Recombinant Human Insulin-Like Growth Factor-I Abolishes Changes in Insulin Requirements Consequent Upon Growth Hormone Pulsatility in Young Adults With Type I Diabetes Mellitus

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To investigate whether recombinant human insulin-like growth factor-I (rhIGF-I) has direct effects on the insulin requirement to maintain euglycemia independent of the growth hormone (GH) level, nine subjects with insulin-dependent diabetes mellitus ([IDDM] seven females; median (range) age, duration of diabetes, and hemoglobin A_{1C} [HbA_{1C}], 16.9 (12.5 to 21.9) years, 11.8 (4.6 to 16.8) years, and 9.8% (7.9% to 14.1%), respectively) underwent two euglycemic studies (6:00 PM to 8:00 AM) after double-blind subcutaneous administration of rhIGF-I/placebo (40 μg/kg). Octreotide infusion (300 ng/kg/h) suppressed endogenous GH, and three identical discrete GH pulses were infused on both nights. Variable-rate insulin infusion maintained euglycemia. Samples were taken every 15 minutes (glucose and GH), 30 minutes (insulin and intermediate metabolites), and 60 minutes (IGF-I and nonesterified fatty acids [NEFA]). Variables were analyzed during the steady-state period of euglycemia (4:00 to 8:00 AM). Data are expressed as the mean ± SEM. The insulin infusion rate and free-insulin level were both significantly reduced after rhIGF-I administration (0.13 ± 0.03 *v* placebo 0.23 ± 0.05 mU/kg/min, $P = .04$, and 8.4 ± 1.3 *v* placebo 12.1 ± 1.4 mU/L, $P = .03$, respectively). GH pulse–related changes in the insulin requirement observed after placebo were not present after rhIGF-I. Glucagon levels were equally suppressed on both nights. Insulin clearance was not altered after rhIGF-I administration. NEFA and ketone levels also were not different on the 2 nights. In conclusion, in adolescents and young adults with diabetes, rhIGF-I administration directly affected insulin requirements independent of GH levels, but had no effect on fatty acid or ketone levels. This difference is related to the abolition of changes in the insulin requirement after GH pulses, and would suggest a complex interaction between GH and IGF-I on insulin action.

THE DAWN PHENOMENON of increased insulin requirements in the early morning in subjects with insulin-dependent diabetes mellitus (IDDM)[1] has been related to growth hormone (GH) secretion.[2] The insulin-antagonistic effects of GH are well characterized,[3,4] and insulin requirements correlate with nocturnal GH secretion[5] and are reversed by agents such as pirenzepine that suppress GH.[6] Increased insulin requirements have been shown to follow GH pulses by about 135 minutes, and GH-pulse and baseline levels affect free fatty acid release and the rate of ketogenesis.[7]

The pathogenesis of GH hypersecretion in adolescents with IDDM is complex, but there is evidence to support a role for reduced negative feedback from low circulating insulin-like growth factor-I (IGF-I) levels.[8] The restoration of IGF-I levels by administration of recombinant human (rh) IGF-I has been shown to result in a concomitant reduction in the GH-pulse amplitude and the insulin requirement to maintain euglycemia.[9,10]

Despite the close relationship between GH and insulin requirements in these studies, it is not possible to exclude a direct effect of rhIGF-I on glucose homeostasis. In vitro studies have shown that IGF-I has effects on glucose uptake distinct from those of insulin.[11] High-dose rhIGF-I exerts insulin-like effects, stimulating glucose uptake and suppressing glucose production.[12-14] rhIGF-I also enhances insulin sensitivity and lipid oxidation.[15]

Thus, rhIGF-I could have direct effects on insulin requirements that are independent of changes in GH secretion. We have therefore undertaken a randomized double-blind, placebo-controlled study of subcutaneous (SC) rhIGF-I in subjects with IDDM in which GH levels were manipulated to be identical during both study periods to enable investigation of the direct effects of rhIGF-I on the insulin requirement to maintain euglycemia.

SUBJECTS AND METHODS

Subjects

Nine subjects with IDDM (two males and seven females; median (range) age and body mass index, 16.9 (12.4 to 21.9) years and 22.9 (19.4 to 28.2) kg/m^2) were studied. All were in late puberty (Tanner stage 4 to 5) and had IDDM for at least 4.5 years but were otherwise healthy. All subjects were on a multiple-injection regimen with evening intermediate-acting insulin (isophane) (9:00 to 10:00 PM) and three injections of soluble insulin daily (before breakfast, lunch, and dinner); the median (range) total daily insulin dose and hemoglobin A_{1C} (HbA_{1C}) were 1.04 (0.74 to 1.48) U/kg/d and 9.5% (7.9% to 14.1%; reference range, 4.3% to 6.1%), respectively. Stimulated C-peptide (blood glucose > 7 mmol/L) was less than 0.09 pmol/L (undetectable in three subjects).

