Metabolic Efficacy of Preprandial Administration of Lys(B28),Pro(B29) Human Insulin Analog in IDDM Patients

A comparison with human regular insulin during a three-meal test period

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OBJECTIVE — The objective of this study was to compare the efficacy of the rapid-acting Lys(B28),Pro(B29) human insulin analog, insulin lispro, with currently available short-acting human insulin in a multiple injection therapy (MIT) regimen with respect to blood glucose and plasma insulin profiles and to serum metabolites (lactate, free fatty acids, glycerol, and β-hydroxybutyrate) in 12 well-controlled type 1 diabetic subjects (8 male, HbA_{1c} 6.8 ± 0.9% [mean ± SD]).

RESEARCH DESIGN AND METHODS — After a run-in period of 4 weeks, patients were treated with either lispro at mealtime or human insulin 30 min before the meal for two periods of 4 weeks in a randomized open-label crossover study. Intermediate-acting insulin (NPH insulin) was given at bedtime. At the end of both study periods, metabolic profiles were assessed from 10:00 P.M. to 7:00 P.M. the next day.

RESULTS — During the treatment periods, glycemic control was stable during lispro but improved during human insulin (ΔHbA_{1c} lispro 0.1 ± 0.48, NS; human insulin −0.41 ± 0.34%, $P < 0.05$). Glucose excursions, as measured by the incremental AUC, during the day and for the 2-h postprandial periods, were lower, although not significantly, for lispro. Insulin profiles demonstrated a faster rise after administration of lispro as compared with human insulin, peaking at 61 ± 11.9 and 111 ± 48.1 min ($P < 0.01$). Glycerol levels showed a slight increase before lunch and dinner, suggestive of enhanced lipolytic activity and compatible with the lower insulin levels.

CONCLUSIONS — Lispro insulin applied in an MIT regimen creates more physiologic insulin profiles and tends to lower the glycemic excursions during the day compared with short-acting insulin. The analog can be applied safely in an MIT regimen, with mealtime intervals up to 5 h.

Recent studies have shown that intensive insulin therapy, resulting in adequate glycemic control, reduces the risks for retinopathy, nephropathy, and neuropathy (1,2), but at the expense of a greatly increased incidence of severe hypoglycemia (3).

A commonly used intensive insulin therapy regimen consists of long-acting insulin (NPH or lente insulin) to supply the basal requirements during the night and multiple short-acting insulin injections to match meal-related insulin requirements (4–6). However, it is hard to achieve normoglycemia because of the pharmacokinetics of the available insulin preparations for subcutaneous administration (7). Insulin preparations with protracted action show a large intraindividual variation of absorption, and the duration of action is too short to ensure adequate basal levels. The available short-acting insulin preparations have various shortcomings, the most evident of which are a delayed onset of action, an inappropriately long time course of action, and a large variability of absorption (8). The absorption of subcutaneous short-acting insulin is influenced by many factors, among which the natural tendency to self-associate to hexamers is of importance (9).

Recently, recombinant DNA techniques have been applied for the production of insulin analogs with fast absorption characteristics. These analogs have in common a reduced tendency to self-associate. Although a large number of these so-called monomeric insulin analogs have been produced, only a few are candidates for the prandial insulin needs in diabetic subjects (10). Among these, Lys(28),Pro(29) human insulin analog (lispro insulin or lispro) has shown to be a promising one. As a result of an inversion of the natural amino acid sequence of the B-chain at B28 (proline) and B29 (lysine), lispro insulin exhibits monomeric behavior in solution (11,12) and displays, in various species, a faster pharmacodynamic action than short-acting human insulin (13–15). These altered pharmacodynamic properties are in concert with the rapid absorption expected from a subcutaneously injected monomeric insulin preparation (16).

Introduction of this insulin analog might prove to be advantageous in a multiple injection therapy (MIT). Taken together, most studies have demonstrated an improved control of postprandial glycemic excursions with lispro insulin but demonstrated no effect on longer-term indexes of glycemic control. Counterregulatory responses to hypoglycemia have been found to be similar for either human insulin or lispro insulin (17–20). Also, the glycemic responses during exercise have been assessed with lispro insulin (21). Fur-

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AUC, area under the curve; FFA, free fatty acid; HBGM, human blood glucose monitoring; MIT, multiple injection therapy; RM-ANOVA, analysis of variance for repeated measures.

thermore, the immunogenecity is not different from that of regular insulin, and toxicity studies have not been able to demonstrate enhanced mutagenicity (22–24).

The pharmacodynamics of lispro suggest that this insulin analog might be able to control postprandial hyperglycemia without enhancing the risk of late postprandial hypoglycemia. However, a relevant basal daytime insulin supply is required to maintain glycemic and metabolic control. In the MIT regimen, this basal supply is provided by the protracted absorption rate of soluble short-acting insulin, which may last for 8 to 12 h (7). The use of a short-acting insulin analog in an MIT regimen rather than regular insulin may therefore result in an unstable control due to insulinopenia 3 to 4 h after administration of the analog.

