

## CLINICAL STUDY

# Models to predict changes in serum IGF1 and body composition in response to GH replacement therapy in GH-deficient adults

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## Abstract

**Objective:** Clinical response to GH therapy in GH-deficient (GHD) adults varies widely. Good predictors of treatment response are lacking. The aim of the study was to develop mathematical models to predict changes in serum IGF1 and body composition (BC) in response to GH therapy in GHD adults.

**Design and methods:** One hundred and sixty-seven GHD patients (103 men, median age 50 years) were studied before and after 12 months of GH treatment. GH dose was tailored according to serum IGF1 concentrations. Good responders (GR) and poor responders (PR) to GH therapy were defined as patients with a response > 60th and < 40th percentile respectively, for changes in serum IGF1 levels (adjusted for GH cumulative dose) and in BC (lean body mass (LBM) and body fat determined using dual-energy X-ray absorptiometry). A logistic regression model was used to predict the probability of being a GR or PR.

**Results:** In the IGF1 prediction model, men (odds ratio (OR) 5.62: 95% confidence interval 2.59–12.18) and patients with higher insulin levels (OR 1.06: 1.00–1.12) were more likely to be GR. The accuracy of the prediction model was 70%. In the BC model, men (OR 10.72: 1.36–84.18) and GHD patients with lower LBM (OR 0.82: 0.73–0.92) and greater height (OR 1.23: 1.08–1.40) at baseline were more likely to be GR. The accuracy of the prediction model was 80%.

**Conclusion:** Accurate mathematical models to predict GH responsiveness in GHD adults were developed using gender, body height, baseline LBM, and serum insulin levels as the major clinical predictors.

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## Introduction

GH therapy offers several benefits to adults with GH deficiency (GHD). However, it is well known that clinical response to GH varies greatly in both children and adults with GHD (1, 2). In children, the primary efficacy of therapy is usually evaluated by growth velocity, whereas, in adults, the end points to define responses to GH therapy are variable and include serum insulin-like growth factor 1 (IGF1), body composition (BC), cardiovascular risk factors, and quality of life (QoL) (3–8).

The reasons for individual differences in response to GH therapy are not known, but are probably influenced by pharmacokinetics of GH and factors acting at the level of the target tissue. The complexity is increased by the fact that some of the actions of GH are directly and others indirectly mediated through the endocrine and paracrine action of IGF1 (9, 10). Previous studies in GHD adults have found an association between the response to GH and clinical and biochemical

parameters, such as body mass index (BMI), age, gender, serum GH-binding protein (GHBP) levels, GH dose, and the route of estrogen replacement in women (2, 11–16). More recently, a genetic predictor, the GH receptor (GHR) polymorphism, has been studied in both children and adults with GHD, showing only a weak influence on the clinical response to GH therapy (17–19) or no influence at all (20–22).

In GHD children, mathematical models have been developed to predict growth response during GH therapy (23, 24). In GHD adults, however, no attempt has been made to produce a probabilistic model to define good responders (GR) and poor responders (PR). Therefore, the aim of the present study was to establish prediction models for some important clinical end points that are used to monitor adult GH replacement therapy. For this purpose, a large cohort of well-characterized GHD adults was used, all of whom are monitored in a prospective long-term clinical trial at a single center. The end points for the study were the serum IGF1 response and the changes in BC, including both a

decrease in total body fat mass (BF) and an increase in lean body mass (LBM), after 12 months of GH replacement.

## Subjects and methods

### Patients

The patients in this study are part of a large longitudinal cohort of adults with hypopituitarism and severe GHD treated at the Sahlgrenska University Hospital, Gothenburg, Sweden. The study was conducted on 343 well-characterized consecutive GHD adult patients registered in the database, who were eligible for GH replacement therapy. From this initial group, those with diabetes mellitus ( $n=15$ ), partial GHD ( $n=8$ ), celiac disease ( $n=1$ ), sleep apnea ( $n=2$ ), a previous history of treatment for Cushing's disease ( $n=21$ ) and acromegaly ( $n=15$ ), compliance problems ( $n=6$ ), and patients with missing data during their 12 months of treatment ( $n=108$ ) were excluded. The final study group consisted of 167 well-characterized GHD adult patients (103 men and 64 women) with diagnosis confirmed by maximum GH peak below  $3 \mu\text{g/l}$  during a GH stimulation test (88% based on insulin tolerance and 12% based on GHRH-pyridostigmine). All the adults with childhood-onset GHD ( $n=19$ ) were retested before entering the GH replacement therapy in adult life.

The most frequent causes of GHD were non-functional pituitary adenoma ( $n=75$ ), idiopathic ( $n=19$ ) craniopharyngioma ( $n=17$ ), and prolactinoma ( $n=15$ ). Twenty-one patients had isolated GHD and 146 had multiple pituitary hormone deficiency. Diabetes insipidus was present in 22% of the patients. When required, patients received adequate and stable therapy with glucocorticoids (cortisone acetate, mean  $\pm$  s.d. dose was  $24.2 \pm 6.3 \text{ mg/day}$ ,  $n=92$  or an equivalent dose of hydrocortisone of  $19.5 \pm 4.9 \text{ mg/day}$ ), thyroid hormone (levothyroxine,  $0.108 \pm 0.04 \text{ mg/day}$ ,  $n=135$ ), sex steroids, and desmopressin, for at least 6 months before beginning GH therapy. Of the 64 women, 35 were receiving oral ( $n=27$ ) or transdermal ( $n=8$ ) estrogen replacement therapy. Thirteen unreplaced women had an intact gonadal axis and 16 were post-menopausal. Of the 103 men, 86 were receiving testosterone by i.m. ( $n=73$ ), transdermal ( $n=10$ ), or oral ( $n=3$ ) route. Fifteen men had an intact gonadotropic axis and 2 had mild hypogonadism, but refused androgen replacement therapy. Informed consent was obtained from all the patients, and the study was approved by the medical ethics committee at Gothenburg University.

