Growth Hormone (GH)-Binding Protein in Prepubertal Short Children Born Small for Gestational Age: Effects of Growth Hormone Treatment*

MARGARET BOGUSZEWSKI, RAGNAR BJARNASON, STEN ROSBERG, LENA M. S. CARLSSON, AND KERSTIN ALBERTSSON-WIKLAND ON BEHALF OF THE SWEDISH STUDY GROUP FOR GROWTH HORMONE TREATMENT†

Department of Pediatrics, International Pediatric Growth Research Center (M.B., R.B., S.R., K.A-W.), and the Department of Medicine, Research Center for Endocrinology and Metabolism (R.B., L.M.S.C.), University of Goteborg, Goteborg, Sweden

ABSTRACT
This study was undertaken to characterize the serum levels of GH-binding protein (GHBP) before and during GH treatment in prepubertal short children born small for gestational age (SGA) and their relationship with growth parameters. Sixty-seven prepubertal short children (49 boys and 18 girls; height SD score, −5.4 to −2.0; age, 2.0–12.8 yr) born SGA, 8 of whom (6 boys and 2 girls) had signs of Silver-Russell syndrome, participated in the study. Total GHBP was measured by a ligand-mediated immunofunctional assay. The mean (SD) change in height SD score during the year before the start of GH treatment (0.1 IU/kg/day) was 0.11 (0.20) SD score, and this value increased to a 0.84 (0.43) SD score during the first year (P < 0.001) and to a 1.27 (0.63) SD score during the 2-yr period of therapy (P < 0.001). The baseline GHBP values ranged from 49–392 pmol/L, and no relationships were found among sex, chronological age, and maximal GH response to an arginine-insulin tolerance test. A positive correlation between GHBP and body composition, expressed as weight for heightSD score, was found in the whole group (r = 0.44; P < 0.05) and in boys (r = 0.44; P < 0.01). No relationship was found between GHBP and spontaneous 24-h GH secretion, in terms of either GH secretion rate or pulsatile pattern, whereas GHBP was positively correlated with insulin-like growth factor I (IGF-I) SD score (r = 0.28; P < 0.05) and IGF-binding protein-3 SD score (r = 0.39; P < 0.01). Using a multiple stepwise linear regression analysis, the model using the IGF-binding protein-3 SD score and the weight for height SD score at the start of GH therapy accounted for 33% of the variance in the baseline GHBP values. A mean increase of 27 (51%) in GHBP levels was found after 1 yr of therapy. However, a high degree of variability in the response of individuals to GH treatment in terms of GHBP levels was observed: in some children GHBP levels increased, whereas in others they decreased. In conclusion, GHBP levels in short prepubertal children born SGA were mostly within the normal range previously reported and correlated directly with body composition. An increase in GHBP levels was observed during GH treatment in some SGA children. No correlation was found between pretreatment GHBP levels and growth response to GH treatment. (J Clin Endocrinol Metab 82: 1014–1019, 1997)


Address all correspondence and requests for reprints to: Dr. Margaret Boguszewski, International Pediatric Growth Research Center, Department of Pediatrics, East Hospital, 416 85 Goteborg, Sweden. E-mail: Margaret.Boguszewski@pediat.gu.se.

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† Participants in the Swedish Study Group for Growth Hormone Treatment: Kerstin Albertsson-Wikland, Jan Alm, Stefan Aronson, Jan Gustafsson, Lars Hagénäs, Anders Håger, Sten Ivarsson, Berit Kristöm, Claude Marcus, Christian Moell, Karl-Olof Nilsson, Martin Ritzén, Torsten Tuuveno, Ulf Westgren, Otto Westphal, and Jan Åman.

A SPECIFIC, high affinity GH-binding protein (GHBP) in human plasma has been identified and characterized by Baumann et al. (1) and Herington et al. (2). Circulating GHBP is identical to the extracellular domain of the cellular GH receptor and it appears to arise primarily from proteolytic cleavage of the membrane-bound GH receptor (3–5). The GHBP plasma concentration shows only minor variations during the day (6), whereas GH is secreted in a pulsatile fashion (7). By complexing with GH in the circulation, GHBP may act to prolong the biological half-life of GH and dampen the oscillations of plasma GH levels caused by episodic pituitary secretion (8).

Studies of GHBP in human fetuses and infants have shown that plasma GHBP levels increase with gestational age and are also influenced by the intrauterine nutritional state (4, 9). The levels of GHBP are low at birth and increase sharply during the first years of life (4, 9, 10). In contrast, the GH concentration is elevated in children during their first days of life, especially under conditions of suboptimal intrauterine growth (11, 12). On the basis of these observations, it has been reported that only about 2% of the circulating GH in human fetuses and infants is bound to GHBP (9).