The objectives of this study were to compare the efficacy of lispro insulin to currently available short-acting human insulin with respect to blood glucose, plasma insulin profiles, and serum metabolites in well-controlled type 1 diabetic patients treated with an MIT regimen consisting of NPH at bedtime and short-acting insulin before meals.

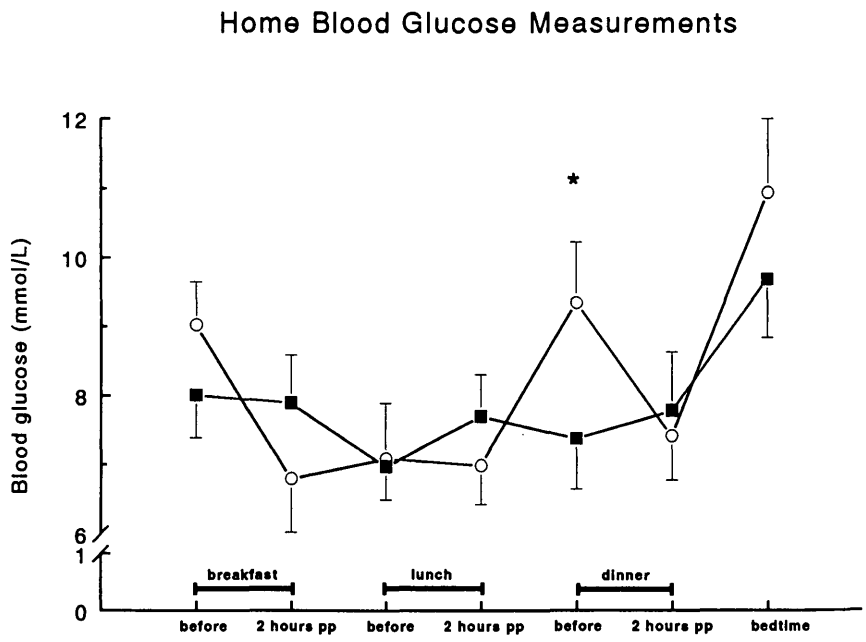

Figure 1—*Home blood glucose measurements (mean ± SE) of the diabetic patients (n = 12) during either lispro (–○–) or human insulin (–■–) treatment (*P ≤ 0.05).*

RESEARCH DESIGN AND METHODS

Patient population

We studied 12 patients with type 1 diabetes from our outpatient clinic (average age at onset 17.8 years; range 7–34). For this study, we included well-controlled patients (HbA_{1c} 6.8 ± 0.9, reference range 4.3–6.1%) treated with MIT consisting of preprandial short-acting insulin and NPH insulin at bedtime. Moreover, they had to have C-peptide levels of <0.07 nmol/l 6 min after glucagon (1 mg i.v.) stimulation and be of normal weight (BMI <30 kg/m^2). Exclusion criteria were serious underlying disease, nephropathy, proliferative retinopathy, pregnancy, and a history of hypoglycemia unawareness or more than two hospitalizations for hypoglycemia in the last year. A healthy nondiabetic control group of six volunteers matched for sex, age, and BMI (kg/m^2), was recruited for assessment of the physiologic profiles. The protocol had been approved by the local ethical committee and the study was conducted in accordance with the Declaration of Helsinki.

Treatment and medication

During the study, patients were treated with Actrapid (Novo Nordisk, Bagsvaerd, Denmark) and Humulin NPH (Eli Lilly, Indianapolis, IN), U100 potency, supplied in cartridges of 1.5 ml. The study material consisted of Lys(B28),Pro(B29) human insulin analog (rDNA) (Eli Lilly). The patients administered the rapid-acting insulin, insulin lispro and Actrapid, in the abdominal region immediately and 15–30 min before meals, respectively. We advised to adjust the dose of insulin in accordance with glycemic needs. The blood glucose values aimed for were fasting, <7.8 mmol/l, and 2-h postprandial, <10.0 mmol/l. The patients administered doses of insulin for each consumption of food (meal or snacks) that contained >20% of the daily caloric intake. Humulin NPH was administered in the thigh region once a day at bedtime. Dose adjustments were made until fasting blood glucose levels of 4.0–7.0 mmol/l were achieved.

Protocol

The study had an open crossover design, with a 4-week run-in period and two study periods of 4 weeks each. During the run-in period, the patients became accustomed to the study requirements, e.g., frequent home blood glucose monitoring (HBGM) twice weekly (measurements before and 2 h after the main meals and at bedtime) and recording the number and severity of hypoglycemic events. The severity of hypoglycemic episodes was graded as follows. grade I: vague feeling, but no action taken; grade II: extra carbohydrates required or an early meal; grade III: assistance of a second person necessary.

