Kiepe D, Ciarmatori S** 2005 Growth hormone/insulin-like growth factor system in children with chronic renal failure. Pediatr Nephrol 20:279–289
35. **Nissel R, Lindberg A, Mehls O, Haffner D; Pfizer International Growth Database (KIGS) International Board** 2008 Factors predicting the near-final height in growth hormone-treated children and adolescents with chronic kidney disease. J Clin Endocrinol Metab 93:1359–1365