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High Serum Levels of Growth Hormone (GH) and Insulin-Like Growth Factor-I (IGF-I) during High-Dose GH Treatment in Short Children Born Small for Gestational Age

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Context: Epidemiological studies have indicated that high serum levels of GH and IGF-I are associated with long-term risks.

Objective: The objective of the study was to evaluate the changes in serum levels of GH during overnight profiles, IGF-I, and IGF binding protein 3 (IGFBP-3) in short small for gestational age (SGA) children during GH treatment with two doses.

Patients: Thirty-six prepubertal short SGA children were the subjects of this study.

Intervention: Subjects received 1 (group A) or 2 (group B) mg GH/m^2·d.

Main Outcome Measures: At baseline and after 6 months of GH treatment, overnight GH profiles were performed, and serum IGF-I and IGFBP-3 levels were measured.

Results: After 6 months, group B had significantly higher GH levels during the profile (mean, maximum, and area under the curve above zero line) than group A ($P < 0.009$). In group B, maximum GH levels increased from 43.9–161 mU/liter ($P < 0.0002$), and in group A, from 57.2–104 mU/liter ($P = 0.002$). During the profile (*i.e.* 12 h per day), children of group B had mean GH levels of 64.4 *vs.* 34.8 mU/liter in group A ($P = 0.001$). The IGF-I and IGF-I to IGFBP-3 ratio SD scores increased significantly in both groups, but were higher in group B than A [1.5 *vs.* 0.2 ($P = 0.002$) and 1.4 *vs.* 0.3 ($P = 0.007$), respectively]. In group B, 74% of the children had IGF-I levels in the highest quintile during GH treatment compared with 19% in group A.

Conclusion: Our study shows that high-dose GH treatment in short SGA children results in high serum GH and IGF-I levels in most children. We recommend monitoring IGF-I levels during GH therapy to ensure that these remain within the normal range. (***J Clin Endocrinol Metab* 91: 1390–1396, 2006**)

MOST CHILDREN BORN small for gestational age (SGA) show catch-up growth to a normal height during the first 2 yr of life, but approximately 10–15% of them remain short with a height below −2 SD scores (1, 2). Disturbances in the GH/IGF axis may play a role in SGA children with persistent short stature (3–10).

It has been demonstrated that GH treatment of short children born SGA results in a normalization of height during childhood, as well as a normal adult height for most of them (6, 11). Recently, Van Pareren *et al.* (11) showed that long-term treatment with a GH dose of 1 mg/m^2·d (~0.033 mg/kg·d) was as effective as the higher dose of 2 mg/m^2·d (~0.067/kg·d) for most children with regard to adult height.

Previous reports have shown that GH treatment of short SGA children leads to increases in serum IGF-I and IGF binding protein 3 (IGFBP-3) levels, which are positively related to the GH dose (4–6). Sas *et al.* (6) reported a rise of the IGF-I and IGFBP-3 SD score up to 1.2 and 0.2, respectively, during GH treatment with 1 mg GH/m^2·d for 1 yr, whereas treatment with 2 mg GH/m^2·d resulted in an IGF-I and IGFBP-3 SD score of 1.9 and 0.5, respectively. After 5 yr of GH treatment, the IGF-I and IGFBP-3 SD scores were 1.7 and 1.0 in the 1-mg GH dose group and to 2.0 and 1.2 in the 2-mg GH dose group, respectively (6).

Although the effects of GH treatment on serum levels of IGF-I and IGFBP-3 in short SGA children have been well studied, no data are available on the effect of GH therapy with various doses on serum GH levels in these children. It has been shown that administration of GH to healthy and GH-deficient adults results in a dose-dependent rise of se-

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Abbreviations: AUC_0, Area under the curve above zero line; BMI, body mass index; CV, coefficient of variation; IGFBP-3, IGF binding protein 3; SGA, small for gestational age.

rum GH levels (12, 13). Therefore, it is expected that short SGA children receiving high-dose GH treatment not only have higher levels of IGF-I, but also higher GH levels.

