

# Prediction of poor growth response to growth hormone treatment in prepubertal short children with growth hormone deficiency and born small for gestational age

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The research presented in this thesis was performed in collaboration with the Belgian Society for Paediatric Endocrinology and Diabetology (BESPEED) and conducted at the Department of Paediatrics, Maastricht University Medical Center, Maastricht, The Netherlands

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- Chapter 6      Criteria for first-year growth response to growth hormone treatment in prepubertal children with growth hormone deficiency: do they predict poor adult height outcome?
- Straetemans S, De Schepper J, Thomas M, Tenoutasse S, Beuloye V, Rooman R, and the members of BESPEED.  
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- Chapter 7      Is a two-year growth response to growth hormone treatment a better predictor of poor adult height outcome than a first-year growth response in prepubertal children with non-acquired growth hormone deficiency?
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- Chapter 8      General discussion and future perspectives
- Chapter 9      Summary
- Chapter 10     Impactparagraaf
- Addendum    Nederlandse samenvatting
- Dankwoord
- Curriculum vitae
- List of publications
- List of abbreviations



## Chapter 1

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General introduction,  
aim and outline of the thesis







## Normal growth and its physiology

Growth is a complex and dynamic process, unique to pediatric medicine, that is influenced not only by growth hormone (GH) but by many intrinsic and extrinsic factors. Growth is the product of a complex interaction of nutrient supply and hormones acting on the growth plates, with surplus energy being converted to muscle or deposited as fat [1]. For bone lengthening to occur the growth plate must be normal, but endocrine factors, such as insulin-like growth factor 1 (IGF-1), thyroxine, sex steroids, but also nutritional factors, such as protein and phosphorus are needed for normal epiphyseal cell division and differentiation. The growth promoting actions of GH thus require adequate nutrition, normal endocrine function and a normal skeleton. The process is easily disrupted and can serve as a marker for pathologies in any system and in the social environment [1].

GH is a single-chain amino acid polypeptide produced by the anterior pituitary. GH release is stimulated by GH releasing hormone, while somatotropin release inhibitory hormone counter-regulates GH release by affecting the timing and amplitude of the GH pulses. Both are neuropeptides produced in the hypothalamus. In the circulation, GH is either free or bound to GH-binding proteins (GHBP). Due to a relatively low binding capacity of GHBP only about 45% of the circulating GH is bound. When bound, it prolongs the half-life of GH and facilitates binding to the GH receptor, which leads to production of IGF-1 in GH sensitive tissues. In the circulation the majority of IGF-1 comes from the liver and circulates as a ternary complex with IGFBP-3 and another protein, acid labile subunit (ALS) that transports IGF-1 in the blood and extends its half-life. IGF-1 binds to the IGF-1 receptor at the growth plate which causes cell division and maturation leading to bone lengthening. Various tissues (e.g. growth plates) express GH receptors, allowing GH to have an effect on growth independent of the hepatic production of IGF-1. Also local production of IGF-1 at the growth plate causes bone lengthening [1, 2].

Bone growth is also regulated by the expression of many genes acting locally in the growth plate. The most recent genome wide association analysis shows more than 400 height associated loci with the growth cartilage being the most strongly implicated tissue [3].

The pubertal growth spurt is caused by gonadal steroids that increase GH secretion two- to threefold and also stimulate IGF-1 production at the growth plate. The production of testosterone and estrogen from the gonads boosts growth of the spine in particular. Estrogen in both sexes matures the epiphyses towards eventual bone fusion after which growth ceases [1, 2]. After reaching adult height, GH production does not cease, however the amplitude of the GH pulses gradually decreases with age [2].

## GH treatment

Human pituitary-derived GH has been used for more than 25 years to promote growth in short children with GH deficiency (GHD), until it was halted in 1985 due to recognition of the association with Creutzfeldt-Jakob disease [4]. From 1985, recombinant human (rh) GH was available and approved for clinical use and also its therapeutic application was expanded, especially in the pediatric population, due to the large availability. Not only GH deficient children, but also children born small for gestational age (SGA), children with idiopathic short stature (not in Europe), and children with growth delay due to chronic renal insufficiency, Turner syndrome, Prader–Willi syndrome, Noonan syndrome and SHOX gene haplo-insufficiency can be treated nowadays with GH [5]. GHD and SGA are the most common indications for GH treatment. Next-generation sequencing has shown that genetic disorders labelled as skeletal dysplasia are also present in patients with a diagnosis of idiopathic short stature. These include, for example, abnormalities in the ACAN gene coding for the growth plate extracellular matrix proteoglycan aggrecan, and the natriuretic peptide receptor-B gene NPR2 [6]. GH treatment is not only given for its growth-promoting effect: in Prader Willi syndrome it is mainly given for its metabolic effects on body composition and muscle strength [7-9]. The starting dose of GH depends on the diagnosis of the condition and is usually calculated according to body weight or body surface area. Some differences in dosing as well as dose adaptations during treatment exist between countries and centers.

## The goal of GH treatment

The aim of GH treatment in the patient's perspective is mainly a rapid and sufficient catch-up growth within the normal reference range, the achievement of an adult height close to the genetic target height based on parental heights and preferably within the normal range, and normalization of body composition, with minimal risks of therapy. GH treatment must also be as patient-friendly as possible, with appropriate injection devices since, up to now, daily subcutaneous injections are required. From the society's perspective, GH treatment should be cost-effective, providing optimal efficacy with the lowest dose. From an ethical and patient quality of life perspective, it is important to avoid a burdensome treatment in children who don't benefit from it.

## The effects of GH treatment

The growth promoting effect of GH depends on the underlying condition and GH dose. GH replacement in GHD children is started at an average height of -3.1 to -3.5 SD, at a mean age of 7.2 to 7.8 years, with a mean dose of 31-33 mcg/kg\*day. The mean height gain ( $\Delta$ Ht) after the first GH treatment year varies from 8.4 to 10 cm/year and from 0.72 to 1.04 standard deviation score (SDS), depending on the severity of GHD [10]. In short SGA children, GH treatment is started in a higher dose (mean 44 mcg/kg\*day), at an average height of -3.5 SD, at an average age of 6.9 years. They have a mean height velocity (HV) of 8.6 cm/year and a mean  $\Delta$ Ht of 0.79 SDS during the first GH treatment year [10]. Many investigators have studied the adult height outcome of GH treatment in GHD children [11-22]: the average (near) adult height is -1.2 SDS, this is 0.35 SDS below the target height; mean total  $\Delta$ Ht is 2.5 SDS after an average duration of 7 years of GH treatment. In SGA children, GH has been shown to improve adult height by 1.6 SDS, reaching a mean (near) adult height of -1.6 SDS, this is 0.6 SDS below the target height [23-30].

Beside its growth promoting effect, GH has many specific metabolic effects as well, including (1) increased mobilization of fatty acids from adipose tissue and increased use of fatty acids for energy, (2) increased rate of protein synthesis in most cells of the body, and (3) increase in fasting and glucose stimulated insulin levels (decrease in insulin sensitivity) mostly without adverse effects on glucose levels [31]. The

effect of these changes in metabolism is reflected in a decrease in fat mass and an increase in fat free mass [32-40]. GH therapy can also increase the basal metabolic rate and total energy expenditure in short time experiments [34].

### The variability of the growth response to GH treatment

There is a large inter individual growth response to GH treatment [22, 41] due to differences in sensitivity to GH or its mediator IGF-1 [42]. Some polymorphisms that alter the function of the genes in pathways have shown to affect growth response to GH therapy. An example is the GH receptor polymorphism, in which exon 3 is either present or absent, and has shown to influence GH signal transduction in vitro and growth response to GH in vivo [43]. However, meta-analyses demonstrate significant variation between reports, highlighting the limitations of studying the effect of a single gene on a complex trait, such as growth [44, 45].

The PREDICT long-term follow-up study used a pharmacogenomic approach and demonstrated that a broad range of growth and metabolism related genes, related in particular to cell signaling, are associated with high or low first-year growth responses to GH treatment in children with GHD [46]. In GHD, 11 genes were significantly associated with the first-year growth response. For example, GRB10 was associated with high response while SOS2 was associated with low response. For each polymorphism, the difference in growth between alleles or genotypes was >1 cm over the first year, representing  $\pm 20\%$  of first-year increment in growth.

The PREDICT validation study supports, in an independent cohort, the association of four of 48 genetic markers with growth response to GH treatment after controlling for clinical/auxological covariates [47]. However, genetic data do not appear to be powerful enough on their own to be used in prediction and clinical management and therefore have limited utility.

Beside intrinsic factors, poor adherence [48, 49], concomitant morbidity (such as mild bone dysplasia) or use of some medications (such as chronic glucocorticoid treatment, dexamphetamine) may also impair the growth response to GH treatment.

## Evaluating the initial growth response to GH treatment

Several auxological changes are being used to assess the first-year growth response, such as the  $\Delta$ Ht standard deviation score (SDS), the observed HV expressed in cm/year or in SDS, or the increase in HV compared to the pretreatment year [10]. A number of definitions of poor first-year growth response have been proposed in clinical trials and consensus statements, such as a  $\Delta$ Ht SDS  $< 0.3$  SD or  $< 0.5$  SD, a first-year HV  $< +0.5$  SD or  $< +1.0$  SD for age and gender, or an increase in HV  $< 3$  cm/year compared to the pretreatment year [50]. These arbitrary cut-off values and the assumption of one size fits all, does not take patient specific parameters into account such as diagnosis or age.

### Predicting the initial growth response to GH treatment

#### a. Prediction of growth response in clinical practice by single parameters

Several efforts have been made to predict the growth response to first-year GH treatment from short term changes in auxological, biochemical and energy expenditure parameters.

1. Auxological changes

Chronological age, pretreatment HV, parental heights and weight status (weight SDS and weight for height SDS) are related to the first year growth response in GHD as well as in short SGA children [51]. However, these individual parameters predict only 22% of the variability in the growth response. Hermanussen et al. showed that 38% of the variability in the first year growth response in children with short stature (mainly with GHD) could be predicted by the change in lower leg length after 8 weeks of treatment [52].

2. Changes in GH related biomarkers

#### Serum IGF-1

Despite the shortcomings of IGF-1 assays, IGF-I values provide information about the severity of GHD and are universally used to monitor GH treatment, both for its efficacy and for its safety [53]. A significant inverse correlation exists between pretreatment IGF-1 levels and the height gain

during GH treatment. However, a cut-off for pretreatment IGF-1 levels to identify poor responders cannot be established [54]. During the first treatment year serum IGF-1 is usually measured in clinical practice at the start and 2-4 months later. A lack of increase in IGF-I usually indicates insensitivity to GH or poor treatment adherence. However, there is a poor correlation between the early changes in serum IGF-I levels and growth rate or treatment outcome [42, 55, 56]. Cohen et al. found a wide range of GH doses required to obtain an average or high normal level of IGF-I, illustrating the difference in sensitivity to GH among patients. Moreover, they showed that even with the same serum IGF-I concentration, patients had very different growth responses, suggesting that there is also a difference in sensitivity to IGF-I. In conclusion, the correlation between serum IGF-I and clinical outcome has been disappointing, highlighting the need for other biomarkers to predict efficacy in individual patients.

#### Serum bone turnover markers

In clinical studies, serum markers of bone turnover such as bone alkaline phosphatase, osteocalcin, carboxy terminal propeptide of type 1 collagen and urinary pyridinoline and deoxypyridinoline [57-59] have been shown to increase during GH treatment, but are not used in daily clinical practice. The GH Research Society concluded that there is insufficient data to support the use of bone markers in monitoring GH therapy [60].

#### Other biomarkers

The influence of IGFBP-3 on growth response appears to be disease dependent [46]. In a study assessing parameters that determine growth response to GH treatment, IGFBP-3 SDS had a positive relationship with  $\Delta$ Ht SDS in GHD [61]. In SGA, van der Kaay et al. showed an association between the first-year  $\Delta$ Ht SDS and the increase in IGFBP-3 SDS [62], however, another study reports no correlation [63]. Additional serum analytes such as ALS, Klotho, and fibroblast growth factor 23 have been shown to change with GH treatment in children, but are not used in daily clinical practice [64, 65].

### 3. Changes in body composition and energy expenditure

Vaisman et al. [32] showed an increase in basal metabolic rate after 2 months of GH treatment in 10 prepubertal boys. In 1991, Gregory et al. [34] demonstrated a significant increase in basal metabolic rate and total energy expenditure after 6 weeks of GH treatment in 15 children (GHD or idiopathic short stature). Hoos et al. [66] showed that change in total body water/height<sup>2</sup> after 6 weeks of GH treatment was valuable in identifying good first-year growth responders. The experience with GH induced changes in body composition and energy expenditure as predictors of poor growth response is however very limited and difficult to incorporate in clinical practice.

### 4. Genetic, maternal or environmental risk factors for being born SGA (e.g. Silver-Russell syndrome, congenital heart defects, maternal infections or smoking during pregnancy) did not explain variances in growth response in SGA children treated with GH [67].

The identification of genetic factors contributing to the variability in growth response can be used to promote individualization of GH treatment for best patient outcome.

## b. Prediction of growth response in clinical practice by multiple parameters

Because growth is so complex and influenced by many factors, single auxological criteria and biomarkers are poor outcome predictors. Therefore, a large number of multiparameter prediction models for first-year growth response have been developed and published [10, 68-79]. The most commonly used prediction models are those developed by Ranke et al. based on data from the Kabi/Pfizer International Growth Study known as KIGS and use readily available clinical parameters. The included factors for the first developed model (GHD) are age, height SDS minus target height SDS, body weight SDS, GH dose, maximum stimulated GH peak, and birth weight SDS [69, 70]. First-year prediction models have also been developed for other indications: SGA [71], Turner syndrome [72], idiopathic short stature [73], chronic kidney disease [74], and recently also Noonan syndrome [75]. These prediction models contain more or less the same parameters,



explaining 61% (GHD), 52% (SGA), 46% (Turner syndrome), 39% (ISS), 37% (chronic kidney disease), and 36% (Noonan syndrome) of the variability of the first-year growth response. Other models have been developed including beside auxological parameters, also biochemical measurements [78, 79]. More recently, combining transcriptomic markers with the clinical phenotype has shown to significantly reduce the predictive error [80]. A disadvantage of these prediction models is that all parameters must be available in order to calculate the predicted growth response.

### Evaluating the initial responsiveness to GH treatment

A simple method to assess the responsiveness (=ability of an individual patient to respond to GH) is the comparison of the patient's observed height velocity during the first year of GH treatment with the published “first-year height velocity for age” curves based on large data registers of patients undergoing GH treatment, such as The Genentech Cooperative Study [81], and KIGS [10]. A height velocity below -1.0 SD on the growth response curve has been considered as a poor response. This method addresses the effect of age, diagnosis, and sometimes gender (with a separate curve for each diagnosis) but ignores the known important influence of, for example, the degree of GHD in idiopathic GHD (iGHD), the height of the parents, and the GH dose. The above-mentioned prediction models for first year height gain do include these parameters and therefore assess responsiveness more accurately.

### The goal of predicting the growth response

The ultimate goal of predictive models should be an estimation of the long-term growth response [82, 83]. Despite the wealth of knowledge gained through these population and indication specific multiparameter growth prediction models, the challenge remains to interpret these growth predictions in terms of final response. No study has yet investigated this relationship. Early detection of a poor final responder provides the opportunity to optimize management by assessing possible causes of inadequate growth and/or GH insensitivity. Cessation of GH treatment could be considered to avoid a burdensome and costly treatment in children who

don't benefit from it. Up to now, these multiparameter growth prediction models have remained in clinical research and academic settings.

## Aim and outline of the thesis

Despite more than 35 years of experience with recombinant human GH treatment, it is still a challenge to predict which children will ultimately have little or no benefit from their GH treatment. This thesis aims to gain more insight in the evaluation of poor growth response to GH treatment in short prepubertal children with GHD and SGA and its ability to predict a poor adult height outcome in children with GHD.

In **chapter 2**, we determine the proportion of poor growth responders after first-year GH treatment identified by different auxological criteria in children with GHD and born SGA and compared these different criteria. In **chapter 3**, we ask the question whether the change in energy expenditure immediately after the start of GH treatment is a predictor of the growth response to GH in GHD and SGA children. In **Chapter 4**, we generate a first-year growth response reference curve for prepubertal Belgian children with iGHD treated with a standard weight-adjusted GH dose and compare this national reference with previously published KIGS growth targets, based on European children [10]. In **Chapter 5**, we validate the KIGS prediction models [82] for near final adult height in children with iGHD after first-year GH treatment with an independent cohort from the Belgian Registry. In **Chapter 6**, we explore the value of different criteria for first-year growth response to GH treatment as predictors of a poor final height outcome after GH treatment in prepubertal children with GHD. In **Chapter 7**, we investigate if lengthening the observation period from one to two years improves the prediction of poor adult height outcome in prepubertal children with non-acquired GHD. In **chapter 8**, we discuss the results of our findings in relation to the most recent literature and propose a practical GH therapy approach after one year of treatment incorporating the first-year growth response and responsiveness. **Chapter 9** consists of a summary of the studies included in this thesis. In **chapter 10** we reflect on the scientific impact of the results of our research. The **addendum** contains the Dutch summary as well as acknowledgements, curriculum vitae, a list of publications, and a list of abbreviations.

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## Chapter 2

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Poor growth response during the first year of growth hormone treatment in short prepubertal children with growth hormone deficiency and born small for gestational age: a comparison of different criteria



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# Poor growth response during the first year of growth hormone treatment in short prepubertal children with growth hormone deficiency and born small for gestational age: a comparison of different criteria

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## Abstract

**Background:** There is no consensus on the definition of poor growth response after the first year of growth hormone (GH) treatment. We determined the proportion of poor responders identified by different criteria in children with GH deficiency (GHD) and born small for gestational age (SGA). The second aim was to analyze the IGF-1 response in poor-growth responders.

**Methods:** First-year height data of 171 SGA and 122 GHD children who remained prepubertal during the first GH treatment year were retrieved from the BESPEED database and analyzed. Criteria for poor first-year response/responsiveness were: change in height ( $\Delta$ Ht) SDS < 0.3 or < 0.5, height velocity (HV) SDS < 0.5 or < 1 based on the population reference, HV SDS < -1 based on the KIGS expected HV curve (HV Ranke SDS), studentized residual (SR) < -1 in the KIGS first-year prediction model.

**Results:**  $\Delta$ Ht SDS < 0.5 gave the highest percentage poor responders (37% SGA, 26% GHD). Although % poor responders were comparable for  $\Delta$ Ht SDS < 0.3, HV SDS < +0.5, HV SDS < +1, SR < -1, and HV Ranke SDS < -1, these criteria did not always identify the same patients as poor responders. Among the poor growth responders 24% SGA and 14% GHD patients had an IGF-1 increase < 40%.

**Conclusions:** The different response criteria yield high but comparable percentages poor responders, but identify different patients. This study does not provide evidence that one criterion is better than another. A limited IGF-1 generation is not the major reason for a poor growth response in the first year of GH treatment in SGA and GHD children.

**Trial registration:** Retrospectively registered.

**Keywords:** Growth hormone treatment, Growth hormone deficiency, Small for gestational age, First-year response, Children

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## Background

Growth hormone (GH) deficiency (GHD) and short stature as a consequence of a small size at birth (SGA) are the most frequent indications for GH therapy in children in Europe. Although in general a substantial fraction of the height deficit is already recovered during the first year of GH treatment in these growth disorders, a high proportion has a poor growth response in the first year of GH therapy [1]. This first year growth response is paramount since it is the major determinant of the gain during the subsequent treatment years and correlates with the final height outcome [2–12].

Traditionally the growth response during the first year of GH treatment is evaluated by auxological parameters, such as the gain in height SDS ( $\Delta$ Ht SDS), the observed height velocity (HV) expressed in cm/year or in SDS, or the increase in HV ( $\Delta$ HV) compared to the pre-treatment year [13]. A number of definitions of poor first-year growth response have been proposed in clinical trials and consensus statements, such as a gain in height  $<0.3$  SD or  $<0.5$  SD, a first-year HV  $<+0.5$  SD or  $<+1.0$  SD for age and gender, or an increase in HV  $<3$  cm/year compared to the pretreatment year [14].

Another more recent method to evaluate the growth promoting efficacy of GH treatment in short children is to compare the observed to the expected growth response defined by certain patient and treatment characteristics, which has been defined as responsiveness, reflecting the ability of an individual person to respond to GH [11, 12, 15]. First year height velocity response curves, determined by age, treatment indication and sometimes gender (Bakker et al. [16], Ranke et al. [13], and Straetemans et al. [17]) have been published. A height velocity below  $-1.0$  SD on the growth response curve has been considered as a poor response.

In an attempt to include even more parameters to determine the responsiveness to GH, Ranke et al. have derived prediction models for the first year response to GH in various treatment indications. They include among other factors birth weight, GH dose and parental heights [18–20]. Responsiveness is expressed as a studentized residual  $[SR = (\text{observed HV} - \text{predicted HV}) / \text{SD of the predicted HV}]$  and a  $SR < -1$  has been considered a poor response [12]. This implies that 16.5% of the patients are poor responders. Although these multivariate prediction models provide a more individualized response target, some patients meet their very poor prediction and are therefore not considered poor responders despite their poor absolute response.

Several conditions might explain a poor growth response to GH administration. With the exception of a poorly responsive growth plate, most conditions such as poor compliance, a hidden chronic disease or a partial GH insensitivity due to abnormalities in the GH-IGF-1

axis will limit a sufficient generation of IGF-1 during GH administration. Different patterns of IGF-1 increase during GH treatment between children with GHD, SGA children and other disorders have been described previously [21, 22]. However, up to now, there have been no previous reports comparing the commonly used measures of poor growth response with measures of poor responsiveness from prediction models and only limited data are available on the IGF-1 increase during GH treatment in relation to the growth response in short GHD and SGA children.

We therefore compared the first year growth response and responsiveness criteria in prepubertal children with SGA and GHD, registered in the database of the Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED). We expected a lower percentage of poor responders using more individualized growth response targets, especially in the SGA group, where GH sensitivity and treatment modalities are more variable. In addition, we evaluated the IGF-1 response during the first year of GH treatment in those children with a poor growth response.

## Methods

### Subjects

The auxological data and first year treatment characteristics of prepubertal children diagnosed with SGA and non-acquired GHD, who had been treated exclusively with recombinant human GH on a daily basis, were retrieved from the Belgian Registry of children treated with GH (BELGROW), which is administrated by BESPEED since 1985. The Registry stores coded data and informed consent was secured prior to data entry. Data of patients who started GH treatment between January 2003 and May 2010 were analyzed.

Diagnosis of SGA or GHD was made by the treating physician after peer-review by the other BESPEED members. All GHD patients had a peak GH concentration  $\leq 10$   $\mu\text{g/L}$  in two provocation tests (glucagon and insulin test). Priming before testing with respectively estrogen and testosterone was done routinely in girls  $\geq 8$  years old and boys  $\geq 9$  years old. GHD patients with and without developmental anatomical anomalies of the pituitary were included. Patients with acquired GHD were excluded. Severe GHD was defined as a peak GH response less than 5  $\mu\text{g/L}$  in both provocation tests. Included SGA children had a birth weight and/or birth length  $< -2$  SD [23] and a height  $< -2.5$  SD at the age of 4 years and at onset of therapy. Prepuberty was defined as having a testicular volume less than 4 ml for boys and Tanner breast stage 1 for girls.

In the GHD group, patients born SGA were excluded. In the SGA group, patients with severe GHD (peak GH  $< 5$   $\mu\text{g/L}$ ) were also excluded. Additional exclusion criteria for all groups were: age  $\geq 10$  years for girls and



$\geq 12$  years for boys at the end of the first year of GH treatment, gestational age  $< 30$  weeks, any chronic disease or genetic syndrome interfering with a normal growth potential, a known poor adherence to GH treatment, concomitant treatment with steroids  $> 12$  mg/m<sup>2</sup>.day (hydrocortisone equivalent), additional previous or current growth promoting therapy such as sex steroids, oxandrolone or aromatase inhibitors. Only patients who remained prepubertal during the first treatment year were considered for analysis.

## Methods

Variables retrieved from the register were (a) status at birth: gender, birth weight and length; (b) genetic background: mother's height (Ht), father's Ht; (c) patient variables at the start of the treatment period: chronological age, Ht, weight (Wt), the highest peak GH concentration in GH provocation tests; (d) first year GH treatment modality: average GH dose ( $\mu\text{g}/\text{kg}\cdot\text{day}$ ) during the first year of GH treatment; (e) Ht, Wt after 1 year of GH treatment. IGF-1 values (ng/mL) before the start and during the first year GH treatment were retrieved from the medical files.

Birth weight for gestational age was transformed into SDS, based on the standards of Niklasson et al. [23]. The midparental height (MPH) was calculated as follows: [father's Ht (cm) + mother's Ht (cm) + 13 for boys/- 13 for girls]/2 [24]. Height, weight, body mass index (BMI), HV, and MPH were converted to SDS using Belgian reference data by Roelants et al. [25].

First-year gain in height ( $\Delta\text{Ht}$ ) SDS and first-year height velocity (HV) (cm/year), were calculated as the increment in height between start of treatment and a measurement made after minimum 9 months and maximum 15 months of GH treatment, subsequently scaled to 12 months.

The observed first-year HV (cm/yr) was expressed as SDS, either using the Flemish HV reference curve [25] or using the reference curves for GH treated prepubertal GHD and SGA children developed by Ranke et al. based on the KIGS database [13]. The latter was calculated as follows: the HV of the child in cm/year minus the mean HV for age and diagnosis divided by the SD for age and diagnosis.

Predicted first-year HV (cm/year) was calculated with the KIGS first-year prediction models for GHD (GH peak included) [18, 19] and SGA [20], provided that all parameters required for the mathematical algorithm were available. These prediction models are available on the Prediction Models Web [26] and on the iGRO website [27]. Differences between observed and predicted HVs were expressed as studentized residuals (SR). SRs were calculated as the observed HV minus the predicted HV, divided by the SD of the predicted HV of the child.

SR is the index of responsiveness (IoR), thus the index of an individual's actual growth versus its unique predicted growth.

The criteria used to define a poor first-year growth response were: (a)  $\Delta\text{Ht} < 0.3$  SD [28], (b)  $\Delta\text{Ht} < 0.5$  SD [13], (c)  $\text{HV} < +0.5$  SD on the population HV reference curves [25], (d)  $\text{HV} < +1.0$  SD on the population HV reference curves [25], (e) observed first-year HV more than 1 SD below the patient's predicted first-year height velocity ( $\text{SR} < -1$ ) [12], and (f)  $\text{HV} < -1.0$  SD for expected first-year height velocity based on diagnosis specific reference data developed by Ranke et al. (HV Ranke SDS) [13].

The patients were divided into three response groups: poor response to all criteria, questionable response (poor response to at least 1 criterion), and good response to all criteria.

The percentage increase in IGF-1 was calculated using the IGF-1 value before the start of GH treatment and the highest IGF-1 value during the first year of GH treatment. A poor IGF-1 response during the first year of GH treatment was defined as an increase of less than 40% after at least 3 months of GH therapy. This cutoff value corresponds to the 10th percentile of IGF-1 increase in GHD patients [29].

## Statistical analysis

The variables were tested for normality with the one-sample Kolmogorov-Smirnov test and are reported as medians (25–75 percentile) or means ( $\pm$  SD). Student's *t* test, one-way ANOVA and Bonferroni correction were used to test for differences between groups when the distribution of data was normal. Otherwise Mann-Whitney-U and Kruskal-Wallis tests were applied. Simple linear correlation analysis was conducted using the Spearman formula. Statistical significance was set at the 5% level ( $p < 0.05$ ). IBM SPSS statistics 21\* software was used for all statistical analyses. The patient population was of sufficient size to detect a 50% lower percentage poor responders for the criterion  $\text{SR} < -1$  compared to the criterion  $\text{HV} < +1.0$  SD ( $\alpha = 0.05$  and  $1-\beta = 0.8$ ).

## Results

### Baseline characteristics

In total, 171 SGA patients and 122 GHD patients met the inclusion and exclusion criteria. Sixty six children were diagnosed with severe GHD (peak GH  $< 5$   $\mu\text{g}/\text{L}$ ). Baseline auxological characteristics at the start of GH treatment are listed in Table 1. For both groups there was a predominance of males (64–66%). Boys started GH treatment at a significantly older age than girls (7.5 vs. 6.6 years, respectively;  $p = 0.01$ ); 26 (=15%) SGA and 19 (=16%) GHD boys were older than 10 years at the start of treatment. At baseline, there was no significant difference in median Ht SDS between SGA and GHD patients (SGA:  $-3.06$  SD, GHD:  $-3.20$  SD). The mean

**Table 1** Characteristics: background, at GH start, after first-year GH treatment

	SCA			GHD (all)			Severe GHD (peak GH < 5 µg/L)			Less-severe GHD (peak GH 5–10 µg/L)															
	n	Mean	SD	p25	Median	p75	n	Mean	SD	Median	p25	p75	n	Mean	SD	Median	p25	p75							
<b>Background</b>																									
Birth weight, SDS	169	-2.56 <sup>1</sup>	0.96	-2.93	-2.03	1.21	-0.44 <sup>1</sup>	0.9	-0.43	-1.21	0.27	65	-0.19	0.94	-0.14	-0.85	0.47	56	-0.74	0.78	-0.77	-1.35	-0.13		
Birth length, SDS	163	-2.77 <sup>1</sup>	1.02	-2.65	-3.41	-2.19	1.12	-0.59 <sup>1</sup>	0.89	-0.58	-1.23	-0.03	61	-0.48	0.87	-0.55	-1.1	0.17	51	-0.71	0.91	-0.83	-1.4	-0.28	
Sex, % male	64						66					64													
Father height, SDS	164	-1.40 <sup>2</sup>	1.12	-1.48	-2.1	-0.47	1.18	-0.85 <sup>1</sup>	1.27	-0.97	-1.66	-0.15	64	-0.72	1.32	-0.67	-1.65	0.24	54	-0.99	1.2	-1.05	-1.95	-0.26	
Mother height, SDS	163	-1.37 <sup>1</sup>	1.11	-1.28	-2.12	-0.61	1.19	-0.77 <sup>1</sup>	1.13	-0.78	-1.53	0.07	64	-0.82	1.16	-0.78	-1.55	0.07	55	-0.72	1.11	-0.61	-1.45	0.07	
MPH, SDS	163	-1.39 <sup>1</sup>	0.85	-1.42	-1.95	-0.85	1.18	-0.82 <sup>1</sup>	0.92	-0.82	-1.56	-0.27	64	-0.96	1.29	-0.86	-1.99	0.02	54	-1.05	0.88	-0.83	-1.87	-0.4	
Maximum GH peak µg/L							122	4.9	2.6	4.8	3.0	7.1	66	2.9	1.4	3.0	1.9	4.1	56	7.4	1.4	7.3	6.0	8.4	
<b>At start GH treatment</b>																									
Age, years	171	7.5	2.3	7.5	5.4	9.2	122	6.7	2.9	6.5	4.4	8.8	66	6.5	3.1	5.9	4.2	8.6	56	6.96	2.8	7.7	5.3	8.9	
Height, SDS	171	-3.21	0.65	-3.06	-3.51	-2.77	1.22	-3.17	0.83	-3.2	-3.69	-2.71	66	-3.33	0.89	-3.32	-3.8	-2.81	56	-2.86	0.7	-2.9	-3.43	-2.59	
Weight, SDS	168	-3.34 <sup>1</sup>	1.21	-3.29	-4.1	-2.47	1.20	-2.53 <sup>1</sup>	1.19	-2.44	-3.36	-1.69	65	-2.57	1.22	-2.49	-3.34	-1.77	55	-2.48	1.15	-2.4	-3.4	-1.6	
BMI, SDS	167	-1.28 <sup>1</sup>	1.2	-2.21	-2.13	-0.41	1.13	-0.33 <sup>1</sup>	1.13	-0.52	-1.06	0.4	62	-1.17	1.04	-0.46	-0.85	0.63	51	-0.53	1.22	-0.74	-1.18	0.27	
Height SDS minus MPH SDS	163	-1.83 <sup>1</sup>	0.87	-1.75	-2.28	-1.21	1.18	-2.36 <sup>1</sup>	1.14	-2.26	-3.04	-1.51	64	-2.58	1.27	-2.41	-3.31	-1.7	54	-2.11	0.9	-2.12	-2.66	-1.42	
GH dose, µg/kg/day	167	38.1	7.2	36.5 <sup>1</sup>	33.5	41.2	120	26.2	3.0	25.8 <sup>1</sup>	24.4	27.4	65	25.8	3.1	2.3	23.8	27.3	55	26.6	2.9	26.0	24.7	27.4	
<b>After first-year GH treatment</b>																									
Height, SDS	171	-2.64	0.71	-2.48 <sup>2</sup>	-2.98	-2.15	1.22	-2.35	0.75	-2.32 <sup>2</sup>	-2.75	-1.91	66	-2.35	0.78	-2.31	-2.92	-1.77	56	-2.35	0.71	-2.34	-2.69	-2.05	
Δ BMI, SDS <sup>3</sup>	167	0.18 <sup>1</sup>	0.47	0.15	-0.15	0.44	1.20	-0.21 <sup>1</sup>	0.59	-0.19	-0.54	0.18	65	-0.27	0.68	-0.23	-0.57	0.2	55	-0.14	0.47	-0.14	-0.48	0.17	
Height SDS minus MPH SDS	163	-1.25 <sup>1</sup>	0.91	-1.15	-1.78	-0.59	1.18	-1.52 <sup>1</sup>	0.89	-1.53	-2.19	-0.89	64	-1.58	1.01	-1.61	-2.47	-0.89	54	-1.45	0.72	-1.5	-1.97	-0.94	
GH dose during first year, µg/kg/day	167	38.1	6.7	36.4 <sup>1</sup>	34.0	41.6	119	26.9	3.2	26.5 <sup>1</sup>	25.0	28.2	64	26.6	2.9	2.64	24.9	28.2	55	27.3	3.5	26.5	25.0	28.4	

SCA small for gestational age, GHD growth hormone deficiency, GH growth hormone, MPH midparental height, BMI body mass index; <sup>1</sup> Increase in BMI during first-year GH treatment; <sup>2</sup> p < 0.001; <sup>3</sup> p < 0.05

average GH dose during the first year of GH treatment for patients with GHD was 26.9  $\mu\text{g}/\text{kg}^*\text{day}$ , which was significantly lower than the dose for patients with SGA (38.1  $\mu\text{g}/\text{kg}^*\text{day}$ ;  $p < 0.001$ ). Children born SGA had a lower weight and BMI at start than children with GHD ( $p < 0.001$ ). Children with GHD had the largest difference between height SDS at start and MPH SDS.