None of the subjects had any evidence of retinopathy (clinical examination by ophthalmologist, with dilation of the pupils), proteinuria/persistent microalbuminuria, or hypertension. Pregnancy was excluded before each study.

The study protocol was approved by the Central Oxford Ethics Committee, and written informed consent was obtained from the subjects and their parents.

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Study Design

This was a randomized double-blind, placebo-controlled study.

Intermediate-acting insulin was withdrawn at least 36 hours before each study, and euglycemia was maintained with regular soluble insulin injections, with the last injection given between 12:00 noon and 1:00 PM on the day of admission. Subjects had a snack at 3:00 PM and were admitted at 4:00 PM, when an intravenous infusion of soluble insulin was commenced. A standardized meal was given at 5:30 PM, and the subjects were then allowed sugar-free soft drinks only until the end of the study.

Each subject was admitted on two occasions (Fig 1) 4 weeks apart, when either rhIGF-I (40 μg/kg; Pharmacia, Stockholm, Sweden) or placebo was administered SC in a double-blind randomized fashion into the anterior aspect of the left thigh at 6:00 PM. Blood glucose levels were "clamped" at 7 mmol/L using a continuous insulin infusion, the rate of which was determined by 15-minute blood glucose levels and a computer program.[16] No glucose was infused overnight. During both study nights, endogenous GH secretion was suppressed with an octreotide infusion (300 ng/kg/h, Sandostatin; Sandoz, Camberley, Surrey, UK) between 6:00 PM and 8:00 AM, and three identical 1-hour GH pulses (9.6 mU/kg/h, Genotropin; Pharmacia) were infused between 8:00 and 9:00 PM, 11:00 PM and midnight, and 2:00 and 3:00 AM.

A second intravenous cannula, placed in a hand vein with the forearm kept in a heated box to arterialize the blood, was used to sample blood before injection of rhIGF-I and thereafter at 15-minute intervals (glucose and GH), 30-minute intervals (free-insulin and metabolites), 60-minute intervals (nonesterified fatty acids [NEFAs] and IGF-I), and 120-minute intervals (glucagon).

Assays

Whole blood glucose was determined at the bedside by the glucose oxidase method (YSI Analyser; Clarendon Scientific, Farnborough, Hampshire, UK). Samples comprising a profile were analyzed in the same batch in duplicate. GH samples were vortexed and separated, and the plasma was stored at −20°C until assayed using a standard diagnostic immunoradiometric assay kit (Netria, St Bartholomew's Hospital, London, UK) and international reference standard 80/505. The detection limit was 0.5 mU/L. Interassay coefficients of variation (CVs) were 9.4%, 7.7%, and 10.5% at 3.5, 15.2, and 77.4 mU/L, respectively; intraassay CVs were 8.0%, 2.0%, and 3.4% at 2.9, 14.3, and 69.4 mU/L, respectively.

Free-insulin levels were measured with a double-antibody radioimmunoassay (Guildhay Antisera, Guilford, Surrey, UK) after precipitation with polyethylene glycol (molecular weight 6000; Sigma, Poole, UK).[16] Interassay and intrassay CVs were 5.5% and 8.6% at 12.2 and 47.2 mU/L and 2.6%, 4.6%, and 5.9% at 19.4, 38.3, and 54.9 mU/L, respectively.

IGF-I levels were measured by radioimmunoassay after acid ethanol extraction. Assay sensitivity was 14 ng/mL. Intraassay and interassay CVs were 11.3%, 6.5%, and 4.7% at 46, 246, and 706 ng/mL and 10.5% 12.1% and 5.1% at 76, 198, and 706 ng/mL, respectively.