Concern has been expressed regarding the possible harmful effects of high serum GH and IGF-I levels for many years (14, 15). Recent epidemiological studies on risk of breast (16), prostate (17), and colon (18) cancer have indicated that serum levels of IGF-I in the upper tertile to quintile are associated with an increased risk of cancer. For that reason, it is important to evaluate the serum levels of GH and IGF-I in GH-treated short SGA children.

Therefore, we studied GH levels during an overnight GH-profile and serum levels of IGF-I and IGFBP-3 in 36 short SGA children, both before and after 6 months of treatment with either 1 or 2 mg GH/m^2·d.

Subjects and Methods

Subjects

The study group comprised 36 prepubertal short children born SGA. Children were included according to the following criteria: 1) birth length and/or birth weight SD score (SD score) below −2 for gestational age, 2) current height SD score below −2.5, 3) height velocity SD score below zero to exclude children with spontaneous catch-up growth, 4) prepubertal stage, defined as Tanner breast stage I for girls and testicular volume less than 4 ml for boys, 5) age between 5–8 yr at start of the study, and 6) an uncomplicated neonatal period, without signs of severe asphyxia (Apgar score >3 after 5 min) or long-term complications of respiratory ventilation such as bronchopulmonary dysplasia. Children with endocrine or metabolic disorders, chromosomal defects, syndromes, and growth failure caused by other conditions (*e.g.* emotional deprivation, severe chronic illness, chondroplasia) were excluded, except for children with Silver-Russell syndrome. The study was approved by the medical ethics committees of the participating centers, and written informed consent was obtained from the parents.

Study design

After stratification for gender, GH-status (maximum serum GH between 20–30 mU/liter *vs.* serum GH >30 mU/liter during a GH stimulation test), and body mass index (BMI) (<−1 SD *vs.* >−1 SD), all 36 children were randomized into two different groups. During 6 months, children of group A (n = 16) received GH therapy with a dose of 1 mg GH/m^2·d and children of group B (n = 20) received a dose of 2 mg GH/m^2·d. GH [Nordiptropin * SimpleXx 15 mg/1.5 ml (biosynthetic human growth hormone, Novo Nordisk A/S, Bagsvaerd, Denmark] was administered sc once daily at bedtime using the Nordipen 15. Overnight GH profiles were performed in all subjects at baseline and after 6 months of GH treatment. Children were admitted to the hospital, and blood for determination of serum GH levels was withdrawn from an indwelling venous catheter at 20-min intervals between 1900 and 0700 h. Children followed their normal eating pattern until midnight. The next morning a fasting blood sample was taken for measurement of IGF-I and IGFBP-3 levels. During the second GH profile, at 6 months after start of GH therapy, the daily sc GH injection was given under observation at 2000 h, 1 h after onset of the GH profile.

Assays

Serum IGF-I and IGFBP-3 were measured using a specific RIA (19) in one laboratory. The intraassay coefficient of variation (CV) was 4% and the interassay CV was 6%. GH levels were measured by IMMULITE 2000 (Diagnostic Products Corporation, Los Angeles, CA), with a lower detection limit of 0.13 mU/liter. The intraassay and interassay CV were 3.7 and 5.7%, respectively.

Calculations

All overnight GH profiles were analyzed using the Pulsar program (20). The area under the curve above zero line (AUC_0), mean, and maximum GH levels were derived. The AUC_0 was divided by three to rescale time into units of 1 h, and was similar when calculated by the trapezoidal method. Serum levels of GH were expressed in milliunits per liter. The serum levels of IGF-I and IGFBP-3 were converted into SD scores to adjust for age and sex, using reference values for healthy children with normal stature determined in the same laboratory (21).

Statistics

Analyses were carried out using the computer statistical package SPSS (version 10.1; SPSS Inc., Chicago, IL) for Windows. Results are expressed as the median (interquartile range), unless indicated otherwise. The Mann-Whitney *U* test was used for differences between groups. Differences between points in time were tested by the Wilcoxon signed rank test. To test for linear relationships between continuous variables, partial correlations were estimated for group A and B together, with adjustment for GH dosage. Multiple linear regression analysis was used to assess multivariable relationships. Factors showing a significant partial correlation with the 6-month change in height SD score were entered into the model. Only results of the best fitting model (in terms of R-squared) are shown. Statistical significance was defined as $P < 0.05$.