It has been shown that children born small for gestational age (SGA) who lack complete catch-up growth postnatally as a group secrete less GH than children born at an appropriate size for gestational age (13, 14), and that their linear growth increases during GH replacement therapy (15, 16). In this study, we characterized serum GHBP concentrations in a cohort of prepubertal short children born SGA and their relationship with growth parameters, spontaneous 24-h GH secretion, and insulin-like growth factor I (IGF-I) and IGF-binding protein-3 (IGFBP-3) levels. The effects of GH treatment on GHBP levels were also evaluated.
Subjects and Methods

Study subjects
A total of 67 prepubertal children born SGA (49 boys and 18 girls), 8 of whom (6 boys and 2 girls) had signs of Silver-Russell syndrome, were investigated at the Children’s Hospital (Goteborg, Sweden). Their mean (sd) chronological age at the start of GH treatment was 6.5 (3.0) yr (range, 2.0–12.8 yr), and their mean (sd) height was 3.4 (0.9) sd score (range, –5.4 to +2.0 sd score), compared with Swedish reference values (17). In this study, SGA is defined as a birth weight and/or a birth length below –2 sd score compared with Swedish reference values for healthy newborns corrected for gestational age (18). The mean (sd) birth weight of the children was 2.8 (1.1) sd score, and their mean (sd) birth length was –3.1 (1.3) sd score. Both the length and weight of 47 children (70%) were below –2 sd score at birth. Ten children were born preterm, that is before 36 weeks 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 malformations and with known or suspected maternal history of alcohol addiction were excluded. Thyroid, kidney, and liver functions were normal, and none of the children had coeliac disease. Mean midparental height was –0.9 (1.0) sd score compared with Swedish reference values (19). Table 1 summarizes the clinical characteristics of the study group.

Study protocol
Pretreatment investigation. A standard arginine-insulin tolerance test (AITT) was performed in all SGA children, and 23 had a maximal GH response (GHmax) below 20 mU/L (10 µg/L). Spontaneous 24-h GH secretion was estimated in these 23 children and also in 31 children (giving of a total 44) with GHmax above 20 mU/L in terms of both secretory rate and pulsatile pattern, as reported previously (13). Briefly, for the SGA children, the mean GH secretion rate was 0.3 U/24 h, whereas for the reference group of normal children, it was 0.7 U/24 h (P < 0.001). The mean area under the curve above the baseline (AUCb) for the SGA children was 88.1 (48.1) mU/L (sd 26.1), whereas for the reference group of normal children, it was 0.7 U/24 h (P < 0.001) and to 1.27 (P = 0.001). The mean area under the curve below the baseline (AUCd) was 27.8 (23.8) mU/L (sd 17.1) for the SGA children, the mean GH secretion rate was 0.3 U/24 h, that is, 0.3 U/24 h (sd 0.2), compared with Swedish reference values for healthy newborns corrected for gestational age (18). The mean (sd) birth weight of the children was 2.8 (1.1) sd score, and their mean (sd) birth length was –3.1 (1.3) sd score. Both the length and weight of 47 children (70%) were below –2 sd score at birth. Ten children were born preterm, that is before 36 weeks 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 malformations and with known or suspected maternal history of alcohol addiction were excluded. Thyroid, kidney, and liver functions were normal, and none of the children had coeliac disease. Mean midparental height was –0.9 (1.0) sd score compared with Swedish reference values (19). Table 1 summarizes the clinical characteristics of the study group.

GH treatment. Recombinant human GH (Genotropin, Pharmacia and Upjohn, Stockholm, Sweden) was administered sc at a dose of 0.1 IU/kg (33 µg/kg) BW daily. All 67 children completed 2 yr of treatment. During the second year of therapy, 6 children were excluded from the 2-yr analysis due to onset of puberty. Blood samples for the measurement of GHBP were collected immediately before the first GH injection, just before the GH injections on day 10, and 1 yr after the initiation of GH therapy. The study was approved by the ethical committee of the Medical Faculty, University of Goteborg. Informed consent was obtained from all children (if old enough) and their parents.

Hormonal measurements

GH concentrations were measured using a polyclonal antibody-based immunoassay (Pharmacia and Upjohn) with the WHO International Reference Preparation 66/217 as the standard. However, some of the children were analyzed using the First International Reference Preparation 80/505 as the standard, and the values obtained from these children were transformed to the 66/217 standard (13).

