Effects of Growth Hormone Treatment in Obese Prepubertal Boys*

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ABSTRACT
Childhood obesity is associated with several abnormalities of the GH axis, including decreased spontaneous secretion, decreased response to exogenous secretagogues, and altered pulsatile pattern of secretion. In adults, GH treatment reduces abdominal obesity and improves insulin sensitivity, as well as blood lipid profiles. Whether GH has similar effects in obese children has not been investigated previously.

In this study, seven prepubertal severely obese boys aged 10–12 yr were treated with GH for 6 months and followed for an additional 6 months. No diet or exercise modifications were initiated. Body fat percentage decreased from 51.3% to 46.1% after treatment (P = 0.03).

The prevalence and severity of childhood obesity are increasing rapidly worldwide (1). Although short-term consequences of moderate childhood obesity are mainly psychosocial, the greatest concern from a public health perspective are long-term effects including cardiovascular disorders, hypertension, hyperlipidemia, glucose intolerance, gall bladder disease, and musculoskeletal disorders, as well as several common forms of cancer (2). Approximately half of the obese school children remain obese as adults (3), and once established in adulthood, obesity can rarely be resolved through voluntary weight loss (4). Thus, early intervention is an attractive strategy to avoid the complications of adult obesity (5).

Only a minute fraction of the obese children have a demonstrable endocrine and/or genetic cause for the excessive adiposity (6). Yet, several twin and adoption studies have demonstrated an important genetic predisposition that, combined with excessive caloric intake and physical inactivity, may result in obesity (7, 8). The mechanisms behind this predisposition are largely unknown. Multiple endocrine alterations, such as increased insulin levels and decreased GH levels, are recognized in obese subjects (9). However, these endocrine abnormalities are reversible on weight loss and, thus, considered as consequences rather than causes of the obese state (10).

Despite normal or even accelerated longitudinal growth and normal serum levels of insulin-like growth factor I (IGF-1), a plethora of abnormalities of the GH axis has been reported in obese children, including decreased spontaneous GH secretion, decreased response to exogenous GH secretagogues, and altered pulsatile pattern of secretion (10, 11). GH treatment of obese adults, who exhibit similar GH axis abnormalities as obese children, reduces abdominal obesity and improves insulin sensitivity, as well as blood lipid profiles (12). Whether GH has similar effects in obese children has not been investigated previously.

Metabolic actions of GH are often divided into early insulin-like and late diabetogenic effects (13). However, no impairment in glucose tolerance has been observed during GH treatment of short stature children with and without GH deficiency, as well as adults with GH deficiency or obesity (12, 14–16). Still there are legitimate concerns that GH treatment of obese children may augment the metabolic risks imposed by the obese state. Accordingly, the present study was designed to examine the effects of GH treatment on body composition, adipose tissue metabolism, glucose metabolism, and blood lipid profiles in prepubertal obese boys.

Subjects and Methods

Patients
Seven prepubertal obese children aged 10–12 yr were included in the study (Table 1). All had a body mass index (BMI) above +3 sd for age and a normal serum level of IGF-I. The exclusion criteria were all sorts of syndromes, history of cancer, medical treatment, and growth velocity below −1 sd. One child presented with pseudotumor cerebri after 3 months of treatment and was excluded from further studies. His symptomatology was completely reversible on withdrawal of treatment.
TABLE 1. Clinical characteristics and serum IGF-I levels of the seven prepubertal boys at entry of the study

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>11 ± 1</td>
<td>10–12</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>63.1 ± 12.5</td>
<td>44.4–80.0</td>
</tr>
<tr>
<td>Percent overweight</td>
<td>89.9 ± 12.6</td>
<td>48.0–142.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>145.4 ± 8.1</td>
<td>130.6–156.0</td>
</tr>
<tr>
<td>BMI (SDS)</td>
<td>+5.9 ± 1.5</td>
<td>+3.9–7.7</td>
</tr>
<tr>
<td>Testis size (mL)</td>
<td>1.86 ± 0.7</td>
<td>1.0–3.0</td>
</tr>
<tr>
<td>IGFI (µg/mL)</td>
<td>267.5 ± 85.7</td>
<td>150–407</td>
</tr>
<tr>
<td>IGFI (SDS)</td>
<td>+0.2 ± 0.9</td>
<td>-1.4–1.2</td>
</tr>
</tbody>
</table>

The blood testosterone level was below 0.7 nmol/L in all participants, except in one boy with a blood level of 1.1 nmol/L.

