Lower growth hormone and higher cortisol are associated with greater visceral adiposity, intramyocellular lipids, and insulin resistance in overweight girls

Madhusmita Misra,1,2 Miriam A. Bredella,3 Patrika Tsai,1 Nara Mendes,1 Karen K. Miller,1 and Anne Kilbansi1

1Neuroendocrine Unit and 2Department of Radiology, Massachusetts General Hospital and Harvard Medical School, and 3Pediatric Endocrine Unit, MassGeneral Hospital for Children and Harvard Medical School, Boston, Massachusetts

Submitted 25 January 2008; accepted in final form 9 June 2008

Obesity is a global problem, and, according to recent estimates, 17% of US children and adolescents are overweight [body mass index (BMI) >95th percentile] and 16.5% are at risk for overweight (BMI between 85th and 95th percentiles) (11, 19). Commensurate with the rising prevalence of overweight, the prevalence of type 2 diabetes is increasing, such that up to 30–50% of all newly diagnosed children with diabetes are classified as having type 2 diabetes, in contrast to <5% before 1994 (13, 23). Although body composition and lipid profiles are markedly altered in overweight compared with normal-weight adolescents, associations of hormonal alterations with body composition and insulin sensitivity changes in overweight teenagers have not been well characterized.

Disorders resulting in growth hormone (GH) deficiency or hypercortisolemia predispose to abdominal fat accumulation and unfavorable lipid profiles, and there are many reports of low GH levels (14, 27, 33, 35) and some reports of high cortisol levels (41) in obese adults. In addition, replacement of GH in GH-deficient children as well as adults with recombinant human GH (rhGH) results in reversal of trunk fat accumulation (38) because of the lipolytic effect of GH (5). Some studies also demonstrate a reduction in trunk fat with rhGH administration in obese adults (4, 14, 33). However, whether GH and cortisol secretory status are determinants of body composition in overweight adolescents has not been much studied. Particularly, there are no reports of peak GH values with formal GH stimulation testing (a dynamic test of GH secretory capacity that tests sufficiency of GH secretion) in overweight vs. normal-weight adolescents. GH levels are affected by nutritional status and are high in undernourished individuals (29). We have also reported that high GH levels are associated with lower trunk fat in undernourished girls (28). These data suggest that overweight adolescents may have low GH levels, which may be related to higher trunk fat and lipid levels. In addition, high cortisol levels have antilipolytic effects (32) and are associated with increased trunk fat (12, 16). Overweight can cause pseudo-Cushing’s syndrome (31), and higher cortisol in overweight adolescents may also contribute to increased trunk fat and higher lipid levels.

Site-specific fat depots have important roles in insulin sensitivity. Trunk fat accumulation has been associated with increased lipid levels and greater severity of insulin resistance in adults. Specifically, subcutaneous adipose tissue (SAT) has been associated with higher lipid levels and visceral adipose tissue (VAT) with a greater degree of insulin resistance (7, 26). However, data in adolescents are limited and conflicting. One study indicated strong associations of SAT with insulin levels (44), whereas other studies reported associations between VAT (43) or intramyocellular lipid (IMCL) (40) with insulin resistance.
We hypothesized that overweight adolescents would have lower GH and higher cortisol levels than normal-weight adolescents, and that these hormonal alterations in overweight adolescents would be related to VAT and IMCL accumulation, higher lipid levels, and greater severity of insulin resistance. We therefore determined GH and cortisol status in overweight vs. normal-weight girls to determine associations of hormones with body composition, IMCL, lipids, and insulin sensitivity.

SUBJECTS AND METHODS

**Subject selection.** Seventeen overweight and 30 normal-weight adolescents (12–18 yr old) were screened for study eligibility. Of the screened subjects, 15 overweight adolescents completed the study visit. These subjects were matched for race, ethnicity, and bone age (within 1 yr) to normal-weight adolescents from the pool of screened subjects, such that the first available control fulfilling match criteria for the corresponding overweight subject was enrolled for the study visit. A telephonic prescreen was used to minimize the number of controls screened to obtain the required number of subjects.

