# Insulin Lispro in CSII

## Results of a Double-Blind Crossover Study

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**Insulin lispro is a human insulin analog that dissociates more rapidly than human regular insulin after subcutaneous injection, resulting in higher insulin levels at an earlier point in time and a shorter duration of action. The aim of the study was to evaluate if this pharmacokinetic difference would translate into better postprandial and overall control in 30 IDDM patients (age, 35.1 ± 1.5 years; male-female ratio, 17:13; BMI, 24.8 ± 0.5 kg/m$^2$; $HbA_{1c}$, 8.03 ± 0.13% at baseline) treated with continuous subcutaneous insulin infusion (CSII; Disetronic H-TRON V100) in a double-blind crossover clinical study. Patients were randomized to insulin lispro or human regular insulin for 3 months before crossing over to the other insulin for another 3 months. All meal boluses were given immediately before breakfast, lunch, and supper. An eight-point blood glucose profile was measured once weekly, and $HbA_{1c}$ levels were measured monthly. At the end of the 3-month treatment period, $HbA_{1c}$ levels were significantly lower with insulin lispro, compared with human regular insulin: 7.66 ± 0.13 vs. 8.00 ± 0.16% ($P$ = 0.0041). While preprandial, bedtime, and 2:00 A.M. values for blood glucose were not significantly different, 1-h postprandial blood glucose was significantly improved after breakfast, lunch, and dinner with insulin lispro, compared with human regular insulin: 8.35 vs. 9.79 mmol/l ($P$ = 0.006), 7.58 vs. 8.74 mmol/l ($P$ = 0.049), and 7.85 vs. 9.01 mmol/l ($P$ = 0.03). The incidence of hypoglycemia per 30 days (blood glucose levels, <3.0 mmol/l) was 8.4 ± 1.3 before randomization, decreasing to 6.0 ± 0.9 for insulin lispro and to 7.6 ± 1.3 for regular insulin during the last month of the study. Two patients in each group reported insulin precipitation. We conclude that insulin lispro improves glycemic control in CSII without increasing the risk of hypoglycemia. *Diabetes* 46:440–443, 1997**

The human insulin analog [Lys(B28), Pro(B29)] insulin (insulin lispro) has an onset of action and a duration that is significantly shorter than that of human regular insulin: 0.3–0.5 vs. 0.5–1.0 h and 3.0–4.3 vs. 6–10 h (1,2). Switching the amino acid sequence of proline and lysine on the B-chain of insulin converts human insulin into a much more rapidly dissociating insulin. While being hexameric at the high concentrations typically found in the insulin vial, insulin lispro dissociates into monomers much more rapidly at the lower concentrations present at the subcutaneous injection site. This results in a more pronounced peak of shorter duration when compared with human regular insulin (3,4). Despite this modification in the structure of the molecule, insulin lispro's biological potency remains fully preserved since receptor binding characteristics and antigenicity are not altered, compared with native human insulin (5,6). When injected before meals in a multiple daily injection regimen, the use of insulin lispro resulted in improved postprandial blood glucose and a reduction in the frequency of hypoglycemic episodes (7–9). However, the majority of studies with insulin lispro failed to demonstrate significant changes in $HbA_{1c}$ levels, despite consistent and uniform decreases in postprandial hyperglycemia. The confounding variables of inadequate basal insulin replacement and lowered rates of hypoglycemia may have been responsible for this apparent contradiction in results.

We therefore decided to employ continuous subcutaneous insulin infusion (CSII) to exploit fully the advantages of this method of insulin replacement in a double-blind crossover clinical trial to evaluate the true impact of insulin lispro on overall glycemic regulation, compared with human regular insulin.

### RESEARCH DESIGN AND METHODS

**Patients.** A group of 17 female and 13 male IDDM patients, aged 35.1 ± 1.5 years (range, 26–51 years), with a body weight of 72.7 ± 1.8 kg (range, 54–90 kg), and a BMI of 24.8 ± 0.5 kg/m$^2$ (range, 21–33 kg/m$^2$), was asked to participate in this study. All patients had at least 3 months of experience with CSII. None of the patients had significant endogenous insulin secretion as assessed by the measurement of fasting C-peptide (<0.2 nmol/l). The average duration of diabetes was 17.5 ± 1.6 years (range, 6–44 years). Patients with severe retinopathy or neuropathy and patients who had more than one severe hypoglycemic episode in the past year were excluded from the study. Mild-to-moderate retinopathy was present in 16 (53%) of the patients and mild-to-moderate neuropathy in 12 (40%) of the patients. Of the 30 patients, 14 patients had been on CSII treatment for >3 months before entry into the study. All other patients were switched to CSII from intensified insulin therapy with pen (7 patients) or syringe (9 patients) 3 months before randomization using human regular insulin (Humulin R). All 30 patients completed the study.