#### Response and responsiveness after the first year of GH treatment

As shown in Table 2, children with GHD had a significantly greater increase in Ht SDS and HV than children with SGA ( $p < 0.001$ ). In the SGA group the mean observed HV is close to the expected HV. In contrast, GHD responded slightly worse than predicted (SR =  $0.35 \pm 1.13$ ;  $p = 0.05$ ).

Children with severe GHD (max. GH peak  $< 5 \mu\text{g}/\text{L}$ ) had a greater increase in Ht SDS ( $0.97 \pm 0.65$  vs  $0.62 \pm 0.42$ ;  $p = 0.001$ ), and a greater HV (cm/yr) ( $10.1 \pm 2.8$  vs  $8.4 \pm 1.9$ ;  $p < 0.001$ ) than the group with less-severe GHD.

There was no significant difference in  $\Delta\text{Ht}$  SDS, nor in HV (cm/yr) between SGA children with only a low birth weight ( $n = 24$ ) and SGA children with only a low birth length ( $n = 38$ ).

#### Comparison of poor response and poor responsiveness criteria

One hundred and six (106) patients (=36%) met at least one of the proposed criteria for poor response. Figure 1 shows the percentage of patients labeled as poor responders according to the different criteria.  $\Delta\text{Ht} < 0.5$  SD gave the highest proportion of poor responders (37% in SGA, 26% in GHD).  $\Delta\text{Ht} < 0.3$  SD generated 15% poor responders in SGA and 12% in GHD.  $\text{HV} < 0.5$  SD was seen in 17% of SGA and in 11% of GHD patients.  $\text{HV} < 1.0$  SD was observed in 25% of SGA and 19% of GHD subjects. Eighteen percent of patients with SGA and 20% of patients with GHD had an observed first-year HV more than 1 SD below the predicted first-year height velocity (SR  $< -1$ ). Fourteen percent of patients with SGA and 12% of patients with GHD had a  $\text{HV} < -1.0$  SD for expected first-year HV based on diagnosis specific reference data developed by Ranke et al. (HV Ranke SDS  $< -1$ ).

Between the SGA and GHD group there were no significant differences in percentages of poor responders. In the SGA group, the percentage of poor responders for the  $\Delta\text{Ht} < 0.5$  SD criterion was significantly different from those for the  $\Delta\text{Ht} < 0.3$  SD,  $\text{HV} < +0.5$  SD, SR  $< -1$  and HV Ranke  $< -1$  SD criteria ( $p < 0.01$ ). In the GHD group, the percentage of poor responders for the  $\Delta\text{Ht} < 0.5$  SD criterion was significantly different from those for the  $\Delta\text{Ht} < 0.3$  SD,  $\text{HV} < +0.5$  SD and HV Ranke  $< -1$  SD criteria ( $p < 0.05$ ).

Although the percentages of poor responders were comparable for the criteria  $\Delta\text{Ht} < 0.3$  SD,  $\text{HV} < +0.5$  SD,  $\text{HV} < +1$  SD, SR  $< -1$ , and HV Ranke  $< -1$  SD in the SGA and GHD group, these specific criteria did not always identify the same patients as poor responders, as shown in Fig. 2. For example, for the criteria  $\Delta\text{Ht} < 0.3$  SD,  $\text{HV} < +1$  SD and SR  $< -1$ , only 17/45 SGA patients and 7/30 GHD patients were identified as poor responders by all three criteria. For the criteria  $\text{HV} < +1$  SD and SR  $< -1$ , respectively 22/45 and 11/30 patients in the SGA and GHD group were identified by both criteria as poor responders.

Poor response to all criteria was observed in 16 (10%) SGA and 7 (7%) GHD patients, questionable response (poor response to at least one criterion) in 49 (30%) SGA and 34 (32%) GHD patients, and good response to all criteria in 96 (60%) SGA and 64 (61%) GHD patients. In the SGA group, age was significantly older in the group with questionable response compared to the group with good response (data not shown). There were no other significant differences between the responder groups in the SGA group. In the GHD group, father height SDS was significantly lower and  $\Delta$  BMI SDS was significantly higher in the group with questionable response compared to the group with good response. There were no other significant differences between the responder groups. IGF-1 could not be compared because this parameter was available in only a minority of the patients (data not shown).

#### IGF-1 response of poor growth responders

Out of the 106 patients who showed a poor growth response for at least one criterion, 70 patients had results of at least two IGF-1 determinations available. There were no significant differences in the growth responses between poor responders with and without available IGF-1 values. For SGA ( $n = 41$ ) and GHD ( $n = 29$ ) patients with a poor first year growth response, the mean increase in IGF-1 was 126% ( $\pm 126$ ) and 176% ( $\pm 193$ ), respectively.

Ten (24%) SGA and 4 (14%) GHD patients had less than 40% increase in IGF-1 during the first year of GH treatment. GHD patients with blunted IGF-1 increase had a significantly lower BMI SDS at start compared to those with a normal increase ( $-1.35$  SD vs  $-0.21$  SD;  $p < 0.01$ ) and had mothers with a taller height ( $0.66$  SD vs  $-1.02$  SD;  $p < 0.01$ ), while no differences in the available auxological parameters were found between SGA children with a poor and a normal IGF-1 increase.

#### Discussion

Depending on the criteria used, between 11 and 26% of short prepubertal GHD children, treated with a mean GH dose of 27  $\text{mcg}/\text{kg}^*\text{d}$  and between 14 and 37% of

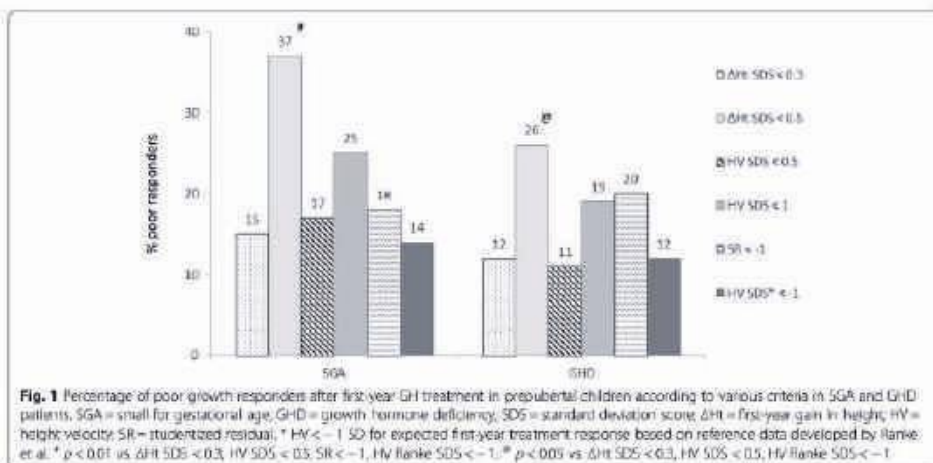




**Table 2** First-year response and responsiveness to GH treatment

	SGA				GHD (all)				Severe GHD (peak GH < 5 µg/L)				Less-severe GHD (peak GH 5–10 µg/L)											
	n	Mean	SD	Median	p25	p75	n	Mean	SD	Median	p25	p75	n	Mean	SD	Median	p25	p75						
<b>Response parameters</b>																								
Δ Height, SDS <sup>a</sup>	171	0.57	0.26	0.56 <sup>1</sup>	0.38	0.77	122	0.83	0.59	0.69 <sup>1</sup>	0.47	1.08	66	0.97	0.65	0.88	0.55	1.31	56	0.62	0.41	0.59	0.38	0.74
HV, cm/year	171	8.1	1.5	8.2 <sup>1</sup>	7.2	9.2	122	9.4	2.6	9.0 <sup>1</sup>	7.6	10.9	66	10.1	2.8	9.9	8.4	12.0	56	8.4	1.9	8.3	7.2	9.5
HV for age and sex, SDS	170	1.98	1.42	2.04 <sup>2</sup>	1.01	2.91	105	2.7	2.03	2.52 <sup>2</sup>	1.27	3.72	57	3.22	2.33	3.06	1.41	4.9	48	2.09	1.39	2.1	0.97	2.78
<b>Parameters of estimated responsiveness</b>																								
HV Rank <sup>b</sup> , SDS	171	-0.09	0.85	-0.08	-0.67 <sup>3</sup>	0.55	118	0.00	0.87	0.04	-0.57	0.33	63	0.03	0.92	-0.02	-0.47	0.64	55	-0.04	0.81	0.04	-0.58	0.37
Studentized residual	159	-0.12	0.94	-0.02	-0.7	0.5	113	-0.35	1.13	0.26 <sup>3</sup>	-0.89	0.2	60	-0.43	1.3	-0.4	-0.93	0.3	53	-0.25	0.9	-0.16	-0.89	0.17

SGA small for gestational age, GHD growth hormone deficiency, GH growth hormone, HV height velocity, gain in height SDS after first-year GH treatment, <sup>a</sup>HV SDS growth targets for first-year GH response, <sup>b</sup>p < 0.001, <sup>c</sup>p < 0.05, <sup>d</sup>p < 0.05 vs. zero

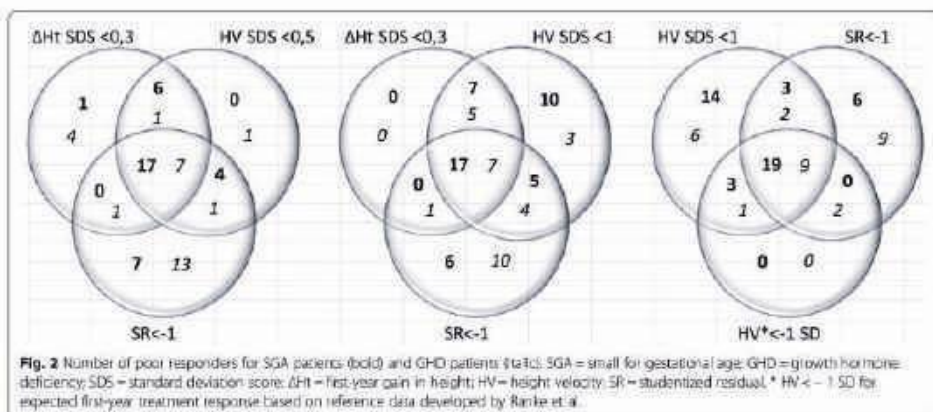


short prepubertal SGA children, treated with a mean GH dose of 38 mcg/kg\*d, were found to be poor responders. ΔHt > 0.5 SD was the most stringent criterion: 26% of GHD and 37% of SGA patients treated in Belgium did not meet this response criterion, whereas the HV Ranke SDS < -1 gave the lowest percentages (12 and 14%).

Our prevalence results are comparable to the findings of Bang et al. [1] who also assessed the criteria for poor growth response in a group of 173 GHD and 54 SGA short prepubertal children from the Nordic countries. Beside the inclusion of SGA born children within the GHD group, the in- and exclusion criteria of this Nordic study are comparable to the data in our Belgian registry

study, explaining to a great extent the similar proportion of poor responders.

Bang et al. [30] have argued that the response to GH should be clinically meaningful, implicating that treatment should diminish rapidly the height difference with peers, implicating a gain in height SDS of at least 0.5 SD during the first year. This criterion is based on the observation that the year to year change in height SDS in normal growing children can go up to 0.3 SD [31]. So to attribute the growth response to GH, the change in height SDS should be at least higher than 0.3 SD. However, since the gain in height SDS is age and diagnosis dependent [1, 16], a fixed cutoff will favor a better response in younger children and in severe GHD.



2

Comparing the annualized HV during the first year on GH with the HV of the pre-treatment year ( $\Delta HV$ , cm/year) might give an approximation of the GH induced HV, except in case a severely HV declining in the pre-treatment year is present, as often seen in severe GHD. Theoretically,  $\Delta HV$  (cm/year) may be the best response parameter to evaluate, however reliable pretreatment height measurements are often unavailable, as was the case in our database.

HV (cm/year) during the first year on GH treatment is highly age dependent [1, 16]. To express HV independent of age and in relation to normal gender related reference values, an SDS for age can be calculated. However, references are usually based on longitudinal studies with relatively small sample sizes or on cross-sectional data.

The ability of an individual patient to respond to GH (the responsiveness) should always be determined in order to evaluate the growth response correctly. For example, a patient with a first-year  $\Delta Ht$  of 0.7 SD would be considered a good responder, but with a SR of, for example,  $-1.2$  this patient proves to have an inadequate response. A weakness of prediction models may be the lack of available patient characteristics needed to calculate responsiveness.

We hypothesized that a more individualized responsiveness criterion would yield 50% less poor responders than the more general response criteria. This hypothesis must be rejected because  $\Delta Ht < 0.3$  SD,  $HV < +0.5$  SD,  $HV < +1$  SD,  $SR < -1$  and  $HV$  Ranke  $SDS < -1$  SD gave the same proportion of poor responders in both treatment indications, although the GH doses are significantly different in both diagnostic groups. This supports the notion that there exists a continuum and overlap between partial GHD and SGA children without a postnatal catch up growth [32].

Although most criteria resulted in the same proportion of poor responders they did not identify the same patients. For example,  $HV < +1$  SD, the reimbursement response criterion of the European Medicines Agency (EMA) for GH treatment in short SGA children, generated a comparable amount of poor responders as the criterion  $SR < -1$  (respectively 25 and 18%). However, only 17 out of 45 of these poor responders fulfilled both criteria. Hence, these parameters cannot be used interchangeably. The fact that there is no concordance between the groups defined by the different criteria is interesting, but not surprising, since the response variables are principally different from the responsiveness parameters.

The long-term evaluation of response to GH has been validated for the KIGS prediction models by showing that SR is the second most important predictor of adult height after GH treatment. All the other proposed criteria for a poor first-year response have not been evaluated for their ability to predict a poor adult height outcome.

In our study, respectively 24 and 14% of the poor responders in the SGA and GHD group were found to have an insufficient IGF-1 increase in the first year. GH insensitivity is hence not a major reason for poor growth response in these children. GHD patients with low IGF-1 increase had a significantly lower BMI SDS at start compared to those with a normal increase. Nutritional constraints are possibly an important cause for the poor IGF-1 response. These children do not have sufficient calories to be able to grow, which may explain the poor growth response. Poor compliance is another possible reason for the poor IGF-1 response and growth response. Because IGF-1 rises within days after GH administration, a normal IGF-1 measurement cannot rule out poor adherence up to a week before the blood collection.

A weakness of this study is the limited amount of available IGF-1 values. However, no significant differences in the growth responses between poor responders with and without available IGF-1 values were observed.

IGF-1 levels after GH might fluctuate with the duration of GH therapy [1]. We therefore have chosen to take the maximum level into account and not a level at fixed duration. To circumvent the problem of non-centralized determination of IGF-1, the percentage increase was calculated on IGF-1 levels determined in the same laboratory.

## Conclusions

In conclusion, with the exception of the  $\Delta Ht < 0.5$  SD cutoff, the tested criteria resulted in the same proportion of poor growth responders in GH treated SGA and GHD patients, but did not always identify the same patients as poor responders. This study does not provide evidence that one criterion is better than another. A critical evaluation of these response parameters and their cutoff values with respect to their capacity to detect a poor final adult height outcome is needed to define the best poor response parameter. A limited capacity in IGF-1 generation did not appear to be a major reason for a poor growth response in both GHD as SGA children.

## Abbreviations

$\Delta Ht$ : Change in height;  $\Delta HV$ : Change in height velocity; BESPEED: Belgian Society for Pediatric Endocrinology and Diabetology; BMI: Body mass index; EMA: European Medicines Agency; GH: Growth hormone; GHD: Growth hormone deficiency; Ht: Height; HV: Height velocity; IQR: Index of responsiveness; MPH: Midparental height; SDS: Standard deviation score; SGA: Small for gestational age; SR: Studentized residual; Wt: Weight

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#### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

#### Authors' contributions

SS, RR, and JDS conceived and designed research. MT made substantial contributions to acquisition of data. SS, RR, and JDS analyzed and interpreted the data. SS, RR, and JDS wrote the manuscript. MT and MC were involved in critical revision of the manuscript for important intellectual content. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

#### Ethics approval and consent to participate

The data were retrieved from the Belgian Registry of children treated with GH (BELGROW), which is administered by BESPEED since 1985. The Registry stores coded data and informed consent was secured prior to data entry.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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## Chapter 3

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Effect of growth hormone treatment on energy expenditure and its relation to first-year growth response in children



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## Effect of growth hormone treatment on energy expenditure and its relation to first-year growth response in children

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### Abstract

**Purpose** The effects of growth hormone (GH) treatment on linear growth and body composition have been studied extensively. Little is known about the GH effect on energy expenditure (EE). The aim of this study was to investigate the effects of GH treatment on EE in children, and to study whether the changes in EE can predict the height gain after 1 year.

**Methods** Total EE (TEE), basal metabolic rate (BMR), and physical activity level (PAL) measurements before and after 6 weeks of GH treatment were performed in 18 prepubertal children (5 girls, 13 boys) born small for gestational age ( $n=14$ ) or with growth hormone deficiency ( $n=4$ ) who were eligible for GH treatment. TEE was measured with the doubly labelled water method, BMR was measured with an open-circuit ventilated hood system, PAL was assessed using an accelerometer for movement registration and calculated ( $PAL = TEE/BMR$ ), activity related EE (AEE) was calculated [ $AEE = (0.9 \times TEE) - BMR$ ]. Height measurements at start and after 1 year of GH treatment were analysed. This is a 1-year longitudinal intervention study, without a control group for comparison.

**Results** BMR and TEE increased significantly (resp. 5% and 7%). Physical activity (counts/day), PAL, and AEE did not change. 11 out of 13 patients (85%) with an increased TEE after 6 weeks of GH treatment had a good first-year growth response ( $\Delta$ height SDS > 0.5).

**Conclusions** GH treatment showed a positive effect on EE in prepubertal children after 6 weeks. No effect on physical activity was observed. The increase in TEE appeared to be valuable for the prediction of good first-year growth responders to GH treatment.

**Keywords** Energy expenditure · Body composition · Metabolism · Growth hormone treatment · Children · First-year growth response

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### Abbreviations

AEE	Activity related energy expenditure
BMR	Basal metabolic rate
Cnts/d	Counts per day
DIT	Diet-induced thermogenesis
DLW	Doubly labelled water
GH	Growth hormone
GHD	Growth hormone deficiency
HV	Height velocity
$\Delta$ Ht	Increase in height
MPH	Midparental height
PAL	Physical activity level
RQ	Respiratory quotient
SD	Standard deviation
SDS	Standard deviation score
SGA	Small for gestational age
TBW	Total body water
TEE	Total energy expenditure

### Introduction

Already for many years, short children with growth hormone (GH) deficiency (GHD) and/or born small for gestational age (SGA) have been treated with recombinant human GH to promote their linear growth. Beside its growth-promoting effect, GH has many specific metabolic effects as well, including (1) increased mobilization of fatty acids from adipose tissue and increased use of fatty acids for energy, (2) increased rate of protein synthesis in most cells of the body, and (3) decreased rate of glucose utilization throughout the body. The effect of these changes in metabolism is reflected in a decrease in fat mass and an increase in fat free mass, as shown in several studies (Vaisman et al. 1994, 1992; Gregory et al. 1991, 1993; Ernst et al. 2012; Khadilkar et al. 2014; Walker et al. 1990; Boot et al. 1997; Hassan et al. 1996).

Beside a change in body composition, it is reasonable to assume that also energy expenditure will be influenced by GH treatment. Total daily energy expenditure (TEE) can be divided into 3 components: (1) basal metabolic rate (BMR), the amount of energy required to maintain all vital body functions at rest with no additional activity; (2) diet-induced thermogenesis (10%) (Westertep 2004); (3) activity related energy expenditure (AEE). However, very little research has been done on changes in energy expenditure caused by GH treatment in children. Vaisman et al. (1994) showed an increase in BMR after 2 months of GH treatment in 10 prepubertal boys. Gregory et al. (1991) were the first and up to now the only who studied GH effects on BMR as well as TEE in 15 children. They demonstrated a significant increase in BMR and TEE after 6 weeks of GH treatment.

It has been shown that changes in body composition can predict the growth response after the first year of GH treatment. Hoos et al. (2003b) showed a strong relationship between the GH induced first-year growth response and the increase in total body water (TBW)/height<sup>2</sup> after 6 weeks in 28 prepubertal children suspected of being GH deficient. Eighty percent of the children with a good growth response (increase in height SDS > 0.7) had a change in TBW/height<sup>2</sup> exceeding the 2 SD reference line of the control group. Additionally, Ernst et al. (2012) showed that the change in TBW after 6 weeks of GH treatment correctly predicted the growth response after the first year in 75% of GHD patients ( $n=88$ ). For children born SGA ( $n=99$ ), a change in TBW of > 0.7 L/m<sup>2</sup> was strongly predictive for a good growth response, but the negative predictive value was low (30%). Gregory et al. (1993) showed in 15 children that not only body composition but also 6 weeks changes in energy expenditure were correlated with height velocity increases at 6 months of GH treatment.

The first aim of this study is to investigate the effects of GH on energy expenditure (BMR, TEE and AEE) and body composition in prepubertal children. Our hypothesis is that the changes in body composition are related to changes in energy expenditure after 6 weeks of GH treatment in children. The second aim of this study is to investigate the relation of the GH induced changes in energy expenditure and the height gain after 1 year. We hypothesize that the increased energy expenditure after 6 weeks of GH treatment can predict the height gain after the first year of GH treatment.

### Subjects and methods

#### Study design

This was a prospective study, approved by the Medical Ethical Research Committee of the University of Maastricht and the Antwerp University Hospital. Informed consent is secured prior to entry in the study. This is a 1-year longitudinal intervention study, without a control group for comparison.

#### Patients

Children visiting the outpatient clinic at the Maastricht University Medical Center and the Antwerp University Hospital were screened by paediatric endocrinologists for participation in the study. Children aged  $\geq 4$  years with GHD and/or born SGA without catch-up growth and who were scheduled for treatment with recombinant human GH on a daily regimen for at least 1 year, were eligible for participation. The diagnosis of GHD was made by the treating paediatric



endocrinologist according to international guidelines, including a height velocity (HV) below the 25th percentile, a low IGF-I concentration, a delayed bone age and a peak GH concentration below 20 mIU/L in 2 GH provocation tests (glucagon, arginine and/or insulin test). Children born SGA without catch-up growth had to meet the following inclusion criteria: (1) a birth length and/or weight  $< -2.0$  standard deviation (SD); (2) height at start of GH treatment  $< -2.5$  SD; (3) height at start of GH treatment  $\geq 1.0$  SD below target height SD score (SDS). Exclusion criteria were: (1) chronological or bone age greater than 8 years for girls and 9 years for boys; (2) puberty during first year of GH treatment (girls Tanner breast stage  $\geq 2$ , boys testicular volume  $\geq 4$  mL); (3) syndromes or diseases that influence growth other than GDH or SGA; (4) concomitant treatment with glucocorticosteroids ( $> 12$  mg/m<sup>2</sup>/day hydrocortisone equivalent) in preceding year or during first-year GH treatment; (5) previous or current treatment with other growth stimulating medications (e.g., sex steroids, oxandrolone, letrozole); (6) other pituitary hormone deficiencies present at start or during first-year GH therapy. If a patient met the inclusion and exclusion criteria, the study was explained to the patients/parents and they were asked whether they were interested in taking part in the study. During the enrollment period only 2 patients did not participate because the parents did not have time for the ventilated hood measurements. Patients were treated with subcutaneous injections of recombinant human GH at a dose of 35  $\mu$ g/kg day for children born SGA, and 25  $\mu$ g/kg day for children with GHD.

## Methods

Auxological parameters (height and weight) were measured at start, after 6 weeks, and after 1 year of GH treatment. A stadiometer accurate to 0.1 cm was used for all height measurements. Weight was measured using an electric scale accurate to 0.1 kg with the patient only wearing underwear.

Birth weight for gestational age was transformed into SDS, based on the standards of Niklasson et al. (1991). The midparental height (MPH) (cm) was calculated as (father's height + mother's height + 13)/2 for boys and (father's height + mother's height - 13)/2 for girls (Cole 1996). Height, weight, body mass index (BMI), MPH and HV were converted to SDS [(patient parameter - mean of the reference population)/SD of the reference population] using the Belgian reference data by Roelants et al. (2009). An increase in height SDS  $< 0.5$  was defined as a poor first-year growth response (Bang et al. 2012).

## Total energy expenditure (TEE) and total body water (TBW)

The doubly labelled water (DLW) method, according to the Maastricht protocol was used for the measurement of body

composition and TEE before and 6 weeks after start of GH treatment. This isotope technique is validated by comparing measurements with results from alternative techniques, and by analysis of the reproducibility within subjects and within observations (Westerterp et al. 1995; Westerterp 1999a). It is the golden standard method. A baseline urine sample was collected. Then, a weighed isotope dose of DLW, a mixture of 10% <sup>18</sup>O and 5% <sup>2</sup>H in water, was orally administered. Children drank the water straight from the bottle (~70 mL) after which the bottle was partly refilled with tap water which was also consumed, to be sure the complete dose of DLW was ingested. The children drank the water in the evening before they went to bed. The next morning, when equilibration of the isotope with the body water had occurred, a urine sample was collected from the second voiding. The DLW and urine samples were stored in air-tight, screw-capped glass containers. TEE was measured over a 2-week period, thus collection of urine samples were repeated at day 8 and 14. Sample analysis requires a sophisticated laboratory with an isotope-ratio mass spectrometer and a sample preparation system. The department of human biology at the Maastricht University in Maastricht, The Netherlands fulfils these requirements and analysed all samples. The samples were analysed in duplicate with an isotope-ratio mass spectrometer (Optima, VG Isogas, Cheshire, UK).

CO<sub>2</sub> production was calculated from the difference in disappearance rates of both isotopes, as calculated from the slope of the elimination curves.

Oxygen consumption was then calculated from measured CO<sub>2</sub> production by assuming an average RQ of 0.85, representative of a normal mixed diet (Black et al. 1986). Energy expenditure was then calculated using Weir's formula (1949).

Fat free body mass was calculated from TBW using the age-specific fat-free mass hydration constants for children by Lohman (1989).

## Basal metabolic rate (BMR) and physical activity level (PAL)

Basal metabolic rate was measured with an open-circuit, ventilated hood system before and 6 weeks after GH treatment (Adriaens et al. 2003). It was measured in the morning after an overnight fast to avoid diet-induced thermogenesis being included in the measurement. The subjects were asked to lie in supine position for 30 min. Oxygen consumption and carbon dioxide production were calculated using the flow through the hood and the oxygen and carbon dioxide concentrations in the incoming and outgoing air using the Omnicol system at the Maastricht University, The Netherlands and the CareFusion, Respiratory Diagnostics, SensorMedics Vmax Encore at the Antwerp University Hospital, Belgium. The Omnicol was calibrated daily and validated weekly using methanol burns. The CareFusion was

calibrated before every measurement. BMR was calculated from oxygen consumption and carbon dioxide production using Weir's equation (Weir 1949). Once TEE and BMR were known, PAL was calculated as TEE/BMR (Human energy requirements. Scientific background papers from the Joint FAO/WHO/UNU Expert Consultation, October 17–24 2001, Rome, Italy 2005).

Physical activity was also assessed using a Direct Life tri-axial accelerometer for movement registration (Tracmor<sup>®</sup>) (Philips New Wellness Solutions; <http://www.directlife.philips.com>) (Bononi et al. 2010; Hoos et al. 2003a). The Tracmor has been developed at the department of Human Biology at the University of Maastricht. It has proved to be an objective and reliable tool for assessing activity levels in free-living subjects (Westertep 1999b). In contrast to other accelerometers, Tracmor was miniaturized to a small ( $3.2 \times 3.2 \times 0.5$  cm) and light (13 g) device, which is important for the subject's comfort (Westertep 2001). The Tracmor<sup>®</sup> was placed at the lower back of the child using an elastic belt. The child was instructed to wear the accelerometer during daytime. At the end of the monitoring period the Tracmor<sup>®</sup> was connected to a personal computer and the recorded data were downloaded using dedicated software. Tracmor<sup>®</sup> output was expressed as activity counts/minute. The Tracmor<sup>®</sup> activity counts/minute were summed over the entire monitoring period and divided by the number of monitoring days to determine the average Tracmor<sup>®</sup> counts per day (Cnts/d).

Activity related energy expenditure (AEE) was calculated as  $(0.9 \times \text{TEE}) - \text{BMR}$ , assuming a diet-induced thermogenesis (DIT) of 10% (Westertep 2004).

### Statistical analysis

The variables are reported as the mean  $\pm$  SD. A Shapiro–Wilk test was used to test for the normal distribution. Differences between groups were tested with a *t* test when the distribution of data was normal, and with a Mann–Whitney *U* test otherwise. Significance is considered at the 5% level ( $p < 0.05$ ). IBM SPSS statistics<sup>®</sup> (version 21) was used for all statistical analyses.

### Results

Eighteen subjects were enrolled. The ventilated hood method was used in all subjects for BMR measurements. The doubly labelled water method was used in all subjects for TEE and body composition measurements. Unfortunately, due to technical problems, the ventilated hood results of 6 subjects were unusable. Therefore, we have BMR results of 12 subjects and TEE and body composition results of 18 subjects.

### Background and baseline characteristics

The background and baseline auxological characteristics of 18 children (5 girls, 13 boys) born SGA ( $n = 14$ ) or with idiopathic GHD ( $n = 4$ ) who started GH treatment are listed in Table 1.

The children started GH treatment at a mean age of 6.4 years and a mean height of  $-2.92$  SD. They were short for their parents (height SDS minus MPH SDS  $-2.00$ ). There was no significant difference between girls and boys.

### Body composition

The body composition of 18 children before and after 6 weeks of GH treatment is given in Table 2. There was a significant increase in body weight after 6 weeks of GH treatment. The increase in TBW ( $0.7 \pm 0.4$  L; 95% CI 0.45–0.86;  $p < 0.001$ ) and FFM ( $0.9 \pm 0.5$  kg; 95% CI 0.6–1.1;  $p < 0.001$ ) after 6 weeks of GH treatment was significant. There was no significant difference between girls and boys. Figure 1 illustrates the changes in TBW and FFM for each individual subject.

