Adverse Effects of Recombinant Human Insulin-Like Growth Factor I in Obese Insulin-Resistant Type II Diabetic Patients

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Data from studies in diabetic rodents and evidence from clinical situations of severe resistance to insulin suggest that insulin-like growth factor I (IGF-I) is able to at least partly overcome insulin resistance. To assess the efficacy of recombinant human IGF-I in subjects with the most common form of insulin resistance, e.g., obese, type II diabetic patients, we administered recombinant human IGF-I (rhIGF) in doses of 120 and 160 μg/kg twice daily for 4–52 days to seven such individuals who had been treated previously with high doses of insulin (>0.7 $U \cdot kg^{-1} \cdot day^{-1}$). Four patients exhibited comparable or enhanced, whereas three had diminished, blood glucose control on rhIGF-I relative to that while on twice daily NPH insulin during the six-week control period. The occurrence of adverse effects in all patients compelled us to discontinue rhIGF-I administration before completing the 8-week treatment period. These adverse effects included edema primarily of the face and hands, mild weight gain, occasional dyspnea, bilateral jaw tenderness, arthralgias and myalgias, fatigue, tachycardia, flushing, orthostatic hypotension, and local burning at the injection site. We conclude that the frequency and severity of side effects associated with administering high-dose subcutaneous rhIGF-I to obese insulin-resistant diabetic patients make it an unacceptable therapeutic agent for these patients despite its ability to produce reasonable blood glucose control in ~50% of them.
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Type II diabetes, non-insulin-dependent diabetes mellitus; IGF-I, insulin-like growth factor I; rhIGF-I, recombinant human insulin-like growth factor I; BP, blood pressure; dBP, diastolic blood pressure; sBP, systolic blood pressure; GCRC, General Clinical Research Center; FBG, fasting blood glucose.

Resistance to exogenous insulin is a common problem in the treatment of obese patients with type II diabetes (1–3). In this condition, the insulin receptor is downregulated, postreceptor events are affected adversely, and increasing doses of exogenous insulin are usually given in an attempt to adequately control blood glucose levels. Unfortunately, these dose increases lead to peripheral hyperinsulinism, which in turn may aggravate insulin resistance at the receptor and postreceptor levels (1).

Insulin-like growth factor I (IGF-I), a molecule with close structural homology to insulin, has its own specific receptor, the type I IGF receptor, through which it elicits a variety of metabolic effects in vitro and in vivo that are similar to insulin (4–7). IGF-I also cross-reacts with the insulin receptor. Studies in two rodent models of diabetes, the BB and the pancreatectomized diabetic rat, indicate that IGF-I is partially able to overcome insulin resistance (8,9). In nondiabetic control animals, IGF-I and insulin have produced similar effects on glucose disposal, glycogen synthesis, and glycolysis, whereas in diabetic animals greater response is observed to IGF-I than to insulin. The mechanism underlying these observations is not clear, but it has been speculated that the type I IGF receptor is normal, whereas the insulin receptor is downregulated in these animal models.

Administration of recombinant human insulin-like growth factor I (rhIGF-I) to normal subjects leads to a dose-dependent decrease in blood glucose levels coincident with a marked suppression of endogenous serum levels of insulin and C-peptide (10,11). Short-term studies in diabetic patients who formerly were treated with diet and oral antidiabetic drugs demonstrate that blood glucose levels have responded well to rhIGF-I, and adverse experiences were minimal in one study (12) or reasonably well tolerated in the other (13). The possibility that IGF-I reverses the cellular defects in severe insulin

resistance is supported further by limited evidence from studies in three women with type A insulin resistance (14) and in one patient with Mendenhall's syndrome (15). In addition, rhIGF-I has affected blood glucose favorably in an adolescent patient in diabetic ketoacidosis, who did not respond to very high doses of insulin, which again suggests that IGF-I can overcome certain states of insulin resistance (16).

