Effects of Insulin-Like Growth Factor I (IGF-I) Therapy on Body Composition and Insulin Resistance in IGF-I Gene Deletion

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ABSTRACT
We have recently reported a patient with a homozygous partial deletion of the insulin-like growth factor-I (IGF-I) gene, resulting in IGF-I deficiency, insulin resistance, and short stature. Recombinant human IGF-I (rhIGF-I) therapy has been shown to improve insulin sensitivity (Si) and growth in other causes of IGF-I deficiency. We now report results of 1 yr of rhIGF-I therapy on body composition, bone mineral density (BMD), insulin sensitivity, and linear growth in this patient. rhIGF-I therapy was initiated at age 16.07 yr (bone age, 14.2 yr); at a starting dose of 40 µg/kg daily, increasing after 3 months to 80 µg/kg daily. Body composition, BMD, markers of bone mineralization, and auxological parameters (height, weight) were measured at 0, 6, and 12 months after start of therapy. Si, acute insulin response to glucose, and glucose effectiveness were determined at baseline, 3 months, and 12 months into therapy. On IGF-I therapy, body mass index increased from 17 kg/m² to 18.6 kg/m². Body composition studies (dual-energy x-ray absorptiometry) revealed an initial decrease in total body fat, from 19.9% at baseline to 15.1% at 6 months; but by 12 months of therapy, this had reversed, with an increase to 21.8%. Si, calculated using Bergman’s minimal model, was substantially reduced at baseline at 1.45 × 10⁻² min⁻¹ (µU/mL) [normal value, 5.1 × 10⁻² min⁻¹ (lean adult male)]. rhIGF-I therapy resulted in a dose-related improvement of Si into the normal range (NR) (rhIGF-I dose: 40 µg/kg-day, Si = 2.06 × 10⁻² min⁻¹; rhIGF-I dose: 80 µg/kg-day, Si = 4.02 × 10⁻² min⁻¹). Baseline reduction in Si was accompanied by elevated acute insulin response to glucose, which also fell in a dose-dependent manner. Baseline BMD was severely reduced when compared with age-matched controls (−4.88 SD); however, calculation of bone mineral apparent density indicated that the true reduction in BMD was minimal. rhIGF-I therapy increased BMD by 17% and bone mineral apparent density by 7%, indicating that IGF-I has a greater effect on bone growth than bone mineralization. Bone turnover markers also increased on rhIGF-I; mean serum osteocalcin: 8.3 ng/mL pretreatment, 21.7 ng/mL after 6 months of rhIGF-I (NR for adult male, 3.4–9.1 ng/mL); mean bone specific alkaline phosphatase: 36.5 U/L pretreatment, 82.2 U/L after 6 months of therapy (NR for adult male, 15–41). Height velocity increased from 3.8 cm/yr pretreatment to 7.3 cm/yr on 80 µg/kg/day of rhIGF-I.

In this patient with severe insulin resistance, therapy with rhIGF-I resulted in beneficial effects on Si, body composition, bone size, and linear growth. These results have implications for IGF-I therapy in a variety insulin resistant states. (J Clin Endocrinol Metab 85: 1407–1411, 2000)
effects of IGF-I. In addition to their role in growth, both GH and IGF-I have effects on glucose and lipid metabolism and bone mineralization (7, 12). This report describes the effects of 12 months of rhIGF-I therapy on this patient’s body composition, bone mineralization, Si, and linear growth.

Subjects and Methods

Patient details

We have previously reported the full details of the case history (1). At the age of 15.75 yr, auxological parameters were as follows: height, 119.1 cm (−6.88 sp); weight, 23.0 kg (−6.49 sp); body mass index, 16.2 kg/m² (−1.9 sp); upper-to-lower segment ratio, 1.07 (mean, 0.98 at 15 yr); triceps skinfold thickness, 6.0 cm (−0.93 sp); and subscapular skinfold thickness, 7.6 cm (−0.0 sp). The patient was mildly dysmorphic, with micrognathia, bilateral ptosis, and a low hairline. There was bilateral clinodactyly and a left-sided single palmar crease. Neurological examination demonstrated severe bilateral sensorineural deafness and mild myopia.

