rhIGF-I Administration Reduces Insulin Requirements, Decreases Growth Hormone Secretion, and Improves the Lipid Profile in Adults With IDDM

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IDDM is associated with elevated circulating levels of growth hormone (GH) and reduced insulin-like growth factor I (IGF-I). GH antagonizes the action of insulin-increasing insulin requirements in IDDM. The effects of subcutaneously administered rhIGF-I on glycemic control, insulin requirements, and GH secretion were studied in eight adults with IDDM. Patients received either placebo or rhIGF-I (50 μg/kg b.i.d.) for 19 days in a randomized, double-blind, parallel-design, placebo-controlled trial. Overnight GH, plasma glucose, free insulin, IGF-I, fructosamine, and lipid profiles were assessed during this period. rhIGF-I therapy increased IGF-I concentration from 117.1 ± 14.2 (mean ± SE) ng/ml (baseline) to 310.5 ± 40.6 and 257.1 ± 41.2 ng/ml on day 5 ($P < 0.01$ vs. baseline) and day 20 ($P < 0.01$ vs. baseline), respectively. After 19 days of rhIGF-I treatment, fructosamine concentrations were unchanged compared with baseline (439 ± 32 vs. 429 ± 35 μmol/l, day −1 vs. day 20, respectively), yet insulin requirements were decreased by ~45% (0.67 ± 0.08 vs. 0.36 ± 0.07 U · kg^{-1} · day^{-1}, day −1 vs. day 19, respectively, $P < 0.005$). After 4 days of rhIGF-I therapy, there was a decrease in free insulin levels (8.38 ± 1.47 vs. 4.98 ± 0.84 mU/l, $P < 0.05$), mean overnight GH concentration (12.6 ± 3.3 vs. 3.8 ± 2.1 mU/l, $P = 0.05$), and total cholesterol and triglycerides (4.68 ± 0.31 vs. 4.25 ± 0.35 mmol/l, $P < 0.05$, 1.27 ± 0.19 vs. 0.95 ± 0.21 mmol/l, $P < 0.001$, respectively). There was no change in any variable in the placebo-treated patients. This study demonstrates that subcutaneous administration of rhIGF-I decreases insulin requirements and improves the plasma lipid profile while maintaining glycemic control in adults with IDDM. The excess nocturnal release of GH, characteristic of IDDM, is also decreased by rhIGF-I therapy.

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CV, coefficient of variation; GH, growth hormone; IGF-I, insulin-like growth factor I; NEFA, nonesterified fatty acid; REE, resting energy expenditure; rhIGF-I, recombinant IGF-I; RIA, radioimmunoassay.

Exogenous rhIGF-I therapy may have a role in the treatment of adults with IDDM, particularly in the setting of abnormal lipids and a high insulin requirement. ***Diabetes*** **46:1453–1458, 1997**

Human insulin-like growth factor-I (IGF-I) shares 48% sequence homology with human proinsulin (1) and exhibits both insulin-like and anabolic properties (2). Recombinant technology has led to the widespread availability of recombinant IGF-I (rhIGF-I), and the effects of this compound have been studied in several conditions, in particular in normal, growth-retarded, and catabolic subjects (3–5) and more recently in patients with IDDM (6,18).

The growth hormone (GH)/IGF-I axis is disordered in IDDM, resulting in low levels of IGF-I and high levels of GH (7). These abnormalities are most evident during periods of poor glycemic control but do not resolve completely, even when control is optimal (8). The liver is the origin of most of the circulating IGF-I, and both insulin and GH are regulators of hepatic IGF-I production (9,10). Evidence suggests that insulin delivery to the liver via the portal system is important for IGF-I generation (11–13). This may explain why patients with IDDM, with systemic insulin delivery, have reduced circulating IGF-I, even during periods of good glycemic control. Reduced negative feedback at the hypothalamic and pituitary levels, in turn, may explain the GH hypersecretion characteristic of IDDM (14).

