Long-Term Impact of GH Treatment during Childhood on Body Composition and Fat Distribution in Young Adults Born SGA

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Context: GH treatment of short children born small for gestational age (SGA) results in a decline in fat mass (FM) and an increase in lean body mass (LBM). It is, however, unknown whether these changes persist into adulthood.

Objective: Our objective was to assess the long-term impact of GH treatment during childhood on body composition and fat distribution.

Patients and Design: A total of 377 young adults participated in this cross-sectional study: 59 previously GH-treated young SGA adults compared to 52 untreated SGA adults with short stature (SGA-S), 161 SGA adults with spontaneous catch-up growth (SGA-CU), and 105 healthy normally-statured controls born appropriate for gestational age (AGA).

Outcome Measures: Body composition and fat distribution were determined by dual-energy x-ray absorptiometry.

Results: Mean (SD) duration of GH treatment was 7.7 (2.4) yr and period after discontinuation 6.8 (1.8) yr. FM, fat distribution, and LBM of GH-treated SGA adults were not significantly different from that of untreated SGA-S adults. GH-treated SGA adults also had a similar FM and fat distribution as SGA-CU adults but a lower LBM. All SGA subgroups had a lower LBM and tended to have a higher FM than healthy AGA controls.

Conclusion: Body composition and fat distribution of previously GH-treated SGA adults was similar to that of untreated SGA-S adults. GH-induced catch-up growth has no unfavorable effect on FM and fat distribution compared with spontaneous catch-up growth. However, our study shows that SGA adults in general may have a different body composition than healthy AGA controls.

Studies on postnatal growth in infants born small for gestational age (SGA) or with intrauterine growth retardation have shown that, although these infants generally show spontaneous catch-up growth in height, approximately 10% of them remain short, with a height below $-2 \text{SD}\) score (SDS) (1, 2). SGA children who remain short tend to have a typical lean appearance with a low body mass index (BMI) (3). We previously showed that this leanness is characterized by a marked reduction of lean body mass (LBM) and to a lesser extent a lower total fat mass (FM) (4). GH treatment of these children resulted in a decline in FM and an increase in LBM, which is consistent with the lipolytic and anabolic properties of GH (4, 5). De Kort et al. (6) showed that this decrease in FM is mainly located in the limbs of GH-treated SGA children, whereas the amount of trunk fat remains stable.

Obesity is a global and increasing problem with major public-health consequences (7). It is a risk factor for sev-
eral adult diseases, including diabetes mellitus type 2, the metabolic syndrome, and cardiovascular diseases. Previous studies showed that growth during infancy is an important determinant of body composition in young adulthood. Faster weight gain in infancy is associated with a greater risk of obesity later in life, whereas birth size is less important (8–10). Infants born SGA, however, are more likely to show catch-up growth in weight than infants born appropriate for gestational age (AGA) and could therefore be at greater risk of developing obesity later in life. Because GH treatment induces catch-up growth, concern has been expressed regarding the long-term effects of GH treatment on body composition (11).

The primary aim of this study was to investigate the impact of GH treatment during childhood on body composition and fat distribution in young adulthood in subjects born SGA, many years after discontinuation of GH. To answer this question, we compared previously GH-treated SGA adults with untreated SGA adults with short stature (SGA-S). We hypothesized that the body composition of GH-treated adults returns to levels of those who were never treated, especially because BMI SDS and waist circumference are comparable for GH-treated and untreated SGA adults with short stature (12). Our second aim was to evaluate whether GH-induced catch-up growth had a different effect on young adult body composition than spontaneous catch-up growth, and whether the various SGA groups had a different body composition and fat distribution than healthy AGA controls.

Subjects and Methods

Subjects

The total study group comprised 377 young adults, divided into 59 previously GH-treated adults born SGA who had previously been participating in a multicenter, double-blind, randomized, dose-response GH trial (13, 14); 52 untreated SGA-S (adult height < −2 SDS); 161 SGA adults with spontaneous catch-up growth (SGA-CU) (adult height > −2 SDS); and 105 healthy, normal-statured adult controls who were born AGA (defined as birth length and adult height > −2 SDS). The SGA-S, SGA-CU, and AGA adults were part of a cohort of young adults participating in a national study evaluating risk factors for diabetes mellitus type 2 and cardiovascular disease, the PROGRAM study (8).

