Improved Postprandial Metabolic Control After Subcutaneous Injection of a Short-Acting Insulin Analog in IDDM of Short Duration With Residual Pancreatic β-Cell Function

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OBJECTIVE — To compare postprandial metabolic control after subcutaneous injection of a short-acting insulin analog [Lys(B289),Pro(B29)] (Lispro) or human regular insulin (Humulin R U-100 [Hum-R]) in insulin-dependent diabetes mellitus (IDDM) of short duration with residual β-cell function.

RESEARCH DESIGN AND METHODS — Six IDDM patients (age 25 ± 2 years, diabetes duration 14 ± 2 months, HbA_{1c} 6.4 ± 0.5%) with residual pancreatic β-cell function (fasting plasma C-peptide 0.19 ± 0.02 nmol/l) were studied on three different occasions. Postbreakfast plasma glucose was maintained at ~7.1 mmol/l by means of intravenous insulin until either 1200 when 0.1 U/kg Hum-R was injected or until 1225 when 0.1 U/kg of either Hum-R or Lispro was injected subcutaneously. Lunch (mixed meal, 692 Kcal) was served at 1230 (0 min). Six nondiabetic control subjects were also studied.

RESULTS — After Lispro administration, the 120-min plasma glucose decreased more (6.1 ± 0.3 mmol/l) than after injection of Hum-R at −30 min (7.7 ± 0.3 mmol/l) or −5 min (9.9 ± 0.2 mmol/l). By the end of the study, plasma glucose was still lower after Lispro was injected (6.7 ± 0.3 mmol/l) than after Hum-R was injected at −30 min (7.6 ± 0.3 mmol/l) or −5 min (7.3 ± 0.2 mmol/l) ($P < 0.05$). Two IDDM patients required glucose to prevent hypoglycemia after being injected with Lispro, but four required glucose after being injected with Hum-R at −5 min (Lispro ~27 mmol glucose infused between 90 and 240 min; Hum-R ~80 mmol between 240 and 390 min). After Lispro, plasma insulin peaked earlier (at 30 min, 342 ± 29 pmol/l) than after Hum-R injection at −30 min (at 90 min, 198 ± 28 pmol/l) and was superimposable on that of nondiabetic subjects. In Hum-R injected at −5 min, plasma insulin peaked later (at 120 min) and subsequently remained greater than in the two other studies.

CONCLUSIONS — Despite the lack of a time interval between injection and meal, Lispro controls postprandial plasma glucose concentration better than Hum-R given 30 min before meals and, to an even greater extent, better than Hum-R given 5 min before meals. In addition, Lispro minimizes the risk of postprandial hypoglycemia, thus closely mimicking the postprandial glucose homeostasis of nondiabetic subjects. IDDM patients with residual pancreatic β-cell function are the ideal candidates for prandial use of Lispro because they can maintain near-normoglycemia longer after subcutaneous analog injection because of residual endogenous insulin secretion.

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FFA, free fatty acid; Hum-R, Humulin R U-100 insulin; IDDM, insulin-dependent diabetes mellitus.

Intensified insulin treatment aiming at near-normoglycemia to prevent long-term diabetic complications (1) has been strongly recommended since the initial clinical manifestation of insulin-dependent diabetes mellitus (IDDM) (2). One good reason is that by reducing glucose-induced insulin resistance (3), therapeutic maintenance of near-normoglycemia in new-onset IDDM favors induction of IDDM remission (4). In turn, remission of IDDM makes it easier to maintain long-term near-normoglycemia (2) because it reduces requirements of exogenous insulin (3,4) and, importantly, contributes to glycemic stability (2).

Rapid-acting insulin at each meal is the most physiological therapeutic approach to achieve near-normoglycemia in IDDM (1). However, a frequent problem in the treatment of new-onset IDDM with regular insulin at meals is the risk for late postprandial hypoglycemia, even after only a few units of insulin. This is the consequence of nonphysiological hyperinsulinemia that occurs late after subcutaneous injection of regular insulin at a time when the meal is nearly totally absorbed (5).

After subcutaneous injection of a short-acting insulin analog [Lys(B28),Pro(B29)] henceforth referred to as Lispro, plasma insulin peaks and decreases earlier than after human regular insulin injection, mimicking the plasma insulin dynamics of nondiabetic subjects in response to meals (6–8). These physiological pharmacokinetics of Lispro result in improved 2-h postprandial blood glucose tolerance and appear to reduce the risk for late hypoglycemia (9). In theory, the earlier plasma insulin bioavailability and the less prolonged hyperinsulinemia after subcutaneous Lispro as compared with after human regular insulin (6–8) should be particularly useful in IDDM patients with residual β-cell function. Because these patients lack appropriate insulin response to meals but to some extent maintain basal insulin secretion between meals, subcutaneous Lispro in-

