Short- and long-term metabolic effects of recombinant human IGF-I treatment in patients with severe insulin resistance and diabetes mellitus

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Abstract

In patients suffering from the genetic syndromes of severe insulin resistance it appears that diabetes develops when the adaptive hypersecretion of insulin fails and often these forms of diabetes will be insensitive to insulin treatment. The objective of the present study was to examine the metabolic and hormonal responses to an unchanged insulin therapy with the addition of a subcutaneous administration of recombinant human IGF-I (rhIGF-I) during (a) a short-term (2 weeks) period with rhIGF-I given twice a day in a high dose (80 μg/kg body weight) in four patients with extreme insulin-resistant diabetes mellitus and (b) during a long-term (10 weeks) period with rhIGF-I given once a day in a low dose (40 μg/kg body weight) in three of the four patients. Two siblings had known mutations in the tyrosine kinase domain of the insulin receptor and a deletion of exon 17 in part of their insulin receptor mRNA, whereas the remaining two patients were suspected to have defects at receptor and/or post-receptor sites. In the short-term study period, plasma glucose levels decreased more than 35% in response to rhIGF-I in all but one patient which was paralleled by reduced levels of serum insulin (25–50%), proinsulin (40–50%) and C-peptide (10–65%) and an improvement in glycaemic control as evaluated by decreased glycosylated haemoglobin and serum fructosamine. During the long-term study period blood glucose-lowering effects of rhIGF-I were seen after 2 weeks of treatment and fasting plasma glucose and serum insulin and C-peptide levels were decreased by 40–55% after 6 weeks in the two siblings with known insulin receptor mutations. After 10 weeks of treatment fasting plasma glucose levels were still decreased whereas fasting serum insulin and C-peptide levels were increased almost to pretreatment values. In conclusion: 2 weeks of high-dose rhIGF-I therapy in insulin-treated patients with severe insulin resistance has a marked lowering effect on fasting plasma glucose and serum insulin levels whereas the metabolic and glycaemic effects of 10 weeks of treatment with low-dose rhIGF-I may be modest and transient.

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Introduction

The genetic syndromes of extreme insulin resistance are commonly associated with acanthosis nigricans, a hyperkeratotic hyperpigmented skin lesion, and ovarian masculinization (1). A series of different mutations in the insulin receptor gene is associated with some of the syndromes of severe insulin resistance, whereas post-receptor molecular defects are likely to be dominant in other cases of severe insulin resistance (1). The insulin resistance in these syndromes is often compensated by a marked increase in endogenous insulin secretion. However, when this adaptation is insufficient frank diabetes mellitus that does not respond adequately to insulin therapy occurs.

Insulin-like growth factor-I (IGF-I) is a 70 amino acid peptide that regulates growth and development as well as metabolism. The actions of IGF-I result from the integration of its effects on cellular proliferation, overall anabolism, and the synthesis of specific macromolecules that support differentiated function (see (2) for review). IGF-I acts through IGF-I or insulin receptors or hybrids of these receptors (3). The IGF-I receptors are present at high concentrations in muscle (2) and IGF-I may thus stimulate glucose transport and glycogen synthesis, primarily via its own receptor (4, 5).

Administration of recombinant human IGF-I (rhIGF-I) to normal subjects leads to a dose-dependent decrease in blood glucose levels and a marked suppression of endogenous serum levels of insulin and C-peptide (6, 7). From studies of patients with extreme insulin resistance due to the type A insulin resistance syndrome, administration of intravenous rhIGF-I resulted in an immediate fall in blood glucose and the markedly elevated circulating levels of insulin and C-peptide fell in a parallel manner (8). Subcutaneous injections of rhIGF-I in
patients with severe insulin resistance and diabetes have also been reported to improve glycaemic control (9).

The present study was undertaken to examine the potential extent of metabolic and hormonal responses to (a) subcutaneous administration of high-dose (80 µg/kg body weight (bw) twice a day) rhIGF-I during a short-term study period (2 weeks) in four patients with extreme insulin resistance syndromes and diabetes mellitus and (b) subcutaneous administration of low-dose (40 µg/kg bw once a day) rhIGF-I during a long-term study period (10 weeks) in three of the same four patients.

