# Use of Insulin Aspart, a Fast-Acting Insulin Analog, as the Mealtime Insulin in the Management of Patients With Type 1 Diabetes

PHILIP RASKIN, MD
RICHARD A. GUTHRIE, MD
LAWRENCE LEITER, MD
ANDERS RIIS, MSC
LOIS JOVANOVIC, MD

OBJECTIVE — To compare long-term glycemic control and safety of using insulin aspart (IAsp) with that of regular human insulin (HI).

RESEARCH DESIGN AND METHODS — This was a multicenter randomized open-label 6-month study (882 subjects) with a 6-month extension period (714 subjects) that enrolled subjects with type 1 diabetes. Subjects administered IAsp immediately before meals or regular HI 30 min before meals; basal NPH insulin was taken as a single bedtime dose in the majority of subjects. Glycemic control was assessed with $HbA_{1c}$ values and 8-point blood glucose profiles at 3-month intervals.

RESULTS — Mean postprandial blood glucose levels (mg/dl ± SEM) were significantly lower for subjects in the IAsp group compared with subjects in the HI group after breakfast (156 ± 3.4 vs. 185 ± 4.7), lunch (137 ± 3.1 vs. 162 ± 4.1), and dinner (153 ± 3.1 vs. 168 ± 4.1), when assessed after 6 months of treatment. Mean $HbA_{1c}$ values (% ± SEM) were slightly, but significantly, lower for the IAsp group (7.78% ± 0.03) than for the regular HI group (7.93% ± 0.05, $P = 0.005$) at 6 months. Similar postprandial blood glucose and $HbA_{1c}$ values were observed at 12 months. Adverse events and overall hypoglycemic episodes were similar for both treatment groups.

CONCLUSIONS — Postprandial glycemic control was significantly better with IAsp compared with HI after 6 and 12 months of treatment. The improvement was not obtained at an increased risk of hypoglycemia. $HbA_{1c}$ was slightly, but significantly, lower for IAsp compared with HI at 6 and 12 months.

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Rapid-acting insulin analogs have been developed to have a peak and duration of activity that more closely coincide with the postprandial blood glucose peak (1–3). The rapid-acting insulin analogs (e.g., insulin aspart [IAsp], insulin lispro, B10) differ from regular human insulin (HI) by having changes in amino acid sequence or composition in the B chain of the insulin molecule. These alterations reduce the stability of the insulin monomer–monomer interaction, leading to a more rapid subunit dissociation and subcutaneous absorption of the insulin (4–6). In IAsp, the proline at position B28 has been replaced by aspartic acid. Because of this modification, its onset of action occurs in ~10–20 min, with maximal serum concentrations reached in ~45 min (7–12).

Previous clinical trials in healthy subjects and in patients with type 1 diabetes have demonstrated that IAsp has a faster onset and shorter duration of action than does HI (13–17). In a previous study in patients with type 1 diabetes receiving IAsp as the mealtime insulin in a multiple-injection regimen, lower postprandial blood glucose levels and improved overall glycemic control were observed in patients treated with IAsp compared with those treated with HI (17). The improved glycemic control was not associated with an increase in the incidence of hypoglycemic episodes in these patients.

The present study was conducted to examine the long-term efficacy and safety of IAsp compared with HI as the mealtime component of an intensive insulin regimen. This article reports the improvement in glycemic control achieved by patients using IAsp, compared with HI, with 6 and 12 months of treatment.

## RESEARCH DESIGN AND METHODS

— This was a randomized open-label parallel-group study conducted at 59 centers in the U.S. and Canada. Subjects with type 1 diabetes were treated with IAsp or HI as part of an intensive insulin regimen for 6 months, and then could continue their assigned treatment in a 6-month extension of the study. The study was performed in accordance with the Declaration of Helsinki and with the approval of local independent review boards. Written informed consent was obtained from all subjects.

### Subjects

The study enrolled 882 men and women, aged 18–75 years, who had type 1 diabetes for at least 18 months. At baseline, subjects

From the Southwestern Medical Center at Dallas (P.R.), University of Texas, Dallas, Texas; Mid-America Diabetes Associates (R.A.G.), Wichita, Kansas; St. Michael's Hospital Health Center (L.L.), Toronto, Ontario, Canada; Novo Nordisk A/S (A.R.), Copenhagen, Denmark; and the Sansum Medical Research Institute (L.J.), Santa Barbara, California.

