Clinical Uses of Insulin-like Growth Factor I

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Insulin-like growth factor I (IGF-I) has acute insulin-like metabolic effects and long-term anabolic actions. The therapeutic potential of recombinant human IGF-I treatment is being investigated in various growth hormone-resistant and insulin-resistant disorders. Recent studies have shown that IGF-I may substitute for growth hormone in promoting linear growth in children with growth hormone insensitivity. The anabolic, protein-sparing action of IGF-I is being evaluated as a potential therapy for adults with catabolic diseases. Patients with insulin-dependent diabetes mellitus have reduced endogenous IGF-I production, and studies are in progress to determine whether treatment with IGF-I in addition to insulin may improve their metabolic/anabolic status. Insulin-like growth factor I treatment may reduce glucose and triglyceride levels in adults with non-insulin-dependent diabetes mellitus and in some patients with extreme insulin resistance. Further studies are needed to evaluate the efficacy and safety of IGF-I treatment in these and other conditions and to provide a better understanding of this hormone's normal physiologic roles and complex relations with growth hormone and insulin.


Dr. Carolyn Bondy (Developmental Endocrinology Branch, National Institute of Child Health and Human Development): Insulin-like growth factor I (IGF-I; somatomedin-C) is an anabolic polypeptide that is structurally homologous to insulin (1). Its actions are mediated primarily by the IGF-I receptor, which is structurally and functionally homologous to the insulin receptor. The ligand-binding domains of these receptors are sufficiently different that each binds its cognate hormone with about ten times more affinity than does the related ligand (2). The signal-transducing, tyrosine kinase domains of the two receptors, however, are very similar (2) and activate common intracellular pathways (3). Thus, it appears that the difference in physiologic effects of insulin and IGF-I are not due primarily to intrinsic differences in signaling capacities of their receptors (4). Furthermore, with a few notable exceptions, both receptors are widely expressed, with some tissues apparently expressing "hybrid" receptors that combine insulin and IGF-I receptor subunits (5, 6). Because insulin and IGF-I are subject to very different regulatory influences and have markedly different patterns of secretion and circulating profiles, hormone bioavailability is probably an important factor in determining the different roles served by IGF-I and insulin. Recombinant human IGF-I recently became available for clinical studies, allowing, for the first time, direct investigation of the metabolic and anabolic effects of IGF-I and its relations with insulin and growth hormone.

Our view of the regulatory relations among IGF-I, growth hormone, and insulin is outlined in Figure 1. Growth hormone and insulin stimulate the constitutive secretion of IGF-I from the liver (7) and IGF-I, in turn, suppresses growth hormone and insulin secretion, even under euglycemic conditions (8-11). In contrast to the highly regulated secretory patterns and fluctuating serum profiles of growth hormone and insulin, circulating IGF-I levels are relatively stable. This stability is due to its constitutive pattern of secretion and to the fact that most circulating IGF-I is bound to high-affinity IGF-binding proteins, which prolong the half-life and titrate the supply of this hormone to its receptors (12, 13). Six IGF binding proteins have been identified, but clinical data are most abundant for IGF-binding protein-3. This IGF-binding protein binds IGF-I and another component, the acid-labile subunit, and forms a high molecular weight ternary complex, which constitutes the primary reservoir of circulating IGF-I. Circulating levels of this complex are positively regulated by growth hormone. Insulin-like growth factor-binding protein-3 binds a smaller fraction of the total circulating IGF-I, but this fraction may be disproportionately influential in terms of the effects of IGF-I on intermediary metabolism, because IGF-binding protein-3 levels are potently suppressed by insulin.

Originally, the somatomedin hypothesis (1) suggested that circulating IGF-I mediates most of the effects of growth hormone on linear growth. Recently, however, growth hormone was found to stimulate the local production of IGF-I in several tissues in addition to the liver in rodents (1), and thus local autocrine or paracrine effects of IGF-I appeared to be important for normal growth. There is, however, little evidence for growth hormone-stimulated IGF-I synthesis in human tissues other than the liver, and the apparent success of systemic IGF-I treatment in producing linear growth in growth hormone-resistant children, discussed in the following section by Dr. Underwood, suggests that neither local IGF-I production nor direct anabolic effects of

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growth hormone are essential for statural growth in children. Local autocrine/paracrine growth processes in humans might be regulated by another member of the insulin family of peptides. Insulin-like growth factor II is structurally closely related to IGF-I (1) and binds the IGF-I receptor with high affinity, but unlike IGF-I it is not regulated by growth hormone. In rodents, IGF-II expression is abundant during embryonic development but is largely suppressed after birth. In humans, however, IGF-II levels are equal to or greater than IGF-I in the circulation and in many tissues during adulthood (1, 14–16).