Research design and methods

Subjects

Four patients with extreme insulin resistance syndromes were recruited for the study. Clinical data are presented in Table 1. The diagnosis was based on (a) the presence of massive hyperinsulinaemia, (b) extreme insulin resistance as evaluated by the euglycaemic hyperinsulinaemic clamp (patients A, C (10) and D) where insulin-stimulated glucose disposal rates were reduced by 95%, 55% and 84% respectively, when compared with a group of patients with non-insulin-dependent diabetes mellitus (NIDDM) (mean ± S.E.M. 325 ± 31 mg/m² per min) as previously reported (11) and (c) unique clinical features. All patients had diabetes mellitus and were treated with regular insulin: patient A, 2-0 U/kg bw per day; patient B, 3-5 U/kg bw per day; patient C, 3-3 U/kg bw per day; and patient D, 0-5 U/kg bw per day. All patients had been seen regularly in the outpatient clinic and no changes in insulin dosage had been made for the last 3 months. None of the patients had evidence of nephropathy or retinopathy at the initiation of the study. Patient A was a Caucasian girl, with menarche occurring at the age of 12 years. She presented with acanthosis nigricans and a mild degree of subcutaneous fat tissue atrophy but a well-developed musculature and she had had known diabetes mellitus for 5 years. Patient B was a Caucasian boy with congenital muscle fibre-type disproportion myopathy and known diabetes mellitus for 4 years (10). Patient C (an older brother to B) was a Caucasian boy likewise with congenital muscle fibre-type disproportion myopathy and known diabetes mellitus for 5 years (10). In both patients B and C a mutation in the tyrosine kinase domain of the insulin receptor inherited from their father and a deletion of exon 17 in part of their insulin receptor mRNA inherited from their mother have been shown (13). Patient D was a Caucasian woman with acquired generalized lipodystrophy and known diabetes mellitus for 3 years. Menarche had occurred at the age of 10 years and the patient had both fasting hypertriglyceridaemia and hypercholesterolaemia for which she was treated with lipid-lowering agents (nicotinic acid derivative and gemfibrozil). Laparoscopy had shown polycystic ovaries and a blood test had shown increased fasting serum levels of androgens. No hirsutism was present.

A pregnancy test in patients A and D was negative at the initiation of the study and during the long-term study (patient D).

Prior to participation, the purpose and risks of the study were carefully explained to the volunteers (and parents of patients A, B and C) and their informed consent was obtained. The protocol was approved by the local Committee of Ethics in Copenhagen and was in accordance with the Helsinki Declaration.

Protocol for short-term IGF-I treatment

All patients were admitted to the Steno Diabetes Center the day before the experimental period (day 0) which lasted for 16 days during which they stayed in hospital. Insulin was discontinued the evening before the experimental period. The patients were given their usual standard diet for diabetic subjects typically containing 50% energy as carbohydrate, 35% as fat and 15% as protein. Besides short walks in the hospital area, no physical exercise was allowed during the entire

<table>
<thead>
<tr>
<th>Table 1 Clinical data of the four patients with severe insulin resistance and diabetes mellitus.</th>
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<tbody>
<tr>
<td>Patient</td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Gender (F/M)</td>
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<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>Known duration of diabetes (years)</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
</tr>
<tr>
<td>Known insulin receptor mutations</td>
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<tr>
<td>Blood pressure (systolic/diastolic) (mmHg)</td>
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</table>

ND, not determined.
study period. Patients fasted from 2400 to 1100 h on
days 0, 1, 2 and 14 and from 2400 to 0730 h on days
3–13 and 15. A dose of 80 μg/kg bw rhIGF-I (K3160)
solution (2 mg/ml; 0·5 ml/cartridge; Pharmacia AB,
Stockholm, Sweden) was administered subcutaneously
into the abdomen at 0800 h on day 1 and then twice a
day at 0800 and 1800 h from day 2 to day 14. From day
4 (at 1730 h) the usual insulin treatment of the patients
was resumed and then continued for the rest of the
experimental period.

Changes in clinical signs and symptoms were care-
fully checked during treatment. Blood samples were
drawn on days 0, 1, 2, 4, 7 and 14 at regular intervals
to determine levels of plasma glucose, serum insulin,
serum C-peptide, serum total IGF-I, plasma IGF-binding
protein (IGFBP)-1, plasma IGFBP-3, serum potassium
and serum phosphate. Moreover, on days 0 and 15
biochemical examinations were performed to determine
fasting levels of serum total cholesterol, serum high-
density lipoprotein (HDL) cholesterol, serum triglyc-
eride, serum sodium, serum proinsulin, as well as serum
fructosamine and glycosylated haemoglobin (HbA1C).
Anti-IGF-I was measured on day 0 and again 2 weeks
after the end of the treatment protocol.