Address correspondence and reprint requests to Philip Raskin, MD, University of Texas, Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., Dallas, TX 75390-8858.

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Abbreviations: ANCOVA, analysis of covariance; HI, regular human insulin; IAsp, insulin aspart.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

were to have a BMI ≤35.0 kg/m$^2$ and an $HbA_{1c}$ level ≤11%. The exclusion criteria included impaired hepatic, renal, or cardiac function, recurrent major hypoglycemia, active proliferative retinopathy, or a total daily insulin dose ≥1.4 IU/kg. Women were excluded if they were pregnant, breast-feeding, or not practicing contraception.

### Treatment

All eligible subjects underwent a 4- to 5-week run-in period during which time they were treated with a multiple-injection regimen consisting of HI (Novolin R; Novo Nordisk, Bagsvaerd, Denmark) as a meal-related insulin and NPH insulin (Novolin N; Novo Nordisk) as the basal insulin. During the run-in and trial periods, HI was administered 30 min before each meal and NPH insulin was administered at bedtime. Subjects were instructed on the proper use of the One Touch II (LifeScan, Milpitas, CA) blood glucose meter to take self-measured blood glucose measurements for insulin dose adjustments. The dosages of both HI and NPH insulin were adjusted by a sliding scale so that subjects might attain the following glycemic targets: fasting/preprandial blood glucose level of 90–144 mg/dl (5–8 mmol/l), postprandial blood glucose level (1–3 h after a meal) of ≤180 mg/dl (≤10 mmol/l), and 2:00 A.M. blood glucose level of 90–144 mg/dl (5–8 mmol/l). After 2 weeks, an additional breakfast dose of NPH insulin could be added to the regimen if satisfactory control of the subject's blood glucose was not attained. The subject's NPH regimen (once or twice a day) was not changed for at least 1 week before receiving study medication and was then maintained for the duration of the study. At the end of the run-in period, the subjects were asked to perform a baseline 8-point blood glucose profile (blood glucose measurements before and 90 min after each meal, at bedtime, and at 2:00 A.M.).

After the run-in period, subjects were randomized, in a 2:1 ratio, to receive either IAsp or HI as their mealtime insulin (2 IAsp subjects:1 HI subject). Subjects randomized to IAsp replaced their dose of HI units during the run-in period with an equal amount of IAsp units during the trial period. Subjects were instructed to inject IAsp immediately before each meal. The abdomen was the recommended injection site for both IAsp and HI, and the thigh was the recommended injection site for NPH insulin. The dose of any study drug was adjusted throughout the trial to attain the same targets of glycemic control as specified in the run-in period.

No lifestyle-adjusting advice (diet or physical activity) was given so that the study could be conducted to test the inherent capabilities of the study medications on a true cross-section of type 1 diabetic individuals, without confounding the data interpretation with the independent effects of lifestyle intervention.

### Efficacy assessments

Efficacy was assessed using 8-point blood glucose and $HbA_{1c}$ values. The 8-point blood glucose profiles were recorded in a diary by the subject on a weekday during the last week of the run-in period and on a weekday before the 6- and 12-month study visits. The prandial blood glucose increment was derived from the 8-point blood glucose measurements by averaging the differences between the blood glucose values just before and 90 min after each of the 3 meals (values before and after all 3 meals were required for inclusion in the analysis). The blood glucose average was calculated as the average of the means of the blood glucose measurements for each subject (at least 6 values from the 8-point profile were required for inclusion in the analysis).

The $HbA_{1c}$ level (assay range 3–18%) was determined using the Bio-Rad Diamat system (Bio-Rad, Hercules, CA) on blood samples at baseline, 3, 6, 9, and 12 months postrandomization (18,19). The daily meal-related and basal insulin doses were also calculated.

### Safety assessments

Safety was assessed based on the recording of adverse events, physical examination findings, clinical laboratory evaluations, and specific and cross-reacting antibodies to IAsp and HI. Specific antibodies to IAsp and HI were determined by radioimmunoassay. Antibody values were expressed as the percent bound radioactivity used to assay the sample in a self-blank subtraction assay (20,21). A value of 100% binding represents an antibody titer of 600 pmol/l that translates into a maximal possible binding of ~1.2 U insulin in the average subject. The value of cross-reacting antibody binding was calculated as the total HI binding that was inhibitable by IAsp.

