Serum leptin in short children born small for gestational age: relationship with the growth response to growth hormone treatment

Margaret Boguszewski¹, Jovanna Dahlgren¹, Ragnar Bjarnason¹,², Sten Rosberg¹, Lena M S Carlsson², Björn Carlsson² and Kerstin Albertsson-Wikland¹ on behalf of the Swedish Study Group for Growth Hormone Treatment

1International Pediatric Growth Research Centre, Department of Pediatrics, and 2Research Centre for Endocrinology and Metabolism, Department of Medicine, University of Göteborg, S-416 85 Göteborg, Sweden

(Correspondence should be addressed to M Boguszewski, International Pediatric Growth Research Centre, Department of Pediatrics, East Hospital, 416 85 Göteborg, Sweden)

Abstract

The product of the obese (ob) gene, leptin, is an adipocyte-derived hormone that is involved in the regulation of appetite and body weight. This study was undertaken in order to describe the basal serum levels of leptin in prepubertal short children born small for gestational age (SGA) and their relationship with growth parameters, before and during growth hormone (GH) treatment. Eighty-nine prepubertal short children (66 boys, 23 girls; height standard deviation score (SDS), −5.4 to −2.0; age, 2.0 to 12.8 years) born SGA, 12 of whom (9 boys, 3 girls) had signs of Silver-Russell syndrome, were included in the study. Serum leptin concentrations were measured by radioimmunoassay. Leptin levels in the children born SGA were compared with those in a reference group of 109 prepubertal healthy children born at an appropriate size for gestational age (AGA). The mean (S.D.) change in height SDS was 0.11 (0.22) during the year before the start of GH therapy (0.1 IU/kg/day) and increased to 0.82 (0.44) during the first year (P<0.001) and to 1.28 (0.59) during the 2-year period of GH therapy (P<0.001). The children born SGA were significantly leaner than the reference group. An inverse correlation was found between leptin and chronological age in the SGA group (r = −0.31, P<0.01). The mean serum level of leptin in the children born SGA who were older than 5.5 years of age was 2.8 mg/l which was significantly lower than the mean value of 3.7 μg/l found in the children born AGA of the same age range. The difference remained after adjustment of leptin levels for sex, age, body mass index (BMI) and weight-for-height SDS (WH SDSSDS). Leptin correlated with WH SDSSDS (r = 0.32, P<0.001) and BMI (r = 0.36, P<0.01) in the reference population, but not in the SGA group. No correlation was found between leptin and spontaneous 24-h GH secretion, insulin-like growth factor (IGF)-I or IGF-binding protein-3 levels, or with fasting insulin or cortisol levels. Leptin levels at the start of GH treatment were correlated with the growth response over both 1 year (r = 0.46, P<0.001) and 2 years (r = 0.51, P<0.001) of GH therapy. Using multiple regression analysis, models including leptin levels at the start of GH treatment could explain 51% of the variance in the growth response after 1 year and 44% after 2 years of GH treatment.

In conclusion, serum leptin levels are reduced in short children born SGA and are inversely correlated with chronological age. Leptin concentrations correlate with the growth response to GH treatment and might be used as a marker for predicting the growth response to GH treatment.

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Introduction

Children born small for gestational age (SGA) have a higher risk of short stature in adulthood in comparison with non-SGA children (1). Although most infants born SGA show catch-up growth in early life, a subgroup will continue to grow slowly, resulting in a short adult height (1–3). They also tend to be thinner and have a reduced amount of body fat compared with children born at an appropriate size for gestational age (AGA) (4, 5). Recently, Lapillonne et al. (6) has shown that total body fat, evaluated by dual-energy X-ray absorptiometry (DXA), is decreased in SGA infants in comparison with total body fat in AGA infants having the same gestational age, confirming anthropometric data.