Table 1—*Clinical characteristics of subjects studied*

	IDDM patients	Nondiabetic subjects
n	6	6
Sex (M/F)	3/3	3/3
Age (years)	25 ± 2	27 ± 2
Diabetes duration (months)	14 ± 2	—
Body mass index (kg/m^2)	21.8 ± 0.5	21.7 ± 1.0
HbA_{1c} (%)	6.4 ± 0.5	3.5 ± 0.2*
Insulin requirements (U/day)	13 ± 3	—
Plasma C-peptide (nmol/l)		
Fasting	0.19 ± 0.02	0.41 ± 0.05*
6 min after intravenous glucagon	0.34 ± 0.04	0.99 ± 0.12*

Data are means ± SE. HbA_{1c} was determined by high performance liquid chromatography method. *$P < 0.05$ vs. IDDM patients.

jection at meals should physiologically replace postprandial insulin without inducing late hyperinsulinemia.

The present series of studies was undertaken in patients with IDDM of short duration who have residual pancreatic β-cell function to *1*) establish whether a subcutaneous injection of Lispro results in a better postprandial glucose tolerance as compared with equimolar doses of human regular insulin (Humulin R U-100 [Hum-R]), and 2) establish whether the residual pancreatic β-cell function in short-term IDDM protects against the relative insulin deficiency and hyperglycemia that occur late after subcutaneous injection of Lispro in C-peptide–negative IDDM patients (10).

RESEARCH DESIGN AND METHODS

— Institutional Review Board approval was obtained for these studies. Informed consent was given by six IDDM patients with residual pancreatic β-cell function and by six nondiabetic control subjects (Table 1). The IDDM patients were recruited from among those attending the outpatient unit of our institution on the basis of duration of IDDM ≤1.5 years, insulin requirements ≤20 U/day, and fasting plasma C-peptide >0.15 nmol/l. At the time of study, the diabetic patients were free of any detectable diabetic complications. They had no other disease apart from diabetes and were not taking any drugs other than insulin. All IDDM patients had been on a therapeutic program of intensified insulin therapy since the early clinical onset of diabetes and were treated with multiple daily insulin injections (regular insulin at each meal and intermediate-acting insulin at bedtime in four patients, regular insulin at breakfast and lunch and premixed insulin [40% regular, 60% NPH] at supper in the two remaining patients). IDDM patients were studied on three different occasions: after subcutaneous injection of Lispro (5 min before a meal) and after Hum-R injection either 30 min before a meal [Hum-R(−30 min)] or 5 min [Hum-R(−5 min)] before a meal. The first two studies (Lispro and Hum-R at −30 min) were performed in random order at 1–2 week intervals. The third study (Hum-R at −5 min) was performed 1.5–2 months after the first two studies were completed. The presence of hypoglycemia (capillary blood glucose read with chemistrips <4 mmol/l) during the week before studies was excluded by daily preprandial and bedtime blood glucose monitoring. The IDDM patients and nondiabetic volunteers were admitted to the Clinical Research Center of the Dipartimento di Medicina Interna e Scienze Endocrine e Metaboliche, University of Perugia, on the morning of the study between 0700 and 0730. They were admitted in the fasting state, put to bed, and studied in the supine position until late evening (1930). Between 0715 and 0745, two venous lines were started. A hand vein of one arm was cannulated retrogradely with a butterfly needle (20 gauge) and maintained in a Plexiglas thermoregulated box (~65°C) for sampling of arterialized venous blood (11). A superficial vein of the contralateral arm was cannulated with a 19-gauge catheter needle for infusion of insulin and/or glucose. These lines were kept patent by an infusion of 0.9% NaCl (30 ml/h) by means of two peristaltic pumps (VM 8000 M, Vial Medical, St-Martin-Le-Vinoux, Grenoble, France). At 0800, an infusion of Hum-R (Humulin R U-100, Eli Lilly, Indianapolis, IN) (diluted to 0.5 U/ml in 2 ml of the subject's blood and 0.9% NaCl to a final volume of 100 ml) was begun using a syringe pump (Harvard Apparatus, Ealing, South Natick, MA) to maintain a plasma glucose concentration between 7.0 and 7.5 mmol/l as previously described (12). This was continued until the prandial dose of insulin was injected subcutaneously at 1200. Between 0815 and 0830, IDDM patients consumed a standard breakfast (100 g milk, 30 g white bread; 186 Kcal, 56% carbohydrate, 26% protein, 18% lipid). On the first two occasions, either Hum-R at −30 min (1200) or Lispro at −5 min (1225) were injected, whereas on the third occasion Hum-R at −5 min (1225) was injected subcutaneously in the abdominal area 2 cm to the left or right of the umbilicus (Eli Lilly, Indianapolis, IN). A dose of 0.1 U/kg was used because this was the dose the IDDM patients would inject for a meal of a size and composition like the one served in the present studies. After the subcutaneous injection of Hum-R or Lispro, the intravenous insulin was stopped. At 1230 (time 0 min), a standard lunch was served (60 g pasta, 80 g veal, 200 g vegetables dressed with 20 g olive oil, 50 g white bread, 150 g apple; 692 Kcal, 54.2% carbohydrate, 17.4% protein, 28.4% lipid) and eaten within 20 min. Nondiabetic