Subjects were asked to record hypoglycemic events in their diaries along with time of day and the blood glucose measurements associated with those events. Hypoglycemic events were defined as minor when the subject had a blood glucose value <45 mg/dl (2.5 mmol/l) or had classical symptoms of hypoglycemia (such as sweating, strong hunger, dizziness, and tremor) and were able to deal with the episode on their own. A major hypoglycemic event was one that the subject could not treat by himself/herself or required administration of parenteral glucose or glucagon.

### Statistical analysis

Glycosylated hemoglobin data were analyzed using analysis of covariance (ANCOVA) with $HbA_{1c}$ at baseline as covariate and treatment and center as fixed effects. The last observation carried forward approach was used for missing data in most analyses. Individual time points of the 8-point blood glucose profile and derived blood glucose end points and insulin dose measures were compared by ANCOVA as above; all values at 6 and 12 months were corrected for baseline differences. Changes in insulin antibodies (to IAsp, HI, and cross-reacting) were compared between treatments using a Student's *t* test. The Mantel-Haenszel $\chi^2$ test was used to compare the number of patients in each treatment group experiencing at least 1 nocturnal (midnight to 6:00 A.M.) major hypoglycemic episode. Results are stated as means ± SEM adjusted for baseline values and center effect, or as mean treatment difference (95% CI), or as indicated.

## RESULTS

### Subjects

Baseline demographic characteristics were similar for both treatment groups (Table 1). Overall, 552 (93%) and 467 (78%) subjects receiving IAsp and 263 (92%) and 208 (73%) subjects receiving HI completed 6 and 12 months of treatment, respectively. Completion and withdrawal rates for both study periods were similar between treatment groups (Table 1).

### Efficacy

With treatment, both groups showed improvement in 8-point blood glucose profiles compared with baseline; the results at 6 and 12 months are shown in Fig. 1. Postprandial blood glucose levels at each of the 3 meals were significantly lower for subjects taking IAsp compared with subjects taking HI. The before-lunch blood glucose value was also significantly lower for the IAsp group at 6 months. Blood glucose levels before breakfast, lunch (during extension

Table 1—*Baseline demographic characteristics and subject enrollment and attrition*

| | IAsp | HI |
|---|---|---|
| *n* | 596 | 286 |
| Age (years) | 38.9 ± 10.5 | 39.9 ± 12.2 |
| Sex (M/F)* | 306 (51)/290 (49) | 152 (53)/134 (47) |
| BMI (kg/m$^2$) | 25.6 ± 3.6 | 25.7 ± 3.2 |
| Caucasian race* | 559 (94) | 266 (93) |
| $HbA_{1c}$ (%) | | |
| Screening | 8.10 ± 1.22 | 8.13 ± 1.35 |
| Baseline | 7.90 ± 1.13 | 7.95 ± 1.25 |
| Duration of diabetes (years) | 15.7 ± 9.7 | 15.8 ± 9.3 |
| Completed 6 months of treatment* | 552 (93) | 263 (92) |
| Total withdrawn*† | 44 (7.4) | 23 (8.0) |
| Adverse event | 3 (0.5) | 2 (0.7) |
| Enrolled in extension trial* | 494 (83) | 220 (77) |
| Completed 12 months of treatment* | 467 (78) | 208 (73) |
| Total withdrawn† (extension)* | 27 (4.5) | 12 (4.2) |
| Adverse event* | 3 (0.5) | 1 (0.3) |

Data are *n*, means ± SD, or *n* (%). *The patient percentages are based on the number of patients initially treated in the 6-month study. †Withdrawal reasons include the following: withdrawal of consent, lack of compliance, lost to follow-up, ineffective therapy, moving away from study center, protocol violation, pregnancy, and adverse event.

period), at bedtime, and at 2 A.M. were not significantly different between the treatment groups but were significantly higher before dinner for subjects treated with IAsp.

The average postprandial blood glucose increments were similar at baseline in the IAsp and HI groups (29 ± 2.3 vs. 31 ± 3.1 mg/dl, mean ± SEM) and decreased at 6 and 12 months for both treatment groups (Fig. 2). Overall, prandial blood glucose increments and increments for each of the 3 individual meals were significantly smaller at 6 and 12 months in the IAsp group than in the HI group (the exception was lunchtime at 12 months). Average blood glucose values were similar for both treatment groups at baseline and decreased slightly at 6 and 12 months for both groups.

