Insulin-Like Growth Factor I and Growth Hormone (GH) Treatment in GH-Deficient Humans: Differential Effects on Protein, Glucose, Lipid, and Calcium Metabolism*

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ABSTRACT

We examined the effects of recombinant human (rh) insulin-like growth factor I (IGF-I) vs. rhGH in a variety of metabolic paths in a group of eight severely GH-deficient young adults using an array of contemporary tools. Protein, glucose, and calcium metabolism were studied using stable labeled tracer infusions of [1-13C]leucine, [6,6-2H]glucose, and 45Ca and 44Ca; substrate oxidation rates were assessed using indirect calorimetry; muscle strength was determined by isokinetic and isometric dynamometry of the anterior quadriceps, as well as growth factors, hormones, glucose, and lipid concentrations in plasma before and after 8 weeks of rhIGF-I (60 μg/kg, sc, twice daily), followed by 4 weeks of washout, then 8 weeks of rhGH (12.5 μg/kg/day, sc); the treatment order was randomized.

In the doses administered, rhIGF-I and rhGH both increased fat-free mass and decreased the percent fat mass, with a more robust decrease in the percent fat mass after rhGH; both were associated with an increase in whole body protein synthesis rates and a decrease in protein oxidation. Neither hormone affected insulinogenic or isometric measures of skeletal muscle strength. However, rhGH was more potent than rhIGF-I at increasing lipid oxidation rates and improving plasma lipid profiles. Both hormones increased hepatic glucose output, but rhGH treatment was also associated with decreased carbohydrate oxidation and increased glucose and insulin concentrations, indicating subtle insulin resistance. Neither hormone significantly affected bone calcium fluxes, supporting the concept that these hormones, by themselves, are not pivotal in bone calcium metabolism. In conclusion, rhIGF-I and rhGH share common effects on protein, muscle, and calcium metabolism, yet have divergent effects on lipid and carbohydrate metabolism in the GH-deficient state. These differences may allow for better selection of treatment modalities depending on the choice of desired effects in hypogonadism. (J Clin Endocrinol Metab 85: 1686–1694, 2000)

Received August 19, 1999. Revision received November 2, 1999. Accepted December 15, 1999.

* This work was supported by NIH Grant RO1-DK-51360 (to N.M.), the Nemours Research Programs (Jacksonville, FL), and the Mayo Clinic General Clinical Research Center (NIH Grant RR-00585).
observed. and treated them with rhIGF-I and rhGH for 8 weeks, each with a 4-week washout period in between. Marked differences in the metabolic effects of these peptides were observed.

Subjects and Methods

Study subjects

These studies were approved by the Nemours Children’s Clinic Clinical Research review committee and the Baptist Medical Center Institutional Review Board. Eight patients with clinical and biochemical evidence of GH deficiency were recruited for these studies after informed written consent was obtained. Their clinical characteristics are summarized in Table 1. Those with other pituitary hormone deficiencies were receiving replacement treatment during these studies. All but two subjects (no. 2 and 6) had childhood-onset GH deficiency. Those patients previously treated with GH had been off GH for at least 1.5 yr before these studies.

Experimental design

For 3 days before admission, subjects were encouraged to consume a weight maintenance diet consisting of approximately 30 Cal/kg and 1 g/kg protein/day; they were admitted to the Wolfson Children’s Hospital Clinical Research Center the afternoon before the first study. Assessment of body composition was obtained using skin fold calipers, bioelectrical impedance analysis, as well as dual emission x-ray absorptiometry (DEXA), using a tissue bar (Hologic, Inc., Waltham, MA). Isokinetic and isometric dynamometry of the anterior quadriceps were performed in our physical therapy department using a Biodex dynamometer (Biodex Corp., Shirley, NY). After a 10-min training session and 30 min of rest, maximum work and torque measures for isometric and isokinetic tests were performed. Isometric tests were performed with 5 contractions of 5 s each, with the knee placed at 45° of flexion, and 10 of rest between contractions. Isokinetic tests were performed for knee extension and flexion at 60°/s for 5 repetitions and at 180°/s for 21 repetitions as described previously (17).