Endocrine investigations revealed elevated GH secretion, both on overnight GH profile (peaks up to 350 mU/L with lack of full suppres-

si on during troughs) and to provocative stimuli (clonidine: peak, 188 mU/L; insulin: peak, 122 mU/L). IGF-I levels were undetectable. IGFBP-3 was normal for age (3.3 mg/L), IGF-II mildly elevated (1430 ng/mL; normal serum pool, 1002 ng/mL), and ALS was normal on immunoblot. Molecular studies revealed a homozygous IGF-I gene dele-

tion involving exons 4 and 5, predicting a severely truncated and abnormal IGF-I peptide. His parents, who were consanguineous, were heterozygous for the deletion.

rhIGF-I therapy was commenced at the age of 16.07 yr (bone age, 14.2 yr). Height was 120.4 cm (−7.44 sp) and Tanner stage of puberty P2, G2, testicular volume (Tvol) 8/10 mL. The starting dose of rhIGF-I was 40 µg/kg by daily sc injection. After 3 months of therapy, an overnight GH profile indicated that GH secretion remained elevated, and the dose was increased to 80 µg/kg-day. A repeat overnight GH profile indicated adequate GH suppression on this dose (11), which was continued for the remaining 9 months of treatment.

Auxology

Height measurements were obtained using a wall-mounted stadi-

ometer. Bone age was assessed using the Tanner-Whitehouse-2 RUS method (13).

Assays

Levels of androgens, sex hormone binding globulin (SHBG), and insulin were measured by standard RIA procedures. Glucose levels were determined by a glucose analyzer. Bone turnover markers (serum osteocalcin and bone specific alkaline phosphatase) were assayed using immunoassays obtained from Metra Biosystems UK (Great Haseley, Oxford, UK).

Bergman-modified minimal model frequent sampling iv glucose tolerance test (FSIGT)

The 180-min FSIGT was used to provide an accurate assessment of β-cell function and Si in the patient. These parameters are calculated after a bolus of IV glucose at 0 min and tolbutamide at 20 min, and computer mathematical analysis of insulin and glucose kinetics using the MINMOD program (the minimal modeling technique). This test has been validated for use in children (14).

The test was performed at three time points: test 1, pretreatment; test 2, after 1 month therapy with IGF-I (dose 40 µg/kg-day); and test 3, after 6 months therapy with IGF-I (dose 80 µg/kg/day). Samples for the analysis of insulin and glucose were taken at the following times (minutes): −15, −10, −5, −1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180. Glucose (300 µg/kg) was injected at t = 0 and tolbutamide (100 mg/kg) at t = 20. The following parameters were calculated using MINMOD: 1) insulin sens-

itivity (Si); 2) glucose effectiveness (Sg); and 3) acute insulin response to glucose (AIRg). The study protocol was approved by the Local Ethics Committee, and informed written consent was obtained from the pa-

ient’s parents.

Determination of bone mineral density (BMD) and body composition

BMD and body composition were determined at three time points (pretreatment, 6 months on treatment, and 12 months on treatment) by dual-energy x-ray absorptiometry using the Lunar Corp. DPX densi-

ometer (Supplied by Aura Scientific, West Lothian, UK). Baseline lum-

bar (L2–L4) BMD was converted to an age-matched sp score using Lunar Corp. pediatric software (control data collected by Lunar Corp.). To correct for bone size, the volumetric BMD [bone mineral apparent density (BMAD)] of the lumbar spine was calculated at each time point, using the formula BMAD = BMC/(Ap)1.5, where BMC = bone mineral content, and Ap = projected area (15).

Adverse effects

Regular ophthalmic and ear, nose, and throat examinations were performed to monitor for the development of papilloedema and tonsillar hypertrophy at 0, 3, 6, and 12 months of therapy.

Results

Changes in body composition on rhIGF-I therapy (Table 1)

Over the first 6 months of rhIGF-I therapy (3 months at 40 µg/kg-day and 3 months at 80 µg/kg-day), there was a marked reduction in total body fat, from 19.9% to 15.1%, which increased during the subsequent 6 months of rhIGF-I therapy (80 µg/kg-day throughout), to result in a net eleva-

tion from baseline at 21.8% (Table 1).