Growth hormone and IGF-I have continuing roles in fuel metabolism and in the maintenance of musculoskeletal mass in adults. Many of the changes in body composition, such as increasing adiposity and decreasing muscle mass, that occur during aging correlate specifically with decreasing levels of these hormones (17). Several clinical situations exist in which the anabolic or metabolic effects of growth hormone, IGF-I, or both may prove to have substantial therapeutic benefit. Starvation, cachexia, hyperalimentation, and insulin-dependent diabetes mellitus are all associated with a state of functional growth hormone resistance in which, despite normal or high growth hormone levels, circulating IGF-I levels are low and do not respond to growth hormone treatment. A common factor in these conditions is under-insulinization of the liver, which impairs normal IGF-I and IGF-binding protein synthesis. Recent clinical trials evaluated the short-term metabolic effects of IGF-I administration in calorically deprived adult volunteers, as described by Dr. Clemmons, and in insulin-dependent diabetic patients, as described by Dr. Bach.

Another area in which IGF-I may have important therapeutic benefit is the hyperglycemic disorders characterized by insulin resistance. In the short term, recombinant IGF-I decreases blood glucose and triglyceride levels in obese patients with non-insulin-dependent diabetes mellitus (11). These salutary effects have been attributed to improved insulin sensitivity due to suppression of growth hormone and insulin secretion by IGF-I and to the direct, insulin-like metabolic effects of IGF-I. A few studies have reported that recombinant IGF-I treatment improves the hyperglycemia of patients with extreme insulin resistance caused by genetic defects in the insulin receptor, thus suggesting that IGF-I may act through its own receptor to regulate blood glucose (18–21). Not all insulin-resistant patients respond well to IGF-I treatment, however, as reported by Drs. Guler and Skarulis in a following section.

Insulin-like Growth Factor I in Growth Hormone-resistant Short Stature

Dr. Louis Underwood (Department of Pediatrics, University of North Carolina, Chapel Hill, North Carolina): We are treating two kinds of patients with short stature secondary to growth hormone insensitivity: patients with Laron-type dwarfism, now called the Laron syndrome (22), and growth hormone-deficient patients in whom large amounts of growth-attenuating antibodies have developed after treatment with growth hormone. Normally, growth hormone binds to the growth hormone receptor to induce hepatic IGF-I production, which in turn stimulates growth and feeds back at the level of the pituitary and hypothalamus to suppress growth hormone secretion (Figure 2). Patients with the Laron syndrome lack functional growth hormone receptors and thus do not respond to growth hormone; their IGF-I levels are very low, growth is slow, and circulating growth hormone levels are high because of decreased feedback suppression of growth hormone by IGF-I (Figure 2). Patients with a deletion of the growth hormone gene may recognize growth hormone as a foreign protein, and large numbers of antibodies may develop that attenuate or obliterate their response to it.

We studied a boy with the Laron syndrome (23) who was very short (111 cm at 9 years) and had the physical appearance of a person with growth hormone deficiency. Basal serum levels of growth hormone were elevated (10 to 12 μg/L) and increased to 40 to 60 μg/L after pharmacologic stimulus. His serum IGF-I level was low (5 to 6 μg/L; normal for age, 100 μg/L), and he had no increase in serum IGF-I after injections of growth hormone. He received growth hormone therapy for 6 months without an increase in growth rate. We admitted him to our Clinical Research Center for 5 weeks and ensured a constant dietary intake. In the second week, he was given three injections of growth
hormone at therapeutic doses, and in weeks 3 and 4 he received continuous infusion of recombinant IGF-I (Genentech, San Francisco, California). This treatment was followed by 1 week of postinfusion observation.

