Reduction of Postprandial Hyperglycemia and Frequency of Hypoglycemia in IDDM Patients on Insulin-Analog Treatment

James H. Anderson, Jr., Rocco L. Brunelle, Veikko A. Koivisto, Andreas Pfützner, Michael E. Trautmann, Louis Vignati, Richard DiMarchi, and the Multicenter Insulin Lispro Study Group

Insulin lispro, an insulin analog recently developed particularly for mealtime therapy, has a fast absorption rate and a short duration of action. We compared insulin lispro and regular human insulin in the mealtime treatment of 1,008 patients with IDDM. The study was a 6-month randomized multinational (17 countries) and multicenter (102 investigators) clinical trial performed with an open-label crossover design. Insulin lispro was injected immediately before the meal, and regular human insulin was injected 30–45 min before the meal. Throughout the study, the postprandial rise in serum glucose was significantly lower during insulin lispro therapy. At the endpoint, the postprandial rise in serum glucose was reduced at 1 h by 1.3 mmol/l and at 2 h by 2.0 mmol/l in patients treated with insulin lispro ($P < 0.001$). The rate of hypoglycemia was 12% less with insulin lispro (6.4 ± 0.2 vs. 7.2 ± 0.3 episodes/30 days, $P < 0.001$), independent of basal insulin regimen or HbA_{1c} level. The reduction was observed equally in episodes with and without symptoms. When the total number of episodes for each patient was analyzed according to the time of occurrence, the number of hypoglycemic episodes was less with insulin lispro than with regular human insulin therapy during three of four quarters of the day ($P < 0.001$). The largest relative improvement was observed at night. In conclusion, insulin lispro improves postprandial control, reduces hypoglycemic episodes, and improves patient convenience, compared with regular human insulin, in IDDM patients. *Diabetes* 46:265–270, 1997

Insulin deficiency in patients with IDDM has been addressed by numerous insulin replacement regimens over the past 75 years. Different regimens with multiple daily injections (MDI) of insulin have been utilized to simulate physiological insulin secretion (1). The inability of MDI to achieve normoglycemia can be attributed partially to the delayed absorption of regular human insulin. Regular human insulin injected before meals results in insufficient plasma levels at the time of the meal but elevated levels in the post-absorptive period. Consequently, the glucose excursion is excessive, and hypoglycemia risk between meals and at night is enhanced. Attempting to optimize the therapy with insulins and treatment regimens currently available increases the risk of severe hypoglycemia, particularly when tight glucose control is achieved (2,3). Mild hypoglycemic episodes impair the sensitivity of patients to recognize hypoglycemic symptoms, thus increasing the risk of severe hypoglycemia (4–6). Severe hypoglycemia is the complication most feared by patients (7). To compensate for the inadequacies of conventional mealtime insulin, the time of the injection should precede the meal by at least 30 min (8–10). This requirement compromises lifestyle and is commonly ignored (11). Short-acting insulin analogs with a rapid peak action and disappearance following subcutaneous injection have been proposed as a better mealtime insulin.

The delayed appearance in the plasma of regular human insulin after subcutaneous insulin injection results from the slow dissociation of insulin hexamers (12). Reversing the natural sequence of proline and lysine in positions B28 and B29 of the B-chain of the insulin molecule (insulin lispro) enhances the hexamer dissociation, which increases the rate of absorption and the onset of action (13). Previous studies using insulin lispro revealed a much more rapid and pronounced insulin peak of shorter duration when compared with regular human insulin (14–16). The glucose lowering was of comparable magnitude, but occurred significantly earlier with insulin lispro. These specific pharmacokinetic properties suggest that insulin lispro is more suitable than regular human insulin to control mealtime hyperglycemia and to reduce the risk of postmeal hypoglycemia.

This crossover study was designed to examine the within-patient effects of insulin lispro and regular human insulin on postprandial hyperglycemia and the rate of hypoglycemic episodes in patients with IDDM.

