Insulin-like Growth Factor-I Improves Glucose and Lipid Metabolism in Type 2 Diabetes Mellitus

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Abstract

Hyperglycemia, hyperinsulinemia, and insulin resistance cause vascular disease in type 2 diabetes mellitus. Dietary treatment alone often fails and oral drugs or insulin enhance hyperinsulinemia. In previous studies, an intravenous bolus of recombinant human insulin-like growth factor-I (rhIGF-I) caused normoglycemia in insulin-resistant diabetics whereas rhIGF-I infusions lowered insulin and lipid levels in healthy humans, suggesting that rhIGF-I is effective in insulin-resistant states. Thus, eight type 2 diabetics on a diet received on five treatment days subcutaneous rhIGF-I (2×120 μg/kg) after five control days. Fasting and postprandial glucose, insulin, C-peptide, proinsulin, glucagon, triglyceride, insulin-like growth factor-I and -II, and growth hormone levels were determined.

RhIGF-I administration increased total IGF-I serum levels 5.3-fold above control. During the control period mean (±SD) fasting glucose, insulin, C-peptide, and total triglyceride levels were 11.0±4.3 mmol/liter, 108±50 pmol/liter, 793±250 pmol/liter, and 3.1±2.7 mmol/liter, respectively, and decreased during treatment to a nadir of 6.6±2.5 mmol/liter, 47±18 pmol/liter, 311±165 pmol/liter, and 1.6±0.8 mmol/liter ($P < 0.01$), respectively. Postprandial areas under the glucose, insulin, and C-peptide curve decreased to 77±13 ($P < 0.02$), 52±11, and 60±9% ($P < 0.01$) of control, respectively. RhIGF-I decreased the proinsulin/insulin ratio whereas glucagon levels remained unchanged. The magnitude of the effects of rhIGF-I correlated with the respective control levels.

Since rhIGF-I appears to improve insulin sensitivity directly and/or indirectly, it may become an interesting tool in type 2 diabetes and other states associated with insulin resistance. (*J. Clin. Invest.* 1992. 90:2234–2241.) Key words: insulin sensitivity • insulin resistance • insulin-like growth factors • noninsulin-dependent diabetes mellitus • proinsulin

Introduction

Noninsulin-dependent (type 2) diabetes mellitus is characterized by hyperglycemia, hyperinsulinemia, and relatively increased proinsulin levels as the result of insulin resistance and β cell dysfunction (1–3). Hyperinsulinemia downregulates insulin receptors of insulin target tissues (1, 4–6) and lowers insulin receptor affinity (6) and tyrosine kinase activity (5, 6) whereas hyperglycemia impairs insulin-mediated glucose disposal and β cell function (7). Hyperinsulinemia was claimed to be an independent cardiovascular risk factor in many (8, 9) but not in all studies (10). Moreover, hyperinsulinemia is often associated with other cardiovascular risk factors such as dyslipoproteinemia (9) and enhanced plasminogen activator inhibitor activity leading to a decreased rate of fibrinolysis (11).

Therapy of type 2 diabetes aims at a loss of body weight by which hyperglycemia, hyperinsulinemia, insulin sensitivity, and glucose tolerance are improved and lipid levels decreased (12, 13). However, compliance with reducing diets is often poor and the beneficial effects short lived so that sulfonylureas or insulin are prescribed. Both enhance hyperinsulinemia (14) and can aggravate insulin resistance directly (5, 15) or indirectly by increasing body weight (16, 17). Therefore, the atherogenic risk rises again (8, 9).

Insulin-like growth factor-I (IGF-I)[1] may interrupt this vicious cycle. IGF-I is a growth-promoting and cell differentiation–enhancing factor which mimics many effects of insulin (18, 19) via the type 1 IGF and/or the insulin receptor (6, 18, 19). An intravenous bolus of recombinant human insulin-like growth factor-I (rhIGF-I) caused hypoglycemia in animals and humans (20, 21), although with a 12-fold lower potency on a molar basis than insulin (20). In severe insulin-resistant diabetics who are unresponsive to intravenous insulin, rhIGF-I decreased blood glucose levels into the normoglycemic range (22). RhIGF-I stimulated glucose uptake during a euglycemic clamp in fasted rats to the same maximum as insulin (23, 24) but was more effective than insulin in diabetic rats (24, 25). Finally, rhIGF-I infusions decreased insulin, C-peptide, and triglyceride levels in healthy subjects without lowering fasting and postprandial glucose levels (26, 27). Thus, insulin secretion was partly uncoupled from glucose levels by the infusion of rhIGF-I. Ready explanations for this phenomenon are the suppression of insulin secretion by rhIGF-I (28), the increase of glucose disposal by rhIGF-I (23, 24), and probably an improvement of insulin sensitivity via decreased insulin, triglyceride, and growth hormone (GH) levels (26, 27, 29).