The elevated GH levels, particularly at night, are thought to result in reduced insulin sensitivity and thus increase insulin requirements, adversely affecting glycemic control (15,16). In addition, elevated levels of GH have been implicated in the development of the long-term microvascular complications of diabetes (17). Exogenous rhIGF-I administration has been shown to decrease GH levels in adolescents with IDDM (18), but it has not been determined whether similar effects would be observed in adult subjects with relatively lower GH levels.

Administration of rhIGF-I has been shown to improve glycemic control in type 2 diabetes (19) and in diabetic subjects with severe insulin resistance (20) and also to decrease levels of insulin and triglyceride in healthy individuals without altering plasma glucose concentration (21,3). The actions of IGF-I may be mediated through several mechanisms, including increasing peripheral glucose disposal (22), decreasing insulin secretion (23), and improving insulin sensitivity, pos-

sibly by decreasing GH secretion (18). This study is the first to examine the effects of rhIGF-I on glycemic control, plasma lipid profiles, GH secretion, and insulin requirements in adult patients with IDDM.

RESEARCH DESIGN AND METHODS

Subjects. Eight adult patients with IDDM participated in a randomized, double-blind, parallel-design, placebo-controlled trial of rhIGF-I treatment. The patients' characteristics are summarized in Table 1. All patients had stable diabetic control with an HbA_{1c} of 7.7 ± 0.5% (range 5.9–9.3; reference range 4.5–6.2), a plasma C-peptide concentration of ≤0.3 µmol/l in the presence of a plasma glucose ≥6 mmol/l, and were on twice-daily subcutaneous soluble and isophane insulin replacement (0.68 ± 0.06; range 0.39–0.89 $U \cdot kg^{-1} \cdot day^{-1}$). The patients were in good general health, without advanced complications of diabetes and with normal thyroid, renal, and hepatic function. The study was approved by the Ethics Committee, Guy's and St. Thomas' NHS Trust, and all patients provided written informed consent.

Experimental protocol. Six patients were randomized to receive rhIGF-I at a dose of 50 µg/kg b.i.d. via subcutaneous injection, and two patients were randomized to receive placebo. The rhIGF-I was provided by Cephalon (West Chester, PA) and was supplied reconstituted in vials at a concentration of 8 mg/ml. Separate injections of insulin and rhIGF-I were self-administered adjacently into the subcutaneous tissue of the abdomen at 0830 and 1830. The dose of rhIGF-I remained constant throughout the study. With the first dose of rhIGF-I/placebo, both the soluble and isophane insulin doses were decreased by 50% with further adjustment based on both laboratory and home blood glucose measurements to maintain adequate blood glucose control throughout the protocol. After a baseline evaluation, rhIGF-I/placebo therapy began on day 1 and continued until day 19, followed by a 4-day washout period up to day 24. Intensive investigations were performed during the first 5 days of the study, and during this period, the patients remained resident in the metabolic unit of the hospital. All subjects received a fixed diet consisting of 30 kcal/kg body weight and made up of 50% carbohydrate, 30% fat, and 20% protein provided as breakfast (0830), lunch (1230), and an evening meal (1830). On the first day (day –1) before commencement of rhIGF-I/placebo, the patients underwent an overnight GH secretion profile, with 30-min sampling intervals, beginning at 2200 and ending at 0730. After 4 days of IGF-I/placebo therapy, an identical overnight GH secretion profile was performed. Venous blood was drawn from indwelling cannulas (Venflon, Viggo, Helsinborg) during the resident phase of the study for the determination of plasma glucose, serum free insulin, plasma cholesterol and triglyceride, and serum IGF-I concentrations. Each morning during this phase (days 1–5), fasting blood samples were taken before rhIGF-I and insulin administration. On the day of admission (day –1) and the follow-up visits to the hospital (days 12, 20, and 24), nonfasting blood samples were taken for these measurements. On all occasions, samples were centrifuged within 30 min and plasma stored at –70°C until analysis. Respiratory gas exchange and resting energy expenditure were measured by indirect calorimetry using a computerized open loop gas analyzer system (Medical Graphics Corporation, MN), and 24-h urinary collections for urea nitrogen were performed on days 1 and 5 to allow calculation of resting energy expenditure and rates of substrate metabolism. After 5 days in the hospital, patients were discharged and returned for continued surveillance on days 12, 20, and 24. Insulin requirements were assessed as total daily dose of insulin required for adequate blood glucose control and were estimated for the first 5 days and each of the surveillance days throughout the study. Plasma fructosamine concentrations were estimated on the day before commencement (day –1) and the final day (day 20) of rhIGF-I/placebo therapy. Retinal photography (45° single field using a Canon CR4 nonmydriatic fundus camera; Canon, Japan) was performed on the first and final days of the study.