Study design and treatment

The total period of the study was 1 yr. The children received recombinant human GH (Saizen; kindly provided by Serono Nordic AB, Solna, Sweden) for 6 months, followed by 6 months of further observation without treatment. The daily dose of GH was 0.1 IU/kg (0.033 mg/kg) administered sc before bedtime. No specific counseling on diet or exercise was provided. The Karolinska Institute Ethics Committee approved the study, and informed consent was obtained from the guardians.

Study protocol

The children were studied as outpatients at seven different time points: before and after 3 weeks, 6 weeks, 3 months, and 6 months of GH treatment, as well as at 9 months and 12 months from the beginning of the study. Physical examination was performed on all visits. BMI was calculated as body weight in kilograms divided by height in meters squared and standardized for age and sex (BMI-SDS) (17). Fasting samples were drawn at all visits for IGFI, glucose, insulin, glycosylated hemoglobin (HbA1c), cholesterol, triglycerides, lipoproteins, TSH, free T4, free T3, testosterone, estradiol, dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione, sex hormone-binding globulin (SHBG), osteocalcin, and alkaline phosphatase. Frequently sampled iv glucose tolerance tests (FSIGTT) were performed before and after 3 weeks, 3 months, and 6 months of treatment. Dual-energy x-ray absorptiometry (DXA) for determination of total body fat, total lean mass, bone mineral content (BMC), and bone mineral density (BMD) were performed before and after 6 weeks, 3 months, and 6 months, as well as at the 9 months and 12 months visits. Overnight serum level curves for GH, cortisol, glucose, and insulin with samples drawn every 30 min were obtained before and after 3 months of treatment. Abdominal sc adipose tissue biopsies were taken for analysis of lipolysis and lipogenesis before and after 3 months of treatment.

DXA

DXA is a scanning technique that measures the differential attenuation of two x-rays as they pass through the body. The procedure differentiates BMC from soft tissue and subsequently divides the latter into fat and lean tissue. Total body composition analysis with DXA (lunar DPX-L, version 1.5E; Lunar Corp. Madison, WI) was performed with patients in the supine position. Body fat content was expressed in both kilograms (fat mass) and percentage of body weight (% fat). Lean soft tissue mass was expressed in kilograms. The relation between fat mass and lean mass was estimated by the ratio of fat mass to lean mass (fat/lean). BMC was expressed as total mass in grams. Bone mineral density (BMD) was expressed as grams per centimeters squared.

Spiroergometry (physical exercise testing)

Spiroergometric testing was performed according to a standardized protocol using continuous cycling test. The initial load was 1 W/kg body weight, followed by stepwise increments every 90 sec. Measurements of blood pressure and heart rate were recorded every 2 min. The highest load recorded during exercise was taken as maximum physical load, $W_{max}$. In all tests, the cycling was terminated due to muscle fatigue.

Insulin-modified FSIGTT

The test was performed as described previously (18–20). The MINMOD software (copyright R. N. Bergman, University of Southern California) (21) was used to calculate insulin sensitivity index ($S_I$) and glucose effectiveness ($S_E$). Insulin sensitivity represents the ability of insulin to enhance net glucose disappearance, whereas glucose effectiveness is a measure of the ability of glucose to enhance its own disappearance at basal insulin. The responsivity of the acute insulin secretion was determined as the peak serum insulin concentration and insulin area under the curve (AUC) during the initial phase of the test (i.e. after glucose infusion and before the injection of exogenous insulin).