On the basis of these limited but provocative studies, we therefore studied the potential efficacy of rhIGF-I in obese type II diabetic individuals who, before the study, were maintained on high doses of insulin reflecting moderate-to-severe insulin resistance. Our study demonstrates that rhIGF-I controls blood glucose in some of these patients, but frequent and moderate-to-severe side effects unfortunately led to the premature termination of the study.

RESEARCH DESIGN AND METHODS

Ten patients with type II diabetes participated in this study. All patients had taken insulin for >2 months, exhibited insulin resistance (daily dose of >0.7 U/kg), and had an HbA_{1c} >8%. None had a history of other significant disease. At the screening, patients underwent an ECG stress test and an ophthalmological exam to rule out proliferative retinopathy. Blood pressure (BP) was <150/95 mmHg and body mass index was ≤45 kg/m^2 in all subjects. The study protocol was approved by the institutional review boards of both participating centers and the General Clinical Research Center (GCRC) Research Committee at the University of Wisconsin, Madison. All patients were properly informed of the nature of the study before signing the approved consent form.

Study design. The study design included a six-week control or run-in phase during which patients received twice daily NPH insulin and weekly counseling on diet and exercise. The doses of NPH insulin were adjusted during this period so that by the end of the sixth week, the majority of patients were as nearly euglycemic as possible under outpatient conditions. In the second or experimental phase, patients were randomized to either continue on NPH insulin or to begin subcutaneous rhIGF-I twice daily for eight weeks. All patients were admitted on the GCRC for the last two days of the control period and the first three days of the experimental period. During this time, fasting and postprandial levels of blood glucose and serum lipids were determined, and ophthalmological exams and ultrasonography of the kidneys and spleen were performed. Postprandial studies followed the ingestion of a test meal consisting of 360 ml of Sustacal liquid (Mead Johnson, Evansville, IN) the morning after a 14-h fast. Creatinine clearances on 24-h urine collections were obtained in both the run-in and experimental periods. The third phase of this study consisted of a four-week washout period designed to return all patients to prestudy condition. Three subjects were randomized to the control group and concluded NPH insulin treatments without adverse responses; their data are not included in this report. Seven subjects were randomized to the rhIGF-I treatment group, and their patient characteristics are seen in Table 1.

TABLE 1
Patient clinical characteristics

Patient (number)	Age	Sex (M/F)	BMI (kg/m^2)	Duration of diabetes (years)	Duration of insulin treatment (years)
1	49	F	38.9	15	<1
2	59	F	45.7	8	6
3	48	M	34.3	9	2
4	56	F	44.4	1.7	1.7
5	52	M	36.7	13	<1
6	56	M	29.6	7	7
7	39	F	35.2	9	<1

rhIGF-I administration. The rhIGF-I used in this study was produced by Chiron (Emeryville, CA), packaged in sterile vials containing 10 mg of lyophilized powder, and stored at 4°C. Patients were instructed on how to reconstitute the drug with 0.9% saline just before administering it. The concentration of the reconstituted rhIGF-I was either 10 or 20 mg/ml, and the injection volumes were between 0.5 and 1.2 ml, depending on the body weight of the patient and the dose of rhIGF-I required to effect reasonable glycemic control. The original dosing scheme, which was based both on data derived from a previous study (13) and preinjection blood glucose levels, is shown in Table 2. Because of the occurrence of adverse experiences in the first three patients, the 160 μg/kg dose was deleted for the last four patients.

Statistical analysis. All data are expressed as means ± SD. Significant differences between means were determined using Student's *t* test.

RESULTS

The adverse effects of administering high-dose rhIGF-I to the seven subjects in this study constitute our most prominent findings. The effects of rhIGF-I on blood glucose and serum lipid levels are mainly summarized in tabular form. Case reports are described in the order the patients were enrolled into the study. Tables 3 and 4 summarize the adverse effects and the metabolic and hemodynamic effects, respectively.