Assays. GH was measured by a double antibody radioimmunoassay (RIA) with a detection limit of 0.5 mU/l. Intra-assay coefficient of variation (CV) was 10.0, 4.0, and 5.4% at 1.7, 12.1, and 22.2 mU/l, respectively. Total IGF-I was measured by double antibody RIA after acid/ethanol extraction, using a commercially available reagent pack (Amersham, Arlington Heights, IL). Standard curves were shown to be reproducible with a range of 0.195–50.00 ng/ml. IGF-I levels in human serum could be quantified with a precision range of 5.1–14.0% CV and an absolute accuracy range of 0.2–22% of the mean expected values. The assay was found to be specific and was not interfered by the presence of IGF-II, insulin, and IGF-binding protein 3. Total cholesterol and triglyceride were measured enzymatically (Boehringer Mannheim, Germany) using a Cobas Fara autoanalyzer (Roche, Milton Keynes, U.K.). Interassay CVs for cholesterol and triglyceride were 2.8 and 3.6% at 2.5 and 8.9 nmol/l; 3 and 2.8% at 1.8 and 3 mmol/l, respectively. HDL cholesterol was measured enzymatically (Boehringer Mannheim, Germany) after precipitation of apolipoprotein B–containing proteins with dextran sulfate/magnesium chloride. LDL cholesterol was estimated using the Friedewald formula (24). Nonesterified fatty acid (NEFA) and glycerol were measured by enzymatic/colorimetric methods using commercially available kits (NEFA, Wako, Neuss, Germany; glycerol, Randox, Co. Antrim, North Ireland) on a Cobas Fara autoanalyzer. Interassay CV was 3.6 and 3.2%, respectively. Samples for free insulin were extracted from serum using 30% polyethylene glycol in 0.05 mol/l barbital buffer (pH 8.6). The insulin was then assayed using a double antibody RIA with an interassay CV <9% and intra-assay CV <6% (25). Plasma glucose concentration and urinary urea nitrogen were measured on an autoanalyzer (Kodak 250, Ortho Clinical Diagnostics, Amersham, U.K.), and rates of substrate utilization were calculated using standard equations (26).

Analysis of GH secretion. Analysis of GH secretion was performed using Pulsar (14) with Wilcoxon's matched pairs signed-rank test used for comparison of variables. Fourier analysis was used to assess the periodicity of GH secretion (27).

Statistics. All data are presented as means ± SE. Statistical analysis was performed on an Excel spreadsheet (Microsoft). Analysis was performed using *t* tests and analysis of variance (for analysis of data from more than two time points). *P* values <0.05 were considered significant.

RESULTS

Clinical. rhIGF-I administration was well tolerated by all subjects. One female patient experienced fluid retention, which resolved with the onset of menses. Four patients (all of whom received rhIGF-I) suffered headache on a least one occasion during the 19 days of treatment, which resolved either spontaneously or after a single dose of a mild analgesic. No episode of severe hypoglycemia or diabetic crisis occurred during the study period. Retinal photography remained unchanged during the study period in all patients and no optic disk swelling was seen.