RESEARCH DESIGN AND METHODS

Patients. Patients were invited to participate if they had IDDM according to WHO criteria (17), were between the ages 12 and 70 years inclusive, and had been on human insulin therapy at least for 2 months. Exclusion criteria included the presence of any other severe disease, pregnancy, a BMI >35 kg/m^2, a daily insulin dose >2.0 U/kg, or a history of clinically significant hypoglycemia unawareness. The patient characteristics are shown in Table 1.

Design. The study was a 6-month open-label multinational (17 countries) and multicenter (102 investigators) randomized crossover trial to compare mealtime treatment of insulin lispro (Humalog, U-100, Eli Lilly & Co., Indianapolis, IN) with regular human insulin (Humulin R, U-100, Eli Lilly & Co.).

From the Lilly Research Laboratories (J.H.A., R.L.B., A.P., M.E.T., L.V., R.D.), Indianapolis, Indiana, and the Department of Medicine (V.A.K.), Helsinki University Hospital, Helsinki, Finland.

Address correspondence to James H. Anderson, Jr., Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285.

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MDI, multiple daily injections.

TABLE 1
Patient characteristics

	Sequence 1	Sequence 2	All
n	508	500	1,008
Sex (%)			
Male	58.3	57.8	58.0
Female	41.7	42.2	42.0
Age (years)	33.3 ± 0.6	33.2 ± 0.5	33.2 ± 0.4
BMI (kg/m^2)	24.2 ± 0.1	24.3 ± 0.1	24.2 ± 0.1
Duration of diabetes (years)	12.2 ± 0.4	11.8 ± 0.4	12.0 ± 0.3
Basal insulin (%)			
NPH	78.1	79.0	78.6
Ultralente	21.9	21.0	21.4

The treatment sequences consisted of multiple premeal dose therapy with regular human insulin for 3 months followed by multiple premeal dose therapy with insulin lispro for an additional 3 months (sequence 1) or vice versa (sequence 2).

The study was not blinded to allow both rapid-acting insulins to be given at the recommended time intervals before the meal (8,10,18). The study was conducted in accordance with the guidelines of "Good Clinical Practice" and the declaration of Helsinki and was monitored by local ethical committees. NPH insulin (Humulin N) or ultralente insulin (Humulin U) were used for basal substitution (both U-100, Eli Lilly & Co.) (Table 1). After a 2- to 4-week lead-in period, patients were randomized to one of the two treatment sequences. The treatment sequences consisted of multiple premeal dose therapy with regular human insulin for 3 months followed by multiple premeal dose therapy with insulin lispro for an additional 3 months (sequence 1) or vice versa (sequence 2) (Table 1).

Insulin administration. Patients injected either insulin lispro immediately or regular human insulin 30–45 min before the meal. Patients administered their basal insulin with a pen (NPH) or syringe (NPH or Ultralente) one or more times per day as determined by the investigator to be appropriate for the patients' needs and meal patterns (Table 2). Patients were allowed to mix premeal and basal insulin in the syringe at the time of the injection, and they were advised to administer all premeal injections subcutaneously in the abdomen. Self-monitoring of blood glucose based on the clinical direction of the investigator was the usual practice and served as the basis for insulin dose adjustments.

Test meal procedure. One- and two-hour blood glucose values were determined after the test meals at baseline and at monthly intervals to evaluate the effect of the study insulin on postprandial glucose control. Tests were conducted in the morning after an overnight fast at the investigator's site. The test meal was similar to the patient's usual breakfast and was kept consistent throughout the study. It was consumed in 5–10 min. The time for postprandial blood glucose measurements started from the beginning of ingestion. Postprandial serum glucose excursions were calculated by subtracting the pretest glucose value from the 1- and 2-h postprandial glucose values. At the baseline test meal, all patients injected regular human insulin. During the study, patients used insulins for the test meals according to their current regimen.