Table 2—*Postbreakfast plasma glucose concentrations and intravenous insulin requirements in the six IDDM patients on the three study days*

	Time of day				
	0900	1000	1100	1200	1225
Plasma glucose (mmol/l)					
Lispro study	11.3 ± 0.8	10.2 ± 0.7	9.7 ± 0.7	7.2 ± 0.3	7.3 ± 0.3
Hum-R(−30 min) study	10.7 ± 0.8	9.8 ± 0.7	8.9 ± 0.6	7.0 ± 0.4	6.5 ± 0.2*
Hum-R(−5 min) study	11 ± 0.7	10.4 ± 0.6	9.2 ± 0.4	6.9 ± 0.3	7 ± 0.3
Insulin infusion ($mU \cdot kg^{-1} \cdot min^{-1}$)					
Lispro study	0.24 ± 0.07	0.22 ± 0.08	0.14 ± 0.06	0.1 ± 0.03	0.02 ± 0.02
Hum-R(−30 min) study	0.25 ± 0.06	0.21 ± 0.06	0.13 ± 0.05	0.10 ± 0.03	0
Hum-R(−5 min) study	0.26 ± 0.06	0.19 ± 0.07	0.12 ± 0.04	0.11 ± 0.02	0.03 ± 0.01

Data are means ± SE. Hum-R was injected either at 1200 [Hum-R(−30 min)] or 1225 [Hum-R(−5 min)], and Lispro was injected at 1225. *$P < 0.05$ vs. Lispro.

control subjects were studied in the same manner as IDDM patients, except they were not injected with exogenous insulin.

Analytical methods

Plasma glucose was measured using a Beckman glucose analyzer (Beckman, Palo Alto, CA). Plasma insulin, C-peptide, and metabolite concentrations were measured by previously described assays (13). To remove antibody-bound insulin in IDDM patients, plasma was mixed with an equal volume of 30% polyethylene glycol immediately after blood collection (14). Plasma glucagon was measured by radioimmunoassay using a commercially available kit (ICN Biomedical, Costa Mesa, CA). HbA_{1c} was determined by a high performance liquid chromatography method (range in nondiabetic subjects 3.8–5.5%).

Calculations

Insulin secretory rate was calculated based on changes in plasma C-peptide concentration, with equations derived from a two-compartment model (15); a distribution space for C-peptide of 80 ml/kg was used. Portal plasma venous insulin concentrations were calculated according to the equation previously described (16).

Statistical analysis

Data are given as means ± SE. A commercially available software package (CSS, Stasoft, Tulsa, OK) was used for statistical analysis. The differences between groups were analyzed using analysis of variance corrected for repeated measures (17).

RESULTS

Plasma glucose concentrations and insulin requirements in IDDM before prandial subcutaneous insulin

Plasma glucose concentrations in the IDDM patients and intravenous insulin requirements before the subcutaneous insulin were no different in the three studies (Table 2).

Postprandial plasma glucose

In nondiabetic subjects, postmeal plasma glucose concentration increased to a peak of 6.3 ± 0.3 mmol/l at 75 min and then decreased to values no different from baseline by 270 min. In the Hum-R(−30 min) study, plasma glucose initially decreased during the 30-min time interval between insulin injection and meal from 7.0 ± 0.2 to 6.5 ± 0.2 mmol/l at 0 min and then reached a nadir 15 min after lunch (5.8 ± 0.2 mmol/l). Subsequently, plasma glucose increased progressively to a peak of 8.1 ± 0.2 mmol/l at 75 min and was 7.6 ± 0.3 mmol/l by the end of study. In the Lispro study, plasma glucose initially increased from 7.3 ± 0.2 to 8.6 ± 0.2 mmol/l at 30 min. It decreased to a nadir of 5.6 ± 0.3 mmol/l at 120 min and was 6.7 ± 0.2 mmol/l by the end of study. In the Hum-R(−5 min) study, plasma glucose increased from 7.2 ± 0.2 mmol/l (0 min) to a peak of 10.3 ± 0.3 mmol/l (90 min) and then decreased to a nadir of 4.8 ± 0.2 mmol/l between 300–330 min during exogenous glucose infusion (see below). Thus, postmeal plasma glucose concentration, both as a 2-h value and as a 0- to 420-min mean value, was lower after Lispro injection as compared with after both Hum-R at −30 min and, to a larger extent, Hum-R at −5 min (Fig. 1 and Table 3).