IGF-I. The baseline IGF-I concentrations (117.1 ± 14.2 ng/ml) were at the lower limit of the normal range for age-matched healthy control subjects (97.9–475.8 ng/ml). Administration of rhIGF-I resulted in a greater than twofold rise in serum IGF-I level, and concentrations remained elevated until day 20 ($P < 0.05$). Throughout the study serum IGF-I concentrations remained within the normal range and values

TABLE 1
Patient demographics and characteristics

Patient	Sex	Age (years)	BMI (kg/m^2)	Duration of diabetes (years)	HbA_{1c} (%)	Insulin (U/kg/day)	Randomization
1	F	30	23	19	7.5	0.67	rhIGF-I
2	F	46	20	11	5.7	0.58	rhIGF-I
3	F	28	32	15	7.6	0.89	rhIGF-I
4	M	49	25	10	5.9	0.39	rhIGF-I
5	M	25	19	21	8.8	0.92	rhIGF-I
6	M	34	26	5	7.5	0.60	rhIGF-I
7	M	44	31	10	9.0	0.65	Placebo
8	M	24	21	6	9.3	0.77	Placebo

returned to baseline 4 days after cessation of therapy (Fig. 1). There was no change in the serum IGF-I concentration in the patients who received placebo.

Insulin requirement and glycemic control. Insulin requirement (assessed as number of units per kilogram per day required for satisfactory glycemic control) decreased by ~45% in patients who received rhIGF-I therapy (0.67 ± 0.08 vs. 0.36 ± 0.07 U · kg^{-1} · day^{-1}, $P < 0.005$, day −1 vs. day 19, respectively). Initially, both soluble and isophane insulins were reduced by 50% and this relationship was maintained throughout the study. The total daily insulin dose for each of the intensive investigation and surveillance days, and the morning plasma glucose values from days 1–5, are displayed in Fig. 2. After the initial 50% reduction in insulin dose, both placebo patients required an immediate increase, achieving baseline insulin replacement values within 48 h. Fasting serum free insulin was lower after 4 days rhIGF-I therapy ($P < 0.05$, Table 2). In the subjects receiving rhIGF-I, mean overnight plasma glucose concentrations (taken every 2 h) were not significantly different during the two GH secretion profiles (6.48 ± 1.80 vs. 8.50 ± 0.50 mmol/l, day −1 vs. day 4, respectively). Plasma fructosamine concentration was similar before commencement and after 19 days of rhIGF-I therapy (439 ± 32 vs. 429 ± 35 μmol/l, respectively).

Growth hormone. The individual overnight GH secretion profiles are displayed for the patients who received rhIGF-I (Fig. 3) and those who received placebo (Fig. 4). Mean overnight GH concentration was significantly decreased after rhIGF-I therapy (12.6 ± 3.3 vs. 3.8 ± 2.1 mU/l, $P = 0.05$, day −1 vs. day 4). When using Pulsar analysis, this reduction was attributable to a reduction in GH peak amplitude (32.5 ± 15.3 vs. 13.4 ± 3.5 mU/l, $P = 0.08$) with no change seen in either the frequency of peaks or length of interval between peaks. Area under the GH curve was significantly decreased by rhIGF-I (59.01 ± 14.84 vs. 19.2 ± 6.76 h · mU^{-1} · l^{-1} · h^{-1}, $P < 0.05$, day −1 vs. day 4, respectively). Fourier analysis demonstrated a maximum periodicity of GH secretion of 270 min, and analysis of the grouped mean data demonstrated no differences in periodicity before or after rhIGF-I administration. No changes in GH secretion were seen in the patients who received placebo.

Plasma lipids. Serum total cholesterol decreased significantly after 4 days of rhIGF-I therapy ($P < 0.05$, Table 2). Similarly, triglyceride values fell after 4 days of rhIGF-I treatment ($P < 0.001$, Table 2). The LDL-to-HDL cholesterol ratio remained unchanged by rhIGF-I (Table 2). No change was seen in total cholesterol or triglyceride in the patients receiving placebo. Nonesterified free fatty acids, lipoprotein(a), and glycerol were unaltered by rhIGF-I therapy (Table 2).

Resting energy expenditure and rates of substrate oxidation. The respiratory quotient was unchanged after 4 days of rhIGF-I, but there was a significant increase in resting energy expenditure ($P < 0.05$, Table 2). No significant changes occurred in the rates of protein, glucose, or fat oxidation in the subjects who received rhIGF-I (Table 2).