Also, any measured blood glucose ≤3.5 mmol/l, with or without symptoms, was considered as a hypoglycemic event. Glycemic control was further evaluated by insulin dosage, hypoglycemic episodes, and HBGM profiles. During the study periods, the patients were randomly allocated to preprandial injections of short-acting insulin or insulin lispro three times daily. This group of well-controlled and educated patients was able to determine their premeal insulin dose requirements on the basis of the nature and size of the anticipated meal and physical activity. The NPH dose was not changed more often than once every 3 days.

At the end of each study period, the patients were hospitalized for a three-meal test period. The patients were admitted to the metabolic ward at 9:30 P.M. the evening before the test. A cannula for intermittent blood sampling was inserted into the antecubital vein of the right arm. A second cannula for glucose administration in case of incipient hypoglycemia was inserted in the other arm. NPH insulin was injected at bedtime. During the night, blood was sam-

pled at 10:00 P.M., midnight, 3:00 A.M., and 6:00 A.M. for assessment of glucose and insulin. In the period before breakfast, three basal samples were obtained for determination of glucose, insulin, glucagon, triglycerides, and metabolites (free fatty acids [FFAs], glycerol, lactate, and β-hydroxybutyrate). Human insulin was injected 30 min before the standardized meals and lispro immediately before the meals. Blood samples were taken after the meal every 15 min for the assessment of blood glucose and serum insulin for 2 h and once per half hour thereafter. The other hormones and metabolites were assessed every 30 min for the first 2 h and once every hour thereafter.

Breakfast consisted of a standard composition (Fortimel pudding and Nutridrink [Nutricia, Zoetermeer, The Netherlands]: 50% carbohydrates, 30% fat, and 20% protein), while the individual caloric intake was calculated by a dietitian, based on a 3-day dietary record.

Measurements

Glycosylated hemoglobin (HbA_{1c}) was analyzed by ion-exchange high performance liquid chromatography (Modular diabetes monitoring system, Bio-Rad Laboratories, Veenendaal, The Netherlands) (25). Blood glucose was determined by a Yellow Springs glucose analyzer (YSI 2300 STAT PLUS, Yellow Springs Instruments, Yellow Springs, OH), whereas HBGM measurements were done by a glucose oxidase method (One Touch II, Lifescan, Milpitas, CA). Serum free insulin was determined using radioimmunoassay (Coat-A-Count, DPC, Los Angeles, CA), as were C-peptide levels (Diagnostic Systems Laboratories, Webster, TX) and plasma glucagon (Linco Research, St. Louis, MO). The latter was modified by an ethanol extraction method to remove big-glucagon. Serum triglycerides and plasma FFAs were measured enzymatically by the GPO-PAP method (Boehringer Mannheim, Mannheim, Germany) and an enzymatic colorimetric method (NEFAC, Wako Chemicals, Neuss, Germany), respectively. Lactate was determined by an enzymatic colorimetric method without deproteinization (Boehringer Mannheim GmbH) from samples collected in tubes containing 5 mg sodium fluoride and 4 mg potassiumoxalate.

Blood samples for plasma glucagon and FFAs were collected in tubes containing EDTA, and 500 KIU of aprotinin (Trasylol, Bayer, Leverkusen, Germany) per milliliter of blood was added for glucagon analysis. An optimized kinetic method was used for automated determination of β-hydroxybutyrate (26). Serum glycerol samples were analyzed using a direct colorimetric procedure using a quinoneimine chromogen system in the presence of glycerol kinase, peroxidase, and glycerol phosphate oxidase (Randox Laboratories, Crumlin, U.K.).