Glucose infusion after prandial subcutaneous insulin injection in IDDM patients

Two IDDM patients in the Lispro study required glucose between 90 and 240 min at the rate of 3.3 ± 0.5 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ to prevent plasma glucose <4.4 mmol/l. Four IDDM patients in the Hum-R(−5 min) study required glucose between 240 and 390 min at the rate of 8.9 ± 0.1 $\mu mol \cdot kg^{-1} \cdot min^{-1}$.

Peripheral arterial plasma insulin, plasma C-peptide, and estimated portal plasma insulin

Baseline peripheral arterial plasma insulin was 46 ± 5 pmol/l in nondiabetic subjects, 38 ± 3 pmol/l in IDDM patients in the Hum-R(−30 min) study, 40 ± 9 pmol/l in the Lispro study, and 39 ± 6 pmol/l in the Hum-R(−5 min) study (NS) (Fig. 2). After lunch, peripheral arterial

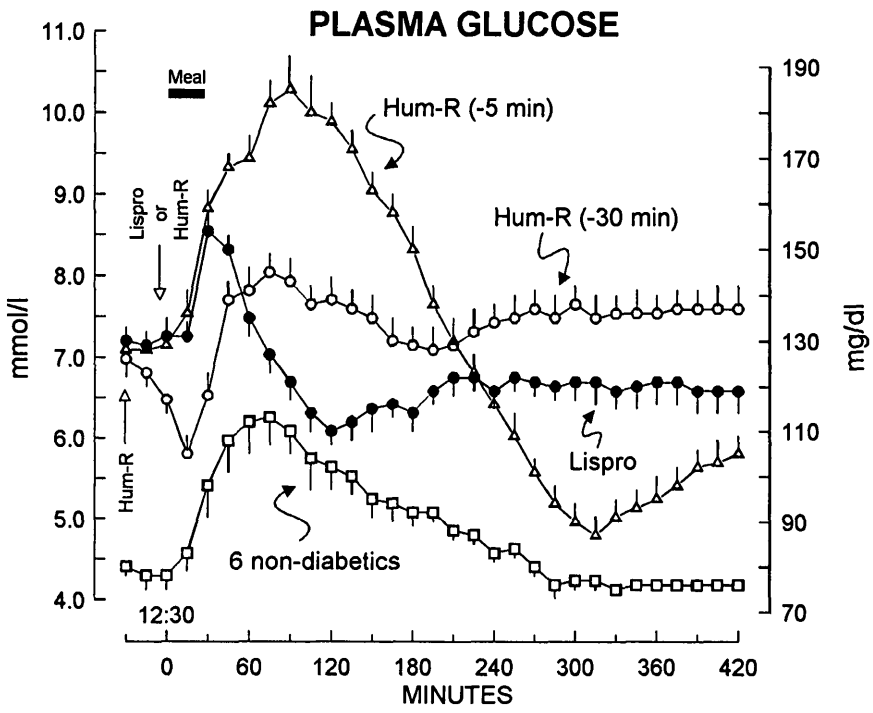

Figure 1—*Plasma glucose concentration after subcutaneous injection of 0.1 U/kg human regular insulin 30 min before a meal [Hum-R(−30 min)] or 5 min before a meal [Hum-R(−5 min)] or Lispro 5 min before a meal (1230, time 0 min) in six patients with a short duration of IDDM and residual pancreatic β-cell function. Six nondiabetic subjects given the same meal as IDDM patients are shown for comparison. Two IDDM patients in the Lispro study and four patients in the Hum-R(−5 min) study required glucose to prevent hypoglycemia (see RESULTS). Data are means ± SE.*

plasma insulin increased in nondiabetic subjects to a peak of 295 ± 41 pmol/l at 90 min and then decreased to baseline values by 300 min. In the Hum-R(−30 min) study, peripheral arterial plasma (free) insulin increased to only 200 pmol/l at 90 min and remained lower in nondiabetic subjects until 150 min. In contrast, in the Lispro study, plasma insulin had already increased at 30 min to a peak of 340 ± 27 pmol/l, a value greater than in nondiabetic subjects (160 ± 47 pmol/l) ($P < 0.05$) and subsequently was at no time different from that in nondiabetic subjects. However, after 180 min, plasma insulin concentration was lower in the Lispro study (47 ± 10 pmol/l) than in the Hum-R(−30 min) study (57 ± 9 pmol/l) (240- to 420-min values), but the difference was not statistically significant. In the Hum-R(−5 min) study, plasma insulin peaked later (120 min) than in the two other studies and after 180 min was greater (93 ± 5 pmol/l) than in the two other studies ($P < 0.05$).