Results

Clinical data

Table 1 lists the baseline clinical data of both GH dosage groups. Children of both groups (A and B) had comparable baseline characteristics. Two children of group B had genetically proven Silver-Russell syndrome. Six children in group A and six children in group B were born preterm.

Growth response to GH therapy

In group A, the height SD score increased significantly from −3.3 (−3.4 to −2.8) at start to −2.8 (−2.9 to −2.3) after 6 months of GH therapy ($P = 0.0004$). Group B showed an increase in height SD score from −3.1 (−3.4 to −2.7) to −2.4 (−2.8 to −2.2) after 6 months ($P < 0.0001$). The change in

TABLE 1. Baseline clinical characteristics of the study groups

	Group A (n = 16; 1 mg GH/m^2·d)	Group B (n = 20; 2 mg GH/m^2·d)
Male/female	9/7	11/9
Gestational age (wk)	37.8 (34.1 to 39.2)	38.0 (33.3 to 39.3)
Birth weight SD score	−1.8 (−3.4 to −1.1)	−2.1 (−2.6 to −1.3)
Birth length SD score	−2.6 (−3.4 to −1.6)	−2.8 (−3.4 to −2.1)
Age at start of GH treatment (yr)	6.2 (5.8 to 7.4)	6.2 (5.4 to 7.7)
Height SD score at start of GH treatment	−3.3 (−3.4 to −2.8)	−3.1 (−3.4 to −2.7)
BMI SD score at start of GH treatment	−0.8 (−2.0 to −0.1)	−1.2 (−2.2 to −0.7)

Data are expressed as median (interquartile range).

TABLE 2. Characteristics of overnight GH release, IGF-I, and IGFBP-3 levels in group A and B at baseline and after 6 months of GH treatment

	Group A (1 mg GH/m²·d)		*P* value[a]	Group B (2 mg GH/m²·d)		*P* value[a]	*P* value[b]
	0 Months	6 Months		0 Months	6 Months		
AUC_0 (mU/liter·12 h)	130 (113–150)	428 (344–638)	0.0004	113 (97.4–138)	791 (668–946)	0.0001	0.0009
Mean GH (mU/liter)	10.8 (9.2–12.5)	34.8 (28.2–52.0)	0.0004	9.6 (8.0–11.3)	64.4 (54.6–76.9)	0.0001	0.001
Max GH (mU/liter)	57.2 (44.4–73.5)	104 (94.3–149)	0.002	43.9 (32.0–53.9)	161 (110–206)	0.0002	0.009
GH >40 mU/liter (h)	0.7 (0.1–1.0)	4.5 (2.9–6.4)	0.0007	0.0 (0.0–0.9)	7.3 (6.0–8.7)	0.0001	0.001
GH <20 mU/liter (h)	2.0 (1.7–2.6)	6.5 (5.7–9.2)	0.0004	1.7 (0.8–2.2)	9.3 (7.7–10.7)	0.0001	0.017
IGF-I SD score	−1.6 (−2.1 to −1.3)	0.2 (−0.5 to 0.7	0.0008	−1.6 (−2.2 to −1.2)	1.5 (0.8–2.1)	0.0001	0.002
IGFBP-3 SD score	−1.5 (−1.7 to −0.8)	−0.2 (−0.7 to 0.2)	0.002	−1.5 (−1.8 to −1.1)	0.5 (0.44–0.68)	0.0001	0.005
IGF-I to IGFBP-3 ratio SD score	−1.1 (−1.7 to −0.6)	0.3 (−0.3 to 1.0)	0.002	−1.0 (−1.6 to −0.4)	1.4 (0.6–2.1)	0.0002	0.007

Data are expressed as median (interquartile range).
[a] Compared to baseline.
[b] Group B *vs.* A after 6 months of GH treatment.

height SD score was significantly higher in group B than in group A ($P = 0.001$).