Subjects were fed dinner at 1800 h and were given 0.3 mg/kg of a stable isotope of calcium (44Ca) orally mixed with milk or juice prepared at least 12 h before equilibration. A urine collection was begun after the oral Ca tracer and continued for the next 28 h. The patients were subsequently fasted except for water ad libitum until the completion of the studies at 1800 h the next day. The following morning (baseline study), at 0600 h, two iv needles were placed in each antecubital vein. One was kept heated for arterialized blood sampling (18). At 0800 h (time zero), three stable isotope tracers were given. One, a primed, dose constant infusion of [6,6-2H2]glucose (33 μmol/kg; 0.33 μmol/kg/min) was begun and continued uninterrupted for the next 240 min. Concomitantly, a primed infusion of [6,6,44Ca]-leucine (4.5 μmol/kg; 0.07 μmol/kg-min) was begun and continued uninterrupted for the next 240 min. Indirect calorimetry was performed three times during the 4 h of isotope infusion using a mouthpiece and a CPX max indirect calorimeter (Medical Graphics, St. Paul, MN). After the isotope infusions were completed, the patients were fed lunch, and one iv line was discontinued. Subjects were subsequently free to move around, and at 1600 h another blood sample was obtained for determination of Ca enrichment. Subjects were then sent home to complete the urine collection. For the next 5 days, twice daily urine samples were obtained for determination of the Ca isotopic enrichments.

After the baseline study and all urine collections were completed, patients were started on rhIGF-I at 60 μg/kg, sc, twice daily. Subjects were instructed to monitor their blood glucose concentrations using home glucose-monitoring equipment for the first week after initiation of rhIGF-I therapy and any other time there were any symptoms of hypoglycemia. They were also instructed to take the rhIGF-I injection with their meals to avoid hypoglycemia. Blood was withdrawn 4 weeks after the initiation of treatment for determination of hormone concentrations and safety laboratories. Eight weeks from the baseline study an identical study was performed. The night before the second study, starting at 2000 h, the second dose of rhIGF-I was substituted for a continuous sc infusion of the peptide at 10 μg/kg-1 h, which was continued uninterrupted for the next 17 h until completion of the studies the following morning. This was done to prevent hypoglycemia during the administration of rhIGF-I while the patients were fasting, while maintaining plasma IGF-I concentrations constant. We have successfully used this strategy in similar experiments (4, 5, 19). Afterward, rhIGF-I treatment was discontinued, and a washout period of 4 weeks was observed without any treatment. Blood samples were again withdrawn at the end of the washout period. rhGH was started as a single sc injection of 12.5 μg/kg at bedtime and was continued for another 8 weeks when the studies were repeated a third time. The treatment order was randomized: D1, baseline study; D2, rhIGF-I for 8 weeks; followed by 4-week washout; and then rhGH was administered for 8 weeks, followed by D3.

Blood and breath samples

The isotopic enrichments of a-ketoisocaproic acid (13C labeled), and 2H2-glucose were measured at ~20, 160, 180, 200, 220, and 240 min. The Ca isotopic enrichments were measured at 0, 5, 10, 15, 20, 30, 40, 60, 120, 180, 240, and 480 min. Plasma IGF-I, IGF-binding protein-1 (IGFBP-1), IGFBP-2, IGFBP-3, insulin, and glucose concentrations were measured three times during the 240 min of tracer infusions. Serum GH concentrations were measured at 10-min intervals for the 4 h of the studies. Serum lipids were also measured while fasting on each study day. Breath samples were obtained for the measurement of expired labeled CO2 at ~20, ~10, ~5, 160, 180, 200, and 220 min. A small aliquot of the urine collected during the 4 h of the morning study was used for determination of urea nitrogen concentration.

Assays

Plasma enrichments of 13C-leuko-ketoisocaproic acid and 2H2-glucose were determined at the Nemours metabolic core laboratory by mass chromatography mass spectrometry as previously described (20, 21). 13CO2 was measured by isotope ratio mass spectrometer as described previously (22). Urinary Ca was determined by flame atomic absorption spectrophotometry at the laboratory of Dr. O’Brien. A dual filament