### Study design

The analysis was performed on data from 167 adult GHD patients retrieved from the Centre of Endocrinology and Metabolism database of the

Sahlgrenska University Hospital. All the patients received recombinant human GH, administered s.c. every evening, with an initial mean  $\pm$  s.d. dose of  $0.25 \pm 0.19 \text{ mg/day}$ , which was titrated according to age- and gender-adjusted IGF1 reference serum concentration after 1 and 4 weeks of GH therapy and every 3 months subsequently in order to maintain serum IGF1 levels between the mean and the upper limit of the normal reference range. For those patients with normal IGF1 at baseline, the dose was given in order to maintain the IGF1 levels within the normal range at all times, never exceeding the upper limit of the reference values. Measurement of BC was performed at baseline and after 6 and 12 months of treatment.

GHD patients were categorized as GR and PR to GH therapy according to absolute changes in the outcome measurements (serum IGF1 and BC) after 12 months of GH treatment. Changes in IGF1 levels ( $\mu\text{g/l}$ ) from baseline were adjusted according to the cumulative GH dose (cGH, mg) that each patient received during the 12 months of treatment using the following formula to calculate IGF1 response ( $\mu\text{g/per mg of GH}$ ):  $\Delta\text{IGF1}/\text{cGH}$  dose.

Using this ratio, patients with IGF1 response above the 60th percentile were categorized as GR and those with a response below the 40th percentile as PR. For BC, patients were classified as GR when LBM increased and BF decreased above the 60th percentile, while in the PR, changes in LBM and BF were below the 40th percentile.

### Biochemical assays

Serum IGF1 levels were determined in serum samples collected in the morning following an overnight fast using a hydrochloric acid-ethanol extraction RIA with authentic serum IGF1 for labeling (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). The detection limit of the assay was  $<20 \mu\text{g/l}$ , and the interassay coefficient of variation (CV) was  $<9.3\%$ . After June 2004, serum IGF1 levels were determined using chemiluminescence immunoassay (Advantage; Nichols Institute Diagnostics). The detection limit was  $<6 \mu\text{g/l}$ , and the interassay CV was  $<8.6\%$ . The individual serum IGF1 levels were transformed into SDS according to age- and gender-adjusted reference values (25).

Serum insulin was measured by immunometric method with chemiluminescence technology (ADVIA Centaur; Bayer Diagnostics) according to the manufacturer's instructions. Interassay CV was  $<5.9\%$ . The detection limit of the assay was between 0.1 and 300 mU/l. All assays were performed at the Department of Clinical Chemistry at Sahlgrenska University Hospital.

### Body composition

Total BF and LBM were assessed at baseline and after 6 and 12 months of GH therapy using dual-energy X-ray

absorptiometry (Lunar DPX-L, Lunar Corporation, Madison, WI, USA). The precision errors (1 s.d.) of the scanner were 1.7% for BF and 0.7% for LBM, which were determined through double examinations of ten healthy subjects (26). Body weight (BW) was measured in the morning to the nearest 0.1 kg, and body height was measured barefoot to the nearest 0.1 cm. The BMI was calculated as BW in kilograms divided by height in meters squared.

**Statistical analysis**

The data were analyzed using the SPSS software for Windows (version 15.0; SPSS Inc., Chicago, IL, USA).

To test for GH treatment effect on IGF1 serum concentrations, BF (kg), and LBM (kg), data at baseline and after 12 months were compared with a paired-samples *t*-test, and the results are presented as mean ± s.d.

The primary end points for this study were the IGF1 response, which was adjusted according to the GH cumulative dose, as previously explained, and the changes in BC (LBM and BF) after 12 months of GH therapy. Between the groups, analyses (GR versus PR) in IGF1 and BC responses were performed. Bivariate analyses (Pearson,  $\chi^2$  and independent samples test) were conducted to test the significance of the association between each predictor and the outcome variables.

Multivariate logistic regression analyses were used to identify significant predictors of the GH response in each outcome variable (27). Predictors were identified as significant if *P* < 0.05. The following variables were tested at baseline: gender, age, BW, body height, BMI, total BF (kg), LBM (kg), insulin levels, peak GH during stimulation test, IGF1 levels, duration of hypopituitarism, number of additional pituitary hormonal deficiencies, surgery, irradiation, sex steroid replacement, thyroxin replacement, glucocorticoid replacement dose, and GH starting dose. The results are presented as odds ratios (OR) with 95% confidence intervals. Two methods of measuring accuracy were presented: the first was the Hosmer and Lemeshow test of goodness-of-fit, which showed that the prediction

models for IGF1 and BC responses were well fitted (*P* > 0.05); the second was the classification tables used to show how well the models identified the GR and PR categories assessing the sensitivity, specificity, and predictive value. Using the specified cut-off value of 0.5, the model categorized a subject into the ‘GR’ category if the estimated probability was 0.5 or more, and categorized a subject into the ‘PR’ category if the estimated probability was < 0.5. The logistic model equation computes the probability of the selected response as a function of the values of the predictor variables. The relationship between the predictor and response variables is not a linear function in logistic regression. The formula used was as follows:

