Metabolic Impact of Growth Hormone Treatment in Short Children Born Small for Gestational Age

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Key Words
Growth hormone · Small for gestational age · Short stature · Metabolic impact

Abstract
Background: Growth hormone (GH) treatment in short children born small for gestational age (SGA) may result in metabolic changes with potential long-term effects. Methods: 149 short SGA children (mean birth weight 2.0 ± 0.6 kg, age 5.5 ± 1.5 years, height standard deviation score (SDS) –3.1 ± 0.6) were randomised to: low-dose GH therapy (0.033 mg/kg/day) for 2 years; high-dose GH therapy (0.100 mg/kg/day) for 1 year, or mid-dose GH therapy (0.067 mg/kg/day) for 1 year. Leptin, ghrelin, insulin-like growth factor-I (IGF-I), IGF binding protein-1 (IGFBP-1), lipids, fasting blood glucose and fasting insulin were assessed at baseline, 12 and 24 months. Results: After 1 year of active treatment, GH significantly reduced serum ghrelin and increased IGF-I SDS and insulin levels. Regression analysis showed an inverse correlation between ghrelin and IGF-I SDS (p < 0.001). Leptin and IGFBP-1 also declined (both p < 0.05). Changes in insulin levels reversed upon discontinuation. Improvements in lipid profile were nonsignificant and fasting blood glucose levels remained within the normal range. Conclusion: In short SGA children, ghrelin and leptin reductions associated with GH treatment may occur through a negative feedback loop of the GH–IGF-I axis. Consequently, via ghrelin and leptin suppression, GH treatment may modify food intake and body composition and potentially improve long-term metabolic outcomes.

Introduction
Growth hormone (GH) treatment is an approved therapy for increasing adult height in short children born small for gestational age (SGA) who fail to experience spontaneous postnatal catch-up growth. These children, who account for approximately 10% of all SGA children, remain short (below –2 standard deviation scores (SDS)) throughout childhood and adulthood if left untreated [1–3]. In this population, GH treatment increases growth velocity and normalises adult height, and appears to be safe and well tolerated [3–11].
Although the main aim of GH treatment in short SGA children is to increase height, additional metabolic effects derived from this therapy may modify food intake, appetite and body composition, and potentially result in favourable long-term metabolic benefits. SGA children with spontaneous catch-up growth appear to be at increased risk for type 2 diabetes, hypertension, hyperlipidaemia and adiposity, all of which are, in turn, risk factors for cardiovascular disease [12–14]. The mechanisms underlying these risks are unclear and most likely depend upon a complex interaction between environmental influences and genetic susceptibility [15]. Several biomarkers have been implicated including leptin, ghrelin and insulin.

Serum levels of leptin, a hormone secreted by adipose tissue [16], are reduced in short children born SGA [17]. GH therapy in short SGA children further decreases leptin levels in a dose-dependent manner, which appears to be correlated with a linear growth response [18]. It has been suggested that GH treatment lowers leptin levels by reducing fat cell mass [18]. Ghrelin is a member of a family of GH secretagogues that stimulate endogenous GH production in normal adults and children [19]. Ghrelin is primarily secreted from the fundus of the stomach, but also from the hypothalamus [19]. However, only the gastric production of ghrelin may probably be detected. Serum levels of ghrelin are higher in short individuals compared with subjects of normal height, suggesting an inverse relationship between ghrelin levels and the amount of circulating GH [20, 21]. Surprisingly, many SGA children have low appetite and low weight for their height, despite higher ghrelin levels [22]. Usually higher levels of ghrelin would be expected to increase adiposity in humans by reducing fat utilisation and increasing food intake as a consequence of its effects on stimulating appetite [23]. Yet it can be speculated that at least in some SGA children, there may exist a certain form of ghrelin resistance.

Insulin resistance and subsequent hyperinsulinaemia are common features in SGA children with rapid weight gain [13, 14, 24–28]. The reduced insulin sensitivity could either cause impairments in the GH-insulin-like growth factor (IGF)–IGF binding protein (IGFBP) axis or be a consequence of those impairments [24–26].