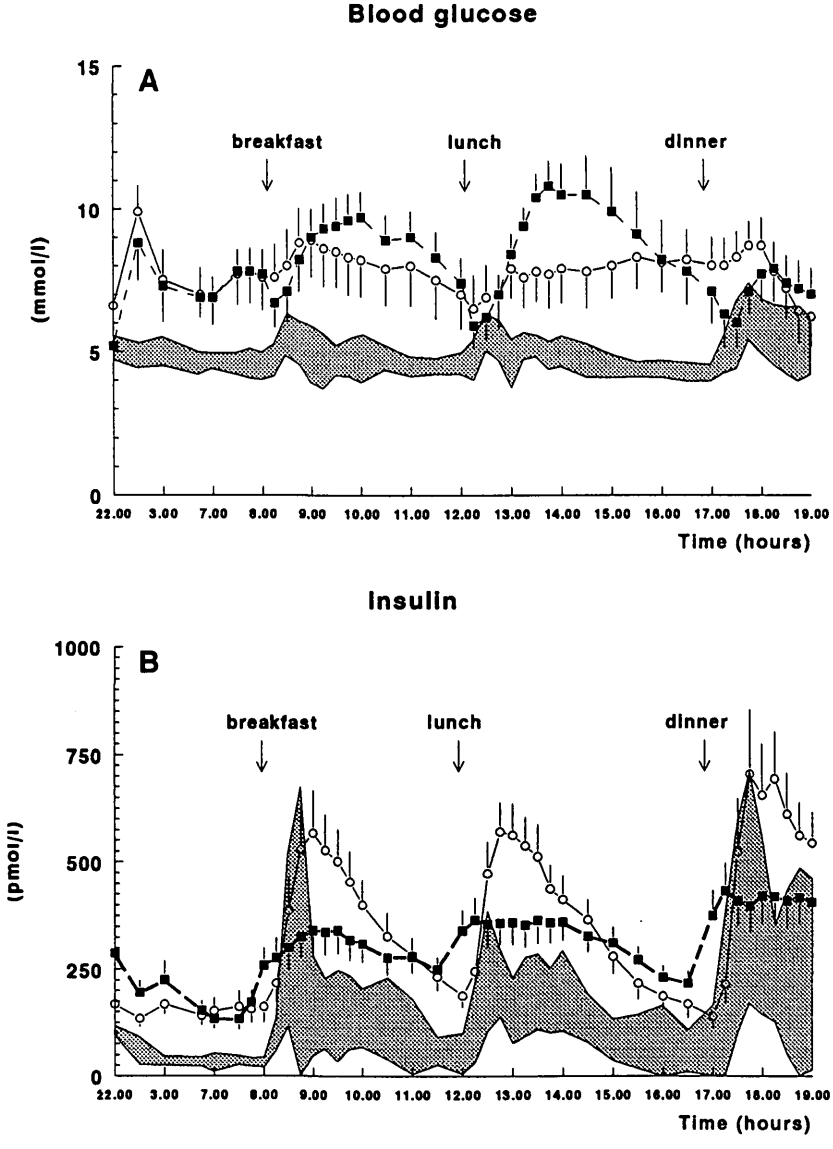

Figure 2—A: *blood glucose curves (means ± SE) of the diabetic patients (n = 12) during hospitalization. The shaded area represents the data of six nondiabetic control subjects (means ± SD), solid line lispro (–O–) and solid line human insulin (–■–) administration.* B: *insulin curves (means ± SE) of the diabetic patients (n = 12) during hospitalization. The shaded area represents the data of six nondiabetic control subjects (means ± SD), solid line lispro (–O–) and solid line human insulin (–■–) administration.*

Calculations and statistical analysis

Data are presented as means ± SD or as stated otherwise. For statistical evaluation of the glycemic and insulin data, the analysis of Hills and Armitage was performed (27). Comparisons between the treatments for metabolites and glucagon were made using the nonparametric Wilcoxon's (matched-pairs) sign-rank test. Both insulin treatments were compared with nondiabetic values by means of the Mann-Whitney *U* test. Also, an analysis of variance for repeated measurements (RM-ANOVA) was performed for the metabolites and glucagon data to test the overall profiles. Therefore, we divided the whole test period in 12 consecutive periods, for which we calculated the area under the curve (AUC)

Table 1—*Pharmacokinetic and pharmacodynamic data of lispro insulin and human regular insulin*

	Insulin			Glucose			
	C_{max}	T_{max}	AUC_{ins}	Preprandial	1-h postprandial	2-h postprandial	AUC_{bg}
Breakfast							
Lispro	615.4 ± 366.9§	61.3 ± 11.9§‖	836 ± 430*	7.6 ± 4.1	8.9 ± 4.6	8.2 ± 4.6	2.8 ± 2.49
Human regular insulin	359.9 ± 197.8	111.3 ± 48.1¶	633 ± 392	7.7 ± 3.1	9.0 ± 3.5¶	9.7 ± 3.2¶	3.6 ± 2.15‡
Control subjects	430.0 ± 305.9	37.5 ± 12.5	461 ± 347	4.5 ± 0.5	4.9 ± 0.9	4.8 ± 0.8	1.2 ± 0.68
Lunch							
Lispro	616.8 ± 257.6†§	53.8 ± 17.5*‖	940 ± 503	7.0 ± 4.3	7.9 ± 3.7	7.9 ± 4.3*	6.8 ± 5.46‖
Human regular insulin	408.3 ± 187.4	106.3 ± 57.4†	813 ± 433‡	7.4 ± 3.1	8.4 ± 2.5¶	10.5 ± 3.9¶	6.5 ± 2.36¶
Control subjects	309.7 ± 88.3	35.0 ± 7.7	445 ± 201	4.6 ± 0.4	4.6 ± 0.8	5.0 ± 0.5	1.3 ± 0.39
Dinner							
Lispro	801.3 ± 528.9§	55.0 ± 18.5§	—	8.0 ± 3.5	8.7 ± 3.5	6.2 ± 3.7	4.4 ± 3.14
Human regular insulin	470.3 ± 232.1	106.3 ± 34.1¶	—	7.1 ± 4.1	7.7 ± 3.2	7.0 ± 3.2	4.6 ± 3.79
Control subjects	515.5 ± 264.9	45.0 ± 16.4	—	4.3 ± 0.3	5.9 ± 1.0	5.2 ± 1.0	2.1 ± 1.31