Leptin, the adipocyte-derived hormone encoded by the obese (ob) gene (7, 8), is thought to act as an afferent satiety signal, regulating appetite and energy expenditure...
in both humans and rodents (8–11). Leptin levels are increased in obese subjects and correlate with the amount of body fat, suggesting that most obese subjects have reduced sensitivity to endogenous leptin (11, 12). Obese children have increased serum leptin concentrations compared with children of normal weight, and the levels correlate directly with fat mass and body mass index (BMI) (13, 14). Leptin levels are also influenced by gender and developmental stage (13). Schubring et al. (15) found that leptin levels were high in maternal serum and cord blood at birth and that placental weight correlated inversely with maternal leptin levels. In addition, cord blood leptin levels correlated directly with birth weight, and it was suggested that leptin is an important regulator of fetal weight and intrauterine growth.

Yu et al. (16) suggested that leptin plays an important role in hypothalamic–pituitary function. Furthermore, leptin can be a metabolic signal that regulates growth hormone (GH) secretion (17). Thus, the study of leptin concentration and its relationship with growth parameters and different hormones in short children born SGA may increase the understanding of the mechanisms behind the lack of catch-up growth in this subgroup of children born SGA.

In this study, we have analysed serum leptin concentrations in a cohort of prepubertal short children born SGA without postnatal catch-up growth, and have studied the relationship between these leptin concentrations and anthropometric measurements, spontaneous 24-h GH secretion, insulin-like growth factor (IGF)-I, IGF-binding protein-3 (IGFBP-3), fasting insulin and cortisol levels. The relationship between leptin concentrations before the start of GH treatment and the growth response to therapy was also evaluated.

Patients and methods

Study subjects

A total of 89 prepubertal children born SGA (66 boys, 23 girls), 12 of whom (9 boys, 3 girls) had signs of Silver-Russell syndrome, were investigated at the Children’s Hospital, Gothenburg, Sweden. Their mean (s.d.) chronological age at the time of the investigation was 6.6 (3.1) years (range, 2.0 to 12.8 years), and their mean (s.d.) height standard deviation score (SDS) was −3.2 (0.8) (range, −5.4 to −2.0 SDS) compared with Swedish reference values (18). Mean (s.d.) weight-for-height SDS (WH₃₀₀ SDS; weight SDS−height SDS) (19) was −0.5 (1.4) and mean (s.d.) BMI (weight in kg/height in m²) was 14.5 (1.5) (Table 1). In this study, SGA is defined as a birth weight and/or a birth length below −2 SDS compared with Swedish reference values for healthy newborns corrected for gestational age (20). The mean (s.d.) birth weight of the children was −2.7 (1.1) SDS and their mean (s.d.) birth length was −2.9 (1.2) SDS. In 60 children (67%), both length and weight were below −2 SDS at birth. Fifteen children were born preterm, that is, before 36 weeks of gestation. The growth of the children has been followed since birth at various neonatal units and at child health-care units in Sweden. None of the children showed complete catch-up growth postnatally. Infants with a known or suspected maternal history of alcohol or drug addiction were excluded. Thyroid, kidney and liver functions were normal and none of the children had coeliac disease. The mean maternal height was −1.0 (1.1) SDS and the mean paternal height was −1.0 (1.3) SDS compared with Swedish reference values (21).

A standard arginine-insulin tolerance test (AITT) was performed in 69 children born SGA, and 24 of them had a maximal GH (GHmax) response below 20 mU/l (10 µg/l). Spontaneous 24-h GH secretion was estimated in 71 children (Table 2), as previously reported (22). Of the 24 children with a GHmax below 20 mU/l (10 µg/l) during the AITT, 7 also had a spontaneous GHmax Peak below 20 mU/l (10 µg/l). In 20 children in whom no AITT was performed, 5 had a spontaneous GHmax peak below 20 mU/l (10 µg/l).

Reference group

A total of 109 prepubertal healthy children (79 boys, 30 girls) born AGA were used as the reference group (Table 1). They were investigated at the Children’s Hospital, Göteborg, Sweden. Their mean (s.d.) chronological age was 9.8 (2.0) years (range, 5.7 to 12.9 years), and their mean (s.d.) height was −1.4 (1.3) SDS (range, −2.5 to 2.5 SDS). They were used as a control group for the children born SGA who were older than 5.5 years of age, that is, within the same age range. Single blood samples for leptin measurements were obtained between 1000 and 1400 h.