We have reported previously that continuous low-dose and discontinuous mid-dose and high-dose GH regimens were associated with similar height gain in short SGA children [29]. In the present study, we extend our research and hypothesise that GH-related changes in the metabolic profile will, in these children, be dose-depen-
after an overnight fast and immediately separated and stored at 
−20°C until assayed without freeze/thaw cycles. All samples of 1 
patient were assayed on the same day in single determination us-
ing kits of the same lot number. The sensitivity of the leptin assay 
was 0.1 ng/ml. The ghrelin assay detected both octanoylated and 
des-octanoylated human ghrelin with a sensitivity of 100 pg/ml. 
The within-assay coefficient of variation was 2.74–4.91% and the 
between-assay coefficient of variation was 7.22–8.30%, depending 
on the concentration of ghrelin in the specimen. IGF-I measure-
ments were standardised according to the assay manufacturer's 
on the concentration of ghrelin in the specimen. IGF-I measure-
ments were standardised according to the assay manufacturer’s 
reference tables and are presented as SDS. For other measure-
mements, the central laboratory’s normal reference ranges were used.

The study was conducted from November 2002 until July 
2006. Data management was conducted by Novo Nordisk A/S.

Results

At study initiation, age (mean ± SD) was 5.5 ± 1.5 
years, height SDS −3.1 ± 0.6 and height velocity SDS −1.9 
± 1.7. The mean birth weight was 2.0 ± 0.6 kg and mean gestational age 37.3 ± 3.4 weeks. Children were ran-
domised into the three treatment groups: low-dose (n = 
51), high-dose (n = 51) and mid-dose (n = 47). 49% of pa-
tients were female. All study participants were pre-puber-
atal at study entry and remained pre-pubertal throughout 
the study period. The main metabolic parameters are 
summarised in table 1.

IGF-I and IGFBP-1

GH therapy was associated with significant changes in 
IGF-I SDS (table 1; fig. 1) between treatment groups both 
at 12 months (p < 0.0001) and at 24 months (p < 0.0001). 
In the low-dose group, the mean increase in IGF-I SDS 
levels remained within the reference range (−2 to 2 SDS), 
but in the other two groups, IGF-I SDS levels rose above 
it after a year of active GH treatment. Upon discontinua-
tion of GH therapy in the high-dose group, mean IGF-I 
SDS declined considerably and fell within the reference range.

In contrast, IGFBP-1 levels declined during active GH 
treatment (table 1; fig. 1). Significant changes appeared 
between treatment groups both at 12 months (p = 0.005) 
and at 24 months (p = 0.01). The mean (± SD) declines in 
IGFBP-1 values for the low-dose, high-dose and mid-dose 
groups were −32.6 ± 67.3, −75.1 ± 88.2 and −68.9 ± 101 
µg/l, respectively, after 1 year of active treatment, sug-
gest ing a dose-dependent effect of GH. At the end of the 
2-year study period after 1 year off therapy, the levels of 
IGFBP-1 in the high-dose group had risen slightly, but 
remained below baseline by −63.8 ± 81.5 µg/l.

Ghrelin and Leptin

The age-specific reference range for ghrelin is wide 
(600–1,400 ng/l). It has been shown previously that short 
children tend to have increased ghrelin levels [31]. There-
fore, not surprisingly, ghrelin levels were above the refer-
ence range in all study groups at baseline. Within the 
study period, the changes were clearly different among 
treatment groups both at 12 months (p < 0.0001) and 
at 24 months (p = 0.0002), with a dose-related decrease 
within the reference range (table 1; fig. 1). The mean 
(± SD) decrease following 1 year of active treatment was 
−442 ± 432 ng/l in low-dose (p < 0.0001), approximately 
a 26% decline; −547 ± 619 ng/l in mid-dose (p = 0.0002), 
approximately a 31% decline, and −812 ± 729 ng/l in 
high-dose patients (p < 0.0001), approximately a 41% 
decline. These results were also suggestive of a dose-depen-
dent action of GH. Upon discontinuation of treatment, 
ghrelin levels rose back to the baseline range (1,838 ± 991 
ng/l) in the high-dose group.