GH levels typically peak at Tanner stages 2 and 3 of puberty in girls, and to control for somewhat earlier puberty reported in overweight than in normal-weight girls, we matched girls for bone age, rather than chronological age. Overweight girls had BMI greater than the 95th percentile for age, and normal-weight girls had BMI between the 15th and 85th percentiles. Menarchal status did not differ between groups. Three overweight and two normal-weight girls were premenarchal. Exclusion criteria were pregnancy, use of medications that may affect GH or cortisol levels (e.g., estrogen, progesterone, and glucocorticoids), significant weight gain or loss (>2 kg) within 3 mo of the study, and presence of diabetes mellitus or thyroid disorders. In each group, 12 were white, 2 were African-American, and 1 was of mixed racial background. For ethnicity, in each group, 13 were non-Hispanic and 2 were Hispanic. We recruited subjects through mass mailings to primary care providers and advertisements in community newspapers and within the Partners HealthCare network. The Institutional Review Board of Partners HealthCare system approved the study, and informed assent and consent were obtained from subjects and parents.

**Anthropometric measurements.** Subjects weighing a hospital gown were weighed to the nearest 0.1 kg on an electronic scale at the General Clinical Research Center (GCRC) of Massachusetts General Hospital. We employed a single stadiometer at the GCRC to measure height to the nearest 0.1 cm and used an average of three measurements. Bone age was assessed using methods of Greulich and Pyle (17).

**Experimental protocol.** On a screening visit at the GCRC of Massachusetts General Hospital, a history was obtained from each subject, a physical examination was performed, and screening laboratory results (thyroid-stimulating hormone, electrolytes, and a complete blood count) were obtained. A normal thyroid-stimulating hormone, fasting glucose <126 mg/dl, and hematocrit >30% were required for study participation.

Eligible subjects were admitted to the GCRC. Fasting blood was drawn for a lipid profile, insulin-like growth factor I (IGF-I), adiponectin, and leptin, and an oral glucose tolerance test (OGTT) was performed using a 1.75 g/kg (maximum 75 g) glucose load. Blood was drawn at 0, 30, 60, 90, and 120 min for determination of glucose and insulin levels. Before the OGTT and with the subjects in a fasting state, body composition was determined using MR imaging (MRI). SAT and VAT were assessed at L4–L5, and soleus IMCL (S-IMCL) was measured using 1H-MR spectroscopy (1H-MRS). 1H-MRS was performed on a Signa 1.5-T MR system (General Electric Medical Systems, Milwaukee, WI) using a standard extremity coil and an optimized PRESS sequence with echo time of 30 ms, repetition time of 3,000 ms, 32 acquisitions, and voxel size of 1.5 ml. The voxel was positioned so as to contain minimal visible interstitial fat, and shaving was performed automatically or manually, resulting in a water line width of 11–12 Hz. Voxels were placed in the soleus muscle. Water presaturation and outer volume suppression were used for metabolite acquisition. Spectral quantification was performed relative to muscle water based on a fit of unsuppressed water signal within the same voxel and to creatine peak at 3.0 ppm.

Dual-energy X-ray absorptiometry (DXA; Hologic 4500, Waltham, MA) was used to assess fat mass, percent trunk fat [(trunk fat/total fat) × 100], and trunk fat-to-extremity fat ratio (T/E) (24, 42). Waist-to-hip ratio (W/H) was determined (waist measurements were taken at the level of the umbilicus, and the maximum hip circumference was measured). Triceps skinfold thickness was obtained using skin calipers. Indirect calorimetry was performed to determine the resting energy expenditure and respiratory quotient. Frequent sampling for GH and cortisol was performed every 20 min between 2300 and 0800 to determine physiological secretory status of these hormones. Then a GH-releasing hormone (GHRH)-arginine stimulation test for GH levels was performed to assess maximal secretory capacity for GH, a test for GH deficiency (1, 6). GHRH was administered at a dose of 1 μg/kg, and then arginine (at a dose of 0.5 g/kg, maximum 30 g) was infused over a 30-min period. Blood was drawn at 0, 30, 60, 90, and 120 min for determination of GH levels. Subjects also collected urine for a 24-h period for free cortisol estimation, i.e., cortisol cleared and filtered by the kidneys and a measure of cortisol excess (34). We calculated the ratio of peak GH (on the GHRH-arginine stimulation test) to cortisol (mean from overnight sampling) as a combined measure of hormonal insult in our subjects, inasmuch as subjects with the lowest GH and highest cortisol levels would be expected to be at greatest risk for alterations in body composition (30).