Case 1. A 49-year-old Hispanic female had a 14-year history of diabetes with peripheral neuropathy. She was moderately obese, but otherwise her physical examination was normal. The patient's stress ECG demonstrated a submaximal heart rate and was considered abnormal but not clinically significant. Her chest X ray and ophthalmological examination were within normal limits. During

TABLE 2
Dosing scheme

Preinjection blood glucose (mM)	rhIGF-I dose (μg/kg)
<5.0	90
≥5.0 to ≤6.7	120
>6.7	160

TABLE 3
Incidence of adverse effects associated with rhIGF-I administration

	Patients (*n*)
Total patients	7
Edema	
Facial	6
Peripheral	4
Temporomandibular joint (pain/tenderness)	6
Arthralgias/myalgias	4
Injection site pain	3
Flushing	3
Postural hypotension	3
Fatigue	2
Headache	2
Dyspnea	2
Erythematous rash	2
Tachycardia	1
Parotid enlargement	1
Hypoglycemia	1

the run-in period, the patient's total NPH insulin dose was gradually increased from 90 to 118 U/day (1.3 U/kg) in an effort to achieve adequate although somewhat erratic control. After this, she began rhIGF-I treatment, 160 μg/kg two times daily, and this was continued for 5 days (total cumulative dose was 1.60 mg/kg). Fasting blood glucose (FBG) values varied widely, but the mean (8.8 ± 4.5 mM) was not different than that during the control period (10.6 ± 5.0 mM). During the 5 days of rhIGF-I administration, the patient experienced mild adrenergic symptoms of hypoglycemia on one occasion associated with an 0400 blood glucose level of 4.3 mM. She also complained of some facial edema, mild bilateral jaw pain, weight gain (1.3 kg), and increasing dyspnea on exertion. For these reasons, her study was terminated. A chest X ray at that time revealed bilateral atelectasis but no pulmonary edema. Echocardiography revealed hypertensive cardiovascular disease characterized by left ventricular hypertrophy and intact left ventricular systolic function, but diminished diastolic compliance. A thallium myocardial perfusion scan suggested possible discrete areas of myocardial injury with no ischemia identified. Catheterization revealed normal coronary artery angiography, moderate aortic stenosis, and elevated left ventricular diastolic blood pressure (dBP) with secondary pulmonary hypertension. The patient subsequently recovered fully and was informed of the need for valve replacement in the future.

TABLE 4
Metabolic and hemodynamic effects of rhIGF-I administration

	Control period (NPH insulin)	Experimental period (rhIGF-I)	*P* value
Serum IGF-I (ng/ml)	134 ± 66	307 ± 112	<0.02
Blood glucose (mM)			
Fasting	9.7 ± 2.3	11.1 ± 3.0	NS
2-h postprandial	14.7 ± 3.9	11.2 ± 2.6	NS
Triglycerides (mM)			
Fasting	2.4 ± 0.4	2.1 ± 0.7	NS
2-h postprandial	2.5 ± 0.5	1.6 ± 0.3	<0.03
Cholesterol (mM)			
Fasting total	5.4 ± 0.7	4.9 ± 0.4	<0.02
Fasting HDL	1.0 ± 0.2	0.9 ± 0.2	<0.01
BP (mmHg)			
sBP	118 ± 9	136 ± 13	NS
dBP	79 ± 3	81 ± 5	NS
Heart rate (min^{-1})	79 ± 10	82 ± 9	<0.05
Creatinine clear (ml/min)	119 ± 47	170 ± 39	NS
Body weight (kg)	106 ± 13	107 ± 14	NS

Data are means ± SD.