He showed no metabolic responses to growth hormone, but he had a marked decrease in urinary excretion of urea and in serum urea nitrogen with IGF-I infusion. His urinary calcium level increased and his urinary phosphate and sodium excretion levels decreased (24). These all are fairly typical growth hormone-like effects and are similar to those that would occur in patients with growth hormone deficiency who are sensitive to growth hormone. Because of the insulin-like effects of IGF-I, he tended to become hypoglycemic when he was infused overnight in a fasting state. However, in the postprandial state, his glucose increased to high levels and his insulin level was suppressed, the latter because of a direct effect of IGF-I on insulin secretion. He was treated with subcutaneous injections of recombinant IGF-I (120 μg/kg every 12 hours). After IGF-I injection, serum IGF-I concentrations were in the normal range for at least 7 hours. In general, however, acute metabolic responses to subcutaneous injections are less pronounced than are those observed with intravenous infusion. He has been treated with IGF-I for nearly 2 years and has grown at a rate of about 10 cm per year, compared with 4.5 cm during the 3 years before treatment (24). Other investigators are studying the effect of IGF-I on growth hormone insensitivity. Laron and colleagues (25) showed that treatment with IGF-I for 3 to 10 months in patients with the Laron syndrome improved growth rates from 2.8 to 5.8 cm per year before treatment to as high as 13.6 cm per year during treatment (Table 1). These investigators also reported that treated patients lose body fat. We now have eight patients being treated with IGF-I, including five with the Laron syndrome and three who have growth-attenuating antibodies to growth hormone (26), all of whom are growing at rates similar to those reported by Laron and colleagues (25). Insulin-like growth factor I appears to be well tolerated by these patients and hypoglycemia is avoided if the patient is fed within 2 or 3 hours of the injection and glucose intolerance is not observed. Several of the children treated with IGF-I had selective growth of adenoid tissue, as indicated by new-onset snoring and, in one case, airway obstruction requiring adenoidectomy.

These studies show that IGF-I promotes growth in patients who are insensitive to growth hormone.
these studies of the responses to exogenous IGF-I, it was not known whether IGF-I exerted its actions through endocrine mechanisms or whether its principal actions occurred at sites of local IGF-I production, by autocrine or paracrine mechanisms (27). Our results lead us to conclude that this growth factor can act by classical endocrine mechanisms and that the endocrine pathway may be dominant for the actions of IGF-I on cartilage and for promotion of statural growth. Our findings, however, do not exclude possible autocrine or paracrine actions of IGF-I on cartilage or other tissues. Our findings also lead us to conclude that the dual effector hypothesis of growth hormone action must be re-evaluated (28). This hypothesis proposes that, in addition to stimulating IGF-I production, growth hormone acts directly on precursor cells to allow them to proliferate in response to IGF-I. The prolonged growth responses of our patients who are insensitive to growth hormone suggests that growth hormone itself is not needed for growth and that all of the actions on statural growth that are ascribed to growth hormone are actually produced by IGF-I.

**Insulin-like Growth Factor I as an Anabolic Agent in Catabolic States**

Dr. David Clemmons (Division of Endocrinology, University of North Carolina): Growth hormone has been proposed as an anabolic therapy for patients with various catabolic conditions, including renal failure, corticosteroid therapy, protein wasting caused by malnutrition, burns, and recovery from surgery or acute illness (29). Because growth hormone may cause suboptimal improvement in these catabolic states (30, 31), other therapeutic strategies have been proposed to improve or augment its anabolic effects. Studies conducted in nutritionally deprived rats and humans have provided some knowledge of the mechanisms that may contribute to suboptimal anabolic response. Fasting results in complete refractoriness to growth hormone, which appears to be mediated by down-regulation of growth hormone receptors (32). In contrast, less severe insults, such as a protein restriction of 60% or a caloric restriction of 50%, induce varying defects, including the inability to generate a normal IGF-I response, abnormal clearance of IGF-I, and refractoriness to IGF-I itself (33, 34). It is not clear which of these mechanisms functions in severe catabolic states.

Although precise strategies to overcome specific deficits in the growth hormone/IGF-I pathway have not been identified, alternative approaches, such as administering IGF-I, have been tested. Six healthy young adult volunteers were fed calorically restricted diets (20 kcal/kg per day) for 2 weeks. During the second week of caloric restriction, IGF-I (Genentech) was infused at a dosage of 12 μg/kg per hour for 16 hours daily for 6 days. When the IGF-I infusion was completed, participants were fed a normal diet for 2 weeks and then the caloric restriction was repeated for another 2-week period; they received a daily injection of growth hormone (50 μg/kg) during the second week. Nitrogen balance improved markedly during both IGF-I and growth hormone treatments (35). Insulin-like growth factor I decreased blood glucose from 4.94 ± 0.91 mmol/L to 3.13 ± 0.44 mmol/L, whereas growth hormone increased blood glucose levels to 5.48 ± 1.0 mmol/L, despite the fact that IGF-I decreased serum C-peptide from 2.14 ± 0.89 mmol/L to 0.97 ± 0.14 mmol/L and growth hormone increased C-peptide to 3.12 ± 0.59 mmol/L. Thus, IGF-I induced substantial hypoglycemia even though C-peptide was suppressed, suggesting that IGF-I, rather than insulin, lowered blood glucose levels. The clinical utility of IGF-I may be limited to those catabolic patients in whom unacceptable degrees of hyperglycemia develop with growth hormone or who have type II diabetes mellitus before therapy is begun.