$$P(\text{event}) = \frac{1}{1 + \exp(-(b_0 + b_1X_1 + b_2X_2 + \dots + b_pX_p))}$$

where *b*<sub>0</sub> is a constant and each model generates a regression coefficient for it; *b*<sub>1</sub>, *b*<sub>2</sub>...*b*<sub>*p*</sub> are the regression coefficients for each predictor; *X*<sub>1</sub>, *X*<sub>2</sub>...*X*<sub>*p*</sub> are the explanatory variables. The computed value *P* ranges from 0 to 1 and represents the probability of a particular outcome, given that set of explanatory variables. The ‘exp ( )’ function is ‘*e*’ (Euler’s constant: 2.718, which is the base of the natural logarithm) raised to a power.

All values presented are two-tailed, and values of < 0.05 are considered to be indicative of statistical significance.

**Results**

**Responses for GH replacement therapy in GR and PR**

IGF1 serum concentrations and LBM (kg) increased, whereas BF (kg) decreased, after 12 months of GH therapy (Table 1). Changes in IGF1 levels from baseline were positively correlated with the 12-month cumulative GH dose (*r* = 0.507, *P* < 0.0001, *n* = 167). After 12 months of GH therapy, the mean serum IGF1 response (calculated by the ratio ΔIGF1/cumulative GH dose) was 1.2 μg/l per mg of GH. The 60th and 40th

**Table 1** Effects of GH replacement during 12 months of treatment on insulin-like growth factor 1 (IGF1) serum concentrations, body fat (BF), and lean body mass (LBM) in 167 adults with GH deficiency.

Variable	Baseline	12-month GH replacement	Changes		P value*
			Mean ± s.d.	Median (range)	
IGF1 levels	110.1 ± 68.7	272.4 ± 120.8	162.2 ± 96.8	151.0 (–32, 481)	< 0.0001
IGF1 (SDS)	–1.6 ± 1.4	1.7 ± 2.3	3.3 ± 2.0	3.0 (–0.7, 9.6)	< 0.0001
LBM (kg)	50.1 ± 11.3	52.5 ± 11.6	2.4 ± 2.9	2.3 (–8.0, 9.4)	< 0.0001
BF (kg)	27.8 ± 9.2	25.5 ± 9.7	–2.3 ± 3.5	–2.1 (–13.5, 9.0)	< 0.0001

Data are presented as mean ± s.d.

\*Baseline and 12 months of GH replacement data on IGF1 serum concentrations, total BF (kg), and LBM (kg) were compared with a paired-samples *t*-test.

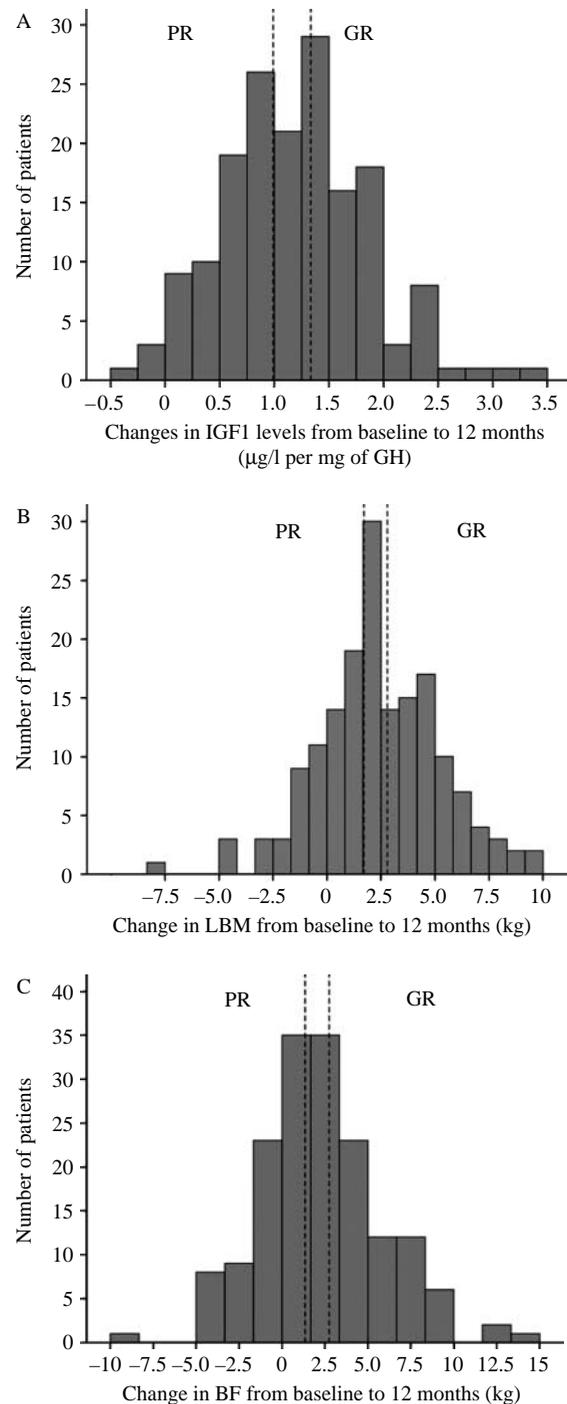
percentile cut-off values to define GR and PR were  $>1.33$  and  $<0.98$   $\mu\text{g/l}$  per mg of GH respectively (Fig. 1A). Of the 167 patients, 67 (52 men, 15 women; mean age  $48.4$  years  $\pm 13.6$ ) were classified as GR and 67 (26 men, 41 women; mean age  $50.3$  years  $\pm 14.6$ ) were classified as PR (Table 2).