Biochemical and other determinations. Serum glucose concentrations were determined by the hexokinase method (19). HbA_{1c} levels were determined using high-performance cation exchange chromatography (reference range, 4.3–6.1%) (20). Both determinations were performed in a central laboratory. Home blood glucose monitoring was performed as determined by the investigator to be appropriate for the patient's needs. Patients recorded an episode of hypoglycemia when they experienced a sign or symptom that they normally associated with hypoglycemia. In addition, a blood glucose measurement during routine blood glucose testing <3.5 mmol/l was counted as hypoglycemia. In total, >92% of these symptomatic episodes were confirmed by a blood glucose measurement of <3.5 mmol/l. In total, 40,628 hypoglycemic episodes were reported by the patients in their diaries, listing time of day, symptoms, severity, and treatment. All hypoglycemic events were analyzed. Severe hypoglycemic episodes were defined as episodes requiring external help and episodes resulting in coma or requiring treatment with intravenous glucose or glucagon.

Statistical methods. A crossover model was used to evaluate both the carryover and the treatment effects (21,22). No evidence of a statistically significant carryover effect was observed. The within-treatment comparisons to baseline were performed using a paired *t* test. The data from all patients were included in the analyses using an intent-to-treat methodology. The analyses were performed using the endpoint value, the last value observed for each patient during each period of the crossover study.

A factorial model incorporating the effects of treatment, basal insulin, and number of basal injections within the crossover model was used for the analyses presented in Table 3. An analysis of covariance model was used to compare the treatments for the mean hypoglycemia rate per 30 days adjusted for HbA_{1c}. The descriptive statistics results are given as means ± SE.

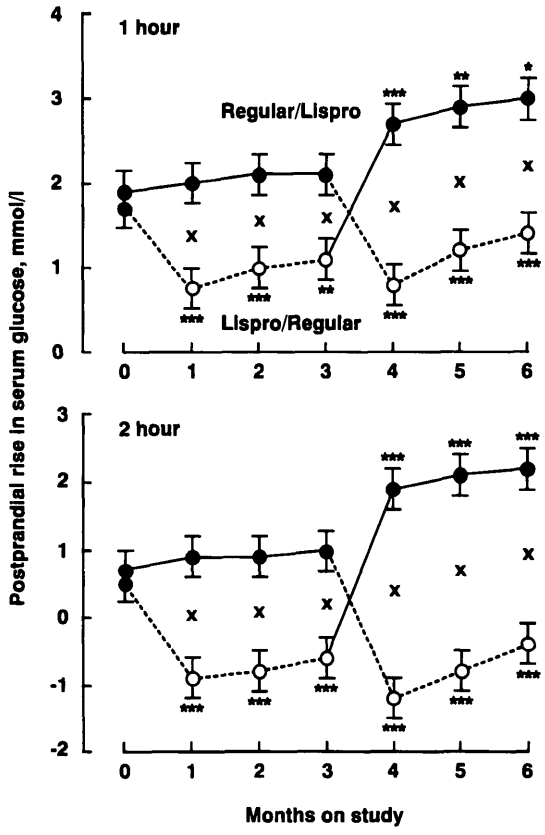

FIG. 1. The 1- and 2-h postprandial serum glucose excursion at each visit during the study. Premeal injections were either regular human insulin (●) or insulin lispro (○). *P < 0.05; **P < 0.01; ***P < 0.001, compared with baseline; $^{\times}P$ < 0.001 between regular human insulin and insulin lispro.

RESULTS

Postprandial rise in glucose. The postprandial increment in serum glucose at each visit of the study is shown in Fig. 1. At baseline, when all patients received regular human insulin, the rise in serum glucose level was similar in both sequence groups. In the sequence 2 group, the rise in blood glucose both 1 and 2 h after the test meal remained unchanged during the first 3 months. When the patients were transferred to insulin lispro therapy, the postprandial rise in blood glucose was significantly less, compared with baseline. In the sequence 1 group, the rise in serum glucose both 1 and 2 h after the test meal was significantly lower than at baseline during insulin lispro therapy. When the patients were transferred to regular human insulin, the rise in serum glucose was significantly higher than at baseline. Throughout the study, the postprandial rise in serum glucose was less during insulin lispro, compared with regular human insulin both 1 and 2 h after the test meal (Fig. 1).

