Recombinant Human Insulin-Like Growth Factor I Has Significant Anabolic Effects in Adults with Growth Hormone Receptor Deficiency: Studies on Protein, Glucose, and Lipid Metabolism*

NELLY MAURAS, VICTOR MARTINEZ, ANNIE RINI, AND JAIME GUEVARA-AGUIRRE

Division of Endocrinology, Nemours Children’s Clinic and Research Programs (N.M., A.R.), Jacksonville, Florida 32207; and the Instituto de Endocrinologia y Reproduccion (V.M., J.G.A.), Quito, Ecuador

ABSTRACT

The physiological effects of insulin-like growth factor I (IGF-I) on intermediate metabolism of substrates have been extensively studied in a variety of experimental situations in man, and its effects on linear growth of children with GH receptor mutations have proven beneficial. However, there is a paucity of data on the metabolic effects of IGF-I as replacement therapy in adults with GH receptor deficiency (Laron’s syndrome). We designed these studies to investigate the in vivo effects of 8 weeks of therapy with recombinant human IGF-I (rhIGF-I) in a unique group of 10 adult subjects with profound IGF-I deficiency due to a mutation in the GH receptor gene (mean ± SEM age, 29.2 ± 2.0 yr; 4 males and 6 females). At baseline, patients had infusions of stable tracers, including L-[13C]leucine, [2H2]glucose, and d3-5-glycerol, as well as indirect calorimetry, assessment of body composition (dual energy x-ray absorptiometry), and measurements of growth factor concentrations. Patients were then discharged to receive twice daily rhIGF-I (60 μg/kg, sc) for the next 8 weeks when the studies were repeated identically. Plasma IGF-I concentrations increased during rhIGF-I treatment from 9.3 ± 1.5 μg/L to 153 ± 23 (P = 0.0001). There was no change in weight during these studies, but a significant change in body composition was observed, with a decrease in percent fat mass (P = 0.003) and an increase in lean body mass (P = 0.001). These were accompanied by increased rates of protein turnover, decreased protein oxidation, and increased rates of whole body protein synthesis, as measured by leucine tracer methods (P < 0.01). These results are similar to those observed in GH-deficient subjects treated with GH. All measures of lipolytic activity and fat oxidation increased during treatment, with an 18% increase in the glycerol turnover rate (P = 0.04), an increase in free fatty acid and β-hydroxybutyrate concentrations, and a significant increase in fat oxidation, as measured by indirect calorimetry (P = 0.04). There were significant decreases in insulin concentrations (P = 0.01) and a reciprocal increase in glucose production rates (P = 0.04) during rhIGF-I, yet plasma glucose concentrations remained constant, suggestive of a significant insulin-like action of this peptide. RhIGF-I was well tolerated by all patients.

In conclusion, 8 weeks of treatment with rhIGF-I had significant positive effects on body composition and measures of intermediate metabolism independent of GH. These results suggest that, similar to GH treatment of adults with GH deficiency, rhIGF-I may be beneficial as long term replacement therapy for the adult patient with Laron’s syndrome. (J Clin Endocrinol Metab 85: 3036–3042, 2000)
growth in children with GH insensitivity (Laron’s syndrome) (2, 3). This condition manifests as profound IGF-I deficiency despite normal or high circulating GH concentrations due to a variety of mutations in the GH receptor gene (12–14). These patients’ physical, biochemical, and linear growth responses to rhIGF-I have been extensively characterized previously both in short term metabolic studies and in long term studies assessing linear growth (2, 3, 15–19). The metabolic effects of GH in the adult with GH deficiency (GHD), the increase in lean body mass, the decrease in adiposity, and the positive cardiovascular/lipid effects, are substantial and have led to the common use of GH in adults with GHD in most western countries (20, 21). Even though the benefit of rhIGF-I treatment promoting linear growth in children with homozygous forms of GH receptor deficiency (GHRD) has been clearly established, the long term use of this peptide for purposes other than linear growth has been less well characterized in the adult (22). We designed these studies to assess the effects of rhIGF-I on protein, glucose, and lipid metabolism and on body composition in a unique population of adult subjects with a homozygous mutation in the GH receptor gene resulting in Laron’s syndrome. Contemporary, stable tracer methodologies were used to study intermediate metabolism before and after more prolonged (8-week) administration of rhIGF-I.