The mean change in LBM in response to GH therapy was  $2.4 \pm 2.9$  kg, with values  $>2.79$  kg (60th) indicating the GR and values  $<1.71$  kg (40th) indicating the PR (Fig. 1B). Sixty-seven GHD patients (57 men, 10 women; mean age  $46.4 \pm 14.4$  years) were classified as GR and 67 (33 men, 34 women; mean age  $50.9 \pm 14.2$  years) were classified as PR for changes in LBM. The mean reduction in BF in response to GH therapy was  $2.3 \pm 3.5$  kg; reduction of BF values  $>2.74$  kg (60th) categorized patients as GR and reductions  $<1.34$  kg (40th) or increments in BF categorized patients as PR (Fig. 1C). Sixty-seven GHD adults (44 men, 23 women; mean age  $49.7 \pm 13.8$  years) were GR and 67 patients (39 men, 28 women; mean age  $48 \pm 15.6$  years) were PR for BF. For BC (LBM+BF), 35 patients (31 men, 4 women; mean age  $49.7 \pm 13.9$  years) were GR (LBM+BF) and 30 (18 men, 12 women; mean age  $50.1 \pm 15.8$  years) were PR (Table 3).

### Prediction model for serum IGF1 response

Height, BW, and LBM at baseline were significantly higher in GR than in PR. GR received a lower daily GH dose and cumulative GH dose after 12 months compared with PR ( $P \leq 0.03$ ). However, these differences were caused by a significantly larger number of men in the GR group (Table 2). No difference was seen in the glucocorticoid replacement dose at baseline between these groups. The comparison between women receiving or not receiving estrogen ( $E_2$ ) did not affect the response in serum IGF1. Furthermore, women taking oral  $E_2$  ( $n=24$ ) required a higher cumulative GH dose to produce the same serum IGF1 response as women who did not receive  $E_2$  ( $n=25$ ,  $154.4 \pm 42.9$  vs  $124.1 \pm 41.5$  mg of GH after 12 months of treatment). The route of  $E_2$  was not analyzed because of the small number of women receiving transdermal  $E_2$  ( $n=7$ ).

Using the logistic regression model, the baseline variables that significantly predicted the individual IGF1 response after 12 months were gender and baseline serum insulin levels (Table 4). Men were 5.6 times more likely to be GR than women (OR: 5.62,  $P < 0.0001$ ). Furthermore, patients with higher insulin levels were more likely to be GR than patients with lower insulin levels (OR: 1.06,  $P = 0.049$ ), even though insulin levels did not differ between the GR and PR (Table 2). Each increase in baseline insulin levels of 1 mU/l increased the probability of being GR by 5.7%. Using the specified cut-off value of 0.5, the sensitivity of the prediction model, i.e. the correctly predicted percentage of patients in the GR category was 77.6%. The specificity of the prediction, i.e. the correctly predicted percentage of



**Figure 1** Variability in IGF1 response and total body fat (BF) changes in response to GH treatment in 167 adults with GH deficiency. (A) Changes in IGF1 levels ( $\mu\text{g/l}$ ) were adjusted according to cumulative GH dose ( $\Delta\text{IGF1}/\text{cGH}$  dose ratio), and were defined as serum IGF1 response. (B) LBM changes after 12 months of GH therapy were calculated as the difference between LBM (kg) at 12 months and LBM at baseline. (C) BF changes after 12 months of GH therapy were calculated as the difference between BF (kg) at baseline and BF at 12 months. The vertical dotted lines show the values at the 40th and 60th percentiles for each response that was used to categorize the patients as poor responders (PR) and good responders (GR) to GH therapy respectively.

**Table 2** Clinical and GH treatment-related characteristics of patients with severe GH deficiency defined as good responders (GR) or poor responders (PR) in serum insulin-like growth factor 1 (IGF1) response to 12-month GH therapy according to the 60th ( $\Delta$ IGF1/cGH dose ratio  $> 1.33$ ) and 40th percentiles ( $\Delta$ IGF1/cGH dose ratio  $< 0.98$ ) respectively.