DISCUSSION

Recombinant rhIGF-I may have therapeutic value in several disorders including GH insensitivity syndromes (4), catabolic states (28), and diabetes (6). This study is the first to address the effects of rhIGF-I on GH secretion and insulin requirements in adults with IDDM. Administration of 50 μg/kg b.i.d. of rhIGF-I resulted in a greater than twofold rise

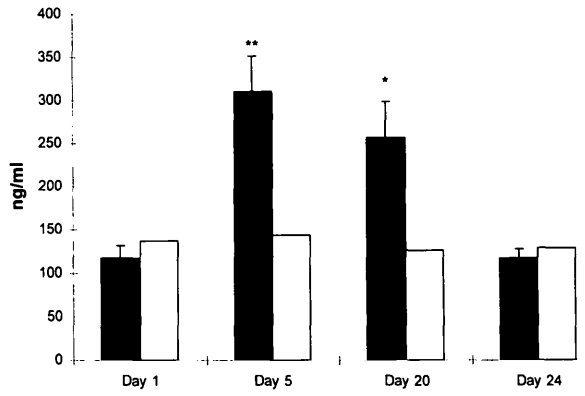

FIG. 1. Serum IGF-I concentration of patients receiving rhIGF-I (■) and placebo (□) at baseline, during treatment, and following treatment. *$P < 0.05$, day 20 vs. day 1; **$P < 0.01$, day 5 vs. day 1.

in circulating IGF-I levels, reaching the upper limit of the physiological range for age-matched healthy subjects. This dose was well tolerated, although higher doses of rhIGF-I (120–160 μg/kg b.i.d.) have been associated with intolerable side effects in patients with type 2 diabetes (29).

The overnight GH profiles of the two subjects who received placebo (patients 7 and 8) displayed a marked variability in the pattern of GH secretion, indicating that the times and amplitude of GH pulses may differ widely on different nights, even in the same individual. Nocturnal GH secretion was markedly reduced with this dose of rhIGF-I indicating, as previously suggested, a negative feedback of exogenous rhIGF-I on GH secretion (30). Similar observations have been recorded after administration of rhIGF-I in

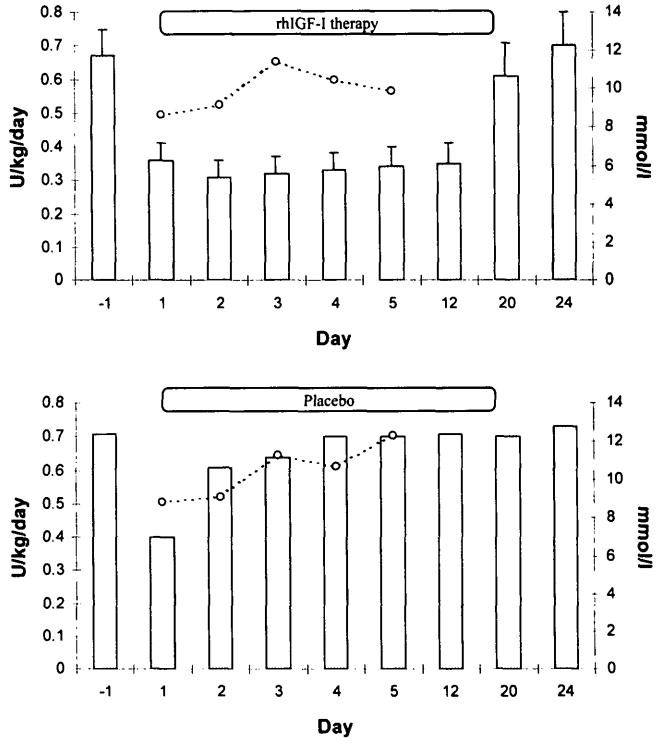

FIG. 2. Total daily insulin requirement (■) and fasting morning plasma glucose concentration (....) in patients who received rhIGF-I and those who received placebo.