Plasma C-peptide concentration increased in response to meals in nondiabetic subjects from 0.44 ± 0.03 to 1.77 ± 0.13 nmol/l at 90 min and remained increased until the end of study (0.79 ± 0.05 nmol/l). Baseline and meal-stimulated plasma C-peptide in IDDM patients was similar in all three studies.

Baseline estimated portal plasma insulin concentrations were no different in the nondiabetic subjects and IDDM patients. After lunch, estimated portal plasma insulin increased earlier in the Lispro study (peak of 453 ± 25 pmol/l at 30 min) than in the Hum-R(−30 min) (335 ± 24 pmol/l at 90 min) or Hum-R(−5 min) study (330 ± 18 pmol/l) ($P < 0.05$) but remained lower than in nondiabetic subjects (peak of 912 ± 67 pmol/l at 90 min) until 360 min.

Plasma glucagon concentrations

Baseline and meal-stimulated plasma glucagon concentrations in nondiabetic subjects and IDDM patients were no different (NS) in the Hum-R and Lispro studies (Fig. 3). Postprandial plasma glucagon increased in all studies between 30 and 180 min ($P < 0.05$). Subsequently, plasma glucagon decreased to baseline values in the Hum-R(−30 min) study (after 210 min), whereas it remained increased until 420 min in all other studies.

Plasma metabolite concentrations

Baseline plasma free fatty acids (FFAs) were lower in IDDM patients (0.26 ± 0.04 mmol/l) than in nondiabetic patients (0.52 ± 0.12 mmol/l) ($P < 0.05$) (Fig. 4). After lunch, plasma FFAs were similarly suppressed in nondiabetic and IDDM patients in all three studies. However, by the end of study, plasma FFAs were still lower

Table 3—*Baseline, 120-min postmeal, and mean 0- to 420-min postmeal plasma glucose (mmol/l) in the three studies of IDDM patients and nondiabetic subjects*

	0 min	120 min	Mean 0–420 min
IDDM patients			
Hum-R(−30 min) study	6.5 ± 0.2	7.7 ± 0.3	7.2 ± 0.3
Lispro study	7.3 ± 0.2	6.1 ± 0.2*	6.8 ± 0.2*
Hum-R(−5 min) study	7.2 ± 0.2	9.9 ± 0.2	7.3 ± 0.2
Nondiabetic subjects	4.3 ± 0.2	5.7 ± 0.3	4.9 ± 0.3

Data are means ± SE. *P < 0.05 vs. Hum-R.