Data are means ± SD. C_{max}, peak plasma insulin concentration (pmol/l); T_{max}, time to C_{max} (min); AUC_{ins}, incremental AUC of insulin (pmol · l^{-1} · h^{-1}) calculated for the periods 7:30 to 12:00 A.M. and 11:30 A.M. to 4:00 P.M., respectively; 1- and 2-h postprandial blood glucose (mmol/l); AUC_{bg}, incremental area under the blood glucose curve for 2 h after meal ingestion (mmol · l^{-1} · h^{-1}). *Lispro versus human regular insulin: $P < 0.05$; †lispro versus control subjects: $P < 0.05$; ‡human regular insulin versus control subjects: $P < 0.05$; §lispro versus human regular insulin: $P < 0.01$; ‖lispro versus control subjects: $P < 0.01$; ¶human regular insulin versus control subjects: $P < 0.01$.

to reduce the degree of freedom.

RESULTS

Glycemic control

Total daily premeal insulin requirements were similar, but the prebreakfast insulin dose was significantly lower for lispro than for human insulin (total 42.8 ± 17.2 vs. 44.7 ± 15.0 IU, NS, and prebreakfast 11.4 ± 5.8 vs. 13.0 ± 5.7 IU, $P = 0.01$). The NPH doses at bedtime were equal: 30.2 ± 10.6 and 30.2 ± 10.3 IU for lispro and human insulin, respectively.

During the run-in period, the HbA_{1c} did not change (at start and after run-in; 6.6 ± 1.0 and 6.7 ± 0.8%). These values remained stable with lispro, but improved significantly with human insulin treatment (change in HbA_{1c}: Δ 0.1 ± 0.48, NS, and Δ −0.41 ± 0.34%, $P = 0.03$, respectively). Besides treatment effects, no carryover or period effects were found for the HbA_{1c} changes.

The results of the HBGM of the last 3 weeks of the two treatment periods are shown in Fig. 1. The mean glucose value was similar for both lispro and human insulin treatments (8.5 ± 4.9 vs. 7.8 ± 4.2 mmol/l, NS), respectively.

Before dinner, blood glucose values rose during lispro, reaching significantly higher values than with human insulin (9.2 ± 3.0 vs. 7.4 ± 2.5 mmol/l, $P = 0.02$). Blood glucose values declined thereafter to similar values 2 h postprandially. Both treatments showed similar blood glucose values at bedtime (10.8 ± 4.0 vs. 9.7 ± 2.9 mmol/l, NS).

The incidence of hypoglycemic episodes was similar at any time point of the study period. For the last 2 weeks of the study period, the reported frequencies were 6.5 ± 4.2 and 6.7 ± 4.6, NS, for lispro and human insulin, respectively. None of these were severe and could be classified as grade II, i.e., could be corrected by additional intake of carbohydrates.

In-hospital metabolic profiles

Blood glucose and serum insulin profiles. The profiles of blood glucose and serum insulin, obtained during hospitalization at the end of each treatment period, are depicted in Fig. 2. The pharmacokinetic data are shown in Table 1.

When comparing lispro with human insulin treatment, the areas under the incremental curves of insulin for the period of 10:00 P.M. to 7:00 P.M. the next day (AUC total) were similar (2,984 ± 1,427 vs. 2,561 ± 1,284 pmol · l^{-1} · h^{-1}, NS), but for the daytime period (8:00 A.M. to 7:00 P.M.), the incremental AUC was higher for lispro (2,557 ± 1,209 vs. 2,004 ± 1,050 pmol · l^{-1} · h^{-1}, $P < 0.01$). Starting at equal fasting serum levels for both treatments, the insulin levels showed a faster rise to higher peak levels, which were achieved at an earlier time point following lispro administration (Table 1). Moreover, the insulin levels returned to basal levels 4.1 ± 0.6 h after administration of insulin lispro, whereas insulin levels after human insulin remained above these levels throughout the day. Predinner values (5 h after prelunch administration) were below the fasting levels at 8:00 A.M. in 10 of the 12 subjects.

Fasting blood glucose levels were not significantly different for both treatments. The mean blood glucose values and the standard deviations of the day profiles (7:30 A.M. to 7:00 P.M.) were 8.2 ± 2.8 vs. 7.7 ± 3.3 mmol/l and 2.2 ± 0.99 vs. 2.4 ± 0.58 mmol/l for lispro and human insulin, respectively. The 2-h postprandial lunch values and blood glucose excursions with lispro administration were significantly lower (7.9 ± 4.3 vs. 10.5 ± 3.9 mmol/l, $P = 0.05$, and 0.9 ± 3.4 vs. 3.2 ± 4.0 mmol/l, $P < 0.05$). Total and incremental areas under the glucose curves are shown in Table 1. The AUCs were all lower for lispro, though not significantly.