Analytical methods

Blood samples were drawn in the morning after an overnight fast. The serum concentration of IGFI was determined by a hydrocholoric acid-ethanol extraction RIA using authentic IGFI for labeling (Nichols Institute Diagnostics, San Juan Capiistrano, CA). The sd score (SDS) for IGFI was calculated from IGFI levels adjusted for age and sex in a normal population (22). Serum cholesterol and triglycerides concentrations were determined with enzymatic methods (Boehringer, Mannheim, Germany). Serum insulin was determined by a RIA (Pharmacia and Upjohn Diagnostics AB, Uppsala, Sweden). Blood glucose was measured by the glucose-6-phosphate dehydrogenase method (Kebo Lab, Stockholm, Sweden). Glycosylated hemoglobin Alc (HbA1c) was determined by high-liquid chromatography (Waters, Millipore AB, Sweden). SHBG, TSH, free T4, and free T3 were measured by timed-resolved fluoroimmunoassays (Wallace Sverige AB, Upplands Väsbys, Sweden). Serum estradiol and dehydroepiandrosterone were measured by a chemiluminescent enzyme immunoassay (Diagnostic Products Corporation, Los Angeles, CA).

Adipocyte metabolism

Isolation of adipocytes and determination of lipolysis. Abdominal sc adipose tissue samples (100–300 mg) were removed after local Citanest anesthesia of the surrounding area. Adipocytes were isolated as described previously (23) and incubated in duplicates for 2 h at 37C in Kreb’s Ringer Phosphate buffer containing albumin (40 g/L), glucose (1 g/L), and ascorbic acid (0.1 g/L) with air as the gas phase. The final adipocyte concentration was 1% (vol/vol). At the end of the incubation, an aliquot of the medium was removed for the analysis of glycerol release, which was used as an index of lipolysis and determined by a very sensitive kinetic bioluminescence method (24). Cell diameter was measured by direct microscopy. Mean cell volume and surface area were calculated as described previously (25).

Determination of insulin-induced inhibition of lipolysis. To study the antilipolytic effect of insulin, lipolysis was induced with 1 µmol/L forskolin. This concentration induces approximately half-maximum stimulation of lipolysis (26). Insulin was added to a final concentration of 10−3–10−6 pmol/L.

Determination of glucose incorporation into lipids (lipogenesis). The lipid incorporation studies were performed at a glucose concentration of 1 mmol/L, that renders glucose transport into the cells rate limiting (27). The adipocytes were incubated at a final concentration of 2% (vol/vol) in Kreb’s Ringer Phosphate buffer containing albumin (40 mg/mL), labeled glucose ([3-3H]-glucose, 5 × 106 cpm, 0.2 µmol/L), unlabeled glucose (1 µmol/L), and insulin (0–10−6 pmol/L). Each incubation was performed in duplicate for 2 h at 37C and stopped by rapidly chilling the vials to 4C. Incorporation of glucose into lipids was determined as described previously (28). Briefly, 45 μL of 6 mol/L H2SO4 and 4 mL saline with 2.5 mg diphenylxazole were added to each vial. The vials were left at room temperature for overnight before the radioactivity was measured by liquid scintillation counting.

Expression of the results

The maximal isoprenaline- and terbutaline-induced lipolysis (responsiveness) were calculated from each individual dose-response curve as glycerol release at the maximum effective stimulatory concentration minus the basal glycerol release. The maximum insulin-induced inhi-
The mean blood glucose level during a 15-h overnight curve was continued observation (n = 1414 KAMEL ET AL. 2000 Vol 85 • No 4).

Table 2. Body composition before, during, and after GH treatment. GH was administered for 6 months, followed by 6 months of continued observation (n = 6)

<table>
<thead>
<tr>
<th>Table 2. Body composition before, during, and after GH treatment. GH was administered for 6 months, followed by 6 months of continued observation (n = 6)</th>
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</thead>
<tbody>
<tr>
<td>Basal</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>BMI (SDS)</td>
</tr>
<tr>
<td>Total body fat %</td>
</tr>
<tr>
<td>Total fat mass (Kg)</td>
</tr>
<tr>
<td>Total lean mass (Kg)</td>
</tr>
<tr>
<td>Total fat:lean ratio</td>
</tr>
<tr>
<td>BMC (Kg)</td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
</tr>
</tbody>
</table>

Data are presented as median, upper, and lower quartiles. Comparisons between data from different time points (6 weeks, 3 months, 6 months, 9 months, and 12 months) were made by Wilcoxon signed rank test.