Thus, rhIGF-I appears to improve insulin sensitivity in healthy subjects and to be particularly effective in insulin-resistant diabetics. In this study, we investigated the effects of rhIGF-I on fasting and postprandial glucose, insulin, C-peptide, proinsulin, glucagon, and triglyceride levels in patients

This work has been presented in part at the 73rd Annual Meeting of the Endocrine Society, Washington, DC, 19–22 June 1991, and at the 27th Annual Meeting of the European Association for the Study of Diabetes, Dublin, Ireland, 11–14 September 1991.

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Received for publication 10 March 1992 and in revised form 15 June 1992.

1. *Abbreviations used in this paper:* AUC, area under the curve; GH, growth hormone; HBA_{1c}, glycosylated hemoglobin; iAUC, incremental AUC; IGF, insulin-like growth factor; IGFBP, IGF-binding protein; MTT, meal tolerance test; rhIGF-I, recombinant human IGF-I.

J. Clin. Invest.

0021-9738/92/12/2234/08 $2.00
Volume 90, December 1992, 2234–2241

with type 2 diabetes mellitus. We found that rhIGF-I decreased fasting plasma glucose and triglyceride levels and improved meal tolerance in the face of markedly lowered fasting and postprandial insulin and C-peptide levels.

Methods

Subjects. Eight patients with type 2 diabetes mellitus gave informed and written consent and participated in this study. Their clinical characteristics are given in Table I. 1–2 wk before the study a physical investigation, electrocardiogram stress test, and hematology and chemistry parameters, including a glycosylated hemoglobin (HbA_{1c}) measurement, confirmed that the type 2 diabetic subjects had no severe diabetic complications and were otherwise healthy. Subjects 3 and 8 were treated for hypertension with angiotensin-converting enzyme inhibitors. All female patients were postmenopausal. The weight of the patients remained constant during 4 wk before the study. The patient's usual treatment for type 2 diabetes consisted of diet alone or diet plus Glibenclamide (Table I) but none of them received insulin. A dietary history of each patient served to calculate the diet that the patients received during the study (see below). The protocol was approved by the Ethics committee of the Department of Internal Medicine of the University Hospital at Zurich.

Experimental protocol. Those patients taking Glibenclamide discontinued the drug 3 d before the study. Throughout the study the patients received a sucrose-free diet of 30 kcal/kg body weight (50% carbohydrates, 30% fat, and 20% protein), which was given as breakfast at 8 am (25% of the total calories), snack at 10 am (10%), lunch at 12 am (25%), snack at 4 pm (10%), dinner at 6:30 pm (25%), and the bedtime snack at 9:30 pm (5%). The composition of the breakfast was identical for each patient throughout the study.

The study lasted 12.5 d and was started with a control period (days 1–5), followed by the rhIGF-I treatment period (days 6–10), and concluded with the wash-out period of 2.5 d (days 11–13). The patients were hospitalized throughout except for days 1–3, on which they came to the hospital for the main meals. Since rhIGF-I affects serum levels of many parameters for several days after its discontinuation, the control and treatment period could not be randomized. Instead, we followed the patients during the wash-out days. In a recent study (26), healthy subjects received intravenous infusions of 7 and 14 μg rhIGF-I/kg per h (equal to 84 and 168 μg/kg two times per day). The higher dose was barely more effective than the lower one. A dose response in a Laron dwarf (30) showed that 16 μg rhIGF-I/kg per h caused fasting hypoglycemia and postprandial hyperglycemia. Therefore, we chose a dose in this study which was between those used in healthy subjects. RhIGF-I, kindly provided by Ciba-Geigy AG (Basel, Switzerland), was dissolved in 0.9% saline (10 mg/ml) and on days 6–10, 120 μg rhIGF-I/kg body weight was subcutaneously injected into the thigh two times per day (7 am and 6:30 pm), except for day 10 when the injection at 6:30 pm was omitted.

After 10 h of fasting, blood was drawn at 7:30 am on days 1, 4, 5, and 8–13, and at 7 am on days 6 and 7 for the analysis of glucose, insulin, C-peptide, proinsulin, glucagon, total triglyceride, total IGF-I and IGF-II, free IGF-I, and GH levels. Fasting plasma glucose was also determined at 7 am during the treatment period and at 7 am on days 11 and 12 in patients 5–8. Additional plasma glucose levels were determined daily before each main meal, at 9:30 pm on days 4–10 in all patients and at 9:30 pm on days 11 and 12 in patients 2 and 5–8.

A meal tolerance test (MTT) was performed on days 4, 5, and 8–12. On these days the snack at 10 am was omitted and was eaten with the breakfast between 8 and 8:30 am, containing 87±11 g carbohydrates (1.2 g/kg). At least 30 min before the start of the MTT, an 18-gauge Venflon (Braun Melsungen AG, Melsungen, FRG) cannula was inserted into a forearm vein to draw blood for the determination of the above-mentioned parameters. GH was determined at 10 and 12 am during MTT.