Samples for NEFAs were separated immediately after sampling and stored at −20°C until assay with a Wako NEFA C kit (Alpha Laboratories, Eastleigh, Hants, UK). The assay detection limit was 10 μmol/L and interassay and intrassay CVs were both 2.5% at 500 and 1,000 μmol/L. Samples for ketones were taken directly into ice-cold 10% perchloric acid, and after separation, they were assayed by standard enzymatic techniques. Interassay and intraassay CVs for the 3-hydroxybutyrate assay were 8.3% and 2.2%, and for the acetoacetate assay, 5.1% and 1.0%, respectively. Plasma glucagon was determined at the Radioimmunoassay Core Facility of the Diabetes Research and Training Center, Washington University School of Medicine (St Louis, MO). The antibody used for the assay has a high specificity for the COOH-terminal portion of the glucagon molecule. Intraassay and interassay CVs for the glucagon assay are less than 10% and less than 11%, respectively. The HbA_{1c} level was measured by high-performance liquid chromatography (Diamat; BioRad Laboratories, Hemel Hempstead, UK). Interassay CVs were 1.9% and 2.3% at HbA_{1c} levels of 6.9% and 11.5%, respectively. Intraassay CVs were 2.7% and 2.3% at HbA_{1c} levels of 7.0% and 11.6%, respectively.

Analysis

Data are expressed as the mean ± SEM. The steady-state period for overnight blood glucose levels was confirmed using two-way ANOVA. This was the period when there was no significant difference in mean plasma glucose levels between the 2 study nights, and during which there was no change in blood glucose with time (4:00 to 8:00 AM).

For the other variables, nonnormal distribution of data was excluded using the Kolmogorov-Smirnov goodness-of-fit test. Comparisons between mean data from the 2 study nights were made using *T* tests for paired samples. Comparisons between profile data from the 2 study nights were made using ANOVA for repeated measures. Insulin clearance was represented by the ratio between the area under the curve (AUC) for the insulin infusion rate and AUC for the free-insulin level.[17] The AUC was calculated using a trapezoid method. Insulin clearance during the steady-state glucose period (4:00 and 8:00 AM) was calculated.

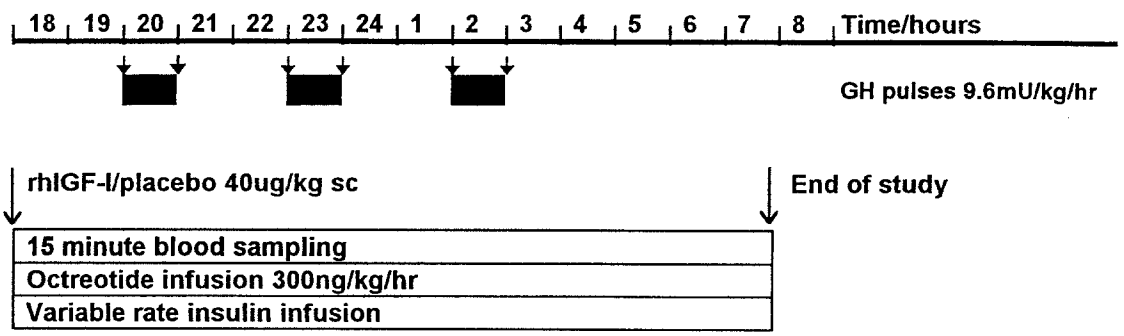

Fig 1. Plan for overnight studies to investigate whether rhIGF-I has effects on the insulin requirement to maintain euglycemia independent of GH. A euglycemic clamp was performed using a variable-rate insulin infusion after double-blind SC administration of IGF-I 40 μg/kg or placebo at 6:00 PM (18:00 hours). Somatostatin analog infusion (300 ng/kg/h) suppressed endogenous GH production, and 3 discrete GH pulses were created by infusion of exogenous GH on both nights.

RESULTS

Glucose settled into the physiological range by 10:00 PM. Glucose levels were more stable after rhIGF-I administration than on the placebo night (Fig 2). A transient increase in glucose occurred on the placebo night between 12:30 and 2:00 AM, despite the fact that insulin infusion rates were also increased on the placebo night at this time. The glucose steady-state period was identified between 4:00 and 8:00 AM, when there was no significant change of glucose levels with time on either night and, furthermore, no significant difference in mean glucose levels between the 2 nights (7.3 ± 0.3 *v* placebo 7.5 ± 0.3 mmol/L, $P = .4$; CV, 16%). None of the subjects had blood glucose less than 3 mmol/L or symptoms of hypoglycemia.

GH and IGF-I Levels

Endogenous GH secretion was suppressed by the octreotide infusion by 8:00 PM, and three distinct GH pulses were observed as a result of the exogenous infusion. Figure 3 illustrates the overnight GH profiles drawn as the mean value for each time point for all nine subjects for each study night. The higher mean value between 6:00 and 8:00 PM on the placebo night was due to a large GH peak in one subject (7:15 PM GH > 120 mU/L), which returned to baseline before the first exogenous GH pulse and subsequently between pulses. There was no obvious cause for this large GH pulse, such as earlier hypoglycemia, that would invalidate this subject's data, and so this subject has not been excluded. The mean ± SEM peak GH value in each pulse was 42 ± 2.7, 46 ± 3.2, and 43 ± 3.5 and 35 ± 7.9, 41 ± 5.4 and 43 ± 7.7 mU/L for the placebo and rhIGF-I night, respectively. These did not differ significantly between the 2 study nights. ANOVA for repeated measures did not identify any significant difference in GH pulses between the 2 nights.