Statistics

Data were analyzed using the Statistical Package for Social Sciences version 5.0 and expressed as median (interquartile range) in the text and tables. Wilcoxon’s rank sum test was used for comparisons between two time points. Friedman ANOVA for repeated measurements was used to analyze changes over time in blood lipid profiles. Significance was defined as P \leq 0.05. In Fig. 3, mean ± sem was used for clarity.

Results

Body composition (Table 2)

The median BMI (SDS) decreased during GH treatment from 6.16 SDS (4.26–7.22) before treatment to 5.75 (4.13–7.03) and 5.56 (4.13–7.20) after 3 and 6 months of treatment, respectively. Total body fat percentage decreased during treatment, followed by a minor rebound after cessation of treatment (Fig. 1). Total lean mass increased during, as well as after, treatment. This indicates that the increase in lean body mass reflects normal growth rather than an effect of GH. The ratio of fat to lean body mass was significantly decreased during treatment and remained so also after discontinuation. Both median BMD and BMC increased during, as well as after, discontinuation of treatment, indicating an age-dependent effect.

Spiroergometry (Table 3)

Spiroergometry (physical exercise) testing was well tolerated by all children. The maximum physical load was increased during, as well as subsequent to, GH treatment, reflecting normal growth of the children.

Whole body glucose homeostasis

No significant effects were elicited by GH treatment on fasting blood glucose levels or HbA1c. Fasting serum insulin level was slightly increased from 11.86 μU/mL (7.95–18.81) before treatment to 18.82 (12.85–34.65) after 3 weeks of treatment (n = 7, P = 0.04), but not at subsequent time points. The mean blood glucose level during a 15-h overnight curve was 6.3 mmol/L (5.2–6.3) at baseline and was not significantly different after 3 months of treatment (5.8, 5.5–6.0). Similarly, the mean serum insulin level was 31.60 μU/mL (25.56–88.11) at baseline and not significantly different after 3 months of treatment (43.74, 32.1–57.23).

Parameters of glucose homeostasis were further investigated by the insulin-modified FSIGTT. Before treatment, the computed insulin sensitivity index was in accordance with previously published data of overweight children of this age group (29, 30). Although there was a trend toward improved insulin sensitivity, neither insulin sensitivity nor glucose effectiveness changed significantly at repeated tests after 3 weeks, 3 months, and 6 months of treatment (Figure 2, A and B). Interestingly, the acute pancreatic β-cell responsivity increased during treatment as estimated during the initial phase of the FSIGTT in terms of attained peak serum insulin concentration, as well as insulin AUC (Table 4).

Biochemical measurements

No significant effects were elicited by GH treatment on free T₃, free T₄, TSH, alkaline phosphatase, androstenidone,
dehydroepiandrosterone sulfate, and SHBG (data not shown). Osteocalcin increased both during and after discontinuation of GH treatment in accordance with normal bone growth (data not shown). Before treatment, the median serum IGF-I concentration of 256 μg/L (212–350) was within the normal range, despite depressed GH levels. The median GH level during an overnight curve increased from 0.2 μmol/L (0.15–0.2) before treatment to 3.0 (0.3–3.4) after 3 months of treatment (P = 0.04). As expected, median IGF-I level increased to 662 μg/mL (548–767, P = 0.02) after 3 weeks, 637 (436–812, P = 0.03) after 6 weeks, and 632 (562–736, P = 0.02) after 3 months of treatment. The overnight serum cortisol curve was not significantly affected as analyzed before and after 3 months of treatment.

Blood lipid profiles
Besides a transient decrease in low-density lipoprotein (LDL) cholesterol after 6 weeks of treatment, no significant effects on the lipid profiles were registered.