Methods. Blood was drawn into tubes containing sodium fluoride and oxalate, centrifuged within 10 min, and immediately analyzed for plasma glucose on a glucose analyzer (Glucose Analyzer 2; Beckman Instruments, Inc., Fullerton, CA). Venous blood was drawn into SST tubes (Becton Dickinson, Meylan Cedex, France). After clot retraction during 30 min at 4°C and centrifugation at 1,550 *g* for 30 min at 4°C, aliquots of serum were stored at −20°C until assayed. Insulin, C-peptide, and GH were determined using commercial RIAs (Medipro AG, Teufen, Switzerland). Triglycerides were hydrolyzed and glycerol was determined by an enzymatic, photometrical determination (Boehringer Mannheim AG, Mannheim, FRG) on a Hitachi 717 (Boehringer, Mannheim, AG). ELISA for proinsulin (31) and RIAs for the determination of glucagon, total IGF-I, total IGF-II, and free IGF-I levels, respectively, were performed as described (26, 32). All samples of one patient were analyzed in duplicate at one to three dilutions within one or two assays. The interassay coefficients of variation were 7.5 and 6.3% for insulin (180 and 680 pmol/liter), 5.1 and 4.1% for C-peptide (360 and 1,110 pmol/liter), 9.0% for proinsulin (between 18 and 28 pmol/liter), 13.8% for GH (320 ng/ml), 13.5% for total IGF-I (between 13 and 27 nmol/liter), 14.0% for total IGF-II (81 nmol/liter), and 12.6% for free IGF-I (2.8 and 12.8 nmol/liter), respectively. HbA_{1c} was determined with a semiautomated cation-exchange column chromatography system (MDMF; Bio-Rad Laboratories, Richmond, CA).

Statistics. All data are presented as mean±SD. The results of this study, comprising eight subjects, cannot be expected to be normally distributed. Therefore, paired differences were analyzed using the two-tailed Wilcoxon's matched pairs signed-rank test. Areas under the curve (AUC) and linear regressions were calculated using the trapezoi-

Table I. Clinical Characteristics of the Patients with Type 2 Diabetes Mellitus

Patient	Sex	Age	BMI	Diabetes	HbA_{1c}*	Previous therapy
		yr	*kg/m²*	*yr*	%	
1	M	50.5	24	8	6.9	Diet, Gc
2	M	46	24	4	10.5	Diet, Gc
3	M	48.5	28	2	6.6	Diet
4	M	41.5	26	0.5	5.8	Diet, Gc
5	F	57	23	10	6.8	Diet, Gc
6	M	40.5	33	5	6.4	Diet
7	M	38	27	10	10.3	Diet, Gc
8	F	60	24	14	11.0	Diet, Gc
Mean ± SD		48±8	26±3	7±5	8.0±2.2	

BMI, body mass index; F, female; Gc, Glibenclamide; M, male.
* Normal range: 4.0–6.4%.

*Table II. Fasting Total IGF-I, Free IGF-I, and Total IGF-II Levels**

Day	Total IGF-I	Free IGF-I	Total IGF-II
		nmol/liter	
1	21.2±7.4	2.3±1.1	99±13
4	20.7±6.4	2.3±1.2	93±15
5	21.3±6.6	2.9±2.2	96±17
6	23.5±7.2	2.5±1.3	100±26
7	98.5±16.3‡	3.9±1.3	49±22‡
8	124.1±23.0‡	7.3±2.6*‡	31±12‡
9	105.6±16.7‡	6.4±1.7*‡	28±13‡
10	106.4±21.2‡	5.2±1.6§	22±8‡
11	55.2±14.3‡‖	2.4±1.5‖	37±11‡
12	33.4±9.5‡‖	2.5±1.5‖	55±12*‡¶
13	24.0±5.2§	2.5±1.2¶	71±14‡¶

* Mean±SD of the fasting total IGF-I, free IGF-I, and total IGF-II levels before (days 1–5), during (days 6–10), and after (days 11–13) treatment subcutaneously with 2 × 120 μg rhIGF-I/kg daily. ‡$P < 0.01$, §$P < 0.05$ vs mean of days 1–5; ‖$P < 0.01$, ¶$P < 0.02$ vs. mean of days 7–10.

dal rule and the method of least squares, respectively. A P value of < 0.05 was considered significant.

Results

All patients tolerated the rhIGF-I treatment well. Body weight and resting and postural blood pressure did not change during the study. An asymptomatic but significant increase of the heart rate by 9 to 17% was noted between days 7 and 12. On day 7, mild tenderness in the area of the parotid gland was reported by all patients. It lasted 3–6 d and was accompanied by a slight swelling of the parotid gland for 3 to 4 d, which was also noticed by four of eight patients.

IGF levels (Table II) remained constant and in the normal range during the control period. Total and free IGF-I levels were significantly increased 24 h after starting rhIGF-I administration, and total IGF-II levels were decreased. On days 8–10, total and free IGF-I levels were 5.3 and 2.5 times above control levels, respectively, whereas total IGF-II levels were decreased to 28%. Free IGF-I levels reached control levels again on day 11, whereas total IGF-I and -II levels were still slightly different from control levels on day 13. During rhIGF-I administration total IGF levels did not markedly change throughout the day, including MTT, whereas free IGF-I levels peaked at 9 am during MTT (Table III). GH levels were clearly decreased by rhIGF-I treatment (Table IV).