| TABLE 1. Clinical and biochemical characteristics of the study subjects |
|-------------------------|---------|-----------------|-----------------|-----------------|------------------|
| Patient no. | Age (yr) | Sex | Diagnosis | Peak GH (ng/mL) |
| 1 | 18.9 | F | Septo optic dysplasia | 0.50 |
| 2 | 33.2 | M | Astrocytoma | 0.30 |
| 3 | 21.3 | F | Craniopharyngioma | 0.06 |
| 4 | 19.6 | M | Optic glioma | 1.10 |
| 5 | 23.0 | M | Idiopathic | 1.46 |
| 6 | 29.6 | M | Idiopathic | 0.16 |
| 7 | 15.5 | M | Idiopathic | 3.00 |
| 8 | 27.0 | M | Hypoplastic anterior pituitary | 0.21 |
| Mean ± SEM | 23.5 ± 2.1 | | | 0.85 ± 0.35 |
thermal ionization quadrupole mass spectrometer (Model THQ, Finnigan MAT, Bremen, Germany) was used to measure the Ca isotopic enrichments as previously described (23). All insulin and lipid concentrations were determined at the immunochemical core laboratory at the Mayo Clinic General Clinical Research Center (Rochester, MN) using commercial kits. IGF-I, IGFBP-1, IGFBP-2, and IGFBP-3 concentrations were measured by radioimmunometric assays at Endocrine Sciences, Inc. (Calabassas Hills, CA), and insulin concentrations were determined by chemiluminescence assay. Serum GH concentrations were measured by a highly sensitive chemiluminescence assay at the University of Virginia Clinical Research Center core laboratory (Charlottesville, VA). Plasma glucose concentrations were measured with a glucose oxidase method using a glucose analyzer (Beckman Coulter, Inc., Palo Alto, CA) at the bedside. Serum lipids [cholesterol, triglycerides, and high and low density (LDL) lipoproteins] concentrations were measured using high performance liquid chromatography methods. Urea nitrogen was measured using a Kodak Ektakem urease method (Eastman Kodak Co., Rochester, NY).

Calculations

The reciprocal pool model was used to estimate rates of whole body protein turnover at steady state as previously described (24). The rate of appearance (Ra) of glucose, a measure of hepatic glucose output, was calculated as: 

$$Ra = \frac{Ei}{Ep} - 1$$

where Ei is the isotopic enrichment of the infusion, Ep is the enrichment of glucose in plasma, and F is the infusion rate.

For the Ca kinetic analysis, the fractional Ca absorption (a) was calculated from the ratio of the cumulative excretion of the oral tracer ($^{44}$Ca) in urine divided by the cumulative excretion of the iv tracer ($^{42}$Ca) as previously described (25, 26).

True Ca absorption was calculated as: 

$$Va = \frac{Vi}{a}$$

where Vi is the dietary Ca intake. Ca kinetic analysis was performed by measuring the isotopic enrichments of the Ca tracers in blood and urine over time using the three-pool multicompartmental model and the simulation analysis and modeling program, SAAM, as previously described (27, 28). Other absorption and kinetic terms used are: Vu, urinary Ca excretion; Vf, endogenous fecal Ca excretion (estimated as 1.5 mg/kg-day) (29); Vo−, the rate of bone Ca deposition; and Vo+ rate of bone Ca resorption.

Substrate oxidation rates for protein, glucose, lipid, and resting energy expenditure were calculated using the rate of gas exchange (VO2 and VCO2) from the indirect calorimetry as previously described (30).

Fat free mass (FFM) and percent fat mass (FM) were measured using DEXA and the tissue bar as well as by the sum of skin folds as described previously (31).

Isotopes and drugs

$\text{L-}[^{1-13}\text{C}])$Leucine (99% enriched; Cambridge Isotopes, Andover, MA), $[6,6-2\text{H}_2]$glucose (99.7% enriched, MSD Isotopes, St. Louis, MO), and $^{42}$Ca/$^{44}$Ca (93.5% and 96% enriched, respectively; Trace Sciences International, Richmond Hill, Canada) were determined to be sterile and pyrogen free and were mixed with 0.9% nonbacteriostatic saline. rhIGF-I (Nutropin; 10 mg/mL) and rhGH (Nutropin; 10 mg/mL) were provided by Genentech, Inc. (South San Francisco, CA).

Statistical analysis

Results are expressed as the mean ± se. Paired Student’s t test was used to estimate differences between baseline studies and rhIGF-I and rhGH treatments for all parameters tested. Wilcoxon signed ranks test was used for those parameters with results not normally distributed. Significance was established at $P < 0.05$.