Adipocyte volume and metabolism (Table 5)
Adipocytes were isolated from an abdominal sc adipose tissue biopsy obtained from each child before and after 3 months of GH treatment.

**Adipocyte volume.** The mean adipocyte volume decreased from 814 pL (557–1070) to 540 pL (480–670) after 3 months of treatment.

**Lipolysis.** Because estimates of adipocyte metabolism depend on the size of the cells (31), data are presented per cell surface area. The basal lipolysis was not affected by treatment, whereas both the maximum isoprenaline- and terbutaline-induced lipolysis were increased approximately 2.5-fold (Fig. 3, A and B). The sensitivity of the adipocytes to isoprenaline (a nonspecific β-adrenergic receptor agonist) was unchanged by treatment (Fig. 4A). However, the sensitivity to terbutaline (a β2-receptor agonist) was significantly increased after treatment (Fig. 4B). There was no effect of treatment on the sensitivity and responsiveness to insulin-induced inhibition of lipolysis.

**Lipogenesis.** The basal and maximum insulin-induced lipogenesis, as well as the insulin sensitivity, were unaffected by treatment.

**Discussion**
We report that 6 months of GH treatment in prepubertal obese boys reduces total body fat percentage without eliciting negative effects on the glucose homeostasis. GH treatment changes body composition, with a marked decrease in total body fat percentage, and reduces abdominal adipocyte size in obese and GH-deficient adults, as well as in short stature children with or without GH deficiency and children with Prader-Willi syndrome (PWS) (12, 32–35). Here, we describe similar findings in obese but otherwise healthy pre-

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**TABLE 3.** Physical exercise testing (spiroergometry) before, during, and after GH treatment. GH was administered for 6 months, followed by 6 months of continued observation (n = 5)

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum heart rate (bpm)</td>
<td>188 (184–197)</td>
<td>200 (191–203)</td>
<td>200 (197–201)</td>
<td>195 (190–199)*</td>
</tr>
<tr>
<td>Maximum systolic blood pressure (mm Hg)</td>
<td>150 (150–157)</td>
<td>160 (153–163)</td>
<td>150 (143–155)</td>
<td>165 (163–168)*</td>
</tr>
<tr>
<td>Maximum physical load W max (watts)</td>
<td>140 (115–145)</td>
<td>142 (130–152)</td>
<td>160 (151–175)*</td>
<td>170 (156–193)*</td>
</tr>
</tbody>
</table>

Data are presented as median, upper, and lower quartiles. Comparisons between data from different time points (3 months, 6 months, and 12 months) were made by Wilcoxon signed rank test.

*P < 0.05.
The reduction of body fat in these children was less pronounced than previously observed in PWS children under GH treatment. However, in the present study no special diet was prescribed. In contrast, because we wanted to study the direct effect of GH, the subjects were instructed not to make dietary changes.

The lipolytic effect of GH is well documented. In hypophysectomized rats, GH restores the decrease in catecholamine-induced lipolysis and the number of β-adrenergic receptors (36, 37). In adults with GH deficiency, GH treatment for 6 months increases responsiveness of the epinephrine-induced lipolysis mainly by increasing the efficiency of the β-adrenergic signaling pathway (38). Furthermore, our data from PWS children with partial GH deficiency shows not to make dietary changes. Reports on the effects of systemic GH treatment on lipogenesis in isolated abdominal adipocytes are confusing. In children with non-GH-deficient short stature and GH deficiency, unaltered insulin-induced lipogenesis with decreased and unchanged basal lipogenesis, respectively, during GH treatment have been described (33, 34). We have previously found an increased insulin-induced lipogenesis in adipocytes from children with PWS after 3 months of GH treatment (39). In contrast, we did not observe any effect of GH treatment on lipogenesis in adipocytes from the obese children in the present study. The basis for this discrepancy is unclear but may reflect that children with PWS are more sensitive to a GH-induced alteration in body composition. PWS children are probably truly GH deficient (40), whereas children with simple obesity have down-regulated GH levels secondary to their obesity state but with preserved normal IGF-I levels and normal growth.