### Subjects and Methods

#### Study subjects

These studies were approved by the clinical research review committee at the Nemours Children’s Clinic, the General Clinical Research Center (CRC) advisory committee at the Mayo Clinic (Rochester, MN), the institutional review board at Baptist Medical Center/Wolson Children’s Hospital (Jacksonville, FL), and the institutional review board at the Institute for Endocrinology and Reproduction (Quito, Ecuador). Subjects were recruited after informed written consent was obtained verbally and in writing in Spanish, the subjects’ native language. A group of 10 adult subjects was recruited by Dr. Guevara-Aguirre in Ecuador, all of whom had been previously identified to be homozygous for the alternative splice site mutation of codon 6 of the GH receptor gene and profound short stature. The genetic, biochemical, and physical characteristics of this patient population have been extensively studied previously (12, 13, 17, 19). Subjects were all in good health, were taking no chronic medications, and had not received any rhIGF-I for at least 3 yr before these studies. Their clinical characteristics are summarized in Table 1.

#### Study design

Subjects traveled in two groups of five with their physicians from Quito to Jacksonville twice over the 10 weeks of these experiments. A full physical exam was performed, and routine blood chemistries and cell counts were made upon arrival at our research center. For 3 days before admission to the Wolfson Children’s Hospital CRC they consumed a weight maintenance diet based upon the dietary histories obtained by the research dietitian consisting of about 30 Cal/kg and 1 g/kg protein-day.

The afternoon before the first study (D1) the subjects were admitted to the Wolfson Children’s Hospital CRC. Assessment of body composition was obtained using skinfold calipers, bioelectrical impedance analysis, as well as dual emission x-ray absorptiometry (DEXA), using a tissue bar (Hologic 2000, Hologic, Inc., Waltham, MA). Dinner was served at 1800 h; subsequently, the patients were fasted except for water ad libitum until the completion of the studies at 1300 h the next day. The next morning (baseline study) at 0800 h, two antecubital veins were cannulated after numbing the skin with an anesthetic cream (EMLA, AstraZeneca, Wilmington, DE). One cannula was kept heated for arterialized blood sampling (23). At 0800 h (time zero), three stable isotope tracers were given. One, a primed, dose constant infusion of [1-13C]leucine (4.5 μmol/kg; 0.07 μmol/kg/min) was begun and continued uninterrupted for the next 240 min. Concomitantly, a primed infusion of [6,6-2H2]glucose (33 μmol/kg; 0.33 μmol/kg/min) was begun and also continued for 240 min. One hundred and twenty minutes into the leucine and glucose tracer infusions, a primed, dose constant infusion of [1,2,3,32H4]glycerol (d4-glycerol) was begun, piggybacked into the same iv line and was continued for 120 min (1.4 μmol/L/kg; 0.1 μmol/L/kg/min). Frequent blood samples were collected for determination of the isotopic enrichment of the different tracers in plasma as well as the concentrations of hormones, substrates, and growth factors, as detailed below. Frequent breath samples were also obtained for determination of 13CO2 enrichment in expired breath. Indirect calorimetry was performed three times during the 4 h of isotope infusion using a mouth piece and a CPX max indirect calorimeter (Medical Graphics, St. Paul, MN). After the isotope infusions were completed, the patients were fed lunch and discharged from the unit.

After the baseline study, all subjects returned to Ecuador and were begun on rhIGF-I at a dose of 60 μg/kg, sc, twice daily; they were closely monitored for the first 24 h by the physicist team in Ecuador. They were then sent home and continued to take twice daily injections of rhIGF-I. 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.

After 8 weeks, the subjects flew back to the CRC in Jacksonville where the studies were repeated identically as at baseline (D2). The only difference was that 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/h using an insulin delivery pump (MiniMed, Inc., Sylmar, CA), which was continued uninterrupted for the next 16 h as part of the completion of the studies the following morning. This was performed 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 previously (4, 9, 24). Each patient served as his/her own control.