The dose-response GH trial started in 1991 and evaluated the effect of two doses of GH, 1 and 2 mg/m² · d, on long-term growth and adult height. The inclusion criteria for the GH trial have been described (13). GH treatment was discontinued when height velocity had dropped below 0.5 cm over the preceding 6 months and when bone age was at least 15 yr for girls and at least 16.5 yr for boys. Patients were included in the present study when they had been treated with GH for more than 4 yr and had discontinued GH treatment for more than 4 yr. Thirty-one of the original 90 participants were not included for the following reasons: one subject had discontinued GH treatment less than 4 yr earlier; five children dropped out during the original GH trial due to lack of motivation (n = 3), precocious puberty (n = 1), or GH insensitivity (n = 1); one subject was not included due to psychosocial problems; four subjects were lost to follow-up; two subjects emigrated; one subject had died due to a road accident; five persons did not respond to the invitation letter, and 12 subjects did not want to participate due to lack of interest. The clinical characteristics of the 59 GH-treated SGA subjects who were included were comparable with those of the 31 subjects who were not included, except for age at discontinuation of GH treatment (15.7 vs. 14.8 yr, respectively; P = 0.001).

The studies were approved by the Medical Research Ethics Committees of the participating centers. Written informed consent was obtained from all participants or their parents.

Measurements

Standing height was measured in the upright position to the nearest 0.1 cm using a Harpenden stadiometer (Holtain, Ltd., Crymmyth, UK). Sitting height (SH) was measured to the nearest 0.1 cm using a Harpenden SH table. SH to height ratio was then calculated and expressed as SDS for age and gender (15). Weight was measured to the nearest 0.1 kg on a digital scale (Servo Balance KA-20-150S, Servo Berkel Prior, Katwijk, The Netherlands). BMI was calculated by dividing weight in kilograms by the square of height in meters and rounded to the nearest tenth. Waist circumference was measured at the level of the umbilicus using a nonextendable measuring tape. All anthropometric measurements were performed at least twice according to standardized methods, after which the mean was calculated. Height, BMI, and waist circumference were expressed as SDs adjusted for age and gender according to Dutch reference data for children (16–18).

In all participants, total FM, trunk FM, limb FM, and LBM were measured on one dual-energy x-ray absorptiometry (DXA) machine (Lunar Prodigy; GE Healthcare, Chalfont St. Giles, UK). Quality assurance was performed daily. For this type of DXA, the intraassay coefficient of variation has been reported to be 0.41–0.88% for fat tissue and 1.57–4.49% for LBM (19).

Statistics

Data are expressed as mean ± SDS. Statistical analyses within the GH-treated SGA group were performed for the GH dosage groups separately (1 vs. 2 mg/m² · d) and for the groups together. Because the outcome variables were the same in both GH dosage groups, data are shown for the groups together. Differences in clinical characteristics between the GH-treated SGA adults, and SGA-S, SGA-CU, and AGA adults were evaluated using independent-samples t tests. Differences in body composition and fat distribution between the GH-treated SGA adults, and the other three subgroups were determined using analyses of covariance, with correction for age, gender, gestational age, and adult height SDS. In the analyses, GH-treated SGA adults were defined as 1 and the other groups as 0.