**Study design.** The study was designed to be a double-blind comparative crossover study. Patients received human regular insulin (Humulin R) for a 1-month run-in period and were then randomized to either regular insulin or insulin

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CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; FFA, free fatty acid; PEG, polyethylene glycol.

lispro for 3 months. After the first 3-month study period, patients were switched to the alternate insulin therapy (Humulin R or insulin lispro) for another 3 months. Patients were asked to change the insulin infusion set every 2 days to reduce the risk of local infection.

Both insulin lispro and human regular insulin premeal boluses were injected 0–5 min before breakfast, lunch, and dinner. Patients were asked to measure blood glucose levels before each meal and at bedtime every day using One Touch II meters (Lifescan Canada, Burnaby, British Columbia, Canada). Throughout the study, patients were followed monthly with $HbA_{1c}$ levels being measured and the treatment regimen being adjusted. A weekly glucose profile (before and 1 h after meals, bedtime, and a 2:00 A.M. measurement) was performed by each patient during the treatment period using One Touch II meters. The target range for glycemia was 4–7 mmol/l before meals and 7–10 mmol/l for the 1-h postprandial glucose levels.

All patients were asked to document their home-monitored blood glucose readings, insulin doses, and hypoglycemic events in a diary.

A subgroup of six patients was hospitalized at the end of each study period and received a standardized 520-kcal test meal (Ensure Plus) to assess postprandial plasma free insulin, glucose, and serum free fatty acid (FFA) responses.

The primary efficacy variables were frequency of hypoglycemia, postprandial blood glucose profile, and hemoglobin $HbA_{1c}$ level. Additional outcome variables included insulin dose and distribution of total daily insulin.

**Statistical methods.** The statistical test to evaluate the two treatments was based on a two-sided test at a type 1 error of 5%. Analysis of variance was used to evaluate continuous and rank-transformed variables using models with treatment-sequence (study group), period, and treatment terms. Variables measured on an ordinal scale were analyzed by Wilcoxon's rank-sum test (treatment-sequence, period, and treatment term were evaluated in three separate analyses). Categorical variables were evaluated by using the $\chi^2$, McNemar's, and/or Fisher's exact tests.

The laboratory test results were classified and tabulated by using center-specific normal ranges. Changes in the laboratory results between enrollment and study termination were evaluated by analysis of variance of the rank-transformed data. $P < 0.05$ was considered significant.

**Assays.** Glycosylated hemoglobin was determined by high-performance liquid chromatography (Variant, Bio-Rad Laboratories, Hercules, CA) with an interassay coefficient of variation of 0.57% at an $HbA_{1c}$ level of 8.80% and a correlation coefficient of 0.989 when compared with the Diamat Analyzer. Plasma free insulin was determined with a double antibody radioimmunoassay assay (BBDC Core Laboratory, University of Toronto, Toronto, Canada) after extraction with polyethylene glycol (PEG). The normal range is 35–250 pmol/l, and the interassay coefficient of variation was 7.2% at 72 pmol/l and 6.6% at 316 pmol/l. A double antibody assay (BBDC Core Laboratory) was used to determine residual secretion of C-peptide in study patients. The normal range is 0.265–1.324 nmol/l. The interassay coefficient of variation was 10% at 0.90 pmol/l.

**Materials.** The U-100 insulin lispro formulation (Eli Lilly, Indianapolis, IN) used in this study contained zinc (0.0197 mg/ml), phosphate buffer (1.88 mg/ml), glycerin (16 mg/ml), and m-cresol (3.15 mg/ml). The pH of this formulation was ~5.65. The control insulin was the commercially available U-100 human regular insulin (Humulin R, Eli Lilly).

All patients used Disetronic H-TRON V-100 (Disetronic Medical Systems, Plymouth, MN) insulin infusion systems, catheters (#100073), and syringes (#100051). Insulin was infused into the abdomen throughout the study, and the infusion site was changed every 2 days.

All patients used One Touch II meters and strips (Lifescan Canada) to monitor capillary glucose levels. The accuracy of the patients' meters was validated against the local laboratory reference method at each visit.