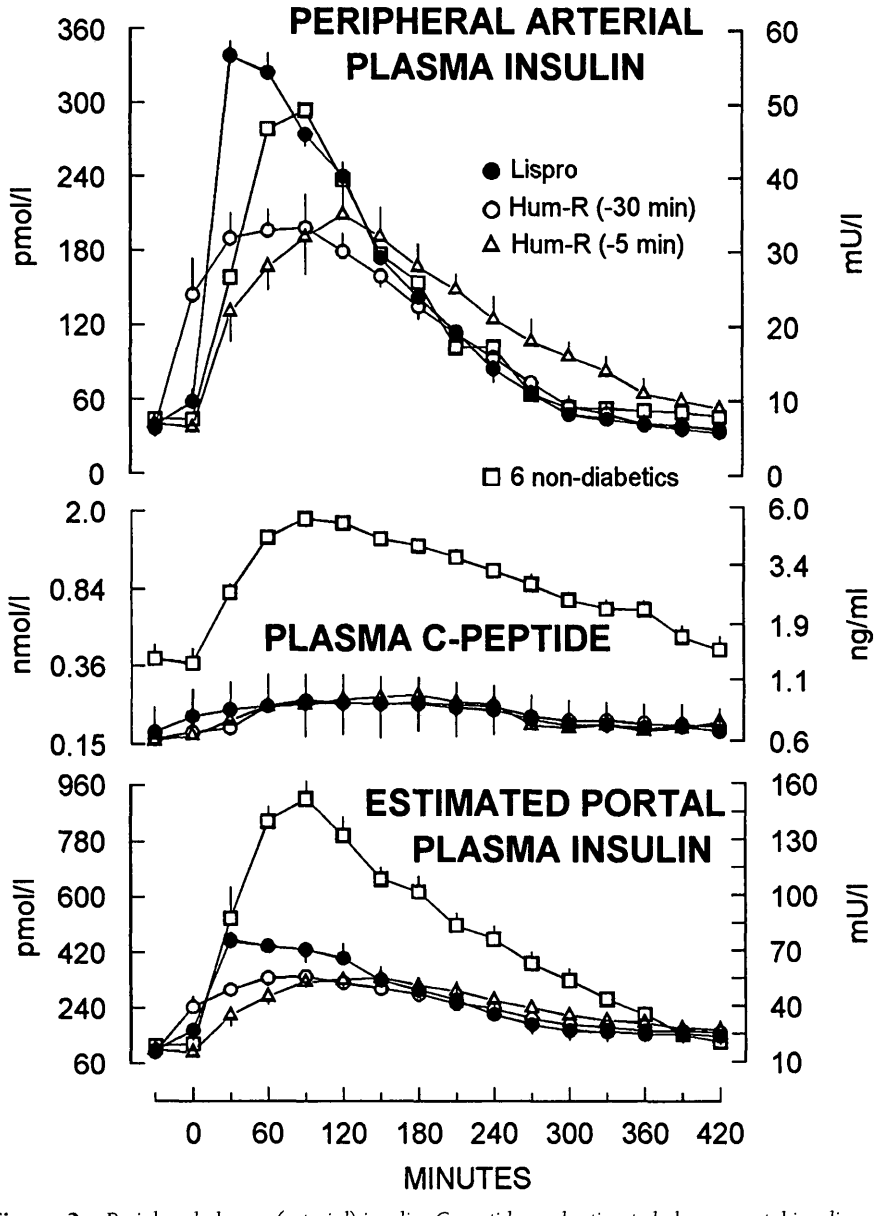

Figure 2—*Peripheral plasma (arterial) insulin, C-peptide, and estimated plasma portal insulin concentrations after subcutaneous injection of Hum-R at −30 min or −5 min or Lispro in six IDDM patients and six nondiabetic subjects (see legend for Fig. 1). The scale of plasma C-peptide is logarithmic. Data are means ± SE.*

than baseline in nondiabetic subjects, whereas they rebounded above baseline in IDDM patients after Lispro and Hum-R(−30 min) injection. Postprandial plasma glycerol concentration was similarly suppressed in nondiabetic subjects and IDDM patients until 120 min but subsequently increased more in IDDM patients in the Hum-R(−30 min) and Lispro studies. In contrast, in the Hum-R(−5 min) study, plasma FFAs and glycerol were no different from that in people without diabetes.

Postprandial plasma β-OH-butyrate concentration was similarly suppressed in nondiabetic subjects and IDDM patients in all three studies until 90 min. Subsequently, plasma β-OH-butyrate concentration increased more in IDDM patients in the Lispro (1.50 ± 0.28 mmol/l) and Hum-R(−30 min) studies (0.98 ± 0.24 mmol/l) than in nondiabetic subjects (0.54 ± 0.39 mmol/l) (420 min, $P < 0.05$). In the Hum-R(−5 min) study, plasma β-OH-butyrate concentration by the end of the study was no different from that of nondiabetic subjects.

Plasma lactate and alanine concentrations increased to similar values after lunch in nondiabetic subjects and IDDM patients and then slowly returned to baseline values by the end of the studies.

CONCLUSIONS —

The present studies demonstrate that in patients with IDDM of short duration who have residual pancreatic β-cell function, the subcutaneous injection of the short-acting insulin analog Lispro results in greater decreases in postmeal hyperglycemia as compared with injection of Hum-R (Fig. 1). This difference is more relevant when Hum-R is given immediately before the meal but is still present when Hum-R is given 30 min before the meal (Table 3).

The first question one might have is whether long-term IDDM treatment with Lispro would decrease the percentage of HbA_{1c}. The results of the present studies, based on the lower postprandial plasma glucose, predict that the decrease of HbA_{1c} after long-term Lispro treatment would be modest and perhaps of disputable biological meaning in terms of protection against long-term microangiopathic complications, at least in IDDM of short duration with residual β-cell function. In fact, these patients usually have HbA_{1c} in an optimal therapeutic range (~6.4% in the present study). However, the favorable effects of Lispro on postprandial plasma glucose, although modest, were observed after injection of the analog at mealtime. In addition, in the present studies, Lispro minimized postprandial hypoglycemia. Thus, one should conclude that Lispro is a more convenient, efficient, and safe insulin prepara-