Figure 2 demonstrates the rise in serum glucose after a test meal at the endpoint for the two sequence groups combined. The rise in serum glucose was 1.3 mmol/l lower 1 h after the

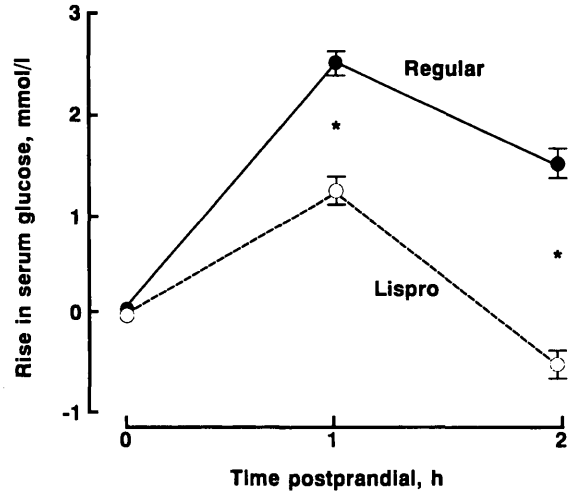

FIG. 2. The rise in serum glucose levels after the test meal at the endpoint for the combined treatment groups. *$P < 0.001$ between regular human insulin and insulin lispro therapy. ●, regular human insulin; ○, insulin lispro.

meal and 2.0 mmol/l lower at 2 h with insulin lispro therapy, compared with regular human insulin. Premeal serum glucose levels were similar during both treatments (Table 2). Thus, due to the lower postprandial rise, serum glucose concentrations both 1 and 2 h after the meal were lower during insulin lispro than regular human insulin therapy (Table 2).

Hypoglycemia. The hypoglycemic rate per 30 days decreased significantly from baseline during each of the insulin lispro treatment periods ($P < 0.05$), but remained unchanged during regular human insulin treatment. There was no carryover effect, and when treatment periods were combined, the frequency of hypoglycemic episodes was less during insulin lispro therapy at every visit than with regular human insulin therapy ($P < 0.001$) (Fig. 3). At the endpoint, the rate of hypoglycemia was 12% less during treatment with insulin lispro (6.4 ± 0.2 vs. 7.2 ± 0.3 episodes/30 days, $P < 0.001$). This difference in the mean hypoglycemia rate per 30 days, adjusted for HbA_{1c}, remained significantly lower during insulin lispro therapy ($P = 0.024$) and was independent of type and number of basal insulin injections (Table 3).

For 85% of all hypoglycemic episodes, blood glucose levels <3.5 mmol/l were documented. When these episodes were analyzed, the frequency of hypoglycemia was significantly less with insulin lispro therapy than with regular human insulin (5.6 ± 0.2 vs. 6.3 ± 0.2 episodes/30 days, $P < 0.001$) for both symptomatic episodes and episodes detected by blood glucose measurements <3.5 mmol/l.

The total number of hypoglycemic episodes occurring during the study in patients on insulin lispro treatment was 19,106, which is 11% lower than the 21,522 episodes during regular human insulin therapy. Patients were unable to self-treat 84 (56 patients) of these episodes during insulin lispro therapy and 119 episodes (73 patients) during regular human insulin therapy. Treatment with intravenous glucose or glucagon was required, or the episode resulted in a coma in 30 episodes (24 patients) during insulin lispro therapy and in 42 episodes (36 patients) during regular human insulin therapy. No significant difference between the treatments was observed for the frequency of severe hypoglycemic episodes.

The total number of episodes for each patient was analyzed according to the time of occurrence throughout the day. The number of hypoglycemic episodes was significantly less with insulin lispro therapy than with regular human insulin therapy during three out of four quarters of the day (Fig. 4). The largest relative improvement was observed at night.

Long-term control. HbA_{1c} improved significantly and equally in both treatment groups during the study (Table 2). The increase in the number of basal injections was associated with lower HbA_{1c} levels ($P = 0.014$), and this difference was observed for both types of basal insulin (Table 3).