Case 2. A 59-year-old white female had a history of diabetes for 8 years, mild hypertension, and peripheral neuropathy. Except for moderate obesity, the patient's physical examination was within normal limits. The patient's stress ECG and chest X ray were normal, whereas her ophthalmological examination showed early cataract formation. During the run-in period, the patient's NPH insulin dose was gradually increased from 64 to 144 U/day (1.2 U/kg) in an effort to achieve satisfactory glycemic control. However, at the end of this 6-week period, her mean blood glucose was still 14.2 ± 1.9 mM. At this time, the patient began rhIGF-I treatment, 160 μg/kg twice daily, and this was continued for 12 days (total cumulative dose was 3.84 mg/kg). Her blood glucose was never well controlled, with the mean FBG at 14.4 ± 3.9 mM. Her study was discontinued because of the onset of dyspnea, facial and hand edema, mild scapular discomfort, mild bilateral jaw pain, transient orthostatic symptoms, and occasional twitching of her legs. The patient subsequently underwent a workup for dyspnea and back pain. A thallium myocardial perfusion scan suggested partial reversible ischemia in the anterior and anterolateral walls. Echocardiography and heart catheterization revealed normal coronary arteries, pulmonary hypertension, and a stiff left ventricle without acute myocardial damage. The back pain was felt to be myofascial in origin and treated accordingly. The patient recovered fully from her symptoms.

Case 3. A 48-year-old white male had a history of diabetes for 9 years, mild hypertension, impotence, and peripheral neuropathy. The patient's physical examination was unremarkable except for mild hypesthesia of the lower extremities. His stress ECG, chest X ray, and ophthalmological examinations were all normal. During the run-in period, the patient's total NPH insulin dose was increased slightly from 80 to 86 U/day (0.8 U/kg). At the end of 6 weeks, he was started on rhIGF-I treatment, 160 μg/kg in the morning and 120 μg/kg in the evening for 4 days (total cumulative dose was 1.09 mg/kg). FBG levels were well controlled at 8.4 ± 0.7 mM. A single determination of 3.3 mM was not associated with symptoms of hypoglycemia. The patient complained of fatigue, headaches, a backache, mild tinnitus, bilateral jaw pain, and edema of his face, tongue, and hands. He also noted some slurred speech and, because of edematous eyelids, was no longer able to insert his contact lenses. His study was terminated because of these adverse effects.

Case 4. A 56-year-old Hispanic female had a history of diabetes for 2 years, peripheral neuropathy, and bilateral cataracts. The patient's physical examination was normal

except for her marked obesity, decreased sensory perception, and deep tendon hyporeflexia in her lower extremities. Her stress ECG and chest X ray were normal, whereas her ophthalmological examination disclosed early cataracts bilaterally. During the run-in period, the patient's total NPH insulin dose of 152 U/day (1.4 U/kg) required only slight alteration to enhance control, and her mean FBG level was 8.1 ± 2.2 mM. She then began rhIGF-I treatment (120 μg/kg two times daily), and this was continued for 14 days (total cumulative dose was 3.36 mg/kg). The patient's blood glucose control gradually deteriorated on rhIGF-I with the mean FBG rising to 14.9 ± 2.8 mM. Because of her unacceptable glycemic control, the study was discontinued. While taking rhIGF-I, the patient experienced some mild facial edema, burning at the injection sites, and moderate back myalgias. Subsequent to discontinuing the study, her midscapular pain was diagnosed as thoracic outlet syndrome possibly related to a preexisting vertebral compression fracture. The patient had a normal sedimentation rate 4 days after the last rhIGF-I administration, but it was elevated (range 35–100 mm) over the next 5 months. Her back pain gradually improved over this time.

Case 5. A 52-year-old white male had a history of diabetes for 14 years, impotence, and hypesthesia of his fingers and toes. Aside from moderate obesity and a mildly enlarged prostate, his physical examination was normal. His stress ECG test disclosed a moderately impaired functional capacity without clinical significance. His chest X ray revealed bilateral hilar calcific granulomas, whereas his ophthalmological examination showed early nonproliferative retinopathy. During the 6-week run-in period, the patient's total NPH insulin dose was 160 U/day (1.0 U/kg), and his mean FBG was 9.2 ± 2.6 mM. He was started on rhIGF-I (120 μg/kg body wt two times daily, and treatment was continued for 52 days (total cumulative dose was 12.48 mg/kg), at which time the study was terminated because of adverse responses. His blood glucose during the experimental period (6.8 ± 2.2 mM) was not different from that during the control period. The patient's weight decreased from 113 to 105.4 kg over the treatment period. Within one week of beginning rhIGF-I treatment, he experienced mild bilateral jaw tenderness and swelling in the region of the parotid glands. During the fourth week, the patient complained of intermittent hand tremors, headaches, malaise, nausea and anorexia, chills, sweating, insomnia, and nonexertional chest pain. Subsequently, he developed increasingly severe bilateral jaw pain and swelling, some injection site pain, and facial flushing occurring ~45 min after his rhIGF-I injections. He also complained of moderate abdominal tenderness and some right upper quadrant distension; myalgias of the lower extremities; arthralgias of the lower back, hips, and knees; trace edema in his legs; and hypesthesia in the right forearm associated with mild localized tenderness.