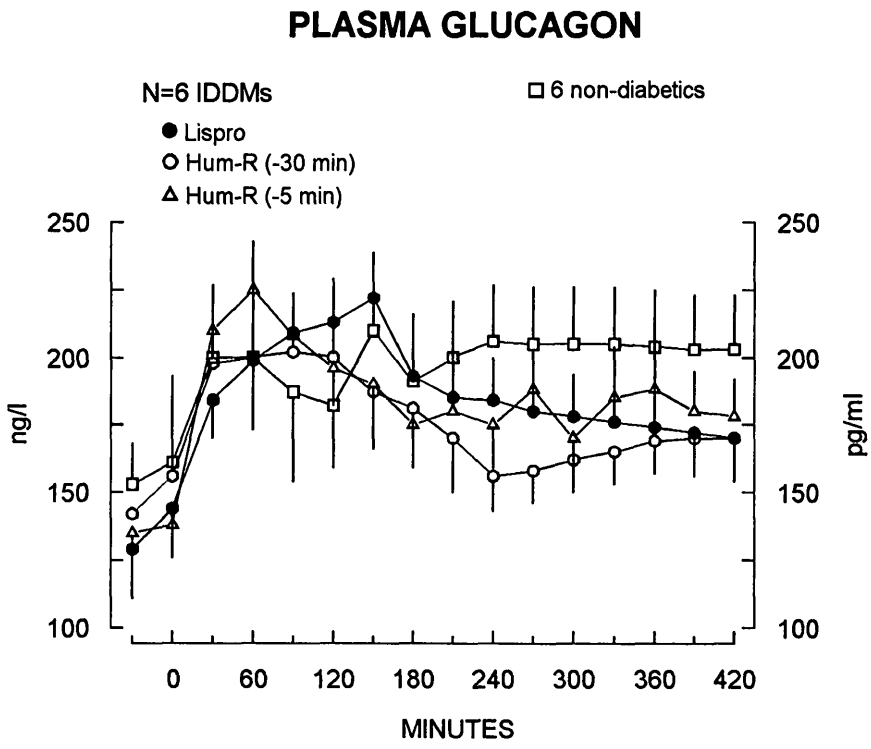

Figure 3—*Plasma glucagon concentrations after subcutaneous injection of Hum-R at −30 min or −5 min or Lispro in six IDDM patients and six nondiabetic subjects (see legend for Fig. 1). Data are means ± SE.*

tion than Hum-R for replacing insulin requirements at meals in IDDM patients, at least in those with short-duration IDDM and residual β-cell function.

Although subcutaneous injection of Lispro is certainly a step forward in the physiological replacement of insulin in IDDM, the present studies show that the postprandial plasma glucose concentration after Lispro was still greater than in nondiabetic subjects (Fig. 1), despite superimposable peripheral plasma insulin concentrations (Fig. 2). However, Lispro was injected in hyperglycemic, not euglycemic IDDM patients. One may speculate that had Lispro been used in strictly euglycemic IDDM patients, postprandial plasma glucose might have been normal. In the present studies, preprandial strict euglycemia in IDDM patients was deliberately avoided because real-life patients should maintain preprandial blood glucose of 2–3 mmol/l above normal to prevent hypoglycemia (18) and hypoglycemia unawareness (19). A second, perhaps more relevant reason for greater postprandial plasma glucose concentration in IDDM patients after Lispro in the present studies is the portal plasma insulin concentration, which in IDDM patients after Lispro injection (as well as after Hum-R) was <50% of that of nondiabetic subjects. Thus, it is likely that it was the portal underinsulinization that accounted for the greater postprandial plasma glucose values in IDDM patients after Lispro as compared with in nondiabetic subjects despite normalization of peripheral plasma insulin. In this regard, it is likely that glucagon did not contribute because its postprandial plasma concentrations after Lispro and Hum-R injections in IDDM patients were no different than those of nondiabetic subjects (Fig. 3). This is at variance with the results of a recent study in which plasma glucagon was found to be greater during prolonged Lispro treatment as compared with during Hum-R treatment in totally C-peptide–negative IDDM patients (8).

One might question whether a greater dose or a longer time interval between injection and meal might have improved postprandial glucose tolerance after subcutaneous injection of Hum-R in the present studies. The answer, of course, is no because of the high risk for hypoglycemia either immediately before or late after the meal. The fact that plasma glucose decreased to ~5.5 mmol/l 15 min after lunch in the Hum-R study (Fig. 1) clearly indicates that the 30-min time intervals between injection and meals used in the present study may increase the risk for preprandial hypoglycemia, at least in patients with IDDM of short duration with residual β-cell function. In fact, having a slightly shorter time interval between injection and meal when using regular insulin would be safer for these patients in real life. On the other hand, the present studies confirm that injection of regular insulin at mealtime deteriorates postprandial glucose control and increases the risk for hypoglycemia (20,21). This reinforces the concept that even patients with IDDM of short duration should be encouraged to allow at least a 20-min time interval between injection of regular insulin and a meal.

The present studies confirm that Lispro reduces the risk for hypoglycemia late after meals, an event often seen when subcutaneous Hum-R is given at mealtime in doses aiming at near-normoglycemia (20,21). This is the result of lower plasma insulin concentrations after 180 min with Lispro as compared with those with Hum-R given at −5 min. In the present studies, two IDDM patients required glucose to prevent hypoglycemia early after the meal. However, the amount of glucose infused with Lispro (~27 mmol between 90 and 240 min) was negligible as compared with the amount infused with Hum-R given at −5 min (~80 mmol between 240 and 390 min).