**Table 1** Subject characteristics

	<i>n</i>	Mean	SD
Gestational age, weeks	17	36.5	3.2
Birth weight, SDS	17	-2.02	1.22
Birth length, SDS	15	-2.18	1.30
Father height, SDS	18	-0.9	1.20
Mother height, SDS	18	-0.86	1.06
MPH, SDS	18	-0.92	0.82
At start GH treatment			
Age, years	18	6.4	1.5
Height, SDS	18	-2.92	0.85
Height SDS minus MPH SDS	18	-2.00	0.81
Weight, SDS	18	-2.51	1.07
BMI, SDS	18	-0.52	0.89
Pretreatment HV, SDS <sup>a</sup>	4	-0.9	0.7
Bone age delay, years <sup>a</sup>	4	1.7	1.1
IGF-1, SDS <sup>a</sup>	4	-2.1	0.3
Maximum GH peak, mIU/L <sup>a</sup>	4	16.6	0.3
GH dose, $\mu\text{g}/\text{kg}$ day	18	35.5	4.4
After first-year GH treatment			
Height, SDS	18	-2.15	0.81
$\Delta$ height, SDS	18	0.73	0.37

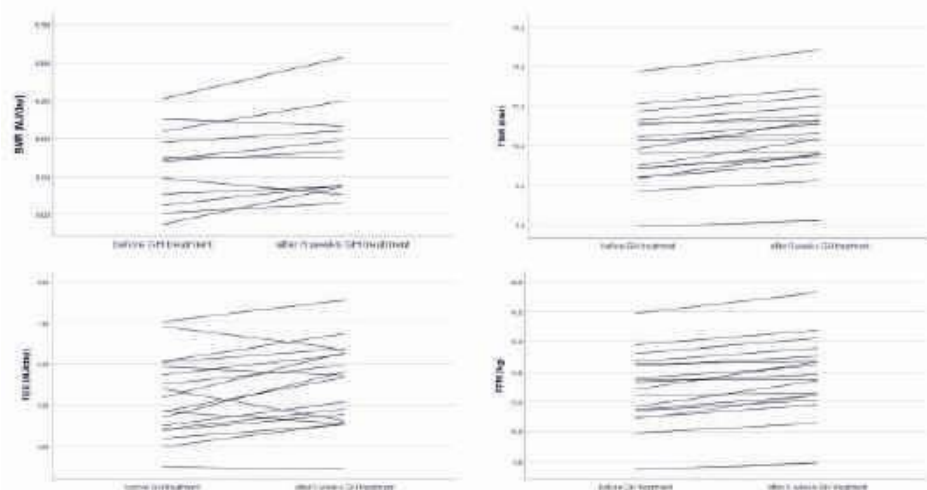
MPH midparental height, GH growth hormone, BMI body mass index, HV height velocity, IGF-1 insulin like growth factor 1,  $\Delta$  height SDS increase in height SDS during first-year GH treatment

<sup>a</sup>Data only of GHD patients

**Table 2** Body composition before and after 6 weeks of GH treatment

	n	Before GH treatment		After 6 weeks GH treatment		Delta			p value
		Mean	SD	Mean	SD	Mean	SD	95% CI	
Body weight, kg	18	16.7	3.4	17.1	3.4	0.5	0.6	0.2 to 0.8	< 0.05
BMI, SDS	18	-0.52	0.89	-0.43	0.81	0.08	0.26	-0.10 to 0.27	n.s.
TBW, L	18	9.9	1.8	10.6	1.9	0.7	0.4	0.5 to 0.9	< 0.001
FFM, kg	18	12.9	2.4	13.7	2.5	0.9	0.5	0.6 to 1.1	< 0.001
FFM, %	18	77.7	5.1	80.5	5.4	2.8	4.3	0.6 to 4.9	< 0.05
FM, kg	18	3.8	1.5	3.4	1.4	-0.4	0.8	-0.84	n.s.
FM, %	18	22.3	5.1	19.5	5.4	-2.8	4.3	-4.9 to -0.6	< 0.05

GH growth hormone, BMI body mass index, TBW total body water, FFM fat free mass, FM fat mass, n.s. not significant, delta value of parameter after 6 weeks of GH treatment minus value of parameter before GH treatment



**Fig. 1** Changes in total body water (TBW), fat free mass (FFM), basal metabolic rate (BMR), and total energy expenditure (TEE) after 6 weeks of growth hormone (GH) treatment for each individual subject

### Energy expenditure

Energy expenditure before and 6 weeks after GH treatment is given in Table 3. After 6 weeks of GH treatment there was a significant mean increase of 5% in BMR [mean increase  $0.18 \pm 0.23$  MJ/day ( $43 \pm 55$  kcal/day); 95% CI 0.03–0.32 MJ/day ( $7–76$  kcal/day);  $p < 0.05$ ;  $n = 12$ ]. There was no significant difference between girls and boys.

TEE also increased significantly (7%) after 6 weeks of GH treatment [mean increase  $0.33 \pm 0.52$  MJ/day ( $79 \pm 124$  kcal/

day); 95% CI 0.07–0.59 MJ/day ( $17–141$  kcal/day);  $p < 0.05$ ].

The increase in BMR was not significantly different from the increase in TEE [difference =  $0.24 \pm 0.67$  MJ/day ( $57 \pm 160$  kcal/day);  $p = 0.249$ ;  $n = 12$ ].

Figure 1 illustrates the changes in BMR and TEE for each individual subject.

The BMR, estimated by the Oxford formula (Henry 2005) was not significantly different from the observed BMR measured by the ventilated hood method before start of GH treatment.



**Table 3** Energy expenditure before and after 6 weeks of GH treatment

	n	Before GH treatment		After 6 weeks GH treatment		Delta			p value
		Mean	SD	Mean	SD	Mean	SD	95% CI	
BMR, MJ/day (kcal/day)	12	3.65 (872)	0.51 (122)	3.82 (912)	0.57 (136)	0.18 (43)	0.23 (55)	0.03 to 0.32 (7 to 76)	<0.05
TEE, MJ/day (kcal/day)	18	5.17 (1235)	0.98 (234)	5.51 (1316)	1.02 (244)	0.33 (79)	0.52 (124)	0.07 to 0.59 (17 to 141)	<0.05
AEE, MJ/day (kcal/day)	12	0.87 (208)	0.45 (107)	1.07 (256)	0.66 (158)	0.19 (45)	0.62 (148)	-0.20 to 0.59 (-48 to 141)	n.s.
PAL	12	1.37	1.13	1.43	0.20	0.05	0.19	-0.07 to 0.17	n.s.
Physical activity, mega-counts/day	12	2706	531	2803	457	-265,240	563,400	-736,254 to 205,775	n.s.

GH growth hormone, BMR basal metabolic rate, TEE total energy expenditure, AEE activity energy expenditure, PAL physical activity level, n.s. not significant, delta value of parameter after 6 weeks of GH treatment minus value of parameter before GH treatment

There was no significant increase in AEE, PAL and Tractor counts per day.

The mean respiratory quotient (RQ) before GH treatment was 0.82; 6 weeks after GH treatment 0.84. This was not significantly different.

#### Energy expenditure in relation to body composition

BMR was strongly related to FFM before start of GH treatment ( $r=0.92$ ,  $R^2=0.84$ , linear equation:  $y=1.21+0.2\times x$ ). After 6 weeks of GH treatment this relation was similar ( $r=0.76$ ,  $R^2=0.58$ , linear equation:  $y=1.49+0.18\times x$ ).

The change in TBW, FFM and FM was not related to the change in BMR and TEE ( $r\leq 0.1$ ,  $R^2\leq 0.01$ ).

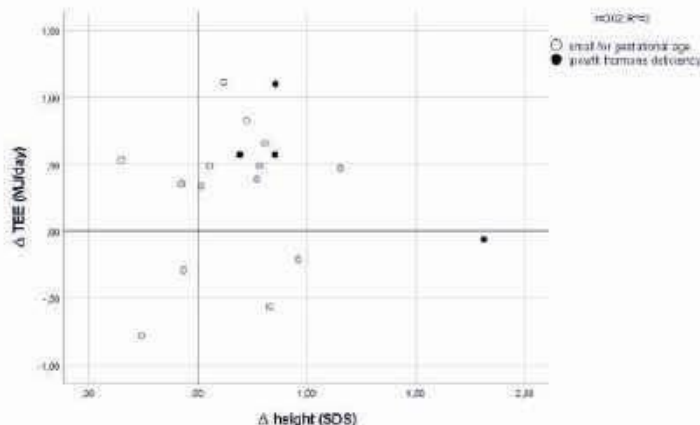
#### Energy expenditure in relation to first-year growth response

After the first year of GH treatment mean height was  $-2.15$  SD. The mean increase in height ( $\Delta$ Ht) SDS was 0.73 SD. Fourteen out of 18 patients (78%) had a good growth response ( $\Delta$ Ht SDS  $> 0.5$ ).

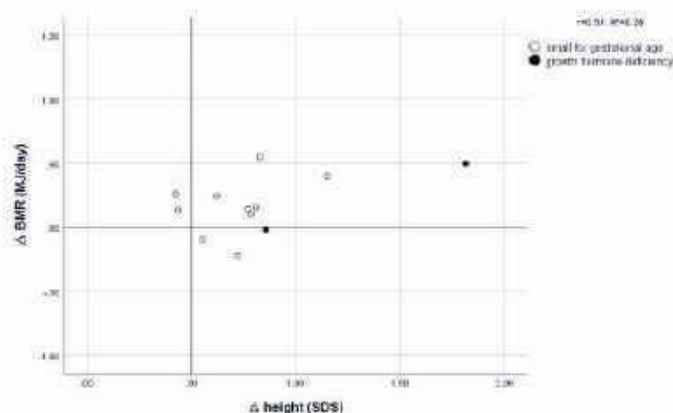
Thirteen out of 18 patients had an increased TEE after 6 weeks of GH treatment. Figure 2 shows that 11 out of these 13 patients (85%) had a good growth response after 1 year of GH treatment. For BMR and AEE this was 7 out of 9 patients and 8 out of 9 patients, respectively ( $n=12$ ) (Figs. 3, 4).

The children with no increase in TEE had varying growth responses and the few patients with poor growth response (4/18) showed varying responses in TEE.

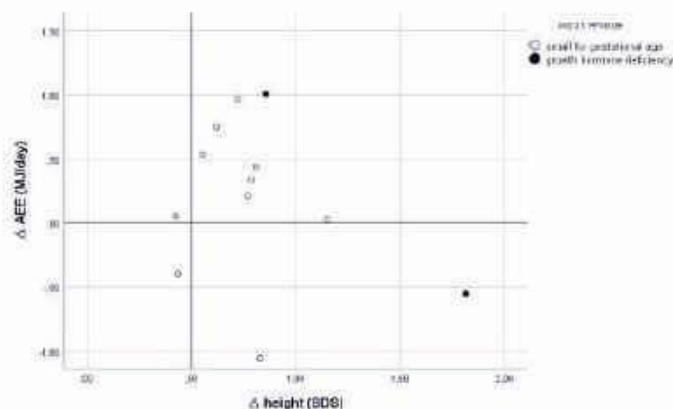
**Fig. 2** Effect of growth hormone treatment on total energy expenditure (TEE) in relation to first-year changes in height SDS ( $\Delta$ Ht SDS)



**Fig. 3** Effect of growth hormone treatment on basal metabolic rate (BMR) in relation to first-year changes in height SDS ( $\Delta$ Ht: SDS)



**Fig. 4** Effect of growth hormone treatment on activity related energy expenditure (AEE) in relation to first year changes in height SDS ( $\Delta$ Ht: SDS)



GH dose was not related to  $\Delta$ TEE ( $r=0.19$ ,  $R^2=0.04$ ) and  $\Delta$ height SDS ( $r=0.12$ ,  $R^2=0.02$ ).

## Discussion

This study shows that 6 weeks of GH treatment has a positive effect on energy expenditure and body composition in children. Body composition changed by an increase in FFM as was demonstrated before in several studies (Ernst et al. 2012; Vaisman et al. 1992, 1994; Gregory et al. 1991, 1993; Walker et al. 1990; Khadifkar et al. 2014; Boot et al. 1997; Hassan et al. 1996). At the same time, total energy

expenditure, measured by the DLW technique and energy expenditure at rest, measured by the ventilated hood method, showed an increase by 7% and 5% respectively. These results are comparable with the few other studies performed. Vaisman et al. (1994) showed a 13% increase in BMR after 2 months of GH treatment in 10 prepubertal boys with subnormal spontaneous GH secretion, and remained stable thereafter. Gregory et al. (1991) demonstrated a significant increase in BMR (12%) and TEE (7%) after only 6 weeks of GH treatment in 15 children (GHD, idiopathic short stature, Turner syndrome).

No relation between  $\Delta$ FFM or  $\Delta$ FM and  $\Delta$ BMR or  $\Delta$ TEE was observed. This is probably due to the relatively small



cohort size and the dispersion of the data. Another explanation might be the relatively long observation period of 6 weeks, since the anabolic effect of GH, indicated by nitrogen retention increases within 24 h and reaches a maximum less than 2 weeks after initiation of treatment, followed by a gradual return of nitrogen excretion toward control levels after 2–3 weeks (Henneman and Henneman 1960). Gregory et al. (1991) found that the increase in BMR was significantly associated only with fat mass and not with fat free mass.

The RQ did not significantly change during GH treatment. However, based on the knowledge that GH increases lipid oxidation and decreases glucose oxidation, and based on the few available literature a decrease of the RQ would have been expected. Acute suppression of RQ during GH infusion has been reported (Jorgensen et al. 1993; Moller et al. 1990) and an increase in RQ following successful transphenoidal surgery in acromegalic patients has been described (Moller et al. 1992b). Additionally, a more prolonged subcutaneous GH administration caused a decreased RQ in adults (Jorgensen et al. 1994; Moller et al. 1992a). To our knowledge, only one report described the effect of subcutaneously administered GH on RQ in children (Carrel et al. 1999). In 35 children with Prader Willi syndrome the RQ decreased after 12 months of GH treatment. We have no clear explanation why the RQ in our cohort did not decrease after 6 weeks of GH treatment.

Hoos et al. (2004) found that children who respond well to GH therapy ( $\Delta$ Ht SDS > 0.7) showed increased physical activity after 2 weeks of therapy as assessed with a tri-axial accelerometer. In contrast, in our study we observed no increase in PAL, Tracmor counts/day, nor in AEE after 6 weeks of GH treatment. Gregory et al. (1991) also concluded that GH has no discernible effect on activity levels. Therefore, it is reasonable to assume that GH has no effect on activity levels in children and that the increased energy expenditure is mainly used to increase metabolism in favour of growth.

We observed that 11 out of 13 children with an increased TEE had a good first-year growth response. On the other hand, good and poor first-year growth responders were indistinguishable from each other when TEE did not increase. Based on these results, the increase in TEE is not a tool to detect poor growth responders, but is very predictive for a good first-year growth response to GH treatment ( $\Delta$ Ht SDS > 0.5).

GH dose could be a possible cause for the differences in growth response, since it has been proven that GH dose affects height velocity during the first treatment year (Ranke 2003). However, GH dose does not explain the variations in first-year growth and  $\Delta$ TEE in our cohort because our patients received the same dose throughout the whole first treatment year (SGA 35 mcg/kg/day and GHD 25 mcg/kg/

day, according to the guidelines), except for 2 patients. As far as we know, the patients were compliant to the GH treatment. Other parameters known to be predictive for first-year height velocity such as age and weight at start of GH treatment, midparental height SDS, and birth weight SDS (Ranke 2009) were not significantly different between our good and poor growth responders.

The actual cause-effect relationship between TEE and growth can not be proven from this data. However, the most prominent metabolic effect of GH is a marked increase in lipolysis with mobilization of large quantities of free fatty acids from the adipose tissue. In addition, in the tissues throughout the body GH enhances the conversion of these fatty acids to acetylcoenzyme A which is used to supply most of the energy for the body cells, thus acting as a potent “protein sparer”. Some research workers have considered the protein-sparing effect to be a major factor that promotes protein deposition and growth (Black et al. 1986). Therefore, it is plausible to assume that an increased TEE leads to growth.

In conclusion, GH treatment showed a positive effect on body composition and energy expenditure in prepubertal children after 6 weeks of treatment. Despite these positive changes we were not able to demonstrate a relation between the increases in both effects of GH. No effect on physical activity was observed. Increase in TEE appeared to be valuable for the prediction of good growth responders to GH treatment.

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**Author contribution** SS, DAS, and W-JMG conceived and designed research. SS, AJGMG-J, and AV conducted experiments. SS, GP, KW, and W-JMG analyzed data. SS, W-JMG, HD, and LJIZ wrote the manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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### Compliance with ethical standards

**Conflict of interest** The funding organization played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

**Data availability statement** The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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## Chapter 4

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Reference curve for the first-year growth response to growth hormone treatment in prepubertal children with idiopathic growth hormone deficiency: validation of the KIGS first-year growth response curve using the Belgian Register for the study of growth and puberty problems



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## Reference Curve for the First-Year Growth Response to Growth Hormone Treatment in Prepubertal Children with Idiopathic Growth Hormone Deficiency: Validation of the KIGS First-Year Growth Response Curve Using the Belgian Register for the Study of Growth and Puberty Problems

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### Key Words

Growth hormone deficiency · Growth response · Growth targets · Growth hormone therapy

### Abstract

**Background:** Comparing observed and expected growth after first-year growth hormone (GH) therapy is useful for identifying a poor growth response to GH. **Aim:** To generate a first-year, age-specific growth response reference curve for prepubertal Belgian children with idiopathic growth hormone deficiency (iGHD) treated with a standard weight-adjusted GH dose and to compare this national reference with the response references derived from KIGS. **Subjects and Methods:** First-year height data of 357 prepubertal children (240 males) with iGHD were analyzed. Smooth reference curves of first-year height velocity (HV) in relation to age were created. Differences with the KIGS targets were evaluated after z-score transformation. **Results:** The observed first-year

HVs were log-normal distributed by age and decreased significantly with age ( $p < 0.001$ ). No GH dose or gender effect was observed ( $p = 0.5$ ). Distance to target height, severity of GHD and occurrence of multiple pituitary hormone deficiencies had a positive effect ( $p < 0.01$ ) on the calculated HV SDS. When applying the KIGS targets for severe iGHD, mean HV SDS was close to zero ( $-0.09 \pm 0.84$ ). **Conclusion:** The developed age-specific growth response curves enable rapid identification of poor response to first-year GH treatment in prepubertal iGHD children. Our results validate the published growth targets derived from the KIGS database.

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### Introduction

Growth hormone deficiency (GHD) is found in 1/3,000 to 1/10,000 children [1]. In Belgium, about 30 patients with GHD are diagnosed yearly. As in other countries, in

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the majority of patients there is no specific cause so they are classified as idiopathic GHD (iGHD) [2, 3]. Since 1986, iGHD children have been treated in most European countries with biosynthetic growth hormone (GH), albeit with different dosing regimens. In Belgium the standard treatment consists of a daily GH dose of 25 µg/kg body weight.

The growth response during the first year of GH treatment is highly important, since it is the major determinant of the height gain during the subsequent years and it correlates with the adult height achieved [2–8]. From the early years of GH therapy, a significant variability in the early growth response between iGHD subjects was observed, even when the biosynthetic form of GH was administered by daily subcutaneous injections with a pen device. Several factors were found to predict the early growth response to GH. Most of these parameters are already known at the start of GH therapy, such as age at start of treatment, the severity of GHD (maximum GH serum levels in stimulation tests and/or serum levels of insulin-like growth factors (IGF) and their binding proteins (IGFBP)), birth weight, weight at start of treatment, GH dose, midparental height and bone age retardation. Markers of bone resorption (e.g. urinary levels of deoxypyridinoline) and serum IGF-1 concentration during the first months of GH therapy are also of predictive value. Based on these specific patient characteristics and treatment modalities, mathematical models for predicting the short-term response have been developed, explaining 61–89% of the variability in observed first-year growth response [9–13]. However, prediction models, including the most widely known KIGS models, may suffer from overfitting, which results in predictions that are too low or too high [14, 15].

Furthermore, these mathematical models are rarely used in clinical practice because often not all of the various parameters needed for the calculation are available and calculation software programs are not easily accessible. In addition, its utility can be questioned for the management of children with GHD, given the limitation of GH dose adaptation in this specific indication (GH is given as a stable weight-adjusted hormonal substitution therapy) and the specific therapeutic aims of GH in this particular growth disorder (correction of a disturbed body composition and metabolic disturbances). However, a comparison of observed growth and expected growth after the first year of GH therapy is useful for rapid identification of a suboptimal growth response, possibly caused by poor compliance, improper administration of GH, additional health problems, poor nutrition, impaired

GH sensitivity due to mutations in the GH-IGF-1 axis genes, or incorrect diagnosis.

Recently, growth response targets, based on the percentile distribution of height velocity during the first year of GH therapy, have been developed from height data in large post-marketing surveillance databases (respectively the NCGS and KIGS database) of prepubertal children with different growth disorders, including iGHD [16, 17]. In Europe, the NCGS targets are of limited value in the evaluation of iGHD children since GH doses prescribed in the United States are up to 50% higher than in Europe. Furthermore, up to now, the KIGS growth targets have not been validated in European countries.

Therefore, the aim of the present study was to generate a country-specific reference curve for prepubertal children with iGHD treated with a standard weight-adjusted GH dose and to compare these with the published KIGS growth targets [17].

## Patients and Methods

### Patients

The relevant auxological data and treatment characteristics of prepubertal children diagnosed with iGHD, who were enrolled in the Belgian Register for the Study of Growth and Puberty Problems since 1986, were retrieved. Informed consent is secured prior to entry in the Register and anonymous use of the data complies with rigorous privacy guidelines. Only prepubertal patients, who had been treated exclusively with recombinant human GH on a daily regimen for at least 1 year and remained prepubertal, defined as testicular volumes <4 ml for boys and Tanner breast stage 1 for girls, during the whole observation year, were included. The diagnosis of iGHD was made by the treating physician according to the KIGS etiology classification system [18]. Patients with and without developmental anatomical anomalies of the pituitary were included. All patients had a peak GH concentration of  $\leq 10$  µg/l. In total, 358 patients with iGHD met the inclusion and exclusion criteria. Only 1 patient was excluded for outlying growth data.

### Methods

First-year height velocity (HV) (cm/year) was calculated as the increment in height between start and after minimum 9 months and maximum 15 months of GH therapy and subsequently scaled to a whole year. Smooth reference curves for the first-year HV were constructed with the LMS method with penalized likelihood [19]. The LMS method removes skewness from the data with a power transformation and summarizes the distribution of HV by age in three smooth curves, the power transform to remove skewness (L), the median (M) and the coefficient of variation (S). The degree of smoothing was determined by the deviance criterion, worm plot and Q-tests [20]. For each subject an age-related HV SDS was calculated as observed value minus median value of the study population divided by standard deviation value of the study population to study the effect of gender, type and severity of GHD. For the validation of the KIGS first-year growth response curve,

**Table 1.** Characteristics: background, at GH start, after 1 year

	iGHD					
	n	mean	SD	median	p10	p90
<b>Background</b>						
Birth weight, SDS	342	-0.75	1.20	-0.70	-2.22	0.70
Father height, SDS	344	-1.10	1.21	-1.17	-2.55	0.49
Mother height, SDS	346	-0.98	1.24	-0.97	-2.63	0.57
MPH, SDS	344	-1.29	1.24	-1.33	-2.84	0.22
Maximum GH peak, µg/l	357	4.9	2.65	4.8	1.2	8.5
<b>At start GH treatment</b>						
Age, years	357	6.6	3.0	6.4	2.3	10.7
Height, SDS	357	-3.45	0.99	-3.36	-4.71	-2.46
Height SDS-MPH SDS	344	-2.15	1.47	-2.06	-3.95	-0.49
Weight, SDS	347	-2.80	1.44	-2.65	-4.64	-1.29
BMI, SDS	347	-0.32	1.17	-0.35	-1.82	1.11
GH dose, µg/kg-day	345	27.6	5.1	26.5	22.4	34.9
<b>After 1 year GH treatment</b>						
Height, SDS	357	-2.54	0.88	-2.45	-3.58	-1.54
Height-MPH SDS	344	-1.24	1.28	-1.18	-2.69	0.22

HV SDS of the subjects was calculated using the KIGS reference data [17].

The other variables retrieved from the registry were (a) status at birth: sex, birth weight and length SDS; (b) genetic background: midparental height (MPH) SDS; (c) patient variables at the start of the treatment period: chronological age, height (Ht) SDS, weight (Wt) SDS, body mass index (BMI) SDS, the highest peak GH concentration of two provocation tests, the presence of other pituitary hormone deficiencies, and (d) treatment modality: average GH dose (µg/kg-day) during the first year of GH treatment.

GHD was defined as isolated if no other pituitary hormone deficiencies and multiple if other deficiencies were present at start or during the first year of GH therapy. For defining severe or less severe GHD, a cut-off value of 5 µg/l of the peak GH at provocation was used.

Birth weight for gestational age was transformed into SDS, based on the standards of Niklasson et al. [21]. The MPH SDS was calculated as follows: (father's Ht SDS + mother's Ht SDS)/1.61 [22, 23]. Height, weight and BMI were converted to SDS using Belgian reference data by Roelants et al. [24].

#### Statistical Analysis

The variables are reported as the median (10–90th percentile) and mean (±SD). A one-sample Kolmogorov-Smirnov test was used to test for the normal distribution. Differences between groups were tested with a t test when the distribution of data was normal, and with a Mann-Whitney U test otherwise. Whenever adjustment for other factors was required, group means were compared with a general linear model. Results of simple and multiple linear regression analysis are expressed as unadjusted and adjusted regression coefficients (B) with the standard error of the estimate. Significance was considered at the 5% level ( $p < 0.05$ ). IBM SPSS Statistics 19<sup>®</sup> software was used for all statistical analyses.

**Table 2.** Observed growth changes after first-year GH treatment

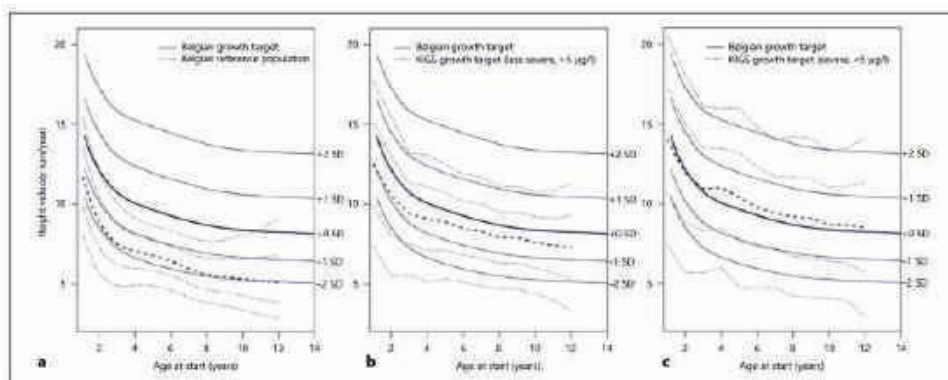
	iGHD					
	n	mean	SD	median	p10	p90
ΔHt SDS <sup>1</sup>	357	0.91	0.59	0.76	0.33	1.64
HV, cm/year	357	9.8	2.5	9.4	6.8	13.2

<sup>1</sup> Gain in height SDS after first-year GH treatment.

## Results

Background and auxological characteristics of the 357 included children (240 males, 117 females) at start of GH treatment are listed in table 1. Their age ranged from 1.2 to 14 years. 66 (19%) of the 347 patients with available birth data were small for gestational age (SGA) (birth weight and/or length  $< -2$  SDS) and 1 was large for gestational age ( $> 2$  SDS). In total, 68 (20%) of the fathers and 59 (17%) of the mothers with available height data had a stature  $< -2$  SD. The median GH peak concentration after provocation was 4.8 µg/l and ranged between 0.2 and 10 µg/l. The median first-year GH dose for the whole group was 27.1 µg/kg-day, the 10th and 90th percentiles were 22.7 and 34.3 µg/kg-day, respectively.

Observed growth changes after the first year of GH treatment are shown in table 2. The HVs were found to



**Fig. 1.** Comparison of HV (cm/year) in prepubertal children with iGHD during the first-year GH treatment as a function of the age at start of GH treatment with HV in the Belgian 'normal' population (a), and with the KIGS growth targets for less severe GHD (b) and severe GHD (c).

be log-normal distributed by age. Smooth reference curves of the HV after the first year of GH treatment in relation to age at start of treatment are shown in figure 1a and the corresponding age-specific growth targets are listed in table 3.

The mean HV SDS was not significantly different between boys ( $0.01 \pm 0.98$ ) and girls ( $-0.08 \pm 1.31$ ) ( $p = 0.5$ ). Mean HV (cm/year) decreased significantly with age from 12.1 cm/year at 2 years to 8.3 cm/year at 12 years ( $p < 0.001$ ). The distance between the median and the +1 and -1 SD lines (around 2.5 and 2 cm respectively) decreased with  $< 0.2$  cm between the ages of 2 and 12 years. As shown in figure 1a, the -1 SD line of HV of iGHD children after first-year GH treatment was around the +1 SD line of HV of the Belgian reference growth curve.

When applying the KIGS targets for severe iGHD (GH peak  $< 5 \mu\text{g/l}$ ) on our population of severe GHD ( $n = 177$ ), the mean HV SDS was significantly higher than zero ( $0.22 \pm 0.86$ ; 95% CI 0.09 to 0.35). No significant difference was noted for the mean HV SDS ( $0.14 \pm 0.98$ ; 95% CI  $-0.01$  to 0.29) when applying the KIGS targets for less severe iGHD (GH peak 5–10  $\mu\text{g/l}$ ;  $n = 169$ ). There was no age dependence. The distribution of SD scores according to the KIGS targets shows some positive skewness, which confirms the log-normal model used by us. When applying the KIGS response targets for severe iGHD on our whole study population, mean HV SDS was  $-0.09 \pm 0.84$ . While using the KIGS targets for less severe iGHD, mean

**Table 3.** HV (cm/year) during the first year of GH treatment in prepubertal children with iGHD according to age at onset of GH treatment

Age years	L	M	S	-2 SD	-1 SD	Mean	+1 SD	+2 SD
1.2	0	14.24	0.155	10.4	12.2	14.2	16.6	19.4
1.5	0	13.30	0.165	9.6	11.3	13.3	15.7	18.5
2.0	0	12.14	0.177	8.5	10.2	12.1	14.5	17.3
3.0	0	10.74	0.196	7.3	8.8	10.7	13.1	15.9
4.0	0	10.07	0.208	6.6	8.2	10.1	12.4	15.3
5.0	0	9.64	0.216	6.3	7.8	9.6	12.0	14.9
6.0	0	9.28	0.222	5.9	7.4	9.3	11.6	14.5
7.0	0	8.97	0.226	5.7	7.1	9.0	11.2	14.1
8.0	0	8.70	0.230	5.5	6.9	8.7	11.0	13.8
9.0	0	8.51	0.232	5.3	6.7	8.5	10.7	13.5
10.0	0	8.39	0.234	5.3	6.6	8.4	10.6	13.4
11.0	0	8.31	0.236	5.2	6.6	8.3	10.5	13.3
12.0	0	8.25	0.237	5.1	6.5	8.3	10.5	13.3
13.0	0	8.20	0.238	5.1	6.5	8.2	10.4	13.2
14.0	0	8.16	0.239	5.1	6.4	8.2	10.4	13.2

HV SDS was  $0.61 \pm 1.19$ . In figure 1b and c, the KIGS targets for iGHD are superimposed on our calculated targets.

Linear regression analysis shows that age, sex, and GH dose have no significant effect on the first-year HV SDS, while distance to target height ( $< -0.8$  SD), severe GHD, and multiple pituitary hormone deficiency (MPHD) each



**Table 4.** Predictors of growth response to treatment with GH according to the Belgian response targets: unadjusted simple linear regression and adjusted multiple regression analysis<sup>1</sup>

	Unadjusted univariate regression coefficients (B) (standard error of the estimate)	Adjusted regression coefficients of multiple regression (B) (standard error of the estimate)
Height SDS at start	-0.23 (0.05)***	-0.17 (0.05)***
Distance to target height <-0.8 SDS <sup>2</sup>	0.63 (0.15)***	0.37 (0.14)**
MPHD	0.57 (0.12)***	0.35 (0.11)**
Severe GHD (GH peak ≤5 µg/l)	0.74 (0.10)***	0.54 (0.10)***
SGA <sup>3</sup>	-0.35 (0.14)***	-0.33 (0.13)**

<sup>1</sup> Age at start, sex and GH dose were also included in the analysis, but were not found to be significant ( $p > 0.05$ ) and were removed from the model with backward selection.

<sup>2</sup> Height SDS at start-MPH SDS <-0.8.

<sup>3</sup> Ten subjects with insufficient data were included as a separate category, but were not significantly different from children without SGA.

\*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

have a positive effect ( $p < 0.01$ ), and SGA and height SDS at start have a negative effect ( $p < 0.01$ ) on HV SDS in both simple and multiple linear regression analysis (table 4).

Children with MPHD ( $n = 83$ ; 23% of total) showed a significantly higher mean growth response than children with isolated GHD ( $n = 274$ ) (HV SDS:  $0.44 \pm 1.04$  vs.  $-0.13 \pm 0.95$ ;  $p < 0.0001$ ). Children with severe GHD (peak GH  $\leq 5$  µg/l;  $n = 188$ ) had a higher mean growth response than children with less severe GHD (peak GH  $> 5$  µg/l;  $n = 169$ ) (HV SDS  $0.34 \pm 0.98$  vs.  $-0.38 \pm 0.88$ ;  $p < 0.0001$ ). There was no significant difference in age at start, sex and GH dose. The differences persisted after correction for height at start, distance to target height, SGA and severity of GHD ( $p < 0.01$ ).