Fasting (Fig. 1) and preprandial plasma glucose levels (11.9±5.6 before lunch and 11.7±5.0 mmol/liter before dinner, respectively) remained constant during the control days, decreased 24 h after starting treatment, reached the nadir (6.6±2.5 fasting, 7.7±3.0 before lunch, and 8.7±2.2 mmol/liter before dinner, respectively) on day 10, and did not markedly increase on days 11 and 12. Fructosamine levels decreased markedly from day 6 (398±200 μmol/liter) to day 10 (319±123 μmol/liter; $P < 0.01$). The difference of the fasting plasma glucose levels between the control and the treatment period correlated with the fasting glucose values during the control period

*Table III. Total IGF-I, Free IGF-I, and Total IGF-II Levels during MTT**

Time	Days 4 and 5	Day 8–10	Day 11	Day 12
Total IGF-I (*nmol/liter*)				
08:00	21±5	116±21‡	52±14‡§	31±9‡§‖
08:30	21±6	130±23	57±14	33±8
09:00	21±5	127±22¶	50±11	35±12
10:00	19±6	122±18**‡‡	48±11¶**	30±6**‡‡
11:00	20±5¶	120±19**	47±12**	29±6**‡‡
12:00	20±5**‡‡	117±20**‡‡	48±10**	30±5
Free IGF-I (*nmol/liter*)				
08:00	2.5±1.1	7.7±1.5‡	2.6±1.3§	2.7±2.1§
08:30	2.5±1.3	9.2±2.7	3.0±1.0	2.4±1.8
09:00	2.3±1.0	9.8±1.7¶	2.8±2.0	2.5±2.3
10:00	2.2±1.0	8.9±1.9	2.8±1.5	2.8±2.0**
11:00	2.6±1.3	8.3±1.7	3.0±1.5	2.1±0.8
12:00	2.7±1.2	7.3±1.1‡‡	3.1±1.6	2.4±1.1
Total IGF-I (*nmol/liter*)				
08:00	93±18	27±11‡	37±8‡	57±16‡§‖
08:30	96±17	28±13¶	43±12¶	62±15
09:00	92±19	27±12**	38±9	60±14
10:00	88±12	26±11**‡‡	39±12	60±12
11:00	92±15	25±9¶**	41±15	61±15
12:00	90±18	25±11**‡‡	45±10¶‡‡	61±15

* Mean±SD of total IGF-I, free IGF-I, and total IGF-II levels before (8 am) and during MTT, before (days 4 and 5), during (days 8–10), and after (days 11 and 12) treatment subuctaneously with 2 × 120 μg rhIGF-I/kg daily. $P < 0.01$ for each time point of the day(s) vs. the respective time points during ‡days 4 and 5, §days 8–10, and ‖day 11, respectively. ¶$P < 0.05$ vs. 8:00, **$P < 0.05$ vs. 8:30, and ‡‡$P < 0.05$ vs. 9:00 of the same day, respectively.

Table IV. GH Levels before, during, and after rhIGF-I Treatment

Time	3 am (n = 4)	7:30 am (n = 8)	10 am (n = 8)	12 am (n = 8)
		ng/ml		
Control period	0.24±0.08	0.49±0.37	0.22±0.05	0.70±1.0
Treatment period	<0.20	0.22±0.05	<0.20	0.23±0.08
Washout period	0.22±0.03	0.20±0.04	<0.20	0.82±1.0

Mean±SD of GH levels at different time points during the day before (control period), during (treatment period), and after (wash-out period) treatment subcutaneously with 2 × 120 μg rhIGF-I/kg daily.

(Fig. 2) and the HbA_{1c} levels of the screening visit ($r = 0.844$, $P < 0.01$). Thus, the absolute decrease of glucose levels was smaller in patients 1 and 3–6, who started with relatively low glucose levels during the control period (7.6±2.8 mmol/liter). These patients reached normal fasting plasma glucose levels on days 9 and 10 (5.2±1.1 mmol/liter).

Fasting insulin and C-peptide levels reached the nadir on days 10 and 9, respectively, increased again on day 11, and reached control values on day 13 (Fig. 1). Fasting triglyceride levels fell to a minimum on day 10 and remained decreased until day 13 (Fig. 1). The decrease of fasting insulin, C-peptide, and triglyceride levels during rhIGF-I treatment correlated with the respective fasting control levels (Fig. 2). In the case of