Overnight GH profiles

Table 2 lists the characteristics of the overnight GH profiles for both GH dosage groups at baseline and after 6 months. At baseline, the AUC_0, mean, and maximum GH levels were comparable for group A and B. After 6 months of GH treatment (when a sc GH injection was given at 2000 h), the AUC_0, mean, and maximum GH levels increased significantly in both groups. All values were significantly higher in group B compared with group A. For example, in group B, mean GH levels increased from 9.6–64.4 mU/liter, and maximum GH levels increased from 43.9–161 mU/liter, whereas group A showed an increase of mean GH levels from 10.8–34.8 mU/liter and of maximum GH levels from 57.2–104 mU/liter.

Figure 1 depicts the mean serum GH levels of both groups at each time point during the overnight GH profiles at baseline

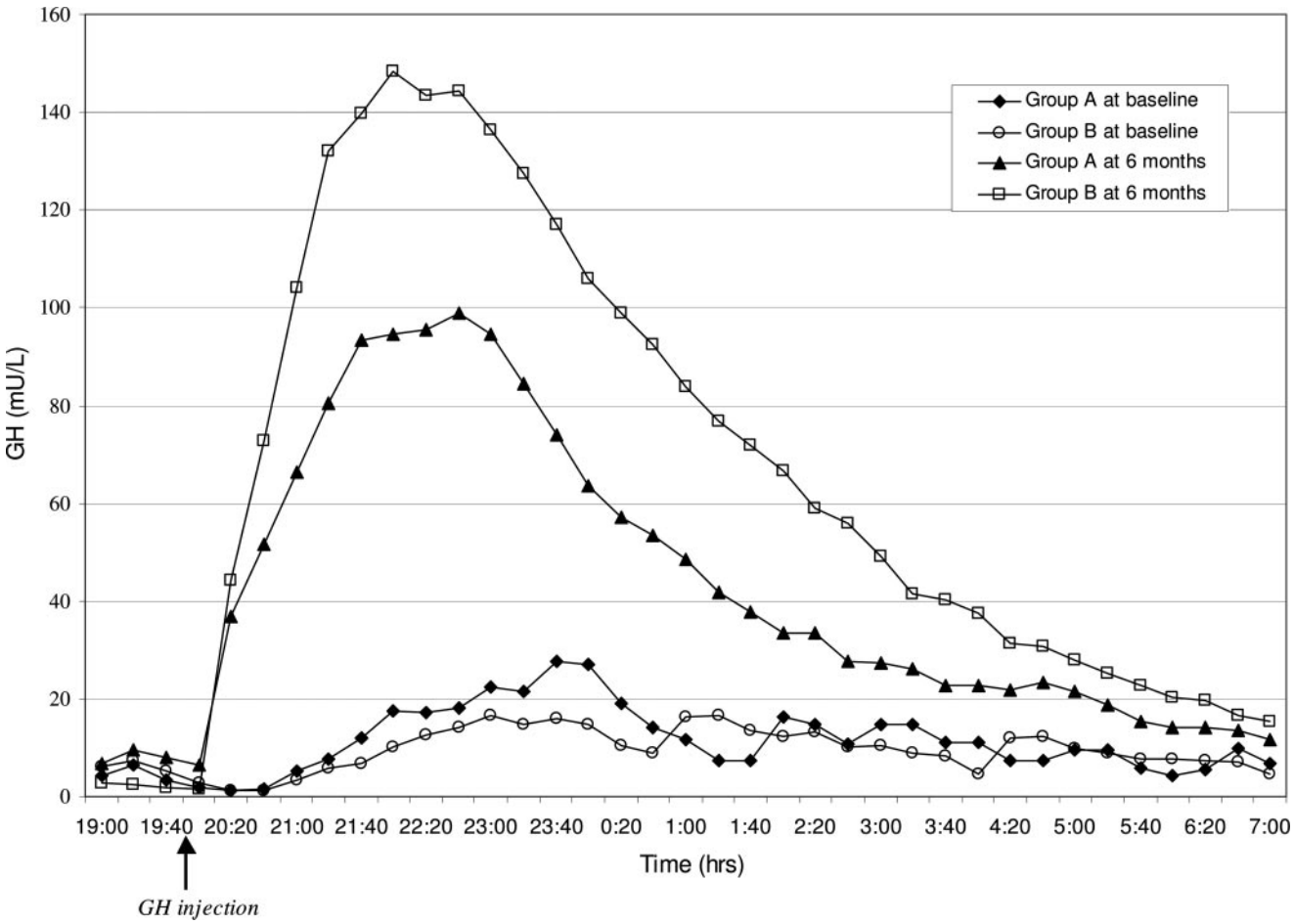

FIG. 1. Mean GH levels for each time point during an overnight GH profile at baseline and after 6 months of GH treatment.