## Discussion

We constructed a smooth curve for the first-year growth response to GH (mean,  $\pm 1$  and  $\pm 2$  SD) as a function of the age at start of GH therapy from the data of prepubertal children with iGHD retrieved from the Belgian Registry, Bakker et al. [16] and Ranke et al. [17] were the first to develop first-year expected HV targets for GHD and other growth disorders treated with GH. Ranke et al. used the data available in the KIGS database from European countries, combined data from males and females and differentiated for severe and less severe iGHD, whereas Bakker et al. used the NCGS data from North America and differentiated for gender and for organic

GHD and iGHD. The higher HV reference curves found in the NCGS study for GHD patients can be explained by the 28% higher GH doses used in the USA (mean GH dose 43 vs. 31 µg/kg/day). Our data do not differ much from the published KIGS targets for less severe GHD, despite the use of different cohorts and smoothing algorithms applied. For severe GHD, our targets are statistically significantly higher ( $p < 0.05$ ), but the clinical effect is rather small (mean HV of 0.22 SDS instead of the expected 0 SDS).

In accordance with most studies evaluating the early growth response to GH in iGHD, gender did not influence the prepubertal growth response to the standard GH therapy [10–13, 17]. Therefore, the same curve can be used for both boys and girls.

We did observe a greater first-year GH response in children with MPHD compared to isolated GHD. This difference persisted after correction for the severity of GHD, age, height at start, MPHD, distance to target height and SGA. This finding is in contrast to the few other studies that have compared the growth response during the first year of GH treatment in prepubertal children with MPHD and isolated GHD. Lee et al. [3] found a comparable growth response in prepubertal children with MPHD and isolated GHD when studying the auxological data of two ongoing prospective worldwide observational studies, including 1,120 and 165 children with respectively isolated GHD and MPHD. A study of the KIGS database by Ranke et al. [25] showed a similar height gain in prepubertal children with idiopathic

MPHD and isolated iGHD after first-year GH treatment. We cannot explain the greater response in our MPHHD group, which persisted after corrections for differences in height at start and distance to target height. Concordant with our study, Darendeliler et al. [26] found a significantly ( $p < 0.001$ ) higher growth response in prepubertal children with MPHHD ( $n = 554$ ) compared to isolated GHD ( $n = 1,619$ ). The children with MPHHD in that study were significantly younger and shorter at start of GH treatment compared to those with isolated GHD. We do not know if the difference in growth response persisted after correction for influencing factors.

Additionally, we found that the first-year growth response to GH was higher in children with a more severe form of GHD, as reflected by the peak GH response after pharmacological stimulation. Because of the known great variability in GH responses to GH stimulation tests and the variation in GH results with different assays, we preferred to develop growth targets combining both severe and less severe GHD. These combined targets are slightly below the KIGS targets for severe iGHD. This can be explained by several factors: (1) the Belgian population also contains patients with less severe GHD, who in general have a poorer response to GH treatment, and (2) the mean GH dose at the start used in the Ranke study is higher (31.4 vs. 27.6  $\mu\text{g}/\text{kg}\cdot\text{day}$ , on average 12% higher). Compared to the KIGS targets for less severe iGHD, the response is higher in the Belgian data and the distribution is wider. This is more the case above the median than below, which confirms the log-normal distribution observed in the Belgian data.

The first-year growth response to GH was higher in children with a smaller stature at start, and a history of non-familial short stature, as previously observed by others [11, 12].

Our data also confirmed the observation by others [11, 27] that the growth response to GH is lower in iGHD children born SGA. It was therefore suggested to treat SGA-iGHD children with a higher dose than non-SGA-iGHD children. The SGA status therefore predominates over the GHD to predict the growth response.

The data from the BSGPE registry are not suitable to study the effect of the GH dose because the dose range that was used in the patients is very narrow due to a strict compliance with the BSGPE treatment protocols and reimbursement regulations in Belgium. Therefore, GH dose is a less important contributor for the prediction of growth response in children with iGHD in Belgium. It is therefore acceptable to compare a patient's growth response to references that do not take the GH dose into account.

Bakker et al. [16] and Ranke et al. [17] showed that the mean pretreatment HV curve approximates the mean  $-2$  SD curve for the first-year HV. Thus, the  $-2$  SD curve represents very little or no gain in HV, and the mean  $-1$  SD curve has been proposed as a reasonable cut-off for defining a poor response. In our opinion, to guarantee catch-up growth toward target height, the growth response should be at least 1 SD above the mean HV for normal growing children, which also corresponds to the  $-1$  SD curve for first-year HV (fig. 1a). We assume that the wider variation in HV observed in GH-treated children when compared to normal growing children is due to relatively large individual differences in response to GH therapy.

Our study has some limitations. Some children with a transient form of GHD may have been included in our analysis, since no systematic retesting was performed at the end of therapy. On the other hand, at the start of therapy all patients responded to strict criteria of GHD. Also no data on compliance are available in our study cohort. In general, compliance with GH injection is rather acceptable during the first years of therapy, especially in prepubertal children [28]. Finally, growth targets could not be established for children below the age of 1.2 years, but this population accounts for less than 2% of treated iGHD patients in Belgium.

In summary, the developed age-specific GH response curves can be used to evaluate the first-year growth response to GH treatment in prepubertal children with iGHD in Belgium. This growth response curve is easy to use in clinical practice, and enables the rapid identification of poor responders to GH treatment, defined by a growth response below  $-1$  SD. The observed growth responses in Belgian children validate the published KIGS targets for first-year growth response in children with iGHD.

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## Chapter 5

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Validation of prediction models for near adult height in children with idiopathic growth hormone deficiency treated with growth hormone – a Belgian Registry study



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Raoul Rooman. *Horm Res Paediatr.* 2016;86(3):161-16





## Validation of Prediction Models for Near Adult Height in Children with Idiopathic Growth Hormone Deficiency Treated with Growth Hormone: A Belgian Registry Study

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### Key Words

Growth hormone deficiency · Growth hormone therapy · Prediction model · Validation · Adult height

### Abstract

**Background/Aim:** To validate prediction models for near final adult height (nFAH) by Ranke et al. [Horm Res Paediatr 2013;79:51–67]. **Methods:** Height data of 127 (82 male) idiopathic growth hormone (GH)-deficient children, treated with GH until nFAH, were retrieved from the database of the Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED). nFAH was predicted after first-year GH treatment, applying prediction models by Ranke et al. Bland-Altman plots and Clarke error grid analyses were performed to assess clinical significance of the differences between observed and predicted nFAH. **Results:** In males, the predicted nFAH was higher than the observed nFAH (difference:  $0.2 \pm 0.7$  SD;  $p < 0.01$ ). In females, there was no significant difference. Bland-Altman analyses showed that the means of the differences between observed and predicted nFAH were close but not equal to zero, with overprediction for smaller heights and underprediction for taller heights. Clarke error grid analysis: in males, 59–61% of the predicted nFAH were within 0.5 SDS and 88% within 1.0 SDS from the observed

nFAH; in females, 40–44% of the predicted nFAH were within 0.5 SDS and 76–78% within 1.0 SDS from the observed nFAH. **Conclusion:** Ranke's models accurately predicted nFAH in females and overpredicted nFAH in males by about 1.5 cm. In most individuals, the predicted nFAH was within 1 SDS of observed nFAH. These models can be of help in giving realistic expectations of adult height.

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### Introduction

Children with a short stature and their parents have in general great expectations about the effect of growth hormone (GH) therapy on final height. In a Belgian study, 76% of parents of short small for gestational age children expected a gain in adult height of  $\geq 10$  cm when starting GH treatment [1]. A long-term negative impact on psychosocial functioning has been described in children when these high expectations are not met [2].

An accurate prediction of the treatment effect on final height at onset or within the first years of GH treatment may help clinicians to give parents and children more realistic expectations. A model that can predict the effect of GH treatment at the onset of therapy would be ideal in

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clinical practice. However, adult height outcome is strongly influenced by the first-year response to GH [3]. Therefore, adult height prediction becomes more accurate if this first-year response is included in the model. Furthermore, a clinically relevant prediction model should be preferentially based on readily available and standardized variables. It should not only explain a large fraction of the variability in treatment response, but must also be easy to use in clinical practice [3]. Lastly, the prediction model must have been validated in the cohort of interest [4, 5].

Ranke et al. [6] developed 2 prediction models for near final adult height (nFAH) in GH-deficient (GHD) patients after 1 year of GH treatment, based on the KIGS data, including, among other variables, the prediction of first-year growth (index of responsiveness).

We here describe the validation of Ranke et al.'s [6] final height prediction models with an independent cohort from the Belgian Registry.

## Patients and Methods

### Patients

The auxological data and GH treatment characteristics of children diagnosed with idiopathic GHD (iGHD) between 1987 and 2005, and who had attained nFAH, were retrieved from the Belgian Registry of GH-treated patients, which is administrated by the Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED), formerly known as the Belgian Study Group for Pediatric Endocrinology (BSGPE). The Registry stores only coded data, and informed consent was secured prior to entry of data in the registry.

nFAH was considered as the height obtained after uninterrupted GH treatment when height velocity (HV) was  $<2$  cm/year, calculated over a period of minimum 9 months, with a chronological age  $>17$  years in boys and  $>15$  years in girls or skeletal age  $>16$  years in boys and  $>14$  years in girls. The diagnosis of iGHD was made by the treating physician according to national guidelines and the KIGS Aetiology Classification System [7], including a HV below the 25th percentile, a low to low-normal IGF-1 concentration, a delayed bone age, and a peak GH concentration  $<20$  mU/l in 2 GH provocation tests (glucagon and insulin test). GHD was defined as isolated if no other pituitary hormone deficiencies were present at the start or during GH therapy. A peak GH response  $<10$  mU/l in both GH provocation tests was considered severe GHD. Both patients with and without developmental anatomical anomalies of the pituitary were included. Inclusion criteria were chosen to reflect the criteria used for the Ranke prediction model: (1) treatment with recombinant human GH on a daily, or 6 days a week, regimen for at least 4 consecutive years, and (2) a prepubertal status during the first year of treatment. Exclusion criteria were: (1) any medication or medical condition other than GHD that could interfere with the growth response to GH. In total, 127 patients (82 males and 45 females) with iGHD (90 with isolated GHD and 37 with multiple pituitary hormone deficiency, MPH) met all the inclusion and exclusion criteria.

### Methods

Variables retrieved from the register were (a) status at birth: gender, birth weight, and length; (b) midparental height (MPH); (c) patient variables at the start of the treatment period: chronological age, height, weight, body mass index (BMI), the highest peak GH concentration of two provocation tests, the presence of other pituitary hormone deficiencies; (d) treatment modality: average GH dose ( $\mu\text{g}/\text{kg}/\text{day}$ ) during the first year of GH treatment, and (e) outcome parameters: the nFAH, in centimeters and expressed as height SDS (Ht SDS), the total  $\Delta\text{Ht}$  SDS, calculated as the nFAH SDS minus Ht SDS at the start of GH therapy, and the final height relative to MPH as an index of achieving genetic height potential, calculated as nFAH SDS minus MPH SDS.

Birth weight for gestational age was transformed into SDS, based on the standards of Niklasson et al. [8]. Height, weight, BMI, and HV were converted to SDS using the Belgian reference data by Roelants et al. [9]. The MPH (SDS) was calculated as follows: (father's Ht SDS + mother's Ht SDS)/1.61 [10, 11]. For the validation of the prediction models, height at the start of GH treatment, father's height, and mother's height were converted to SDS using reference data by Prader [12].

Observed first-year HV (cm/year) was calculated as the increment in height between the start of treatment and a measurement made after minimum 9 months and maximum 15 months of GH therapy, subsequently scaled to 12 months. Predicted first-year HV (cm/year) was calculated using the tool that can be found at [www.growthpredictions.org](http://www.growthpredictions.org), which uses the KIGS first-year prediction models [13]. Studentized residuals (SR) were calculated as follows: SR with GH peak:  $[\text{observed HV (cm/year)} - \text{predicted HV (cm/year)}]/1.46$ , and SR without GH peak:  $[\text{observed HV (cm/year)} - \text{predicted HV (cm/year)}]/1.72$ .

Predicted nFAH was calculated according to the Ranke model derived from the KIGS database [6]. There are 2 prediction formulas, as follows: the first one includes the maximum GH level during a GH provocation test and uses the following equation:  $\text{nFAH SDS} = 2.34 + [0.34 \times \text{MPH, SDS (Prader)}] + [0.18 \times \text{birth weight, SDS}] + [0.59 \times \text{height at the start of GH treatment, SDS (Prader)}] + [0.29 \times \text{first-year SR with maximum GH}] + [1.28 \times \text{mean GH dose, mg/kg/week}] + [-0.37 \times \ln \text{maximum GH level to provocation test, } \ln \mu\text{g/l}] + [-0.10 \times \text{age at the start of GH treatment, years}]$ . The second prediction equation does not take the results of the GH provocation test into account:  $\text{nFAH SDS} = 1.76 + [0.40 \times \text{MPH, SDS (Prader)}] + [0.21 \times \text{birth weight, SDS}] + [0.53 \times \text{height at the start of GH treatment, SDS (Prader)}] + [0.37 \times \text{first-year SR without maximum GH}] + [1.15 \times \text{mean GH dose, mg/kg/week}] + [-0.11 \times \text{age at the start of GH treatment, years}]$ .

### Statistical Analysis

The variables are reported as the median (10th–90th percentile) and mean ( $\pm$ SD). A one-sample Kolmogorov-Smirnov test was used to test for normal distribution. Differences between groups were tested with a t test when the distribution of data was normal, and with a Mann-Whitney U test otherwise.

Bland-Altman plots were constructed to assess agreement between the observed and predicted nFAH and to look for proportional bias [14, 15].

Clarke error grid analysis was performed to assess the clinical significance of the differences found between the observed and predicted nFAH. Zone A (= no fault) was arbitrarily defined as a difference between observed and predicted nFAH SDS of  $<0.5$  SD,

**Table 1.** Background and baseline characteristics of the study population

	Total					MPHD					Isolated GHD							
	n	median	p10	mean	SD	n	median	p10	mean	SD	n	median	p10	mean	SD			
<i>Background</i>																		
Birth weight, SDS	127	-0.55	-2.08	0.95	-0.66	121	37	-0.52	-1.96	0.58	114	90	-0.60	-2.35	1.07	-0.69	1.24	
Birth length, SDS	112	-0.88	-2.38	1.04	-0.75	127	33	-0.83	-2.35	0.73	106	90	-0.95	-2.52	1.05	-0.78	1.33	
Father height, SDS	127	-1.20	-2.55	-0.11	-1.23	113	37	-1.05 <sup>c</sup>	-2.16	0.63	106	90	-1.32	-2.68	-0.22	-1.40	1.12	
Mother height, SDS	127	-1.11	-2.66	0.24	-1.13	121	37	-0.78 <sup>c</sup>	-3.34	0.88	156	90	-1.11	-2.61	0.23	-1.22	1.02	
MPH, SDS	127	-1.52	-3.02	-0.07	-1.47	116	37	-1.07 <sup>d</sup>	-3.06	0.72	141	90	-1.66	-2.77	-0.31	-1.62	1.00	
Maximum GH peak, µg/l	127	4.6	1.2	8.6	4.8	2.7	37	2.9 <sup>b</sup>	1.1	6.1	3.2 <sup>b</sup>	1.9	5.6	1.8	8.8	5.4	2.7	
<i>At the start of GH treatment</i>																		
Age, years	127	7.0	2.3	11.0	7.1	3.1	37	5.9 <sup>c</sup>	1.7	9.6	5.9 <sup>c</sup>	2.6	7.7	2.7	11.2	7.5	3.2	
Height, SDS	127	-3.42	-5.11	-2.48	-3.58	1.00	37	-3.73 <sup>d</sup>	-5.75	-2.36	-3.97 <sup>d</sup>	1.34	90	-3.30	-4.55	-2.61	-3.42	0.78
Height SDS minus MPH SDS	127	-2.36	-4.09	-0.93	-2.39	1.27	37	-2.93 <sup>d</sup>	-5.25	-1.13	-3.08 <sup>d</sup>	1.61	90	-2.22	-3.13	-0.78	-3.08	1.61
Weight, SDS	127	-2.71	-5.09	-1.38	-3.02	1.51	37	-2.91	-6.33	-1.05	-3.32	1.90	90	-2.64	-4.88	-1.44	-2.89	1.31
BMI, SDS	119	-0.28	-1.99	0.87	-0.43	1.09	33	0.07	-1.76	1.25	0.16	115	86	-0.36	-2.00	0.64	-0.53	1.06
GH dose, µg/kg/day	127	27.6	23.6	35.5	28.7	4.8	37	27.9	22.6	38.2	29.4	5.7	90	27.4	23.7	34.9	28.4	4.4
<i>At nFAH</i>																		
Age, years	127	17.5	15.0	19.2	17.4	1.5	37	17.9 <sup>d</sup>	15.9	19.2	17.8 <sup>d</sup>	1.3	90	17.2	14.8	19.3	17.2	1.6
nFAH all, SDS	127	-1.63	-3.05	-0.16	-1.63	1.06	37	-1.39 <sup>d</sup>	-2.97	0.26	-1.35 <sup>d</sup>	1.22	90	-1.77	-3.08	-0.26	-1.74	0.98
nFAH males, cm	82	169.7	160	178.4	169.5	6.7	27	171.7	161.8	181.7	171.9	7.6	55	169.1	160	175.0	168.3	6.0
nFAH males, SDS	82	-1.63	-3.13	-0.35	-1.70	1.01	27	-1.39	-2.87	0.10	-1.36	1.15	55	-1.77	-3.12	-0.91	-1.87	0.90
nFAH females, cm	45	157	149.4	167	157.8	6.8	10	157.2	152.4	167.7	158.7	8.7	35	157.0	149.6	166.3	157.5	6.3
nFAH females, SDS	45	-1.62	-2.91	0.07	-1.49	1.15	10	-1.58	-2.40	0.19	-1.34	1.46	35	-1.62	-2.86	-0.03	-1.53	1.07
Total ΔH SDS <sup>e</sup>	127	1.79	0.83	3.45	1.96	1.24	37	2.26 <sup>b</sup>	1.13	4.73	2.62 <sup>b</sup>	1.41	90	1.59	0.59	2.92	1.69	1.06
nFAH SDS minus MPH SDS	127	-0.37	-1.70	0.69	-0.43	0.97	37	-0.42	-1.89	1.06	-0.46	1.08	90	-0.35	-1.53	0.68	-0.42	0.93
BMI, SDS	119	-0.09	-1.89	1.32	-0.23	1.27	37	-0.06	-1.67	1.42	-0.13	1.31	82	-0.10	-1.94	1.27	-0.27	1.25
Duration of GH therapy, years	127	9.6	5.3	13.7	9.6	3.1	37	10.9 <sup>c</sup>	7.3	15.4	10.9 <sup>c</sup>	2.8	90	8.8	5.0	13.6	9.0	3.1
Duration of GH therapy before puberty, years	125	5.2	1.9	9.4	5.4	2.9	37	6.7 <sup>c</sup>	2.7	10.9	6.6 <sup>c</sup>	2.8	88	4.4	1.5	8.6	4.8	2.8

MPHD = Multiple pituitary hormone deficiency; GHD = growth hormone deficiency; MPH = midparental height; GH = growth hormone; BMI = body mass index; nFAH = near-final adult height. The reference by Roslants et al. [9] was used for the SDS calculations except for birth weight and birth length SDS for which Nilklässon et al. [8] was used. <sup>a</sup> Gain in Ht SDS from the start of GH treatment until nFAH. <sup>b</sup>  $p < 0.001$ ; <sup>c</sup>  $p < 0.05$ ; <sup>d</sup>  $p < 0.05$  for comparison between MPHD and isolated GHD.





zone B (= acceptable fault) was defined as a difference between observed and predicted nFAH SDS between 0.5 and 1 SD, and zone C (= unacceptable fault) was defined as a difference between observed and predicted nFAH SDS of >1 SD. The height SD for adults was taken from the Prader curve of 20-year olds: for adult men, 1 SD is 6.9 cm, and for adult females, 1 SD is 5.9 cm.

Significance was considered at the 5% level ( $p < 0.05$ ). The IBM SPSS Statistics 21<sup>®</sup> software was used for all statistical analyses.

## Results

### Background and Baseline Characteristics

The background and baseline auxological characteristics are listed in table 1, with data of isolated GHD ( $n = 90$ ) and MPH (  $n = 37$ ) given separately. Children with MPH started GH therapy at a younger age ( $p < 0.05$ ), were shorter ( $p < 0.05$ ), and had taller parents ( $p < 0.05$ ) than children with isolated GHD.

### Final Height Outcome Data

The near adult height data are listed in table 1. The mean duration of GH therapy was 9.6 years, with a mean duration before pubertal onset of 5.4 years. Children with MPH had a significantly longer mean duration of GH therapy than those with isolated GHD (10.9 vs. 9.0 years;  $p < 0.01$ ) due to a younger mean age at the start of GH therapy (5.9 vs. 7.5 years;  $p < 0.05$ ). Girls reached nFAH earlier than boys (16.5 vs. 17.8 years;  $p < 0.001$ ). The mean nFAH for boys was  $169.5 \pm 6.7$  cm ( $-1.70 \pm 1.01$  SDS), and the mean nFAH for girls was  $157.8 \pm 6.8$  cm ( $-1.49 \pm 1.15$  SDS). The median total increase in Ht SDS was 1.79, and the mean nFAH SDS minus MPH SDS was  $-0.43$ . On average, children with MPH had a greater median total  $\Delta$ Ht SDS and a greater mean nFAH than children with isolated GHD, but there was no difference in nFAH corrected for MPH.

### Validation of the Ranke Prediction Models for nFAH

The Ranke nFAH predictions with both formulas (with and without maximum GH) were not significantly different from the observed nFAH in females. In contrast, the predicted nFAH was significantly higher than the observed nFAH in males (model with GH peak: difference:  $0.20 \pm 0.67$ ; 95% CI 0.06–0.35;  $p < 0.01$ ; model without GH peak: difference:  $0.22 \pm 0.66$ ; 95% CI 0.07–0.36;  $p < 0.01$ ).

The Bland–Altman analyses show that the means of the differences between the observed and predicted nFAH are close but not equal to zero; on average, the predicted nFAH is higher than the observed nFAH in males and

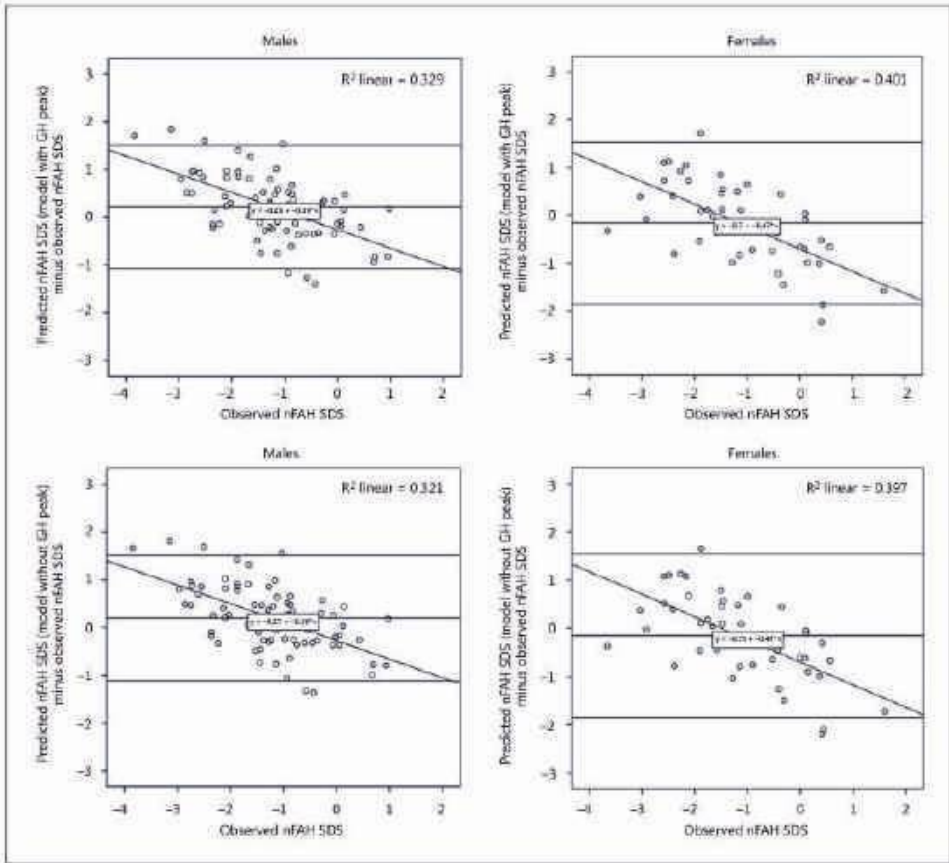
lower in females (fig. 1). For both formulas, the Bland–Altman analyses also show a proportional bias in both genders, with an overprediction for the smaller adult heights and an underprediction for the taller individuals. This proportional bias falls within the CI for the mean difference for observed nFAH values between  $-4.0$  and  $+1.5$  SDS (fig. 1).

The Clarke error grid analyses are shown in figure 2. In males, 59% of the predicted nFAH values (model with GH peak) and 61% (model without GH peak) are in zone A (<0.5 SD difference from observed nFAH), 29% (model with GH peak) and 27% (model without GH peak) of the predictions are in zone B (0.5–1 SD difference from observed nFAH), and 12% (model with and without GH peak) of the values are in zone C (>1 SD difference from observed nFAH). In females, 40% (model with GH peak) and 44% (model without GH peak) of the predicted nFAH are in zone A, 38% (model with GH peak) and 31% (model without GH peak) are in zone B, and 22% (model with GH peak) and 24% (model without GH peak) are in zone C.

## Discussion

We found that in Belgium, children with iGHD, either isolated or part of a MPH, when treated with a mean GH dose of  $28.7 \mu\text{g}/\text{kg}/\text{day}$  and at least 1 year before pubertal onset gained around 1.8 SDS in height. Although these children were treated before pubertal onset, they remained short compared to their peers (nFAH SDS:  $-1.6$  on Belgian references), but they almost reached their MPH (nFAH minus MPH SDS:  $-0.4$ ). The final adult height outcome of the studied cohort was higher in MPH than in isolated iGHD. Although we used quite strict criteria for near final height, some patients may have gained some height afterwards and their ultimate final height outcome may be better.

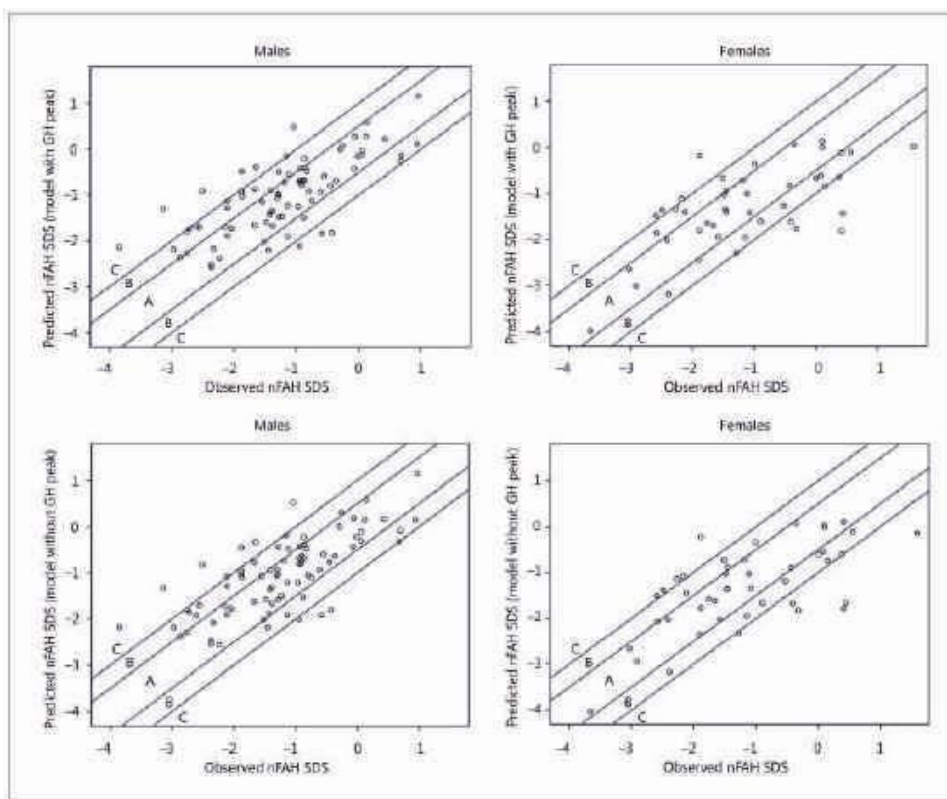
In the last decades, several prediction models for nFAH in GHD patients treated with GH have been developed [6, 16–21]. Thomas et al. [16] developed a model based on a rather small cohort ( $n = 61$ ) of Belgian GHD children. Carel et al. [17] developed a model based on a cohort ( $n = 1,885$ ) of the French National database that contains 10 parameters. De Ridder et al. [18] analyzed the data of the Dutch growth database and described models for prepubertal and pubertal children at the start and after the first year of GH treatment. Carrascosa et al. [19] retrieved data from 184 Spanish children from different medical centers and described a model at the end of the



**Fig. 1.** Bland-Altman plots. The horizontal lines show the mean differences and the 95% confidence intervals. Upper panels: prediction models including the GH peak; lower panels: prediction models without GH peak. All SDS calculations are based on Prader et al. [12].

second treatment year as well as a model at the onset of the pubertal growth spurt, predicting the Ht SDS gain to be achieved at adult height age. Blethen et al. [20] described a model derived from the Genentech study ( $n = 121$ ). Cutfield et al. [21] developed models for children with isolated GHD ( $n = 1,091$ ) and MPHD ( $n = 604$ ) based on the KIGS database. These models could not be

validated in our Belgian cohort because they did not include the first-year response [12, 17–21], they used several parameters that were not always available in the Belgian Registry (e.g. bone age within 3 months of GH start [18], BMI, and height at the onset of the pubertal growth spurt [19]), and/or because they included patients treated with only 3 doses of GH per week [17, 20], and/or because



**Fig. 2.** Clarke error grid analyses. Upper panels: prediction models including the GH peak; lower panels: prediction models without GH peak. Zone A: difference between predicted and actual nFAH SDS < 0.5. Zone B: difference between predicted and actual nFAH SDS 0.5–1.0. Zone C: difference between predicted and actual nFAH SDS > 1.0. All SDS calculations are based on Prader et al. [12].

they contain parameters not usable to predict adult height at 1 year of GH treatment, such as the total duration of GH treatment [20, 21] and the 2-year growth response to GH [19].

We validated both clinically and statistically the Ranke prediction model for adult height in this Belgian cohort. A clinically validated model is likely to be more useful than a statistically validated one [5]. Statistical analysis of our outcome data showed no significant difference between ob-

served and predicted nFAH for females. For males, the predicted nFAH is 0.20–0.22 SD (1.4–1.5 cm) higher than the observed nFAH. This difference is statistically significant, but the absolute error does not make the method invalid for clinical practice. Alternatively, one may choose to subtract 0.2 SD from the height predictions in males. However, this does not reduce the number of unacceptable (zone C) predictions in the Clarke error grid analysis, since it creates more underpredictions (data not shown).



The Bland-Altman analysis shows a proportional bias for both genders and both formulas (with and without GH peak in the stimulation test). This bias is rather mild and falls within the confidence limits for the mean difference between the predicted and the observed nFAH, at least for the range of final height data that are mostly encountered in clinical practice (i.e. -4.0 to +1.5 SDS). Therefore, it is not necessary to correct for this bias [15].

For the Clarke error grid analysis, we arbitrarily determined the zone A as a difference between predicted and observed nFAH <0.5 SDS. Prediction errors of <1 SD are still acceptable if compared to other methods for final height prediction, such as the Tanner and Whitehouse and the Greulich-Pyle Bayley-Pinneau prediction models [22, 23].

The Clarke error grid analyses show that 59–61% of males and 40–44% of females have a predicted nFAH which deviates from the initially predicted nFAH by <0.5 SD (about 3–3.5 cm). In males, 88% of the predictions fall within 1 SD of the observed nFAH (error grid zones A and B). The prediction error is larger for females than for males; 76–78% of the predictions fall within 1.0 SD of the observed nFAH in females. In our opinion, Ranke's prediction models for both genders are clinically valid, since only 12% of males and 22–24% of females in the Belgian Registry cohort have an observed nFAH which deviates >1 SD (6.9 cm for males and 5.9 cm for females) from the predicted nFAH.