On cessation of rhIGF-I treatment, the patient recovered slowly, reporting the presence of mild bilateral jaw tenderness for approximately three weeks, and continued chills and arthralgias for five to six weeks. Seven weeks after discontinuing rhIGF-I treatment, the patient's only complaint was mild, preexisting hypesthesia in both lower extremities. Laboratory studies performed to determine the etiology of the patient's adverse responses revealed several abnormalities, including a slight eosinophilia two days before and one week after starting rhIGF-I treatment, and a mildly elevated sedimentation rate (19–28 mm) for two months after the conclusion of rhIGF-I administration. The rheumatoid factor and serum antinuclear antibody titers were positive 4 weeks after starting rhIGF-I treatment and remained so until 60 days after discontinuing it. No baseline determinations before rhIGF-I treatment had been obtained. A magnetic resonance imaging of the lumbar region to rule out an abscess as the cause of lower back pain disclosed a slight bulging of the L4/L5 intervertebral disk. Ophthalmological exam and ultrasound measurements of the kidneys and spleen size before and after rhIGF-I treatment were not significantly different.

Case 6. A 56-year-old white male had a 7-year history of diabetes, mild hypertension, and impotence. Except for mild obesity and deep tendon hyporeflexia in the lower extremities, the patient's physical examination was within normal limits. His stress ECG revealed a mildly impaired functional capacity without clinical significance, whereas his chest X ray and ophthalmological examination were normal. During the 6-week run-in period, the patient's mean FBG was 8.8 ± 3.1 mM on a total NPH insulin dose of 65 U/day (0.7 U/kg). He began rhIGF-I treatment at a dose of 120 μg/kg two times daily and continued for 6 days (the total cumulative dose was 1.32 mg/kg). The FBG value during rhIGF-I treatment (8.4 ± 1.4 mM) was comparable to that during the run-in period. After the second day of rhIGF-I administration, the patient complained of mild headache, facial flushing and edema, erythema and edema of the hands, dry mouth, orthostatic hypotension, near syncope with rapid position change, decreased energy, constipation, and bilateral jaw tenderness. Because of these adverse effects, rhIGF-I treatment was terminated after the sixth day.

Case 7. A 39-year-old white female had a 9-year history of diabetes, hypesthesia of her fingers and toes, and intermittent sciatica. Aside from moderate obesity, the remainder of her physical examination was normal. The patient's stress ECG, chest X ray, and ophthalmological examinations were all within normal limits. During the run-in period, the patient's total NPH insulin dose was increased from 96 to 142 U/day (2.5 U/kg) to achieve reasonable glycemic control. The patient then began rhIGF-I treatment (120 μg/kg two times daily), but because her blood glucose control rapidly deteriorated to >16.7 mM on the third day, her rhIGF-I was discontinued after 4 days. In addition to the patient's lack of adequate blood glucose control, she experienced mild erythema and edema of both forearms, edema of the hands, some tachycardia, presyncopal symptoms, pain at the injection sites, an episode of blurry vision, flushing, and mild left jaw tenderness.

DISCUSSION

This study in obese insulin-resistant type II diabetes patients was terminated early because of adverse expe-

riences associated with twice daily subcutaneous injections of high doses of rhIGF-I. The most frequent adverse effects associated with the rhIGF-I administration include edema, bilateral jaw tenderness, arthralgias, myalgias, fatigue, dyspnea, tachycardia, flushing, orthostatic hypotension, and local burning at the injection site.