## RESULTS

**Skin reactions and insulin stability.** The number of mild skin reactions at the injection site was 16 with insulin lispro and 15 with regular insulin. There was no abscess or other serious cutaneous adverse effect. Discoloration or precipitation of insulin in the reservoir or catheter was reported twice for each study drug during the 3 months of treatment. This did not lead to obstruction or to significant hyperglycemia.

**Insulin dose and body weight.** The basal, meal-related, and total daily insulin doses are depicted in Fig. 1. There was no significant difference between doses for insulin lispro and human regular insulin. The doses for insulin lispro versus human regular insulin were 5.5 ± 0.4 vs. 6.0 ± 0.4 U before breakfast, 5.6 ± 0.5 vs. 5.6 ± 0.4 U before lunch, and 6.8 ± 0.4 vs. 6.7 ± 0.4 U before supper. The daily basal infusion rate was

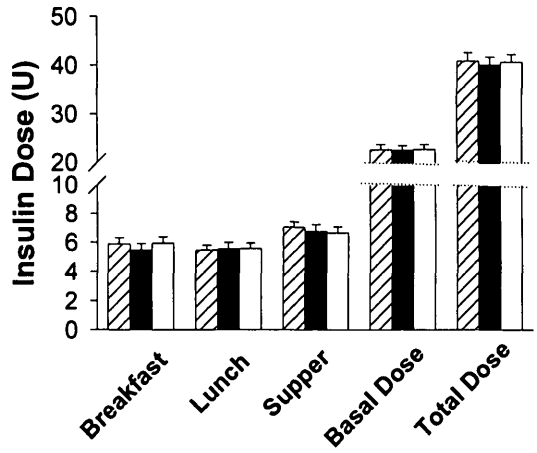


**FIG. 1. Meal-related, basal, and total daily insulin doses in 30 patients treated with insulin lispro (■) or human regular insulin (□) for 3 months as compared to baseline (▨). All values are presented as means ± SE.**

22.6 ± 1.0 U for insulin lispro vs. 22.7 ± 1.1 U for human regular insulin. The total daily insulin dose was 40.4 ± 1.7 U with insulin lispro vs. 40.8 ± 1.6 U with human regular insulin.

Body weights were 72.7 ± 1.8 kg at the beginning of the study and remained unchanged after 3 months on insulin lispro (72.6 ± 1.8 kg) or human regular insulin (72.8 ± 1.8 kg).

**Blood glucose levels.** All patients were asked to assess pre- and 1-h postprandial, bedtime, and a 2:00 A.M. blood glucose profile every week throughout the entire study period. Postprandial blood glucose levels were significantly lower with insulin lispro, compared with regular insulin (Fig. 2). Presupper and 2:00 A.M. values tended to be somewhat higher with insulin lispro, but the differences were not statistically significant.

**Glycosylated hemoglobin.** The pre-study average level of glycosylated hemoglobin ($HbA_{1c}$) was 8.03 ± 0.13%. During treatment with human regular insulin, $HbA_{1c}$ did not change (8.00 ± 0.16%; Fig. 3). In contrast, $HbA_{1c}$ decreased with insulin lispro treatment (7.66 ± 0.13%). The difference of 0.34% in $HbA_{1c}$ after treatment with insulin lispro, compared with human regular insulin, was significant ($P = 0.0041$).

**Hypoglycemia.** Hypoglycemia was defined in this study as blood glucose values <3 mmol/l or the development of any symptoms compatible with hypoglycemia. The frequency of hypoglycemia per 30 days was 12.7 ± 1.6 before randomization into the study. During the study, the rate of hypoglycemia decreased with both study drugs (Fig. 3). For patients on insulin lispro, it dropped to 8.6 ± 1.4 per 30 days being significantly ($P = 0.035$) lower than at baseline. For patients on human regular insulin, the rate of hypoglycemia dropped to 10.8 ± 1.8 per 30 days during the last month of treatment. The difference to baseline or to insulin lispro was not statistically significant. When only hypoglycemia as confirmed by blood glucose measurements was analyzed, the results were similar. The hypoglycemia rate was 8.4 ± 1.3 at baseline decreasing to 6.0 ± 0.9 for insulin lispro ($P = 0.03$ vs. baseline) and to 7.6 ± 1.3 (NS vs. baseline or insulin lispro) for regular insulin during the last month of the study. There were no episodes of severe hypoglycemia as defined by Diabetes Control and Complications Trial (DCCT) criteria (10).