In conclusion, children with iGHD, when treated at least for 4 years with GH and 1 year before pubertal onset, had a significant median total height gain of 1.8 SD. Their final height was still relatively short compared to their peers (mean nFAH -1.6 SD) but only slightly below their

MPH. The Ranke prediction model for nFAH after the first year of GH therapy accurately predicted nFAH in females and overpredicted nFAH in males by 0.2 SDS (about 1.5 cm). In most individuals, the nFAH prediction after GH therapy was within 1 SDS of the observed nFAH. Therefore, the Ranke prediction models are useful in clinical practice for predicting nFAH after 1 year of GH treatment.

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#### Disclosure Statement

The authors have no conflict of interest to disclose.

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## Chapter 6

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Criteria for first-year growth response to growth hormone treatment in prepubertal children with growth hormone deficiency: do they predict poor adult height outcome?



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# Criteria for First-Year Growth Response to Growth Hormone Treatment in Prepubertal Children With Growth Hormone Deficiency: Do They Predict Poor Adult Height Outcome?

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**Objective:** Several criteria for first-year growth response (FYGR) to growth hormone (GH) treatment have been proposed. We explored which FYGR criteria predicted best the final height outcome after GH treatment in prepubertal children with GH deficiency (GHD).

**Design and methods:** Height data of 129 GHD children (83 boys) who attained adult height and had been treated with GH for at least 4 consecutive years with at least 1 year before pubertal onset, were retrieved from the Belgian GH Registry. The FYGR parameters were: (1) increase in height ( $\Delta$ Ht) SDS, (2) height velocity (HV) SDS, (3)  $\Delta$ HV (cm/year), (4) index of responsiveness (IoR) in KIGS prediction models, (5) first-year HV SDS based on the KIGS expected HV curve (HV KIGS SDS), (6) near final adult height (nFAH) prediction after first-year GH treatment. Poor final height outcome (PFHO) criteria were: (1) total  $\Delta$ Ht SDS  $< 1.0$ , (2) nFAH SDS  $< -2.0$ , (3) nFAH minus midparental height SDS  $< -1.3$ . ROC curve analyses were performed to define the optimal cut-off for FYGR parameters to predict PFHO. Only ROC curves with an area under the curve (AUC) of more than 70% were further analyzed.

**Results:** Twelve, 22 and 10% of the children had respectively a total  $\Delta$ Ht SDS  $< 1$ , nFAH SDS  $< -2$ , and nFAH minus midparental height SDS  $< -1.3$ . The AUC's ranged between 73 and 85%. The highest AUC was found for first-year  $\Delta$ Ht SDS to predict total  $\Delta$ Ht SDS  $< 1$ , and predicted nFAH SDS to predict nFAH SDS  $< -2$ . The currently used FYGR criteria had low specificities and sensitivities to detect PFHO. To obtain a 96% specificity, the cut-off value (and sensitivity) of FYGR parameters were:  $\Delta$ Ht SDS  $< 0.35$  (40%), HV SDS  $< -0.85$  (43%),  $\Delta$ HV  $< 1.3$  cm/year (36%), IoR  $< -1.57$  (17%), HV KIGS SDS  $< -0.89$  (40%) to predict total  $\Delta$ Ht SDS  $< 1$ ; predicted nFAH SDS (with GH peak)  $< -1.94$  (25%),

predicted nFAH SDS (without GH peak)  $< -2.02$  (25%) to predict nFAH SDS  $< -2$ . At these cut-offs, the amount of correctly diagnosed poor final responders equals the amount of false positives.

**Conclusion:** First-year growth response criteria perform poorly as predictors of poor final height outcome after long-term GH treatment in prepubertal GHD children.

**Keywords:** growth hormone treatment, growth hormone deficiency, children, first-year growth response criteria, adult height outcome

## INTRODUCTION

Growth hormone deficiency (GHD) in children is mostly idiopathic and is treated with daily growth hormone (GH) injections for a mean duration of 4 to 11 years (1–8). GH treatment is therefore not only burdensome for the patients and their families, it is also costly. In addition, not every child benefits from GH treatment and the poor responder rate in GHD has been found to be between 10 and 30% (9, 10). It is therefore common practice to evaluate the response to GH therapy after 1 year to detect poor responders in order to reassess the diagnosis, adapt the GH dose or stop the treatment to avoid unnecessary daily injections and expenses. The evaluation is usually done after 1 year of treatment because it is known that the first year response is an important determinant of the total treatment height outcome (11).

Several methods exist to evaluate this first year response such as increase in height ( $\Delta$ Ht) SDS,  $\Delta$  height velocity (HV), HV SDS on the population HV reference curve, and HV SDS on the predicted HV for idiopathic GHD curve (12, 13). A parameter (index of responsiveness, IoR) has been introduced that compares the observed first year HV to a predicted HV derived from prediction models (14, 15). More recently, models have been proposed that predict the near final height outcome after the first treatment year (16). All these methods for evaluation of first-year growth response use arbitrary decision values that are not based on their ability to predict a final height outcome. Up to now, the value of these first-year growth response and responsiveness parameters as predictors of a poor final height outcome after long-term GH treatment in GHD patients has not been analyzed.

We therefore set out to determine the sensitivity and specificity of these first year growth response (FYGR) criteria at their proposed threshold levels to detect a poor final height outcome (PFHO), defined by different criteria. In addition, we performed ROC analyses to calculate the decision levels at a desired 95% specificity.

## MATERIALS AND METHODS

### Materials

The auxological data and GH treatment characteristics of prepubertal children diagnosed with GHD, who were enrolled in the Registry of the Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED) since 1986, were retrieved. This registry was approved by the ethical committee of the Brussels

University and the University Hospital Brussels in Belgium. The legal representatives of all subjects gave written informed consent to have their data registered in a national registry and to use their data for scientific purposes in accordance with the Declaration of Helsinki. All data are pseudonymised to comply with rigorous privacy guidelines. Only patients, who had been treated with recombinant human GH on a daily regimen for at least 4 consecutive years and at least 1 year before pubertal onset and who had attained final adult height were included. Growth hormone was only of recombinant origin in all cases. GHD patients with and without developmental anatomical anomalies of the pituitary were included, but those with acquired GHD were excluded. Other exclusion criteria were any medication or medical condition other than GHD that can affect growth, interruption of GH treatment for more than 6 months, and smallness for gestational age. In total, 129 patients (83 males and 46 females) with GHD (81 with isolated GHD and 48 with multiple pituitary hormone deficiency) met the inclusion and exclusion criteria.

### Methods

The diagnosis of GHD was made by the treating physician and peer-reviewed at the monthly meeting of BESPEED, according to the KIGS etiology classification system (17). All patients had a peak GH concentration of  $< 10 \mu\text{g/l}$  after glucagon and/or insulin stimulation. Pubertal onset was defined as testicular volumes  $\geq 4 \text{ ml}$  for boys and Tanner breast stage  $\geq 2$  in girls.

Variables retrieved from the registry were (a) status at birth: sex, birth weight and length; (b) father's and mother's height (Ht); (c) pre-treatment Ht when measured between 6 and 18 months before GH treatment; (d) patient variables at the start of the treatment period: chronological age, Ht, weight (Wt), body mass index (BMI), the highest peak GH concentration during a provocation test, the presence of other pituitary hormone deficiencies, and (e) treatment modality: average GH dose ( $\mu\text{g/kg}\cdot\text{day}$ ) during the first year of GH treatment.

Birth weight for gestational age was transformed into SDS, based on the standards of Niklasson et al. (18). Midparental height (MPH) was calculated as follows: (father's Ht + mother's Ht + 13 for boys/–13 for girls)/2 (19). Height, weight, BMI, MPH, and HV were converted to SDS using Flemish reference data by Roelants et al. (20).

Near (n) FAH was defined as the height attained when HV was less than 2 cm/year, calculated over a period of minimum 9 months, and when the child had a chronological



**TABLE 1 |** Characteristics: background, at GH start, after first year, at nFAH.

	n	Median	p25	p75	Mean	SD
<b>Background</b>						
Gestational age, weeks	123	40.0	38.0	40.0	38.7	2.8
Birth weight, SDS	122	-0.29	-0.86	0.34	-0.20	0.89
Birth length, SDS	110	-0.38	-1.02	0.46	-0.25	0.96
Father height, SDS	124	-1.20	-1.79	-0.19	-1.03	1.17
Mother height, SDS	124	-0.78	-1.62	-0.27	-0.91	1.13
MPH, SDS	124	-1.10	-1.70	-0.41	-0.99	0.93
maximum GH peak, $\mu\text{g/l}$	129	4.0	2.1	6.9	4.4	2.7
<b>At start GH treatment</b>						
Age, years	129	6.6	4.7	8.7	6.8	2.6
Height, SDS	129	-3.31	-3.89	-2.73	-3.39	0.85
Height minus MPH, SDS	124	-2.34	-2.99	-1.71	-2.39	1.07
BMI, SDS	129	-0.42	-1.20	0.34	-0.36	1.11
GH dose, $\mu\text{g/kg}\cdot\text{day}$	129	27.0	24.5	31.1	28.0	5.4
HV during pretreatment year, $\text{cm}/\text{year}$	107	5.0	3.8	6.0	5.2	2.0
<b>After first-year GH treatment</b>						
Height, SDS	129	-2.34	-2.80	-1.90	-2.39	0.80
Height minus MPH, SDS	124	-1.29	-1.98	-0.74	-1.38	0.94
$\Delta$ BMI, SDS <sup>a</sup>	129	-0.21	-0.56	0.07	-0.27	0.57
<b>Growth response</b>						
$\Delta$ height, SDS <sup>b</sup>	129	0.99	0.57	1.38	1.00	0.52
$\Delta$ HV, $\text{cm}/\text{year}$	107	4.6	3.1	7.0	5.1	3.3
HV, $\text{cm}/\text{year}$	129	10.4	8.2	12.0	10.2	2.5
HV for age and sex, SDS	115	1.51	0.09	3.50	1.91	2.23
<b>Responsiveness</b>						
HV for first-year GH treatment <sup>c</sup> , SDS	129	0.26	-0.31	0.91	0.31	0.88
Index of responsiveness (with GH peak)	123	0.02	-0.59	0.71	0.07	1.13
Index of responsiveness (without GH peak)	123	0.13	-0.51	0.90	0.21	1.13
<b>Prediction of nFAH</b>						
Predicted nFAH (with GH peak) <sup>d</sup>	123	-0.87	-1.37	-0.36	-0.84	0.87
Predicted nFAH (without GH peak) <sup>d</sup>	123	-0.85	-1.41	-0.37	-0.85	0.87
<b>At nFAH</b>						
Age, years (boys)	83	18.3	17.6	19.2	18.9	2.3
Age, years (girls)	46	16.3	15.5	17.7	16.7	1.7
Age stop GH treatment, years (boys)	83	16.8	16.1	17.6	16.9	1.3
Age stop GH treatment, years (girls)	46	15.3	14.7	16.4	15.6	1.3
Growth since stop GH treatment, $\text{cm}$	129	0.6	0.0	1.1	1.3	2.4
Duration GH therapy, years	129	9.9	7.5	11.7	9.7	2.6
Duration GH therapy before pubertal onset, years	122	5.5	3.2	7.8	5.6	2.7
nFAH, SDS (A21)	129	-1.46	-2.02	-0.67	-1.40	1.10
nFAH, SDS (CA)	129	-1.19	-1.91	-0.41	-1.17	1.08

(Continued)

**TABLE 1 |** Continued

	n	Median	p25	p75	Mean	SD
nFAH minus MPH, SDS (A21)	124	-0.38	-0.96	0.23	-0.39	0.94
nFAH minus MPH, SDS (CA)	124	-0.17	-0.70	0.45	-0.16	0.94
Total $\Delta$ height, SDS <sup>a</sup> (A21)	129	1.84	1.19	2.69	1.99	1.13
Total $\Delta$ height, SDS <sup>a</sup> (CA)	129	2.05	1.55	2.97	2.23	1.09
BMI, SDS (A21)	110	-0.55	-1.47	0.29	-0.49	1.36
BMI, SDS (CA)	110	-0.15	-1.05	0.61	-0.19	1.27

GH, growth hormone; nFAH, near final adult height; SDS, standard deviation score; MPH, midparental height; BMI, body mass index; HV, height velocity;  $\text{cm}$ , centimeter; A21, SDS calculated at age 21 years; CA, SDS calculated at chronological age; <sup>a</sup>change in BMI SDS after first-year GH treatment; <sup>b</sup>gain in height SDS after first-year GH treatment; <sup>c</sup>growth targets for first-year GH response by Ranke et al.; <sup>d</sup>prediction model for nFAH by Ranke et al.; <sup>e</sup>gain in height SDS from start of GH treatment until nFAH.

age >17 years in boys and >15 years in girls. nFAH SDS was calculated in 2 different ways: (1) using the chronological age (CA), (2) using the growth reference data at age 21 years (A21).

The FYGR parameters were: (1) increase in height ( $\Delta$ Ht) SDS, (2) height velocity (HV) ( $\text{cm}/\text{year}$ ), (3) HV SDS, (4)  $\Delta$ HV ( $\text{cm}/\text{year}$ ), (5) index of responsiveness (IoR) in KIGS prediction models, (6) first-year HV SDS based on the KIGS expected HV curve (HV KIGS SDS), (7) near final adult height (nFAH) prediction after first-year GH treatment.

First-year gain in height ( $\Delta$ Ht) SDS and first-year HV ( $\text{cm}/\text{year}$ ), were calculated as the increment in height between start and after minimum 9 months and maximum 15 months of GH therapy and subsequently scaled to 12 months.  $\Delta$ HV ( $\text{cm}/\text{year}$ ) was calculated as the HV during the first year of GH treatment minus the HV during the pretreatment year. The HV during the first year of GH treatment was plotted on the Flemish HV curve (20), and on the reference curve for the HV during the first year of GH treatment developed by Ranke et al. (15), and its SDS value was calculated. Predicted HV was calculated using the KIGS prediction models for idiopathic GHD (14, 15), if all parameters required for the mathematical algorithm were available. Differences between observed and predicted HVs were expressed as index of responsiveness (IoR), calculated as the observed HV minus the predicted HV, divided by the SD of the predicted HV of the child. The predicted nFAH was calculated after the first year of GH treatment, using the prediction models by Ranke et al. (16). For the prediction models, observed heights (height at start, height after first year, parental heights, and nFAH) were converted to SDS using reference data by Prader et al. (21) and the MPH SDS was calculated with the Cole formula: (father height SDS + mother height SDS)/1.61.

The long-term growth response to GH was evaluated by three different, but complementary methods: (1) nFAH, expressed as a height SDS; (2) total  $\Delta$ Ht SDS, calculated as the nFAH SDS minus height SDS at start of GH treatment;



(3) nFAH SDS minus MPH SDS, an index of achieving genetic height potential.

A poor near final height outcome to GH treatment was defined as: (1) total  $\Delta$ H SDS  $< 1$ , (2) nFAH  $< -2$  SD of the population mean, or (3) nFAH SDS minus MPH SDS  $< -1.3$ .

### Statistical Analysis

The variables are reported as the median (25–75th percentile) and mean ( $\pm$ SD). A Shapiro-Wilk test was used to test for the normal distribution. Differences between groups were tested with a *t*-test when the distribution of data was normal, and with a Mann-Whitney *U*-test otherwise. ROC curve analyses were performed to examine the relationship between sensitivity and specificity for the different FYGR parameters and PPHO criteria and to determine the test cut-off values that had a 95% specificity. The minimum AUC was set at 0.7. Significance was considered at the 5% level ( $p < 0.05$ ). MedCalc<sup>®</sup> and IBM SPSS Statistics 25<sup>®</sup> software was used for all statistical analyses.

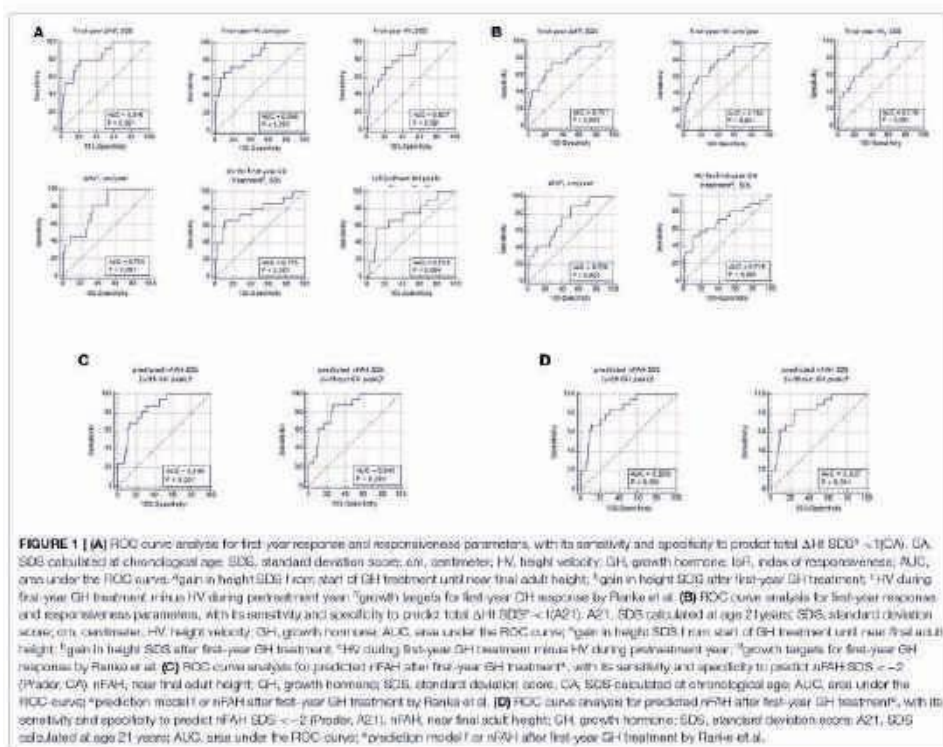
## RESULTS

### Background Characteristics

The background and auxological characteristics of 129 included GHD children (83 males, 46 females) are listed in Table 1. GH therapy was initiated at a mean age of 6.8 years, a median height SDS of  $-3.31$  and a median height minus MPH SDS of  $-2.34$ . The mean GH dose at start was 28  $\mu$ g/kg/day.

### First-Year Response and Responsiveness to GH Treatment (Table 1)

After the first year of GH therapy, the median  $\Delta$ H SDS was 0.99, the mean ( $\pm$ SD) first-year HV was 10.2 cm/year ( $\pm 2.5$ ) or 1.91 SD ( $\pm 2.23$ ), and the mean  $\Delta$ HV was 5.1 cm/year ( $\pm 3.3$ ). The mean HV SDS on the first-year GH treatment response curve by Ranke et al. was 0.31 ( $\pm 0.88$ ). The mean IoR was respectively 0.07 ( $\pm 1.13$ ) and 0.21 ( $\pm 1.13$ ), for the formula with and without max. GH peak. The mean predicted nFAH SDS was  $-0.84$  ( $\pm 0.87$ ) with, and  $-0.85$  ( $\pm 0.87$ ) without the maximum GH peak included.



**TABLE 2A |** ROC curve analysis: cut-off values for first-year response and responsiveness parameters, with its sensitivity and specificity to predict total  $\Delta$ Ht SDS < 1<sup>a</sup> (CA).

$\Delta$ Ht <sup>b</sup> , SDS	Sensitivity (%)	Specificity (%)	HV, cm/year	Sensitivity (%)	Specificity (%)	HV for age and sex, SDS	Sensitivity (%)	Specificity (%)
0.20	20	100	5.9	13	100	-1.93	14	100
0.28	33	98	6.5	33	98	-1.00	29	97
0.35	40	95	6.6	40	97	-0.85	43	95
<b>0.50</b>	<b>60</b>	<b>86</b>	6.8	47	95	-0.38	57	88
0.57	73	82	7.4	60	90	0.09	71	80
0.61	80	79	8.0	67	85	<b>1.00</b>	<b>78</b>	<b>67</b>
1.00	87	54	8.9	80	68	1.22	86	63
1.03	93	50	10.8	93	49	2.48	93	45
1.14	100	43	11.0	100	45	2.56	100	43
AUC: 85% (95% CI: 77–90%)			AUC: 85% (95% CI: 77–91%)			AUC: 83% (95% CI: 75–89%)		
$\Delta$ HV <sup>c</sup> , cm/year	Sensitivity (%)	Specificity (%)	HV for first-year GH treatment <sup>d</sup> , SDS	Sensitivity (%)	Specificity (%)	IoR (without GH peak)	Sensitivity (%)	Specificity (%)
-2.3	27	100	-1.57	13	100	-2.24	0	100
1.2	36	97	-1.14	20	98	-1.82	8	97
1.3	36	95	<b>-1.00</b>	<b>33</b>	<b>97</b>	-1.57	17	95
1.6	45	92	-0.83	40	95	<b>-1.28</b>	<b>17</b>	<b>92</b>
<b>3.2</b>	<b>45</b>	<b>74</b>	-0.68	53	90	-0.97	58	90
3.8	72	69	-0.19	73	73	-0.40	67	75
4.9	82	49	0.43	87	46	0.43	83	40
5.1	100	49	1.03	93	24	0.69	92	32
			1.46	100	12	1.16	100	21
AUC: 79% (95% CI: 70–88%)			AUC: 78% (95% CI: 70–85%)			AUC: 73% (95% CI: 64–81%)		

CA, SDS calculated at chronological age; SDS, standard deviation score; cm, centimeter; HV, height velocity; GH, growth hormone; IoR, index of responsiveness; AUC, area under the ROC curve; CI, confidence interval. <sup>a</sup>gain in height SDS from start of GH treatment until near final adult height; <sup>b</sup>gain in height SDS after first-year GH treatment; <sup>c</sup>HV during first-year GH treatment minus HV during pretreatment year; <sup>d</sup>growth targets for first-year GH response by Ranke et al. **bold**, currently used FYGR criteria; *italic*, FYGR criteria at 95% specificity.

## Final Height Outcome After GH Treatment

Near FAH after GH treatment is listed in **Table 1**. The mean duration of GH therapy was 9.7 years, with a mean duration before pubertal onset of 5.6 years. nFAH was attained at a mean age of 16.7 years in girls and 18.9 years in boys. For girls, mean nFAH was 157.6 cm  $\pm$  7.0 (-1.52 SD  $\pm$  1.19, and -1.34  $\pm$  1.15, resp. for A21 and CA). For boys, mean nFAH was 172.1 cm  $\pm$  7.1 (-1.33 SD  $\pm$  1.06, and -1.08 SD  $\pm$  1.04, resp. for A21 and CA). Twenty six and 22% of patients had a nFAH < -2.0 SD, resp. for A21 and CA. Mean nFAH SDS minus MPH SDS was -0.39 (A21) and -0.16 (CA). Twelve and 10% of patients had a nFAH SDS minus MPH SDS < -1.3, resp. for A21 and CA. The median total increase in height SDS was 1.99 (A21) and 2.23 (CA). Median total  $\Delta$ Ht SDS was comparable in girls and boys [mean difference 0.13 SD (A21) and 0.22 SD (CA);  $p = 0.5$ ]. Sixteen and 12% of patients had a total  $\Delta$ Ht SDS < 1, resp. for A21 and CA.

## Logistic Regression Analysis

ROC curve analysis was performed for all first-year response and responsiveness parameters [ $\Delta$ Ht SDS, HV for age and sex (cm/year and SDS),  $\Delta$ HV (cm/year), HV SDS for first-year GH

treatment, IoR, predicted nFAH SDS] in relation to the studied poor final outcome parameters (total  $\Delta$ Ht SDS < 1, nFAH SDS < -2, and nFAH SDS—MPH SDS < -1.3) (**Figures 1A–D**). Only ROC-curves with an AUC  $\geq$  70% were further analyzed.

**Tables 2A–D** show the thresholds with their sensitivity and specificity of the different tests vs. the different outcomes. The thresholds for the tests currently proposed in the literature are set in bold.

**Tables 2A,B** show cut-off values for first-year response and responsiveness parameters, with its sensitivity and specificity to predict total  $\Delta$ Ht SDS < 1 (CA and A21). The first-year response criterion  $\Delta$ Ht SDS < 0.5 had a relatively low specificity (86%) to predict a total  $\Delta$ Ht SDS < 1. The corresponding sensitivity was 60%. The other proposed first-year response and responsiveness criteria had a specificity of 67–97%, with corresponding sensitivities of 17–78%.

To predict a total  $\Delta$ Ht SDS < 1 (CA) with a 95% specificity (in italic) the following threshold levels were found:  $\Delta$ Ht < 0.35 SD; HV < 6.8 cm/year; HV < -0.85 SD for age and sex;  $\Delta$ HV < 1.3 cm/year; HV < -0.83 SD for first-year GH treatment by Ranke et al.; IoR (without GH peak) <

**TABLE 2B** | ROC curve analysis: cut-off values for first-year response and responsiveness parameters, with its sensitivity and specificity to predict total  $\Delta$ Ht SDS  $<1^a$  (A21).

$\Delta$ Ht, SDS <sup>b</sup>	Sensitivity (%)	Specificity (%)	HV, cm/year	Sensitivity (%)	Specificity (%)	HV for age and sex, SDS	Sensitivity (%)	Specificity (%)
0.20	14	100	5.9	10	100	-1.93	10	100
0.30	29	98	6.6	29	98	-0.94	35	98
0.37	43	95	6.7	33	95	-0.60	40	95
<b>0.50</b>	<b>48</b>	<b>86</b>	7.6	52	90	-0.22	50	85
0.60	62	80	8.3	62	80	0.11	60	80
0.69	71	73	8.9	67	70	0.60	65	73
0.99	81	56	9.9	81	61	<b>1.00</b>	<b>70</b>	<b>68</b>
1.03	86	51	10.8	86	50	1.48	80	60
1.14	90	44	11.0	90	45	2.56	90	43
1.22	95	39	11.1	95	42	2.63	95	40
1.56	100	16	12.9	100	17	3.50	100	29
AUC: 79% (95% CI: 71–85%)			AUC: 78% (95% CI: 70–85%)			AUC: 78% (95% CI: 69–85%)		

$\Delta$ HV <sup>c</sup> , cm/year	Sensitivity (%)	Specificity (%)	HV for first-year GH treatment <sup>d</sup> , SDS	Sensitivity (%)	Specificity (%)
-2.4	18	100	-1.57	10	100
1.4	29	95	<b>-1.00</b>	<b>29</b>	<b>98</b>
1.8	35	90	-0.63	33	95
<b>3.0</b>	<b>41</b>	<b>79</b>	-0.59	52	89
3.4	47	74	-0.32	57	81
3.9	65	67	-0.19	62	73
4.4	71	61	0.14	71	60
5.1	82	50	0.43	81	46
6.0	88	40	1.03	90	24
6.9	94	30	1.46	95	12
7.3	100	27	1.85	100	4
AUC: 73% (95% CI: 63–81%)			AUC: 72% (95% CI: 63–79%)		

A21, SDS calculated at age 21 years; SDS, standard deviation score; HV, height velocity; cm, centimeter; GH, growth hormone; AUC, area under the ROC curve; CI, confidence interval; <sup>a</sup>gain in height SDS from start of GH treatment until near final adult height; <sup>b</sup>gain in height SDS after first-year GH treatment; <sup>c</sup>HV during first-year GH treatment minus HV during pretreatment year; <sup>d</sup>growth targets for first-year GH response by Rankin et al. *ibid.*, currently used FYGR criteria; *ibid.*, FYGR criteria at 95% specificity.

-1.57. The corresponding sensitivities were respectively 40, 47, 43, 36, 40, and 17%. The total  $\Delta$ Ht SDS of the good final responders who were wrongly diagnosed as poor final responders (according to the above criteria) varied between 1.08 and 2.57.

Tables 2C,D show cut-off values for predicted nFAH after first-year GH treatment, with its sensitivity and specificity to predict nFAH SDS  $<-2.0$  (Prader, CA and A20). A predicted nFAH after first-year GH treatment  $<-1.94$  SD (model with GH peak) and  $<-2.02$  (model without GH peak) predicted nFAH SDS  $<-2$  (CA) with 95% specificity and 25% sensitivity. The nFAH SDS of the good final responders who were wrongly diagnosed as poor final responders (according to the above criteria) varied between -1.98 and -1.28.

For all FYGR parameters in relation to nFAH minus MPH SDS  $<-1.3$ , the AUC's were  $<70\%$  and therefore not further analyzed.

## Comparison of the Good and the Poor Final Height Responders

The patients having a total  $\Delta$ Ht SDS in the highest quartile had a significantly lower height SDS at start of GH treatment compared with the patients in the lowest  $\Delta$ Ht SDS quartile ( $-3.78$  SD vs.  $-3.03$  SD;  $p < 0.001$ ) (Table 3). They also had a significantly higher first-year  $\Delta$ Ht SDS (1.50 SD vs. 0.61 SD;  $p < 0.001$ ). Therefore, they reached a comparable height SDS after the first year of GH treatment ( $-2.28$  SD vs.  $-2.41$  SD;  $p = 0.5$ ). The total  $\Delta$ Ht was 3.71 SD for the good (highest quartile) and 0.98 SD for the poor (lowest quartile) total  $\Delta$ Ht responders. The poor total  $\Delta$ Ht SDS responders had a significantly lower birth weight, shorter parents, and a less severe GHD. They started GH at an older age, with a taller height, and lower BMI, and received GH for a shorter period than the good total  $\Delta$ Ht SDS responders.

The patients in the highest quartile nFAH SDS had a significantly higher height SDS at start compared to the patients



**TABLE 2C** | ROC curve analysis: cut-off values for predicted nFAH after first-year GH treatment<sup>a</sup>, with its sensitivity and specificity to predict nFAH SDS < -2 (Prader, CA).

Predicted nFAH SDS (with GH peak) <sup>a</sup>	Sensitivity (%)	Specificity (%)	Predicted nFAH SDS (without GH peak) <sup>a</sup>	Sensitivity (%)	Specificity (%)
-2.62	19	100	-2.53	25	100
-1.94	25	95	-2.02	25	95
-1.74	44	91	-1.77	44	91
-1.65	63	90	-1.70	63	90
-1.28	75	79	-1.51	69	83
-1.17	81	74	-1.21	81	76
-1.04	88	68	-1.20	88	74
-0.87	94	55	-0.78	94	52
-0.69	100	47	-0.64	100	44

AUC: 86% (95% CI: 77–90%)      AUC: 84% (95% CI: 77–90%)

nFAH, near final adult height; GH, growth hormone; SDS, standard deviation score; CA, SDS calculated at chronological age; AUC, area under the ROC-curve; CI, confidence interval; <sup>a</sup>prediction model for nFAH after first-year GH treatment by Rankie et al. *italics*, FYGR criteria at 95% specificity.

**TABLE 2D** | ROC curve analysis: cut-off values for predicted nFAH after first-year GH treatment<sup>a</sup>, with its sensitivity and specificity to predict nFAH SDS < -2 (Prader, A20).

Predicted nFAH SDS (with GH peak) <sup>a</sup>	Sensitivity (%)	Specificity (%)	Predicted nFAH SDS (without GH peak) <sup>a</sup>	Sensitivity (%)	Specificity (%)
-2.62	16	100	-2.53	21	100
-1.95	21	85	-1.91	26	95
-1.67	63	91	-1.70	63	91
-1.50	68	88	-1.51	68	85
-1.28	74	80	-1.25	74	77
-1.04	84	69	-1.20	84	75
-0.87	89	56	-0.78	89	53
-0.69	95	47	-0.64	95	44
-0.61	100	41	-0.48	100	38

AUC: 84% (95% CI: 76–90%)      AUC: 84% (95% CI: 76–90%)

nFAH, near final adult height; GH, growth hormone; SDS, standard deviation score; A20, SDS calculated at age 21 years; AUC, area under the ROC-curve; CI, confidence interval; <sup>a</sup>prediction model for nFAH after first-year GH treatment by Rankie et al. *italics*, FYGR criteria at 95% specificity.

in the lowest quartile nFAH SDS (-3.10 SD vs. -3.88 SD;  $p < 0.01$ ) (Table 3). Delta height SDS after the first year, at onset of puberty and at nFAH was significantly higher in the good responders. They had also taller parents and more severe GH.

## DISCUSSION

In this study of a cohort of GHD patients treated with GH extracted from the Belgian Registry we found that the mean nFAH was still below average and 10–22% of the patients had a poor final height outcome. ROC-analysis showed that

the currently used FYGR criteria had low specificities and sensitivities to detect PFHO.

Our final height outcome data in Belgian patients are comparable with the results of a Swedish (2) and Canadian (4) study, using the same criteria for nFAH, where idiopathic GHD children were treated with a similar GH dose for a mean period of 8.6 and 5.4 years, respectively: up to 84 and 90% obtained a nFAH SDS > -2. We previously reported in a smaller group of Belgian idiopathic GHD patients a comparable nFAH (170.4 cm in males and 158 cm in females after a mean treatment duration of 5.2 years) and a similar response rate (84% had a nFAH within normal limits) (22).