The magnitude of increment of IGF-I due to 1 year of 
active GH therapy significantly correlated with decreas-
ing ghrelin levels (p < 0.001; fig. 2). Only the baseline lev-
el of ghrelin (p < 0.001) and treatment dose (p = 0.036) 
had a statistical adjusting effect on the correlation. None 
of the other measures had significant adjusting effects 
(sex: p = 0.92, baseline IGF-I SDS: p = 0.09, baseline BMI: 
p = 0.58, baseline glucose: p = 0.24, baseline insulin: p = 0.57, 
baseline leptin: p = 0.12). When adjusting for base-
line level of ghrelin and treatment dose, the change of 
ghrelin was still significantly influenced by change in 
IGF-I SDS (p = 0.0016) with a 92 ng/l ghrelin decrease for 
each increase of 1 SDS of IGF-I.

Leptin changes were significantly different among 
treatment groups both at 12 months (p = 0.004) and at 24 
months (p = 0.002). Leptin levels declined in the two
Table 1. Results for selected metabolic parameters at baseline, 12 months and 24 months stratified by treatment group

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>low-dose GH 0.033 mg/kg/day for 0–24 months (n = 51)</th>
<th>high-dose GH 0.100 mg/kg/day for 0–12 months (n = 51)</th>
<th>mid-dose GH 0.067 mg/kg/day for 12–24 months (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IGF-I SDS scores</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>–1.4 (0.6)</td>
<td>–1.1 (0.9)</td>
<td>–1.2 (1.0)</td>
</tr>
<tr>
<td>Range minimum/maximum</td>
<td>–2.3/0.5</td>
<td>–2.1/2.1</td>
<td>–2.3/2.3</td>
</tr>
<tr>
<td>N ≥2 SDS (%)</td>
<td>5 (9.8)</td>
<td>2 (4.0)</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>N ≥2 SDS/2 SDS (%)</td>
<td>46 (92.2)</td>
<td>47 (94.0)</td>
<td>39 (83.0)</td>
</tr>
<tr>
<td>N &gt;2 SDS (%)</td>
<td>0</td>
<td>1 (2.0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>12 months</td>
<td>0.9 (1.9)</td>
<td>3.3 (2.1)</td>
<td>–0.9 (1.2)</td>
</tr>
<tr>
<td>Range minimum/maximum</td>
<td>–1.7/9.4</td>
<td>–1.8/10.9</td>
<td>–2.5/3.0</td>
</tr>
<tr>
<td>N ≥2 SDS (%)</td>
<td>0</td>
<td>0</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>N ≥2 SDS/2 SDS (%)</td>
<td>37 (74.7)</td>
<td>11 (22.4)</td>
<td>36 (80.0)</td>
</tr>
<tr>
<td>N &gt;2 SDS (%)</td>
<td>10 (21.3)</td>
<td>38 (77.6)</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>24 months</td>
<td>0.8 (2.1)</td>
<td>–0.6 (1.0)</td>
<td>2.9 (2.8)</td>
</tr>
<tr>
<td>Range minimum/maximum</td>
<td>–2.3/8.5</td>
<td>–2.4/1.8</td>
<td>–0.9/10.6</td>
</tr>
<tr>
<td>N ≥2 SDS (%)</td>
<td>1 (2.1)</td>
<td>3 (6.3)</td>
<td>0</td>
</tr>
<tr>
<td>N ≥2 SDS/2 SDS (%)</td>
<td>37 (74.7)</td>
<td>45 (93.8)</td>
<td>15 (35.7)</td>
</tr>
<tr>
<td>N &gt;2 SDS (%)</td>
<td>9 (19.1)</td>
<td>0</td>
<td>27 (64.3)</td>
</tr>
<tr>
<td><strong>IGFBP-1, µg/l</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>152.1 (71.2)</td>
<td>181.7 (99.1)</td>