Fasting serum insulin levels were lower in the nondiabetic control subjects than in the diabetic subjects treated with either lispro or human insulin (36.5 ± 7.6 vs. 156.1 ± 119.2 and 145.6 ± 84.7 pmol/l, $P < 0.01$). Moreover, the total area under the incremental curve (AUC total) was lower than for lispro and human insulin in the diabetic subjects: 1,553 ± 822 vs. 2,984 ± 1,426 and 2,561 ± 1,293 pmol · l^{-1} · h^{-1} ($P = 0.05$ and $P = 0.06$, respectively). For the daytime period (8:00 A.M. to 7:00 P.M.), only the difference between control subjects and lispro treatment remained significant: 1,402 ± 460 vs. 2,567 ± 1,209 and 2,005 ± 1,051 pmol · l^{-1} · h^{-1}, $P = 0.03$,

NS (control subjects versus lispro and human insulin, respectively). During the night (10:00 P.M. to 7:00 A.M.), total incremental AUC values were higher for human insulin than for lispro: 536 ± 410 vs. 425 ± 353 pmol · l^{-1} · h^{-1}, $P < 0.05$.

Metabolites and glucagon. Serum triglycerides showed the same pattern during the day for both treatments. Triglycerides during lispro treatment did not differ significantly from normal values. Fasting and most daytime triglyceride values during human insulin treatment were significantly lower than in the control group, whereas the ANOVA for repeated measurements showed a tendency (lispro vs. control subjects, $P = 0.06$) (Figs. 3 and 4).

Glycerol curves were similar for diabetic and nondiabetic subjects (RM-ANOVA). Comparing the insulin treatments, the values during lispro were higher at 12:00 A.M. and 12:30, 5:00, and 5:30 P.M. Although the total incremental AUC of glycerol was not different, the incremental AUC for the breakfast period (8:00–12:00 A.M.) was higher with lispro treatment (lispro versus human insulin, 32.4 ± 14.6 vs. 14.8 ± 12.3 mol · l^{-1} · h^{-1}, $P < 0.01$).

FFA levels for both treatments were not different from the normal values (RM-ANOVA). Values during lispro treatment tended to be higher at 12:30 and 5:30 P.M. (lispro versus human insulin, 0.27 ± 0.26 vs. 0.15 ± 0.07 mmol/l, $P = 0.09$, and 0.36 ± 0.33 vs. 0.18 ± 0.14 mmol/l, $P = 0.06$), as were the postprandial increments (FFA) for the postbreakfast and postlunch periods, respectively (lispro versus human insulin, 0.24 ± 0.22 vs. 0.11 ± 0.09 mmol/l, $P = 0.05$, and 0.36 ± 0.33 vs. 0.18 ± 0.14 mmol/l, $P = 0.06$).

Though β-hydroxybutyrate values at 12:00 A.M. and 12:30 P.M. were higher for lispro as compared with human insulin (0.10 ± 0.08 vs. 0.05 ± 0.02 mmol/l, $P < 0.05$, and 0.14 ± 0.15 vs. 0.06 ± 0.03 mmol/l, $P = 0.01$), RM-ANOVA did not show differences. The lactate and glucagon profiles were identical in both treatments and did not differ from control subjects (RM-ANOVA).