To avoid the problem of hypoglycemia and possibly improve the anabolic response to IGF-I, we wanted to determine if a combination of growth hormone and IGF-I would be safer and more efficacious. The rationale for this approach was based on the view that growth hormone and IGF-I have unique anabolic actions and that they have opposite effects on glucose metabolism. Seven healthy adult volunteers were studied during caloric restriction in a protocol exactly parallel to that described previously, except that IGF-I alone (administered as in the previous study) was compared with IGF-I infusion plus growth hormone injections (36). The diet restriction reduced nitrogen balance to +139 ± 48 mmol/L. The growth hormone and IGF-I combination caused substantially greater nitrogen retention (252 ± 43 mmol/L per day) than did IGF-I alone (108 ± 29 mmol/L per day). Combined growth hormone and IGF-I treatment also caused substantial urinary potassium conservation, which suggests that most of the protein accretion occurred in muscle and connective tissue. Furthermore, all participants who received the growth hormone and IGF-I combination had a positive nitrogen balance, whereas none had a positive balance with growth hormone or IGF-I alone. The mean capillary blood glucose level with growth hormone and IGF-I treatment was 4.3 ± 1.0 mmol/L compared with 3.8 ± 0.8 mmol/L with IGF-I alone.

As in the previous study, IGF-I caused a marked decline in C-peptide, whereas no change was seen with the growth hormone and IGF-I combination, suggesting that the combination maintained a more normal carbohydrate metabolism. Peak serum IGF-I levels were substantially higher with the growth hormone and IGF-I combination (1854 ± 708 ng/mL compared with 1092 ± 503 ng/mL). Insulin-like growth factor-binding protein-3 associates with an acid-labile subunit (37), and levels of both decreased in the group receiving IGF-I alone but increased and remained stable in the group treated with growth hormone and IGF-I. Both groups had similar side effects, which were limited to edema and jaw pain, but only participants receiving IGF-I alone had symptomatic hypoglycemia.

Several mechanisms might account for this enhanced response. 1) Higher serum IGF-I levels were achieved with combined growth hormone and IGF-I. 2) Growth hormone may have direct anabolic actions on muscle and skeletal tissues. 3) The growth hormone and IGF-I combination may be more effective in improving tissue IGF-I levels, and this change may be more important than increasing serum IGF-I concentrations. 4) Clear-
ance of IGF-I may be markedly altered by the coad-
ministration of growth hormone, which stabilizes the
ternary IGF-binding complex, potentially providing sus-
tained metabolic action. 5) Combined growth hormone
and IGF-I results in substantially greater serum insulin
concentrations, and maintaining insulin concentrations
may augment the anabolic effect of IGF-I.

The growth hormone and IGF-I combination offers
hope for patients who are severely catabolic and refrac-
tory to either hormone alone or who are at risk for
hypoglycemia with IGF-I alone. The results also sug-
gest that chronic conditions such as short stature in
children with relative growth hormone insensitivity may
respond to combined growth hormone and IGF-I ther-
apy, which is safe and more efficacious. Whether this
degree of improvement can be achieved in multiple
clinical situations must be determined.