**Biochemical assessment.** We used RIA to assess insulin [Diagnostic Products, Los Angeles, CA; intra-assay coefficient of variation (CV) = 3.1–9.3%, sensitivity = 1.2 μIU/ml], adiponectin (Linco Diagnostics, St. Charles, MO; lowest detectable concentration = 0.001 ng/ml, CV = 6.4–8.4%), leptin (Linco Diagnostics; intra-assay CV = 3.4–8.3%, sensitivity = 0.5 ng/ml), and cortisol (Diagnostic Products; limit of detection = 1 μg/dl, sensitivity = 0.21 μg/dl, CV = 2.5–4.1%) and an immunoradiometric assay to measure GH (Diagnostic Systems Laboratories, Webster, TX; intra-assay CV = 3.1–5.4%, sensitivity = 0.01 ng/ml) and IGF-I (Diagnostic Systems Laboratories; intra-assay CV = 3.9–7.0%, sensitivity = 2.06 ng/ml). Lipid profiles and glucose levels were obtained from the hospital laboratory with use of published methods. UFC over 24 h was measured in the hospital laboratory by the GammaCoat 125I-RIA (Diasorin, Stillwater, MN; detection limit = 1 μg/dl, CV = 7%). All samples were stored at −80°C until analysis in duplicate.

Measures of insulin resistance [fasting insulin-to-glucose ratio, homeostasis model assessment of insulin resistance (HOMA-IR), and corrected insulin response (CIR)] and insulin sensitivity (QUICKI) were calculated. HOMA-IR was calculated as [(fasting glucose (mmol/l) × fasting insulin (μU/ml))/22.5, CIR as (insulin at glucose peak – 2.5) / (glucose peak – 70)], and QUICKI as 1/log fasting glucose + log fasting insulin) (15, 21).

**Statistical methods.** Values are means ± SD. JMP version 4 (SAS Institute, Cary, NC) was used for statistical analysis. Student’s t-test was used for analysis of differences between means for two groups. Data that were not normally distributed (GH, cortisol, and insulin resistance data) were logarithmically transformed and then subjected to the t-test. Pearson correlations were conducted to determine associations between different variables for normally distributed data and after logarithmic transformation of data not normally distributed. Stepwise regression modeling was also performed. P < 0.05 was used to denote significance.
RESULTS

Clinical characteristics. Clinical characteristics for overweight and normal-weight adolescents are summarized in Table 1. The groups were matched per study design for maturity, as assessed by bone age and Tanner stage, because GH, IGF-I, and insulin resistance parameters vary with maturity (9, 18, 36). As an expected consequence and given the known effects of overweight on maturity, overweight girls were younger than normal-weight girls. Overweight girls had significantly higher weight and BMI than controls. BMI ranged from 25.4 to 49.0 kg/m² in overweight girls and from 18.2 to 25.3 kg/m² in normal-weight adolescent girls.

W/H, triceps skinfold thickness, total fat, percent trunk fat, T/E, VAT, SAT, and S-IMCL were higher in overweight adolescents than in controls. Insulin and glucose levels during the OGTT are shown in Fig. 1. Measures of insulin resistance, insulin area under the curve (AUC), and glucose AUC, as well as insulin resistance parameters vary with maturity, as assessed by bone age and Tanner stage, because log peak GH and GH-AUC correlated inversely with BMI standard deviation score (BMI-SDS) in overweight girls (r = 0.63, P = 0.0005) and in the entire group (r = 0.54, P = 0.002).