Edema was mainly located in the face, especially periorbitally, and in the hands and fingers; generally, much less edema was seen in dependent body parts. Weight changes were highly variable and correlated poorly with symptoms. Of the seven subjects, five gained weight (range 0.4–7.5 kg), and two others lost weight (1.6 and 7.6 kg, respectively). This variability raised the suspicion that the edema seen with rhIGF-I administration was at least partly caused by vascular leakage rather than gross fluid overload. Furthermore, the observation that one patient had tongue edema in the absence of fluid retention in his legs lends additional support to the notion that rhIGF-I causes edema, not by a simple fluid overload, but rather by a second as yet undefined mechanism. On the other hand, two patients demonstrated pulmonary fluid overload that was revealed as mild pulmonary hypertension on cardiac catheterization even though chest X rays were not very impressive. Note, however, that one of these patients was diagnosed with moderate aortic stenosis that was unrecognized previously. It seems likely, therefore, that patients with preexisting cardiac conditions may have an increased risk of pulmonary fluid overload when treated with high doses of rhIGF-I.

Bilateral jaw tenderness and occasional swelling in response to rhIGF-I administration have been reported in recent trials (12,13,17), and the same symptoms were encountered in this study. Anatomically, this observation is most likely related to the parotid glands. Although no studies investigating the effects of rhIGF-I on salivary glands in rodents have been published, an eight-week course of rhIGF-I treatment in lambs resulted in an increase in the weight of their salivary glands. Macroscopically, these organs were normal (P.D. Gluckman, unpublished observation), and the mechanism underlying this phenomenon remains speculative. However, the fact that jaw tenderness and swelling observed in patients usually vanished within a few days after cessation of rhIGF-I administration suggests strongly that it is a transient process, such as the transudation of fluid into the parotids.

Arthralgias, myalgias, and fatigue are common symptoms in acromegalic patients. The etiology of these complaints in acromegalics is not clearly defined. However, normal adults (18) and hypopituitary patients (19) treated with supraphysiological doses of growth hormone experienced similar symptoms. It seems reasonable, therefore, that arthralgias, myalgias, and fatigue are at least partly related to elevations of serum levels of IGF-I. Previous studies have indicated that rhIGF-I also has cardiovascular side effects. These include modest increases in heart rate (10,12,13), tachycardia with palpitations (20), and orthostatic hypotension (13). In our study, the mean increase in heart rate for all patients was small but statistically significant. Symptoms of orthostatic hypotension were reported by three patients during rhIGF-I treatment. Although two of these patients also had pathological drops in BP during the run-in phase, symptoms were noted only while these patients were treated with rhIGF-I.

rhIGF-I exerts pronounced effects on kidney function (13,21). Our finding of an increased glomerular filtration rate in four of five patients from whom we had sufficient data in this study did not reach statistical significance but is consistent with previous reports in normal (21) and type II diabetic (13) subjects. Because the induction of hyperfiltration may be harmful to diabetic patients, the effects of rhIGF-I in this patient population would require careful study to be sure it does not have an adverse effect.

Other potentially adverse effects of rhIGF-I involve the retina. One study has shown that diabetic patients with advanced retinopathy had higher circulating IGF-I levels than patients without retinopathy (22), whereas another observed that intraocular levels of IGF-I were higher in diabetic patients with retinopathy than those without retinopathy (23). A recent study demonstrated that the blood-retinal barrier changed significantly in normal subjects given a continuous subcutaneous infusion of rhIGF-I ($10\ \mu g \cdot kg^{-1} \cdot h^{-1}$) over 5 days; fluorescein angiography revealed a substantial increase of the plasma penetration ratio (24).