At 6 months, the $HbA_{1c}$ values (corrected for baseline) were slightly, but significantly, lower with IAsp than with HI (7.78 ± 0.03 vs. 7.93% ± 0.05, $P = 0.005$). Values of $HbA_{1c}$ were also significantly lower with IAsp than with HI at 12 months (7.78 ± 0.04 vs. 7.91% ± 0.06, $P = 0.046$).

Mean doses of IAsp and HI remained relatively constant throughout the study, at ~0.42 U/kg, whereas the mean dose of basal insulin (NPH) increased marginally in both treatment groups. The mean NPH dose increased from 0.244 ± 0.005 U/kg at baseline to 0.306 ± 0.006 U/kg for the IAsp group at 12 months and from 0.261 ± 0.010 to 0.305 ± 0.011 U/kg for the HI group. Because the 2 treatment groups had different baseline NPH doses, the change in basal NPH dose from baseline to 12 months was slightly, but significantly, higher with the IAsp group than with the HI group. After correcting for baseline differences, the mean basal NPH dose at 12 months for the IAsp group was significantly higher than that for the HI group (IAsp: 0.314 ± 0.006 vs. HI: 0.296 ± 0.006 U/kg, treatment difference is 0.018 U/kg, 95% CI [0.004–0.033], $P = 0.011$). When the $HbA_{1c}$ values were adjusted for total insulin dose (largely affected by the NPH dose), the $HbA_{1c}$ value of the IAsp group was less than that of the HI group (7.78 ± 0.04 vs. 7.90 ± 0.06, $P = 0.080$). Although the difference was not significant, the lower $HbA_{1c}$ values in the IAsp group could partly be explained by the increase in insulin dose.

A small percentage of subjects (<4% of either treatment group) were treated with doses of NPH twice a day. An ANCOVA analysis of the influence of number of daily NPH injections on $HbA_{1c}$ showed that IAsp-treated subjects, but not HI-treated subjects, on a twice-a-day NPH regimen obtained lower $HbA_{1c}$ levels than subjects on a once-a-day NPH regimen (IAsp, 7.34 ± 0.18 vs. 7.81 ± 0.03%, $P < 0.05$; HI, 7.82 ± 0.23 vs. 7.94 ± 0.05%, not significant) at 6 months. A similar trend was seen at 12 months, but was not significant.

## Hypoglycemia

Of the subjects, ~90% in each treatment group had 1 or more minor hypoglycemic episodes, whereas ~20% of subjects in each group experienced a major episode. The occurrences of major and minor hypoglycemic episodes per patient year for subjects in the IAsp group (major, 0.91; minor, 43.44) were similar to those seen in the HI group (major, 1.13; minor, 45.48) during the 6-month study. The number of episodes per patient year decreased during the extension study but remained similar between treatment groups (major episodes: IAsp group, 0.62; HI group, 0.67; minor episodes: IAsp group, 36.12; HI group, 36.60).

Although a similar percentage of subjects in each treatment group had a major hypoglycemic episode by 6 months, fewer subjects in the IAsp group than in the HI group (4 vs. 8%, respectively, $P = 0.013$) experienced a major hypoglycemic episode during the night (from midnight until 6 A.M.). Conversely, subjects in the IAsp group tended to have slightly more major episodes during daytime hours compared with the HI group, but the observed differences were not significant. During the 6-month extension period, the risk of having a major nocturnal hypoglycemic episode became similar for both groups. However, more subjects in the HI group with a major nocturnal hypoglycemic episode during the first 6 months chose not to enroll in the extension trial (10 of 23 in the HI group compared with 4 of 24 in the IAsp group).

## Safety

The overall frequency and type of adverse events were comparable for the 2 treatment groups. After 1 year of treatment in this open-label trial, ~90% of the subjects in each treatment group had reported 1 or more adverse events, the most common of which were the following: upper respiratory tract infections, headaches, and accidental injuries. Most of these events were mild in severity and not considered to be related to treatment with IAsp or HI.