Blood samples

Leptin measurements during 24-h sampling

Out of the 89 children born SGA, 71 (52 boys, 19 girls) were evaluated using 24-h blood sampling for determination of GH secretory patterns as part of an investigation of their short stature, as previously reported (22). Serum leptin concentrations were measured in single samples collected between 1000 and 1400 h on the same day. In 18 children, the 24-h sampling was not performed; in these children, leptin was measured in samples taken immediately before the start of GH treatment.

Leptin measurements at start of GH treatment

Sixty-three short children born SGA (47 boys, 16 girls) were treated with recombinant GH (Genotropin, Pharmacia & Upjohn, Stockholm, Sweden), which was administered subcutaneously at a dose of 0.1 IU/kg (33 µg/kg) daily. All children completed 2 years of treatment, but eight children were excluded from the
2-year growth response analysis due to the onset of puberty. For correlations between serum concentrations of leptin and the growth response to GH treatment, the leptin concentrations were those measured in samples taken immediately before the first GH injection.

Blood samples for measurements of IGF-I and IGFBP-3 were taken at the time of 24-h sampling and at the start of GH treatment. Morning samples for measurements of cortisol (0600 h) were obtained in parallel to the 24-h profiles. Samples for measurement of insulin were taken at 0600 h after an overnight fast.

Serum samples for all hormone measurements were stored at $-20^\text{o}$C until assayed.

The study was approved by the Ethical Committee of the Medical Faculty, University of Göteborg. Informed consent was obtained from all children (if old enough) and their parents.

**Hormone measurements**

Leptin concentrations in serum were determined in duplicate by radioimmunoassay (RIA) (Human Leptin RIA Kit, Linco Research, Inc., St Charles, MO, USA). The assay has a detection range of 0.22 to 100 µg/l with an intra-assay coefficient of variation (CV) of 7.0% at 2.4 µg/l and 4.9% at 14.0 µg/l. The corresponding interassay CV values were 9.0% and 5.0%.

GH concentrations were measured using a polyclonal antibody-based immunoradiometric assay (Pharmacia & Upjohn, Uppsala, Sweden) with the WHO International Reference Preparation 66/217 as standard. However, some of the samples were analysed using the First International Reference Preparation 80/505 as standard, and the values obtained from these samples were transformed to the 66/217 standard (22).

IGF-I concentrations were measured by an IGFBP-blocked RIA without extraction and in the presence of an approximately 250-fold excess of IGF-II (Mediagnost GmbH, Tübingen, Germany) (23). Serum IGFBP-3 concentrations were determined using an RIA method as reported previously (Mediagnost GmbH) (23). As serum levels of IGF-I and IGFBP-3 are age-dependent, all values were converted into SDS using reference values for prepubertal healthy children (24).

Insulin concentrations were measured by RIA (Pharmacia & Upjohn, Uppsala, Sweden). Cortisol concentrations were determined by RIA (Farmos Diagnostica, Åbo, Finland). Measurements of insulin and cortisol were performed in the Department of Clinical Chemistry at Sahlgrenska Hospital, Göteborg (accredited laboratory No. 1240 according to European home EN 45001).

**Statistical methods**

Data are presented as means (S.D.). Because of non-normal distribution of serum leptin concentrations, leptin data are presented as mean, median and quartiles (25th and 75th). The correlations between leptin and the other variables were evaluated by the Spearman rank correlation coefficient. For all other correlations, Pitman’s non-parametric permutation test (25) was used and Pearson’s correlation coefficient was calculated. For comparison of leptin levels from the children born SGA with the reference group controlling for chronological age, sex, WH SDSSDS and BMI, Mantel’s technique of pooling (26) applied to Wilcoxon’s rank sum test was used (25). Fisher’s non-parametric permutation test was used for comparisons between groups. A multiple stepwise linear regression analysis was used as a multivariate method to identify predictors of the growth response for the 1- and 2-year periods of GH treatment. In this analysis, a log transformation of serum leptin levels was performed to normalize the distribution.