Near FAH was taken as a proxy of FAH as an outcome parameter, as many patients usually stop GH treatment and disappear from follow-up when growth slows down to less than 2 cm per year and before adult height is reached (23). To overcome this problem, nFAH SDS could be calculated at a reference age of 21 years instead of the actual chronological age. This underestimates the real Ht SDS since most adolescents will still gain a few centimeters. On the other hand, since the mean height of the reference population also increases between 16 and 21 years, nFAH SDS at the actual chronological age will overestimate the real Ht SDS. We therefore calculated nFAH SDS both with age set at 21 years (worst case scenario) and at chronological age (best case scenario), accepting that the first method will underestimate and the second will overestimate the actual FAH SDS.

This ROC-analysis showed that the classically proposed threshold levels for first-year growth response and responsiveness parameters had a low sensitivity and specificity to predict a poor near final height outcome. For example, first-year  $\Delta$ Ht SDS < 0.5 had a sensitivity of 60%. This means that 60% of the poor final responders (total  $\Delta$ Ht SDS < 1.0) had a poor first-year response (first-year  $\Delta$ Ht SDS < 0.5), and 40% (100-sensitivity) of the poor final responders had a good first-year response (first-year  $\Delta$ Ht SDS > 0.5). The corresponding specificity was 86%, meaning 86% of the good final responders had a good first-year response, and 14% (100-specificity) of the good final responders had a poor first-year response. Thus, first-year  $\Delta$ Ht SDS < 0.5 correctly identified 60% of the poor final responders, but misdiagnosed 14% of the good final responders as poor responders. In order to misdiagnose good final responders as few as possible (5%), we decided to set the specificity of the FYGR parameters at 95% and determined the test cut-off values. At these newly defined threshold values, the sensitivity to detect poor final height responders decreased considerably. Of course, every physician can choose the specificity required by the local circumstances. The FYGR threshold values that best predicted total  $\Delta$ Ht SDS < 1 with a 95% specificity were:  $\Delta$  Ht SDS < 0.35; HV SDS < -0.85, HV for first-year GH treatment SDS < 0.83, and  $\Delta$  HV < 1.3 cm/year. On the other hand, predicted nFAH SDS (with GH peak) < -1.94, and predicted nFAH SDS (without GH peak) < -2.02 performed best to detect nFAH < -2 SD (Prader) with a 95% specificity. These criteria only correctly identify 25–43% (=sensitivity) of the patients with a poor final outcome (= 3.8–5.2% of the total population). At a specificity of 95%, 5% of good final responders is wrongly diagnosed as poor final responder (=4.2–4.4% of

**TABLE 3 |** Comparison of poor and good final responders.

Background	25% poorest total ΔHt SDS <sup>1</sup>			25% best total ΔHt SDS <sup>1</sup>			p-value	25% poorest nFAH SDS <sup>1&amp;c</sup>			25% best nFAH SDS <sup>1&amp;c</sup>			p-value
	n	Mean	SD	n	Mean	SD		n	Mean	SD	n	Mean	SD	
Birth weight, SDS	28	-0.53	0.73	30	-0.05	0.89	<0.05							
Father height, SDS	29	-1.43	1.04	30	-0.41	1.19	<0.01	29	-1.66	1.21	30	0.35	1.01	<0.001
Mother height, SDS	29	-1.42	0.99	30	-0.54	1.05	<0.01	29	-1.67	1.04	30	0.17	0.90	<0.001
MPH, SDS	29	-1.43	0.89	30	-0.50	0.92	<0.001	29	-1.66	0.91	30	0.24	0.80	<0.001
Maximum GH peak, µg/L	32	6.4	2.4	32	2.7	1.6	<0.001	32	4.8	2.9	32	3.0	1.9	<0.01
<b>At start GH treatment</b>														
Age, years	32	7.2	2.4	32	5.8	2.3	<0.05							
Height, SDS	32	-3.03	0.71	32	-3.78	0.8	<0.001	32	-3.88	0.89	32	-3.10	0.91	<0.01
Height minus MPH, SDS	29	-1.54	0.83	30	-3.25	0.97	<0.001	29	-2.25	1.33	30	-3.19	0.81	<0.01
BMI, SDS	32	-0.69	0.96	32	-0.07	1.08	<0.05							
HV during pretreatment year, cm/year	27	5.7	2.1	25	4.8	2.2	0.2	27	5.2	2.1	28	4.8	2.2	0.5
<b>After first-year GH treatment</b>														
Height, SDS	32	-2.41	0.63	32	-2.28	0.83	0.5	32	-2.98	0.80	32	-1.65	0.72	<0.001
Height minus MPH, SDS	29	-0.91	0.79	30	-1.76	1.06	<0.01							
<i>Growth response</i>														
Δ height, SDS <sup>2</sup>	32	0.61	0.36	32	1.50	0.44	<0.001	32	0.90	0.47	32	1.45	0.47	<0.001
Δ HV, cm/year	27	2.9	3.0	25	7.8	3.1	<0.001	27	4.6	3.4	25	7.8	3.3	<0.01
HV, cm/year	32	8.3	1.8	32	12.6	1.9	<0.001	32	9.4	2.3	32	12.7	2.0	<0.001
HV for age and sex, SDS	31	0.35	1.60	26	4.20	1.73	<0.001	31	1.24	2.03	26	4.36	1.96	<0.001
<i>Responsiveness</i>														
HV for first-year GH treatment <sup>c</sup> , SDS	32	-0.16	0.87	32	0.89	0.80	<0.001	32	0.02	0.94	32	1.01	0.83	<0.001
Studentized residual (with GH peak)	29	-0.24	1.07	30	0.73	1.24	<0.01	29	-0.11	1.16	30	0.76	1.26	<0.01
Studentized residual (without GH peak)	29	-0.34	0.93	30	0.99	1.08	<0.001	29	-0.01	1.09	30	1.00	1.19	<0.01
<i>Prediction of nFAH</i>														
Predicted nFAH (with GH peak) <sup>d</sup>	29	-1.20	0.57	30	-0.37	0.77	<0.001	29	-1.56	0.77	30	0.36	0.64	<0.001
Predicted nFAH (without GH peak) <sup>d</sup>	29	-1.21	0.57	30	-0.39	0.79	<0.001	29	-1.57	0.79	30	0.35	0.66	<0.001
<b>At puberty onset</b>														
Duration GH therapy before puberty, years	31	4.9	2.5	32	6.7	2.5	<0.01							
Height, SDS	31	-2.10	0.67	31	-0.84	1.00	<0.001	31	-2.40	0.86	31	-0.31	0.85	<0.001
Δ height, SDS	31	0.94	0.46	31	2.91	0.96	<0.001	31	1.48	0.79	31	2.87	1.18	<0.001
<b>At nFAH</b>														
Duration GH therapy, years	32	8.9	2.5	32	11.0	2.2	<0.01							
nFAH, SDS <sup>e</sup>	32	-2.31	0.71	32	-0.30	0.95	<0.001	32	-2.34 <sup>h</sup>	0.49	32	0.90 <sup>k</sup>	0.49	<0.001
nFAH, SDS <sup>3</sup>	32	-2.05	0.71	32	-0.11	0.88	<0.001	32	-2.26 <sup>h</sup>	0.50	32	0.99 <sup>k</sup>	0.47	<0.001
nFAH minus MPH, SDS <sup>e</sup>	29	-0.78	0.67	30	0.17	0.99	<0.001	29	-1.04 <sup>h</sup>	0.93	28	0.31 <sup>k</sup>	0.95	<0.001
nFAH minus MPH, SDS <sup>3</sup>	29	-0.53	0.73	30	0.41	0.96	<0.001	29	-0.96 <sup>h</sup>	0.91	28	0.40 <sup>k</sup>	0.92	<0.001
Total Δ height <sup>4</sup> , SDS <sup>e</sup>	32	0.71	0.47	32	3.48	0.85	<0.001	32	1.76 <sup>h</sup>	0.87	32	4.12 <sup>k</sup>	1.16	<0.001
total Δ height <sup>4</sup> , SDS <sup>3</sup>	32	0.98	0.42	32	3.71	0.71	<0.001	32	1.84 <sup>h</sup>	0.84	32	4.20 <sup>k</sup>	1.14	<0.001
BMI, SDS <sup>e</sup>	25	-0.99	1.16	28	-0.05	1.17	<0.01							
BMI, SDS <sup>f</sup>	25	-0.63	1.03	28	0.21	1.14	<0.01							

Characteristics: background, at GH start, after first year, at puberty onset, at nFAH GH, growth hormone; nFAH, near final adult height; SDS, standard deviation score; MPH, midparental height; BMI, body mass index; HV, height velocity; SDS, standard deviation score; cm, centimeter; <sup>1</sup> SDS calculated at 21 years; <sup>2</sup> SDS calculated at chronological age; <sup>3</sup> SDS calculated with Prader references; <sup>4</sup> change in BMI SDS after first-year GH treatment; <sup>5</sup> gain in height SDS after first-year GH treatment; <sup>6</sup> growth targets for first-year GH response by Ranke et al.; <sup>7</sup> prediction model for nFAH by Ranke et al.; <sup>8</sup> gain in height SDS from start of GH treatment until nFAH.

## FLOW CHART PATIENT SELECTION

*n* = 1230, idiopathic GHD (iGHD) not secondary to a treatment of a tumor or not HSD3 with or without symptoms

Idiopathic GHD with syndromes or diagnostic features (*n* = 157)

*n* = 1073, idiopathic GHD, idiopathic congenital hypopituitarism (ICGHD), idiopathic growth hormone insensitivity (IGHI), idiopathic isolated hypopituitarism (IIH)

Start GH before 1995 (*n* = 45)

*n* = 998

SGA (*n* = 132)

*n* = 895

Age at start GH < 2 year (*n* = 87)

*n* = 795

Age at start GH treatment > 11 year (males) (*n* = 94); > 12 year (females) (*n* = 133)

*n* = 698

Duration of GH < 4 year or stimulation < 5 months (*n* = 47)

*n* = 614

Age at IFRH < 15 year (males) and < 17 year (females) or GH treatment not stopped (*n* = 242)

*n* = 272

GH peak in provocation test > 10 ng/ml or only 1 provocation test performed (*n* = 14)

*n* = 258

Too many missing data (*n* = 2)

*n* = 256

Not prepubertal after 1 year GH therapy (*n* = 7) or pubertal stage unknown (*n* = 8)

*n* = 235

GH treatment not daily or not recombinant human GH (*n* = 51)

*n* = 214

No adult height achieved as height velocity < 2 cm/year (*n* = 28)

*n* = 192

the total population). At these cut-offs the amount of correctly diagnosed poor responders equals the amount of false positives due to the relatively low prevalence of poor responders.

Several parameters, such as birth weight, midparental height, age at start, max. GH peak in provocation test, height at start, and IFR after the first year of GH treatment were found to differ between patients with a good or a poor final height outcome. Not surprisingly, these parameters are also used in prediction models for rFAH, such as in the model by Ranke et al. (16).

However, these parameters were found to only explain 60% of the variability. An incorrect diagnosis of GHD or the presence of another growth limiting condition at start of GH as well as several conditions during the GH course, such as GH dose adaptations during the first year, poor compliance after the first year of GH treatment as well as variability in pubertal onset, pubertal growth and bone age progression may all explain the poor predictability of the FAH outcome in GH treated children.

This is the first study evaluating the final height predictability of the currently used first year growth response parameters, putting them in a new long-term perspective. However, this study has also several shortcomings. Treatment adherence and the persistence of the GHD were not assessed routinely in the studied cohort. Secondly, the size of the cohort was rather small, despite the national recruitment of patients.

Despite FYGR criteria were found not to be suitable for detecting poor or good final responders without too many misdiagnoses, it is still important to evaluate first-year response to GH to identify poor compliance, improper administration of GH, additional health problems, poor nutrition, impaired GH sensitivity due to mutations in the GH-IGF-1 axis genes, incorrect initial diagnosis, etc.

In conclusion, the currently used first-year growth response and responsiveness parameters perform poorly as predictors of a poor final height outcome after long-term GH treatment in prepubertal GHD children, due to low sensitivities and/or specificities and the low prevalence of poor responders in this group. The FYGR parameters may perform better in indications with more poor responders or when more stringent criteria for poor near final height outcome (e.g.,  $\Delta$ Ht SDS > 1.5) are used.

## DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of the University of Brussels and University Hospital of Brussels. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

SS, JD, MI, SF, VB, and IJR contributed to the conception, design of the study and wrote sections of the manuscript. SS and MI organized the database. SS performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Chapter 7

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Is a two-year growth response to growth hormone treatment a better predictor of poor adult height outcome than a first-year growth response in prepubertal children with growth hormone deficiency?







# Is a Two-Year Growth Response to Growth Hormone Treatment a Better Predictor of Poor Adult Height Outcome Than a First-Year Growth Response in Prepubertal Children With Growth Hormone Deficiency?

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**Objective:** The first year response to growth hormone (GH) treatment is related to the total height gain in GH treated children, but an individual poor first year response is a weak predictor of a poor total GH effect in GH deficient (GHD) children. We investigated whether an underwhelming growth response after 2 years might be a better predictor of poor adult height (AH) outcome after GH treatment in GHD children.

**Design and methods:** Height data of GHD children treated with GH for at least 4 consecutive years of which at least two prepubertal and who attained (near) (n)AH were retrieved from the Belgian Register for GH treated children (n = 110, 63% boys). In ROC analyses, the change in height ( $\Delta$ Ht) SDS after the first and second GH treatment years were tested as predictors of poor AH outcome defined as: (1) nAH SDS < -2.0, or (2) nAH SDS minus mid-parental height SDS < -1.3, or (3) total  $\Delta$ Ht SDS < 1.0. The cut-offs for  $\Delta$ Ht SDS and its sensitivity at a 95% specificity level to detect poor AH outcome were determined.

**Results:** Eleven percent of the cohort had a total  $\Delta$ Ht SDS < 1.0. ROC curve testing of first and second years  $\Delta$ Ht SDS as a predictor for total  $\Delta$ Ht SDS < 1.0 had an AUC > 70%. First-year  $\Delta$ Ht SDS < 0.41 correctly identified 42% of the patients with poor AH outcome at a 95% specificity level, resulting in respectively 5/12 (4.6%) correctly identified poor final responders and 5/98 (4.5%) misclassified good final responders (ratio 1.0).  $\Delta$ Ht SDS after 2 prepubertal years had a cut-off level of 0.65 and a sensitivity of 50% at a 95% specificity



level, resulting in respectively 6/12 (5.5%) correctly identified poor final responders and 5/98 (4.5%) misclassified good final responders (ratio 1.2).

**Conclusion:** In GHD children the growth response after 2 prepubertal years of GH treatment did not meaningfully improve the prediction of poor AH outcome after GH treatment compared to first-year growth response parameters. Therefore, the decision to re-evaluate the diagnosis or adapt the GH dose in case of poor response after 1 year should not be postponed for another year.

**Keywords:** growth hormone treatment, growth hormone deficiency, children, growth response, poor adult height outcome

## INTRODUCTION

The goal of growth hormone (GH) treatment in a GH deficient (GHD) child is to attain a true catch-up growth, resulting in an adult height (AH) close to target height (1). The pattern of GH induced growth consists of a first phase of accelerated growth, which allows the child to approach its target height in a number of years and is followed by a phase of maintenance growth where height velocity (HV) is normal. Several studies have evidenced that this GH induced growth acceleration diminishes rapidly, which is called the waning effect (2, 3). This waning has been explained by a GH receptor desensitization, but its determinants have been poorly studied in children with GHD.

In clinical practice, the first-year growth response is most often used to evaluate the individual response to GH treatment (4, 5), allowing the early identification of GHD patients who may not respond to a physiological GH replacement and/or are not GHD. However, we recently showed that the currently used first-year growth response and responsiveness parameters have a low sensitivity and/or specificity to predict a suboptimal adult height outcome after long-term GH treatment in prepubertal GHD children (6).

Many issues may negatively influence the first year response to GH treatment, including GH injection problems, an inappropriate GH starting dose, a hidden growth limiting disease, or additional hormonal deficiencies appearing during GH therapy (e.g. central hypothyroidism) (7). Correction of these conditions in the second year may result in an improved linear growth during the second year. In addition, a less pronounced waning effect in the second year of GH treatment might also explain why some children with an inadequate first-year growth response do have an adequate AH outcome.

We therefore investigated in prepubertal children with a non-organic GHD: 1) the contribution of the first 2 years of GH therapy to the total height increase, 2) the magnitude and determinants of the waning of the growth response during the second year, and 3) the eventual improvement of poor adult height prediction after two years of GH therapy in comparison with the prediction after one year of GH treatment. We hypothesized that the growth response after 2 years of GH treatment may be a better predictor of poor adult height outcome than the first year response, as in some patients a less pronounced waning in the second year might compensate a failing first year growth response to GH therapy.

## MATERIALS AND METHODS

### Materials

The auxological data and GH treatment characteristics of children diagnosed with GHD, collected by the members of the Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED) in a national database, called Belgrow, since 1986 were retrieved. This study was approved by the ethical committee of Brussels Free University and the University Hospital Brussels in Belgium. All subjects gave written informed consent in accordance with the Declaration of Helsinki. In the registry, all data are pseudonymized to comply with rigorous privacy guidelines. Only patients who had been treated exclusively with daily recombinant human GH for at least 4 consecutive years of which at least two were prepubertal and who had attained (near) AH (nAH) were included. The patients were mostly treated in a time period when the dose for GHD in Belgium was fixed to 25 mcg/kg \* day. GHD patients with central malformations (e.g. anomalies of the pituitary and/or stalk) and patients with idiopathic GHD as well as patients with congenital GHD related to genetic alterations (e.g. GH gene mutations) were included, but those with acquired GHD of known cause (related to e.g. a brain tumor, brain irradiation, brain trauma) were excluded. Other exclusion criteria were any medication or known medical condition other than GHD that could affect growth, interruption of GH treatment for more than 6 months, and a birth weight and/or birth length below  $-2$  SD. Girls aged  $\geq 12$  years and boys aged  $\geq 13$  years at the end of the second GH treatment year were excluded. In total, 110 patients (69 males and 41 females) with non-acquired GHD (66 with isolated GHD and 44 with multiple pituitary hormone deficiency) met the inclusion and exclusion criteria.

### Methods

The diagnosis of GHD was made by the treating physician and peer-reviewed by BESPEED members (8). All patients had a peak GH concentration of  $< 10$   $\mu\text{g/L}$  after both glucagon and insulin stimulation. Pubertal onset was defined as testicular volumes  $\geq 4$  ml for boys and Tanner breast stage  $\geq 2$  in girls.

Birth weight for gestational age was transformed into SDS, based on the standards of Niklasson et al. (9). The MPH was calculated according to Tanner et al. as follows: (father's height + mother's height + 13 for boys/-13 for girls)/2 (10). Height, weight, BMI, and MPH were converted to SDS using Flemish reference data (11).



nAH was defined as the height attained when HV was less than 2 cm/year, calculated over a period of minimum 9 months, and chronological age >17 years in boys and >15 years in girls. nAH SDS was calculated in two different ways, using the Flemish reference data: (1) for the chronological age (CA), (2) for an age of 21 years (A21).

The change in height ( $\Delta$ Ht) SDS was calculated after the first and second prepubertal year of GH therapy, provided that the height data were available within a 9–15 month interval for that year and scaled to respectively 12 and 24 months.

The final outcome of the GH treatment was evaluated by three different methods: (1) nAH, expressed as a height SDS; (2) total  $\Delta$ Ht SDS, calculated as the nAH SDS minus height SDS at start of GH treatment; (3) nAH SDS minus midparental height (MPH) SDS, an index of achieving the genetic height potential. A poor final treatment outcome was defined as total  $\Delta$ Ht SDS <1.0, nAH SDS – MPH SDS <–1.3, and nAH SDS <–2.0.

Receiver operating characteristic (ROC) curve analyses were performed for  $\Delta$ Ht SDS after the first and second prepubertal years as a predictor for the defined poor adult height outcome parameters. We have previously published the results of ROC analyses of the first year only, in a cohort overlapping the cohort of this study (6).

### Statistical Analysis

The variables are reported as the median (25–75th percentiles) and mean ( $\pm$  SD). A Shapiro–Wilk test was used to test for the normal distribution. ROC curve analyses were performed to examine the relationship between sensitivity and specificity for the different test parameters and the different outcome parameters. Only pairs with an area under the ROC-curve (AUC)  $\geq 70\%$  were further analyzed. In order to misdiagnose only 5% of good responders, a specificity level of 95% was chosen to calculate the corresponding cut-off values for  $\Delta$ Ht SDS. Linear regression analyses were performed to study the relationship between the growth responses and possible explanatory variables. Significance was considered at the 5% level ( $p < 0.05$ ). MedCalc<sup>®</sup> and IBM SPSS Statistics 25<sup>®</sup> software was used for all statistical analyses.

## RESULTS

### Clinical Characteristics

The background and auxological characteristics of 110 included GHD children (69 males, 41 females) are listed in **Table 1**. GH therapy was initiated at a mean age of 6.2 years and at a median height SDS of –3.47, which was 2.47 SDS below the MPH SDS. The mean GH dose at start was 28  $\mu\text{g}/\text{kg}\cdot\text{day}$ . The mean duration of GH therapy was 10.2 years, with a mean duration before pubertal onset of 6.2 years. Girls entered puberty spontaneously at a mean age of 11.3 years ( $n = 35$ ), boys at a mean age of 12.5 years ( $n = 45$ ). Puberty was hormonally induced at a mean age of 12.9 years in girls ( $n = 5$ ) and 13.9 years in boys ( $n = 20$ ). nAH was attained at a mean age of 16.7 years in girls and 18.7 years in boys.

### Response to GH Treatment During the First Two Years of Treatment

The median  $\Delta$ Ht SDS after the first treatment year was 1.03, while the median  $\Delta$ Ht SDS during the second year was 0.43 (**Table 1**). **Figure 1** shows the individual data and the correlation between  $\Delta$  height SDS during the first and second GH treatment years. The  $\Delta$ Ht SDS during the second year correlated moderately ( $r = 0.553$ ;  $p < 0.001$ ) with the first year height increase. Patients with a lower than median  $\Delta$ Ht SDS (<1.03 SD) during the first treatment year had a median second year  $\Delta$ Ht SDS of 0.29 SD, which was 0.33 SD lower than the first year; their median  $\Delta$ Ht SDS after 2 years was 0.95. In contrast, patients with a higher than median first-year  $\Delta$ Ht SDS (>1.03) had a median second year  $\Delta$ Ht SDS of 0.57 SD, which was 0.77 SD lower than the first year; their median  $\Delta$ Ht SDS after 2 years was 2.01. Of the 55 patients with a higher than median first-year  $\Delta$ Ht SDS, 19 had a lower than median second-year response (shown in quadrant D in **Figure 1**), while 17/55 patients with a lower than median first-year  $\Delta$ Ht SDS had a higher than median second year increase (shown in quadrant A). Only 4/110 patients had a second year  $\Delta$ Ht SDS that was higher than the first year  $\Delta$ Ht SDS.

### Determinants of the Waning Effect During the Second Year

The first year  $\Delta$ Ht SDS correlated negatively with maximum GH peak in the GH stimulation tests, age at start, height minus MPH SDS at start, height SDS at start, and correlated positively with BMI SDS at start, mid parental height SDS and GH dose at start (**Table 2**). Whereas the height SDS increase in the second year correlated positively with first-year  $\Delta$ Ht SDS and negatively with maximum GH peak, height minus MPH SDS at start, height SDS at start, and age at start. The waning effect, calculated by the difference between  $\Delta$ Ht SDS in the second year and  $\Delta$ Ht SDS in the first year, was positively correlated with first-year  $\Delta$ Ht SDS, height SDS after the first and second years, BMI SDS at start, and correlated negatively with age at start, height minus MPH at start, maximum GH peak, and height SDS at start.

### Response to GH Treatment During the Whole Treatment Period

**Figure 2** compares the height SDS at start of GH treatment, after the first and second GH treatment years, at pubertal onset and at near AH. After one and two years of GH therapy, the median  $\Delta$ Ht SDS was respectively 1.03 and 1.44. At onset of puberty, median  $\Delta$ Ht SDS was 1.80. The median  $\Delta$ Ht SDS at nAH was 2.09 for chronological age (CA), but 1.86 when extrapolated to the age of 21 years (A21). The 2 year  $\Delta$ Ht SDS accounted thus for 69% (CA)–77% (A21) of the total increase in height SDS. Twenty five percent of the patients had a  $\Delta$ Ht SDS <1.0 at 2 years, 20% at pubertal onset, and 11% (CA)–16% (A21) at nAH.

After two years 46% of the patients had a height SDS <–2.0 and 35% at pubertal onset, whereas at the moment of nAH, 25% (CA) and 28% (A21) of the patients had a height SDS <–2.0. The median difference of the height SDS with the MPH SDS gradually diminished over time after the first and second

**TABLE 1** | Characteristics: background, at GH start, after 1<sup>st</sup> year, after 2<sup>nd</sup> year, at pubertal onset, at nAH.

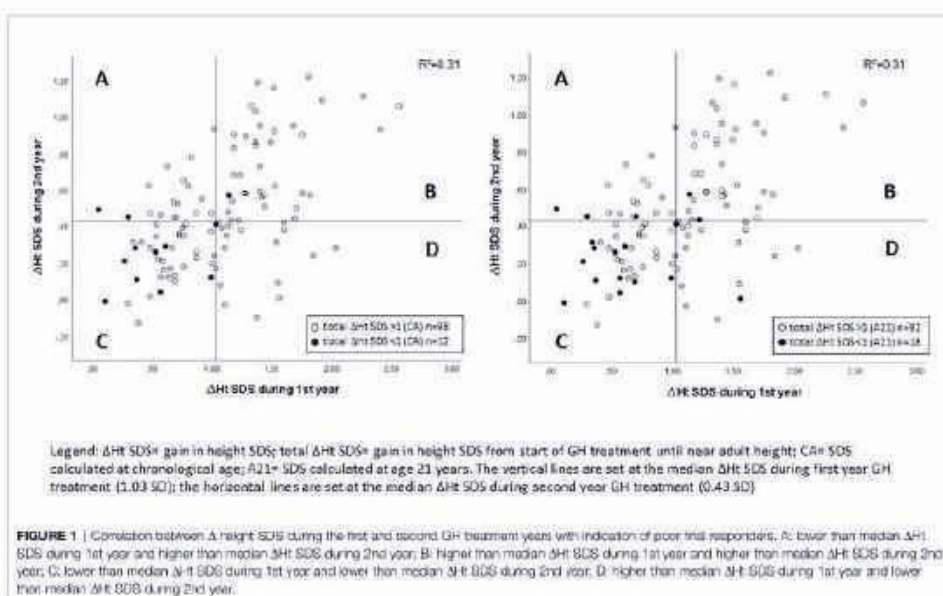
	n	median	p25	p75	mean	SD
<b>Background</b>						
gestational age, weeks	104	40.0	38.0	40.0	38.5	2.9
birth weight, SDS	103	-0.27	-0.77	0.25	-0.18	0.89
birth length, SDS	93	-0.27	-0.77	0.25	-0.24	0.95
father height, SDS	105	-1.20	-1.80	-0.15	-1.03	1.17
mother height, SDS	105	-0.78	-1.62	-0.27	-0.91	1.16
MPH, SDS	105	1.05	-1.71	-0.45	-0.99	0.95
maximum GH peak, µg/L	110	3.9	2.1	6.7	4.3	2.7
<b>at start GH treatment</b>						
age, years	110	6.1	4.6	8.2	6.2	2.3
height, SDS	110	-3.44	-3.99	-2.80	-3.47	0.86
height minus MPH, SDS	105	-2.44	-3.10	-1.75	-2.47	1.11
BMI, SDS	110	-0.42	-1.20	0.41	-0.33	1.11
GH dose, µg/kg.day	110	27.0	24.5	31.1	28.0	5.5
<b>after first year GH treatment</b>						
height, SDS	110	-2.36	-2.91	-1.89	-2.42	0.83
Δ height, SDS <sup>a</sup>	110	1.03	0.65	1.40	1.05	0.50
Δ height velocity, cm/year	95	4.8	3.1	7.2	5.2	3.2
height minus MPH, SDS	105	-1.34	-2.03	-0.73	-1.41	0.98
<b>after second year GH treatment</b>						
height, SDS	110	-1.92	-2.52	-1.47	-1.95	0.88
Δ height, SDS <sup>b</sup>	110	1.44	0.95	2.01	1.52	0.72
Δ height velocity, cm/year	110	-2.5	-3.6	-1.3	-2.5	1.9
height minus MPH, SDS	105	-0.94	-1.62	-0.28	-0.94	0.97
<b>at puberty onset</b>						
age onset spontaneous puberty (females), years	35	11.4	10.6	12.1	11.3	1.0
age puberty induction (females), years	5	13.0	11.8	13.9	12.9	1.0
age onset spontaneous puberty (males), years	45	12.7	12.0	13.1	12.5	1.0
age puberty induction (males), years	20	14.0	13.3	14.2	13.9	1.2
duration GH therapy before puberty, years	105	6.3	4.4	8.2	6.2	2.4
height, SDS	104	-1.52	-2.29	-0.97	-1.52	1.09
Δ height, SDS <sup>c</sup>	104	1.80	1.14	2.65	1.94	1.03
height minus MPH, SDS	99	-0.49	-1.27	0.06	-0.52	1.11
<b>at nAH</b>						
age, years	110	17.9	16.9	18.9	18.0	2.2
age, years (females)	41	16.5	15.2	17.8	16.7	1.8
age, years (males)	69	18.3	17.1	19.2	18.7	2.2
age stop GH treatment, years	110	16.5	15.4	17.4	16.4	1.5
age stop GH treatment, years (females)	41	15.2	14.5	16.5	15.5	1.4
age stop GH treatment, years (males)	69	16.8	16.1	17.6	16.9	1.3
growth since stop GH treatment, cm	106	0.5	0.0	1.2	1.3	2.5
duration GH therapy, years	110	10.2	8.2	12.0	10.2	2.4
nAH CA, SDS	110	-1.21	-1.97	-0.39	-1.21	1.12
nAH A21, SDS	110	-1.53	-2.22	-0.67	-1.44	1.14
nAH CA minus MPH, SDS	105	-0.20	-0.72	0.46	-0.19	0.99
nAH A21 minus MPH, SDS	105	-0.42	-0.99	0.22	-0.43	0.98
Δ height (onset puberty until nAH CA), SDS	104	0.26	-0.18	0.81	0.28	0.26
Δ height (onset puberty until nAH A21), SDS	104	0.02	-0.55	0.71	0.05	0.84
total Δ height CA, SDS <sup>d</sup>	110	2.09	1.56	3.00	2.27	1.11
total Δ height A21, SDS <sup>d</sup>	110	1.86	1.18	2.74	2.03	1.16
BMI CA, SDS	95	-0.11	-1.12	0.65	-0.16	1.33
BMI A21, SDS	95	-0.50	-1.53	0.33	-0.46	1.42

GH, growth hormone; MPH, midparental height; BMI, body mass index; nAH, near adult height; SDS, standard deviation score; cm, centimeter; A21, SDS calculated at age 21 years; CA, SDS calculated at chronological age; <sup>a</sup>gain in height SDS from start until after first-year GH treatment; <sup>b</sup>gain in height SDS from start until after second year of GH treatment; <sup>c</sup>gain in height SDS from start of GH treatment until onset puberty; <sup>d</sup>gain in height SDS from start of GH treatment until nAH.

prepubertal years of GH treatment until pubertal onset, respectively 1.34, 0.94, and 0.49 SDS. At start, 87% of the patients had a height – MPH SDS <–1.3, after two years this percentage decreased to 35%, and at pubertal onset it was 23% of the patients. Finally, 12% (CA) and 14% (A21) of the patients had a nAH – MPH SDS <–1.3.

### Response to GH Treatment in Isolated GHD Versus MPH

Of 110 patients, 44 had multiple pituitary hormone deficiencies that were supplemented. ΔHt SDS after 1 year, ΔHt SDS after 2 years, and total ΔHt SDS were comparable between the group with isolated GHD and MPH (Table 3).