Results

There was no apparent difference in the trend of any of the parameters measured depending on the treatment order of rhIGF-I or rhGH; hence, data were grouped for analysis according to the hormone received. Figure 1 shows the plasma IGF-I concentrations in eight GH-deficient patients studied at baseline and 8 weeks after rhIGF-I, after a 4-week washout, and after 8 weeks of rhGH treatment. There was no difference in IGF-I concentrations between baseline values and those obtained after 4 weeks of washout.

Plasma IGF-I concentrations returned to baseline levels in the study subjects after 4 weeks of discontinuation of hormone treatment.

Body composition and muscle strength (Table 2)

There was a modest increase in weight after rhIGF-I treatment, but not after rhGH. There were comparable trends in body composition using either DEXA or sum of skin folds; hence, data are shown for DEXA only. Body composition, however, changed comparably after either hormone, with a 3.1-kg (6%) increase in FFM after rhIGF-I and a 3.6-kg (6.8%) increase after rhGH ($P < 0.01$ for both) and decreases in %FM of 1.2% and 3% after rhIGF-I and rhGH, respectively. The decrease in %FM was greater after rhGH than after rhIGF-I ($P = 0.02$ between the two hormone treatments). There were no detectable changes in isometric or isokinetic measures of muscle strength of the leg extensors or leg flexors (data for the latter not shown).

Protein kinetics (Table 3)

There were no changes in the Ra of leucine, a measure of whole body proteinolysis, after rhIGF-I; yet there was a clear trend toward higher protein turnover after rhGH administration ($P = 0.06$). Protein oxidative rates decreased comparably with both hormones (approximately $-27$–$-29\%$) with increases in nonoxidative leucine disposal, a measure of whole body protein synthesis, after the administration of both hormones; this was more pronounced after rhGH.

Substrate oxidation and energy expenditure rates

Clear differences in the metabolic effects of these hormones on intermediate metabolism in the GHD state were observed. Carbohydrate oxidation rates were unaltered after rhIGF-I treatment, whereas they decreased after rhGH [baseline, 18.2 ± 3.7 Cal/FFM-day; rhIGF-I, 15.3 ± 4.1 ($P = NS$);
Table 2. Changes in body composition (by DEXA) and muscle strength [by isokinetic (IK) and isometric (IM) dynamometry of the leg extensors] in GHD subjects at baseline and after treatment with rhIGF-I and rhGH for 8 weeks each

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>rhIGF-I</th>
<th>rhGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body composition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>81.3 ± 7.2</td>
<td>83.8 ± 7.4</td>
<td>82.9 ± 7.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.2 ± 2.2</td>
<td>29.0 ± 2.1</td>
<td>28.7 ± 2.2</td>
</tr>
<tr>
<td>FFM (kg)</td>
<td>51.8 ± 5.4</td>
<td>54.9 ± 5.7</td>
<td>55.4 ± 6.2</td>
</tr>
<tr>
<td>% FM</td>
<td>34.7 ± 4.1</td>
<td>33.5 ± 4.0</td>
<td>31.7 ± 4.5</td>
</tr>
<tr>
<td>Muscle strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IM ext (Nm)</td>
<td>127.6 ± 17.3</td>
<td>139.6 ± 21.0</td>
<td>132.6 ± 22.7</td>
</tr>
<tr>
<td>IK ext 60 °/s (Nm)</td>
<td>152.7 ± 27.4</td>
<td>151.4 ± 24.0</td>
<td>154.2 ± 27.4</td>
</tr>
<tr>
<td>IK ext 180 °/s (Nm)</td>
<td>116.4 ± 17.0</td>
<td>111.6 ± 13.3</td>
<td>118.4 ± 17.9</td>
</tr>
</tbody>
</table>

Data from the rhIGF-I and rhGH were compared against baseline.

a P < 0.05 vs. baseline.
b P ≤ 0.01 vs. baseline.
c P ≤ 0.001 vs. baseline.

d P = 0.06 vs. baseline.