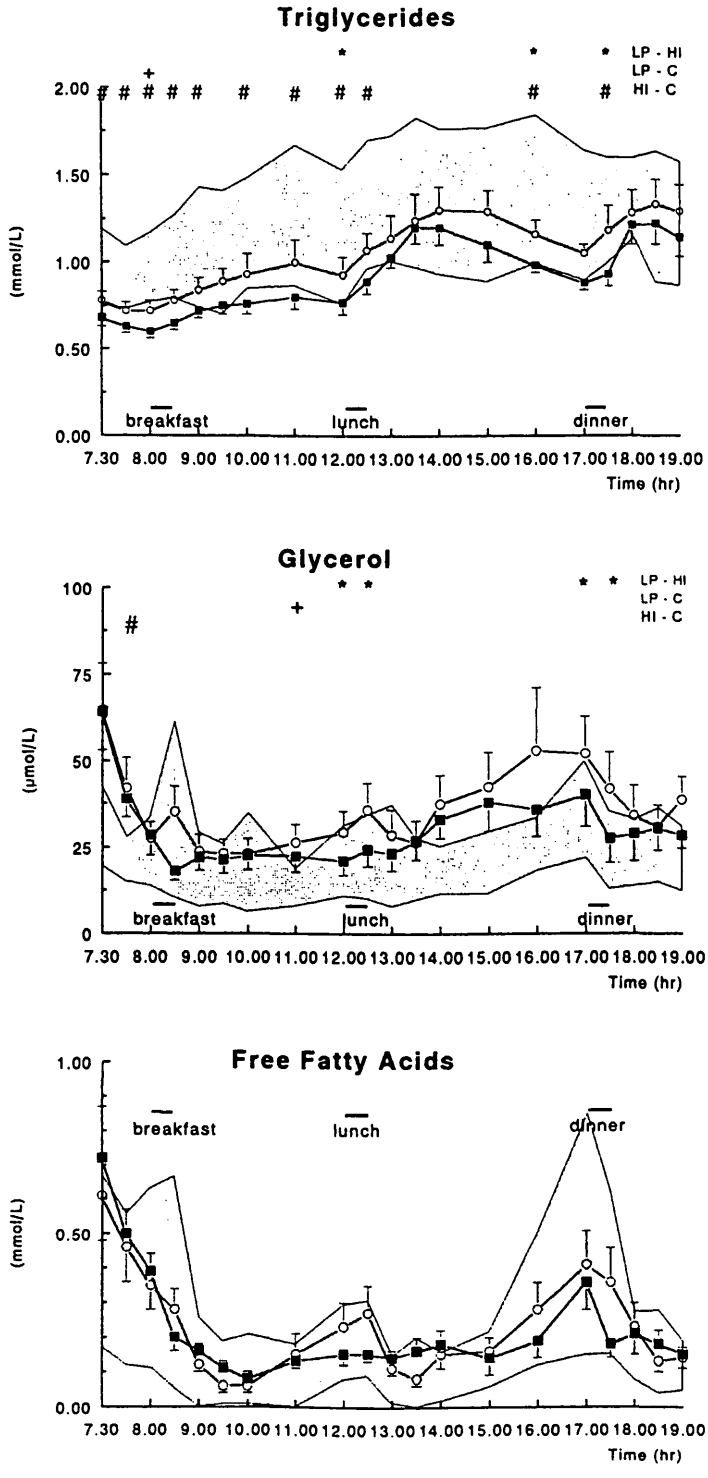

Figure 3—*Triglycerides, glycerol, and FFA levels (means ± SE) in diabetic patients (n = 12) during hospitalization. The shaded area represents the data of six nondiabetic control subjects (means ± SD), solid line lispro (–○–) and solid line human insulin (–■–) administration. Significance is assessed among groups (★, lispro-human insulin [LP-HI]; +, lispro-control subjects [LP-C]; #, human insulin-control subjects [HI-C], P < 0.05).*

CONCLUSIONS — The main aim of this study was to assess the metabolic efficacy of lispro insulin as compared with human regular insulin in an MIT regimen, applying only one basal NPH insulin injection at bedtime.

The basal insulin delivery between the main meals in an MIT regimen is supplied by the protracted absorption of soluble short-acting insulin, which may last for 8–12 h (7). Whether the pharmacokinetics of lispro insulin will allow its use in an MIT regimen, thus without causing deterioration of glycemic and metabolic control before the subsequent meal, had not been studied previously.