Combined Insulin-like Growth Factor I and Insulin
Therapy in Insulin-dependent Diabetes Mellitus

Dr. Mark A. Bach (Developmental Endocrinology
Branch, National Institute of Child Health and Human
Development): Many young patients with insulin-depen-
dent diabetes mellitus have some degree of growth hor-
mones resistance, as shown by decreased circulating
IGF-I levels, despite increased levels of growth hor-
mone, and by an inability to produce an appropriate
increase in IGF-I in response to exogenous growth hor-
mone (38-40). This functional refractoriness to growth
hormone is also seen in starvation and may be due to
insufficient portal vein insulin for normal hepatic IGF-I
synthesis. Because increased growth hormone levels ex-
acerbate hyperglycemia (41) and because low IGF-I lev-
els may also contribute to deficient fuel metabolism and
growth hormone, we hypothesized that treatment of young
diabetic patients with recombinant IGF-I and insulin
might improve their metabolic/anabolic status and re-
duce the risks of overinsulinization. To evaluate the
feasibility of such an approach, we examined the effects
of short-term infusions of IGF-I on growth hormone,
IGF system parameters, and insulin requirements in
insulin-dependent diabetic and pubertal stage-matched
healthy adolescents.

The study (9) included six healthy volunteers and four
patients with insulin-dependent diabetes mellitus (mean
glycated hemoglobin levels, 10.1% ± 0.4%). Participants
were maintained on their normal diets and studied dur-
ing and after daily 10-hour (0800 to 1800 h) subcutane-
ous infusions of saline or IGF-I (20 μg/kg per hour) for
2 sequential days each. At baseline, IGF-I levels in
diabetic patients were approximately 40% lower (P <
0.001) and IGF-II levels were approximately 13% higher
(P < 0.05) than in controls. The diabetic patients were
managed on a sliding scale of regular insulin, and an
average 60% reduction in insulin dose was needed to
maintain baseline blood glucose levels during IGF-I in-
fusions. Blood glucose was not substantially different in
either group during IGF-I infusion compared with base-
line. Insulin-like growth factor I was well tolerated by
all participants, none of whom had hypoglycemia or
other adverse effects. Levels of IGF-I increased ap-
proximately three times by the end of the daily IGF-I
infusion. The rates of increase and decrease in IGF-I
levels were identical in the healthy and diabetic partic-
pants, and as IGF-I levels increased, IGF-II levels de-
creased sharply in both groups. In the diabetic patients,
IGF-binding protein-1 levels increased more than two-
fold after 2 days of IGF-I infusions, whereas no sub-
stantial increase in this binding protein was observed in
healthy participants. Insulin-like growth factor-binding
protein-1 is normally suppressed by insulin (12, 13), but
whereas the diabetic patients received about 60% less
insulin than usual during IGF-I infusion, healthy partic-
ants also had a reduction of approximately 60% in
endogenous insulin secretion. Peripheral insulin levels
were similar in the two groups, but the healthy partic-
ants were expected to have higher portal insulin levels
than were the diabetic patients, and thus they may have
maintained some suppression of hepatic IGF-binding
protein-1 synthesis. Because IGF-I bound to IGF-bind-
ing protein-1 appears to be involved in short-term gly-
cemic regulation (13), this increase may benefit diabetic
patients. Additional studies are needed, however, to
determine whether the increase in IGF-binding protein-1
levels can be sustained during long-term IGF-I treat-
ment. Insulin-like growth factor-binding protein-3 levels
did not change during IGF-I treatment in this short-term
study.

Finally, both groups had marked suppression of sponta-
neous overnight and arginine-stimulated growth hor-
mone secretion when circulating IGF-I levels were ele-
vated (9). In the short term and with the relatively high
IGF-I levels achieved in this study, IGF-I treatment is
well tolerated and has substantial growth hormone-sup-
pressing and insulin-sparing effects in pubertal diabetic
patients. Although the primary defect in insulin-depend-
ent diabetes mellitus is insulin deficiency, treatment
with peripheral insulin may not normalize some liver
functions, such as IGF-I synthesis, that depend on the
presence of high portal insulin levels. To determine if
treatment of young diabetic patients with IGF-I and
insulin will promote better metabolic/anabolic balance
than treatment with insulin alone, while potentially
avoiding some of the undesirable effects of overinsulin-
zation, long-term studies based on an IGF-I supple-
mentation regimen that normalizes IGF-I and growth
hormone levels are needed. Close monitoring of the
development of retinal and renal diabetic complications
and of growth patterns are necessary to evaluate the
safety and utility of IGF-I adjuvant treatment in diabetic
adolescents.