Fig. 1. Insulin and glucose levels at different times during the oral glucose tolerance test in adolescent overweight (black line) and normal-weight (gray line) girls. Insulin and glucose levels were higher in overweight than in normal-weight girls. Significances for insulin data are from comparison of logarithmically converted data: *P < 0.05; **P < 0.01; ***P < 0.001.

Table 1. Clinical characteristics of overweight and normal-weight (control) adolescent girls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Overweight Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>16.1 ± 1.6</td>
<td>13.7 ± 1.7</td>
<td>0.0005</td>
</tr>
<tr>
<td>Bone age, yr</td>
<td>15.8 ± 1.7</td>
<td>15.1 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Tanner stage (breasts)</td>
<td>4.6 ± 1.0</td>
<td>4.3 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.5 ± 2.0</td>
<td>34.4 ± 7.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>0.0 ± 0.5</td>
<td>3.7 ± 1.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>REE, kcal</td>
<td>1.390 ± 1.82</td>
<td>1.813 ± 237</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Body composition measurements

Clinical measurements

Triceps skinfold thickness, mm 17.1 ± 4.11 25.9 ± 5.1 <0.0001
W/H 0.79 ± 0.05 0.90 ± 0.08 0.0004
DXA measures

Total fat mass, kg 16.3 ± 3.4 39.3 ± 13.6 <0.0001
T/E 0.36 ± 0.58 44.6 ± 6.6 0.0007
MR measures

SAT, g 145.8 ± 56.8 449.4 ± 174.9 <0.0001
VAT, g 20.5 ± 8.8 46.8 ± 18.7 <0.0001
VAT/SAT 0.30 ± 0.05 0.10 ± 0.03 0.03
1H-MRS S-IMCL 9.2 ± 5.0 13.6 ± 4.7 0.03

OGTT

Log insulin AUC, μIU·ml⁻¹·120 min⁻¹ 3.66 ± 0.16 4.01 ± 0.30 0.006
Log fasting insulin or glucose, μU/ml or mg/dl 1.24 ± 0.18 0.87 ± 0.50 0.01
Log HOMA-IR -0.003 ± 0.178 0.40 ± 0.482 0.005
Log CIR -0.14 ± 0.31 0.09 ± 0.25 0.03
Log QUICKI -0.41 ± 0.03 -0.47 ± 0.06 0.003

Serum lipids

Serum cholesterol, mg/dl 144.1 ± 21.2 156.5 ± 23.8 NS
Serum triglycerides, mg/dl 55.5 ± 20.0 91.5 ± 47.9 0.01
Serum LDL, mg/dl 74.7 ± 18.7 92.1 ± 22.5 0.03
Serum HDL, mg/dl 58.2 ± 10.5 44.5 ± 13.4 0.004

Values are means ± SD of 15 subjects in each group. BMI, body mass index; SDS, standard deviation score; REE, resting energy expenditure; W/H, waist-to-hip ratio; T/E, trunk-to-extremity fat ratio; MRS, MR spectroscopy; S-IMCL, soleus intramyocellular lipid; OGTT, oral glucose tolerance test; SAT and VAT, subcutaneous and visceral adipose tissue; DXA, dual-energy X-ray absorptiometry; AUC, area under the curve; HOMA-IR, homeostasis model assessment of insulin resistance; CIR, corrected insulin response; NS, not significant.
Log mean serum GH levels from overnight frequent sampling and fasting IGF-I did not differ between groups (Table 2) and were not predicted by BMI.

IGF-I levels correlated strongly with log peak GH ($r = 0.84$, $P = 0.0003$) but less strongly with log mean GH ($r = 0.54$, $P = 0.04$) levels in overweight girls and for the group as a whole ($r = 0.55$ and $0.52$, $P = 0.002$ and $0.005$, respectively).

Log peak GH levels on the GHRH-arginine test correlated strongly and positively with log mean GH levels from overnight frequent sampling in overweight girls ($r = 0.89$, $P < 0.0001$). Associations were weaker for the group as a whole ($r = 0.48$, $P = 0.02$) than in overweight girls.