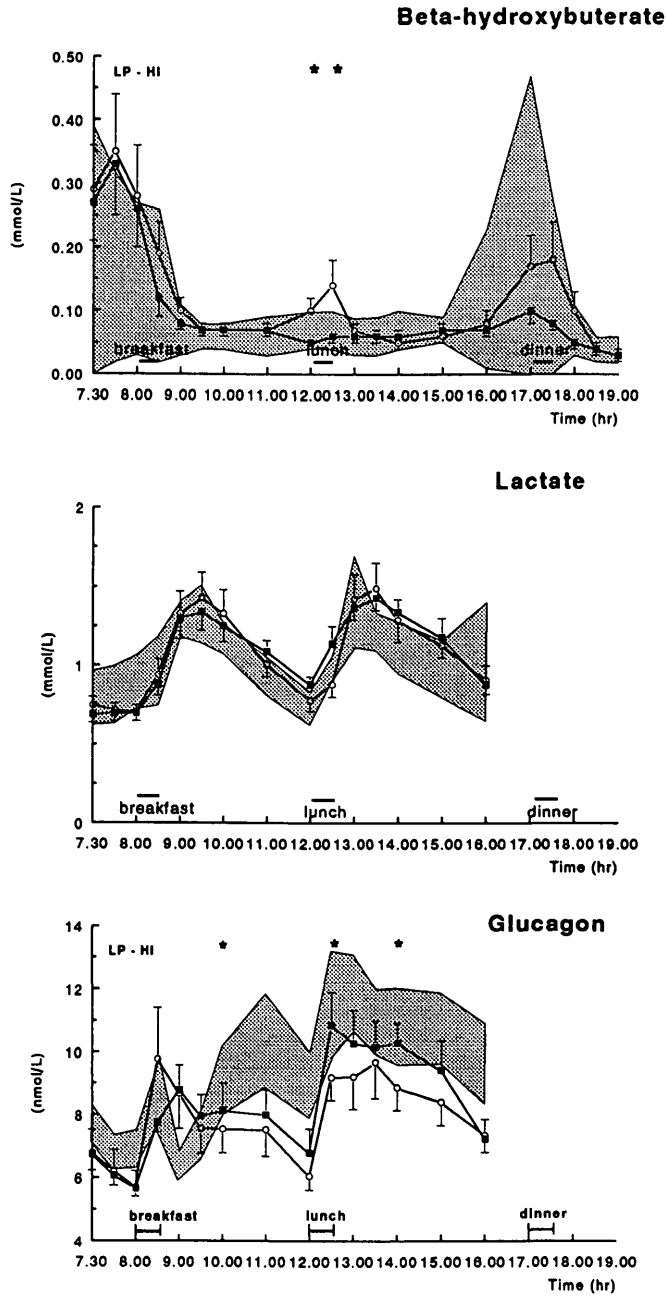

Figure 4—*β-hydroxybutyrate, lactate, and glucagon levels (means ± SE) in diabetic patients* (n = *12*) *during hospitalization. The shaded area represents the data of six nondiabetic control subjects (means ± SD), solid line lispro* (–○–) *and solid line human insulin* (–■–) *administration. Significance is assessed among the lispro-human insulin [★, LP-HI] groups,* $P < 0.05$.

During the study, the patients were advised to adjust the dose of insulin in accordance with HBGM and aim for the set values. When converting from human insulin to lispro insulin, patients started with the same dose, assuming equipotency of both insulin species (12,14,23). During lispro treatment, the required prebreakfast dose was less than with human insulin. In general, there was no need to adjust the NPH insulin dose at bedtime; fasting blood glucoses were not different for both treatments. In our study, the incidence rates of mild hypoglycemia were not different for both treatments. Brunelle et al. (17) recently reported a lower rate of mild hypoglycemic events with lispro insulin than with human insulin in patients achieving improved glycemic control during a 1-year follow-up. In our study, we could not demonstrate any differences in the occurrence rate of mild hypoglycemia, possibly due to the low number of patients.

Glycemic control, as reflected in HbA_{1c} values, was stable during lispro but improved during human insulin treatment. The more frequent HBGM during the study may have resulted in a further lowering of the HbA_{1c} percentages during treatment with human insulin, despite the 4-week run-in period. A recently presented 1-year trial comparing lispro treatment to regular insulin reported that at least equal long-term glycemic control is obtainable (18). Also, it should not be expected that a meal-related insulin applied in an MIT regimen would cause a major change in overall control.

In addition, HBGM showed more fluctuations in glycemic levels during the day and in particular at the end of the day during lispro treatment. The higher predinner glucose values seen with lispro insulin substitution returned to similar 2-h postprandial values. This was confirmed by the clinical profiles, which were performed under well-controlled conditions.

The clinical profiles showed that the three premeal injections of lispro insulin resulted in early and high insulin peaks, returning to basal levels 4–5 h after administration. However, these more physiological insulin profiles were not fully reflected by an improvement of the glucose profiles. Only the 2-h postprandial excursions were significantly smaller with lispro. In this study, the circumstances were optimized for human insulin by administering this insulin exactly 30 min before the meal. This way, we took full advantage of human insulin, avoiding the lag time in insulin absorption, whereas in daily life, most patients take their human insulin 0–15 min before their meals. A study by Heinemann et al. (28) showed that giving either insulin preparaion immediately before the meal caused clear differences in glucose excursions and AUC of glucose. Because meal intervals at home might have been longer than the studied interval of 5 h, it may have resulted in low insulin availability during lispro treatment, which then in turn was reflected by elevated premeal glucose values. Finally, the composition and energy content of the meals were probably less constant than that in the hospital.

Earlier studies comparing the efficacy of various insulin treatment regimens in well-educated patients (6,29–31) could not demonstrate an apparent improvement of blood glucose control. Differences in stabil-

ity, as measured with the standard deviation of daily blood glucose profiles or excursions, are reported but were not necessarily accompanied by a change in HbA_{1c} (32,33).

Preprandial serum triglycerides were lower during human insulin treatment than those of nondiabetic subjects, whereas the triglycerides during lispro treatment did not differ from those of control subjects. Slightly higher values were also observed in studies comparing intraperitoneal delivery with subcutaneous insulin therapy (34–37). The finding of lower values than those in the control subjects is probably caused by the combination of good glycemic control achieved in these patients and peripheral hyperinsulinemia. This combination causes a suppression of FFA and glycerol flux to the liver and an increase of lipoprotein lipase activity, stimulating the clearance of triglyceride-rich lipoproteins. Hyperinsulinemia suppresses glycerol levels also during human insulin treatment. During lispro treatment, we measured a slight elevation of glycerol levels before the meals, suggesting enhanced lipolysis because of the low insulin levels. Even if the differences noted in the measured metabolites—FFAs, lactate, and β-hydroxybutyrate—were less important (RM-ANOVA did not show significancy), the overall profiles in all patients are suggesting to be closer to normal with lispro than with human insulin treatment.

In conclusion, this study demonstrates that lispro can be safely applied in an MIT regimen with mealtime intervals up to 5 h. When longer intervals are expected, the addition of NPH insulin should be considered either as an extra injection in the morning or as premixed combination therapy.

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