Total GHBP was measured by a ligand-mediated immunofunctional assay as described previously (21), using reagents from Genentech (South San Francisco, CA).

IGF-I was measured by an IGFBP-blocked RIA without extraction and in the presence of an approximately 250-fold excess of IGF-II (Mediagnost, Tübingen, Germany) (22). IGFBP-3 was determined using a RIA method reported previously (Mediagnost) (22). As serum levels of IGF-I and IGFBP-3 are age dependent, all values were converted into a sd score using our reference values from prepubertal healthy children (20).

Statistical methods

Data are presented as means (sd), unless otherwise stated. Correlations were tested using Pitman’s nonparametric permutation test (23). Pearson’s correlation coefficients were estimated. The Wilcoxon rank sum test was used for comparisons between groups, and the Wilcoxon signed rank test was used for evaluation of changes over time. A multiple stepwise regression analysis was used as a multivariate method to explain the variability in baseline GHBP levels.

Results

Growth response to GH therapy

The change in height sd score per yr (Δ height sd score) is used to describe the growth response. The Δ height sd score during the year before the start of GH treatment was 0.11 (0.20) sd score, and this value increased to 0.84 (0.43) sd score during the first year of GH therapy (P < 0.001) and to 1.27 (0.63) sd score during the 2-yr period of treatment (P < 0.001). Consequently, the mean height attained increased from –3.37 (0.87) sd score at the start of treatment to –2.52 (0.87) sd score after 1 yr and –2.11 (0.92) sd score after 2 yr of GH treatment.

Table 1. Clinical characteristics of the SGA children at birth and at the start of GH treatment

<table>
<thead>
<tr>
<th></th>
<th>All SGA (n = 67)</th>
<th>&lt;6 yr of age (n = 32)</th>
<th>&gt;6 yr of age (n = 35)</th>
<th>Girls (n = 18)</th>
<th>Boys (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver-Russell syndrome (n)</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>6.5 (3.0)</td>
<td>2.9 (1.0)</td>
<td>8.9 (1.9)</td>
<td>6.0 (3.0)</td>
<td>6.7 (3.0)</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>18/49</td>
<td>9/23</td>
<td>9/26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ht SD score</td>
<td>–3.4 (0.9)</td>
<td>–3.8 (0.9)</td>
<td>–3.0 (0.6)</td>
<td>–3.8 (0.8)</td>
<td>–3.2 (0.8)</td>
</tr>
<tr>
<td>Wt SD score</td>
<td>–2.4 (0.8)</td>
<td>–3.1 (0.6)</td>
<td>–1.9 (0.6)</td>
<td>–2.9 (0.7)</td>
<td>–2.3 (0.8)</td>
</tr>
<tr>
<td>Wt for ht SD score</td>
<td>0.01 (1.0)</td>
<td>0.5 (0.9)</td>
<td>0.4 (0.9)</td>
<td>0.5 (0.5)</td>
<td>0.2 (1.1)</td>
</tr>
<tr>
<td>Midparental ht SD score</td>
<td>–0.9 (1.0)</td>
<td>–0.7 (1.1)</td>
<td>–1.2 (1.0)</td>
<td>–1.5 (1.1)</td>
<td>–0.7 (0.9)</td>
</tr>
<tr>
<td>Birth length SD score</td>
<td>–3.1 (1.3)</td>
<td>–3.6 (1.4)</td>
<td>–2.5 (0.9)</td>
<td>–3.0 (1.0)</td>
<td>–3.1 (1.4)</td>
</tr>
<tr>
<td>Birth wt SD score</td>
<td>–2.8 (1.1)</td>
<td>–3.1 (1.1)</td>
<td>–2.5 (1.0)</td>
<td>–2.7 (0.9)</td>
<td>–2.8 (1.1)</td>
</tr>
<tr>
<td>AITT, GHmax &lt;20 mU/L</td>
<td>23</td>
<td>8</td>
<td>15</td>
<td>5</td>
<td>18</td>
</tr>
</tbody>
</table>

Values are given as the mean (sd).

a P < 0.001 vs. children older than 6 yr of age.

b P < 0.01 vs. boys.

c P < 0.05 vs. boys.

d P < 0.05 vs. children older than 6 yr of age.

e P < AITT, Arginine-insulin tolerance test.
Basal serum GHBP levels

The mean pretreatment level of GHBP in the children with Silver-Russell syndrome did not differ from that in SGA children without signs of the syndrome. The pretreatment GHBP values ranged from 49–392 pmol/L and did not vary with sex, age (Fig. 1), and GH max during an AITT (Table 2). No correlation was found between basal GHBP levels and the growth response to GH treatment.