Table 3. Protein kinetic data (micromoles per kg/min) in GHD subjects

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>rhIGF-I</th>
<th>rhGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucine Ra</td>
<td>1.49 ± 0.11</td>
<td>1.57 ± 0.13</td>
<td>1.86 ± 0.13</td>
</tr>
<tr>
<td>Leucine oxidation</td>
<td>0.26 ± 0.03</td>
<td>0.19 ± 0.02</td>
<td>0.19 ± 0.02</td>
</tr>
<tr>
<td>NOLD</td>
<td>1.23 ± 0.10</td>
<td>1.38 ± 0.12</td>
<td>1.68 ± 0.13</td>
</tr>
</tbody>
</table>

Ra measures proteolysis, NOLD (nonoxidative leucine disposal) measures whole body protein synthesis rates.
a P = 0.06 vs. baseline.
b P ≤ 0.001 vs. baseline.
c P = 0.02 vs. baseline.

Discussion

The effects of rhIGF-I were directly compared with those of rhGH in a wide array of metabolic pathways in young adults with profound GH deficiency treated with these hormones for 8 weeks each. There were significant similarities in the metabolic effects of these peptides on body composition and muscle strength, protein, and calcium metabolism for e.g., yet there were marked differences on lipid and carbohydrate metabolism effects, as measured with the present tools of study, again supportive of the concept that IGF-I mediates only some of the metabolic actions of GH in vivo.

Body composition and protein metabolism

Body composition, as measured by DEXA, was comparably affected after rhIGF-I and rhGH treatment, with measurable increases in FFM and decreased %FM even after 8 weeks of continuous therapy. This strongly suggests that long term rhIGF-I treatment may have beneficial effects comparable to those of rhGH on body composition in GH-deficient subjects, particularly as it pertains to FFM accumulation. There appears to be a more robust decline in %FM after rhGH than after rhIGF-I. Even though DEXA cannot compartmentalize if these changes were due solely to changes in lean soft tissue vs. water, the changes in FFM were accompanied by a 20% increase in the total rate of whole body protein synthesis, as measured by the leucine tracer studies, indicating that both hormones affect large body protein pools. These results are similar to those ob-


**TABLE 4.** Glucose rate of appearance (Ra) and insulin and glucose concentrations in GHD patients during rhIGF-I/rhGH treatment

<table>
<thead>
<tr>
<th>Glucose Ra (mg/kg-min)</th>
<th>Baseline</th>
<th>rhIGF-I</th>
<th>rhGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.45 ± 0.09</td>
<td>1.94 ± 0.24a</td>
<td>1.78 ± 0.10a</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/100 mL)</td>
<td>86 ± 3</td>
<td>30 ± 4</td>
<td>94 ± 1a</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>9.2 ± 3.0</td>
<td>3.6 ± 1.5a</td>
<td>14.2 ± 3.5b</td>
</tr>
</tbody>
</table>

a P < 0.001 vs. baseline.

b P < 0.001 vs. baseline.

**TABLE 5.** Absorption and kinetics of Ca using stable tracer data in GHD subjects

| Vi | 1238 ± 275 | 1286 ± 241 | 1179 ± 237 |
| Va | 492 ± 135  | 469 ± 81   | 499 ± 89   |
| Vu | 110 ± 25   | 253 ± 39a  | 167 ± 39   |
| Vo | 1068 ± 185 | 1353 ± 196 | 1274 ± 45  |
| vo | 908 ± 218  | 1279 ± 219 | 1056 ± 140 |

All units are milligrams per day except α, which has no units.
Vi, Dietary Ca intake; α, fractional Ca absorption; Va, total Ca absorption; Vu, urinary Ca excretion; Vo”, bone Ca deposition; Vo”, bone Ca resorption.

a P < 0.005.

**Muscle strength**

Skeletal muscle has few GH receptors, yet type I IGF-I receptors are rather ubiquitous in skeletal tissue, suggesting that IGF-I is the main mediator of the actions of GH in myocytes (37). In the present studies we raised plasma IGF-I concentrations to levels observed in the midst of puberty, particularly after rhIGF-I, yet there were no detectable changes in skeletal muscle strength in these individuals, as neither isokinetic nor isometric measures of strength were altered by rhGH or rhIGF-I treatment. These results parallel those observed in elderly subjects treated with rhGH (38) and in GH-deficient subjects treated with rhGH for up to 6 months where similar measures of muscle strength were used (39, 40). Even though the length of treatment (8 weeks each) might arguably not be enough to detect an effect on muscle strength, in similar experiments conducted by us in healthy subjects rendered intentionally hypogonadal pharmacologically, we detected significant decreases in muscle strength after only 10 weeks of sustained hypogonadism (17). The latter suggests that sex steroids may play a more pivotal role than the GH/IGF-I axis in enhancing skeletal muscle strength in humans. There are, to our knowledge, no published results to date on similar trials using rhIGF-I examining muscle strength; however, the present results suggest that neither rhIGF-I nor rhGH per se affects muscle strength in the absence of significant exercise training. The use of these...
agents as ergogenic agents thus appears unsubstantiated by the available data.