<td>165.6 (101)</td>
</tr>
<tr>
<td>Range minimum/maximum</td>
<td>23.5/361.7</td>
<td>13.7/570.0</td>
<td>19.3/474.0</td>
</tr>
<tr>
<td>12 months</td>
<td>121.3 (66.0)</td>
<td>109.0 (67.5)</td>
<td>141.3 (67.9)</td>
</tr>
<tr>
<td>Range minimum/maximum</td>
<td>9.2/340.9</td>
<td>3.6/358.6</td>
<td>41.1/354.9</td>
</tr>
<tr>
<td>24 months</td>
<td>111.2 (40.8)</td>
<td>121.4 (52.6)</td>
<td>96.4 (66.3)</td>
</tr>
<tr>
<td>Range minimum/maximum</td>
<td>53.0/244.0</td>
<td>28.4/297.8</td>
<td>61.3/547.8</td>
</tr>
<tr>
<td><strong>Ghrelin, ng/l</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1,714 (741)</td>
<td>1,967 (1,028)</td>
<td>1,791 (904)</td>
</tr>
<tr>
<td>12 months</td>
<td>1,293 (630)</td>
<td>1,150 (482)</td>
<td>1,773 (799)</td>
</tr>
<tr>
<td>24 months</td>
<td>1,283 (585)</td>
<td>1,838 (991)</td>
<td>1,172 (530)</td>
</tr>
<tr>
<td><strong>Leptin, µg/l</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.7 (3.6)</td>
<td>3.6 (4.4)</td>
<td>2.6 (1.9)</td>
</tr>
<tr>
<td>12 months</td>
<td>3.4 (4.8)</td>
<td>3.3 (4.1)</td>
<td>3.5 (3.4)</td>
</tr>
<tr>
<td>24 months</td>
<td>3.5 (4.0)</td>
<td>5.0 (6.3)</td>
<td>2.7 (3.5)</td>
</tr>
<tr>
<td><strong>HDL cholesterol, mmol/l</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.5 (0.3)</td>
<td>1.5 (0.3)</td>
<td>1.4 (0.3)</td>
</tr>
<tr>
<td>12 months</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.3)</td>
<td>1.5 (0.3)</td>
</tr>
<tr>
<td>24 months</td>
<td>1.4 (0.3)</td>
<td>1.4 (0.3)</td>
<td>1.4 (0.3)</td>
</tr>
<tr>
<td><strong>LDL cholesterol, mmol/l</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.9 (0.6)</td>
<td>3.2 (0.7)</td>
<td>2.9 (0.7)</td>
</tr>
<tr>
<td>12 months</td>
<td>2.9 (0.5)</td>
<td>2.8 (0.6)</td>
<td>2.9 (0.7)</td>
</tr>
<tr>
<td>24 months</td>
<td>2.7 (0.5)</td>
<td>2.9 (0.5)</td>
<td>2.6 (0.6)</td>
</tr>
<tr>
<td><strong>Total cholesterol, mmol/l</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.7 (0.8)</td>
<td>5.0 (0.9)</td>
<td>4.7 (0.6)</td>
</tr>
<tr>
<td>12 months</td>
<td>4.6 (0.7)</td>
<td>4.5 (0.8)</td>
<td>4.6 (0.8)</td>
</tr>
<tr>
<td>24 months</td>
<td>4.6 (0.7)</td>
<td>4.7 (0.8)</td>
<td>4.4 (0.8)</td>
</tr>
<tr>
<td><strong>Fasting glucose, mmol/l</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.6 (0.6)</td>
<td>4.7 (0.6)</td>
<td>4.6 (0.4)</td>
</tr>
<tr>
<td>12 months</td>
<td>4.8 (0.5)</td>
<td>5.0 (0.5)</td>
<td>4.8 (0.6)</td>
</tr>
<tr>
<td>24 months</td>
<td>4.8 (0.4)</td>
<td>4.6 (0.4)</td>
<td>4.8 (0.6)</td>
</tr>
<tr>
<td><strong>Fasting insulin, IU/ml</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.1 (2.8)</td>
<td>2.7 (1.9)</td>
<td>2.8 (3.3)</td>
</tr>
<tr>
<td>12 months</td>
<td>5.3 (3.5)</td>
<td>8.9 (5.0)</td>
<td>4.1 (6.3)</td>
</tr>
<tr>
<td>24 months</td>
<td>6.3 (4.7)</td>
<td>4.3 (2.9)</td>
<td>8.2 (5.4)</td>
</tr>
</tbody>
</table>