Blood pressure and heart rate were measured daily
after 10 min of rest in the supine position. The meas-
urements were carried out with an appropriately sized
cuff using an automatic, electronic device (UA-751;
Takeda Medical, Tokyo, Japan).

Examination of the fundus including stereo photo-
graphs with dilated pupils and checks for papillodea-
ema were performed before and at the end of the study.

Protocol for long-term IGF-I treatment

Six months after the short-term study, patients B, C and
D volunteered for a second IGF-I treatment. They were
given rhIGF-I (40 μg/kg bw) subcutaneously into the
abdomen at 0800 h once a day for 10 weeks. The usual
insulin treatment of the patients was continued
unchanged for the whole study period. Patients were
seen regularly (0, 2, 6 and 10 weeks) in the out-patient
clinic and were asked to measure blood glucose, body
weight and blood pressure every second day at home.
Examination of the fundus including stereo photo-
graphs with dilated pupils and checks for papilloede-
a and analysis of urine albumin excretion were performed
at each visit to the out-patient clinic. Glomerular
filtration rate measurements were performed before
and after the study period. In order to evaluate β-cell
function, and indirectly to evaluate peripheral insulin
sensitivity, an intravenous glucose tolerance test (IVGTT)
was performed at day 0 and after 6 and 10 weeks of
treatment after a 10-h overnight fast with measure-
ment of plasma glucose, serum insulin and C-peptide
concentrations. Furthermore, fasting blood samples
were drawn on the same days for analysis of biochem-
ical variables as mentioned above.

IVGTT

The IVGTT (0·3 g/kg bw) lasted for 90 min. Venous
blood was sampled at baseline and 2, 3, 4, 5, 6, 7, 8, 9,
10, 11, 12, 15, 20, 25, 30, 40, 50, 60, 70, 80 and
90 min after the glucose injection, for measurements of
plasma glucose, serum insulin and serum C-peptide
levels. In addition, serum proinsulin levels were
measured at baseline.

Analytical methods

Glucose in plasma was measured by an automated
glucose oxidase method (Granunest; Merck, Darmstadt,
Germany). Intact insulin in serum was measured by
applying an enzyme-linked two-site immunoassay (Dako
Diagnostics Ltd, Ely, Norfolk, UK) (14). The method
uses two murine monoclonal antibodies that bind to
two different epitopes on the insulin molecule. The
immunoassay is specific and no des(31,32-) or intact
proinsulin are detected by the assay. Serum C-peptide
was analyzed by RIA (15) using a polyclonal antibody
M 1230 (16, 17). Serum proinsulin was determined by
ELISA with a broad specificity including all four pro-
insulin conversion intermediates (65–99%) with intact
proinsulin (100%) (18). For measurement of serum
values of insulin, proinsulin and C-peptide, the detection
limit and coefficients of variation were 5 pmol/l and
0·09, 1·2 pmol/l and 0·09, 60 pmol/l and 0·08 respec-
tively. HbA1C was measured using Bio-Rad Variant
(Bio-Rad, Hercules, CA, USA), normal range 4·1–6·4%.
Fasting serum levels of total cholesterol, HDL chole-
sterol, triglycerides, sodium, potassium, plasma phos-
phate and fructosamine were analyzed using routine
methods.