Calcium flux

Calcium tracer studies have been extensively used in a variety of experimental situations in humans and offer the advantage of allowing the assessment of bone calcium fluxes in a noninvasive way (23–26, 29, 41, 42). Using these tools, measures of calcium absorption (Va), bone calcium deposition (Vo⁺), and bone calcium resorption (Vo⁻) did not change after rhIGF-I or after rhGH therapy, suggesting that these peptides do not significantly affect bone calcium metabolism in the short term. Previous studies of the effects of GH on bone have yielded somewhat conflicting results, some showing no effect of GH on bone mass after 6 months of therapy, and others showing an actual decrease in bone mineral density after treatment (40). Histomorphometric analysis of transiliac bone biopsies in GH-deficient patients treated with rhGH for 1 yr showed that only cortical thickness, not trabecular bone, increases after GH therapy (43). It is now clear that GH increases bone formation in GH-deficient states only after prolonged treatment (>18 months) (9). IGF-I, on the other hand, has not change after rhIGF-I or after rhGH therapy, suggesting that these peptides do not significantly affect bone calcium absorption and bone calcium deposition in the short term in the GH-deficient state. The observed increase in urinary calcium excretion with rhIGF-I is probably related to the increased renal filtration typically observed after rhIGF-I treatment (47). The physiological relevance of this observation would require further study, but chronic rhIGF-I treatment may need careful assessment of calcium balance.

Substrate oxidation rates and energy expenditure

rhIGF-I and rhGH had divergent effects on other pathways of intermediate metabolism, as measured by gas exchange and indirect calorimetry. Carbohydrate oxidation rates were decreased after rhGH, but not rhIGF-I, administration in these subjects. This is probably secondary to the relative insulin resistance caused by rhGH therapy, whereas the insulin-like effect of rhIGF-I compensated for the suppressed insulin production during rhIGF-I treatment. Hepatic glucose production (glucose Ra), on the other hand, was increased after both hormones, indicating that the hepatic sensitivity to insulin was diminished during both treatments, albeit possibly by different mechanisms: during rhGH by increased insulin resistance, and during rhIGF-I by diminished portal insulin secretion. This increase in hepatic glucose production after both rhGH and rhIGF-I is comparable to that observed after short term (7-day) rhIGF-I treatment in healthy volunteers reported by us previously (19). However, the present results contrast with those observed in GH-deficient subjects treated with both hormones reported previously (13), in whom there was no detectable effect of either hormone on carbohydrate oxidation when measured by the same tools, and hepatic glucose output was increased only after rhGH. The latter difference mostly likely relates to the length of treatment, as the present model of treatment for 8 weeks each was substantially longer than the 7 days previously reported, allowing the changes in insulin sensitivity to become apparent. rhIGF-I has been clearly shown to increase insulin sensitivity in healthy subjects (48). These results sug-