For subsequent correlational analysis of GH with parameters of body composition, insulin resistance, and lipids, log peak GH and log GH-AUC (from the GHRH-arginine test) demonstrated similar associations with various variables, and because peak GH is of greater clinical significance in diagnosing GH insufficiency than integrated overnight GH secretion, only associations of peak GH are reported (see below). In addition, because subjects with the lowest GH and highest cortisol levels would be expected to have the greatest measures of body fat, insulin resistance, and lipids, we also examined the log (peak GH-to-mean cortisol) ratio as an integrated measure of GH and cortisol effects.

In overweight girls, log leptin correlated inversely with log peak GH ($r = -0.80$, $P = 0.001$), log mean GH ($r = -0.53$, $P = 0.04$), and IGF-I ($r = -0.70$, $P = 0.004$).

**Associations between body composition measures.** Strongest associations of DXA and clinically assessed body composition measures with MRI measures of body composition were as follows in overweight girls: SAT was associated with total fat ($r = 0.97$, $P < 0.0001$) and triceps skinfold thickness ($r = 0.71$, $P = 0.01$), VAT with W/H ($r = 0.78$, $P = 0.004$) and triceps skinfold thickness ($r = 0.61$, $P = 0.03$), and S-IMCL with W/H ($r = 0.82$, $P = 0.004$) and T/E ($r = 0.75$, $P = 0.005$). Other associations were weaker and are not reported. Associations were even stronger when the group as a whole was assessed for all parameters except S-IMCL.

For the rest of the analysis, we have used MRI and MRS measures of body fat, namely, VAT, SAT, and S-IMCL, for association analysis with GH and cortisol parameters, given the greater accuracy of these measures of body composition.

**Associations of GH and cortisol with body composition measures.** In overweight adolescents, only weak associations of log mean cortisol were observed with VAT ($r = 0.55$, $P = 0.08$), but this association reached significance for the group as a whole ($r = 0.53$, $P = 0.01$). Log peak GH, IGF-I, and log (peak GH-to-cortisol) ratio were inversely associated with VAT, SAT, and S-IMCL (Table 3) within overweight girls and in the group as a whole and also with triceps skinfold thickness, W/H, percent trunk fat, and T/E (details not reported).

### Table 2. Hormones in overweight and normal-weight (control) adolescent girls

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Overweight Subjects</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log peak GH (GHRH-arginine test), ng/ml</td>
<td>1.55 ± 0.28</td>
<td>1.28 ± 0.33</td>
<td>0.03</td>
</tr>
<tr>
<td>Log peak baseline GH (GHRH-arginine test), ng/ml</td>
<td>1.51 ± 0.31</td>
<td>1.27 ± 0.34</td>
<td>0.06</td>
</tr>
<tr>
<td>Log GH AUC (GHRH-arginine test), ng·ml$^{-1}$·120 min$^{-1}$</td>
<td>7.82 ± 0.66</td>
<td>7.22 ± 0.81</td>
<td>0.04</td>
</tr>
<tr>
<td>Log mean serum GH frequent sampling, ng/ml</td>
<td>-0.03 ± 0.31</td>
<td>0.03 ± 0.33</td>
<td>NS</td>
</tr>
<tr>
<td>Serum IGF-I, ng/ml</td>
<td>623 ± 130</td>
<td>687 ± 168</td>
<td>NS</td>
</tr>
<tr>
<td>Log mean serum cortisol frequent sampling, μg/dl</td>
<td>0.85 ± 0.04</td>
<td>0.91 ± 0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Log 24-h UFC, μg/24 h</td>
<td>1.47 ± 0.17</td>
<td>1.61 ± 0.13</td>
<td>0.02</td>
</tr>
<tr>
<td>Log peak GH/mean cortisol</td>
<td>0.68 ± 0.32</td>
<td>0.30 ± 0.35</td>
<td>0.01</td>
</tr>
<tr>
<td>Log leptin, ng/ml</td>
<td>0.96 ± 0.20</td>
<td>1.59 ± 0.20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log adiponectin, ng/ml</td>
<td>0.97 ± 0.13</td>
<td>0.91 ± 0.03</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SD of 15 subjects in each group. GH, growth hormone; GHRH, GH-releasing hormone; IGF-I, insulin like growth factor I; UFC, urinary free cortisol.