Changes in bone mineralization on rhIGF-I therapy (Table 2)

Lumbar BMD at baseline was severely reduced, compared with age-matched controls (L2–L4 region, 0.58 g/cm²; sp score, −4.88). BMAD at baseline was 0.14 g/cm³. Appropriate age- and sex-matched control values for BMAD have not been published; however, this value compares with a BMAD of 0.165 g/cm³ ± 0.114 sp in 75 female subjects (mean age, 24.4 yr), calculated using the same formula (15). Over the 1 yr of therapy, BMD increased by 17% and bone mineral content by 26%. BMAD increased by 7%. Markers of bone formation and turnover (serum osteocalcin and bone specific alkaline phosphatase) increased substantially by 6 months.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>IGF-I dose (µg/kg/day)</th>
<th>Duration of therapy (months)</th>
<th>Weight (kg)</th>
<th>Body mass index (kg/m²)</th>
<th>Total lean body mass (kg)</th>
<th>Total body fat (kg)</th>
<th>Total body fat (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.07</td>
<td>0</td>
<td>0</td>
<td>24.3</td>
<td>16.7</td>
<td>17.9</td>
<td>4.60</td>
<td>19.9</td>
</tr>
<tr>
<td>16.55</td>
<td>80</td>
<td>6</td>
<td>26.0</td>
<td>16.9</td>
<td>20.8</td>
<td>3.85</td>
<td>15.1</td>
</tr>
<tr>
<td>17.07</td>
<td>80</td>
<td>12</td>
<td>30.1</td>
<td>18.6</td>
<td>22.1</td>
<td>6.41</td>
<td>21.8</td>
</tr>
</tbody>
</table>
By 12 months, levels remained above baseline but were lower than the 6-month values.

Changes in Si and secretion on rhIGF-I therapy (Table 3, Fig. 1)

Before initiation of rhIGF-I therapy, there was fasting hyperinsulinemia [insulin, 28.9 mU/L (normal range, NR, for stage 2 puberty, 8–18)], although plasma glucose (mean, 4.9 mmol/L) and glycated hemoglobin [3.2% (NR, 3–5%)] were normal. Administration of both iv glucose and tolbutamide resulted in an exaggerated insulin response. Using the MINMOD program, Si was markedly reduced, and AIRg was greatly elevated. Sg was normal. There was a dose-dependent improvement in Si and AIRg to rhIGF-I therapy, the higher (80 μg/kg-day) dose resulting in a fall of Si into the NR for age and puberty status. SHBG was initially undetectable and increased almost into the normal adult range.

Changes in linear growth and maturation during rhIGF-I therapy (Table 4)

 Pretreatment height velocity was 3.8 cm/yr. On rhIGF-I (40 μg/kg for 3 months), height velocity increased modestly to 4.2 cm/yr. After the increase in rhIGF-I dose to 80 μg/kg, there was a more pronounced increase in height velocity, to 7.3 cm/yr. Puberty progressed from G2, PH2, Tvol 8/10 to G4, PH4, Tvol 12/12 over the 12 months of therapy.
TABLE 4. Changes in height and bone age during 1 yr of rhIGF-I therapy

<table>
<thead>
<tr>
<th>Age</th>
<th>IGF-I dose (μg/kg·day)</th>
<th>Height (cm)</th>
<th>Height velocity (cm/yr)</th>
<th>Bone age (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.07</td>
<td>Start 40</td>
<td>120.4</td>
<td>3.8</td>
<td>14.2</td>
</tr>
<tr>
<td>16.33</td>
<td>↑ to 80</td>
<td>121.5</td>
<td>4.2</td>
<td>14.6</td>
</tr>
<tr>
<td>16.55</td>
<td>80</td>
<td>123.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17.07</td>
<td>80</td>
<td>126.9</td>
<td>7.2</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Adverse effects

The patient reported no significant adverse effects of rhIGF-I therapy. In particular, no hypoglycemic episodes occurred after rhIGF-I injection, as observed in rhIGF-I therapy of patients with GHRD (8). Regular ophthalmologic and ear, nose, and throat examinations revealed no evidence of papilloedema or adenotonsillar hypertrophy.