Insulin-like Growth Factor I Treatment in
Non-Insulin-dependent Diabetes Mellitus

Dr. Hans-Peter Guler, (Ciba-Geigy Pharmaceuticals,
Summit, New Jersey): Earlier studies showed that
IGF-I decreases blood glucose levels in healthy persons
(42) and in diabetic patients whose anti diabetic medica-
tion is removed and who are treated with IGF-I, at least
in the short term (43). Based on these studies, it was
hypothesized that IGF-I could have beneficial effects on
blood glucose control and possibly on serum lipid levels
in type II or non-insulin-dependent diabetes mellitus. It
was also proposed that IGF-I could circumscribe insulin
resistance in these mostly obese patients by reducing hyperglycemia partly through the IGF-I receptor. A trial was conducted with seven non-insulin-dependent diabetic patients at two centers (Dr. D. S. Schalch, University of Wisconsin, Madison, Wisconsin, and Dr. S. Schwartz, Diabetes and Glandular Disease Research Center, San Antonio, Texas). Study patients had type II diabetes, were between 39 and 56 years old, had been treated with insulin for 2 months to 6 years, and had body mass indices ranging from 29.6 to 45.7 kg/m². To achieve optimal blood glucose control, the study began with a 6-week run-in phase of intermediate-acting insulin treatment twice daily, at the end of which morning fasting blood glucose (mean ± SD) was 10.4 ± 4.6 mmol/L and daily insulin dose (mean ± SD) was 1.16 ± 0.35 U/kg. For the subsequent trial phase, patients received IGF-I at a dose of either 160 or 120 μg/kg administered twice daily before morning and evening meals.

One patient included in the IGF-I injection protocol was treated for 52 days, but all others received IGF-I for a shorter period (4 to 14 days), with some terminations needed because of adverse side effects. The one patient who has received IGF-I for a relatively long time is described in some detail, whereas information on the others is discussed briefly. Data from all patients are summarized in Table 2. Patient 5 was a 52-year-old man treated with 1.3 U/kg per day of insulin in the last week of the run-in period, with fasting blood glucose measurements generally less than 8.3 mmol/L. He was treated with 120 μg/kg of IGF-I twice daily, and morning fasting blood glucose levels ranged from 5.0 to 14.4 mmol/L, slightly higher than in the run-in phase. Postprandial blood glucose profiles were similar with insulin and IGF-I, and fasting lipid levels did not change substantially during IGF-I therapy. Clinically, this patient did well during the first 4 to 6 weeks of IGF-I treatment. Except for minor tenderness and some pain in both jaw angles and slight swelling in the area of the parotid glands, he had no side effects. In the last 2 to 3 weeks, however, adverse effects appeared, including arthralgia in his hips and knees, generalized myalgia, exhaustion, lower back pain, and chills for up to 30 minutes several times each day. He recovered fully after several weeks of supportive treatment with analgesics. In the other patients, blood glucose was as well controlled with 160 μg/kg of IGF-I as with insulin, whereas patients receiving 120 μg/kg were less well controlled (Table 2). The pattern of adverse effects was similar in all patients, including jaw tenderness and edema of the face and hands; one patient also reported a transient increase in the size of his tongue associated with slurred speech. Two patients had dyspnea and weight gain; one of them was later found to have moderate aortic stenosis.

When administered at a dose of 160 μg/kg twice daily, IGF-I appears to control blood glucose nearly as well as insulin in obese, non-insulin-dependent diabetic patients, but adverse experiences led to early termination of this trial in all participants. We conclude that IGF-I is not suitable for monotherapy of non-insulin-dependent diabetes mellitus but that using IGF-I with insulin could be a next step in the evaluation of IGF-I in the treatment of these patients.

Insulin-like Growth Factor I Treatment in Extreme Insulin Resistance

Dr. Monica Skarulis (Diabetes Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland): Extreme insulin resistance results from either mutations in the insulin receptor gene or from defects in postreceptor sites critical for glucose metabolism (44, 45). The clinical course of patients with extreme insulin resistance is characterized by poor control of blood glucose despite the administration of large doses of insulin. Hypothetically, IGF-I could improve glucose metabolism in patients with defective insulin receptors by stimulating glucose uptake in skeletal muscle through IGF-I receptors (46). If a postreceptor site abnormality is the cause of the resistance, the effect of IGF-I on glucose metabolism depends on whether the defective pathway is unique to the insulin receptor or shared by both receptor types.