Variables	Serum IGF1 response at 12 months			P value
	All (n=167)	GR (n=67)	PR (n=67)	
Gender: men (%)/women (%)	103 (61.7)/64 (38.3)	52 (66.7)/15 (26.8)	26 (33.3)/41 (73.2)	<0.0001
Age (years)	48.8±14.4 (49.9)	48.4±13.6 (49.1)	50.3±14.6 (51.2)	NS
Duration hypopituitarism (years) <sup>a</sup>	7.4±9.4 (2)	8.6±9.7 (3)	7.3±9.6 (2)	NS
Additional deficiencies (n) <sup>b</sup>	2.1±1.1 (2)	2.3±1.0 (3)	2.0±1.1 (2)	NS
Body weight (kg)	81.6±16.0 (81.0)	83.5±13.9 (82.3)	77.4±16.7 (74.5)	0.02
Height (cm)	172.6±10.0 (172.0)	173.8±8.9 (175.1)	169.1±10.3 (167.3)	0.001
BMI (kg/m <sup>2</sup> )	27.3±4.3 (26.9)	27.6±3.7 (26.9)	27.1±5.0 (26.9)	NS
BF (kg)	27.8±9.2 (26.9)	27.2±7.8 (27.0)	28.2±9.8 (27.5)	NS
LBM (kg)	50.1±11.3 (50.4)	52.4±9.7 (52.6)	45.9±11.7 (42.8)	0.001
Insulin (mU/l)	10.0±7.4 (7.4)	11.6±9.2 (8.4)	8.8±5.8 (6.5)	NS
Peak GH (µg/l)	0.66±0.74 (0.35)	0.56±0.68 (0.3)	0.7±0.7 (0.5)	NS
IGF1 (µg/l)	110.1±68.7 (101.0)	120.5±72.3 (112.0)	94.9±57.9 (86)	NS
IGF1 (SDS)	-1.6±1.4 (-1.6)	-1.45±1.5 (-1.6)	-1.8±1.1 (-1.7)	NS
Glucocorticoid replacement (mg/day)	19.5±4.9 (20.0)	19.8±5.4 (20.0)	19.1±4.7 (20.0)	NS
GH starting dose (mg)	0.25±0.2 (0.17)	0.23±0.17 (0.17)	0.24±0.2 (0.17)	NS
GH dose at 12 months (mg/day)	0.44±0.16 (0.40)	0.39±0.14 (0.33)	0.46±0.16 (0.42)	0.004
GH cumulative dose (mg) <sup>c</sup>	141.0±56.7 (128.1)	126.4±48.1 (119.0)	144.2±57.0 (132.0)	0.03
$\Delta$ IGF1 (µg/l)	162.2±96.8 (151.0)	225±83.4 (203)	85.6±58.6 (80)	<0.0001
$\Delta$ IGF1 (SDS)	3.3±2.0 (3.0)	4.6±1.7 (4.0)	1.7±1.2 (1.6)	<0.0001
$\Delta$ BF (kg)	2.3±3.5 (2.1)	2.3±3.6 (2.2)	2.4±3.5 (2.2)	NS
$\Delta$ LBM (kg)	2.4±2.9 (2.3)	2.6±2.9 (2.4)	1.9±2.7 (1.7)	NS

Data are presented as mean±s.d. (median).

NS, no significant difference was found.

$\Delta$ IGF1 and  $\Delta$ LBM represent value at 12 months – value at baseline.  $\Delta$ BF = BF at baseline – BF at 12 months.

<sup>a</sup>Defined as the time from the discovery of the first anterior pituitary hormone deficiency to the time of this study.

<sup>b</sup>Additional deficiencies: number of additional pituitary deficiencies.

<sup>c</sup>The cumulative GH dose that each patient received during the study.

patients in the PR category was 59.7%. Overall, this prediction model correctly classified 68.7% of the cases.

The estimated equation for serum IGF1 response to 12 months of GH therapy is as follows:

$$P(\text{GR\_IGF1}) = \frac{1}{1 + (e)^{-(-1.60 + 1.73 \times \text{gender} + 0.06 \times \text{insulin levels})}}$$

In the equation,  $P(\text{GR\_IGF1})$  is the predicted probability of being a GR in IGF1.

Gender: men = 1 and women = 0; serum insulin levels are at baseline (mU/l); and 'e' is 2.718.

GR if estimated probability  $P(\text{GR\_IGF1})$  is  $\geq 0.5$ , and PR if  $P(\text{GR\_IGF1})$  is  $< 0.5$ .

### Prediction model for treatment response in BC

There was a significant gender difference in LBM response, with only 10 (22.7%) out of 44 women in the GR group and only 33 (36.7%) out of 90 men in the PR group ( $P < 0.0001$ ). GR were taller and had lower BMI, BF, and insulin levels at baseline compared with PR. Analysis of post-treatment variables showed that GR received a higher daily GH dose and cumulative GH dose after 12 months compared with PR. Moreover, GR in LBM had more pronounced changes in BF with GH therapy than PR ( $P = 0.001$ ). No difference was seen in

the glucocorticoid replacement dose at baseline between the GR and PR groups. The statistical analysis was also performed excluding the two men with untreated mild hypogonadism, and no changes in the results were observed.

The logistic regression analyses showed that gender, BMI, and BF at baseline were the significant predictors of LBM changes after 12 months of GH replacement therapy (Table 4). Men were 11.7 times more likely to be GR than women (OR: 11.67,  $P < 0.0001$ ). GHD patients with lower BMI at baseline were more likely to be GR than patients with higher BMI (OR: 0.65,  $P < 0.0001$ ). Each increase in BMI at baseline of 1 kg/m<sup>2</sup> decreased the probability of being GR by 35.3%. Patients with higher BF at baseline were more likely to be GR than patients with lower BF at baseline (OR: 1.17,  $P = 0.003$ ). Each increase in total BF at baseline of 1 kg increased the probability of being GR by 16.5%. The sensitivity and specificity were 71.6 and 77.6% respectively. Overall, this prediction model correctly classified 74.6% of the cases.