The effect of the duration of GH treatment on total FM, trunk FM, limb FM, and LBM was analyzed using multiple regression analyses, corrected for possible confounders (age, gender, gestational age, height SDS, weight SDS, birth length SDS, and birth weight SDS). The interaction term birth length SDS × adult height SDS was added to the multiple regression model to ensure that the effect of these variables was modeled correctly (20). Oral
TABLE 1. Unadjusted clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>GH-treated SGA (n = 59)</th>
<th>Untreated SGA-S (n = 52)</th>
<th>P valuea</th>
<th>SGA-CU (n = 161)</th>
<th>P valueb</th>
<th>AGA controls (n = 105)</th>
<th>P valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>34/25</td>
<td>18/34</td>
<td></td>
<td>72/89</td>
<td></td>
<td>34/71</td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td>36.6 (3.8)</td>
<td>37.9 (3.0)</td>
<td>0.051</td>
<td>36.6 (3.6)</td>
<td>0.892</td>
<td>39.4 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight SDS</td>
<td>−2.7 (1.0)</td>
<td>−2.3 (0.8)</td>
<td>0.013</td>
<td>−2.3 (0.7)</td>
<td>0.011</td>
<td>−0.1 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth length SDS</td>
<td>−3.5 (1.3)</td>
<td>−3.0 (0.9)</td>
<td>0.031</td>
<td>−2.7 (1.0)</td>
<td>&lt;0.001</td>
<td>−0.3 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>22.5 (2.0)</td>
<td>20.9 (1.7)</td>
<td>&lt;0.001</td>
<td>20.9 (1.7)</td>
<td>&lt;0.001</td>
<td>20.9 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height SDS</td>
<td>−1.6 (1.1)</td>
<td>−2.5 (0.6)</td>
<td>&lt;0.001</td>
<td>−0.4 (0.9)</td>
<td>&lt;0.001</td>
<td>0.1 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>0.3 (1.2)</td>
<td>0.3 (1.6)</td>
<td>0.999</td>
<td>0.3 (1.4)</td>
<td>0.857</td>
<td>0.1 (0.9)</td>
<td>0.191</td>
</tr>
<tr>
<td>Waist circumference SDS</td>
<td>−0.3 (1.3)</td>
<td>−0.2 (1.4)</td>
<td>0.923</td>
<td>0.4 (1.2)</td>
<td>&lt;0.001</td>
<td>0.2 (1.0)</td>
<td>0.018</td>
</tr>
<tr>
<td>Ratio SH/height SDS</td>
<td>1.6 (1.3)</td>
<td>1.6 (1.2)</td>
<td>0.950</td>
<td>0.7 (2.8)</td>
<td>0.028</td>
<td>0.2 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>−0.4 (1.0)</td>
<td>−0.5 (0.9)</td>
<td>0.583</td>
<td>−0.4 (0.9)</td>
<td>0.828</td>
<td>−0.4 (1.0)</td>
<td>0.874</td>
</tr>
</tbody>
</table>

Data are expressed as mean (SDS).

a Differences between GH-treated SGA and untreated SGA-S.
b Differences between GH-treated SGA and SGA-CU.
c Differences between GH-treated SGA and AGA controls.

Results

Clinical characteristics

The clinical characteristics of the four subgroups are shown in Table 1. GH-treated SGA adults were 22.5 (2.0) yr old. At the start of GH treatment, mean height SDS was −3.0, and mean age at start of GH treatment was 8.0 yr. The mean (SDS) duration of GH treatment was 7.7 (2.4) yr and the period after discontinuation of GH 6.8 (1.8) yr. GH-treated SGA adults had a significantly smaller size at birth (birth weight and/or birth length) than the SGA-S, SGA-CU, and AGA adults.

At time of the present follow-up study, previously GH-treated SGA adults were 1.6 yr older than untreated SGA-S adults, SGA-CU adults, and AGA controls. GH-treated SGA adults were taller than the untreated SGA-S adults and shorter than the SGA-CU adults and AGA controls.

GH-treated SGA adults had a similar SH to height ratio SDS as SGA-S and SGA-CU adults. This ratio was higher in SGA adults, either GH-treated or not, than in AGA controls. At the time of the present study, waist circumference SDS of GH-treated adults was similar to that of SGA-S adults but differed from those of SGA-CU and AGA adults. BMI SDS and serum IGF-I level SDS of the GH-treated SGA adults were comparable to those of the other three subgroups.

Body composition

Unadjusted body composition data are shown in Table 2. The differences between the GH-treated SGA adults and the other subgroups are given after correction for age, gender, gestational age, and adult height SDS.

GH-treated SGA vs. SGA-S

Total FM of GH-treated SGA adults was similar to that of untreated SGA-S adults. Fat distribution (trunk FM and limb FM) was also comparable for GH-treated SGA and untreated SGA-S adults. Unadjusted LBM seems to be higher in GH-treated SGA than in untreated SGA-S adults. However, after necessary adjustments for age, gender, gestational age and height SDS, the adjusted LBM of GH-treated SGA adults tended to be lower than untreated SGA adults (GH-treated vs. SGA-S β = −2188; P = 0.063). After additional adjustment for birth weight SDS and birth length SDS, because GH-treated SGA adults were the smallest at birth, this difference disappeared (P = 0.130).