Several reports have suggested that IGF-I may be used to treat such patients (18-21). These reports are in contrast with our study of five patients with severe insulin resistance, in which the acute effects of IGF-I (30 μg/m² per minute) on glucose use and hepatic glucose production were compared with equimolar concentrations of insulin (500 mU/m² per minute) under con-

Table 2. Summary of Results of Insulin-like Growth Hormone Factor I Treatment in Seven Obese Patients with Non-insulin-dependent Diabetes Mellitus*

<table>
<thead>
<tr>
<th>Patient</th>
<th>BMI, kg/m²</th>
<th>Days†</th>
<th>Dose, μg/kg</th>
<th>Dose, mg</th>
<th>Morning Blood Glucose‡</th>
<th>Reason for Termination</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>38.9</td>
<td>5</td>
<td>160</td>
<td>17.3</td>
<td>Same</td>
<td>Jaw pain, dyspnea, edema (face)</td>
</tr>
<tr>
<td>2</td>
<td>45.7</td>
<td>11</td>
<td>160</td>
<td>26.2</td>
<td>Same</td>
<td>Jaw pain, back pain, dyspnea, orthostasis, edema (face, hands)</td>
</tr>
<tr>
<td>3</td>
<td>34.3</td>
<td>4</td>
<td>160</td>
<td>17.8</td>
<td>Same</td>
<td>Jaw pain, edema (face, hands, tongue)</td>
</tr>
<tr>
<td>4</td>
<td>44.4</td>
<td>14</td>
<td>120</td>
<td>10.9</td>
<td>Higher</td>
<td>Myalgia, back pain, edema (face)</td>
</tr>
<tr>
<td>5</td>
<td>36.7</td>
<td>52</td>
<td>120</td>
<td>13.5</td>
<td>Higher</td>
<td>Generalized aches, jaw pain</td>
</tr>
<tr>
<td>6</td>
<td>29.6</td>
<td>5</td>
<td>120</td>
<td>11.8</td>
<td>Same</td>
<td>Edema (face, hands)</td>
</tr>
<tr>
<td>7</td>
<td>35.2</td>
<td>10</td>
<td>120</td>
<td>10.8</td>
<td>Higher</td>
<td>Edema (face, hands, forearms)</td>
</tr>
</tbody>
</table>

*BMI = body mass index.
† Number of days of treatment before termination due to reasons listed in the last column.
‡ Fasting blood glucose values compared with previous values while taking insulin.
tions of euglycemic clamp (47). A well-characterized patient with type A insulin resistance (44), homozygous for a point mutation in the alpha-subunit of the insulin receptor (which results in an 80% to 90% decrease in the number of receptors expressed on the cell surface), showed no increase in glucose use when challenged with either insulin or IGF-I. The least insulin-resistant patient, a woman with acquired lipoatrophic diabetes, had an increase in glucose use during both insulin and IGF-I clamps, although insulin was more effective than IGF-I at the doses studied. Two other patients with lipoatrophic diabetes and one patient with uncharacterized extreme insulin resistance had no increase in glucose use during IGF-I infusion. Furthermore, hepatic glucose production was not suppressed during IGF-I treatment in any of our patients, despite the fact that free IGF-I levels known to induce hypoglycemia were attained in all patients. Insulin and C-peptide levels decreased during the IGF-I infusion.

In a study of the long-term use of subcutaneous IGF-I in an 8-year-old with the Rabson-Mendenhall syndrome, 250 µg/kg was administered twice daily for 15 months (48). This patient, found to have mutations in both alleles of the insulin-receptor gene, had uncontrolled diabetes and growth retardation despite therapy with more than 400 units of insulin daily. Therapy with IGF-I was begun after intravenous IGF-I (100 µg/kg) but not insulin (0.15 U/kg) caused hypoglycemia. The prolonged administration of IGF-I increased IGF-I levels from 5 to 50 µg/L (normal, 110 to 565 µg/L). Daily fasting and preprandial glucose measurements continued to range from 11.1 to 27.8 mmol/L and polyuria, glycosuria, and ketonuria persisted. Glycated hemoglobin remained at about 13.9% (normal, <7.6%). Insulin-like growth factor I did not suppress insulin and C-peptide levels. Despite uncontrolled diabetes during IGF-I therapy, linear growth was improved as the patient grew from 3.5 to 2.5 standard deviations from the mean for his age. No adverse effects were noted while he received therapy.