Besides a transient increase in fasting insulin levels after 6 weeks of treatment, no disturbances in glucose homeostasis during treatment were observed. Most notably, there was no effect on insulin sensitivity as determined by the FSIGTT. This lack of diabetogenic effect is in concert with studies of both short stature non-GH-deficient children (15) and girls with Turner’s syndrome (41). On the contrary, we observed increased β-cell responsivity after GH treatment. Previous studies have suggested a decreased β-cell capacity in children with GH deficiency with a beneficial effect of exogenous GH (42, 43). Whether this is valid also for obese children calls for further investigation. Nevertheless, changes in body composition, as well as putative effects on the β-cell capacity, may counter negative effects on insulin sensitivity. In concert with this, GH treatment of obese adults improves insulin sensitivity (12).

Obesity is associated with high levels of LDL- and very LDL-cholesterol, as well as low levels of high-density lipoprotein-cholesterol (44). Similar blood lipoprotein profiles are found in patients with GH deficiency, and GH treatment of these patients restores the LDL- and high-density lipoprotein-cholesterol to normal (45). An increased LDL-receptor expression and activity in hepatocytes as demonstrated in

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**TABLE 4. β-Cell responsivity assayed by the frequently sampled iv glucose tolerance test (FSIGTT) during 6 months of GH treatment**

<table>
<thead>
<tr>
<th>Lipolysis</th>
<th>Basal</th>
<th>3 weeks</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin concentration (μU/mL)</td>
<td>13.99 (8.04–17.00)</td>
<td>22.03 (11.48–37.03)</td>
<td>20.95 (15.07–53.53)</td>
</tr>
<tr>
<td>Peak insulin concentration (μU/mL)</td>
<td>200.2 (108.8–240.4)</td>
<td>250.4 (96.9–385.3)</td>
<td>230.3 (155.0–274.8)</td>
</tr>
<tr>
<td>Insulin AUC (μU/mL/10 min)</td>
<td>1190.0 (280.5–1650.0)</td>
<td>1425.0 (559.0–2119.5)</td>
<td>1290.0 (874.0–1600.0)</td>
</tr>
<tr>
<td>Insulin AUC (μU/mL/20 min)</td>
<td>2092.0 (549.0–2696.0)</td>
<td>2434.0 (1071.0–3733.0)</td>
<td>2317.0 (1565.5–2777.0)</td>
</tr>
</tbody>
</table>

Data are presented as median, upper, and lower quartiles. Comparisons between data from different time points (3 weeks, 3 months, and 6 months) were made by Wilcoxon signed rank test (n = 5).

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**TABLE 5. Effect of GH treatment (3 months) on isoprenaline- and terbutaline-induced lipolysis, insulin-induced inhibition of lipolysis, insulin-induced lipogenesis, and cell volume in isolated adipocytes (n = 7)**

<table>
<thead>
<tr>
<th>Lipolysis</th>
<th>Basal</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoprenaline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>1.3 (0.7–1.6)</td>
<td>1.7 (0.8–2.8)</td>
</tr>
<tr>
<td>Maximum</td>
<td>3.3 (2.3–6.9)</td>
<td>7.9 (4.5–13.7)</td>
</tr>
<tr>
<td>EC_{50} (nmol/L)</td>
<td>8.0 (5.0–20.0)</td>
<td>5.0 (0.2–8.0)</td>
</tr>
<tr>
<td>Terbutaline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>1.3 (1.1–3.4)</td>
<td>1.8 (1.3–3.2)</td>
</tr>
<tr>
<td>Maximum</td>
<td>1.9 (1.3–2.4)</td>
<td>4.7 (2.8–6.2)</td>
</tr>
<tr>
<td>EC_{50} (nmol/L)</td>
<td>1.0 (0.8–4.0)</td>
<td>0.5 (0.3–0.9)</td>
</tr>
<tr>
<td>Insulin-induced inhibition of lipolysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>2.9 (1.2–8.0)</td>
<td>5.3 (2.4–9.1)</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.5 (0.1–2.8)</td>
<td>0.7 (0.4–2.9)</td>
</tr>
<tr>
<td>EC_{50} (nmol/L)</td>
<td>0.01 (0.01–0.1)</td>
<td>0.01 (0.001–0.01)</td>
</tr>
</tbody>
</table>