Discussion

This paper describes the effects of 1 yr of rhIGF-I therapy on body composition, bone mineralization, Si, and growth in this patient with severe IGF-I deficiency secondary to a homozygous partial deletion of the IGF-I gene.

A marked reduction in Si, using the modified FSIGT devised by Bergman and co-workers, confirmed that this patient was significantly insulin resistant before the onset of rhIGF-I therapy. Marked hypersecretion of insulin, in response to glucose and tolbutamide, was observed, suggesting exaggerated β-cell reactivity, a feature often associated with insulin-resistant states (16). Sustained exposure to elevated GH levels is well described to reduce Si, as seen in conditions such as acromegaly (17–19). An increase in the direct effects of GH, secondary to the elevation in GH secretion at baseline, thus provides the likely explanation for the insulin resistance of this patient. This hypothesis is supported by the dose-dependent improvement in Si observed during rhIGF-I therapy. Elevated GH secretion is thought to be one explanation for the insulin resistance observed in adolescent insulin-dependent diabetes mellitus, and rhIGF-I therapy has been shown to improve glycemic control in this condition (20).

SHBG levels, reduced to below the limits of assay detection at baseline, increased into the NR for age and pubertal stage during rhIGF-I therapy. This may reflect either the fall in insulin or GH levels during therapy, both of which have an inverse relationship with SHBG (21–23).

IGF-I has been described to have both short-term antilipolytic and long-term lipolytic effects (12). Patients with severe GHD and GHRD tend to have increased adiposity, most likely secondary to the lack of the direct antilipolytic effect of GH (24). The body fat content of our patient, at 19.9%, is considerably less than that of prepubertal GHRD children in a recent study, in whom the mean total body fat was 28.3% (7). In the first 6 months of IGF-I therapy, his total body fat fell, but by 12 months there had been a net increase. This gain in body fat, suggesting an overall lipogenic effect of treatment, may be secondary to the fall in GH levels induced by rhIGF-I, which for the first 3 months of therapy were inadequately suppressed on the lower dose of rhIGF-I.

The measurement of BMD, using dual-energy x-ray absorptiometry scanning in short children and adults, is confounded by the effects of reduced bone size and may lead to underestimation of true bone density (25). The effect of reduced bone size on the calculation of BMD can be overcome, however, by the calculation of BMAD (15). Both children and adults with GHD have been reported to have reduced BMAD, suggesting that GH, either acting directly on bone tissue and/or mediated by IGF-I, plays an important role in bone mineralization (26–28). Children with GHRD have also been reported to have low BMD, which improves with rhIGF-I therapy (7); however, BMD was not adjusted for height in this study. In contrast, a recent study of adults with GHRD demonstrated no reduction in BMAD, compared with controls, thereby questioning the role of the GH-IGF-I axis in bone mineralization (29). Our patient had a low BMD, compared with age-matched controls at baseline. However, his baseline BMAD was only mildly reduced, compared with a reference population of young adult women. During rhIGF-I therapy, BMD and BMC increased markedly and BMAD less so, suggesting that much of the apparent increase in BMD was, in fact, attributable to an increase in bone size. As puberty progressed from Tanner stage 2 to stage 4 during the period of therapy, the modest increase in BMAD may well be secondary to the effects of puberty, which has been shown to be associated with an increase in BMAD (30), rather than an effect of rhIGF-I therapy. Thus, rhIGF-I had a much greater effect on bone growth than on bone mineralization.

A growth response to rhIGF-I was clearly seen, with a near doubling of growth velocity on the higher (80 μg/kg-day) dose of rhIGF-I. Considering that the patient was in puberty at the time of rhIGF-I administration, this growth response is perhaps less than might be expected for a similar individual with severe GHD receiving hGH therapy for the first time. Direct GH actions are intact in our patient, and rhIGF-I clearance is normal. However, systemic rhIGF-I therapy cannot correct the lack of local IGF-I production, and this may be the explanation for the suboptimal growth response.

In summary, this paper reports the results of rhIGF-I therapy for 1 yr in this unique patient with IGF-I gene deletion. The main benefits of therapy were an improvement in body composition and normalization of Si. rhIGF-I has the potential to improve metabolic status in a variety of insulin-resistant states.

Acknowledgments

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References

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