Fig. 2. Growth hormone (GH)-releasing hormone (GHRH)-arginine stimulation test in adolescent overweight and normal-weight girls. A: GH levels at different points of the GHRH-arginine stimulation test were lower in adolescent overweight (black line) than in normal-weight (gray line) girls. Significances are from comparison of logarithmically converted data: *$P < 0.05$; **$P < 0.01$. B: log peak GH levels were lower in adolescent overweight (black bar) than in normal-weight (gray bar) girls. *$P < 0.05$. 

AJP-Endocrinol Metab • VOL 295 • AUGUST 2008 • www.ajpendo.org
Figure 3 shows the inverse associations of log peak GH with VAT in overweight girls and the group as a whole. In a regression model that included log peak GH, log mean cortisol, and BMI-SDS, in overweight girls, independent associations of BMI-SDS and log mean cortisol with SAT (accounting for 80.3% and 11.7% of the variability, respectively, \( P = 0.0001 \) and 0.02) were observed; log peak GH and BMI-SDS accounted for 78% and 9.5% of the variability of VAT values (\( P = 0.02 \) and 0.05), and log peak GH contributed to 34% of the variability of S-IMCL (\( P = 0.04 \)). Similar, but weaker, associations were observed for the group as a whole and are not reported.

Log leptin was strongly associated with SAT (\( r = 0.79, P = 0.0001 \)), VAT (\( r = 0.61, P = 0.02 \)), and S-IMCL (\( r = 0.62, P = 0.03 \)) in overweight girls, and strong associations were also observed for the group as a whole (not reported).

Associations of GH and cortisol with measures of insulin resistance. In overweight girls and the group as a whole, log peak GH was inversely related and log mean cortisol was positively related to measures of insulin resistance, including log fasting insulin/glucose, log CIR, and log HOMA-IR, and only associations with log HOMA-IR are reported (Table 3). Similarly, log peak GH was positively related and log mean cortisol was inversely related to QUICKI, a measure of insulin sensitivity, in overweight girls and in the group as a whole. Strongest associations were observed for log (peak GH-to-mean cortisol) ratio with insulin resistance measures, indicating possibly combined effects of these hormones on insulin resistance parameters. Log UFC, in contrast to log mean serum cortisol, was not associated with measures of insulin resistance. Interestingly, GH, IGF-I, and cortisol did not predict adiponectin levels in overweight girls or in the group as a whole.

In addition, given conflicting data in the literature, we also examined associations of insulin resistance (as assessed by HOMA-IR) and adiponectin with clinical, DXA, and MR measures of body composition. In overweight girls, percent trunk fat, T/E, W/H, and VAT (but not total fat, SAT, S-IMCL, or triceps skinfold thickness) were positively associated with log HOMA-IR (Table 4). For the group as a whole, all measures of body composition were positively associated with HOMA-IR. However, associations were stronger with central than with peripheral measures of adiposity. On regression modeling with VAT, log peak GH, and log mean cortisol entered into the model, log mean cortisol was the sole and independent variable associated with measures of HOMA-IR, contributing to 49% of its variability. Addition of S-IMCL to the regression model did not add to the variability explained for log HOMA-IR.

![Figure 3](http://ajpendo.physiology.org/)

**Fig. 3.** Relationship of log peak GH (GHRH-arginine test) with visceral adipose tissue in overweight girls and all girls. Log peak GH levels correlated strongly and inversely with visceral adipose tissue.
In overweight girls, log adiponectin correlated inversely with total fat mass \((r = -0.73, P = 0.003)\) and with SAT \((r = -0.65, P = 0.02)\). For the entire group, we observed inverse associations between log adiponectin and total fat, triceps skinfold thickness, SAT, and VAT \((r < -0.40, P < 0.05)\).