Few subjects withdrew from the trial because of adverse events: 6 (1%) subjects from the IAsp group and 3 (1%) subjects from the HI group. Four subjects in the IAsp group reported events (weight gain, accidental injury, pruritus, and hyperglycemia) that were mild in severity but considered to have a possible relationship to the study medication. All other adverse events leading to withdrawal were considered unrelated to the study drugs.

There were no clinically significant differences between treatments with respect to

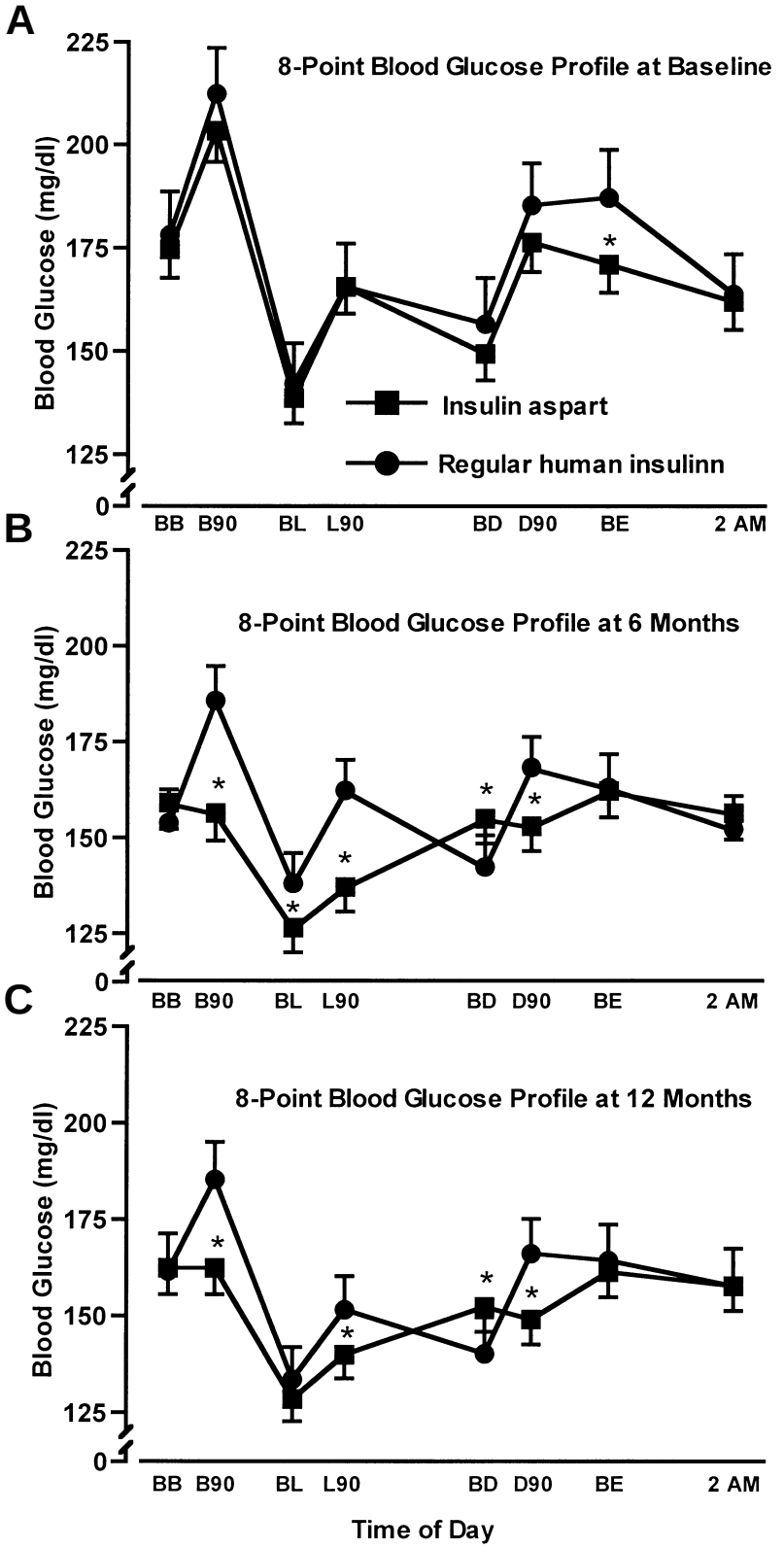


**Figure 1**—*Comparison of 8-point mean blood glucose profiles (mean ± 2 SEM) for IAsp and HI at baseline (*A*), 6 months (*B*), and 12 months (*C*). *Statistically significant ($P < 0.05$) difference between treatment groups. Number of subject data values used to prepare each profile: IAsp: 546, 555, and 490 for baseline, 6 months and 12 months, respectively; HI: 255, 258, and 215 for baseline, 6 months, and 12 months, respectively. Abbreviations: B90, 90 min after breakfast; BB, before breakfast; BD, before dinner; BE, at bedtime; BL, before lunch; D90, 90 min after dinner; L90, 90 min after lunch.*

changes in vital signs, physical parameters, clinical laboratory findings, or electrocardiogram evaluations during the 12 months. An increase in BMI after 12 months was small, but similar, for subjects in both treatment groups receiving IAsp and HI (0.44 vs. 0.48 kg/m$^2$).

Specific antibodies to IAsp and HI remained at a relatively low level (1% binding) for both treatment groups throughout the 12 months of the trial. Mean (± SEM) cross-reacting antibody binding was ~16.6% ± 1 for both treatment groups at baseline. Binding in the HI group remained at ~16% ± 1 during the trial. At 3 months, the mean of cross-reacting