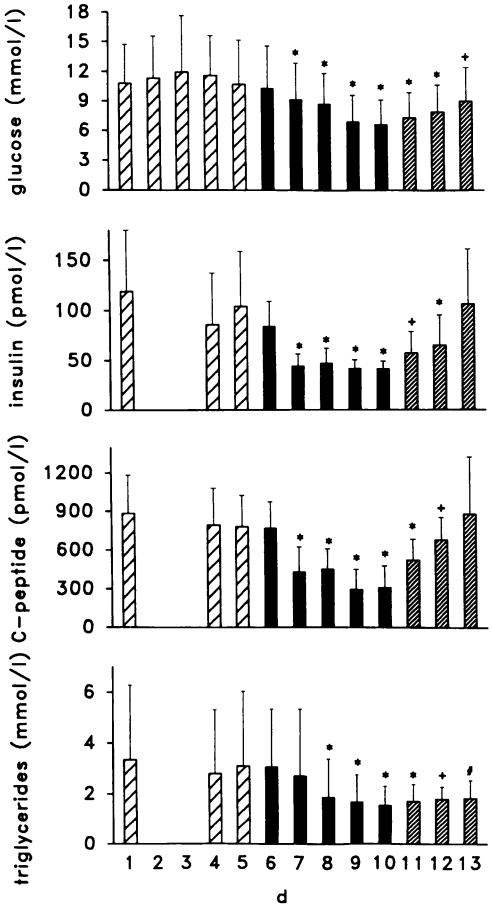

Figure 1. Effects of rhIGF-I on fasting glucose, insulin, C-peptide, and triglyceride levels. Mean + SD of plasma glucose (*top panel*), insulin (*upper middle panel*), C-peptide (*lower middle panel*), and total triglyceride levels (*bottom panel*) in eight type 2 diabetics before (*coarsely hatched bars*), during (*solid bars*), and after (*hatched bars*) treatment subcutaneously with 2 × 120 μg rhIGF-I/kg daily. $*P < 0.01$, $^{+}P < 0.02$, $*P < 0.05$ vs. control.

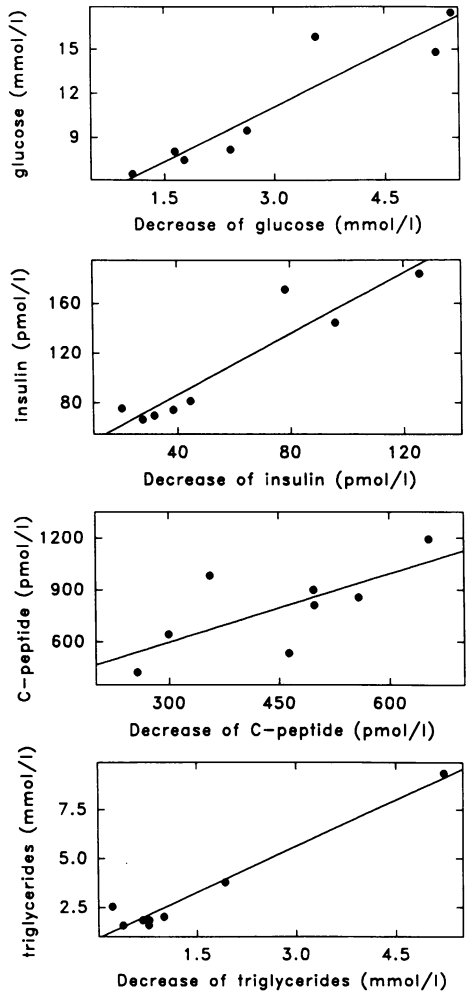

Figure 2. Decrease of fasting glucose, insulin, C-peptide, and triglyceride levels during rhIGF-I treatment compared with the control levels. The differences between the mean fasting plasma glucose, insulin, C-peptide, and total triglyceride levels during the control and the treatment period are correlated with the fasting plasma glucose (*top panel:* $y = 2.49x + 3.64$, $r = 0.932$, $P < 0.001$), insulin (*upper middle panel:* $y = 1.23x + 38$, $r = 0.938$, $P < 0.001$), C-peptide (*lower middle panel:* $y = 1.32x + 202$, $r = 0.711$, $P < 0.05$), and total triglyceride levels (*bottom panel:* $y = 1.57x + 0.92$, $r = 0.976$, $P < 0.001$) during the control period. Each circle represents the value of one subject.

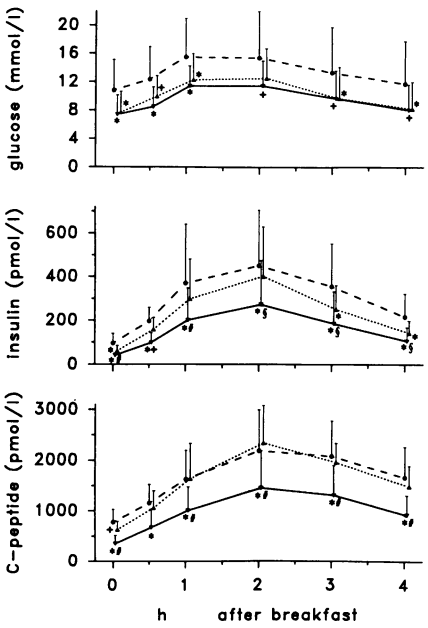

Figure 3. Effects of rhIGF-I on postprandial glucose, insulin, and C-peptide levels. Plasma glucose (*top panel*), insulin (*middle panel*), and C-peptide levels (*bottom panel*) in eight type 2 diabetics before (0 h) and during a MTT (standard breakfast). The values represent the mean + SD of the two MTTs on days 4 and 5 during the control period (*coarsely hatched line, circles*), three MTTs on days 8–10 during treatment subcutaneously with 2 × 120 μg rhIGF-I/kg daily (*solid line, downward triangles*), and two MTTs on days 11 and 12 during the wash-out period (*dotted line, upward triangles*). $^{*}P < 0.01$, $^{+}P < 0.05$ vs. control, $^{\#}P < 0.01$, $^{\S}P < 0.05$ vs. wash-out.