GH-treated SGA vs. SGA-CU

GH-treated SGA adults had a similar total FM and fat distribution as SGA-CU. LBM was lower in GH-treated SGA adults than in SGA-CU adults.
The EMM for all body composition parameters and differences between the SGA subgroups and the healthy AGA controls are shown in Figs. 1–4. These EMM are adjusted for several variables such as adult height SDS and gender. Because the subgroups differ in, for example, gender and adult height SDS, it is important and more valuable to show these adjusted values. All SGA subjects had a higher adjusted total FM and adjusted limb FM than healthy AGA controls, but these differences were significant only for the SGA-CU adults compared with AGA controls ($P < 0.001$). Adjusted trunk FM was also higher in all SGA subgroups but did not reach significance in the SGA-S adults ($P < 0.100$), probably due to a lower number of subjects. In addition, all SGA subgroups had a lower adjusted LBM than healthy AGA controls.

**Duration of GH treatment**

Within the GH-treated SGA adults, multiple regression models were used to determine the influence of the duration of GH treatment on body composition. The duration of GH treatment did not have an effect on total FM ($P = 0.063$), trunk FM ($P = 0.847$), and limb FM ($P = 0.032$), after adjustment for possible confounders (age, gender, gestational age, birth length SDS, birth weight SDS, adult height SDS, and adult weight SDS), many years after discontinuation of GH.

**Discussion**

This study compared the body composition and fat distribution of previously GH-treated SGA adults, at 6.8 yr after discontinuation of GH treatment, with those of untreated SGA-S, SGA-CU, and healthy AGA controls. FM, fat distribution, and LBM of GH-treated SGA adults were not significantly different from those of untreated SGA-S. As indicated by Willemsen et al. (21), significant changes in body composition occur in previously GH-treated SGA adults after stopping GH treatment. They showed that at 6 months after GH discontinuation (mean age subjects 16 yr), fat percentage and FM had increased, whereas LBM had decreased. In a group of 10 SGA subjects who were treated with GH for a period of 3 yr, Leger et al. (5) also showed a tendency to a decreased LBM and a significant increase in adipose tissue 3 months after GH discontinuation. These changes are opposite to those that occur during GH treatment in SGA children (22), i.e., an increase in LBM and a decrease in FM (4, 5).

In our cohort of young adults many years after discontinuation of GH, differences between GH-treated SGA and untreated SGA-S.

In the analyses, GH-treated SGA adults are defined as 1 and the other groups as 0. Data are expressed as mean (SDS). $P$ values are adjusted for age, gender, gestational age, and adult height SDS.

<table>
<thead>
<tr>
<th></th>
<th>GH-treated SGA</th>
<th>Untreated SGA-S</th>
<th>$P$ value\textsuperscript{a}</th>
<th>SGA-CU</th>
<th>$P$ value\textsuperscript{b}</th>
<th>AGA controls</th>
<th>$P$ value\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>59</td>
<td>52</td>
<td>161</td>
<td>105</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total FM (g)</td>
<td>15211 (8502)</td>
<td>15808 (8743)</td>
<td>−942</td>
<td>17210 (9923)</td>
<td>−1456</td>
<td>14296 (6671)</td>
<td>2752 (0.098)</td>
</tr>
<tr>
<td>Trunk FM (g)</td>
<td>8002 (4738)</td>
<td>7591 (4405)</td>
<td>−208</td>
<td>8522 (5168)</td>
<td>−419</td>
<td>6668 (3253)</td>
<td>1905 (0.037)</td>
</tr>
<tr>
<td>Limb FM (g)</td>
<td>6620 (3773)</td>
<td>7613 (4339)</td>
<td>−730</td>
<td>8043 (4784)</td>
<td>−996</td>
<td>6969 (3370)</td>
<td>836 (0.262)</td>
</tr>
<tr>
<td>LBM (g)</td>
<td>43715 (9788)</td>
<td>38004 (7529)</td>
<td>−2188</td>
<td>46909 (9494)</td>
<td>−1981</td>
<td>48200 (9431)</td>
<td>−3364 (0.001)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Differences between GH-treated SGA and untreated SGA-S.