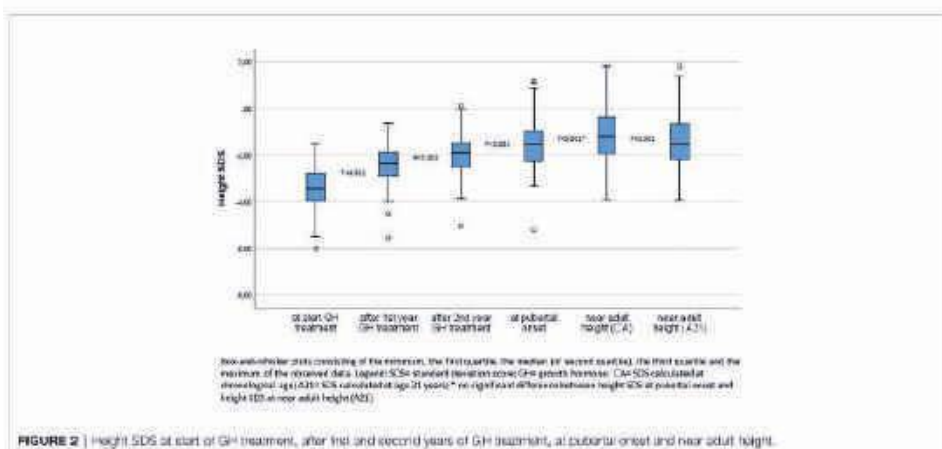


**TABLE 2** | Linear regression analyses for the prediction of first and second year  $\Delta$ Ht SDS and the wearing effect during the second GH treatment year in prepubertal GH-T patients.

predictors	R <sup>2</sup>	p-value	correlation pos/neg
<b>first-year <math>\Delta</math>Ht SDS<sup>a</sup></b>			
maximum GH peak	0.302	<0.001	-
age at start	0.219	<0.001	-
height minus MPH SDS at start	0.216	<0.001	-
height SDS at start	0.129	<0.001	-
BMI SDS at start	0.073	<0.01	+
father height SDS	0.06	<0.05	+
MPH-SDS	0.046	<0.08	+
GH dose at start	0.036	<0.08	+
<b><math>\Delta</math>Ht SDS during second year<sup>b</sup></b>			
first-year $\Delta$ Ht SDS	0.326	<0.001	+
maximum GH peak	0.301	<0.001	-
height minus MPH SDS at start	0.191	<0.001	-
height SDS at start	0.103	0.001	-
age at start	0.049	<0.05	-
<b>wearing effect<sup>c</sup></b>			
first-year $\Delta$ Ht SDS	0.618	<0.001	+
age at start	0.161	<0.001	-
height SDS after first year	0.072	<0.01	+
height minus MPH SDS at start	0.035	<0.01	-
maximum GH peak	0.033	0.01	-
height SDS after second year	0.05	<0.05	+
height SDS at start	0.036	<0.05	-
BMI at start	0.037	<0.05	+

<sup>a</sup>gain in height SDS after 1 year of GH treatment; <sup>b</sup>gain in height SDS after 2 years of GH treatment; <sup>c</sup>wearing effect, first-year  $\Delta$ Ht SDS minus  $\Delta$ Ht SDS during second year; GH, growth hormone; GAD, GH deficient; R<sup>2</sup>, the coefficient of determination; pos, positive correlation; neg, negative correlation; MPH, mid parental height; BMI, body mass index.





**FIGURE 2 |** Height SDS at start of GH treatment, after first and second years of GH treatment, at pubertal onset and near adult height.

### Prediction of a Poor Adult Height Outcome

ROC curve analysis was performed for  $\Delta$ Ht SDS after the first and second prepubertal years of GH treatment in relation to the studied poor final outcome parameters (total  $\Delta$ Ht SDS <1, nAH SDS <-2, and nAH SDS - MPH SDS <-1.3). Only ROC-curves related to total  $\Delta$ Ht SDS <1.0 had an AUC  $\geq 70\%$  (varying between 78 and 82%) and were further analyzed (Figure 3).

Tables 4A, B show the cut-off values for  $\Delta$ Ht SDS after 1 and 2 prepubertal years of GH treatment, with their sensitivity and specificity to predict total  $\Delta$ Ht SDS <1.0 (CA and A21). The sensitivity to predict total  $\Delta$ Ht SDS <1.0 (CA) with a specificity of 95% was 42 and 50%, resulting in respectively 5/12 (4.6%) and 6/12 (5.5%) correctly identified poor final responders. At a 95% specificity level, 5/98 (4.5%) of the good final responders were misclassified as poor responders. If the SDS was calculated on age 21, the corresponding sensitivities were 33% after the first year and 44% after two years of GH treatment, giving respectively 6/18 (5.4% and 8/18 (7.2%) correctly diagnosed poor final responders. At a 95% specificity level, 5/92 (4.2%) of the good final responders were misclassified as poor responders. The ratio correctly diagnosed poor final responders/misclassified good

final responders (1.0 at one year and 1.2 at two years) did not improve after two years of GH treatment.

As shown in Figure 1, eight of 12 patients with a total height increase of <1 (CA) had both a below median  $\Delta$ Ht SDS after one and at two years of treatment.

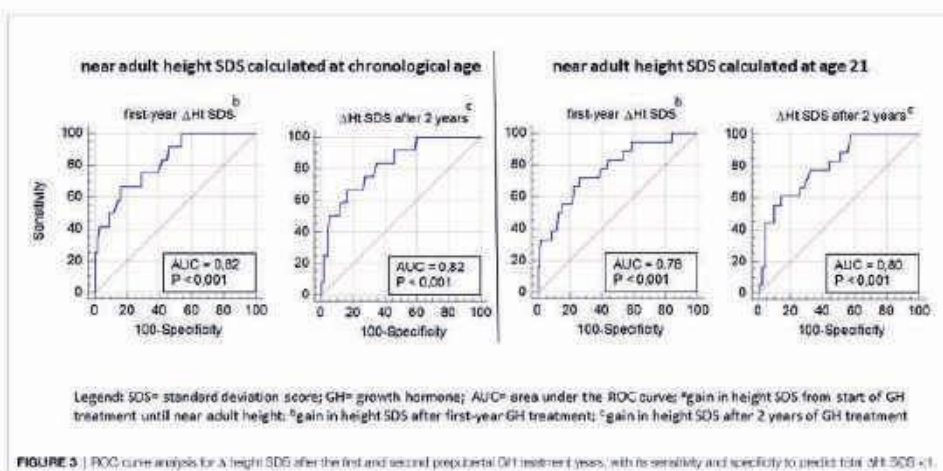
### DISCUSSION

The first year response to GH, in general represented as  $\Delta$ Ht SDS, is used by many clinicians to identify those children who may or may not benefit from long-term GH treatment. The first year response is also often used as a *post hoc* diagnostic criterion of GHD, especially in children with an idiopathic form of GHD. Although the first year response could be used to guide GH dosing, the current practice is to keep GH dosage stable over-time on a body weight or body surface basis (in general between 0.25 and 35  $\mu$ g/kg/day) in GHD patients, at least in Belgium and several other European countries (12–14). While the first year growth response to GH is highly associated with the adult height outcome, it is a weak predictor for a poor growth outcome as an

**TABLE 3 |** Response to GH treatment in isolated GHD versus MPH/D.

	Isolated GHD (n = 66)			MPHD (n = 44)			p-value
	median	p25	p75	median	p25	p75	
$\Delta$ Ht SDS after 1 year <sup>a</sup>	1.04	0.66	1.36	1.02	0.61	1.39	n.s.
$\Delta$ Ht SDS after 2 years <sup>a</sup>	1.40	1.07	1.90	1.47	0.92	2.07	n.s.
total $\Delta$ Ht BCS ICA <sup>b</sup>	0.14	1.09	2.97	0.04	1.09	3.20	n.s.
total $\Delta$ Ht BCS A21 <sup>b</sup>	1.86	1.20	2.60	1.81	1.14	2.79	n.s.

GH, growth hormone; GHD, growth hormone deficiency; MPH/D, multiple pituitary hormone deficiencies; SDS, standard deviation score; ICA, in height SDS from start until first year of GH treatment; A21, in height SDS from start until second year of GH treatment; ICA, SDS calculated at chronological age; A21, SDS calculated at age 21 years; n.s., not significant.



**FIGURE 3 |** ROC curve analysis for  $\Delta$  height SDS after the first and second prepubertal GH treatment years, with its sensitivity and specificity to predict total  $\Delta$ HI SDS  $< 1$ .

**TABLE 4A |** ROC curve analysis: cut-off values for  $\Delta$ HI SDS after 1 and 2 years of prepubertal GH treatment, with its sensitivity and specificity to predict total  $\Delta$ HI SDS  $< 1$  (A2).

$\Delta$ HI after 1 year, SDS <sup>a</sup>	sensitivity (%)	specificity (%)	$\Delta$ HI after 2 years, SDS <sup>a</sup>	sensitivity (%)	specificity (%)
0.27	77	100	0.10	6	100
<b>0.47</b>	<b>83</b>	<b>98</b>	<b>0.72</b>	<b>44</b>	<b>98</b>
0.64	80	89	0.79	56	90
1.22	94	41	1.65	94	43
1.66	100	16	1.71	100	42
AUC: 78% (95% CI: 66–85%) n = 110 (F = 18 – G = 92)			AUC: 60% (95% CI: 75–87%) n = 110 (F = 18 – G = 92)		

GH, growth hormone; AUC, area under the ROC curve; CI, confidence interval; <sup>a</sup>gain in height SDS from start of GH treatment until near adult height; <sup>b</sup>gain in height SDS after 1 year of GH treatment; <sup>c</sup>gain in height SDS after 2 years of GH treatment; A2, SDS calculated at age 21 years; n, number of patients; F, total  $\Delta$ HI SDS  $< 1$ ; G, total  $\Delta$ HI SDS  $> 1$ ; *bold*, values of 95% specificity.

**TABLE 4B |** ROC curve analysis: cut-off values for  $\Delta$ HI SDS after 1 and 2 years of prepubertal GH treatment, with its sensitivity and specificity to predict total  $\Delta$ HI SDS  $< 1$  (A1).

$\Delta$ HI after 1 year, SDS <sup>a</sup>	sensitivity (%)	specificity (%)	$\Delta$ HI after 2 years, SDS <sup>a</sup>	sensitivity (%)	specificity (%)
0.27	35	100	0.10	6	100
<b>0.41</b>	<b>42</b>	<b>98</b>	<b>0.64</b>	<b>80</b>	<b>98</b>
0.63	30	91	0.79	88	88
1.03	92	54	1.46	92	54
1.14	100	46	1.71	100	46
AUC: 62% (95% CI: 74–80%) n = 110 (F = 12 – G = 98)			AUC: 62% (95% CI: 74–80%) n = 110 (F = 12 – G = 98)		

GH, growth hormone; AUC, area under the ROC curve; CI, confidence interval; <sup>a</sup>gain in height SDS from start of GH treatment until near adult height; <sup>b</sup>gain in height SDS after 1 year of GH treatment; <sup>c</sup>gain in height SDS after 2 years of GH treatment; A1, SDS calculated at chronological age; n, number of patients; F, total  $\Delta$ HI SDS  $< 1$ ; G, total  $\Delta$ HI SDS  $> 1$ ; *bold*, values of 95% specificity.

individual basis, as we previously reported in a cohort overlapping the cohort of this study (6). In this study, we investigated if a lower waning effect in the second year might compensate for a lower first year response in prepubertal children with GHD, translating in a better predictability of a poor total height gain after two years of GH treatment.

A waning effect was observed in the majority of the patients in our study; only 3.6% of the GHD patients had a second year  $\Delta$ HI SDS that was higher than the first year  $\Delta$ HI SDS. The waning effect was greater in those with a more impressive height gain in the first year, which occurred more often in younger patients, in patients with a more severe GHD, and a greater height deficit

in relation to their parental height. These results are consistent with previous studies in prepubertal patients with GHD (15, 16), with the exception of the absent association with the first year GH dose. The absent association with the GH dose in our study can be explained by the uniform dosing around 25  $\mu\text{g}/\text{kg}\cdot\text{day}$ . However, previous attempts trying to overcome this waning effect in GHD patients by modifying the dose or the frequency of the GH regimen have not been very efficacious, as the dose response relationship diminishes during the second year (17, 18).

We confirmed that the majority of the height gain in GH treated GHD children occurs during the first 2 years of treatment (19). In our study, 69% (CA) – 77% (A21) of the total height gain was obtained in the first 2 years. We showed that there was still some improvement in the percentages of children obtaining a normal height or a height within the expected target range after two years of treatment.

Despite its important contribution to the total height gain, the height increase after two years of treatment did not greatly improve the sensitivity to predict a poor growth outcome at the end of treatment: the sensitivity to detect with 95% specificity a poor total height increase at the end of treatment increased from 42% after one year to only 50% after two years of treatment. This finding can be explained by our observation that the waning effect observed during the second treatment year is in general lower in patients with a below average first-year response than in patients with an above average first-year response, explaining the only moderate correlation between the first year growth response and second year growth response. In most studies, the best predictor of the second year growth response was the first year response (16, 20). However, we observed that about a third of the above median first year growth responders grow slower than the median during the second treatment year. This might be explained among other factors by a declining adherence (21).

Despite the 8% (CA) – 12% (A21) increase in sensitivity for the second-year  $\Delta\text{Ht}$  SDS compared to first-year  $\Delta\text{Ht}$  SDS, the ratio correctly diagnosed poor final responders/misclassified good final responders did not change with a longer treatment duration due to the low (11–16%) prevalence of poor final responders. We hypothesize that predictability of poor final outcome will be better in a cohort with a higher prevalence of poor growth response, e.g. children born small for gestational age without catch-up growth or Turner syndrome. To illustrate this argument, if the poor response rate would have been 30% in this cohort (33 poor responders and 77 good responders) we would have identified 16 poor responders (13.6%) correctly and misclassified four good responders (3.6%)(at CA), a much better risk benefit ratio.

The patients remained short compared to their peers (mean nFAH SDS:  $-1.21$  (CA) and  $-1.44$  (A21) on Belgian references), but they almost reached their target height [nFAH minus MPH SDS:  $-0.19$  (CA) and  $-0.43$  (A21)]. This is consistent with other reports studying final height after GH treatment (19, 22–24).

This is the first study to evaluate the predictability of poor adult height outcome after two prepubertal GH treatment years in GHD children. This study has some shortcomings. Firstly, neither treatment adherence nor persistence of GHD was assessed routinely in the studied cohort. Secondly, the size of the cohort was rather small despite the national recruitment of patients. Near AH was taken as a proxy of AH as many patients usually stop GH

treatment and disappear from follow-up when growth slows down to less than 2 cm per year and before AH is reached (25). To overcome this problem, nAH SDS could be calculated at a reference age of 21 years instead of the actual chronological age. This underestimates the real height SDS since most adolescents will still gain a few centimeters. On the other hand, since the mean height of the reference population also increases between 16 and 21 years, nAH SDS at the actual chronological age will overestimate the real height SDS. We therefore calculated nAH SDS both with age set at 21 years (worst case scenario) and at chronological age (best case scenario), accepting that the first method will underestimate and the second will overestimate the actual AH SDS.

In conclusion, the growth response after two prepubertal years of GH treatment did not meaningfully improve the prediction of poor near adult height outcome compared to the one year response. The decision to re-evaluate the diagnosis of GHD or adapt the GH dose in case of poor height response after 1 year should not be postponed for another year, as the prediction after two years has no added value in GHD children.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

This study was approved by the ethical committee of Brussels Free University and the University Hospital Brussels in Belgium. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

## AUTHOR CONTRIBUTIONS

SS, RR, and JS contributed to the conception and design of the study. SS organized the database. SS performed the statistical analysis. SS wrote the first draft of the manuscript. SS, RR, and JS wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Chapter 8

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### General discussion and future perspectives





Recombinant human growth hormone (GH) was first administered to children more than 35 years ago. Since then, more than 150000 children have been treated worldwide. In recent decades a lot of knowledge has thus been gathered about the effects and outcome of GH treatment. However, despite its frequent use, we still cannot properly predict which children will ultimately have an excellent or poor growth response to GH. There are still gaps in our knowledge and new questions have emerged. This thesis aims to add new insights to the existing knowledge on the growth response to GH treatment. We initially compared the predictive power of different poor-first-year-response criteria and used the longitudinal growth data from the Belgian Registry to develop national reference curves for first-year growth response to GH treatment. We also explored the possibility that changes in energy expenditure after the start of GH treatment can predict the first-year growth response in children. Subsequently, we validated one of the most frequently used prediction models for near adult height (the KIGS model) and focused on the relation between early and late response to GH treatment: do growth response criteria during the early years predict poor adult height outcome in children with GH deficiency (GHD)? An insight in the predictors of the growth response to GH is needed as the strategy of GH therapy using standard doses has evolved to individualized GH dosing, depending on a more detailed diagnosis and validated predictors of the growth response to GH.

## First-year response to GH treatment

There is a great variability not only in the endogenous production of GH, but also in the sensitivity to GH. This results in a highly variable growth response, both among as between diagnostic groups qualifying for GH therapy [1-3]. So there is a continuum where on one side the production of GH is high but the sensitivity is low (GH resistance) and on the other side the production is low and the sensitivity is high (GHD).

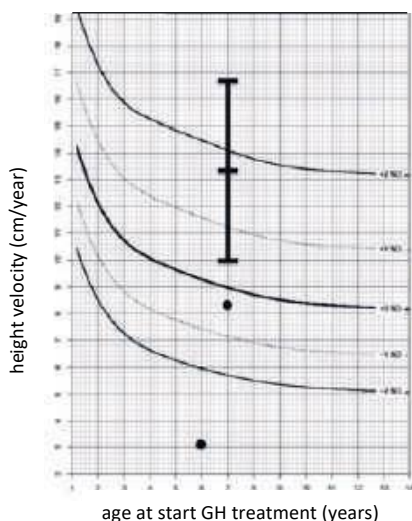
In clinical practice the growth response to GH treatment is assessed after the first year of treatment to detect poor responders in order to reassess the diagnosis, adapt the GH dose or stop the treatment to avoid unnecessary daily injections and expenses. There is however no general consensus on the definition of a poor



first-year growth response. Several criteria have been proposed by several investigators. Ranke et al. [4] proposed a first-year increase in height ( $\Delta$ Ht) standard deviation score (SDS)  $< 0.3$  (for less severe GHD and small for gestational age (SGA)) and  $\Delta$ Ht SDS  $< 0.4$  (for severe GHD) as criteria for poor response. Bang et al. [5] have argued that the response to GH should be clinically meaningful. The year to year change in height SDS in normal growing children can go up to  $0.3$  SD [6], so to attribute the growth response to GH, the increase in height SDS should be at least higher than  $0.3$  SD. Therefore, Bang et al. proposed  $\Delta$ Ht SDS  $< 0.5$  as the poor response criteria for both GHD and SGA. Bakker et al. suggested that patients with a first-year height velocity (HV) SDS  $< -1.0$  observed during GH treatment for a specific diagnosis, age and gender should be labelled as poor responders [7]. An advisory board held in Dubai in 2017 proposed to compare the height gain with the individualized prediction; alternatively, they suggested to consider  $\Delta$ Ht SDS  $< 0.3$  or  $< 0.5$  as the lower limit of an acceptable catch-up growth in children with GHD and SGA [8]. The European Medicines Agency uses first-year HV SDS  $> +1$  for age and gender as the response criterion to continue GH treatment in SGA children. Our comparative study in both GHD and SGA children showed that  $\Delta$ Ht SDS  $< 0.5$  is the most stringent criterion, giving the highest proportion of poor responders (26% in GHD and 37% in SGA) compared to other most commonly used poor first-year response criteria (HV SDS  $< 0.5$  or  $< 1$ ), which resulted in a much lower amount of poor growth responders (11-19% in GHD, 17-25% in SGA). We also showed in this study for the first time that the different response criteria do not always identify the same patients as poor responders. We however could not provide evidence that one criterion might be better than another since the adult height outcome was not available. The most commonly used first-year response criteria in clinical practice, an increase in height SDS and height velocity SDS during the first year of treatment are not adapted to specific patient characteristics (e.g. parental heights), nor do they give any information about whether or not the observed response is sufficient for a specific patient, in other words whether the observed response is in line with the expected response. In order to be able to make a statement on eventual GH (in)sensitivity, resulting in an eventual GH dose adaptation or stop of treatment, the responsiveness must be taken into account.

Responsiveness is the ability/capacity of an individual patient to respond to GH based on his/her individual characteristics. A first step to a more individualized GH treatment is to compare the GH response to the response of children of the same gender, age, and diagnosis [4, 7]. We therefore developed age-specific height velocity curves for prepubertal GHD children which are easy to use in clinical practice and enable rapid identification of poor response to first-year GH treatment, defined by a HV SDS  $< -1$ . A more accurate way to assess responsiveness is the use of prediction models for

first-year HV [9-12]. The most commonly used models are of KIGS (Kabi/Pfizer International Growth Study), a registry containing growth data of European children treated with GH. These models take more individual patient parameters into account to predict a patient's response to GH treatment and permit the calculation of an index of responsiveness (IoR), also called studentized residual (SR), which is the difference between the predicted and observed height increase. This IoR allows thus a more individualized interpretation of the growth response to GH, informing whether the observed response corresponds to the predicted response. For example, a patient with a first-year  $\Delta$ Ht SDS of 0.6 would be considered a good responder based on first-year response criteria ( $>0.3-0.5$ ), and with a HV SDS of  $-0.4$  on the Belgian expected first-year HV curve would be considered an average responder compared to other GHD children of the same age treated with GH, but with an IoR of  $-2.94$  this patient has an inadequate response ( $<-1.28$ ) and was expected to grow even more (figure 1).



**Figure 1.** HV of a female GHD patient plotted on the Belgian first-year HV curve for GHD children treated with GH, and compared with the predicted first-year HV ( $\pm 2$  SD) (horizontal error bars) obtained by the KIGS prediction model (without GH peak). Patient details: age at start GH treatment, 6.0 years; height at start,  $-3.32$  SD; weight at start,  $-3.02$  SD; birth weight,  $+0.64$  SD; GH dose,  $0.025$  mg/kg\*day; midparental height,  $+1.43$  SD; HV before treatment,  $3.1$  cm/year; HV during first treatment year,  $8.3$  cm/year (lower dot, before treatment; upper dot, after first-year treatment).

On the other hand, these prediction models and IoR have also their limitation for daily use. A first weakness of these prediction models may be the lack of one or more patient characteristics needed to calculate the predicted growth response. Another important weakness is that they can only partially predict the variation in treatment response, explaining 45-61% of the variability by the KIGS models for GHD and 52% for SGA. Furthermore, the IoR does not say anything about the absolute magnitude of the response. A patient that gains only 0.3 SD but is predicted to have only 0.3 SD of gain will be scored as a good responder but the real gain of the treatment would still be minimal.

To increase the predictive value of the models, more sophisticated models have been proposed. Some models incorporated in addition to clinical auxological characteristics GH induced changes in biochemical parameters after some months in an attempt to improve the predictability power. One of these combined auxological and biochemical models is the Cologne model, which also contains biochemical markers of bone metabolism, before and during the first 3 months of GH treatment, and was shown to explain up to 89% of the variability [13]. Jung et al. [6] advised to assess the responsiveness to GH treatment already after 3 months of GH treatment instead of 1 year in order to be able to adjust the GH dose and optimize the first-year response, at a time when these children are most sensitive to respond to a higher dose. They predicted first-year HV after 3 months of GH treatment using this Cologne prediction model [13], and showed that GH dose increase at 3 months in children born SGA with predicted poor first-year response ( $\Delta\text{Ht SDS} < 0.75$ ) maintained a catch-up growth and achieved a first-year  $\Delta\text{Ht SDS}$  comparable with the group of children who had been predicted good first-year responders. But even when on a fixed high dose, some patients (16%) did not achieve a good first-year response. However, the biochemical bone parameters are not standard determinations and need 24 h urine collections, limiting their feasibility in clinical practice.

Kristrom et al. [14] have investigated the effect of GH dosing guided by individual responsiveness. At the start of GH treatment, they predicted the height which would be achieved after 2 years of GH treatment in a group of 153 short children (75% GHD, 25% ISS). If the predicted height was lower or higher than the height goal (=mid parental height (MPH) SDS) then the starting dose was adjusted to

achieve the height goal (doses 17-100 mcg/kg\*day). This caused 32% reduction of the growth response variability, but the mean GH dose and the mean height minus MPH SDS was comparable with the fixed GH dose group (43 mcg/kg/d).

Other investigators have studied whether even earlier GH induced metabolic changes, such as increase in total body water (TBW), basal metabolic rate (BMR), and total energy expenditure (TEE), which occur already 2-6 weeks after initiation of GH treatment, might be better as well as earlier predictors than changes in bone markers, which are classically measured after 3 months [15-17]. Ernst et al. showed that the change in TBW after 6 weeks of GH treatment correctly predicted the first-year growth response in 75% of GHD patients (n=88), while a change in TBW of  $>0.7 \text{ l/m}^2$  after 6 weeks of GH treatment was strongly predictive for a first-year  $\Delta\text{Ht SDS}$  of  $> 0.7 \text{ SDS}$  in SGA children (n=99) [17]. Gregory et al. demonstrated that 6 week changes in fat mass, BMR, and TEE were significantly correlated with 6 month increases in height velocity [15]. We also observed in a study of 13 children with GHD or short stature related to SGA that 11 patients with an increased TEE, measured after 6 weeks, had a good first-year growth response ( $\Delta\text{Ht SDS} > 0.5$ ). However, good and poor first-year growth responders were indistinguishable from each other when TEE did not increase. Based on these initial results, the increase in TEE does not appear to be a promising new tool for the early detection of poor growth responders.

Another strategy for a more individualized approach in prescribing GH therapy is an insulin-like growth factor 1 (IGF-1) based dosing of GH treatment, but studies comparing the effectiveness of IGF-1 based dosing compared with that of standard weight-based dosing on adult height have not yet been done [18]. Moreover, there is a poor correlation between the early changes in serum IGF-I levels, GH doses and growth rate [3, 19].

Since parental height is a determinant in the prediction models and height is largely hereditary, it is plausible that genetic variation could influence the response to GH. Dauber et al. have completed the largest genetic study to date of response to GH [20]. They were unable to replicate previous associations, nor did they identify any new variants that were clearly and robustly associated with GH response. However, some associations reached genome-wide significance in secondary analyses and merit further investigation, and their data raised the

hypothesis that variation in glycosylation pathways may regulate the response to GH. Larger sample sizes will be needed to more definitively identify genetic factors that robustly influence the response to GH.

In conclusion, our studies confirmed the great variability in first-year response and responsiveness to GH treatment, but could not provide evidence that one first-year response criterion is better than another. A critical evaluation of these response parameters and their cutoff values with respect to their capacity to detect a poor adult height outcome is therefore needed to define the best poor response parameter.

### The relation between first-year response and final outcome after continued GH treatment

Although the first-year growth response (FYGR) to GH treatment is one of the most important determinants of the GH treatment outcome [11, 21-25], it is unknown which of the proposed first-year response parameters predict a poor treatment outcome with the highest reliability. Therefore, we searched for the most suitable poor FYGR criterion, based on a poor final height outcome, in GHD children. In order to misdiagnose good final responders as few as possible (5%), we decided to set the specificity of the FYGR parameters at 95% and determined the test cutoff values. Of course, every physician can choose the specificity required by the local circumstances. We found that each of the poor FYGR criteria, i.e.  $\Delta\text{Ht SDS} < 0.35$ ,  $\text{HV SDS} < -0.85$ , increase in HV  $< 1.3$  cm/year,  $\text{IoR} < 1.57$ ,  $\text{HV KIGS SDS} < -0.83$ , gave just as many correctly diagnosed poor final responders (total  $\Delta\text{Ht SDS} < 1$ ) as misclassified good final responders (total  $\Delta\text{Ht SDS} > 1$ ), due to the low sensitivity (25-43 %) and the relatively low prevalence of poor responders. Therefore, in children with GHD we cannot use the classically used first-year response criteria in daily practice to define a poor responder in the end. We hypothesize that predictability of poor final outcome could be better in a cohort with a higher prevalence of poor growth response. If the poor response rate would have been 30% in our cohort (33 poor responders and 77 good responders) we would have identified 16 poor responders (13.6%) correctly and misclassified 4 good responders (3.6%), resulting in a much better risk benefit



ratio. This higher rate of poor response is seen in SGA patients and poor responders prediction may be more useful in this indication. Unfortunately, the Belgian Registry did not yet have enough final height data for the SGA indication to check this hypothesis.

We additionally analyzed whether the prediction of poor final responders might improve by extending the observation period for height gain to 2 years in children with GHD. We found that 27% of the patients with a lower than median first-year  $\Delta$ Ht SDS had a higher than median second year increase and a good final adult height outcome. A waning effect was observed in almost all patients in our study (96%) and was greater in those with a more impressive height gain in the first year. Those with a poorer first-year height gain showed a lower waning effect in the second year partly compensating for the lower first-year response. This observation explains in part the poor predictive value of the first-year growth response for the long-term outcome.

Kaplowitz et al. [26] concluded that for GHD children the first-year HV SDS was not a potent predictor of the second year HV SDS to use first-year HV alone to decide on GH continuation. They observed that 63% of those who grew poorly in the first year (HV SDS < -1) but who continued treatment grew satisfactorily ( $-1 \leq$  HV SDS  $\leq$  +1; 91%) or well (HV SDS > 1; 9%) during the second year.

Prediction models for near adult height have also been established for GHD children after the first year of GH treatment, based on changes in auxological and biochemical parameters [11, 27]. The parameters used in the KIGS prediction models for near adult height are the index of responsiveness, midparental height, birth weight, height and age at start, average GH dose during the first treatment year, and severity of GHD, explaining 60% of the variability. We validated these KIGS prediction models using the Belgian registry for GH treated children and concluded that they accurately predict near adult height in females and overpredict near adult height in males by about 1.5 cm. Therefore, these prediction models are useful for predicting near adult height after the first year of GH treatment in clinical practice.

## Proposal for optimized management of GH treatment in GHD

The more recent recommendations and guidelines on short stature management in the context of GH treatment have highlighted the medical need to personalize and individualize treatment based on an individual patient's characteristics in order to optimize treatment outcomes, most importantly, improving height gain [8-11, 18, 28, 29]. Although these recommendations have been published in the last decade, the individualized approach is still not common practice in Belgium and the Netherlands.

With the insights gained during our studies, we propose an optimized strategy for an individualized approach for identification and management of poor first-year response in GHD children, as presented in table 1.

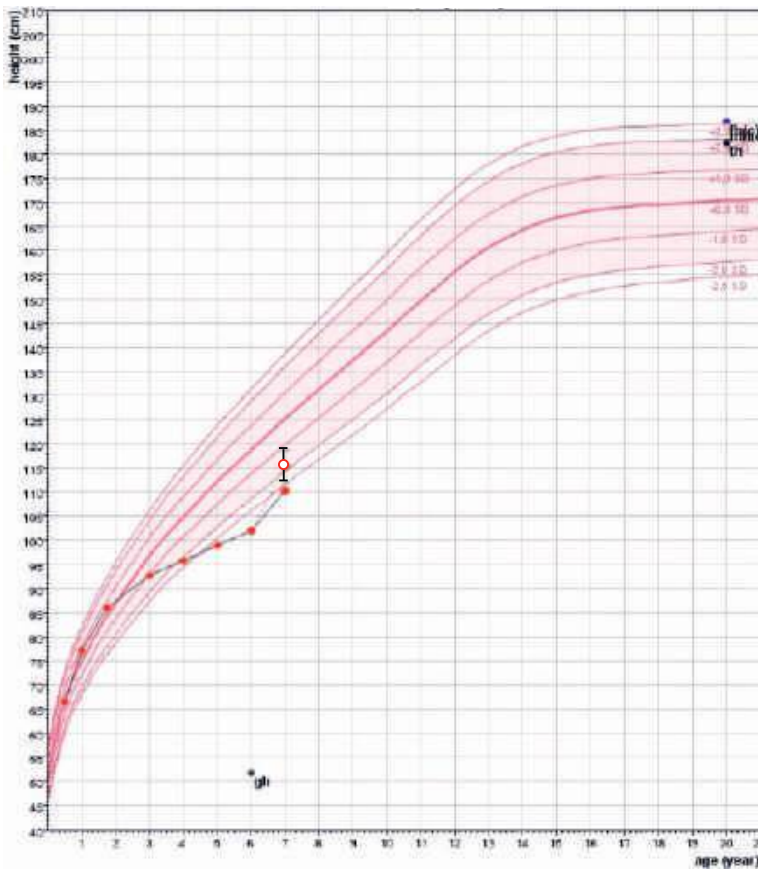
In GHD children, the recommended starting GH dose is 22-35  $\mu\text{g}/\text{kg}\cdot\text{day}$  [18]. At the start of GH treatment, the first-year growth response should be predicted, using the KIGS prediction model [11]. Certain growth curve software (e.g. Growth Analyser) have a tool that predicts the height after the first year of GH treatment using the KIGS prediction models. The predicted height with its standard deviations appears readily on the growth curve (e.g. figure 2). If the predicted increase in height SDS (predicted height SDS minus height SDS at start) is poor ( $\Delta\text{Ht SDS} < 0.4^*$ ) the starting GH dose can be increased to achieve a more satisfactory predicted first-year height gain. On the other hand, if the predicted height increase is more than satisfactory ( $\Delta\text{Ht SDS} > +1.4^{**}$ ), it is cost effective to choose the lowest GH dose at which a satisfactory predicted first-year HV is achieved.

During the first year, besides determining the height, sitting height and weight, the treatment adherence should be evaluated (history taking, IGF-1 measurement).