The mechanism of better postprandial glucose tolerance after Lispro as compared with after Hum-R is easily ex-

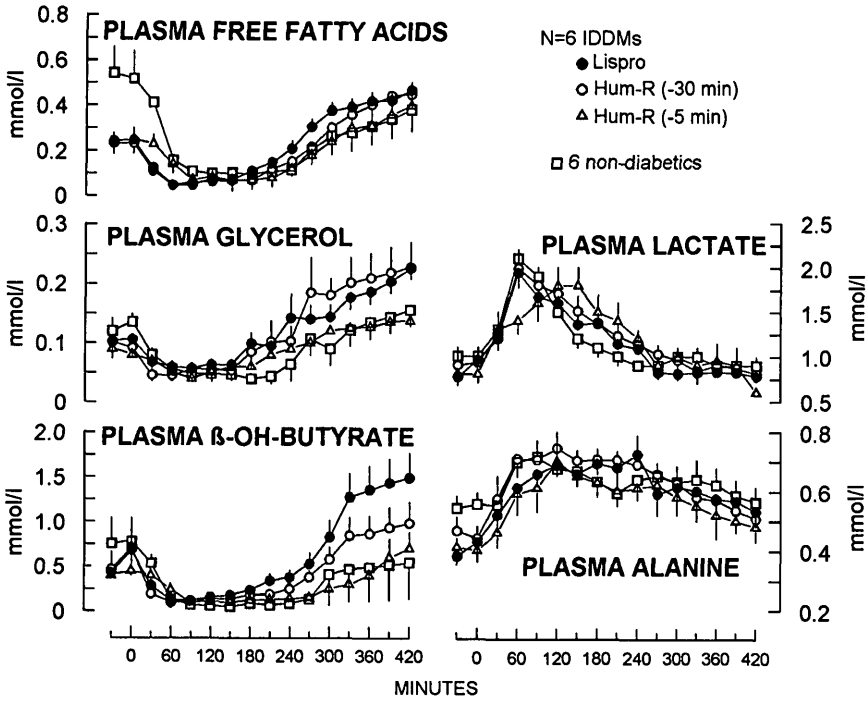

Figure 4—*Plasma metabolite concentrations after subcutaneous injection of Hum-R at −30 min or −5 min or Lispro in six IDDM patients and six nondiabetic subjects (see legend for Fig. 1). Data are means ± SE.*

plained by the more physiological insulin pharmacokinetics of Lispro. In contrast to the postprandial hypoinsulinemia observed after Hum-R between 0 and 180 min, the postprandial peak of peripheral plasma insulin after Lispro injection was superimposable on that of nondiabetic subjects (Fig. 2). Thus, the results of the present studies confirm the previous observation that it is the early plasma insulin peak in response to a meal that is critical to postprandial plasma glucose tolerance (20,22,23).

However, a greater biological effect of Lispro as compared with that of Hum-R cannot be totally excluded (10). Because in the present studies two IDDM patients required intravenous glucose after Lispro, it would appear wise to start a 10% smaller dose of Lispro than of Hum-R when IDDM patients are first transferred from regular to Lispro insulin, at least for patients with short IDDM duration and residual pancreatic β-cell function.

In the present studies with Lispro, plasma glucose concentration did not increase late after lunch (between 240 and 420 min). This is different from the marked increase in plasma glucose observed in totally C-peptide–negative IDDM patients studied under similar experimental conditions, i.e., late after Lispro, paralleling a decrease in plasma insulin concentration (10). It is reasonable to assume that such a difference is explained by the residual endogenous insulin secretion of the IDDM patients in the present studies, as indicated by the plasma C-peptide concentrations. In this regard, it is interesting that even a modest residual plasma C-peptide concentration (~0.2 nmol/l) indicates endogenous insulin secretion significant enough to maintain near-normoglycemia in the transition from the absorptive to the postabsorptive phase. This observation is the rationale behind treating IDDM patients with short disease duration and residual β-cell function with short-acting insulin at each meal rather than with intermediate or long-acting insulin. In contrast, in totally C-peptide–negative IDDM patients, basal insulin between meals must be replaced to prevent exaggerated late postmeal hyperglycemia after Lispro administration (10).

In summary, subcutaneous prandial administration of the short-acting insulin analog Lispro in patients with IDDM of short duration who have residual pancreatic β-cell secretion offers several advantages over the conventional Hum-R. First, Lispro can be injected with a meal. This contributes to a normal lifestyle for an IDDM patient and, most importantly, protects the patient from the risk of preprandial hypoglycemia, which may occur when a time interval of 30 min between insulin injection and a meal is observed in patients who are near-normoglycemic at the time of injection (20). Second, postprandial glucose tolerance improves. Third and most important, Lispro minimizes the risk for the postprandial hypoglycemia that may easily occur 4–6 h after injection of Hum-R at mealtime in doses aiming at the target near-normoglycemia of intensive insulin therapy and may therefore prevent hypoglycemia unawareness in IDDM (19).

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