There was a sustained increase in IGF-I after rhIGF-I administration, with peak levels of 460.4 ± 26.9 ng/mL at 11:00 PM on the rhIGF-I night, compared with a peak of 302.2 ± 19.1 ng/mL at 8:00 PM after placebo. Mean levels during the steady-state period (4:00 to 8:00 AM) were 395 ± 23, versus placebo 255 ± 20 ng/mL ($P < .001$, Fig 3). IGF-I levels did not change significantly with time during the glucose steady-state period on either night.

Effect of rhIGF-I Administration on Insulin Requirements

There was a significant reduction in both the insulin infusion requirement to maintain the steady-state glucose level

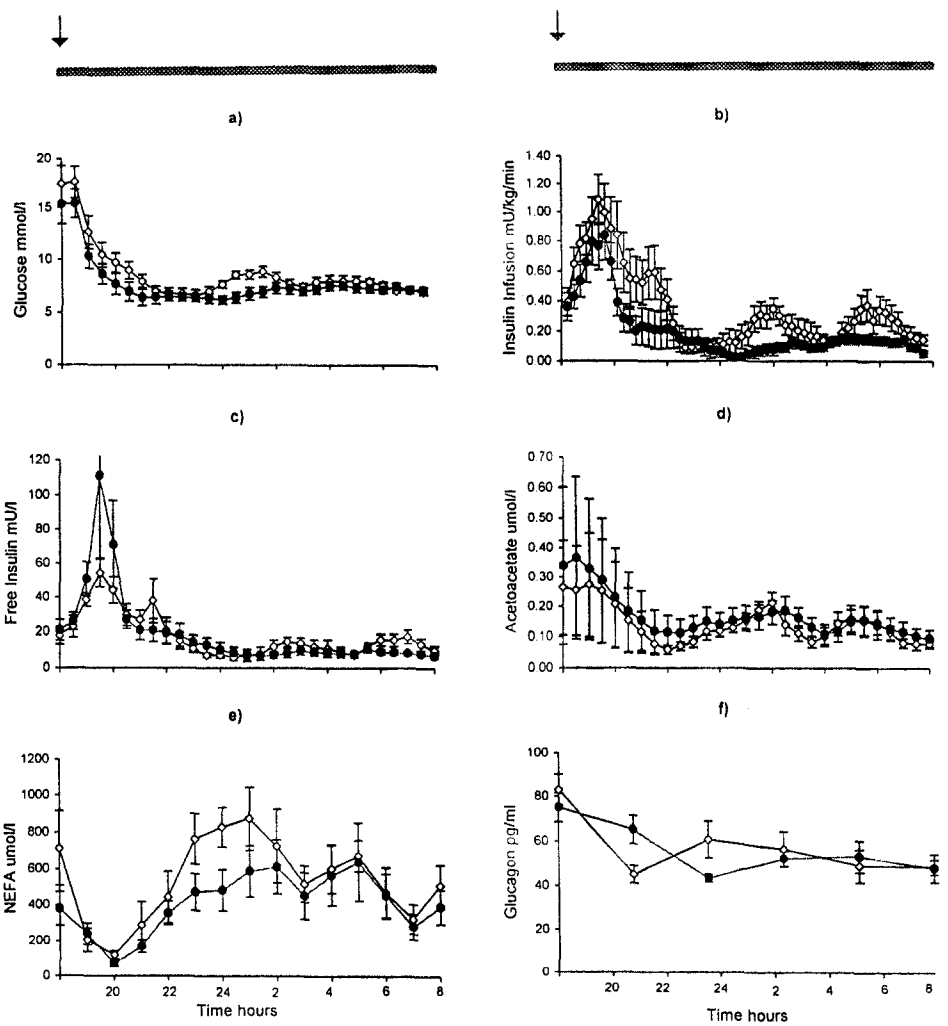

Fig 2. Overnight profiles for (a) glucose, (b) insulin infusion rate, (c) free-insulin, (d) acetoacetate, (e) NEFA, and (f) glucagon after administration of placebo (◇) or rhIGF-I 40 μg/kg SC (●) at 18:00 hours (6:00 PM; indicated by arrow) in 9 adolescents with IDDM during euglycemic clamp studies involving continuous insulin and octreotide infusions (—) and 3 60-minute exogenous GH pulses at 20:00, 23:00, and 02:00 hours. (8.00 PM, 11:00 PM, and 2:00 AM).