During the short-term study period, total serum IGF-I,
plasma IGFBP-1, plasma IGFBP-3 and anti-IGF-I were
all analyzed using RIAs (performed by Pharmacia AB).
For IGF-I (normal range: 119–262 ng/ml) the detection
limit for undiluted samples was 20 ng/ml and the intra-
and interassay coefficients of variation (at a concentra-
tion of 200 ng IGF-I/ml) were 0·03 and 0·10 respec-
tively. The cross-reactivity for IGF-II was approxi-
ately 1%, whereas for insulin, proinsulin and smaller
IGF-I fragments the cross-reactivity was negligible. For
IGFBP-1 (normal range: 6·74–12·46 ng/ml) the mea-
suring range was 1·8–178 ng/ml and the intra-
and interassay coefficients of variation were 0·03 and 0·13
respectively. Cross-reactivity for plasma IGFBP-3 was
below 0·003%. For plasma IGFBP-3 (normal range:
3·21–5·15 mg/ml) the measuring range was 0·075–
128 μg/ml and the intra- and interassay coefficients of
variation were 0·05 and 0·07 respectively. Cross-
reactivity for IGFBP-1, IGFBP-2 and IGFBP-4 was
below 0·3%. Samples for anti-IGF-I yielding a titre of
≥1·0 were considered positive for anti-IGF-I, a titre
below ≤1·0 was not significantly increased. Measuring
range for positive control rabbit serum was ≥3 μg/l.
Table 2 Clinical and metabolic responses to 14 days of combined treatment with the usual insulin dose and rhIGF-I (80 μg/kg bw twice a day) in four patients with severe insulin resistance.

<table>
<thead>
<tr>
<th></th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
<th>Patient D</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 15</td>
<td>Day 0</td>
<td>Day 15</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>48.0</td>
<td>49.0</td>
<td>23.0</td>
<td>23.1</td>
</tr>
<tr>
<td>S-fructosamine (μmol/l)</td>
<td>595</td>
<td>509</td>
<td>355</td>
<td>292</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>16.4</td>
<td>14.8</td>
<td>10.7</td>
<td>9.3</td>
</tr>
</tbody>
</table>

**Fasting**
P glucose (mmol/l) 14.8 12.1 9.3 4.2 16.8 5.6 15.1 9.5
S insulin (pmol/l) 2820 2980 3870 2190 2080 1590 281 139
S proinsulin (pmol/l) 53 75 318 160 93 54 156 87
S C-peptide (pmol/l) 1115 1535 2165 760 1465 1554 173 847
S IGF-I (ng/ml) 91 245 309 819 913 1554 173 847
P IGFBP-1 (ng/ml) 37.0 32.0 10.0 14.0 12.0 7.0 10.4 7.0
P IGFBP-3 (mg/l) 2.45 3.91 4.88 6.81 5.55 9.61 6.81 7.01
Anti-IGF-I (titre) — 0.0 — 0.0 — 0.0 — 0.2
IGF-I/IGFBP-3 ratio 0.037 0.063 0.063 0.120 0.165 0.162 0.025 0.121
S total chol. (mmol/l) 4.2 4.3 3.1 2.9 4.3 3.1 6.2 4.4
S HDL chol. (mmol/l) 2.52 2.93 1.45 1.19 2.09 1.28 0.32 0.54
S triglycerides (mmol/l) 1.1 0.7 0.5 0.5 0.9 0.5 12.7 4.4
S phosphate (mmol/l) 1.47 1.44 1.69 2.14 1.53 1.83 1.34
S potassium (mmol/l) 3.9 4.2 4.0 3.9 4.2 4.0 4.1 4.0
S sodium (mmol/l) 142 139 141 140 138 138 138 139

* Impossible to analyze due to lipaemic plasma; S = serum; P = plasma; chol. = cholesterol.

Figure 1 Effects of the administration of subcutaneous rhIGF-I (80 μg/kg bw twice a day) in combination with the usual insulin treatment for 14 days on fasting (a) plasma glucose, (b) serum insulin, (c) serum C-peptide and (d) serum total IGF-I in four patients with severe insulin resistance and diabetes mellitus. From day 4 (at 1730h) the usual insulin doses of the patients were resumed and then continued for the rest of the experimental period. Patient A (V), patient B (O), patient C (Δ) and patient D (□).
The intra- and interassay coefficients of variation for positive test were 0.05 and 0.15 respectively. During the long-term study period, total serum IGF-I and plasma IGFBP-1 were analyzed as described previously (19, 20).

Results

**Short-term metabolic and hormonal responses to IGF-I treatment**

HbA1C, which had been severely elevated (HbA1C >10%) in all patients for more than 6 months, decreased in all participants in the study after 14 days of combined rhIGF-I and insulin treatment (Table 2). The reduction in hyperglycaemia was further confirmed by measuring serum fructosamine (Table 2).