Data are mean (±SD), except where range and n are given. * Significant change among treatment groups p < 0.05.
groups that received GH therapy in the first year (table 1; fig. 1); in contrast, leptin rose during the first year off therapy in the mid-dose GH, and declined upon GH start. At the end of the study period, leptin values remained significantly above baseline both in the mid-dose and high-dose subgroups (0.1 ± 3.1 and 1.1 ± 5.9 μg/l, respectively; p = 0.002).

**Lipids**
GH-elicited changes in serum levels of HDL, LDL and total cholesterol were similar and nonsignificant among groups at both 12 and 24 months.

**Fasting Glucose and Insulin**
Fasting glucose levels remained within the normal range in all treatment groups throughout the study (table 1). No significant differences among groups could be detected. Fasting insulin levels rose in all groups during active GH treatment, in a dose-dependent fashion (table 1; fig. 1). The changes were different among treatment groups both at 12 months (p < 0.0001) and at 24 months (p = 0.0005). All increases remained within the reference range. After active treatment in the high-dose group, insulin levels declined at study end to within 1.7 ± 3.3 IU/ml of the baseline measure.
creases in body fat in the course of GH treatment have been associated with decreased ghrelin and treatment dose affected this relationship. Lower ghrelin levels was not influenced by gender or BMI. Only baseline ghrelin and treatment dose affected this relationship.

However, in the other groups, the relationship between ghrelin and IGF-I axis was attributed to a negative feedback loop of the GH–IGF-I axis in short SGA and children results in a disproportionate increase in body fat instead of lean tissue, particularly abdominal adiposity, raising their risk for insulin resistance, type 2 diabetes, obesity and cardiovascular disease as adults [13, 14, 40, 41]. Short SGA children who receive GH treatment may reach a normalised adult height without the increased risks for overweight and increased fat mass.

Regarding the increase in leptin observed during the first year off therapy in the mid-dose GH treatment group, leptin levels are affected by age, gender, body mass index and pubertal status [42]. Since our study cohort included children aged 3–8 years, one would expect that in both girls and boys leptin would naturally increase in the control group, as indicated in figure 1. When treatment was initiated in the mid-dose group, leptin decreased as in the other groups. The results of this study indicated that leptin rises if untreated, and GH therapy prevents it from increasing.

Consistent with our study’s finding of a significant correlation between declining ghrelin levels and rising IGF-I SDS levels (p < 0.001), Engström et al. [37] reported a correlation between these parameters in adults with GH deficiency. The relationship between ghrelin and IGF-I was attributed to a negative feedback loop of the GH–IGF-I axis on ghrelin secretion [37] and the reduction in ghrelin was ascribed to the GH-promoting effects on glucose production, lipolysis and, possibly, insulin secretion [37]. Other results from observational cross-sectional, as well as interventional, studies have also suggested a potential inverse relationship between ghrelin and IGF-I [20, 21, 43]. Likewise, our results support the existence of a negative feedback loop of the GH–IGF-I axis in short SGA children who receive GH treatment. However, there may be an additional factor contributing to increasing IGF-I levels with GH administration, besides the ghrelin–GH–IGF-I feedback loop. Boonstra et al. [44] have shown that SGA children treated with GH naturally increase their appetite while on therapy. IGF-I is also influenced by nutritional status [45].