antibody binding for the IAsp group increased significantly to 22.3% ± 0.9 (between treatment difference 5.85%; 95% CI [4.06–7.64]), with 21% of the patients having an increase ≥10% above their baseline value. The increase for the IAsp group was attributed, in large part, to 22 subjects (4% of IAsp-treated subjects in the extension) with cross-reacting antibody binding >40%. Notably, the IAsp dose did not need to be increased for these subjects to maintain efficacy. Overall, mean cross-reacting antibody levels in the IAsp group had decreased to 19.6% ± 0.8 at 6 months and had returned to near-baseline levels (16.8 ± 0.8) at 12 months.

CONCLUSIONS — The rapid-acting insulin analogs have been designed as mealtime insulins and are currently best suited to control the rapid rise in postprandial blood glucose. This study showed that the new analog, IAsp, provided significantly improved postprandial glycemic control compared with HI when used as the mealtime insulin in a multiple-injection regimen. Although the bias from use of patient diaries in an open-label study cannot be discounted, the finding of improved postprandial glycemic control associated with IAsp use is consistent with published data of other rapid-acting insulin analogs (22,23). In addition, previous studies in subjects with type 1 diabetes using IAsp as the mealtime insulin have demonstrated improved postprandial blood glucose control using a variety of pharmacodynamic end points, including postprandial blood glucose excursions up to 4 h (17,24).

In this study, subjects experienced a slight improvement in mean $HbA_{1c}$ values during the 4- to 5-week run-in period, indicating that subjects benefited from the multiple-injection regimen and entered into the treatment period in relatively good glycemic