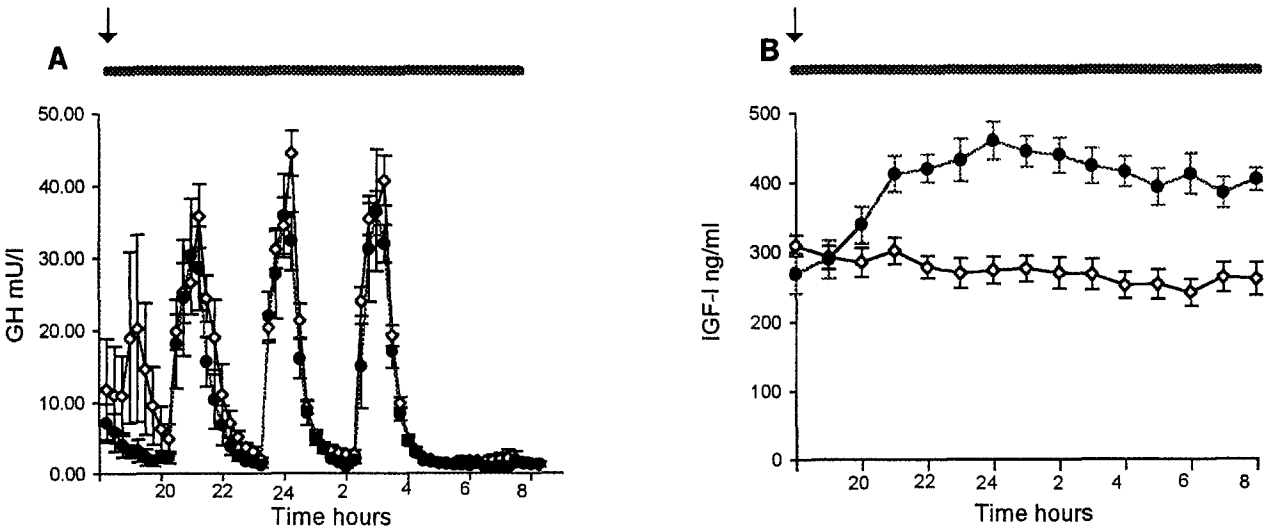

Fig 3. Overnight profiles for (A) GH and (B) IGF-I after administration of placebo (◇) or rhIGF-I 40 μg/kg SC (●) at 18:00 hours (6:00 PM; indicated by arrow) in 9 adolescents with IDDM during euglycemic clamp studies involving continuous insulin and octreotide infusions (—) and 3 60-minute exogenous GH pulses at 20:00, 23:00, and 02:00 hours (8:00 PM, 11:00 PM, and 2:00 AM).

(0.13 ± 0.03 *v* placebo night 0.23 ± 0.05 mU/kg/min, $P = .04$) and the free-insulin level (8.4 ± 1.3 *v* placebo night 12.1 ± 1.4, $P = .03$; Table 1 and Fig 4) after rhIGF-I administration. An inspection of the overnight profiles for the insulin infusion rate (Fig 2) shows that there is a marked difference in the pattern of the insulin requirement with time. ANOVA identifies a significant difference in the change in the insulin requirement with time on the placebo night ($P = .03$); there was no such significant change with time after rhIGF-I administration. Although the insulin infusion rates between the GH pulses did not differ on the 2 nights during the glucose steady-state period, insulin requirements did increase approximately 2 hours after the third GH pulse on the placebo night. A similar increase in the insulin requirement also occurred after the second GH pulse on the placebo night, although it is not possible to comment on changes in the insulin requirement following the first GH pulse because of variability in the insulin requirement at the beginning of the study. No such increases in insulin requirements were seen following the identical GH pulses after rhIGF-I administration.

There was no significant difference in insulin clearance during the steady-state glucose period (4:00 to 8:00 AM) after rhIGF-I administration (Table 1).