**Plasma free insulin, glucose, and FFA levels following a test meal.** The insulin dose given before the test meal

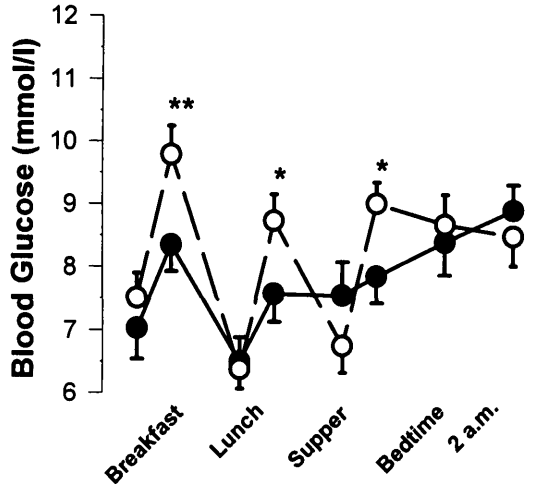


**FIG. 2. Eight-point home-assessed blood glucose profile in 30 patients using either insulin lispro (●) or human regular insulin (○) with CSII. All values depicted represent the means ± SE of 12 different profiles as assessed once weekly by every patient during each 3-month study period.**

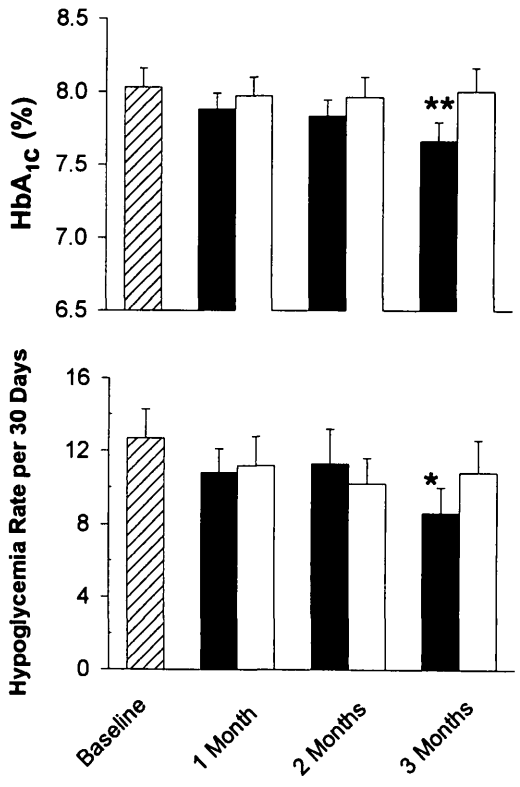


**FIG. 3. Glycosylated hemoglobin levels and rate of hypoglycemia in 30 CSII patients at baseline and after 1, 2, and 3 months of treatment with insulin lispro (■) or human regular insulin (□). All values are presented as means ± SE. **$P$ = 0.0041, insulin lispro versus human regular insulin; *$P$ = 0.035, lispro at month 3 versus month 1 or 2.**

tended to be slightly lower but not significantly different with insulin lispro (5.8 ± 4.1 U), compared with human regular insulin (6.6 ± 2.8 U), while the basal insulin infusion rates with insulin lispro (1.0 ± 0.2 U/h) and human regular insulin (1.0 ± 0.3 U/h) were similar (Fig. 4). Levels of free plasma insulin under insulin lispro were highest at 45 min (287 ± 69 pmol/l), compared with 150 min (294 ± 56 pmol/l) under human regular insulin (Fig. 4). The glycemic response to the test meal was markedly reduced with insulin lispro from the 60-min time point on. FFA levels were dramatically lower with insulin lispro from 30 min until 180 min after the meal, compared with human regular insulin, reflecting the earlier onset of the antilipolytic effect with insulin lispro.

## DISCUSSION

The physiological replacement of insulin continues to be an elusive goal (11). The recent demonstration in prospective controlled randomized clinical trials that glycemic control dramatically improves patient outcome, as measured by retinopathy, nephropathy, and neuropathy, has heightened the imperative of improving insulin replacement (12). Although multiple injections of insulin and CSII are only one component of an intensive diabetes management program, these insulin injection regimens provide the patient with the flexibility of adjusting insulin therapy in response to premeal glycemic levels, the calculated carbohydrate content of the meal, and anticipated exercise. Human regular insulin is currently the insulin of choice as the premeal bolus insulin. Unfortunately, its pharmacokinetics are less than optimal for this purpose. Its peak action has variably been reported as being 2–4 h and may last up to 6–8 h (13–16). To accommodate for this deficiency in pharmacokinetics, patients are asked to administer their dose of insulin 30–40 min before eating. This clearly is inconvenient and often entirely impractical.