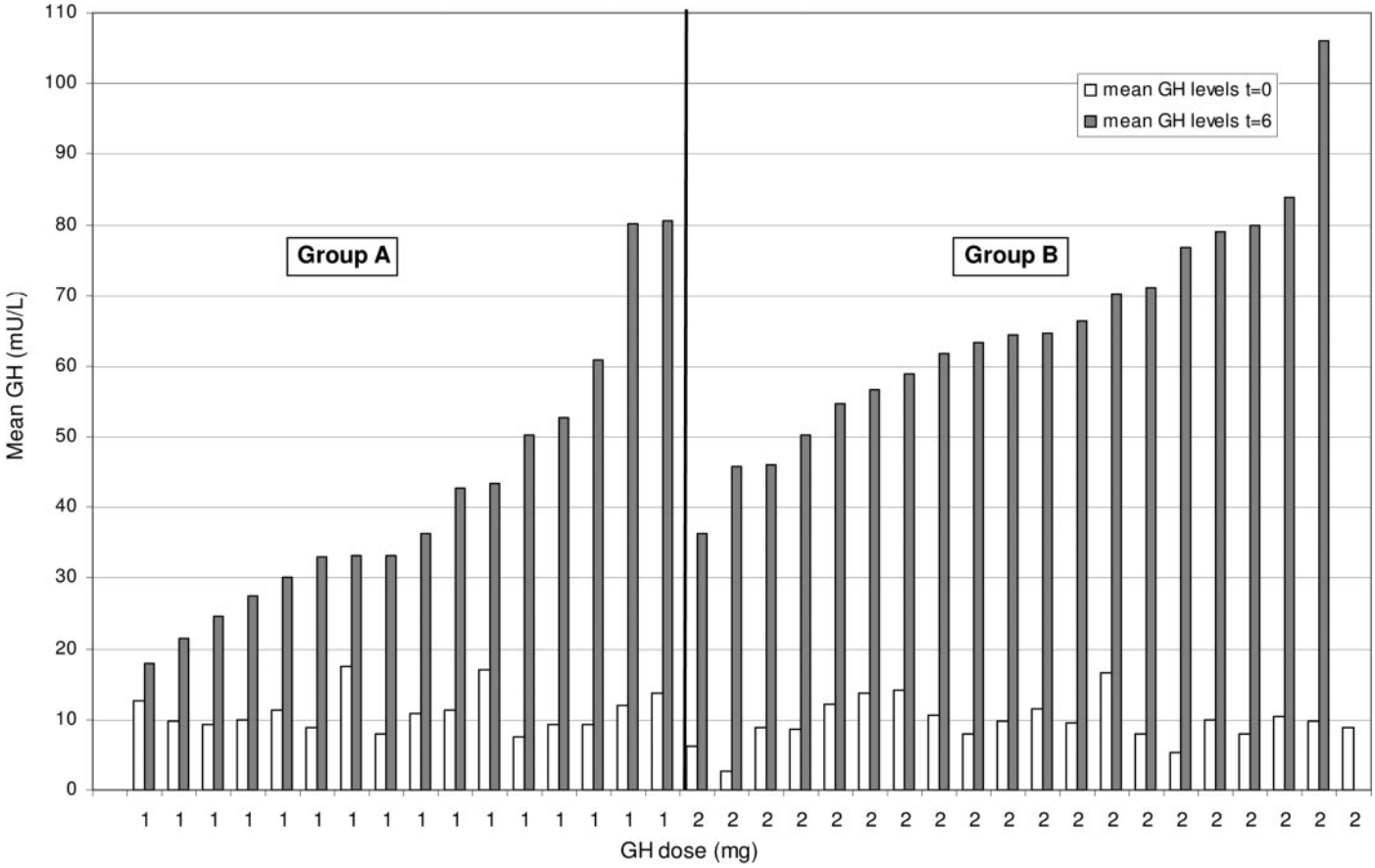

FIG. 2. Mean GH levels for each individual during an overnight GH profile before and after 6 months of GH treatment.

and after 6 months. After sc GH injection at 2000 h, GH levels remained above 40 mU/liter for 7.3 h in group B compared with 4.5 h in group A ($P = 0.0008$), and above 20 mU/liter for 9.3 h in group B compared with 6.5 h in group A ($P = 0.017$). Figure 2 shows the individual mean GH levels during the overnight GH profiles for each child, with the children ranked per group. During GH treatment, a wide interindividual variation in mean GH levels was seen. Two subjects in group A and one in group B showed strikingly high mean serum GH levels compared with the other children of their group.

IGF-I and IGFBP-3 levels and IGF-I to IGFBP-3 ratio

Serum levels of IGF-I and IGFBP-3 and the IGF-I to IGFBP-3 ratio, expressed as SD scores, are shown in Table 2. Baseline IGF-I and IGFBP-3 SD scores were comparable for group A and B and significantly lower than zero ($P = 0.0001$ to 0.0009). After 6 months of GH treatment, the IGF-I and IGFBP-3 SD scores increased significantly in both GH dosage groups compared with baseline, but were significantly higher in group B than in group A. In group B, the IGF-I SD score increased from −1.6 to 1.5 and the IGFBP-3 SD score increased less markedly from −1.5 to 0.5. Both SD scores were significantly higher than zero ($P = 0.005$ and 0.009). In contrast, in group A, the IGF-I SD score increased from −1.6 to 0.2 