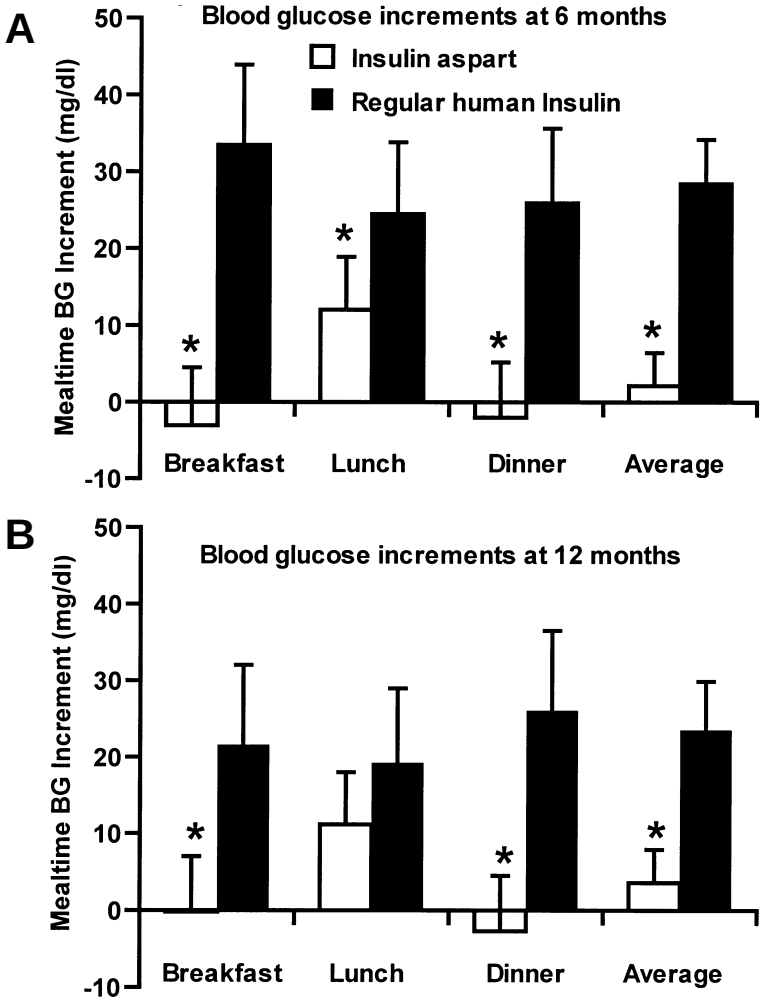


**Figure 2**—*Mean (±2 SEM) blood glucose increment (90-min postprandial blood glucose value–premeal blood glucose value) after 6 (*A*) and 12 (*B*) months of treatment. The average increment is the mean of the 3 mealtime increments for each subject. *Statistically significant ($P < 0.05$) difference between treatment groups. Number of subject data values used to prepare increments: for IAsp: 555 and 490 at 6 and 12 months, respectively; for HI: 260 and 215 at 6 and 12 months, respectively.*

control. With long-term treatment, $HbA_{1c}$ values for the IAsp group were slightly, but significantly, lower than those of the HI group. The lower $HbA_{1c}$ may be partly attributed to the slightly greater increase in basal NPH insulin used in the IAsp group. It is not surprising that a basal-bolus regimen using a rapid-acting mealtime insulin, instead of HI, would require an increase in basal insulin to control the interprandial blood glucose levels. Further lowering of $HbA_{1c}$ levels was observed in a subgroup of IAsp-treated subjects receiving injections of NPH twice a day. These findings are consistent with results of studies specifically addressing the optimization of NPH insulin use (dose and frequency) in basal-bolus regimens utilizing a rapid-acting analog (25).

Tighter glycemic control of mealtime blood glucose by IAsp resulted in significantly smaller blood glucose increments at all meals but was not associated with any increased incidence of hypoglycemic episodes compared with HI. In a previous study in subjects with type 1 diabetes receiving IAsp as their mealtime insulin, there were significantly fewer major hypoglycemic episodes associated with IAsp use compared with HI use (17). In the present study, the risk of major nocturnal hypoglycemia was 50% lower for subjects in the IAsp group compared with the HI group at 6 months. At 12 months, the incidence of major nocturnal hypoglycemia decreased for the HI group. However, the decreased incidence may be attributed to the refusal of HI-treated subjects with high risk of major nocturnal hypoglycemia in the initial 6-month study to enter into the extension. Similar reductions in nocturnal hypoglycemic episodes have been reported for the insulin lispro analog (26).

Cross-reactive antibodies increased for the IAsp-treated subjects. The increase appeared to occur within the first 3 months of treatment, after which levels gradually returned to near-baseline values. The increase in the overall mean values was largely caused by increases observed in a small group of IAsp-treated subjects. Although the reason for the rise in specific antibodies is unknown, the increase in antibodies did not seem to have any adverse consequences. No adjustment to insulin dose was needed for subjects in this group, nor did they have deterioration of glycemic control or an increase in hypoglycemia.

Rapid-acting analogs provide patients with the convenience of insulin injection immediately before their meals. This convenience should help patients with compliance of their mealtime dosing. In a clinical trial, patients who were switched from a basal-bolus regimen using insulin lispro analog to one with HI as mealtime insulin had a significant decrease in treatment satisfaction (27). The decrease in patient satisfaction was also accompanied by a decrease in glycemic control.

The results of this study indicate that insulin aspart, as the mealtime component of an intensive insulin regimen, provided improved postprandial glycemic control compared with HI. Insulin aspart allowed mealtime injection without compromising standard safety parameters or otherwise bringing about an increase in hypoglycemic episodes or adverse events.

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