Insulin dose. There was a small increase in the basal insulin dose during insulin lispro therapy (Table 2). For both treat-

TABLE 2
Endpoint parameters by therapy

	Baseline	Endpoint insulin lispro	Endpoint regular human insulin
Serum glucose (mmol/l)			
Premeal	12.4 ± 0.2	11.6 ± 0.2*	11.3 ± 0.2*
1 h postprandial	14.1 ± 0.2	12.9 ± 0.2*†	13.9 ± 0.2
2 h postprandial	13.0 ± 0.2	11.2 ± 0.2†	12.9 ± 0.2
HbA_{1c} (%)	8.5 ± 0.1	8.2 ± 0.1‡	8.2 ± 0.1‡
Daily insulin dose (U/kg)			
Premeal	0.36 ± 0.01	0.36 ± 0.01	0.36 ± 0.01
Basal	0.32 ± 0.01	0.35 ± 0.01*†	0.33 ± 0.01*
Total	0.68 ± 0.01	0.71 ± 0.01*†	0.69 ± 0.01*
Premeal injections/day (% of patients)			
≤2	14.3	10.3	11.7
3	75.1	76.2	76.5
≥4	10.5	13.5	11.9
Basal injections/day (% of patients)			
≤1	58.1	53.6	56.0
≥2	41.9	46.4§	44.0
Weight (kg)	71.2 ± 0.4	71.5 ± 0.4	71.8 ± 0.4

Data are means ± SE or %. *$P < 0.001$ vs. baseline; †$P < 0.001$ vs. regular; ‡$P < 0.01$ vs. baseline; §$P < 0.05$ vs. regular. Because of the crossover design, the baseline value is the same for both groups.

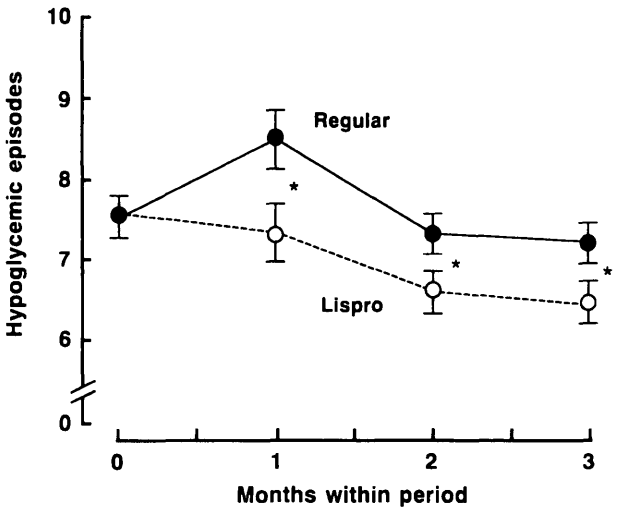

FIG. 3. The number of hypoglycemic episodes per patient per 30 days during the combined treatment periods. During the entire study, the rate of hypoglycemia was significantly lower (*P < 0.001) during treatment with insulin lispro, compared with regular human insulin. ●, regular human insulin; ○, insulin lispro.

ment groups, the premeal insulin dose was equal and remained stable during the entire study.

Adverse events. There were no differences in type and frequency of adverse events between treatments. The most common adverse events—headache, pharyngitis, infection, rhinitis, flu syndrome, pain, accidental injury, and diarrhea—were reported by 5–15% of the patients. The study was completed by 95.2% of the patients, with no difference in discontinuations between the two treatment groups.

DISCUSSION

A goal in the treatment of diabetes is to achieve good metabolic control without increasing the risk of hypoglycemia. The DCCT recently demonstrated the difficulty of achieving optimal HbA_{1c} levels without increasing hypoglycemic risk (3), particularly at night (23). Hypoglycemia is the most common side effect of insulin therapy, regardless of the intensity of the treatment. It can be estimated that an average IDDM patient will experience 3,500 episodes of mild hypoglycemia, 30–70 episodes of severe hypoglycemia, and a coma three to seven times during a period of 40–45 years of living with diabetes (23,24). Patients fear severe hypoglycemia as much as complications such as kidney failure or blindness.