Relationship among serum GHBP levels, height, and body composition. GHBP levels correlated inversely with the pretreatment height SD score in the whole SGA group (r = −0.28; P < 0.05); further, this correlation was stronger for SGA children younger than 6 yr (r = −0.52; P < 0.01), who were also shorter (Table 1 and Fig. 1, middle panel). Body composition was expressed as the weight for height SD score. The mean pretreatment weight for height SD score for the boys was 0.2 ± 0.39, whereas in girls no relationship was observed between these parameters (Fig. 1, bottom panel).

Variability of the baseline GHBP concentrations. To explain the variability in the GHBP concentrations at the start of GH therapy, stepwise regression analysis was applied to all variables that correlated with the baseline GHBP levels with P < 0.05 (Table 3). IGFBP-3 levels, expressed as a SD score, and the weight for height SD score at the start of therapy were entered into the model and accounted for 33% of the variance in the baseline GHBP levels (r² = 0.33; SD of the residual = 66).

Changes in GHBP levels during GH treatment

The individual serum GHBP levels before treatment and after 10 days and 1 yr of GH replacement therapy are shown in Fig. 3. A high degree of variability in the individual GHBP response to GH treatment was observed. The mean GHBP level at the start of GH therapy was 153 (69) pmol/L, and this did not change significantly after 10 days of therapy [mean, 143 (54); range, 57–259 pmol/L], whereas the mean value after 1 yr of therapy was 185 (104) (range 66–507 pmol/L; P < 0.01). The mean percent increase up to 1 yr of treatment was 26 (45) (range, −42% to 193%) for the children without signs of Silver-Russell syndrome and 35 (74) (range, −69% to 202%) for the children with signs of the syndrome. No correlation was found between the percent changes in GHBP levels and the growth response to treatment. However, a positive correlation was found between GHBP levels after 1 yr of treatment and the first year growth response to GH therapy (r = 0.33; P < 0.05).

Discussion

Children born SGA are at increased risk of short stature, and the causes of this growth failure have been investigated by several researchers. Disturbances in GH secretion and reduced serum concentrations of IGF-I and IGFBP-3 in SGA children have been reported (13, 14, 20). Recent studies suggest that abnormalities at the level of the GH receptor and GHBP concentration may be one explanation for the growth failure in short children (24, 25); however, no data on GHBP levels in short SGA children have been reported. In this report, we have described the basal levels of GHBP and their
changes during GH treatment in prepubertal short children born SGA.

A broad range of serum GHBP levels, from 49–392 pmol/L, was found among the SGA children, and these levels were mostly within the range previously reported for normal children (25). Despite the high variability of GHBP levels among all SGA children (8-fold), the values for each child varied within narrower limits (3-fold), even during GH treatment. Our data are in accordance with previous reports suggesting that GH secretion is probably not a major long term regulator of serum GHBP levels (26, 27).

Serum levels of GHBP increase with gestational age, are very low in newborns and increase rapidly during the first 3 months of life (4, 9). Further increases have been observed during childhood in most (10, 24–27), but not all (28, 29), studies. In our group of SGA children, this age-dependent phenomenon was not found. The majority of the reports cited above were based on data from normal children with a

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**TABLE 2.** GHBP concentrations in children born SGA analyzed separately for sex, age, and GH max during an arginine-insulin tolerance test (AITT)

<table>
<thead>
<tr>
<th>GHBP (pmol/L)</th>
<th>Girls</th>
<th>Boys</th>
<th>&lt;6 yr</th>
<th>&gt;6 yr</th>
<th>&lt;20 mU/L</th>
<th>&gt;20 mU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>192 (67)</td>
<td>156 (79)</td>
<td>162 (69)</td>
<td>169 (85)</td>
<td>172 (81)</td>
<td>162 (76)</td>
</tr>
<tr>
<td>Range</td>
<td>89–313</td>
<td>49–392</td>
<td>49–313</td>
<td>50–392</td>
<td>50–344</td>
<td>49–392</td>
</tr>
<tr>
<td>n</td>
<td>18</td>
<td>49</td>
<td>32</td>
<td>35</td>
<td>23</td>
<td>44</td>
</tr>
</tbody>
</table>

**TABLE 3.** Correlation coefficients between different variables and the GHBP concentrations at baseline

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean (SD)</th>
<th>Correlation coefficient</th>
<th>( r )</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-BP-3 (ng/mL)</td>
<td>67</td>
<td>2585.4 (791.9)</td>
<td>0.37</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>IGF-BP-3 (SD score)</td>
<td>67</td>
<td>-0.4 (1.0)</td>
<td>0.39</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>IGF-I (ng/mL)</td>
<td>67</td>
<td>99.9 (55.7)</td>
<td>0.35</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>IGF-I (SD score)</td>
<td>67</td>
<td>-0.5 (1.2)</td>
<td>0.28</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Ht (SD score)</td>
<td>67</td>
<td>-3.4 (0.9)</td>
<td>-0.28</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Wt for ht SD score</td>
<td>67</td>
<td>0.01 (1.0)</td>
<td>0.28</td>
<td>&lt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

\( ^a \) By Pitman’s permutation test.