The index weight-for-height SDS was developed from the age-specific linear regression between weight SDS and height SDS (weight SDS = β · height SDS), where β is the slope between weight SDS and height SDS. The index can be expressed in SDS (WH SDSSDS) using the residual S.D. around the regression line. After correcting weight SDS for the slope β, the correlation coefficient between the index and the height SDS becomes zero (19, 27).

**Results**

**Leptin levels and gender**

A significant difference in leptin levels was found between boys and girls, both in the SGA group and in the reference population. The mean level for SGA boys was 2.8 µg/l (median 2.4, quartiles 2.1 and 3.0 µg/l), whereas for the SGA girls the corresponding values were 3.5 µg/l (median 3.2, quartiles 2.6 and 4.0 µg/l) ($P<0.01$). The difference remained significant after adjustment for age, WH SDSSDS and BMI.

**Leptin levels and age**

An inverse correlation was found between leptin levels and chronological age ($r=-0.31$, $P<0.01$) in the children born SGA, but not in the reference group. The leptin levels in the children born SGA who were younger than 5.5 years of age ($n=37$; mean 3.3 µg/l, median 3.0 µg/l, quartiles 2.5 and 3.5 µg/l) were significantly higher ($P<0.001$) compared with those in the oldest SGA children (mean 2.8 µg/l, median 2.4 µg/l, quartiles 2.0 and 2.8 µg/l). Figure 1 shows the serum concentrations of leptin for the children born SGA in relation to their chronological age and compared with the reference group. As described above, the mean leptin level for the oldest children born SGA was 2.8 µg/l, which was significantly below the mean value of 3.7 µg/l (median 3.1 µg/l, quartiles 2.7 and 4.0 µg/l) for the reference population ($P<0.001$). After adjustment of
leptin levels for chronological age and sex, the difference between groups was still significant (P < 0.001). The leptin levels in the children with Silver-Russell syndrome did not differ from those in the children born SGA without signs of the syndrome.

Leptin levels and WHSDS SDS and BMI

Table 1 summarizes the clinical characteristics of the children born SGA and the reference group born AGA. The children born SGA were significantly leaner than the reference group. No relationship was found between leptin levels and WHSDS SDS or BMI in the children born SGA (Fig. 2, top panels), whereas leptin levels correlated with WHSDS SDS (r = 0.26, P < 0.01) and BMI (r = 0.36, P < 0.01) in the reference children (Fig. 2, bottom panels). After adjustment of leptin levels for age, sex, WHSDS SDS and BMI, a significant (P < 0.001) difference in leptin levels was still found between the children born SGA and the reference population.

Leptin levels and other hormones

Table 2 summarizes the hormone measurements in the study group and their relationships with the baseline leptin levels. No correlation was found between leptin levels and spontaneous 24-h GH secretion, nor with IGF-I or IGFBP-3 levels. Serum concentrations of leptin did not correlate with fasting serum insulin or serum cortisol levels.

Leptin and the growth response to GH treatment

The change in height SDS per year (∆ height SDS) was used to describe growth. The ∆ height SDS during the year before the start of GH treatment was 0.11 (0.22) (range, −0.44 to 0.52) and increased to 0.82 (0.44) (range, 0.16 to 2.27) during the first year of GH therapy (P < 0.001) and to 1.28 (0.59) (range, 0.14 to 3.25) during the 2-year period of treatment (P < 0.001). Leptin concentrations were available in 43 children after 2 years of GH therapy. Leptin levels decreased in 32 children, although the difference between levels at the start and after 2 years of treatment was not significant (P = 0.08). Leptin levels at the start of GH treatment correlated strongly with both the 1-year (r = 0.46, P < 0.001) and 2-year (r = 0.51, P < 0.001) growth response, expressed as ∆ height SDS (Fig. 3).