Table 1. Mean ± SEM Values From the Steady-State Glucose Period (4:00-8:00 AM) for the Placebo Night and rhIGF-I Night

Steady-State Value (4:00-8:00 AM)	Placebo Night	rhIGF-I Night	*P*
Glucose (mmol/L)	7.5 ± 0.3	7.3 ± 0.3	NS
IGF-I (ng/mL)	255 ± 20	395 ± 23	<.001
Insulin infusion (mU/kg/min)	0.23 ± 0.05	0.13 ± 0.03	.04
Free-insulin (mU/L)	12.1 ± 1.4	8.4 ± 1.3	.03
Insulin clearance (mL/min/kg)	37.6 ± 4.2	39.4 ± 8.2	NS
NEFA (μmol/L)	510 ± 55	623 ± 85	NS
Acetoacetate (mmol/L)	0.12 ± 0.02	0.12 ± 0.04	NS
β-Hydroxybutyrate (mmol/L)	0.21 ± 0.06	0.24 ± 0.09	NS
Glucagon (pg/mL)	52 ± 4.4	53 ± 4.1	NS

Effect of rhIGF-I Administration on Intermediate Metabolites, Fat Metabolism, and Circulating Glucagon Levels

Despite the changes in insulin requirements, circulating free-insulin, and IGF-I levels, there was no significant change in intermediate metabolites or NEFAs after rhIGF-I administration for either the circulating mean levels at 4:00 to 8:00 AM (Table 1) or the overnight profiles (Fig 2). Circulating glucagon levels were suppressed during the octreotide infusion, and there was no significant difference in circulating mean levels at 4:00 to 8:00 AM (Table 1 and Fig 2).

DISCUSSION

In this double-blind, placebo-controlled study, the design ensured that IGF-I levels, although low on the placebo night, were restored to within the normal late-pubertal range on the night of rhIGF-I administration. Octreotide and GH were infused at the same rate on both nights to ensure identical GH peaks comparable to those found in nondiabetic adolescents (30 to 50 mU/L), ie, lower than those usually seen in adolescents with IDDM.[18] In this model, both the insulin infusion requirement and free-insulin level in the glucose steady-state period were significantly reduced after rhIGF-I administration, whereas NEFA and ketone levels remained unchanged. Furthermore, these data demonstrate that rhIGF-I may interact with GH effects on insulin action. This study therefore provides further evidence of the complex interplay between insulin and the GH/IGF-I system in subjects with IDDM, in particular evidence of the direct effects of rhIGF-I on glucose homeostasis independent of GH levels.

Oscillations in the insulin requirement overnight can be seen in the present study on the placebo night (Fig 2). These changes are similar to those we observed in previous studies where a variable-rate insulin infusion was used to maintain stable blood glucose levels without infusion of glucose.[7,9] Distinct changes in insulin requirements can be seen after the second and third GH pulses, although any similar changes following the first

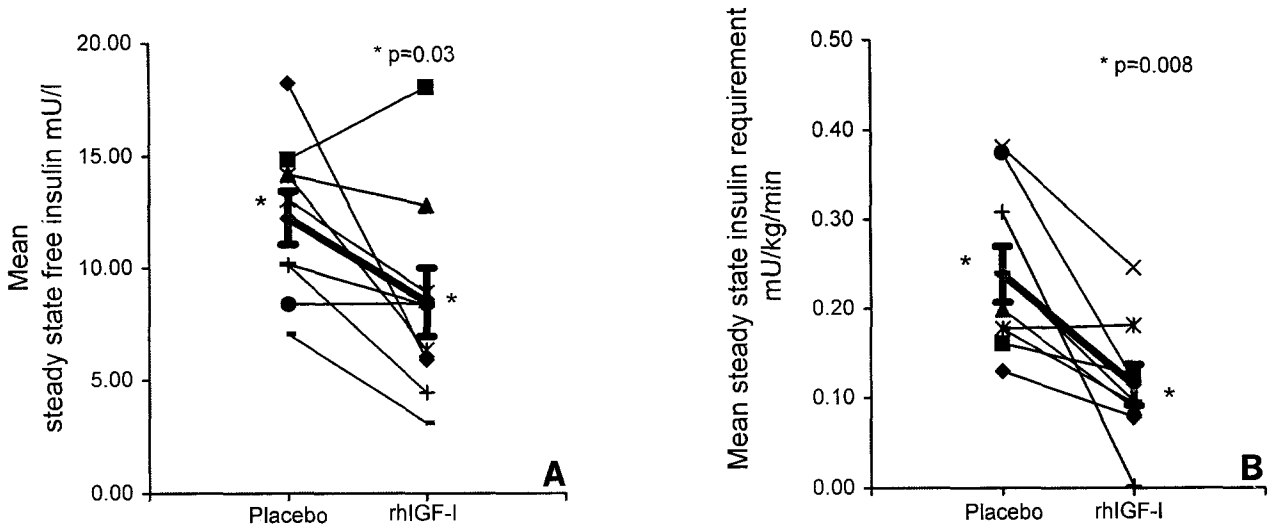

Fig 4. Changes in mean steady-state (4:00-8:00 AM) (A) free-insulin and (B) insulin infusion rate after administration of placebo or rhIGF-I 40 μg/kg SC in 9 adolescents with IDDM during euglycemic clamp studies involving continuous insulin and octreotide infusions and 3 60-minute exogenous GH pulses at 20:00, 23:00, and 02:00 hours (8:00 PM, 11:00 PM, and 2:00 AM) on both study nights. Individual data are shown, with the mean ± SEM in bold.