In BF response, GR were significantly taller than the PR ( $P = 0.049$ ). Analysis of post-treatment variables showed that the daily GH dose and the cumulative GH dose after 12 months were similar in the GR and in the PR groups. GR in BF had more pronounced changes in LBM with GH therapy than PR ( $P = 0.04$ ). No difference was seen in the glucocorticoid replacement dose at

**Table 3** Clinical and GH treatment-related characteristics of patients with severe GH deficiency defined as good responders (GR) if their responses were >60th percentile in both lean body mass (LBM) and body fat (BF) changes to 12-month GH therapy and poor responders (PR) if their responses were <40th percentile.

Variables	Body composition			P value
	All (n=167)	GR (n=35)	PR (n=30)	
Gender (male (%)/female (%))	103 (61.7)/64 (38.3)	31 (63.3)/4 (25)	18 (36.7)/12 (75)	0.008
Age (years)	48.8±14.4 (49.9)	49.7±13.9 (50)	50.1±15.8 (53.5)	NS
Duration hypopituitarism (years) <sup>a</sup>	7.4±9.4 (2)	6.4±8.8 (2)	5.2±7.2 (2)	NS
Additional deficiencies (n) <sup>b</sup>	2.1±1.1 (2)	2.0±1.1 (2)	2.2±1.0 (2.5)	NS
Body weight (kg)	81.6±16.0 (81.0)	84±13.8 (84.1)	85.7±18 (88.3)	NS
Height (cm)	172.6±10.0 (172.0)	178.3±8.5 (180.2)	171.5±10 (172.0)	0.004
BMI (kg/m <sup>2</sup> )	27.3±4.3 (26.9)	26.3±2.9 (26.4)	29.2±5.4 (31.0)	0.01
BF (kg)	27.8±9.2 (26.9)	26.3±8.1 (25.4)	29.1±9.7 (30.2)	NS
LBM (kg)	50.1±11.3 (50.4)	53.3±9.3 (54.8)	53.0±12.2 (52.0)	NS
Insulin (mU/l)	10.0±7.4 (7.4)	7.3±5.3 (5.5)	12.5±9.5 (10.5)	0.005
Peak GH (μg/l)	0.66±0.74 (0.35)	0.5±0.5 (0.3)	0.7±0.8 (0.6)	NS
IGF1 (μg/l)	110.1±68.7 (101.0)	99.0±63.4 (82.0)	110.0±70.5 (109.5)	NS
IGF1 (SDS)	-1.6±1.4 (-1.6)	-1.9±1.3 (-2.0)	-1.4±1.4 (-1.4)	NS
Glucocorticoid replacement (mg/day)	19.5±4.9 (20.0)	19.3±4.6 (20)	21.1±4.6 (20)	NS
GH starting dose (mg)	0.25±0.2 (0.17)	0.34±0.3 (0.17)	0.22±0.18 (0.17)	NS
GH dose at 12 months (mg/day)	0.44±0.16 (0.40)	0.46±0.16 (0.49)	0.39±0.15 (0.33)	NS
GH cumulative dose (mg) <sup>c</sup>	141.0±56.7 (128.1)	168.9±77.2 (149.4)	130.9±52.5 (119.1)	0.02
ΔLBM (kg)	2.4±2.9 (2.3)	5.3±1.6 (5.0)	-0.4±1.9 (-0.1)	<0.0001
ΔBF (kg)	2.3±3.5 (2.1)	6.0±2.8 (2.8)	-1.5±2.2 (-1.0)	<0.0001
ΔIGF1 (μg/l)	162.2±96.8 (151.0)	207.8±92.1 (209)	144.1±91.1 (130.5)	0.007
ΔIGF1 (SDS)	3.3±2.0 (3.0)	4.3±1.9 (4.4)	2.9±1.9 (2.5)	0.004

Data are presented as mean±s.d. (median).

NS, no significant difference was found.

ΔIGF1 and ΔLBM represent value at 12 months—value at baseline. ΔBF=BF at baseline—BF at 12 months.

<sup>a</sup>Defined as the time from the discovery of the first anterior pituitary hormone deficiency to the time of this study.

<sup>b</sup>Additional deficiencies are the number of additional pituitary deficiencies.

<sup>c</sup>The cumulative GH dose that each patient received during the study.

baseline between the GR and PR groups. In the logistic regression model, body height was the only significant predictor for BF changes after 12 months of GH replacement therapy (Table 4). Taller patients were more likely to be GR than shorter patients. Each increase in height of 1 cm increased the probability of being GR by 3.6%. Using the specified cut-off value of 0.5, the sensitivity of the prediction was 58.2%, and the specificity was 58.2%. Overall, this prediction model correctly classified 58.2% of the cases.

For BC changes (LBM+BF), there was a significant gender difference, with only 4 (25%) of 16 women belonging to the GR group, and only 18 (36.7%) of 49 men were classified as PR ( $P=0.008$ ). GR were taller, had a lower BMI, and had lower serum insulin levels at baseline compared with PR. Moreover, GR received a higher cumulative GH dose after 12 months compared with PR (Table 3).