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Fig. 2. Baseline GHBP levels in SGA children vs. GH secretion rate, vs. AUCb (only the children with a GH max response to an AITT above 20 mU/L), vs. IGF-I SD score, and vs. IGFBP-3 SD score. The lines represent the linear regression of baseline GHBP vs. IGF-I SD score (continuous line), vs. AUCb (dotted line), and vs. IGFBP-3 SD score (broken line).
broader age range than those in our study, but the reason for the discrepancy among results is not entirely clear.

Nutrition has an important regulatory effect on GHBP levels. Massa et al. (9) examined cord serum from 69 infants and suggested that the intrauterine nutritional state influences GHBP levels. Other studies showed a positive correlation between GHBP levels and body mass index, that is weight (kilograms)/height (centimeters)$^2$, in both prepubertal and pubertal healthy children (10, 27, 28, 30). Moreover, serum GHBP levels are decreased in patients of low weight with anorexia nervosa and return to nearly normal levels after refeeding (31). In our study, the weight for height $sd$ score was used to avoid the influence of height on the results (32). A positive correlation was found between basal GHBP levels and weight for height $sd$ score in the whole SGA group and in boys, whereas no correlation could be found in girls. One reason for this difference could be the narrower range of weight for height $sd$ score in girls than in boys in our study.

Interestingly, using stepwise regression analysis to explain the variability in the baseline GHBP, we found that weight for height $sd$ score and IGFBP-3 concentration, expressed as the $sd$ score, accounted for 33% of the variance in baseline GHBP levels. IGFBP-3 is a GH-dependent IGFBP, and its levels are reduced in undernutrition (31). These findings further support an influence of nutrition on GHBP levels.

In our study, an inverse relationship was found between the spontaneous GH secretion expressed as the AUC$^b$ and GHBP levels in the subgroup of SGA children with a $G_{\text{max}}$ response to an AITT above 20 mU/L, as has previously been shown for normally growing boys, aged 7–18 yr (30). However, we did not find any correlation between GHBP and GH secretion in the whole group of children born SGA or in those with a $G_{\text{max}}$ response to an AITT below 20 mU/L. In another report by Martha et al. (26), these investigators suggested that plasma GHBP levels are relatively stable for a given individual and that the GH secretion rate may be adjusted according to the prevailing GHBP/receptor level to determine the individual growth rate and height potential. In this study, we found that GHBP levels in the SGA children were largely within the range reported previously for normal children and were inversely correlated with the pretreatment height $sd$ score. In addition, in a recent report, we have shown that children born SGA who lack complete catch-up growth postnatally secrete less GH than healthy children born at an appropriate size for gestational age (13). These data may indicate that the interaction between GH production and GHBP is lost in some SGA children and can explain in part their growth failure.

In agreement with previous reports (15, 16), the SGA children in this study showed a significant increase in linear growth during the 2-yr period of GH treatment, although there was much variability in the degree of growth response. Martha et al. (26) showed that plasma GHBP levels are an important determinant of the growth response to GH in GH-deficient children and suggested that GHBP may serve as a predictor of the therapeutic response to GH. However, the effect of GH treatment on GHBP levels is not entirely clear. Some reports, using other methods, have shown that GHBP levels rise after GH treatment in children with (33) and without (34) GH deficiency. In contrast, other studies, using large numbers of children, found GHBP levels to be unchanged after long term GH therapy (26, 35). Although we found a statistically significant increase (27%) in GHBP after 1 yr of therapy, there was no consistency among the patients, with some children showing an increase in GHBP, and others showing a decrease. However, a positive correlation was found between the growth response and GHBP levels after 1 yr of therapy.

In conclusion, GHBP levels in short prepubertal children born SGA were mostly within the normal range previously reported and correlated directly with body composition. An increase in GHBP levels was observed during GH treatment in some SGA children, and there was a positive correlation between the growth response and GHBP levels after 1 yr of therapy. Further studies are required to elucidate the interaction between GH production and GHBP in children born SGA.

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