and the IGFBP-3 SD score from −1.5 to −0.2, both being not statistically different from zero anymore. Seventy-four percent of the children of group B had serum IGF-I levels in the highest quintile (> 0.84 SD score), and 37% had levels above 2 SD score compared with only 19% ($P = 0.0014$) and 6% ($P = 0.034$) of the children of group A, respectively.

At baseline, the IGF-I to IGFBP-3 ratio SD score was significant lower than zero in both groups ($P = 0.002$ and 0.0001). After 6 months of GH treatment, the IGF-I to IGFBP-3 ratio SD score increased significantly in both groups compared with baseline, but was significantly higher in group B than in group A. In group B, there was an increase from −1.0 to 1.4, which was significantly higher than zero ($P = 0.001$). In contrast, in group A, the IGF-I to IGFBP-3 ratio SD score increased from −1.1 to 0.3 and was no longer statistically different from zero. Sixty-three percent of children of group B had an IGF-I to IGFBP-3 ratio in the highest quintile (> 0.84 SD score) and 32% above 2 SD score, compared with 25% ($P = 0.026$) and 0% ($P = 0.015$) of the children in group A, respectively.

At baseline, the IGFBP-3 SD score correlated significantly with the AUC_0 ($r = 0.48$, $P = 0.003$), mean ($r = 0.51$, $P = 0.002$), and maximum GH levels ($r = 0.57$, $P = 0.000$), but no correlation was found after 6 months. In contrast, the IGF-I and IGF-I to IGFBP-3 ratio SD scores did not correlate with serum GH levels, neither at baseline, nor at 6 months.