In the type A insulin-resistant patient, IGF-I did not stimulate glucose metabolism through IGF-I receptors as expected. This finding suggests that IGF-I may work through the insulin receptor in skeletal muscle as well as in the liver (49) and adipose tissue (50) and that its activity is limited by the degree of insulin resistance. Another possibility, probably operative in lipoatrophic diabetes, is that the effect of IGF-I is limited by critical postreceptor abnormalities shared by the insulin and IGF-I receptor pathways. In addition to the possibilities stated above, the lack of efficacy of long-term administration of IGF-I in the patient with the Rabson-Mendenhall syndrome may be related to the dose studied and the absence of IGFBPs to prolong the half-life of IGF-I in the circulation. The effects of IGF-I on glucose metabolism in insulin-resistant patients may be as heterogeneous as the syndrome itself, and thus it cannot be assumed that all patients with insulin resistance will benefit from this therapy.

Conclusions

Dr. Bondy: This conference reviewed data on IGF-I treatment in conditions involving different degrees of growth hormone or insulin insensitivity. Investigations of other potential clinical applications of IGF-I, including the treatment of osteoporosis, immune deficiency, peripheral neuropathy, and acute renal failure, are just beginning. Results of studies to date suggest that IGF-I can substitute for growth hormone in promoting growth in children with growth hormone insensitivity, thus supporting the role of circulating IGF-I as a mediator of the effect of growth hormone on somatic growth. Prolonged follow-up is necessary, however, to evaluate fully the growth pattern of children receiving IGF-I. Whether children with short stature associated with functional growth hormone resistance, such as is seen in chronic disease states, may benefit from treatment with IGF-I or IGF-I combined with growth hormone must be determined. Children have been treated with recombinant IGF-I for as long as 2 years and the only adverse effect that has been noted is adenoid enlargement, apparently due to a selective effect of IGF-I in promoting the growth of lymphoid tissue. Ultrasound evaluation has revealed splenic enlargement in some children, but this has not been clinically evident. Adults experience a range of adverse effects, primarily due to soft tissue edema, which are not seen in children. The most prominent and consistent complaint associated with IGF-I treatment in adults is jaw pain, probably caused by parotid inflammation. Nerve entrapment, presumably due to soft tissue swelling, has been observed in a few patients, but these and other side effects, such as arthralgias, have resolved after withdrawal of IGF-I treatment. Hypoglycemia does not appear to be a problem as long as IGF-I is not used in fasting patients. Experience with IGF-I treatment is limited and the risks of long-term treatment are not known.

Pilot studies in calorically restricted normal volunteers suggest that growth hormone and IGF-I combination therapy may be useful in treating the protein-wasting catabolic states that affect patients in the intensive care unit setting and with chronic diseases, but further study of the effects of these agents in such patients is needed. Preliminary study of the effects of IGF-I treatment in insulin-dependent diabetes mellitus indicates that this hormone may have insulin-sparing effects; however, additional studies are needed to evaluate the effects of normalization of IGF-I levels on long-term metabolic control and diabetic complications. The role of IGF-I as a hypoglycemic agent in the spectrum of insulin-resistant diabetes is being studied actively. Insulin-like growth factor I treatment clearly reduces blood glucose in non-insulin-dependent diabetes mellitus, but its use as a sole agent in some patients may be limited by side effects. Lower doses of IGF-I in combination with other hypoglycemic agents or diet and exercise regimens might be more successful in these obese patients. The latter approach appears particularly attractive because augmenting IGF-I levels might be expected to enhance muscular strength and exercise capacity. Although several studies found that IGF-I effectively controlled blood glucose in nonobese patients with extreme insulin resistance (18-21), the National Institute of Diabetes and Digestive and Kidney Diseases experience in treating patients with the most extreme forms of insulin resistance has been largely negative.
Even if it does not prove to be clinically useful in these patients, the study of the effects of IGF-I in patients with defined genetic lesions causing insulin resistance should help delineate the relation between insulin and IGF-I receptors.

Finally, these studies show clearly that the therapeutic effects of IGF-I must be evaluated in the context of ambient growth hormone, insulin, and IGF-binding protein activities. Administration of recombinant IGF-I at levels sufficient to reduce growth hormone secretion causes loss of the anti-insulin effects of growth hormone and reduces IGF-binding protein-3 ternary complex levels. This latter effect ultimately may limit effective treatment with exogenous IGF-I because, when not bound in a ternary complex, IGF-I is rapidly cleared. In addition, IGF-I reduces insulin secretion, which leads to increased IGF-binding protein-1 levels. Further definition of the physiologic effects and therapeutic potential of IGF-I must consider all these perturbations and the role of additional IGF-binding proteins present in the circulation, about which there is little information.

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