In the logistic regression model, gender, body height and LBM at baseline contributed significantly to the response in BC (Table 4). Men were 10.7 times more likely to be GR than women (OR: 10.72,  $P=0.024$ ). Taller patients were more likely to be GR than shorter patients (OR: 1.23,  $P=0.001$ ). Each increase in body height of 1 cm increased the probability of being GR by 23.4%. Patients with higher LBM at baseline were less likely to be GR (OR: 0.82,  $P=0.001$ ), meaning that each increase in LBM of 1 kg at baseline led to a

17.9% decrease in the probability of being GR. Using the specified cut-off value of 0.5, the sensitivity of the prediction was 88.6%, and the specificity was 70%. Overall, this prediction model correctly classified 80% of the GR or PR cases in both LBM and BF. The logistic regression equation is as follows:

$$P(\text{GR}_{\text{BC}}) = \frac{1}{1 + (e)^{-(-28.08 + 0.21 \times \text{height} - 0.20 \times \text{basal LBM} + 2.37 \times \text{gender})}}$$

In the equation,  $P(\text{GR}_{\text{BC}})$  is the predicted probability of being a GR in BC; gender: men=1 and women=0; height (cm); LBM at baseline (kg); 'e' is 2.718. GR if estimated probability  $P(\text{GR}_{\text{BC}}) \geq 0.5$ , and PR if  $P(\text{GR}_{\text{BC}}) < 0.5$ .

## Discussion

We searched for clinical predictors of serum IGF1 and BC responses to GH replacement therapy in a large cohort of well-characterized adults with severe GHD who were treated for 12 months at a single center. We developed prediction models by logistic regression analysis for serum IGF1 and BC changes to GH therapy. The mathematical model for serum IGF1 response was a function of gender and baseline serum insulin levels. The best predictors for LBM changes in response to GH

therapy were gender, BMI, and BF at baseline, and the only significant predictor for BF changes was body height. The mathematical model for changes in both BF and LBM was a function of gender, body height, and LBM at baseline. The IGF1 and BC prediction models developed in the study correctly classified 70–80% of GHD patients as GR or PR to GH replacement therapy.

It is likely that other parameters should be included in the prediction models. These parameters may be members of the GH axis, such as GHP (2) or polymorphisms in some gene encoding factors involved in GH action. Recently, we examined the role of the GHR polymorphism in the response to GH therapy in adults with GHD, but no influence of this polymorphism was observed (22). Another study, however, has indicated that the GHR polymorphism may have some impact on GH sensitivity in adults (19). Therefore, further studies are required to study the potential role of other candidate genes and to validate the performance of the mathematical models in prospective cohorts of adults with GHD.

Previous studies have shown a significant overlap of serum IGF1 levels between normal individuals and adult GHD patients, especially with increasing age (28–30). By using serum IGF1 as a dose titration monitor, subjects with normal baseline levels are usually allowed a smaller dose of GH, whereas those who have the lowest serum IGF1 levels at baseline are more likely to receive the highest maintenance dose of GH (31). Therefore, in order to obtain comparable responses for statistical analysis, we used the ratio between the GH-induced change in IGF1 levels from baseline to 12 months and the 12-month cumulative

GH dose that each patient received. A similar approach had been used to define GH response or sensitivity in previous studies (14, 32). We chose to use the cumulative dose, as it would reflect the total dose exposure during the period under study, and we used the cumulative GH dose in the denominator because the highest correlation coefficient was found between the changes in serum IGF1 and the cumulative GH dose in the whole cohort. Another strategy was applied in the study by Meyer *et al.* (33), in which the ratio of IGF1 levels to daily GH dose after 12 months was used.

In our patients, the best predictors of a good response in serum IGF1 were gender and basal insulin levels. This is in accordance with previous studies showing men to be more responsive to GH than women (2, 12–14). Both *in vivo* and *in vitro* models have shown that hepatic gene expression after GH administration is sexually dimorphic (34). Despite the fact that oral estrogen replacement attenuates the serum IGF1 response to GH (16), estrogen replacement was not found to be of importance in our prediction model. This may have been due to the dose titration schedule and the statistical approach of adjusting the changes in IGF1 levels after 12 months of GH replacement according to the cumulative dose of GH. GHD patients with higher baseline serum insulin levels were more likely to be GR in serum IGF1 response. This might be an effect of insulin upregulating the surface availability of the GHR in human liver cells (35). Moreover, insulin by itself might increase IGF1 gene transcription in hepatocytes (36).

In children, growth velocity and final height are two major end points for GH therapy. In adults, however,

**Table 4** Significant baseline predictors for serum insulin-like growth factor 1 (IGF1), lean body mass (LBM), and body fat (BF) responses (changes) to 12-month GH replacement therapy using logistic regression analyses.

Predictors	Regression coefficient	Odds ratio (95% CI)	P value	Goodness-of-Fit test
<b>IGF1 response</b>				
Constant ( $\beta$ )	-1.60			0.674
Gender	1.73	5.62 (2.59, 12.18)	<0.0001	
Basal insulin (mU/l)	0.06	1.06 (1.00, 1.12)	0.049	
<b>LBM response</b>				
Constant ( $\beta$ )	5.98			0.726
Gender	2.46	11.67 (3.94, 34.55)	<0.0001	
Basal BMI (kg/m <sup>2</sup> )	-0.44	0.65 (0.52, 0.80)	<0.0001	
Basal BF (kg)	0.15	1.17 (1.05, 1.29)	0.003	
<b>BF response</b>				
Constant ( $\beta$ )	-6.08			0.738
Height (cm)	0.04	1.04 (1.00, 1.07)	0.05	
<b>Body composition response (LBM + BF)</b>				
Constant ( $\beta$ )	-28.08			0.702
Gender	2.37	10.72 (1.36, 84.18)	0.024	
Height (cm)	0.21	1.23 (1.09, 1.40)	0.001	
Basal LBM (kg)	-0.20	0.82 (0.73, 0.92)	0.001	