The decline in IGFBP-1 levels is most likely the consequence of the increase in insulin levels observed during periods of active GH treatment. It is well established that in time of scarcity helps to explain the metabolic observations of Engström et al. [37] and Møller and Jørgensen [38]. Our data are consistent with that hypothesis and also with previous data showing an increase in lean body mass and a decrease in fat mass in short SGA children following GH treatment [39]. Recent evidence suggests that spontaneous catch-up growth experienced by SGA infants and children results in a disproportionate increase in body fat instead of lean tissue, particularly abdominal adiposity, raising their risk for insulin resistance, type 2 diabetes, obesity and cardiovascular disease as adults [13, 14, 40, 41]. Short SGA children who receive GH treatment may reach a normalised adult height without the increased risks for overweight and increased fat mass.

Despite the well-known association between SGA and long-term metabolic consequences, there have been just a limited number of studies published so far on the metabolic influences of GH therapy in short children born SGA [32–34]. In this comparative, prospective analysis of short pre-pubertal GH-treated SGA children randomised to different treatment regimens, GH treatment induced significant and dose-dependent decreases in ghrelin and leptin levels, both of which are substantially involved in metabolic regulation. We hypothesise that these changes may account for an important part of the impact of GH therapy on the metabolic profile in these children, namely influencing lipid mobilisation and glucose production through decreased ghrelin and leptin. In the present study, the reverse correlation between IGF-I and ghrelin levels was not influenced by gender or BMI. Only baseline ghrelin and treatment dose affected this relationship.

Reductions in the levels of leptin and ghrelin in the course of GH treatment have been associated with decreases in body fat [18, 35–37]. Since ghrelin is an appetite stimulant, a decrease in the levels of this hormone may promote a more healthy energy balance in short children born SGA. The reduction in fat mass, reported in other studies [35–37], may be due to the metabolic-enhancing effects of GH on lipolysis and glucose production [37]. The evolutionary development of GH among humans in utilising carbohydrates and protein for fuel in times of energy surplus and switching to the use of lipids...
serum IGFBP-1 levels are controlled by insulin and, to a lesser degree, by glucose [26]. The dose-dependent influence of insulin on IGFBP-1 levels, however, appears to be limited to the duration of GH treatment [34].

The increase in fasting insulin levels observed in this study, while still remaining within normal ranges, is in line with the known acute effect of GH on insulin signaling. The rise in insulin levels reverted upon GH discontinuation, as previously reported [46, 47]. It should be noted that the morning sample for measuring insulin and glucose levels was taken approximately 10–14 h after the GH dose. Since maximum serum GH concentrations occur 2–8 h after dose administration [48], it is likely that insulin and glucose levels would decline further throughout the day. Further investigations to determine the 24-hour glucose and insulin profiles following GH dosing may be warranted to determine the overall impact of GH therapy on insulin and glucose levels.

In contrast with previous studies that reported GH-induced persistent benefits on lipid profile in short SGA children [5, 34], we observed only slight, nonsignificant improvements in total cholesterol and LDL cholesterol levels. It is likely that longer GH treatment is needed to detect significant changes in the lipid profile, and may also explain the persistent benefits observed after treatment is stopped [32].

Conclusion

In short SGA children, GH treatment appears to reduce ghrelin levels through a negative feedback loop of the GH–IGF-I axis and is associated with beneficial effects on lipolysis and glucose production that also lower levels of leptin, increasing lean body mass and reducing fat mass. Glucose levels remained within normal limits in this study, and the changes in insulin levels were reversible upon treatment discontinuation. As the results suggest that at least some of the GH-induced metabolic changes are dose-dependent, with a tendency to vanish after discontinuation of treatment, GH administration throughout childhood with carefully selected GH dosages appears to be an advantageous clinical practice in short SGA children. Further research is warranted to clarify the effect of GH treatment on lipid levels and confirm the long-term benefits of GH on metabolic risks in this population.

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