After 7 days of treatment, fasting plasma glucose was normalized in patient B and on day 15 fasting plasma glucose was decreased by 45%. No major change in fasting plasma glucose concentration was seen in patient A (82%) whereas the decrease in patients C and D was 33 and 63% respectively (Fig. 1a). Fasting serum insulin concentration decreased in patients C, B and D whereas no change was seen in patient A (76, 57, 49 and 106% of baseline values respectively) (Fig. 1b). Comparable results were seen with regard to fasting serum C-peptide concentration (138, 35, 77 and 89% in patients A, B, C and D respectively) (Fig. 1c). In all patients, a marked, but highly variable, increase was seen in fasting serum IGF-I concentrations from day 0 to day 15 (patient A, 269%; patient B, 265%; patient C, 170%; patient D, 490%) (Fig. 1d) and in serum plasma IGFBP-3 levels (patient A, 160%; patient B, 239%; patient C, 173%; patient D, 103%).

**Long-term metabolic and hormonal responses to IGF-I treatment**

After 2 weeks of insulin treatment in combination with rhIGF-I therapy in a dose which was 25% of that used during the short-term study, fasting plasma glucose was clearly decreased in all patients (data compared with day 0), in particular in patient B (decreased by 35% compared with baseline) (data not shown). During the following 4 weeks a further decrease was observed in patients B (48%) and C (54%) whereas plasma glucose was almost unaltered in patient D (decreased by 20%). After 10 weeks of treatment a small increase was seen in patients B and C and in patient D plasma glucose rose to pretreatment level. Parallel changes were observed for serum insulin and C-peptide levels in patients B and C whereas no changes were seen in patient D (Table 3).

HbA1C, which had been elevated in all patients for more than 3 months, decreased in all study participants after 14 days of combined rhIGF-I and insulin treatment and remained decreased during the study period (Table 3). The reduction of hyperglycaemia was further confirmed by measuring serum fructosamine.
In all patients, highly variable fluctuations were seen in fasting serum IGF-I concentrations from day 0 to week 10 (Table 3). No changes were seen in fasting serum IGFBP3 levels in patients B and D, whereas a small increase was seen in patient C (24%) after 10 weeks of IGF-I treatment (Table 3).

**IVGTT during long-term rhIGF-I treatment**

IVGTT tests were performed in all three patients at the initiation of the study and after 6 and 10 weeks of treatment. A clear decrease in plasma glucose area under the curves (AUC) was seen in patients B (39%) and C (41%) and to a lesser extent in patient D (21%) after 6 weeks of rhIGF-I treatment despite lower fasting serum insulin levels (Table 3). After 10 weeks of treatment a small increase was seen when compared with results after 6 weeks. For serum insulin and C-peptide AUC, smaller decreases were seen after 6 weeks of treatment (5–26 and 12–34% respectively). However, after 10 weeks of treatment, AUC values for serum insulin and C-peptide were comparable with pretreatment levels (Table 3).

**IGF-I effects on the cardiovascular system**

Short-term rhIGF-I treatment (days 1–15: 80 μg/kg bw twice a day) had effects on blood pressure and/or heart rate in some of the patients when compared with baseline levels (day 0) (data not shown). The effects were most marked in patient B with an increase in heart rate, expressed as a percentage of baseline levels, of 187% and on systolic and diastolic blood pressure of 132% and 118% respectively. An increase in heart rate was also seen in patient A (129%) and patient C (109%), whereas heart rate was unaffected by rhIGF-I treatment in patient D (94%). Systolic and diastolic blood pressure was slightly increased in patient A (109% and 112% respectively) and patient C (115% and 119%) whereas a small decrease was seen in patient D (79% and 81%). Only patient D complained of intermittent symptoms of increased heart rate.

During the long-term study period with rhIGF-I (40 μg/kg bw once a day) blood pressure and heart rate, measured every second day by the patients, remained unchanged during the whole period.

**Other adverse effects of rhIGF-I treatment**

During the short-term study, patient B reported a single episode of mild headache on day 1 and in the evening of day 1 vomiting occurred. Patient D, who was suffering from paroxysmal attacks of migraine (hemicrania), reported intermittent mild headache during the short-term study period and also episodes of nausea. These symptoms had disappeared by the last days of the study period.

During the long-term study period no side-effects were reported or observed in the three patients.