Relationship between the growth response and other variables

Partial correlations were made for group A and B together, with adjustment for GH dose. The change in height SD score

correlated significantly with the height SD score at start (r = −0.34, $P = 0.044$), age at start (r = −0.50, $P = 0.002$), AUC_0 at start (r = −0.34, $P = 0.044$), mean GH levels at start (r = −0.36, $P = 0.034$), and the baseline IGF-I (r = −0.47, $P = 0.004$), and IGFBP-3 SD scores (r = −0.51, $P = 0.002$). No significant partial correlation was found between gain in height SD score and the following parameters: birth weight and birth length SD score; target height SD score; maximum GH levels at start; baseline IGF-I to IGFBP-3 ratio SD score; AUC_0 at 6 months; mean and maximum GH levels at 6 months; IGF-I, IGFBP-3, and IGF-I to IGFBP-3 ratio SD scores at 6 months; and the 6-month changes in GH levels, IGF-I, IGFBP-3, and IGF-I to IGFBP-3 ratio SD scores.

Using multiple regression, the following variables were the best predictors of the 6-month increase in height SD score during GH treatment: GH dose (group B *vs.* group A) ($\beta = 0.51$, $P = 0.0002$), age (in years) at start of the study ($\beta = -0.370$, $P = 0.0043$), and IGF-I SD score at start ($\beta = -0.34$, $P = 0.0079$). These three variables explained 55% of the variation of the 6-month change in height SD score.

Discussion

Our study shows that short SGA children receiving high-dose GH treatment (2 mg/m^2·d) have very high mean serum GH levels of 64.4 mU/liter during 12 h per day. High-dose GH treatment also resulted in serum IGF-I levels and an IGF-I to IGFBP-3 ratio in the highest quintile (>0.84 SD score) in 74 and 63% of the children, respectively.

This is the first report describing serum GH levels after GH administration in prepubertal short SGA children. We found great interindividual variations in mean serum GH levels among the short SGA children in both GH dosage groups. Comparable individual variations in GH levels after sc GH injection have previously been reported in GH-deficient children and were attributed to different mechanisms of the degradation of GH at the site of injection or in the circulation (22). Two children in group A and one child in group B had extremely high GH levels compared with the other children in the groups. Higher serum GH levels have been described when the GH injection was administered im instead of sc (23). It is possible that the GH administration in these two children was not completely sc as in the other children, but partly intramuscular at the time of the overnight profile. Their IGF-I levels were not different compared with the other children.

Previous studies concerning GH levels during GH treatment have mainly been performed in healthy adults (24, 25), GH-deficient patients (12, 23, 26), and in girls with Turner syndrome (27). The short SGA children in our study showed remarkably high mean and maximum serum GH levels after sc GH injection. Vahl *et al.* (28) found an inverse correlation between serum GH levels after a single GH dose and age as well as intraabdominal fat mass. This might partly explain the higher mean and maximum GH levels in our study group, which consisted of young prepubertal SGA children with a reported lower fat mass and a lower BMI SD score than their peers (29).

In the high-dose group, mean serum GH levels were 64.4 mU/liter during the 12 h of the GH profile, and remained above 20 mU/liter for more than 9 h, indicating that short SGA children treated with 2 mg GH/m^2·d have elevated GH levels for a great part of the day. At the end of the overnight GH-profiles, 11 h after the sc GH injection, serum GH returned to near baseline levels in both groups. For comparison, overnight GH levels in normal prepubertal boys and girls are 10.5 and 10.8 mU/liter, respectively, and increase during puberty, reaching maximum values of 17.1 mU/liter in boys and 20 mU/liter in girls (30).

In the 2-mg GH dose group, 63% of the children had IGF-I levels and 74% an IGF-I to IGFBP-3 ratio in the highest quintile (> 0.84 SD score) after GH treatment, and approximately 30% of them even had levels above 2 SD scores. In contrast, almost all children of the normal GH dose group had IGF-I levels and/or an IGF-I to IGFBP-3 ratio SD score within ±1 SD score.