#### Blood and breath samples

The isotopic enrichments of α-ketosaccharic acid ([13C]KIC), and [2H]glucose were measured at –20, 160, 180, 200, 220, and 240 min. The isotopic enrichments of d4-glycerol were measured in plasma samples obtained at 60, 190, 200, 210, 220, 230, and 240 min. Plasma IGF-I, IGF-II, IGF-binding protein-1 (IGFBP-1), IGFBP-2, IGFBP-3, insulin, and glucose concentrations were measured three times at 0, 120, and 240 min during the tracer infusions. Serum GH concentrations were measured at hourly intervals for the 4 h of the studies. β-Hydroxybutyrate and free fatty acid concentrations were measured in plasma samples at –20 and 120 min. 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, 150, 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 the urea nitrogen concentration.

#### Assays

Plasma enrichments of [13C]KIC, [2H]glucose, and d4-glycerol were determined at the Nemours metabolic core laboratory by gas

---

**TABLE 1. Clinical characteristics of the study subjects**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Ht (cm)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>18.3</td>
<td>154</td>
<td>27.0</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>24.8</td>
<td>158</td>
<td>19.5</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>22.3</td>
<td>157</td>
<td>22.9</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>37.1</td>
<td>130</td>
<td>31.7</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>35.2</td>
<td>110</td>
<td>26.1</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>26.3</td>
<td>116</td>
<td>23.3</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>27.1</td>
<td>116</td>
<td>17.8</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>30.8</td>
<td>126</td>
<td>20.4</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>33.9</td>
<td>116</td>
<td>28.4</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>36.6</td>
<td>116</td>
<td>26.4</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>29.2</td>
<td>121</td>
<td>24.4</td>
</tr>
<tr>
<td>± SEM</td>
<td></td>
<td>2.0</td>
<td>2</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Hormones and growth factors

Significance was established at the given growth factor. The range of GH concentrations observed under columns D1 and D2.

**TABLE 2.** Hormones and growth factors of subjects with GH receptor deficiency before (D1) and after 8 weeks of rhIGF-I administration (D2).

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-I (μg/L)</td>
<td>[155–432 M, 87–368 F]</td>
<td>9.3 ± 1.5</td>
<td>153 ± 23</td>
</tr>
<tr>
<td>IGFBP-3 (mg/L)</td>
<td>[2.2–4.2]</td>
<td>1.3 ± 0.1</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>IGFBP-1 (µg/L)</td>
<td>[10–150]</td>
<td>49 ± 10</td>
<td>83 ± 13</td>
</tr>
<tr>
<td>IGFBP-2 (µg/L)</td>
<td>[215–518]</td>
<td>552 ± 84</td>
<td>1115 ± 123</td>
</tr>
<tr>
<td>IGF-II (IGF-II µg/L)</td>
<td>[288–736]</td>
<td>188 ± 23</td>
<td>63 ± 5</td>
</tr>
<tr>
<td>Mean GH (μg/L)</td>
<td>9.5 ± 3.2</td>
<td>0.3 ± 0.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak GH (μg/L)</td>
<td>23.5 ± 8.8</td>
<td>0.6 ± 0.2</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**Graph:**

Fig. 1. Plasma IGF-I concentrations in GHRD patients before (D1) and after (D2) 8 weeks of twice daily sc rhIGF-I. The thick bars on the y-axis represent the lower limits of normal for male (M) and female (F) subjects.
measurements via indirect calorimetry, lipid oxidation rates increased from $19.2 \pm 3.8$ Cal/FFM·day to $27.6 \pm 4.4$ ($P = 0.04$; Fig. 2). Plasma lipid concentrations remained invariant during rhIGF-I treatment: total cholesterol, $179 \pm 11$ mg/dL on D1 and $176 \pm 11$ on D2; HDL, $47 \pm 3$ mg/dL on D1 and $46 \pm 4$ on D2; LDL, $112 \pm 10$ mg/dL on D1 and $109 \pm 8$ on D2; triglycerides, $100 \pm 15$ mg/dL on D1 and $106 \pm 24$ on D2 ($P = NS$ for all comparisons).