**Discussion**

This study demonstrates that short-term rhIGF-I treatment of patients with extreme insulin resistance may improve or even normalize fasting plasma glucose levels. The improvement in the present study was accomplished even though the fasting serum insulin levels fell more than 25% in response to rhIGF-I in three of the four patients during the short-term study and more than 40% for at least 6 weeks in two of the three patients during the long-term study. The fall in fasting plasma glucose levels during rhIGF-I treatment may, in part, account for the decrease in serum insulin concentrations. However, the presence of IGF-I receptors on pancreatic beta cells (21) suggests that an inhibitory effect of IGF-I on insulin secretion may also add to lower circulating insulin levels. Moreover, human studies have shown that relatively small doses of IGF-I are able to reduce insulin and glucagon secretion during euglycaemia (5).

Although the long-term study showed improvement in the metabolic control in two of the three patients for at least 6 weeks, it also showed that the glucose- and insulin-lowering effects of rhIGF-I in the patients examined may be transient, at least when IGF-I was given in a dose which was 25% of the original dose. An increase in fasting serum insulin and C-peptide to near pretreatment levels was observed at the end of the 10-week study period and this finding was paralleled by an increase in fasting plasma glucose levels, although fasting plasma glucose levels were still 35% lower than pretreatment levels in the two patients.

Previous studies of patients with extreme insulin resistance syndromes have shown comparable effects of rhIGF-I treatment on carbohydrate metabolism (8, 9, 22). However, compared with healthy subjects, the decline in plasma glucose after rhIGF-I infusion is much slower in insulin-resistant subjects (23). This difference in glucose kinetics after rhIGF-I administration in healthy subjects may be explained by a normal function of both insulin and IGF-I receptors whereas, in patients with known defective insulin receptor functions (type A syndrome and leprechaunism) in terms of insulin binding and/or kinase activity, it has been suggested that IGF-I may exert its blood glucose-lowering effect through IGF-I receptors or hybrids of IGF-I and insulin receptors (8, 9). In two of the patients in the present study (B and D) a mutation in the tyrosine kinase domain of the insulin receptor and a deletion of exon 17 in part of their insulin receptor mRNA have been shown (13). These patients were furthermore characterized by very high concentrations of fasting serum insulin. It seems likely that IGF-I in these patients may exert its blood glucose-lowering effect partly through IGF-I receptors but also through those of the insulin receptors.
which have normal functions. In patient A, who was characterized by having acanthosis nigricans, the fasting serum insulin levels were comparable to those in the two boys but the insulin receptor status has not been examined. Only about 50% of patients with acanthosis and severe insulin resistance appear to have mutations in the insulin receptor (1). Compared with the two boys with known insulin receptor mutations, patient A had a clearly different response to short-term effects of IGF-I as no change was seen in plasma glucose or serum insulin levels after 2 weeks of treatment.

In patient D, diagnosed as having acquired generalized lipodystrophy (Lawrence syndrome), the fasting serum insulin levels were mildly increased compared with the other participants. As in patient A, the insulin receptor status was not examined in this patient. Only a very limited number of studies of patients with this syndrome has been published. A severe impairment in insulin-stimulated glucose disposal rate during clamp conditions has been demonstrated in these patients but insulin binding to the insulin receptor seems variable and only modestly impaired (1). Taken together, it seems that the insulin resistance in patient D may be due to more basic defects in the insulin signalling network which may involve both abnormalities in carbohydrate and lipid metabolism. rhIGF-I treatment for 2 weeks improved both glucose and lipid metabolism in this patient.