The crossover design of this study allowed each patient to serve as his or her own control, thus minimizing between-patient variability. The open-label design was necessary to allow patients to inject premeal insulin at the optimal times. This had the potential to introduce a bias into the study. However, test meals were performed at the investigator's site to ensure the correct timing of insulin injections, which minimized potential bias. The insulin analog, insulin lispro, is more rapidly absorbed from the injection site in the subcutaneous tissue and has a shorter and more predictable duration of action than regular human insulin (18,25). Therefore, if regular human insulin had been injected closer to the meal, as often occurs in clinical practice (9,11), this would have increased the treatment difference in postprandial glucose outcome.

This study demonstrated that the postprandial rise in serum glucose is significantly smaller after insulin lispro therapy. Blood glucose levels returned to premeal values earlier after the meal when insulin lispro was given immediately before the meal, compared with an injection of regular human insulin even 30 min before the meal. The lowering of the 2-h postprandial blood glucose below baseline after insulin lispro was beneficial because of the elevated premeal values. However, the effect of insulin lispro on postprandial glycemia is dose-dependent, and the dose can be adapted, depending on a premeal blood glucose concentration.

During therapy with insulin lispro the overall rate of hypoglycemia was significantly lower, compared with regular human insulin treatment. This was consistent whether symptomatic episodes or episodes with blood glucose levels <3.5 mmol/l without symptoms were analyzed. In addition, when episodes were analyzed for the time of occurrence, lispro resulted in reduced or equal frequency during all periods. The greatest relative decrease could be seen at night. The lower hypoglycemia rate with insulin lispro was independent of basal insulin regimen or HbA_{1c}. A lesser rate of hypoglycemia during insulin lispro therapy can be explained by comparing the time-action of the two insulins. Regular human insulin has a duration of action of up to 10 h, whereas the duration of action of insulin lispro is 4–5 h (14). Therefore, regular human insulin activity can significantly overlap with basal insulin activity between meals and especially at night. In

Table 3
Hypoglycemia rate and HbA_{1c} by type and the number of injections of basal insulin

	Premeal therapy	NPH ≤1 daily	NPH ≥2 daily	Ultralente ≤1 daily	Ultralente ≥2 daily
n		376	349	132	67
Hypoglycemic episodes/patient/30 days*					
	Insulin lispro	4.8 ± 0.3	7.1 ± 0.4	7.4 ± 0.7	9.2 ± 1.1
	Regular	5.3 ± 0.3	7.8 ± 0.5	8.8 ± 0.8	10.6 ± 1.2
HbA_{1c} (%)†					
	Insulin lispro	8.4 ± 0.1	8.1 ± 0.1	8.3 ± 0.2	8.2 ± 0.2
	Regular	8.3 ± 0.1	8.1 ± 0.1	8.4 ± 0.1	8.0 ± 0.2
Basal insulin ($U \cdot kg^{-1} \cdot day^{-1}$)*					
	Insulin lispro	0.28 ± 0.01	0.43 ± 0.01	0.32 ± 0.01	0.36 ± 0.02
	Regular	0.27 ± 0.01	0.41 ± 0.01	0.31 ± 0.01	0.35 ± 0.02

Data are means ± SE. *P < 0.001 insulin lispro vs. regular human insulin therapy; †P < 0.05 once daily vs. ≥2 times daily.