**Associations of GH and cortisol with lipid parameters.** In overweight girls, log peak GH correlated weakly with triglycerides \((r = -0.49, P = 0.09)\) and correlated more strongly with HDL \((r = 0.65, P = 0.02)\), and, similarly, IGF-I was inversely associated with triglycerides \((r = -0.55, P = 0.03)\) and positively associated with HDL \((r = 0.77, P = 0.0008)\). Log mean cortisol was positively associated with LDL and total cholesterol \((r \geq 0.60, P \leq 0.03)\) and was the single variable independently associated with lipids on regression modeling (with SAT, VAT, peak GH, and mean cortisol entered into the model), accounting for 49\%, 37\%, and 59\% of the variability of LDL, total cholesterol, and HDL, respectively. In the present study, correlations were not observed between lipids and body composition measures.

For the group as a whole, associations of lipids with hormones were similar: triglycerides were inversely associated with log peak GH \((r = -0.54, P = 0.003)\) and positively associated with log mean cortisol \((r = 0.41, P = 0.046)\). HDL was positively associated with log peak GH \((r = 0.56, P = 0.002)\). LDL and total cholesterol were positively associated with log mean cortisol \((r \geq 0.51, P = 0.01)\). In contrast to the overweight girls alone, in the combined group, triglycerides and LDL were positively associated and HDL was inversely associated with all measures of body composition except S-IMCL (data not reported). On regression modeling, log mean cortisol was independently associated with total and LDL cholesterol, accounting for 24\% and 50\% of the variability, respectively, whereas VAT was independently associated with triglycerides and HDL, accounting for 33\% and 55\% of the variability, respectively.

In addition, log leptin levels correlated positively with triglycerides \((r = 0.47, P = 0.009)\) and LDL \((r = 0.49, P = 0.006)\) and correlated inversely with HDL \((r = -0.56, P = 0.002)\) for the group as a whole, but not in overweight girls alone.

**DISCUSSION**

Our data indicate that lower peak GH and higher cortisol levels in overweight adolescents are independently associated with higher regional fat mass, measures of insulin resistance, and serum lipids. We are the first to report lower basal and peak GH levels with the GHRH-arginine stimulation test in overweight than in normal-weight adolescent girls, consistent with reported inverse associations of GH with low body weight (29). These data are also consistent with studies of GH stimulation testing in obese adults (10, 39). However, contrary to our expectations and other studies (20), overnight integrated GH secretion was not lower in overweight than in normal-weight girls. GH levels typically peak at Tanner stages 2 and 3 of puberty in girls, and to control for the somewhat earlier puberty reported in overweight than in normal-weight girls, we matched girls for bone age and also included similar numbers of pre- and postmenarchal girls in the two groups. Differences in pubertal maturity, therefore, cannot account for the differences in peak stimulatory capacity of GH or the lack of difference in overnight GH levels between the groups.

The discordance between results of the GHRH-arginine stimulation test and overnight frequent sampling may be a consequence of differences in what these tests assess. The GHRH-arginine test measures maximal secretory capacity of GH to pharmacological stimuli and is an established test for GH deficiency. In contrast, nighttime GH sampling measures physiological GH secretion but is not a good test of GH deficiency. It is possible that maximal secretory capacity of GH is decreased in overweight girls before physiological secretory capacity is affected. In fact, our subjects were certainly not as heavy as those in some other studies showing decreased overnight GH secretion (2, 20). In addition, nighttime GH secretion is always higher than daytime GH secretion, and it may be that assessment of GH secretion over 24 h would have shown a difference between the groups, with lower GH levels in overweight girls.

Mean IGF-I levels did not differ between overweight and normal-weight girls, consistent with another study in overweight adolescents (2). Within overweight girls, we found strong positive associations of IGF-I with log peak GH on the GHRH-arginine test and log mean GH from frequent sampling overnight. It is therefore possible that greater severity of overweight may be associated with lower IGF-I levels in adolescents in association with lower GH levels. In addition, IGF-I secretion is driven not only by GH status, but also by nutritional status, and differences attributable to low GH secretory capacity in overweight girls may not be manifest because of overoptimal nutritional status. Overnutrition should be associated with higher IGF-I levels, which may, by negative feedback, cause a decrease in GH secretion, which in turn may lower IGF-I levels. There may therefore be a negation of nutritional effects on IGF-I levels because of GH status, but these effects may also con-
tribute to a lack of difference in IGF-I levels between the groups.