Although rhIGF-I administration was adjusted to body weight in all patients, the increase in circulating levels of IGF-I and changes in plasma concentrations of IGFBP-1 and IGFBP-3 and the metabolic effects were very different among the patients after 14 days of high-dose (80 µg/kg bw twice a day) IGF-I treatment. The metabolic effects of IGF-I are modulated by the concentrations of IGFBPs. These binding proteins are regulated by, for example, nutritional status, age, and a series of hormones including insulin and growth hormone (24). Free serum IGF-I concentration is inversely correlated with plasma IGFBP-1 concentrations and plasma IGFBP-1 acts as an inhibitor of the insulin-like actions of IGF-I (3). Plasma IGFBP-1 levels are increased in conditions associated with decreased serum insulin levels, e.g. in poorly controlled diabetes. Moreover, plasma IGFBP-1 levels are decreased following intravenous and oral glucose loads, mixed meals or during a euglycaemic insulin clamp (3, 24). Fasting serum insulin and IGFBP-1 levels are inversely correlated in children and young adults (24). In the present study, all patients were characterized by having high fasting serum insulin levels at entry and at the end of the study period and fasting plasma IGFBP-1 levels were also decreased in all patients except in patient A. In patient A, where only small changes were seen in serum insulin and serum C-peptide and plasma glucose levels during the study, the plasma IGFBP-1 level was markedly increased both before and at the end of the study period. The increased levels of plasma IGFBP-1 in combination with low levels of plasma IGFBP-3 and serum IGF-I, the latter probably in part due to an increased clearance of free serum IGF-I, may explain the lack of major effects of rhIGF-I treatment in this patient. Furthermore, severe insulin resistance at the level of the liver may also have decreased the inhibitory effect of insulin on the IGFBP-1 production by the liver as well as the insulin clearance (24, 25). In the other patients, fasting levels of plasma IGFBP-1 were low which may have increased the free serum IGF-I concentrations and thereby may have stimulated glucose uptake in skeletal muscle and other insulin-sensitive tissues.

From animal experiments it has been shown that IGF-I is the major regulator of plasma IGFBP-3. The effect of growth hormone on IGFBP3 seems to be indirect and mediated through IGF-I (3, 24). However, the effects of IGF-I on plasma IGFBP-3 seem less predictive, possibly due to the influence of growth hormone and nutritional status. Intravenous infusion or subcutaneous injection of rhIGF-I have been reported to decrease plasma IGFBP-3 levels, to cause small increases (24) or to cause no change in plasma IGFBP-3 levels (26). Plasma IGFBP-3 levels are increased during puberty and acromegaly and decreased in growth hormone deficiency and diabetes (3). In the present study, all but one (A) patient were characterized by having very high fasting levels of plasma IGFBP-3 at entry to the study and in all patients an increase was seen in fasting plasma IGFBP-3 after 14 days of rhIGF-I treatment. The abnormal low levels of plasma IGFBP-3 in patient A at entry to the study together with low levels of serum IGF-I may be due to dysregulated diabetes and/or to a defect in growth hormone-induced stimulation of IGF-I/IGFBP-3 production. Furthermore, low levels of plasma IGFBP-3 increase the clearance of IGF-I leading to reduced circulating IGF-I levels. Patient A had no phenotypic sign of growth retardation. Whether an increased plasma IGFBP-3 protease activity is present in the serum of the patient can only be speculated upon.

IGF-I has noticeable effects on the cardiovascular system, increasing both heart rate and stroke volume producing an increased cardiac output (25, 27), possibly through IGF-I receptors expressed in cardiovascular tissue (28). Whether a stimulation of the sympathetic activity takes place due to rhIGF-I infusion during hyperglycaemia is not known. No stimulation has been seen during euglycaemia in man (27). In the present short-term study, rhIGF-I treatment had effects on blood pressure and/or heart rate in some of the patients when compared with baseline levels (day 0). The effects were most marked in patient B with both an increased heart rate (187% above basal) and increased systolic and diastolic blood pressure (132% and 118% above basal respectively). In the other participants the changes were only minor. During the long-term study, with a much smaller rhIGF-I dose, no effects on the cardiovascular system were observed. These observations clearly indicate that the adverse effects of IGF-I treatment are in part dose-dependent.
Only a few long-term studies of high-dose (0·1–0·4 mg/kg bw twice a day) rhIGF-I treatment of patients with severe insulin-resistance syndromes (up to 16 months) (9) or NIDDM patients (up to 52 days) have been performed (12). In these studies adverse effects were reported. In the study of patients with extreme insulin resistance only minor adverse effects were noted (weight gain, malaise during fasting), but in the study of NIDDM patients the adverse effects of rhIGF-I treatment were so frequent and severe (e.g. oedema, occasional dyspnœa, arthralgias, tachycardia, flushing) that the study had to be discontinued. Circulating serum IGF-I levels during long-term IGF-I treatment of patients with NIDDM or severe insulin resistance are elevated two- to fivefold when compared with healthy individuals (9, 12, 24). It is therefore of importance to monitor the effects of these elevated levels of serum IGF-I carefully since IGF-I may be involved in the regulation of renal function and growth and in promoting proliferative retinopathy and renal hyperthrophy in patients with diabetes mellitus (7, 24).

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References

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