Glucose metabolism

There was maintenance of normoglycemia despite suppression of circulating insulin concentrations in the fasted state after rhIGF-I therapy: plasma glucose concentrations: D1, $88 \pm 2$ mg/dL; D2, $88 \pm 4$ (or D1, $4.9 \pm 0.1$ mmol/L; D2, $4.9 \pm 0.2$); insulin concentrations: D1, $5.4 \pm 1.5$ μU/mL; D2, $2.4 \pm 0.7$ ($P = 0.01$; or D1, $32.4 \pm 9.0$ pmol/L; D2, $14.4 \pm 4.2$). Glucose Ra, a measure of hepatic glucose production, was increased after rhIGF-I therapy from $1.95 \pm 0.15$ mg/kg·min to $2.36 \pm 0.18$ ($P = 0.00001$). Glucose oxidation rates were decreased from $25 \pm 4$ Cal/FFM·day to $17 \pm 5$ ($P = 0.04$) after chronic rhIGF-I therapy.

Comparison with GHD and normal subjects

Some of the responses of the subjects with GHRD to rhIGF-I were compared with those of a group of 8 GHD adults treated with rhGH (12.5 μg/kg·day, sc) and rhIGF-I (60 μg/kg twice daily, sc) for 8 weeks, each reported previously [mean age, 23.5 ± 2.1 yr; 6 males and 2 females; body mass index (BMI), 28.2 ± 2.2 kg/m²] (31). Data were also compared with those of a group of 10 healthy males (mean age, 23.7 ± 0.5 yr; BMI, 25.2 ± 0.9 kg/m²) who participated in similar studies, some of which have been reported previously (32). The data from the experiments were gathered identically as in the present GHRD subjects. Figure 3, left panel, shows the changes in IGF-I concentrations in the 3 groups of subjects, the right panel shows the fasting insulin concentrations, and Fig. 4 shows the rates of nonoxidative leucine disposal, a measure of whole body protein synthesis.

Table 3. Changes in body composition, as measured by DEXA, and whole body protein kinetics, as measured by [13C]leucine infusions (micromoles per kg/min), in 10 adult patients with GHRD

<table>
<thead>
<tr>
<th></th>
<th>D1</th>
<th>D2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body composition</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>35.5 ± 2.3</td>
<td>35.7 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Fat-free mass (kg)</td>
<td>17.4 ± 0.9</td>
<td>18.4 ± 0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>% Fat mass</td>
<td>47.1 ± 3.1</td>
<td>45.7 ± 3.1</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Protein kinetics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucine Ra</td>
<td>1.24 ± 0.12</td>
<td>1.39 ± 0.10</td>
<td>0.004</td>
</tr>
<tr>
<td>Leucine oxidation</td>
<td>0.28 ± 0.04</td>
<td>0.22 ± 0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>NOLD</td>
<td>0.95 ± 0.09</td>
<td>1.16 ± 0.08</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Fig. 2. The upper left panel shows the rates of glycerol turnover, a measure of lipolysis, before (D1) and after (D2) 8 weeks of rhIGF-I in 10 subjects with Laron’s syndrome as measured by $d_5$-glycerol tracer studies. The upper right panel shows rates of lipid oxidation, as measured by indirect calorimetry; the lower left panel shows the changes in free fatty acid concentrations, and the lower right panel shows the changes in β-hydroxybutyrate during the same experiments.
Safety profile

These doses of rhIGF-I were well tolerated in all subjects. After the initiation of treatment there were complaints of occasional headaches, tachycardia, and soft tissue swelling, the latter most likely secondary to fluid retention. These symptoms were all transient and well tolerated. No patient discontinued the medication because of them. General chemistries, blood counts, thyroid profile, and sex steroid concentrations remained invariant during these studies.