An odds ratio > 1 indicates an increased probability of being GR. CI, confidence interval. The Goodness-of-Fit test (Hosmer & Lemeshow) showed that the prediction models for IGF1 and body composition (LBM + BF) responses were well fitted ( $P > 0.05$ ).

responses to GH therapy involve different outcome variables, and any criteria for GR and PR have to be arbitrarily defined. In previous studies, GH replacement in GHD adults has been shown to promote, on average, an LBM increase of 2–5.5 kg and a BF reduction of 4–6 kg, with doses varying from 5 to 25 µg/kg per day (37). In our study, we obtained similar changes in BC, with a Gaussian distribution of response. Hence, the 60th and 40th percentiles were chosen as cut-offs to define GR and PR because in this model 20% of patients with similar average outcomes were excluded from the analysis, leaving a sample of good size and significant statistical power to design the statistical models. With the cut-off values at the 60th and 40th percentiles, we had a higher degree of differentiation between the GR and PR response values.

Consistent with other studies (37, 38), the increase in LBM and decrease in BF were sustained after 12 months of GH replacement. Gender, baseline BMI, and BF were the most important predictors of LBM response to GH therapy. Lower BMI at baseline predicted good response in LBM. This finding is in agreement with a previous study, which also demonstrated that patients with the lowest baseline BMI (below the lower quartile, 24.4 kg/m<sup>2</sup>) benefited the most in terms of progressive and significant increases in LBM (38). Higher BF at baseline was also a weak predictor of good response in LBM. It is known from previous studies that young and male patients exhibit the most marked increase in LBM in response to GH treatment (2, 38). However, in our study, age was not a predictor of the LBM changes. Previous studies have shown that changes in total BF in response to GH is dependent on GH dose (39–41) and gender (12), whereas the magnitude of BF changes is influenced by the duration of treatment (39). Moreover, the amount of BF is known to vary according to body height, BW, gender, and age (42, 43). In our study, the logistic regression model revealed that taller patients had greater changes in BF in response to GH. Gender did not contribute significantly to the logistic regression model in BF response. There is still, however, the possibility of an indirect influence of gender in this prediction model because the proportion of men was twice the proportion of women in the GR group.

We have also developed a model to predict those patients who were GR in both LBM and BF, which includes gender, body height, and baseline LBM. Men and GHD patients with lower LBM at baseline were more likely to be GR in both LBM and BF changes.

Previous studies have shown that a mean glucocorticoid replacement dose of at least 20 mg of hydrocortisone augments the metabolic perturbations associated with hypopituitarism and untreated GHD (32). It is possible that the reported adverse changes in BC, intermediary metabolism, and insulin sensitivity which characterize the adult hypopituitary state may be partly related to glucocorticoid overreplacement in

addition to the effects of GHD. The mean hydrocortisone equivalent dose in our study was 19 mg/day, and we found no significant impact of the glucocorticoid dose on serum IGF1, LBM, and BF responses after 12 months of GH therapy.

The response to GH therapy in adults might be judged by many different end points not included in this study, such as changes in QoL, lipids, and bone mineral density. We decided to study BC and serum IGF1 as our end points because they are among the best validated and most objective parameters used in clinical practice. Impairment in QoL is, however, a prominent feature of adult GHD and often the main reason for initiating GH replacement (37). We did not include QoL as an end point because the patients' subjective perception concerning QoL was likely to be multifactorial in origin (44), and previous studies had found treatment response in QoL to be proportional to the baseline deviation from normality (45, 46). In our models, we clearly observed that a patient could be a GR in one parameter and a PR in the other, indicating a need for different prediction models for each studied outcome. This is in agreement with previous observations showing poor correlations between improvement in QoL and biochemical, metabolic or BC changes during adult GH replacement therapy (44–47).

Together, the clinical predictors of GH therapy in GHD adults were gender, serum insulin, BMI, and BF at baseline. Although gender was by far the strongest predictor, our findings also indicate that a patient's metabolic status at baseline influences responsiveness to GH. One likely possibility that has not been formally investigated is the importance of insulin sensitivity in response to GH replacement. Insulin sensitivity has a profound impact on the lipid metabolism of the adipocyte and could therefore influence the lipolytic response to GH. The availability of free fatty acids could in turn affect the anabolic response to GH/IGF1 (48). Therefore, significant changes in BF and LBM are to be expected in lean GHD subjects with good insulin sensitivity.

The proportion of adults with GHD receiving GH replacement therapy varies considerably from one country to another and even among centers in the same country. There are many reasons for these distinct approaches, including the heterogeneous nature of the disease, the large individual variation in the responses to therapy and the costs of treatment. Therefore, it would be of great importance to have a good way of selecting patients who would benefit most from GH replacement. Our study is devoted to creating such a strategy to identify these individuals. Our hope is that a combination of several parameters, easily accessible in clinical practice, may help clinicians when it comes to deciding whether to initiate GH replacement and improve the safety and efficacy of this type of therapy (49).

## Declaration of interest

E J L Barbosa, J Koranyi, and B-Å Bengtsson have nothing to declare. H Filipsson received lecture fees from Nycomed, Novo Nordisk, and Pfizer. C L Boguszewski consults for Merck Serono. G Johannsson consults for Merck Serono, has equity interests in DuoCort AB, and received lecture fees from Pfizer, Novo Nordisk, and Eli Lilly.

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