### TABLE 6. Hormones, growth factors, and plasma lipid concentrations in GHD patients

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Baseline</th>
<th>rhIGF-I</th>
<th>rhGH</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (ng/mL)</td>
<td>121 ± 38</td>
<td>742 ± 127&lt;sup&gt;a&lt;/sup&gt;</td>
<td>386 ± 58&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IGFBP-1 (ng/mL)</td>
<td>21 ± 9</td>
<td>30 ± 11</td>
<td>17 ± 12</td>
</tr>
<tr>
<td>IGFBP-2 (ng/mL)</td>
<td>340 ± 78</td>
<td>813 ± 160&lt;sup&gt;a&lt;/sup&gt;</td>
<td>241 ± 48</td>
</tr>
<tr>
<td>IGFBP-3 (ng/mL)</td>
<td>2.23 ± 0.33</td>
<td>2.30 ± 0.42</td>
<td>3.45 ± 0.34&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IGF-II (ng/mL)</td>
<td>408 ± 88</td>
<td>106 ± 15&lt;sup&gt;b&lt;/sup&gt;</td>
<td>411 ± 39</td>
</tr>
<tr>
<td>Mean GH (ng/mL)</td>
<td>0.47 ± 0.18</td>
<td>0.24 ± 0.15</td>
<td>1.61 ± 0.55&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peak GH (ng/mL)</td>
<td>1.00 ± 0.49</td>
<td>0.14 ± 0.07</td>
<td>2.62 ± 0.53&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total cholesterol (mg/100 mL)</td>
<td>177 ± 14</td>
<td>188 ± 21</td>
<td>175 ± 11</td>
</tr>
<tr>
<td>LDL (mg/100 mL)</td>
<td>112 ± 13</td>
<td>135 ± 21</td>
<td>89 ± 10&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>HDL (mg/100 mL)</td>
<td>39 ± 4</td>
<td>37 ± 4</td>
<td>39 ± 3</td>
</tr>
<tr>
<td>Triglycerides (mg/100 mL)</td>
<td>126 ± 19</td>
<td>131 ± 27</td>
<td>182 ± 33&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> P < 0.002.
<sup>b</sup> P < 0.01.
<sup>c</sup> P < 0.03.
<sup>d</sup> P < 0.05.
gest that rhIGF-I may be advantageous over rhGH as a replacement therapy in GH-deficient subjects who also have carbohydrate intolerance. This observation would require further study.

Protein oxidation rates decreased comparably in both treatment arms, similar to the results observed in the leucine tracer studies. This suggests that both hormones affect protein metabolism comparably.

Lipid oxidation rates were increased only after the administration of rhGH, not rhIGF-I. This contrasts with the report by Hussain et al. (19) in GH-deficient subjects treated with both hormones, in whom lipid oxidation rates increased significantly after both. Again, the significantly more prolonged treatment scheme in the present studies probably explains these differences, as there are no type I IGF-I receptors in adipocytes (8); hence, any short term increase in lipid oxidation observed after 7 days of treatment was attributed to the decrease in insulin production caused by rhGH with the consequent increase in lipolysis and presumably lipid oxidation (19). In the present treatment paradigm, rhGH had a more pronounced effect than rhIGF-I on lipid oxidation and a modest, but significantly greater, decrease in %FM. The latter suggests that rhIGF-I may affect body composition differently than rhGH by promoting protein/muscle accretion and causing a nutrient shift, from adipose to lean body tissue, whereas GH acts in both adipocytes and whole body protein directly. Resting energy expenditure was unchanged after long term treatment with either hormone, underscoring the shift in nutrient utilization with preservation of total energy used.

The difference between the effects of rhIGF-I reported here and those observed in normal volunteers might also be due to the differences in the pharmacokinetics of IGF-I in the GH-deficient state. We recently reported our data from pharmacokinetic studies in GH-deficient patients treated with rhIGF-I, several of whom also participated in the present study, and showed that GH deficiency is associated with normal absorption and distribution of IGF-I, yet faster elimination kinetics than normal subjects (49); hence, one would expect an even faster clearance of IGF-I in GH-deficient subjects after discontinuation of treatment.

Hormones, growth factors, and plasma lipids

rhIGF-I and rhGH had divergent effects on the circulating concentrations of IGFBPs and GH, as previously observed (50); after rhIGF-I treatment, IGF-I concentrations were more increased than after rhGH as well as IGFBP-2 administration, whereas IGF-II concentrations were decreased only after rhIGF-I treatment, and IGFBP-3 levels were increased only after rhGH treatment. Interestingly, only prolonged rhGH, not rhIGF-I, had a significant lowering effect on the LDL concentration in these GH-deficient subjects.