Some of the adverse effects in response to rhIGF-I administration have been described previously by us and others (12,13), but they were only mild in nature. However, these studies were of short duration with rhIGF-I administration for only 5 days. Two recent studies that used rhIGF-I in patients with severe insulin resistance have been published. In one study (25), two type A patients received rhIGF-I at a dose of 100 μg/kg two times daily for 3 weeks. In the other (26), 11 patients with extreme insulin resistance were given rhIGF-I in doses of 100–400 μg/kg two times daily for up to 16 months. Biochemical responses were excellent: Hyperglycemic patients experienced lower blood glucose as well as C-peptide and insulin levels, whereas normoglycemic subjects had marked reductions of endogenous insulin secretion without hypoglycemia. Adverse experiences, if any, seem to have been minimal in these studies. Patients in one of these studies (26) were of either normal or less than ideal body weight, in contrast to the obesity of the subjects in our study. The discrepancy between the frequency and severity of side effects presented in this study and the virtual absence of such in the above-mentioned studies (25,26) may be the result of the administration of much higher doses of rhIGF-I relative to lean body mass used in our study. However, it does not seem likely that a reduction in the dose of rhIGF-I used in our study would have maintained blood glucose levels in an acceptable range while reducing adverse side effects. For example, 2 of the 4 patients treated with 120 μg/kg two times daily of rhIGF-I experienced an obvious deterioration of blood glucose control, whereas a third patient was reasonably well controlled on this dose, although not as well as when on NPH insulin. In the fourth patient, glycemic control during rhIGF-I administration

was comparable with that on NPH insulin until the study was discontinued on the sixth day because of adverse effects. Only one mild hypoglycemic episode occurred during our study, which points to the fact that IGF-I has a much lower hypoglycemic potency than insulin (27).

In summary, this study has demonstrated that rhIGF-I is a blood glucose-lowering agent in some, though not all, obese insulin-resistant type II diabetic patients. However, the total dose of rhIGF-I ($\geq$240 $\mu g \cdot kg^{-1} \cdot day^{-1}$) required to provide reasonable blood glucose control was not well tolerated. Adverse experiences were frequent and led to discontinuing the study in all seven patients. Potential adverse effects of rhIGF-I on the retinas and kidneys of such patients would require additional studies.