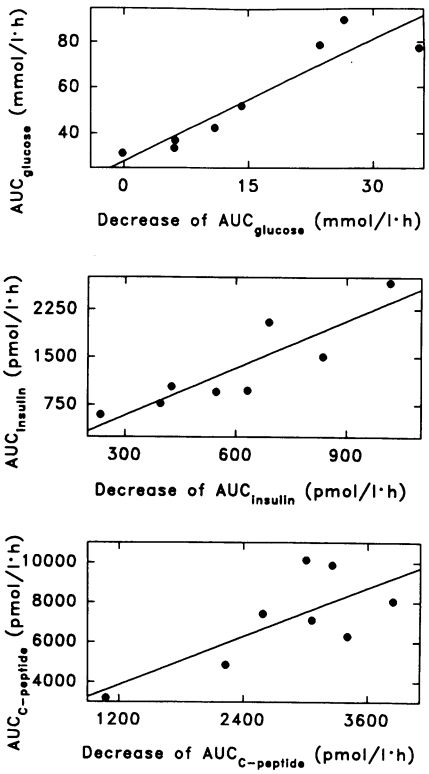

Figure 4. Decrease of the postprandial area under the glucose, insulin, and C-peptide curve during rhIGF-I treatment versus the respective area during the control period. The areas under the glucose ($AUC_{glucose}$), insulin ($AUC_{insulin}$), and C-peptide ($AUC_{C\text{-}peptide}$) curve during MTT and the differences between these AUCs during the control and the treatment period were calculated. The AUCs during the control period are plotted versus the decrease of the $AUC_{glucose}$ (*top panel:* $y = 1.78x + 27.8$, $r = 0.924$, $P < 0.001$), $AUC_{insulin}$ (*middle panel:* $y = 2.48x - 157$, $r = 0.879$, $P < 0.01$), and $AUC_{C\text{-}peptide}$ (*bottom panel:* $y = 2.03x + 1429$, $r = 0.735$, $P < 0.05$) during rhIGF-I treatment. Each circle represents the value of one subject.

triglycerides, the correlation remained almost significant ($r = 0.73$, $P = 0.56$) even if the data pair of the patient with clearly increased fasting triglyceride levels was excluded from statistical analysis.

During rhIGF-I administration, postprandial glucose, insulin, and C-peptide levels were markedly decreased but only glucose levels remained decreased during the wash-out period (Fig. 3). The decrease of both total AUC and incremental AUC (iAUC) for glucose, insulin, and C-peptide during rhIGF-I treatment (Table V) cannot solely be explained by the decreased fasting levels. The diminution of the $AUC_{glucose}$ during rhIGF-I treatment was related to the fasting plasma glucose levels ($r = 0.846$, $P < 0.01$) and to the $AUC_{glucose}$ during the control period (Fig. 4). The differences of the $AUC_{insulin}$ and of the $AUC_{C\text{-}peptide}$ between the control and the treatment period correlated with the respective AUC during the control period (Fig. 4).

Fasting and postprandial proinsulin levels and the proinsulin/insulin ratio were clearly decreased during rhIGF-I administration as well as on day 12 (Table VI).

Table V. Total and Incremental Area Under the Glucose, Insulin, and C-peptide Curve during the MTT before, during, and after rhIGF-I Treatment

	Days 4 and 5	Days 8–10	Day 11	Day 12
$AUC_{glucose}$ (*mmol/liter per h*)	55±23	40±13§	41±14‡	44±17$^{\ddagger **}$
$iAUC_{glucose}$ (*mmol/liter per h*)	15±5	11±2§	13±4	14±4
$AUC_{insulin}$ (*pmol/liter per h*)	1,322±712	725±504‡	1,069±598	1,122±604$^{\|}$
$iAUC_{insulin}$ (*pmol/liter per h*)	921±511	547±481‡	805±478¶	855±520
$AUC_{C\text{-}peptide}$ (*pmol/liter per h*)	7,117±2,353	4,309±1,819‡	6,468±1,645¶	7,137±1,993¶
$iAUC_{C\text{-}peptide}$ (*pmol/liter per h*)	4,045±1,563	2,994±1,459‡	4,498±1,373¶	4,436±1,575**

AUC and iAUC for glucose, insulin, and C-peptide during the MTT before (days 4 and 5), during (days 8–10), and after (days 11 and 12) treatment subcutaneously 2 × 120 μg rhIGF-I/kg daily. $^{\ddagger}P < 0.01$, $^{\S}P < 0.02$, $^{\|}P < 0.05$ vs. days 4 and 5; $^{\P}P < 0.01$, $^{**}P < 0.05$ vs. days 8–10.