To explain the variance in growth response to GH treatment, stepwise regression analysis was applied to all variables correlated with the ∆ height SDS with a P value less than 0.1 (Table 3). In the first model, chronological age at the start of GH treatment and maternal height, expressed in SDS, accounted for 46% of the variance in the 1-year growth response (R² = 0.46, s.d. of the residual=0.34). With the addition of leptin levels at the start of therapy (model 2), the R²

| Table 1 | Clinical characteristics at the start of the investigation in short children born SGA without signs of Silver-Russell syndrome (SGA), with signs of the syndrome (SR) and in the reference group born AGA. |
|---|---|---|---|---|
| **Age (years)** | **Height (SDS)** | **Weight (SDS)** | **WHSDS SDS (SDS)** | **BMI (kg/m²)** |
| SR (n = 12) | Mean (S.D.) | 4.1 (2.4) | −3.8 (1.0) | −3.7 (1.2) <sup>ab</sup> | −1.0 (1.5) <sup>c</sup> | 14.5 (1.8) <sup>c</sup> |
| | Range | 2.0 to 10.5 | −5.0 to −2.1 | −5.3 to −0.9 | −2.7 to 1.9 | 12.5 to 17.9 |
| SGA (n = 77) | Mean (S.D.) | 7.0 (3.0) | −3.0 (0.8) | −2.6 (1.1) <sup>a</sup> | 0.5 (1.3) <sup>c</sup> | 14.5 (1.5) <sup>c</sup> |
| | Range | 2.2 to 12.8 | −5.4 to −2.0 | −5.3 to 0.2 | −4.0 to 3.0 | 11.7 to 19.6 |
| SGA + SR (n = 89) | Mean (S.D.) | 6.6 (3.1) | −3.2 (0.8) | −2.8 (1.1) <sup>a</sup> | −0.5 (1.4) <sup>c</sup> | 14.5 (1.5) <sup>c</sup> |
| | Range | 2.0 to 12.8 | −5.4 to −2.0 | −5.3 to 0.2 | −4.0 to 3.0 | 11.7 to 19.6 |
| Reference group (n = 109) | Mean (S.D.) | 9.8 (2.0) | −1.4 (1.3) | −1.0 (1.3) | 0.1 (1.2) | 16.0 (1.8) |
| | Range | 5.7 to 12.9 | −2.5 to 2.5 | −2.9 to 2.8 | −2.1 to 4.7 | 12.7 to 23.0 |

<sup>a</sup> P < 0.0001 vs reference group; <sup>b</sup> P < 0.001 vs SGA non-SR group; <sup>c</sup> P < 0.001 vs reference group.
value increased to 0.51. In model 3, 24-h GH profiles were included, as were maternal height SDS, chronological age at the start of GH treatment, and spontaneous GH secretion, expressed as the area under the curve above the baseline (AUCb), and accounted for 48% of the variability of the 1-year growth response. For the 2-year period, the variables available at the start of GH therapy, with the exception of leptin levels, were analysed (model 4). Only chronological age at the start of therapy entered the model and accounted for 27% of the variance in the growth response. However, the $R^2$ value increased to 0.44 when leptin levels at the start of therapy were included (model 5). The estimated regression equations for the growth response based on the various predictors in each model are shown in Table 4.

Figure 2 Relationships between serum leptin concentrations and weight-for-height SDS (WH SDS SDS) and body mass index (BMI) in children born SGA (O, upper panels) and in the reference group (●, lower panels). The solid line represents the linear regression.

Table 2 Correlation coefficients between different measurements and the baseline leptin levels in short prepubertal children born SGA.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean (± s.d.)</th>
<th>Range</th>
<th>$r$</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h GH profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH max (mU/l)</td>
<td>71</td>
<td>29.6 (16.1)</td>
<td>9.8–89.4</td>
<td>–0.00</td>
<td>ns</td>
</tr>
<tr>
<td>GH secretion rate (U/24 h)</td>
<td>71</td>
<td>0.32 (0.16)</td>
<td>0.09–1.06</td>
<td>–0.19</td>
<td>ns</td>
</tr>
<tr>
<td>Number of GH peaks</td>
<td>71</td>
<td>8.4 (2.0)</td>
<td>4.0–14.0</td>
<td>0.10</td>
<td>ns</td>
</tr>
<tr>
<td>Baseline GH level (mU/l)</td>
<td>71</td>
<td>1.1 (0.9)</td>
<td>0.1–4.6</td>
<td>0.05</td>
<td>ns</td>
</tr>
<tr>
<td>AUCb (mU/l 24 h)</td>
<td>71</td>
<td>86.4 (38.7)</td>
<td>29.8–208.5</td>
<td>–0.02</td>
<td>ns</td>
</tr>
<tr>
<td>AITT–GH max (mU/l)</td>
<td>69</td>
<td>30.5 (20.4)</td>
<td>5.0–118.4</td>
<td>0.07</td>
<td>ns</td>
</tr>
<tr>
<td>IGF-I (SDS)</td>
<td>69</td>
<td>5.2 (3.3)</td>
<td>1.5–12.1</td>
<td>0.02</td>
<td>ns</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>48</td>
<td>333.8 (121.2)</td>
<td>142.7–647.0</td>
<td>0.08</td>
<td>ns</td>
</tr>
</tbody>
</table>