pulse were obscured by the high insulin levels during the early part of the night. GH pulse–related changes were not identified at all on the rhIGF-I night, and this absence of the expected increase in the insulin requirement after GH pulses accounts for the significant reduction in the insulin requirement to maintain euglycemia after rhIGF-I administration. In previous studies, the insulin-antagonistic effect of GH has been shown to be related to plasma GH levels with regard to both duration and response in normal and IDDM subjects.[4] The onset of insulin-antagonistic action was delayed by 2 hours with GH peaks of 75 and 150 mU/L and by 4 hours with a peak of 45 mU/L in subjects with IDDM, but the maximal response was seen at a GH peak of 75 mU/L in normal subjects.[3,4] Oscillations in the insulin requirement overnight are related to this GH effect,[7] and the delayed time of onset, time of maximal effect, and duration of the insulin-antagonistic effect all implicate GH as a key player in the pathogenesis of the dawn phenomenon.[19] Insulin infusion requirements and free-insulin levels were reduced even on the placebo night compared with those observed in a very similar group of subjects with IDDM described by Cheetham et al.[9] This may be explained by the octreotide infusion and suppression of glucagon secretion, or by the lower peak GH levels produced by exogenous GH pulses in this study. However, the difference in insulin requirements on the 2 nights cannot be explained by the octreotide infusion or glucagon levels, as these were the same on both nights. There is a well-established association between insulin sensitivity and GH levels,[20,21] but in the present study GH pulsatility was predetermined and identical on both nights, and therefore, the reduction in the insulin requirement cannot be explained by feedback effects on GH levels. Nor would it be entirely consistent with a direct hypoglycemic effect of rhIGF-I, as the reduction in the insulin requirement might then be expected to be consistent throughout the period when IGF-I levels were increased. This did not occur, but IGF-I replacement abolished the changes in insulin sensitivity that would be expected to follow GH pulses. This suggests a complex direct mechanism of action such as an interaction between GH and IGF-I effects on insulin postreceptor events. Unfortunately, the effect of rhIGF-I on insulin requirements in the absence of GH could not be explored, because previous experience has demonstrated a marked increase in insulin sensitivity and tendency to hypoglycemia in this model.[7]

One possible mechanism of interaction could be changes in insulin clearance that would reflect the availability of insulin to its receptor. Insulin clearance has recently been reported to increase overnight in IDDM,[22] although many of the early reports implicating changes in insulin clearance in the dawn phenomenon were discounted because of problems with the Biostator.[21,23] IGF-I itself may have a direct effect on insulin clearance through competition for hepatic insulin removal mechanisms.[24] This is supported by in vitro studies demonstrating that IGF-I interferes with insulin degradation in human hepatoma cell cultures[25] and preparations of rat liver and kidney plasma membranes.[26,27] Somatostatin infusion has also been shown to reduce insulin clearance,[28] although in this study there was an identical somatostatin infusion on both study nights. Insulin clearance rates in the current study were relatively high, although a wide range is reported for a healthy population (2 to 30 mL/min kg[17]). However, we did not identify a significant change in insulin clearance following rhIGF-I administration, but since there was great interindividual variability in insulin clearance in our small group of subjects, it is not possible to draw any firm conclusions regarding the possible effect of rhIGF-I on insulin clearance, and this clearly warrants further study.

