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

Chapter 9

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 (ΔHt) 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. ΔHt SDS <0.5 gave the highest percentage poor responders (37% SGA, 26% GHD). Although % poor responders were comparable for ΔHt 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 (ΔHt 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 ± 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) ΔHt SDS, (2) HV SDS, (3) ΔHV (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 ΔHt 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: ΔHt SDS <0.35 (40%), HV SDS <-0.85 (43%), ΔHV <1.3 cm/year (36%), IoR <-1.57 (17%), HV KIGS SDS <-0.83 (40%) to predict total ΔHt 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 ΔHt SDS as a predictor for total ΔHt SDS <1.0 had an area under the curve >70 % and were further analyzed. First-year ΔHt 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). ΔHt 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.