\textsuperscript{b} Differences between GH-treated SGA and SGA-CU.

\textsuperscript{c} Differences between GH-treated SGA and AGA controls.
uation of GH treatment, FM and LBM levels were similar to those of untreated SGA-S. So despite an increase in FM and decrease in LBM after discontinuation of GH treatment, previously GH-treated SGA adults have a similar body composition as those who remained untreated. Furthermore, duration of GH treatment did not have any effect on body composition in young adulthood.

GH-treated SGA adults had a similar total FM and fat distribution as SGA-CU, which indicates that GH-induced catch-up growth has no unfavorable effect on FM compared with spontaneous catch-up growth. GH-treated SGA adults had, however, a lower LBM than SGA-CU adults, which is in line with the body composition of SGA children with short stature characterized by, among other things, a reduced LBM.

Furthermore, all SGA adults (GH-treated, SGA-S, and SGA-CU) tended to have a higher total FM and a higher trunk FM and limb FM than healthy AGA controls and had a lower LBM than the control subjects. These observed differences in body composition and fat distribution between SGA adults and controls probably indicate that SGA adults in general have a different body composition than healthy AGA controls. Using DXA trunk FM as a surrogate for abdominal FM and knowing that abdominal obesity is a risk factor for the development of metabolic abnormalities (23, 24), our study suggests that all SGA-born adults might have a higher risk of developing diabetes mellitus type 2 and cardiovascular diseases than normal-statured healthy AGA controls.

The SGA-CU subjects had the highest amount of FM (total, trunk, and limb) of all three SGA subgroups and differed most significantly from healthy AGA controls. This is in line with previous research by Leunissen et al. (8) and Ibáñez et al. (25, 26) who reported that SGA-CU gained more body adiposity and abdominal fat than AGA infants. Previous systematic reviews have also described a very consistent association between rapid weight gain during infancy and subsequent adiposity risk in childhood and later life (27–29).

To our knowledge, this is the first study investigating the long-term effects of GH on body composition many years after discontinuation of treatment in adults born SGA. Because body composition is greatly influenced by age, gender, and height (16), differences in body composition were evaluated after correction for these variables. Because gestational age was significantly different between the four subgroups and previous research suggests that gestational age might be of influence on later body composition (30), we also adjusted for this possible confounder in our analyses.

The GH-treated SGA subjects started GH treatment relatively late, around 8 yr of age. Our results demonstrate that GH treatment does not have an unfavorable effect on body composition in young adulthood, many years after stopping GH. However, the beneficial effects of GH on body composition during treatment, i.e., an increase in LBM and a decrease in FM, did not remain either. It has been suggested that the adverse effects of poor intrauterine growth on the adipose tissue is most prominent in the first years of life. Ibáñez et al. (31) showed that girls born SGA, aged 2–8 yr, tend to follow an altered developmental trajectory that may lead to abnormal fat storage in puberty and adulthood. One could speculate that the lack of a positive effect of GH treatment on body composition, many years after its discontinuation, might be due to the fact that GH treatment was not started in the early years of life. Nowadays, some studies start GH treatment in (much) younger SGA children (32–34). It would be interesting to evaluate whether these children have a different adipose tissue development, particularly in the long term.

In conclusion, our study shows that at 6.8 yr after discontinuation of long-term GH treatment, body composition of previously GH-treated SGA adults is similar to that of untreated SGA-S. These data are reassuring, because they suggest that long-term GH treatment of SGA children with short stature does not have an unfavorable effect on body composition in young adulthood. Second, our study

**FIG. 3.** EMM of limb FM of the three SGA subgroups compared with AGA controls (with 95% CI), adjusted for age, gender, gestational age, and height SDS. *, P < 0.001 compared with AGA controls.

**FIG. 4.** EMM of LBM of the three SGA subgroups compared with AGA controls (with 95% CI), adjusted for age, gender, gestational age, and height SDS. *, P < 0.001 compared with AGA controls; #, P < 0.05 compared with AGA controls.
shows that SGA adults in general may have a different body composition from healthy AGA controls. It remains to be elucidated how body composition and fat distribution develop when these subjects become older.

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