Table VI. Proinsulin Levels and Proinsulin/Insulin Ratio before, during, and after rhIGF-I Treatment

	Proinsulin		Proinsulin/insulin ratio	
	7:30 am	10:00 am	7:30 am	10:00 am
	pmol/liter			
Day 4	24±13	67±33	0.75±1.12	0.22±0.17
Day 5	23±13	67±28	0.38±0.36	0.21±0.12
Day 9	8±5‡	28±15‡	0.26±0.30§	0.16±0.11§
Day 10	7±5‡	30±20‡	0.19±0.18‡	0.15±0.11‖
Day 12	12±5‡	54±33	0.37±0.41§	0.21±0.23

Mean±SD of fasting (7:30 am) and postprandial (10:00 am) proinsulin levels and the proinsulin/insulin ratio before (days 4 and 5), during (days 9–10), and after (day 12) treatment subcutaneously with 2×120 μg rhIGF-I/kg daily. ‡$P < 0.01$, §$P < 0.02$, ‖$P < 0.05$ vs. days 4 and 5.

Fasting glucagon levels did not change during rhIGF-I administration (not shown).

The insulin/glucose ratio can be considered as an index of tissue sensitivity to insulin (33). The fasting insulin/glucose ratio (mean±SD) during the control period was $11.7 \pm 9.2 \times 10^6$ and decreased to $6.3 \pm 2.6 \times 10^6$ during the treatment period ($P < 0.01$). The ratio decreased similarly in the postprandial state during rhIGF-I administration (not shown). The fasting and postprandial C-peptide/insulin ratio was not changed by rhIGF-I administration as can be deduced from the data in Figs. 1 and 3.

Discussion

RhIGF-I exerts insulin-like effects in isolated cells and organs, and in the intact organism (18–21). Free IGF-I levels are markedly increased after an intravenous bolus of rhIGF-I whereby glucose disposal via type 1 IGF and insulin receptors is stimulated (6, 18), causing hypoglycemia in animals and humans (20, 21). In diabetics with severe insulin resistance, normoglycemia after an intravenous rhIGF-I bolus results mostly from the interaction of free IGF-I with type 1 IGF receptors (22). During a euglycemic clamp in fasted rats, rhIGF-I and insulin increased glucose uptake similarly (23), but rhIGF-I was clearly more effective than insulin in diabetic rats (24, 25). In the present study, rhIGF-I administration lowered fasting plasma glucose levels and improved meal tolerance despite markedly decreased insulin and C-peptide levels (Figs. 1 and 3).

Elevated IGF-I levels are not always associated with insulin-like effects. In acromegaly, GH excess increases total IGF-I levels into the same range as rhIGF-I administration did in this study (34) but GH excess causes insulin resistance and impaired glucose tolerance in the presence of elevated insulin levels (35). On the other hand, suppressed GH levels after treatment of acromegaly (35) or during rhIGF-I administration (Table IV and reference 26) lower insulin levels and improve glucose tolerance (26, 35).

Furthermore, serum IGF-binding proteins (IGFBPs), which are important regulators of IGF action, undergo different changes during GH excess and rhIGF-I administration, respectively. In this and previous studies rhIGF-I administration elevated free IGF-I serum levels (Tables II and III, and reference 26) and increased IGFBP-1 and -2 serum levels (36) by way of decreased insulin levels (37, 38). Thus, serum levels of free IGF-I are increased during rhIGF-I infusions, and IGFBP-1 and -2, which have a short half-life, carry relatively large amounts of the total serum IGF-I (39). Free IGF-I and IGF-I bound to IGFBP-1 were shown to cross the vascular barrier of the rat heart (40) so that during rhIGF-I administration a large portion of IGF-I may stimulate glucose disposal in muscle via type 1 IGF and/or insulin receptors (6, 18, 19). This increase of free IGF-I and the changed IGF-I distribution among IGFBPs could counterbalance the diminished insulin levels with respect to glucose disposal (Figs. 1 and 3). In contrast, increased GH levels in acromegaly induce IGFBP-3 and the acid-labile subunit of the IGFBP-3 complex (34, 36, 41) with a high IGF-binding capacity (41). The concomitantly increased insulin levels (35) suppress IGFBP-1 and -2 production (42) and lower their serum levels. Hence, IGF-I in acromegaly is mostly bound to the IGFBP-3 complex and, in that form, stimulates anabolic and growth processes (43) rather than glucose metabolism.