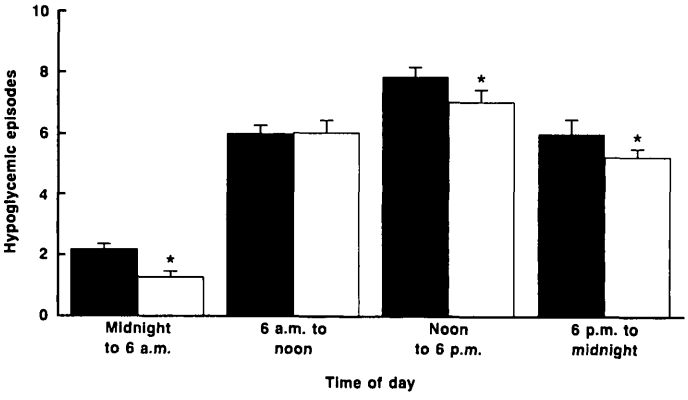

FIG. 4. The distribution of hypoglycemic episodes per patient throughout the day over the course of the entire study. ■, regular human insulin; □, insulin lispro. *$P < 0.001$.

some IDDM patients who have prolonged between-meal intervals, the shorter duration of insulin lispro may result in postabsorptive hyperglycemia. This may be compensated for by changes in the basal insulin regimen.

The reduced hypoglycemia rate in IDDM patients may have a number of beneficial consequences. First, the safety and quality of life of patients is improved. This is particularly the case if nighttime hypoglycemic risk is reduced, as was demonstrated in the current study with insulin lispro therapy. Psychological morbidity (26) and higher levels of anxiety described in patients with recurrent hypoglycemia (27) may be improved. Second, even mild episodes of hypoglycemia reduce the symptoms and counterregulatory responses of a subsequent hypoglycemic episode, thus increasing risk of severe hypoglycemia (5,6,28). There is evidence that normal awareness of hypoglycemia can be restored by the scrupulous avoidance of low blood glucose (29,30). Third, the reduced risk of hypoglycemia and the ability to inject insulin lispro closer to the meal may allow more appropriate adjustments of insulin doses to achieve better metabolic control. Thus, the reduction of hypoglycemia by insulin lispro can both enhance the well-being and improve the prognosis of patients with IDDM.

Patients participating in this study had fairly good metabolic control at baseline, and HbA_{1c} levels improved equally during insulin lispro and regular human insulin treatment. Because of better postprandial control, one would have anticipated a greater decrease during insulin lispro therapy than with regular human insulin. Several factors may have contributed to the equal decrease in HbA_{1c} levels in the two treatment groups. First, the differences in postprandial hyperglycemia may not have been large enough to result in a lower HbA_{1c}. However, recent data in patients with gestational diabetes indicate that an improvement in postprandial hyperglycemia can result in a substantial decrease in glycated hemoglobin levels (31). Second, the treatment periods were of short duration, only 3 months per insulin. Similarly, no difference in HbA_{1c} has been observed in another short-term study that compared a rapid-acting insulin analog and regular human insulin (32). This time period may be too short to observe major differences in long-term metabolic control. Third, since HbA_{1c} is a measure of the average glycemia, in the insulin lispro group, the decrease in postprandial excursions may have been counterbalanced by a decrease in hypoglycemic excursions. Fourth, multiple injection regimens consist of mealtime and basal insulin therapy. This study was specifically designed to examine mealtime insulin treatment without attempts to optimize basal insulin therapy. Long-term use of insulin lispro with improved basal insulin regimens may lead to a greater improvement of HbA_{1c} than was observed in this short-term study.

With the exception of a decreased risk of hypoglycemia, insulin lispro has a similar safety profile to that of regular human insulin. No adverse events specific for insulin lispro were observed in this study. Insulin lispro has been virtually indistinguishable from regular human insulin when assessed for immunogenicity in patients (33), toxic effects during reproductive and developmental periods in animals (34), and the ability to promote cell growth (35).

The current study indicates that insulin lispro improves postprandial glucose control and reduces the frequency of hypoglycemia in patients with IDDM. In addition, the ability to inject insulin lispro immediately before the meal decreases the inconvenience of insulin therapy and may allow more appropriate adjustments of doses according to dietary changes. Its pharmacokinetic and glucodynamic characteristics and the current data suggest that insulin lispro can be considered a step forward toward optimal insulin therapy.