Within overweight girls and for the group as a whole, there were inverse associations between GH concentrations and measures of body fat, consistent with similar reports in obese adults (25, 35) and with the greater truncal adiposity reported in GH-deficient children (38) and adults (8). One study in children related decreased GH secretion to higher trunk fat using DXA (37) but did not assess regional fat mass more specifically using MRI or MRS. It remains unclear whether lower GH concentrations in overweight conditions lead to increased trunk fat accumulation or whether greater truncal adiposity leads to decreased GH secretion. In our regression model, log peak GH was independently associated with VAT and S-IMCL and log mean cortisol with SAT. Because association studies cannot determine causation, studies of rhGH administration are necessary to determine whether, within overweight girls, rhGH administration will lead to a decrease in VAT and central adiposity measures. Certainly, rhGH administration in conditions of GH deficiency is associated with a decrease in trunk fat (8, 38), and rhGH administration in adults with visceral adiposity leads to a decrease in visceral fat (14, 33). GH levels were also inversely associated with measures of insulin resistance and with lipid levels on simple correlational analysis but were not independently associated with these measures on regression modeling. We observed no associations of GH with adiponectin.

As hypothesized, UFC (a measure of cortisol excess) was higher in overweight than in normal-weight girls. Mean serum cortisol concentrations (an integrated measure of cortisol secretion overnight) were also higher but did not reach statistical significance. Within overweight girls, log mean cortisol concentrations were inversely and independently associated with SAT, consistent with greater adiposity reported in conditions of cortisol excess, such as Cushing’s syndrome. Of importance, log mean cortisol levels were also independently related to measures of insulin resistance and lipids on the basis of our univariate and multiple regression models. In contrast, we found no associations of cortisol with adiponectin, which was associated inversely only with measures of body fat. Although similar associations have been reported in prepubertal children (3), there are no previous reports of associations of cortisol with insulin resistance and lipids in pubertal children. Given the decrease in insulin sensitivity at puberty and pubertal alterations in fat mass, these data are important from a physiological perspective. Of interest, the associations of cortisol with insulin resistance and lipid parameters in our study were independent of effects of body composition and GH levels.

Consistent with data reported by other investigators (20, 22), we found inverse associations of GH and IGF-I with leptin, and it remains unclear whether high leptin levels cause a decrease in peak GH secretion in overweight girls or whether lower GH concentrations are associated with increased fat mass and, therefore, higher leptin levels. In addition, in overweight girls, we observed strong associations of insulin resistance with VAT, trunk fat, and W/H (central measures of adiposity), rather than with S-IMCL or SAT (peripheral measures of adiposity), consistent with reports from Weiss et al. (43) but not reports from other investigators (44). Similarly, for the group as a whole, associations of central measures of adiposity with HOMA-IR were stronger than associations of peripheral measures.

We report, for the first time, decreased peak stimulatory capacity of GH in adolescent overweight girls compared with normal-weight girls as assessed using peak GH levels following the GHRH-arginine test and also report higher urinary cortisol levels in this population. We demonstrate that low peak GH and high overnight cortisol concentrations are strongly associated with measures of body composition, insulin resistance, and lipids. These data indicate a potential therapeutic role for rhGH therapy and measures to reduce cortisol levels in overweight adolescent girls.

ACKNOWLEDGMENTS

We thank the nurses, Bionutrition staff, and administrative staff of the GCRC for help with the study protocol. We are grateful to our subjects, without whom the study would not have been possible.

GRANTS

This work was supported in part by National Institutes of Health Grants M01-RR-01066, K23-RR-018851, and F32-DK-072816 and a grant from the Boston Obesity Nutrition Research Center.

REFERENCES