* Spearman rank correlation; ns, not significant.
1 $AUC_b$, area under the curve above the baseline; 2 Samples taken at 1000 h; 3 samples taken at 0600h.
Discussion

This study shows that short children born SGA have reduced serum leptin concentrations in comparison with those in children born AGA. In addition, leptin levels correlate directly with the growth response to GH treatment (the higher the leptin levels, the better the growth response).

The short children born SGA were thinner than the reference population. In addition, their serum leptin

Table 3 Correlation coefficients between different variables and the one-year and two-year growth response to GH treatment in children born SGA.

<table>
<thead>
<tr>
<th></th>
<th>One-year growth response</th>
<th>Two-year growth response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>r</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63</td>
<td>−0.55</td>
</tr>
<tr>
<td>Diff SDS*</td>
<td>63</td>
<td>−0.51</td>
</tr>
<tr>
<td>Height SDS</td>
<td>63</td>
<td>−0.28</td>
</tr>
<tr>
<td>Height SDS Father</td>
<td>63</td>
<td>0.27</td>
</tr>
<tr>
<td>Mother</td>
<td>63</td>
<td>0.47</td>
</tr>
<tr>
<td>Mid-parental</td>
<td>63</td>
<td>0.42</td>
</tr>
<tr>
<td>Log leptin (μg/l)</td>
<td>63</td>
<td>0.52</td>
</tr>
<tr>
<td>IGF-I (ng/ml)</td>
<td>60</td>
<td>−0.33</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>60</td>
<td>−0.02</td>
</tr>
<tr>
<td>IGFBP-3 (ng/ml)</td>
<td>60</td>
<td>−0.32</td>
</tr>
<tr>
<td>IGFBP-3 SDS</td>
<td>60</td>
<td>0.02</td>
</tr>
<tr>
<td>AITT - GHmax (mU/l)</td>
<td>50</td>
<td>−0.07</td>
</tr>
<tr>
<td>24-h GH profile AUC0 (mU/l/24 h)</td>
<td>53</td>
<td>−0.27</td>
</tr>
<tr>
<td>GHmax (mU/l)</td>
<td>53</td>
<td>0.24</td>
</tr>
<tr>
<td>GHt (U/24 h)</td>
<td>53</td>
<td>−0.42</td>
</tr>
</tbody>
</table>

1 Diff SDS, difference between the individual height SDS at baseline and mid-parental height SDS; 2 AUC0, area under the curve above the baseline; 3 GHt, GH secretion rate.

* Pitman’s permutation test; ns, not significant.
indicating that leptin is a signal responsible for approximately 50% just before the onset of puberty, children (13) and in adults (29). Recently, Mantzoros et al. have shown that leptin levels in boys rose by 24-h GH profile 0.13 + 0.06 × chronological age at GH start – 0.33 × mother height SDS – 0.002 × AUC ob.3. In our study, the higher leptin concentration found in girls may indicate that the girls are nearer to the start of puberty than boys.

The relationship between insulin and leptin levels is not totally understood. Positive effects of insulin on expression of the ob gene in rat adipose tissue and on leptin levels in humans have been reported (31, 32), but these findings have not been supported by others (33, 34). Considine et al. (12), using large numbers of obese and non-obese subjects, found that fasting serum insulin had no influence on leptin concentrations after adjustment for the percentage of body fat. In the present group of children born SGA, no correlation was found between leptin and fasting insulin, cortisol or GH concentrations. As the regulation of body weight involves various hormones, including insulin, cortisol and GH (35), it might be that in children born SGA the leptin levels reflect the balance between those hormones enhancing lipid accumulation and those stimulating lipid depletion, rather than each of these hormones separately.