The development of insulin analogs with significantly more rapid absorption characteristics and a shorter duration of action was expected to improve postprandial hyperglycemia (17–20). Early in development, stability and toxicity problems (21,22) hampered clinical implementation. The development of insulin lispro (1,2) appears to provide an analog with advantageous pharmacokinetics and no apparent toxicity.

The present study demonstrated that improving postprandial hyperglycemia results in an improvement in overall glycemic control, as assessed by $HbA_{1c}$, without additional risk for hypoglycemia. This is in contrast to the findings of the DCCT, where a decrease in $HbA_{1c}$ was associated with an increased risk of hypoglycemia. The overall rate of hypoglycemia per 30 days, the severity of symptoms, and insulin doses were similar with the two study insulins. The difference in $HbA_{1c}$ levels of 0.34%, although small, translates into a risk reduction for developing retinopathy of ~20% based on a risk analysis of the DCCT data (12,24). Thus, a reduction of $HbA_{1c}$ as shown in the present study may very well be clinically relevant.

It is also notable that the reduction of $HbA_{1c}$ was achieved despite preprandial or fasting blood glucose values, which tended to be slightly higher with insulin lispro, particularly before supper. This is probably a consequence of insulin lispro's shorter duration of action, compared with human regular insulin. Similar observations have been reported in previous clinical studies when insulin lispro has been given before meals and basal insulin requirements have been replaced with NPH insulin (24,25) and in a short-term 6-day CSII study that compared human regular insulin to the short-acting insulin analog B28Asp (26). The failure in some of these studies to improve $HbA_{1c}$ may be because of the combination of inadequate adjustment of basal insulin replacement and a decreased frequency of low blood glucose values in patients treated with insulin lispro (8,9). As a consequence,

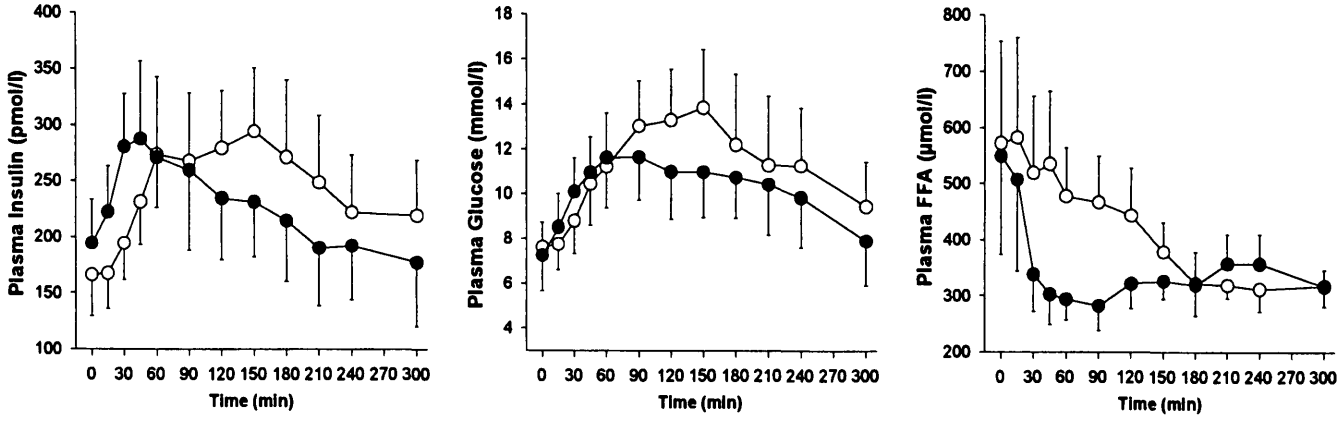


**FIG. 4. Plasma free insulin, glucose, and FFA levels in six patients after a standardized test meal while being treated with either insulin lispro (●) or human regular insulin (○). Insulin was injected 5–0 min before the test meal that was given at $t = 0$. All values are presented as means ± SE.**

more precise adjustments of basal insulin replacement to adapt for insulin lispro's pharmacokinetics might further improve overall glycemic control without increasing hypoglycemia risk. On a cautionary note, it is important to keep in mind that the interruption of CSII insulin delivery with insulin lispro might result in more rapid onset and/or greater degree of hypoglycemia, compared with human regular insulin (27).

We concluded that the use of insulin lispro in CSII resulted in improved glycemic control without an increased rate of hypoglycemia when administered at the start of the meal. Insulin lispro should therefore be considered the insulin of choice for CSII.

## ACKNOWLEDGMENTS

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