After the first year of GH treatment, both the magnitude of the growth response and responsiveness should be assessed. A poor response is considered as a  $\Delta\text{Ht SDS} < 0.4^*$  and poor responsiveness is considered an  $\text{IoR} < -1.57^*$ . If 1 or more parameters of the prediction model are unavailable, the responsiveness can be determined by plotting the observed HV on the Ranke expected HV curve and comparing the observed HV with the predicted HV, based on age and diagnosis. A HV SDS  $< -0.83^*$  on the Ranke expected HV curve is considered a poor

responsiveness. The response should then be evaluated in function of the patient's responsiveness and action should be taken upon findings (see table 1).

After the second GH treatment year the growth response of the poor first-year responders needs to be re-evaluated. If the  $\Delta$ Ht SDS after 2 years of GH treatment is  $< 0.6^*$  then cessation of GH treatment needs to be considered.



**Figure 2.** Height for age growth curve of a female GHD patient treated with GH since the age of 6 years. The mean predicted height after the first treatment year (open circle) and  $\pm 2$  SD (horizontal error bars) are plotted on the curve. Patient details: height at start, -3.32 SD; weight at start, -3.02 SD; birth weight, +0.64 SD; GH dose, 0.025 mg/kg\*day; midparental height, +1.43 SD; HV before treatment, 3.1 cm/year; HV during first treatment year, 8.3 cm/year; first-year  $\Delta$ Ht SDS 0.6; IoR - 2.94.

**Table 1. Proposal for optimized management of GH treatment in GHD**

**At start of GH treatment**

**Predict first-year growth response using 25 µg/kg\*day**

prediction model (KIGS [30]):

first-year HV (cm/year) = 12.41 + (-0.36 x age at onset, years) + (0.47 x birth weight, SDS) + (1.45 x ln(GH dose), IU/kg\*week) + (-0.6 x [height, SDS - MPH, SDS]) + (0.28 x weight, SDS) (error SD 1.72 cm/year)

or use tool (e.g. Growth Analyser®)

**Adjust GH dose to obtain a predicted Δ height SDS within the normal range**

Predicted ΔHt SDS <0.4: increase the GH dose until predicted ΔHt SDS > 0.4

Predicted ΔHt SDS >1.4: decrease the GH dose to achieve predicted ΔHt SDS +1.4

**During first-year GH treatment**

**Evaluate adherence** (history taking, IGF-1)

**After first-year GH treatment**

**Evaluate first-year response**

Poor response = ΔHt SDS < 0.4

**Evaluate first-year responsiveness**

Poor responsiveness = loR < -1.57

HV SDS < -0.83 on Ranke expected HV curve

**Predict adult height in poor responders with a poor responsiveness**

prediction model (KIGS [11]):

near adult height SDS (Prader)= 2.34 + [0.34 x MPH, SDS (Prader)] + [0.18 x birth weight, SDS] + [0.59 x height at start of GH treatment, SDS (Prader)] + [0.29 x first-year studentized residual with max. GH] + [1.28 x mean GH dose, mg/kg\*week] + [-0.37 x ln max GH level to provocation test, ln µg/L] + [-0.10 x age at start of GH treatment, years]).

Short predicted adult height = < -2 SDS\* (Prader references [31])

## Evaluate response in function of responsiveness

		Responsiveness	
		good	poor
Response	good	<p>good growth, as expected</p> <p>no further evaluation necessary</p> <p>continue GH in similar dose if serum IGF-1 allows</p>	<p>good growth, but less than expected</p> <p>evaluate possible causes of inadequate growth (e.g. poor compliance, co-morbidity, psychosocial well-being, use of growth limiting medication,...) and act upon findings</p> <p>continue GH in similar dose if serum IGF-1 allows</p>
	poor	<p>poor growth, but as expected</p> <p>patient has an intrinsic poor sensitivity to GH</p> <p>increase GH dose if serum IGF-1 allows</p>	<p>poor growth and less than expected</p> <p>evaluate possible causes of (severe) insensitivity to GH (e.g. IGF1R-mutation, skeletal disease,...) and inadequate growth (e.g. poor compliance, co-morbidity, psychosocial well-being, use of growth limiting medication,...) and act upon findings</p> <p>consider stop GH treatment if no treatable cause is found and/or short predicted adult height</p>

## After second-year GH treatment

### **Re-evaluate growth response for first-year poor responders**

$\Delta$ Ht SDS after 2 years  $<0.6$ : consider stop GH treatment if no treatable cause of poor response is found

\* The cutoff values are based on the results of our research, taking the final outcome into account [32-34].\*\* The cutoff value is based on the results of our research: first-year  $\Delta$ Ht SDS  $>1.4$  is 1 SDS above the mean in GHD children [first-year  $\Delta$ Ht SDS (mean  $\pm$  1 SD) =  $0.83 \pm 0.59$ ] [35].

## General conclusion

First-year growth response and responsiveness to GH treatment are highly variable, both between and within diagnostic groups. Although the first-year growth response is an important determinant of the ultimate height gain, in GHD children a poor first-year response is not a reliable predictor of poor final height outcome and extending the prediction period to 2 years improves the predictive value marginally. The identification of poor responders during the first years, and possibly earlier, remains important, both to discover eventual underlying causes of poor response and to adjust the GH treatment if necessary, in a period when patients are most sensitive to GH. A poor first-year growth response in combination with a poor responsiveness, might be a reason for stopping GH treatment if no underlying cause is found to avoid a costly useless treatment with potential adverse effects. Future studies investigating the causes of the variability in response and responsiveness and the effect of the individualized approach on adult height will provide more realistic expectations in short children starting a GH treatment.



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## Chapter 9

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### Summary







In **chapter 1** the physiology of normal growth, which is a very complex process unique to pediatrics is described. The history, indications, and goals of growth hormone (GH) treatment are discussed and the different ways in which the growth response to GH treatment can be assessed is introduced, with their advantages and disadvantages. Finally, the objectives of our studies evaluating the growth response to GH treatment in short children with GH deficiency (GHD) and smallness for gestational age (SGA) are discussed.

**Chapter 2** describes the growth response to first-year GH treatment in short prepubertal children with GHD (n=122) and born SGA (n=171). Since there is no consensus on the definition of poor growth response we compared the proportion of poor responders identified by different criteria: change in height ( $\Delta$ Ht) standard deviation score (SDS) <0.3 or <0.5, height velocity (HV) SDS <0.5 or <1 based on the population reference, HV SDS <-1 based on the expected HV curve derived from KIGS, a registry containing growth data of European children with iGHD and SGA (HV Ranke SDS), studentized residual (SR) <-1 in the KIGS first-year prediction model.  $\Delta$ Ht SDS <0.5 gave the highest percentage poor responders (37% SGA, 26% GHD). Although % poor responders were comparable for  $\Delta$ Ht SDS <0.3, HV SDS <+0.5, HV SDS <+1, SR <-1, and HV Ranke SDS <-1, these criteria did not always identify the same patients as poor responders. Among the poor growth responders 24% SGA and 14% GHD patients had an insulin-like growth factor 1 (IGF-1) increase <40%. We concluded that the different response criteria yield high but comparable percentages poor responders, but identify different patients. This study does not provide evidence that one criterion is better than another. A limited IGF-1 generation is not the major reason for a poor growth response in the first year of GH treatment in SGA and GHD children.

**Chapter 3** contains a 1 year intervention study, without a control group for comparison, investigating the effect of GH treatment on energy expenditure (EE) and its relation to first-year growth response in children. Total EE (TEE), basal metabolic rate (BMR), and physical activity level (PAL) measurements before and after 6 weeks of GH treatment were performed in 18 short prepubertal children (5 girls, 13 boys) born SGA (n=14) or with GHD (n=4) who were eligible for GH treatment. TEE was measured with the doubly labelled water method, BMR was measured with an open-circuit ventilated hood system, PAL was assessed using an

accelerometer for movement registration and calculated ( $PAL = TEE/BMR$ ), activity related EE (AEE) was calculated ( $AEE = (0.9 * TEE) - BMR$ ). GH treatment showed a positive effect on BMR and TEE in prepubertal children after 6 weeks. No effect on physical activity was observed. We concluded that increase in TEE appeared to be valuable for the prediction of good first-year growth responders ( $\Delta Ht\ SDS > 0.5$ ) to GH treatment, but might be of less value in detecting poor growth responders.

**Chapter 4** shows the created smoothed reference curves of first-year HV in relation to age for prepubertal Belgian children with idiopathic (i) GHD treated with a standard weight-adjusted GH dose. This national reference was compared with the response references derived from KIGS, a registry containing growth data of European children with iGHD. The observed first year HVs of 357 prepubertal children (240 males) with iGHD were log-normal distributed by age and decreased significantly with age. No GH dose or gender effect was observed. Distance to target height, severity of GHD and occurrence of multiple pituitary hormone deficiencies had a positive effect on the observed HV SDS. The developed age-specific growth response curves enable rapid identification of poor response to first-year GH treatment in prepubertal iGHD children. Our results also validated the published growth targets derived from the KIGS database.

In **chapter 5** prediction models for near adult height (nAH) by Ranke et al. were validated. These prediction models enable the prediction of final height after the first year of GH treatment in children with GHD. We retrieved height data of 127 (82 male) iGHD children, treated with GH until nAH from the Belgian national GH treatment database. Bland Altman plots and Clarke error grid analyses were performed to assess clinical significance of the differences between observed and predicted nAH. In males, predicted nAH was higher than observed nAH (difference:  $0.2\ SD \pm 0.7$ ;  $p < 0.01$ ). In females, there was no significant difference. Bland Altman analyses showed that the means of the differences between observed and predicted nAH were close, but not equal to zero with overprediction for smaller heights and underprediction for taller heights. Clarke error grid analysis showed that in males 59-61% of predicted nAH were within 0.5 SDS and 88% within 1.0 SDS from observed nAH; in females, 40-44% of predicted nAH were within 0.5 SDS and 76-78% within 1.0 SDS from observed nAH. In conclusion, Ranke's models accurately predicted nAH in females and

overpredicted nAH in males by about 1.5 cm. In most individuals, predicted nAH was within 1 SDS of observed nAH.

In **chapter 6** we further explored which first-year growth response (FYGR) criteria predicted best the final height outcome after GH treatment in prepubertal children with GHD. Therefore, height data of 129 GHD children (83 boys) who attained adult height and had been treated with GH for at least 4 consecutive years with at least one year before pubertal onset were retrieved from the Belgian GH Registry to determine the sensitivity and specificity of these FYGR criteria at their proposed threshold levels to detect a poor final height outcome (PFHO). The studied FYGR parameters were: (1)  $\Delta$ Ht SDS, (2) HV SDS, (3)  $\Delta$ HV (cm/year), (4) index of responsiveness (IoR) in KIGS prediction models, (5) first-year HV SDS based on the KIGS expected HV curve (HV KIGS SDS), (6) nAH prediction after first-year GH treatment. Twelve, 22 and 10% of the children had a PFHO defined respectively as a total  $\Delta$ Ht SDS  $<1$ , nAH SDS  $<-2$ , and nAH minus midparental height SDS  $<-1.3$ . ROC curve analyses showed that the currently used FYGR criteria had low specificities and sensitivities to detect PFHO. To obtain a 95% specificity, the cut-off value (and sensitivity) of FYGR parameters were:  $\Delta$ Ht SDS  $<0.35$  (40%), HV SDS  $<-0.85$  (43%),  $\Delta$ HV  $<1.3$  cm/year (36%), IoR  $<-1.57$  (17%), HV KIGS SDS  $<-0.83$  (40%) to predict total  $\Delta$ Ht SDS  $<1$ ; predicted nAH SDS (with GH peak)  $<-1.94$  (25%), predicted nAH SDS (without GH peak)  $<-2.02$  (25%) to predict nAH SDS  $<-2$ . At these cut-offs, the amount of correctly diagnosed poor final responders equals the amount of false positives. We concluded that FYGR criteria perform poorly as predictors of PFHO after long-term GH treatment in prepubertal GHD children.

In **chapter 7**, our research on the prediction of poor adult height outcome after GH treatment in GHD children is continued by an evaluation after two years of treatment. Height data of GHD children treated with GH for at least 4 consecutive years of which at least 2 were prepubertal and who had attained nAH (n=110) were retrieved from the Belgian Register for GH treated children. In ROC analyses, the first and second year  $\Delta$ Ht SDS as a predictor for total  $\Delta$ Ht SDS  $<1.0$  had an area under the curve  $>70$  % and were further analyzed. First-year  $\Delta$ Ht SDS  $<0.41$  correctly identified 42% of the patients with a poor AH outcome at a 95% specificity level, resulting in respectively 5/12 (4.6%) correctly identified poor final

responders and 5/98 (4.5%) misclassified good final responders (ratio 1.0).  $\Delta$ Ht SDS after 2 prepubertal years had a cut-off level of 0.65 and a sensitivity of 50% at a 95% specificity level, resulting in respectively 6/12 (5.5%) correctly identified poor final responders and 5/98 (4.5%) misclassified good final responders (ratio 1.2). We concluded that the growth response after 2 prepubertal years of GH treatment did not meaningfully improve the prediction of poor adult height outcome after GH treatment compared to first-year growth response parameters in prepubertal GH treated children with non-acquired GHD.

**Chapter 8** discusses the most important findings of our studies in view of current literature. We emphasize the clinical implications of the evaluation of the first-year response to GH therapy and propose an optimized integrated management for the first and second year GH treatment in GHD children, based on the growth response, the responsiveness and expected adult height outcome.







## Chapter 10

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### Impactparagraaf





It is common practice to evaluate the growth response to growth hormone (GH) treatment in children after the first year to detect poor responders in order to reassess the diagnosis, adapt the GH dose or stop the treatment to avoid unnecessary daily injections and expenses. While for the physician the purpose of assessing the growth response is multifold, for the patient/caregivers the most important question is whether the patient has grown "well". However, there is no agreement as to which criterion is most appropriate for this purpose. Consequently, different physicians use different criteria, or sometimes none at all. In this thesis we compared the different criteria for growth response after the first year of GH treatment and concluded that these criteria gave high and comparable percentages poor responders but may identify different patients. This study does not provide evidence that one criterion is better than another. Thus, a patient may be labeled a poor responder by a physician using criterion A, while not being considered a poor responder by a physician using criterion B. In addition, a good response for one patient may be different from a good response for another patient. This depends on the responsiveness (= the ability of a person to respond to GH) and is determined by, among other things, the age and the indication for GH treatment. We developed age-specific growth response curves for prepubertal idiopathic GH deficient (GHD) children which correspond to the published growth targets derived from the KIGS database. These curves can be used by physicians to rapidly identify patients with poor response to first-year GH treatment. However, until now these curves have not been used frequently because they are not integrated into existing growth curve software programs. Implementing this would increase ease of use and consequently its use.

In order to identify poor growth responders much earlier than after the first treatment year, we tried to find GH induced metabolic changes which predict the first-year growth response. We showed that GH treatment had a positive effect on basal metabolic rate and total energy expenditure (TEE) in prepubertal children after 6 weeks. The increase in TEE appeared to be valuable for the prediction of good first-year growth responders but not for poor responders to GH treatment. Therefore, these metabolic criteria cannot be used as predictors for poor response.

Another question that patients and/or their care givers often ask is whether the patient will have a normal final height and preferably also what the final height will be. We validated Ranke's prediction models predicting the near adult height (nAH). Ranke's models accurately predicted nAH in females and overpredicted nAH in males by about 1.5 cm. In most individuals, predicted nAH was within 6.8 cm (= 1 SDS) of observed nAH. These models can be of help in giving realistic expectations of adult height.

The diagnosis "poor responder" may result in discontinuation of GH treatment after the first year. However, current criteria do not take into account the ultimate growth response after years of GH treatment. We were the first to investigate the value of the different first-year growth response (FYGR) criteria as predictors of a poor final height outcome after long-term GH treatment in GHD patients. We showed that the amount of correctly diagnosed poor final responders (=poor responder after first year AND poor final responder) equals the amount of falsely diagnosed poor final responders (=poor responder after first year BUT good final responder). Therefore, FYGR criteria perform poorly as predictors of poor final height outcome after long-term GH treatment in prepubertal GHD children and alone should not be used to decide to discontinue treatment. We hypothesized that a lower waning effect in the second year might compensate for a lower first year response, translating in a better predictability of a poor total height gain after two years of GH treatment. However, we found that the growth response after 2 prepubertal years of GH treatment did not meaningfully improve the prediction of poor adult height outcome after GH treatment compared to first-year growth response parameters. We concluded that the evaluation of the growth response should not be postponed for another year, as the prediction after 2 years has no added value in GHD children.

With the insights obtained from the results of these studies, we have drawn up an advice for an optimized strategy for an individualized approach for identification and management of poor first-year response in GHD children. Responsiveness (using prediction models or our developed expected height velocity curves) should play a prominent role in the assessment of first-year growth response, which has rarely been the case in clinical practice until now. This way, the first-year growth response will be interpreted more correctly, resulting in more

adequate management as suggested in our advice. After the second treatment year, reevaluation of the growth of poor responders who had a treatment adjustment after the first year should take place and action taken upon findings. This could lead to a better cost effectiveness of this yet expensive GH treatment and less burden for the patient and his family.

These new insights were shared with other healthcare professionals through the published articles, several presentations at (inter)national conferences and this thesis. However, an update of the (inter)national guidelines regarding the interpretation of the first-year growth response would only really lead to a change in mindset and treatment behavior of health care professionals.

Furthermore, it would be worth re-evaluating the indications for GH treatment. Since response and responsiveness are highly variable, even within diagnostic groups, decisions about GH treatment could also be made on the likelihood of benefit, depending not only on diagnosis and sufficiency of GH secretion, but also on the responsiveness to GH. This way children with idiopathic short stature with a good predicted first-year height velocity could benefit from GH treatment. In our new proposal for management of poor responders we suggest that discontinuation of GH treatment in children with poor growth response and poor responsiveness should be considered. This way an expensive treatment with marginal or no benefit will be avoided in poor responders while short children with expected good response, who currently have no access to GH treatment, could benefit from it.





## Addendum

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Nederlandse samenvatting

Dankwoord

Curriculum Vitae

List of publications

List of abbreviations





## Samenvatting

In **hoofdstuk 1** wordt de fysiologie van normale groei beschreven, dat een zeer complex proces is, uniek voor kindergeneeskunde. De geschiedenis, indicaties en doelen van groeihormoon (GH) behandeling worden besproken en de verschillende manieren voor beoordelen van de groeirespons worden geïntroduceerd, met de voor- en nadelen. Ten slotte worden de doelstellingen van de studies besproken.

**Hoofdstuk 2** beschrijft de groeirespons na eerstejaars GH-behandeling bij kleine prepuberale kinderen met groeihormoondeficiëntie (GHD) (n = 122) en dysmatuur geboren zonder inhaalgroei (SGA) (n = 171). Aangezien er geen consensus is over de definitie van een slechte groeirespons, werden de proporties slechte groeiresponders, geïdentificeerd aan de hand van verschillende criteria, vergeleken: toename in lengte ( $\Delta$ Ht) standaard deviatie score (SDS)  $<0.3$  of  $<0.5$ , lengtegroeisnelheid (HV) SDS  $<0.5$  of  $<1$  gebaseerd op de populatie-referentie, HV SDS  $<-1$  gebaseerd op de HV-referentiecurve verworven uit de KIGS-database, een database die groeigegevens van Europese kinderen met GHD en SGA bevat (HV Ranke SDS), "studentized residual" (SR)  $<-1$  in het KIGS eerstejaars predictiemodel.  $\Delta$ Ht SDS  $<0.5$  gaf het hoogste percentage slechte responders (37% SGA, 26% GHD). Hoewel het percentage slechte responders vergelijkbaar was voor  $\Delta$ Ht SDS  $<0.3$ , HV SDS  $<+0.5$ , HV SDS  $<+1$  SR  $<-1$  en HV Ranke SDS  $<-1$ , identificeerden deze criteria niet altijd dezelfde patiënten als slechte responders. Onder de slechte groeiresponders had 24% van de SGA en 14% van de GHD-patiënten een insulin-like growth factor 1 (IGF-1) toename  $<40\%$ . We concludeerden dat de verschillende responscriteria hoge maar vergelijkbare percentages slechte responders opleveren, maar verschillende patiënten identificeren. Dit onderzoek levert geen bewijs dat het ene criterium beter is dan het andere. Een beperkte toename van de IGF-1-waarde is niet de belangrijkste reden voor een slechte groeirespons in het eerste jaar van GH-behandeling bij SGA- en GHD-kinderen.

**Hoofdstuk 3** beschrijft een 1-jaar durende longitudinale interventiestudie, zonder vergelijkingsgroep, waarin het effect van groeihormoonbehandeling op het energiegebruik en de relatie met de eerstejaars groeirespons bij kinderen wordt

onderzocht. Totaal energiegebruik (TEE), basaal metabolisme (BMR) en fysiek activiteitsniveau (PAL) metingen voor en na 6 weken GH-behandeling werden uitgevoerd bij 18 prepuberale dysmature (n=14) of groeihormoondeficiënte (n=4) kinderen (5 meisjes, 13 jongens) die in aanmerking kwamen voor GH-behandeling. TEE werd gemeten met de dubbel gelabeld watermethode, BMR werd gemeten met een open circuit geventileerde kap, PAL werd beoordeeld met behulp van een accelerometer voor bewegingsregistratie en berekend ( $PAL = TEE/BMR$ ), activiteit gerelateerd energiegebruik (AEE) werd berekend ( $AEE = (0.9 * TEE) - BMR$ ). GH-behandeling toonde een positief effect op BMR en TEE bij prepuberale kinderen na 6 weken. Er werd geen effect op fysieke activiteit waargenomen. De toename in TEE bleek waardevol te zijn voor de voorspelling van goede eerstejaars groeiresponders ( $\Delta Ht SDS > 0.5$ ) op GH-behandeling.

**Hoofdstuk 4** toont de gecreëerde referentiecurves van de lengtegroeisnelheid tijdens het eerste jaar GH-behandeling in relatie tot de leeftijd voor Belgische prepuberale kinderen met idiopathische (i) GHD die werden behandeld met een standaard, voor gewicht gecorrigeerde, GH-dosis. Tevens werden deze nationale referentiecurves vergeleken met de gepubliceerde referentiecurves verworven uit de KIGS-database. De waargenomen eerste jaars groeisnelheden van 357 prepuberale kinderen (240 jongens) met iGHD waren log-normaal verdeeld naar leeftijd en namen significant af met de leeftijd. Er werd geen GH-dosis of geslachtseffect waargenomen. De afstand tot doellengte, de ernst van GHD en het optreden van meervoudige hypofysehormoondeficiënties hadden een positief effect op de geobserveerde lengtegroeisnelheid SDS. De ontwikkelde leeftijdsspecifieke groeiresponscurves maken een snelle identificatie mogelijk van GHD-kinderen met een slechte respons na eerstejaars GH-behandeling. Onze resultaten valideren de gepubliceerde groeiresponscurves die zijn ontwikkeld uit de KIGS-database.

In **hoofdstuk 5** worden predictiemodellen voor eindlengte, ontwikkeld door Ranke et al., gevalideerd. Deze predictiemodellen maken het mogelijk de uiteindelijke lengte te voorspellen na het eerste jaar GH-behandeling bij kinderen met GHD. Met lengtegegevens uit de Belgische database (BESPEED) van 127 kinderen (82 jongens) met idiopathisch GHD, behandeld met GH tot eindlengte, werd na het eerste jaar GH-behandeling de eindlengte voorspeld met behulp van

de predictiemodellen van Ranke et al. Bland Altman plots en Clarke error grid analyses werden uitgevoerd om de klinische significantie van de verschillen tussen waargenomen en voorspelde eindlengte te beoordelen. Bij mannen was de voorspelde eindlengte hoger dan de waargenomen eindlengte (verschil:  $0.2 \text{ SD} \pm 0.7$ ;  $p < 0.01$ ). Bij vrouwen was er geen significant verschil. Bland Altman analyses toonden aan dat de gemiddelden van de verschillen tussen waargenomen en voorspelde eindlengte dichtbij nul, maar niet gelijk aan nul waren, met overschatting voor kleinere lengtes en onderschatting voor grotere lengtes. Clarke error grid analyses toonden aan dat bij mannen 59-61% van de voorspelde eindlengte binnen 0.5 SDS lag en 88% binnen 1.0 SDS van de waargenomen eindlengte; bij vrouwen lag 40-44% van de voorspelde eindlengte binnen 0.5 SDS en 76-78% binnen 1.0 SDS van de waargenomen eindlengte. Concluderend kan gesteld worden dat Ranke's predictiemodellen nauwkeurig de eindlengte bij vrouwen voorspellen en bij mannen de eindlengte overschatten met ongeveer 1.5 cm. Bij de meeste patiënten lag de voorspelde eindlengte binnen 1 SDS van de waargenomen eindlengte. Deze modellen kunnen behulpzaam zijn bij het geven van realistische verwachtingen van eindlengte.

**Hoofdstuk 6** onderzoekt welke criteria voor de eerstejaars groeirespons het beste de uiteindelijke lengte na GH-behandeling voorspelden bij prepuberale kinderen met GHD. Tot nu toe zijn verschillende criteria voor de eerstejaars groeirespons op GH-behandeling voorgesteld, maar hun waarde als voorspellers van een slechte uiteindelijke lengte-uitkomst na langdurige GH-behandeling bij GHD-patiënten is nog niet geanalyseerd. Hiertoe werden lengtegegevens opgehaald uit het Belgische GH-register van 129 GHD-kinderen (83 jongens) die volwassen lengte bereikten en gedurende ten minste 4 opeenvolgende jaren met GH waren behandeld met ten minste één jaar vóór de puberteit. De sensitiviteit en specificiteit van de eerstejaars groeirespons criteria werd bepaald bij hun vooropgestelde afkapwaarden om een slechte uiteindelijke lengte-uitkomst te detecteren. De eerstejaars groeirespons parameters waren: (1)  $\Delta \text{Ht SDS}$ , (2) HV SDS, (3)  $\Delta \text{HV (cm/jaar)}$ , (4) "index of responsiveness" (IoR) in KIGS-voorspellingsmodellen, (5) eerstejaars HV SDS gebaseerd op de KIGS verwachte HV-curve (HV KIGS SDS), (6) voorspelling van de bijna uiteindelijke volwassen lengte (nAH) na eerstejaars GH-behandeling. Twaalf, 22 en 10% van de kinderen hadden een slechte uiteindelijke lengte-uitkomst, respectievelijk gedefinieerd als

een totale  $\Delta$ Ht SDS <1, nAH SDS <-2, en nAH minus midparentale lengte SDS <-1.3. ROC-curve analyses lieten zien dat de momenteel gebruikte eerstejaars groeiresponscriteria lage specificiteiten en sensitiviteiten hadden om slechte uiteindelijke lengte-uitkomst te detecteren. Om een specificiteit van 95% te verkrijgen, waren de afkapwaarde (en sensitiviteit) van de eerstejaars groeiresponsparameters:  $\Delta$ Ht SDS <0.35 (40%), HV SDS <-0.85 (43%),  $\Delta$ HV <1.3 cm / jaar (36 %), IoR <-1.57 (17%), HV KIGS SDS <-0.83 (40%) om totale  $\Delta$ Ht SDS <1 te voorspellen; voorspelde nAH SDS (met GH-piek) <-1.94 (25%), voorspelde nAH SDS (zonder GH-piek) <-2.02 (25%) om nAH SDS <-2 te voorspellen. Bij deze afkapwaarden is het aantal correct gediagnosticeerde slechte eindresponders gelijk aan het aantal valse positieven. Daarom presteren de eerstejaars groeiresponscriteria slecht als voorspellers van slechte uiteindelijke lengte-uitkomst na langdurige GH-behandeling bij prepuberale GHD-kinderen.

In **hoofdstuk 7** werd het onderzoek naar de voorspelling van een slechte uiteindelijke lengtewinst na GH-behandeling bij GHD-kinderen voortgezet. Er werd onderzocht of de groeirespons na 2 jaar GH-behandeling een betere voorspeller zou zijn dan de eerstejaars respons. Lengtegegevens van GHD-kinderen behandeld met GH gedurende minstens 4 opeenvolgende jaren, waarvan minstens 2 prepuberaal, en die (bijna) de eindlengte hadden bereikt, werden opgehaald uit het Belgisch register voor met GH behandelde kinderen. In ROC-analyses hadden de lengtewinst ( $\Delta$ Ht-SDS) van het eerste en tweede jaar als voorspeller voor totale lengtewinst <1.0 een gebied onder de curve (AUC) > 70% en werden deze verder geanalyseerd. Eerstejaars  $\Delta$ Ht SDS <0.41 identificeerde 42% van de patiënten met een slechte uiteindelijke lengtewinst correct, met een specificiteit van 95%, resulterend in respectievelijk 5/12 (4.6%) correct geïdentificeerde slechte eindrespondenten en 5/98 (4.5%) verkeerd geïdentificeerde goede eindrespondenten (ratio 1.0).  $\Delta$ Ht SDS na 2 prepuberale jaren had een afkapwaarde van 0.65 en een sensitiviteit van 50% bij een specificiteit van 95%, resulterend in respectievelijk 6/12 (5.5%) correct geïdentificeerde slechte eindrespondenten en 5/98 (4.5%) verkeerd geïdentificeerde goede eindrespondenten (ratio 1.2). We concludeerden dat de groeirespons na 2 prepuberale jaren GH-behandeling de voorspelling van een slechte uiteindelijke lengtewinst na GH-behandeling niet significant verbeterde in



vergelijking met eerstejaars groeiresponsparameters bij prepuberale GH-behandelde kinderen met niet-verworven GHD.

Ten slotte worden in **hoofdstuk 8** de belangrijkste bevindingen van dit proefschrift besproken en bediscussieerd. De klinische implicaties van de evaluatie van de eerstejaars groeirespons op GH worden benadrukt en een geoptimaliseerd geïntegreerd beleid voor het eerste en tweede jaar GH-behandeling bij GHD-kinderen wordt voorgesteld op basis van de groeirespons, de responsiviteit en de verwachte uiteindelijke lengte uitkomst.



## Dankwoord

Eindelijk is het zover, mijn proefschrift is afgerond! ☺

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## Curriculum Vitae

Saartje Straetemans werd op 27 mei 1977 geboren in Bree, België. Daar groeide ze op met haar ouders en broer. In 1995 behaalde ze haar diploma secundair onderwijs aan het Koninklijk Atheneum te Maaseik. Van 1995 tot 1998 studeerde ze geneeskunde aan het Limburgs Universitair Centrum en van 1998 tot 2003 aan de Universiteit Antwerpen. Ze behaalde haar diploma arts cum laude.

Van 2003 tot 2005 werkte zij als arts-assistent niet in opleiding op de afdeling kindergeneeskunde van het Viecuri Medisch Centrum te Venlo en het Onze Lieve Vrouwe Gasthuis te Amsterdam. Van 2005 tot 2010 specialiseerde zij zich tot kinderarts in het Jeroen Bosch ziekenhuis in 's Hertogenbosch (opleider: wijlen dr. Hans Hoekstra), het Koningin Paola kinderziekenhuis en het Universitair ziekenhuis Antwerpen (opleider: wijlen prof. dr. José Ramet). In 2010 begon ze met haar fellowship kinderendocrinologie in het Universitair ziekenhuis Gent (opleider: prof. dr. J. De Schepper). Tijdens dit fellowship startte ze haar onderzoek binnen de kinderendocrinologie, in samenwerking met de Belgian Society for Pediatric Endocrinology and Diabetology (BESPEED, toen nog BSGPE), onder supervisie van prof. dr. Raoul Rooman en prof. dr. Jean De Schepper.

In 2012 startte ze haar carrière als kinderendocrinoloog in het Maastricht Universitair Medisch Centrum (de eerste 6 maanden als fellow). In 2014 en 2015 was ze tevens 1 dag per week consulent kinderendocrinologie in het Universitair ziekenhuis Antwerpen en in 2015-2016 in het Radboud UMCN. Ze zette haar onderzoek voort, dit groeide uit tot een promotietraject. Ze presenteerde haar onderzoek op verschillende nationale en internationale congressen.

In 2017 werd haar zoon Timon geboren.



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## List of abbreviations

$\Delta$	increase in
A21	age 21 years
AEE	activity related energy expenditure
AH	adult height
ALS	Acid label subunit
AUC	area under the curve
BESPEED	Belgian Society for Pediatric Endocrinology and Diabetology
BMI	body mass index
BMR	basal metabolic rate
CA	chronological age
DLW	doubly labelled water
EE	energy expenditure
FFM	fat free mass
FM	fat mass
FYGR	first-year growth response
GH	growth hormone
GHBP	growth hormone binding protein
GHD	growth hormone deficiency
Ht	height
HV	height velocity
i	idiopathic
IGF-1	insulin-like growth factor
IoR	index of responsiveness
KIGS	Kabi/Pfizer International Growth Study
MPH	midparental height
nAH	near adult height
nFAH	near final adult height
PAL	physical activity level
PFHO	poor final height outcome
RQ	respiratory quotient
SGA	small for gestational age
SDS	standard deviation score

SR	studentized residual
TBW	total body water
TEE	total energy expenditure
Wt	weight