Children born SGA have an increased risk of short stature in adulthood in comparison with non-SGA children (1–3). A particular subgroup of children born SGA are those with the dysmorphic features of Silver-Russell syndrome (small and triangular face, clinodactyly and asymmetry of the body), whose mean final height is lower than their target height (36). We have shown that children born SGA who fail to achieve complete catch-up growth postnatally secrete less GH than healthy children born AGA of both normal and short stature (22). In addition, they have lower levels of IGF-I and IGFBP-3 than children born AGA of normal height (24). In the present study, the children born SGA had a significant increase in linear growth during the 2 years of GH treatment, in agreement with previous studies (37, 38), although there was much variability in the magnitude of the growth response. Since the

**Table 4** Estimated regression equations for the one-year and two-year growth response to GH treatment in children born SGA.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>R²</th>
<th>s.d. of the residual</th>
<th>Estimated regression equation for the growth response, expressed as change in height SDS</th>
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</thead>
<tbody>
<tr>
<td><strong>One-year growth response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Model 1 Pretreatment variables</td>
<td>62</td>
<td>0.46</td>
<td>0.34</td>
<td>1.50 – 0.07 × chronological age at GH start + 0.19 × mother height SDS</td>
</tr>
<tr>
<td>Model 2 Pretreatment variables plus leptin</td>
<td>62</td>
<td>0.51</td>
<td>0.32</td>
<td>0.98 – 0.059 × chronological age at GH start + 0.79 × log leptin level at GH start + 0.16 × mother height SDS</td>
</tr>
<tr>
<td>Model 3 Pretreatment variables plus leptin and 24-h GH profile</td>
<td>52</td>
<td>0.48</td>
<td>0.34</td>
<td>1.55 – 0.06 × chronological age at GH start + 0.13 × mother height SDS – 0.002 × AUC ob.3</td>
</tr>
<tr>
<td><strong>Two-year growth response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4 Pretreatment variables</td>
<td>52</td>
<td>0.27</td>
<td>0.25</td>
<td>1.00 – 0.05 × chronological age at GH start + 0.56 + 0.10 × log leptin level at GH start – 0.04 × chronological age at GH start</td>
</tr>
<tr>
<td>Model 5 Pretreatment variables plus leptin</td>
<td>52</td>
<td>0.44</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Model 6 Pretreatment variables plus leptin and 24-h GH profile</td>
<td>42</td>
<td>0.49</td>
<td>0.17</td>
<td>0.81 – 1.04 × GH secretion rate – 0.06 × Diff SDS*</td>
</tr>
</tbody>
</table>

* Diff SDS, difference between the individual height SDS at baseline and mid-parental height SDS.
introduction of recombinant GH therapy, much effort has been made to predict the growth response to GH therapy and to identify short children who will respond to treatment (24, 39, 40). In our previous report (24), chronological age at the start of GH therapy (the younger the child, the better the growth response), the mother’s height expressed as SDS (the taller the mother, the better the growth response) and the 24-h GH secretion rate (the lower the GH secretion rate, the better the growth response) were the strongest predictors. In the present study, we show that the serum leptin concentration at the start of GH treatment is another factor that could be included in the prediction models, especially when 24-h GH profiles are not available. Furthermore, for the 2-year growth response, the leptin level before treatment was an even stronger predictor of the response than was chronological age at the start of GH therapy, increasing the $R^2$ value from 27% to 44%. These findings are consistent with the hypothesis that leptin may be involved in growth regulation and that it can be used as a predictor of the growth response to GH treatment: the higher the leptin level, the better the growth response.

In conclusion, serum leptin levels are reduced in prepubertal short children born SGA and are inversely correlated with chronological age. Leptin concentration correlates with the growth response to GH treatment and can be used as a marker for predicting the growth response to GH treatment in short children born SGA.

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