The pattern of circulating levels of ketone bodies we describe is consistent with previous reports that have identified a peak in intermediate-metabolite levels in the middle of the night followed by a further increase prebreakfast in both normals and diabetics.[29] However, circulating levels of ketones were higher on both nights in the current study than in studies reported in the

literature. Edge et al[6] reported middle-of-the-night peak levels of 277 ± 48 and 111 ± 48 μmol/L with and without pirenzepine, compared with peak β-hydroxybutyrate levels in the current study of 390 ± 80 and 350 ± 70 μmol/L after placebo and rhIGF-I, respectively. This would suggest that there is incomplete suppression of ketogenesis by the reduced circulating levels of free-insulin, despite the fact that blood glucose levels were controlled, although the target plasma glucose was 7 mmol/L, and so were not completely suppressed. The effect of GH on circulating ketone body levels has been explored in studies using pirenzepine[6] or somatostatin[30] to abolish endogenous GH secretion. These studies demonstrated that although fasting levels were determined by the insulin concentration, the early-night peak was related to GH.[6] In addition, an increase in ketone bodies but no increase in NEFAs during GH administration has been reported.[31] Prolonged exposure to GH in insulin-deficient diabetics has also been shown to have an effect on ketogenesis independent of its effect on lipolysis,[32] which is suppressed if there is sufficient insulin. The kinetics of the effect of a GH pulse on lipid intermediates was shown to differ from its effects on insulin sensitivity in humans, with a maximal increase in glucose uptake at 20 minutes but a maximal increase in lipid metabolites at 120 to 160 minutes.[33] GH, rather than insulin, has therefore been shown to be the predominant effector in ketogenesis and lipolysis, and since the GH pulses were the same on both nights, this would explain the observation that there was no difference in ketone or NEFA levels between the 2 study nights in the current investigation.

Thus, although rhIGF-I had a significant effect on the insulin requirement to maintain euglycemia, it had no identifiable effect on GH-stimulated lipolysis or ketogenesis, and this, in turn, may be explained by the varying distribution of receptors in different tissues. IGF-I receptors are abundant in muscle,[34] but the concentrations are reduced in the adult liver[35] and in adipose tissue.[36,37] In vitro studies suggest that the effects of rhIGF-I on glucose transport and metabolism are mediated through its own receptor and not the insulin receptor,[38] whereas acute effects of rhIGF-I on adipocytes are mediated through the insulin receptor.[39] Other studies also provide indirect evidence for the action of IGF-I in adipose tissue via the insulin receptor.[36,40] However, data concerning the direct effects of rhIGF-I administration on lipolysis are conflicting, with no change in NEFA in rats,[41] whereas in normal humans a transient small reduction in NEFA[42] and a significant reduction[13] have been described. Other studies have also suggested that adipose tissue is relatively resistant to IGF-I compared with muscle.[36,40,43] In rat and human adipose tissue, IGF-I–insulin potency ratios of the order 1:100 and 1:1,000, respectively, have been described.[39,44] Our data are therefore consistent with the hypothesis that rhIGF-I acts directly through the type 1 receptor—hence its effect on blood glucose levels but not on lipolysis.

Other factors known to affect not only insulin sensitivity but also ketogenesis and lipolysis are somatostatin and glucagon. Somatostatin has been shown to have a direct hepatic effect on ketogenesis[31] and may also affect free fatty acids directly.[45,46] Circulating NEFA levels have themselves been shown to be important regulating factors of hepatic ketogenesis.[47] In the current study, octreotide and circulating NEFA levels were identical on both nights. IGF-I has been shown to have an effect on glucagon levels, but in this study glucagon levels were equally suppressed by somatostatin on both study nights.

IGF-I bioactivity and bioavailability are modulated by its binding proteins, and alterations in circulating binding protein levels and hence IGF bioactivity could explain the alterations in the insulin requirement noted in the current study. In IDDM, circulating levels of the GH-dependent IGF-binding protein-3 (IGFBP-3) are low but levels of the insulin-dependent IGFBP-1 are high.[48] IGFBP-1, an inhibitor of IGF-I activity, responds to changing glucose and insulin levels and may contribute to the dawn phenomenon.[49] IGFBP levels are altered following rhIGF-I administration[50,51] and thus may be involved in the mechanisms mediating the changes in insulin requirements observed. The role of IGFBPs in alterations of the insulin requirement following rhIGF-I administration in IDDM requires further investigation.

In conclusion, this randomized double-blind, placebo-controlled study of rhIGF-I administration in adolescents and young adults with IDDM provides further support for the role of excess GH and IGF-I deficiency in changes in the insulin requirement overnight and the dawn phenomenon. It supports the hypothesis that IGF-I deficiency may be implicated in those changes, and that the effect of GH on insulin sensitivity in IDDM may be related to IGF-I deficiency. rhIGF-I replacement has direct effects on the insulin requirement, and these effects are largely the result of abolition of the changes in the insulin requirement induced by GH pulses, suggesting subtle interplay of GH and IGF-I on insulin action. rhIGF-I replacement in IDDM promises to shed light on the putative role of IGF-I in the regulation of glucose metabolism, and may prove to be of therapeutic value.[52]

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