TABLE 2
Plasma lipid concentrations, serum free insulin, REE, respiratory quotient, and substrate oxidation in the rhIGF-I–treated patients

	Day 1	Day 5	*P* value
Total cholesterol (mmol/l)	4.68 ± 0.31	4.25 ± 0.35	<0.05
Triglycerides (mmol/l)	1.27 ± 0.19	0.95 ± 0.21	<0.001
LDL-to-HDL cholesterol ratio	2.17 ± 0.18	2.28 ± 0.29	NS
Lipoprotein(a) (mg/l)	18.33 ± 7.7	19.17 ± 8.51	NS
Nonesterified fatty acids (mmol/l)	0.71 ± 0.09	0.78 ± 0.14	NS
Glycerol (μmol/l)	68.45 ± 16.45	74.29 ± 19.72	NS
Free insulin (mU/l)	8.38 ± 1.47	4.98 ± 0.84	<0.05
Resting energy expenditure (kcal · kg^{-1} · day^{-2})	24.5 ± 1.5	30.6 ± 2.4	<0.05
Respiratory quotient	0.86 ± 0.05	0.85 ± 0.03	NS
Protein oxidation (mg · kg^{-1} · min^{-1})	0.79 ± 0.07	0.79 ± 0.06	NS
Glucose oxidation (mg · kg^{-1} · min^{-1})	2.31 ± 0.69	2.42 ± 0.78	NS
Fat oxidation (mg · kg^{-1} · min^{-1})	0.54 ± 0.28	0.96 ± 0.26	NS

Data are means ± SE. n = 6.