Discussion

Relatively short term (8-week) daily administration of rhIGF-I had substantial, positive effects in IGF-I-deficient adults with GH receptor mutations. Rates of protein synthesis increased significantly; body composition changed with increased lean body mass and decreased adiposity without changes in total body weight. Rates of lipolysis and lipid oxidation also increased after rhIGF-I, suggestive of a nutrient shift and a net protein anabolic effect. Glucose production rates increased with long-term treatment, yet there was no hyperglycemia despite persistent insulinopenia. The expected increase in glucose resulting from this increase in hepatic glucose production was probably negated by increased glucose transport, suggestive of a compensatory increase in insulin-like sensitivity during treatment.

These patients with GH receptor mutations had GH concentrations that were significantly suppressed during rhIGF-I treatment, whereas the GH-dependent growth factors were unaltered; hence, they represent a unique biological model that allows the measurement of IGF-I effects without the confounding effects of GH. Treatment with rhIGF-I resulted in normalization of the plasma IGF-I concentrations in most of the subjects studied and a near-normalization in the others, without any measurable alteration in IGFBP-3 concentrations and a marked decline in circulating GH concentrations. These data are similar to previously reported results after short-term treatment with this peptide and after prolonged treatment for linear growth purposes (3, 33).

The observed changes in body composition, with increased lean body mass and decreased adiposity, were not accompanied by total body weight changes and are remarkable considering that subjects were treated for only 8 weeks. These changes were similar to those observed in GHD patients treated with rhGH and rhIGF-I for 8 weeks, each at similar doses reported by us recently (31) and not dissimilar from those observed after more prolonged treatment with rhGH in adults with GHD (21). Five adults treated with rhIGF-I at twice the dose used here were also reported to have decreased adiposity, as measured by skinfold thickness, after 6–9 months (22). Interestingly, rhIGF-I treatment of Laron’s syndrome subjects resulted in increased protein breakdown and protein synthesis rates, with a net protein anabolic effect. These results differ from the selective increase in protein synthesis rates observed after rhIGF-I in healthy individuals (4) and GHD subjects (31) and may be secondary to the chronic relative insulinopenia observed during treatment.
during treatment, as insulin administration typically suppresses proteolysis (34).

The effects of 8 weeks of chronic rhIGF-I treatment on all measures of fat metabolism in this cohort of GHRD subjects is perhaps the most intriguing. Using stable isotopes of glycerol, measurement of glycerol turnover allows the estimation of rates of lipolysis at the whole body level. The breakdown of stored triglyceride in the adipocyte results in the release of both free fatty acids and glycerol, and as there is no glycerol kinase in the adipocyte (hence, reesterification of the released glycerol is not possible within the fat cell), the measurement of the rate of appearance of glycerol is used as a measure of whole body lipolysis. Using this tool, lipolytic rates were increased during rhIGF-I treatment, and this difference was most obvious when the data were expressed per kg FM, highlighting the sensitivity of adipose tissue to the antilipogenic effects of IGF-I. There was minimal change in FFA concentrations, yet the glycerol Ra increased, and as glycerol concentrations did not change, it may be that some of the effect of the treatment was to increase the effectiveness of FFA utilization, such that despite greater release of the products of lipolysis the utilization was increased so as to maintain the same concentration.

Measures of gas exchange and indirect calorimetry in these subjects also revealed a significant increase in the oxidation of lipids; there was also an increase in the concentrations of ketone bodies (β-hydroxybutyrate), which, taken in aggregate, suggest that not only is there mobilization and breakdown of stored lipids, but there is also increased oxidation of the broken fat. As there appear to be no functional type 1 IGF-I receptors in the adipocyte (11), and both GH and insulin concentrations are suppressed during rhIGF-I treatment, these data suggest that these effects on fat metabolism are secondary to chronic relative insulin deficiency during rhIGF-I treatment. This is congruent with recent data in rats that show that IGF-I reduces fat mass via inhibition of the lipogenic capacity of adipocytes and inhibition of insulin secretion (35). Even though the plasma lipid profiles remained unchanged in these subjects during treatment, the beneficial effects of IGF-I replacement on fat metabolism deserve further long-term study.