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REFERENCES

1. DeFronzo RA, Ferranini E: Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care* 14:173–94, 1991
2. Reaven G: Banting Lecture 1988: role of insulin resistance in human disease. *Diabetes* 37:1595–1607, 1989
3. Kaplan NM: The deadly quartet: upper-body obesity, glucose intolerance, hypertriglyceridemia and hypertension. *Arch Intern Med* 149:1514–20, 1989
4. Bach LA, Rechler MM: Insulin-like growth factors and diabetes. *Diabetes Metab Rev* 8:229–57, 1992
5. Turkalj I, Keller U, Ninnis R, Vosmeer S, Stauffacher W: Effect of increasing doses of rhIGF-I on glucose, lipid, and leucine metabolism in man. *J Clin Endocrinol Metab* 75:1186–91, 1992
6. Rennert NJ, Caprio S, Sherwin RS: IGF-I inhibits glucose stimulated insulin secretion but does not impair glucose metabolism in normal humans. *J Clin Endocrinol Metab* 76:804–806, 1993
7. Boulware SD, Tamborlane WV, Sherwin RS: Diverse effects of insulin-like growth factor I on glucose, lipid and amino acid metabolism. *Am J Physiol* 262:E130–33, 1992
8. Rosetti L, Frontoni S, Dimarchi R, DeFronzo RA, Giaccari A: Metabolic effects of IGF-I in diabetic rats. *Diabetes* 40:444–48, 1991
9. Jacob RJ, Sherwin RS, Bowen L, Fryburg D, Fagin KD, Tamborlane WV, Shulman GI: Metabolic effects of IGF-I and insulin in spontaneously diabetic BB/w rats. *Am J Physiol* 260:E262–68, 1991
10. Kerr D, Tamborlane WV, Rife F, Sherwin RS: Effect of insulin-like growth factor I on the responses to and recognition of hypoglycemia in humans: a comparison with insulin. *J Clin Invest* 91:141–47, 1993
11. Zenobi PD, Graf S, Ursprung H, Froesch ER: Effects of insulin-like growth factor I on glucose tolerance, insulin levels and insulin secretion. *J Clin Invest* 89:1908–13, 1992
12. Zenobi PD, Jaeggi-Groisman SE, Riesen WF, Roder ME, Froesch ER: Insulin-like growth factor I improves glucose and lipid metabolism in type II diabetes mellitus. *J Clin Invest* 90:2234–41, 1992
13. Schalch DS, Turman NJ, Marcsisin VS, Heffernan M, Guler H-P: Short-term effects of recombinant human insulin-like growth factor I on metabolic control of patients with type II diabetes mellitus. *J Clin Endocrinol Metab* 77:1563–68, 1993
14. Schoenle EJ, Zenobi PD, Torresani T, Werder EA, Zachman M, Froesch ER: RhIGF-I reduces hyperglycemia in patients with extreme insulin resistance. *Diabetologia* 34:675–79, 1991
15. Quin JD, Fisher BM, Paterson KR, Inoue A, Beastall GH, MacCuish AC: Acute response to rhIGF-I in a patient with Mendenhall's syndrome. *N Engl J Med* 323:1425–26, 1990
16. Usala AL, Madigan T, Burguera B, Sinha MK, Caro JF, Cunningham P, Powell JG, Butler BC: Brief report: treatment of insulin resistant diabetic ketoacidosis with insulin like growth factor I in an adolescent with insulin dependent diabetes. *N Engl J Med* 327:853–57, 1992
17. Kupfer SR, Underwood LE, Baxter RC, Clemmons DR: Enhancement of the anabolic effects of growth hormone and insulin-like growth factor I by use of both agents simultaneously. *J Clin Invest* 91:391–96, 1993
18. Lehmann S, Cerra FB: Growth hormone and nutritional support: adverse metabolic effects. *Nutr Clin Pract* 7:27–30, 1992
19. Salomon F, Cuneo RC, Hesp R, Sonksen PH: The effect of treatment with rhGH on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med* 321:1797–1803, 1989
20. Ebeling PR, Jones JD, O'Fallon WM, Janes CH, Riggs BL: Short-term effects of rhIGF-I on bone turnover in normal women. *J Clin Endocrinol Metab* 77:1384–87, 1993
21. Hirschberg R, Brunori G, Kopple JD, Guler HP: Effects of IGF-I on renal function in normal men. *Kidney Int* 43:387–97, 1993
22. Merimee TJ, Zapf J, Froesch ER: Insulin-like growth factors–studies in diabetics with and without retinopathy. *N Engl J Med* 309:527–30, 1983
23. Grant M, Russell B, Fitzgerald C, Merimee TJ: Insulin-like growth factors in vitreous: studies in control and diabetic subjects with neovascularization. *Diabetes* 35:416–20, 1986
24. Hussain MA, Studer K, Messmer EP, Froesch ER: Changes in the blood retinal barrier under treatment with IGF-I in healthy men (Abstract 3). In *Fourth International Symposium on Insulin, IGF's and Their Receptors, Woodshole MA, 1993* American Diabetes Association, Alexandria, VA
25. Morrow L, O'Brien M, Molles D, Flier J, Moses A: Recombinant human (rh)IGF-I improves hyperglycemia and insulin sensitivity in severe insulin resistance (Abstract 47). In *Fourth International Symposium on Insulin, IGF's and Their Receptors, Woodshole MA, 1993* American Diabetes Association, Alexandria, VA
26. Kuzuya H, Mtsuura N, Sakamoto M, Makino H, Sakamoto Y, Kadowaki T, Suzuki Y, Kobayashi M, Akasawa Y, Nomura M, Yoshimasa Y, Kasuga M, Goji K, Nagataki S, Oyasu H, Imura H: Trial of IGF-I therapy for patients with extreme insulin resistance syndromes. *Diabetes* 42:696–705, 1993
27. Guler HP, Zapf J, Froesch ER: Short-term metabolic effects of rhIGF-I in healthy adults. *N Engl J Med* 317:137–40, 1987