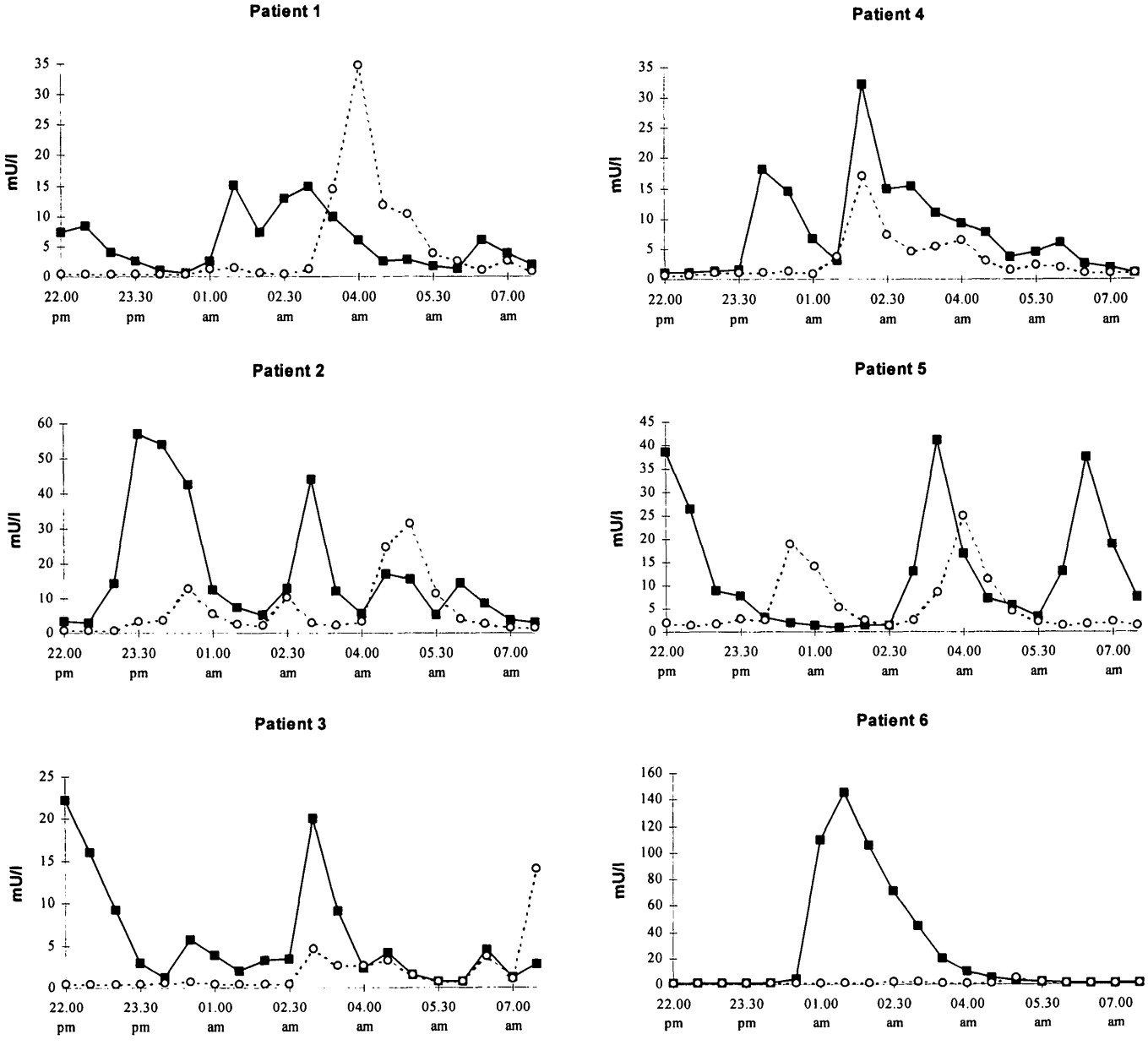

FIG. 3. Individual overnight GH secretion profiles at baseline (— ■ —) and at day 4 (- - ○ - -) for the six patients who received rhIGF-I. The profiles are presented in order of patient number as appears in Table 1.

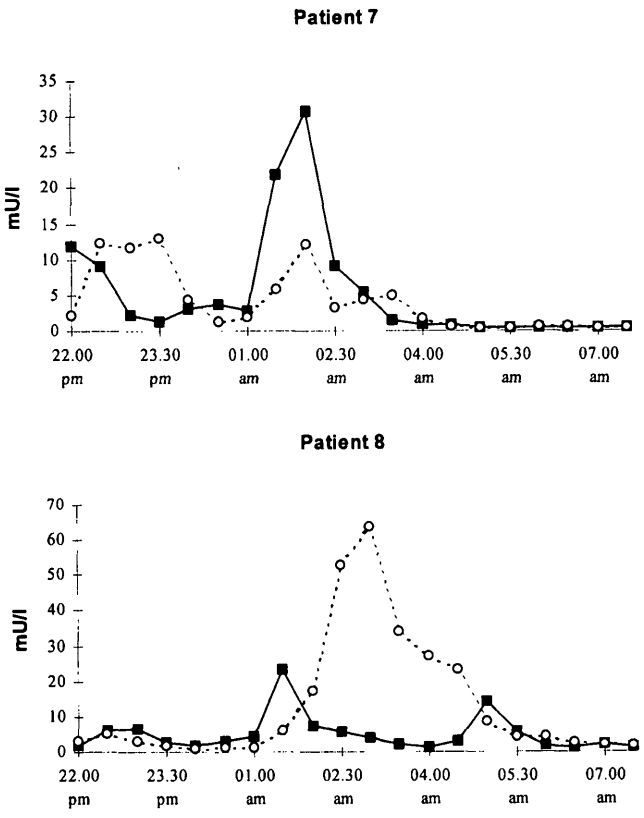

FIG. 4. Individual overnight GH secretion profiles at baseline (— ■ —) and at day 4 (- - ○ - -) for the two patients who received placebo. The profiles are presented in order of patient number as appears in Table 1.

adolescents with IDDM (18). The decrease in GH observed in this study has several implications. As glycemic control and insulin requirements are affected by GH, the decrease in circulating GH may allow for an improvement in diabetic control, and as insulin antagonism is decreased, a further reduction in insulin requirement may be possible. In addition, evidence exists that GH may contribute to the pathogenesis of diabetic complications, in particular, retinopathy (31). It is possible that the reduction of GH levels with correction of the relative IGF-I deficiency of IDDM may have protective effects from the development of the long-term complications of IDDM.