Fasting and postprandial insulin and C-peptide levels may also have been lowered indirectly due to the decreased plasma glucose levels during rhIGF-I administration. Furthermore, IGF-I has been shown to directly suppress insulin secretion in the perfused rat pancreas (28). In contrast, our data suggest that IGF-I has no marked effect on glucagon secretion. Improved metabolic control (17) and the partial suppression of insulin secretion may have been responsible for the decreased fasting and postprandial proinsulin levels and proinsulin/insulin ratio (Table VI), suggesting a beneficial effect of rhIGF-I on β cell function in type 2 diabetes. On the other hand, suppression of insulin secretion by rhIGF-I may be such that the diminished and delayed postprandial insulin response results in glucose intolerance. This was reported in a child with Laron-type dwarfism in whom an infusion of 16 μg rhIGF-I/kg per h caused fasting hypoglycemia and, at the same time, glucose intolerance (30). We observed in a recent study in healthy humans that a dose of 14 μg rhIGF-I/kg per h shifted the glucose peak slightly to the right after a glucose challenge but did not markedly change glucose levels (26). The small rhIGF-I dose in this study was not diabetogenic in type 2 diabetics but (near-)normalized plasma glucose levels in the face of clearly lowered insulin and C-peptide levels (Figs. 1 and 3).

A moderate decrease of insulin levels during dieting and weight loss improves insulin sensitivity of hyperinsulinemic patients with type 2 diabetes and obesity (4, 12). Likewise, nondiabetics with low normal insulin levels are more sensitive to insulin than those with high normal levels (44). Furthermore, insulin sensitivity is also improved by lowering glucose (7) and triglyceride levels (45). In this study, rhIGF-I decreased fasting and postprandial glucose, insulin, and triglyceride levels, i.e., effects each of which could by itself have improved insulin sensitivity. The effect of rhIGF-I was more marked in those diabetics with high starting levels of these metabolic parameters (Figs. 2 and 4). This finding confirms results in healthy humans in whom rhIGF-I lowered insulin levels better, the higher their fasting insulin levels were before treatment (26). It is, however, in sharp contrast with the effects of insulin, which decreases higher glucose levels less effectively than those that are only slightly elevated. Finally, the fasting insulin levels during the control period and on the last wash-out day were comparable. They were accompanied by hyperglycemia during the

control period and euglycemia on the last wash-out day when free IGF-I levels were back to normal but glucose, insulin, triglyceride, and GH levels still decreased. All these findings support the hypothesis that rhIGF-I may improve insulin sensitivity indirectly.

It would have been preferable to randomize the control and treatment period of this study to avoid a possible bias due to the change of the diet. However, this was impossible because of the long-lasting effects of rhIGF-I after its discontinuation. A major bias in our nonrandomized study design can be excluded for the following reasons: The diet during the study was calculated on the basis of the dietary history of each patient so that no big dietary changes occurred. Patients did not lose weight during the control or treatment period. Blood glucose levels were similar during the first 3 d on diet, during which the patients came to the hospital only for the main meals, as on day 4 and 5, during which the patients were hospitalized.

Weight loss is the most reasonable therapeutic approach to most overweight type 2 diabetic patients. It improves insulin sensitivity and glucose tolerance and lowers insulin, glucose, and triglyceride levels (12, 13). However, these improvements often do not last very long and sulfonylureas or insulin are added. These agents are well known to lower glucose levels, yet with some risk of hypoglycemia (16). In this study with rhIGF-I treatment, no hypoglycemia occurred although near-normoglycemia was achieved. Furthermore, sulfonylureas and insulin enhance hyperinsulinemia (14), can aggravate insulin resistance directly (5, 15) or indirectly by increasing body weight (16, 17), and, thereby, increase the atherogenic risk (8, 9). Since in this short-term study rhIGF-I lowered not only glucose and triglyceride but also insulin levels, all of which are considered to be cardiovascular risk factors (8, 9), rhIGF-I treatment could, in the long run, have beneficial effects on cardiovascular morbidity and mortality.

Thus, rhIGF-I treatment has obvious theoretical advantages compared with conventional therapies of type 2 diabetes mellitus. However, this is a short-term study and we do not know whether the positive effects of rhIGF-I on glucose and lipid metabolism in type 2 diabetics persist during prolonged administration and whether the stimulation of retinal endothelial and smooth muscle cell proliferation by rhIGF-I in vitro (46, 47) may have a harmful corollary in vivo. The same holds true for the increased heart rate during rhIGF-I administration (see Results), which remains unexplained and may increase the risk for myocardial ischemia. An association between total IGF-I serum levels and diabetic complications was found in some (48) and not in other studies (49, 50). Furthermore, the suppression of GH during rhIGF-I administration may be beneficial for diabetics since GH has been implicated in the pathogenesis of diabetic complications (51).

The possibility of interrupting the vicious cycle of insulin resistance, hyperinsulinemia, and hyperglycemia by rhIGF-I administration is exciting. However, we obviously need long-term trials and very careful retinal, renal, and cardiovascular monitoring before rhIGF-I can be investigated in a larger group of patients with type 2 diabetes mellitus.

Acknowledgments

We thank Dr. J. Furrer for allowing us to study two of his patients; Dr. P. Holzmann, Ms. S. Graf, Ms. Y. Glatz, and Mr. A. Lenz for technical assistance; and Ms. S. Vosmeer and Dr. U. Keller for the determination of glucagon levels. The help of the nurses on the metabolic ward is highly appreciated.

This work was supported by the Swiss National Science Foundation (grant 31-9095.87) and by Ciba-Geigy AG (Basel, Switzerland).

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