In another group of short SGA children receiving 1 and 2 mg GH/m^2·d, Sas *et al.* (6) also showed an increase of the IGF-I SD score up to 1.2 and 1.9 in the first year and up to 1.7 and 2.0 after 5 yr, respectively, indicating that these levels remain at the same SD level when GH treatment is given for many years. de Zegher *et al.* (5) reported a 3- to 6-fold increase of IGF-I levels after 2 yr of high-dose GH treatment with 2 and 3 mg/m^2·d, respectively. In all reports, there was also a significant increase of the IGF-I to IGFBP-3 ratio (5, 6).

We found a clear correlation between baseline GH levels and the baseline IGFBP-3 SD score, but not with the IGF-I SD score, which is in agreement with previous studies (3, 8, 31). This might suggest that IGFBP-3 levels are a more valuable measure for the endogenous GH secretion in short SGA children.

The 6-month change in height SD score was inversely related to mean GH levels at start and the baseline IGF-I, IGFBP-3, and the IGF-I to IGFBP-3 ratio SD scores, indicating that children with lower levels of GH and IGF-I were more sensitive to GH treatment. No correlation was found between the growth response and the increases in GH, IGF-I, and IGFBP-3 levels. This may suggest a reduced GH and/or IGF-I receptor sensitivity, particularly in those children with higher GH and IGF-I levels in combination with a poorer growth response. Another explanation may be that IGF-I receptors in some short SGA children are already maximally stimulated, meaning that a further increase of GH and IGF-I levels has no extra effect. Previous reports concerning the relationship between growth response to GH therapy and the GH/IGF-I axis are contradictory. Some studies suggest that the catch-up growth during GH treatment is independent of the GH/IGF-I axis (6, 11, 26). However, other studies have shown a clear correlation between the growth response and baseline IGF-I levels (4, 31) or changes in IGF-I levels during GH treatment (32).

Concern has been expressed regarding the possible detrimental effects of persistently high serum levels of GH and IGF-I (14, 15). Epidemiological studies have suggested that high serum levels of GH and IGF-I might increase cancer risk in human beings, especially when IGFBP-3 levels are low (17, 18). Serum IGF-I levels in the upper tertile to quintile have been associated with increased risk of breast, prostate, and colon cancer (16–18). These findings were supported by Renehan *et al.* (33) who did a systematic review and meta-

regression analysis of the association between concentrations of IGF-I and IGFBP-3 levels and cancer risks.

In contrast, low serum levels of GH and IGF-I, as found in individuals with a T1663A polymorphism in the human GH1 gene, are associated with a decreased risk of colorectal cancer (34).

Most short SGA children receiving GH treatment with 2 mg/m^2·d have high GH levels for many hours per day and IGF-I levels in the upper quintile (> 0.84 SD score). As the majority of these children will be treated for 10–12 yr until adult height is reached, serum GH and IGF-I levels will be elevated during their childhood and adolescence. Children treated with the higher GH dose for many years might therefore be at increased risk for complications in later life.

Recently, GH treatment for short children born SGA with persistent short stature has been approved by the European Agency for the Evaluation of Medicinal Products. However, there is still debate about the optimal GH dose for these children. In the United States, the higher GH dose of 2 mg/m^2·d has been approved by the Food and Drug Administration, whereas we have recently shown that treatment with a GH dose of 1 mg/m^2·d was as effective as 2 mg/m^2·d with regard to reach a normal adult height (11). In a recent epianalysis, it has been shown that height gain is less dose dependent over the long term than over the short term (35). For that reason, there is no evidence to support long-term treatment with the higher GH dose for all short SGA children with regard to adult height improvement.

In conclusion, our study shows that GH treatment with 2 mg GH/m^2·d in short SGA children results in high serum GH levels for 12 h per day and IGF-I levels and/or an IGF-I to IGFBP-3 ratio in the highest quintile (>0.84 SD score) in 74 and 63% of the children, respectively, whereas treatment with a dose of 1 mg GH/m^2·d completely normalizes IGF-I and IGFBP-3 levels (±1 SD score). The long-term risks of high GH and IGF-I levels in short SGA children are still unknown. Therefore, we recommend monitoring IGF-I levels during GH therapy to ensure these remain within the normal range. GH treatment could be started at a lower dose with individual adjustment based on growth response and IGF-I levels.

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