The aim throughout the protocol was to maintain blood glucose control so that the effects of rhIGF-I alone could be demonstrated. This was achieved as overall glycemic control, as assessed using plasma fructosamine, remained unchanged. The effects on GH secretion may result in an improvement in diabetic control, but a longer-term study is necessary to determine whether this is the case. rhIGF-I had a profound insulin-sparing effect, with subjects decreasing their insulin requirement on average by ~45%. Although rhIGF-I administration in normal subjects has been shown to reduce insulin secretion directly (23), IGF-I also has a direct insulin-like action resulting in hypoglycemia and this may be the predominant feature allowing for a reduction in insulin replacement. Assuming that rhIGF-I has a glycemic potency 8% that of insulin (32), a total daily dose of 100 μg · kg^{-1} · day^{-1} of rhIGF-I is equivalent to 5.9 μg · kg^{-1} · day^{-1} (0.15 U · kg^{-1} · day^{-1}) of insulin for the patients in this study. The reduction in insulin requirement, however, was ~0.31 U · kg^{-1} · day^{-1}, suggesting that the hypoglycemic action of rhIGF-I was not solely attributable to insulin-like activity. We attribute this difference to the reduction in GH concentration, contributing to an increase in insulin sensitivity. The reduction in insulin requirement has therapeutic implications. Evidence exists that hyperinsulinemia is associated with atherogenesis and cardiovascular complications (33,34). A decrease in insulin therapy allowing for a reduction in systemic insulin concentration may decrease the rate of development of such complications. Importantly, in vitro studies have demonstrated stimulation of retinal endothelial and vascular smooth muscle proliferation by rhIGF-I (35,36), and it is not yet known whether rhIGF-I administration will accelerate atherogenesis and development of microvascular complications, in particular retinopathy, in patients with IDDM.

Resting energy expenditure (REE) increased by ~22% in the patients who received rhIGF-I. Similar increases in REE have been reported in studies of the effects of rhIGF-I (10 μg · kg^{-1} · h^{-1} via continuous subcutaneous infusion) in normal subjects (37) and adults with GH deficiency (38). In these studies, glucose oxidation was unchanged and protein oxidation decreased, but a large increase in fat oxidation occurred and may have accounted for the change in REE. There was no significant change in fat oxidation in the present study, possibly reflecting the small sample size, but the dose of rhIGF-I was significantly lower than in previous studies (37,38). Alternative explanations for the rise in REE include increased energy expenditure as a result of increased cardiac work or possibly rhIGF-I–mediated conversion of thyroxine to triiodothyronine; however, no data is available to support these hypotheses.

The effects on the patient's lipid profiles are of considerable interest. A marked reduction was seen in plasma total cholesterol and triglyceride concentrations after only 4 days of rhIGF-I therapy, but there was no significant change in the LDL-to-HDL ratio. Despite the reductions in cholesterol and triglyceride, the concentration of lipoprotein(a) was unaffected. Studies of the effect of rhIGF-I on circulating levels of free fatty acids (NEFA) have produced inconsistent results. In normal humans, an intravenous injection (100 μg/kg) produced only a transient decrease in NEFA (34), whereas an intravenous infusion (24 μg · kg^{-1} · h^{-1}) resulted in a sustained decrease (39). Others have reported increased plasma NEFA concentrations after subcutaneous infusions of rhIGF-I (10 μg · kg^{-1} · h^{-1}) for up to 1 week (37,38). The similar free fatty acid (NEFA) concentration seen in this study before and after rhIGF-I is surprising because NEFA levels may have been expected to rise in the presence of the reduced insulin concentration (since IGF-I is less potent than insulin in lowering NEFA [40]). However, because GH has lipolytic effects (41), the reduction in overnight GH secretion would be expected to decrease NEFA levels and this may account for the unchanged NEFA concentrations. As dyslipidemia is a frequent accompaniment of both type 1 and type 2 diabetes, the lipid-lowering effect of rhIGF-I further adds to the therapeutic potential of this compound in the treatment of diabetes.

In summary, the administration of rhIGF-I decreases insulin requirements and circulating free insulin concentrations in adult patients with IDDM. A subcutaneous rhIGF-I dose large enough to decrease insulin requirements by 45%

is well tolerated and is not associated with an alteration in glycemic control over a 19-day period. rhIGF-I administration results in a marked reduction in the excessive overnight GH secretion of IDDM. Plasma cholesterol and triglyceride concentrations are also reduced. rhIGF-I may have a clinical application in the management of IDDM, particularly in the setting of insulin resistance and an adverse lipid profile.

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