There was a modest, yet significant, increase in the glucose Ra, a measure of hepatic glucose production, in these patients. This is similar to the increase observed after rhIGF-I treatment of normal (9) and GHD subjects (31, 36) reported by us previously and strongly suggests that there is relative suppression of insulin concentrations at the portal level. The fact that glucose concentrations remained normal and there was no hyperglycemia despite an increase in glucose production rates during these 8-week experiments suggest, however, that IGF-I actively participates in glucose transport. The latter could be either through the insulin receptor (7) or through its own type 1 receptor (8). Di Cola et al. studied insulin receptor-deficient mice and showed that IGF-I caused a prompt and sustained decrease in plasma glucose levels, similar to that in mice with intact insulin receptors (8). They also observed that in skeletal muscle, IGF-I treatment caused phosphorylation of IGF-I receptors and increased the levels of the phosphatidylinositol-3-kinase p85 subunit, consistent with the possibility that IGF-I stimulates glucose uptake in a phosphatidylinositol-3-kinase-dependent manner. It is likely that the sustained glucose transport and persistent normoglycemia observed here reflect this action of rhIGF-I in humans through both the insulin and the IGF-I receptor. Based on these data, the long-term use of rhIGF-I in the adult with GHRD should not have deleterious effects on carbohydrate tolerance. Further studies on long-term safety in the adult are needed.

Compared with GHD subjects reported previously (31), it appears that the metabolic deficiencies observed are more severe in GHRD states. Even though there are substantial increases in rates of protein synthesis after rhIGF-I, e.g., compared to GHD patients treated with rhGH and rhIGF-I, the best normalization of these rates was observed in the GHD subjects treated with rhGH. It is noticeable that rhIGF-I treatment of the GHD subjects resulted in the largest increase in plasma IGF-I concentrations, followed by rhGH treatment in GHD subjects and lastly rhIGF-I treatment of GHRD patients. There are, however, comparable increases in NOLD per U increase in IGF-I for the GHRD patients treated with rhIGF-I as for the GHD patients treated with rhGH, supportive of the idea that IGF-I mediates the protein anabolic actions of GH in man (4, 24). Adult GHD subjects treated with rhIGF-I studied by us using the same doses as those reported here showed normal absorption and distribution of IGF-I, yet faster elimination kinetics than normal subjects (37), similar to results observed in GHRD subjects reported previously (38). However, the rise in plasma IGF-I concentrations observed in this cohort, even though not fully normal in three patients, is appropriate, and the metabolic effects observed are substantial, suggesting that a dose of 60 μg/kg twice daily may be appropriate for long-term studies in this patient population. Whether complete normalization of the metabolic derangement of these patients could be overcome with years of rhIGF-I therapy remains to be fully studied. However, considering the pivotal role of this hormone in a multiplicity of metabolic functions in vivo, the actual, albeit limited, availability of this peptide, and the standard practice of endocrinology to replace hormone-deficient states, it behooves us to perform the necessary long-term studies in the affected adults with this syndrome. The ultimate effects on the quality of life of these patients would also need to be assessed.

In conclusion, we studied intermediate metabolism of proteins, sugars, and lipids in a group of severely IGF-I-deficient subjects treated with rhIGF-I for 8 weeks. IGF-I affects protein, glucose, and lipid metabolism independent of GH and has positive anabolic effects in this condition. These results suggest that rhIGF-I may be beneficial for long-term replacement of the adult with Laron’s syndrome.

Acknowledgments

We are grateful to Brenda Sager and the biochemical core laboratory at the Nemours Children’s Clinic for sample analysis, to Burnese Rutledge and the expert nursing staff at Wolfson Children’s Hospital for their dedicated care of our patients, to Susan Welch for assistance with the care of the patients during admissions, to Dr. Mark Hartman at Eli Lilly & Co. for his enthusiastic support of this study, to Dr. George Klee and the immunoochemical core laboratory at the Mayo Clinic (Rochester, MN) for immunoassay support, to Dr. Johannes Veldhuis and Ginger

The Endocrine Society. Downloaded from press.endocrine.org by [individualUser.displayName] on 27 March 2014, at 08:25 For personal use only. No other uses without permission. All rights reserved.
Bauler at the University of Virginia General Clinical Research Center core laboratory for the measurement of GH concentrations, and to Genentech, Inc., for continued supply of the study drug.

References