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APPENDIX: THE MULTICENTER INSULIN LISPRO STUDY

The following individuals and their site personnel participated in the Multicenter Insulin Lispro Study. *Australia:* K.M. Bowen, Newcastle; D.P. Cameron, Wolloongabba; A.J. Nankervis, Parkville; A.P. Roberts, Adelaide; P. Zimmet, Caulfield Vic. *Austria:* M.H. Borkenstein, Graz; G. Schernthaner, Vienna; W.K. Waldhäusl, Vienna. *Belgium:* I.H. De Leeuw, Edegem; F. Fery, Bruxelles; A. Scheen, Liege; G. Somers, Brussels. *Canada:* I.M. Fettes, Toronto; H.D. Tildesley, Vancouver; E.L. Toth, Edmonton. *Finland:* J. Viikari, Turku. *France:* J.J. Altman, Paris; P.F. Bougneres, Paris; P. Drouin, Dommartinlestoul; P. Fossati, Lille; P.J. Guillausseau, Paris; E. Marechaud, Poitiers; J.P. Riou, Lyon; J.L. Selam, Paris; P.B. Vialettes, Marseille. *Germany:* J. Beyer, Mainz; K. Federlin, Giessen; R.D. Fussganger, Ulm; F.A. Gries, Duesseldorf; H.U. Jastram, Kaiserslautern; I. Koop, Marburg; R. Landgraf, Munich; C. Rosak, Frankfurt; H. Schatz, Bochum; B. Schulze-Schleppinghoff, Essen; F.J. Seif, Tubingen; F. Stoeckmann, Goettingen. *Israel:* A. Karasik, Tel Hashomer; S. Weitzman, Beersheba. *Italy:* D. Andreani, Rome; G. Bompiani, Palermo; G. Crepaldi, Padova; R. Giorgino, Bari; A.V. Greco, Rome; R. Lauro, Rome; D. Maingay, Blaricum; M. Mancini, Napoli; G. Menzinger, Rome; M. Muggeo, Verona; G. Pagano, Torino; L. Sacca, Napoli; A. Tiengo, Padova; R. Vigneri, Catania. *Netherlands:* D.W. Erkelens, Utrecht; E.N. Janssens, Dordrecht; J.F. Lekkerkerker, Enschede; A.J. Spijker, Roermond. *New Zealand:* A.R. Daniels, Auckland. *Norway:* I. Folling, Trondeim. *South Africa:* F.B. Bonnici,

Observatory Cape; W.F. Mollentze, Bloemfontein; R. Moore, Durban; M.A. Omar, Durban; L.I. Robertson, Durban. *Spain:* R. Astorga, Seville; A. de Leiva, Barcelona; A. Jara, Madrid; J.A. Vazquez, Baracaldo; E. Villardell, Barcelona. *Sweden:* C.D. Agardh, Lund. *United Kingdom:* W.D. Alexander, Sidcup; A.H. Barnett, Birmingham; J. Cassar, Isleworth; G.A. Hitman, London; C.M. Kesson, Langside; J.P. O'Hare, Bath; K.M. Shaw, Cosham; J.K. Wales, Leeds. *United States:* S. Arslanian, Pittsburgh, PA; E.J. Bastyr, Galveston, TX; T.C. Blevins, Austin, TX; P.A. Boyce, Indianapolis, IN; S.J. Brink, Chestnut Hill, MA; D.H. Clarke, Salt Lake City, UT; T. DeClue, Tampa, FL; A.J. Garber, Houston, TX; R.A. Guthrie, Wichita, KS; D.G. Johnson, Tucson, AZ; A. Krosnick, Princeton, NJ; L.G. Linarelli, San Diego, CA; D.K. McCulloch, Seattle, WA; N.H. Mezitis, New York, NY; P. Raskin, Dallas, TX; M.L. Reeves, Chattanooga, TN; S. Rosenblatt, Irvine, CA; D. Schimel, Lake Bluff, IL; J.S. Skyler, Miami, FL; G.E. Sonnenberg, Milwaukee, WI; F.W. Whitehouse, Detroit, MI; B. Zimmerman, Rochester, MN.

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