We believe the washout period to be adequate to allow the effects of the two hormones to be detected. Even though the baseline study was not repeated before the initiation of the second hormone cycle, plasma IGF-I concentrations were measured and had clearly returned to baseline in the study subjects after 4 weeks of washout. Previously published studies assessing the effects of both of these hormones have used similar or shorter washout periods. Kupfer et al. (12), when studying healthy, GH-sufficient, calorically deprived volunteers, treated these subjects with either rhIGF-I alone or rhGH and rhIGF-I combined in random order with a 3-week washout in between and observed enhancement of the combination treatment on nitrogen balance studies. Moreover, Hussain et al. (13) evaluated intermediate metabolism in GH-deficient adults using a paradigm without any washouts, i.e., 7 days of observation, followed by 7 days of daily rhIGF-I, then 7 days of rhGH and 7 days of combined treatment. These investigators found divergent effects on lipid and glucose metabolism produced by the two treatment modalities. Also, Lucidi et al. (36), while investigating the relative dose response for rhGH in GH-deficient adults, used a paradigm of 1 week of treatment, 2–3 weeks of washout, and then another dose of rhGH. Differential effects of the two doses on protein metabolism were observed. In addition, Chapman et. al. (51) examined the temporal relation between discontinuation of rhIGF-I treatment and resumption of normal GH production in normal volunteers and found a rebound in GH production within 5–7 days after discontinuation. We have studied GH-deficient subjects, who show a marked decrease in the GH-dependent proteins, IGFBP-3 and acid-labile subunit during rhIGF-I administration and have shown normal absorption and distribution of IGF-I, yet faster elimination kinetics than normal subjects (49); hence, one would expect an even faster clearance of IGF-I in GH-deficient subjects after discontinuation of treatment.

If the metabolic effects observed after both hormones had been in parallel, then there could be legitimate concern about the adequacy of the washout period, but in the present work there were marked differences in specific metabolic paths after 8 weeks of each hormone, making the findings perhaps more compelling. There were clear differences in carbohydrate metabolism. There were no detectable effects on carbohydrate oxidation after rhIGF-I, yet a significant decrease after rhGH. Lipid oxidation did not change after rhIGF-I, yet it increased after rhGH. Insulin concentrations decreased after rhGH, yet they increased after rhGH. IGFBP-2 increased only after rhGH-I, not after rhGH. IGFBP-3 increased only after rhGH-I. LDL cholesterol decreased only after rhGH and not after rhIGF-I treatment. Taken in aggregate, the observed dichotomy of effects of both hormones is probably the result of the specific hormone treatment and not due to the carryover effect of the previous hormone administered.

Summary and conclusions

A direct comparison of the metabolic effects of IGF-I and GH in GH-deficient subjects shows that both hormones, in the doses administered, decrease the %FM and increase FFM; however, rhGH had a more potent effect in decreasing adiposity. Both are associated with an increase in whole body protein synthesis rates and a decrease in protein oxidation. Neither hormone
affected isokinetic or isometric measures of skeletal muscle strength. However, rhGH was more potent than rhIGF-I at increasing lipid oxidation rates and improving plasma lipid profiles. Both hormones increased hepatic glucose output, but rhGH treatment was also associated with decreased carbohydrate oxidation and increased glucose and insulin concentrations, indicating subtle insulin resistance. Neither hormone significantly affected bone calcium fluxes, supporting the concept that these hormones by themselves are not pivotal in bone calcium metabolism. In conclusion, rhIGF-I and rhGH share common effects on protein, muscle, and calcium metabolism, yet have divergent effects on lipid and carbohydrate metabolism in the GH-deficient state. These differences may allow for better selection of treatment modalities depending on the choice of desired effects in hypopituitarism.

Acknowledgments

We are grateful to Burnese Rutledge and the expert nursing staff of the Wolfson Children’s Hospital Clinical Research Center for their dedicated care of our patients, Brenda Sager and the Nemours Biochemical Core Laboratory for the metabolic laboratory analysis, to Paul M. Marthas, Jr., at Genentech, Inc., for supplying us with study drugs, to Gigi Bauer and Dr. Johannes D. Veldhuis at the General Clinical Research Center core laboratory at the University of Virginia for the measurement of the serum GH concentrations, and to Darlene Lucas and Dr. George Klee at the Mayo Clinic immunochemical core laboratory for the measurement of the immunoassays.

References

41. Mauzus N, Vieira NE, Yergey AL. 1997 Estrogen therapy enhances calcium


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Erratum

In the article “Normocortisolemic Cushing’s syndrome initially presenting with increased glucocorticoid receptor numbers” by Ron S. Newfield, George Kalaitzoglou, Teresa Licholai, David Chilton, Javed Ashraf, E. Brad Thompson, and Maria I. New (The Journal of Clinical Endocrinology & Metabolism 85:14–21), the authors regret that acknowledgement of the extensive editorial assistance of Laurie Vandermolen was inadvertently omitted. The authors wish to express their appreciation for her help in the publication of this manuscript.