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Lipolysis was determined as glycerol release (μmol/μm²·2 h × 10⁻¹¹) and lipogenesis as glucose incorporation into lipids (μmol/μm²·2 h × 10⁻¹¹). Data are presented as median, upper, and lower quartiles. Comparison between data before and after treatment were made by Wilcoxon signed rank test.
human, as well as in hypophysectomized rats, treated with GH may explain the beneficial effect on LDL-cholesterol (46). In this study, we found merely a transient decrease of LDL-cholesterol during treatment. Similarly, lack of continuously decreased total cholesterol in obese adults during treatment with GH for 9 months have been reported (12).

When adipocyte function was studied in vitro, we found an increased maximal catecholamine-induced lipolysis in adipocytes isolated from obese children after 3 months of GH

**Fig. 3.** Dose-response curves for isoprenaline (A) and terbutaline (B) before (■) and after 3 months of GH treatment (○) (n = 7). Adipocytes were incubated with increasing concentrations of isoprenaline and terbutaline, and glycerol release to the medium was determined. The values are presented as mean ± SEM. The maximum isoprenaline- and terbutaline-induced lipolysis increased after treatment (P = 0.02).

**Fig. 4.** Concentrations of isoprenaline (A) and terbutaline (B), respectively, resulting in half-maximal stimulation of lipolysis (EC_{50}) before, as well as after, 3 months of GH treatment (n = 7). The EC_{50} for terbutaline was significantly decreased after treatment (P = 0.04).
treatment. Moreover, the sensitivity to terbutaline-induced lipolysis, but not isoprenaline-induced lipolysis, was increased, which indicates that the lipolytic effect of GH may be related to a stimulatory effect on β-2-adrenergic receptors. It has previously been demonstrated that lipolysis in vivo in obese children is less responsive to epinephrine infusions (47). GH levels were markedly reduced in obese children in this study, which confirms numerous of previous studies (10, 11). Because epinephrine primarily acts on β-2-adrenergic receptors and our data may indicate that GH selectively up-regulates β-2-adrenergic lipolysis, the decreased response to epinephrine in obese children probably is due to altered GH levels and not a primary cause of obesity, as previously suggested (47). In support of this, weight reduction in obese adult females results in up-regulation of β-2-adrenergic receptors in fat cells (48). Because weight reduction is associated with restoration of circulating GH levels (10, 11), the disturbed β-2-adrenergic function is likely due to a reduced GH tone. Our data differs from previously published reports of unaltered catecholamine-induced lipolysis after 3 months of GH treatment in short stature children with or without GH deficiency (33, 34). Several possible factors may explain this discrepancy. Firstly, we expressed our data “per cell surface area,” and not per cell, because estimates of adipocyte metabolism depend on the size of the cells (31). The size of the abdominal adipocytes decreased significantly also in the previous studies (33, 34), and expressing the results per cell may, thus, be misleading. Secondly, our patients were less heterogeneous in terms of age, sex, diagnosis, and body composition (e.g. adipocytes of obese children may be more sensitive to alterations in body composition with a different reaction to GH than nonobese children).

In conclusion, GH treatment for 6 months of obese prepubertal boys reduces total body fat percentage, possibly via stimulation of catecholamine-induced lipolysis, with minimal or no effect on whole body insulin sensitivity and glucose homeostasis. Whether long-term GH treatment is an effective strategy to avoid complications of childhood obesity needs further investigations.

Acknowledgments
We thank Dr. Anette Asplund-Carlson (King Gustaf V Research Institute, Karolinska Hospital) for kind assistance in analyzing data from the FSIPTT.

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