# Mixing Insulin Aspart With Detemir Does Not Affect Glucose Excursion in Children With Type 1 Diabetes

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**OBJECTIVE** — We hypothesized that insulin detemir mixed with aspart had equivalent effects on blood glucose as if being given as separate injections in pediatric type 1 diabetes patients.

**RESEARCH DESIGN AND METHODS** — Fourteen children with type 1 diabetes were randomly assigned to either Study A (mixed insulins) or Study B (separate insulins) for the first 10 days and crossed over for the last 10 days. Each subject underwent continuous glucose monitoring on the last 72 h of each study.

**RESULTS** — The 48-h area under the curve (mmol/hour/l), M-value, and mean amplitude of glucose excursion (mmol/l) for Study A versus Study B were 457 ± 70 versus 469 ± 112 ($P$ = 0.58), 39.67 ± 15.37 versus 39.75 ± 9.69 ($P$ = 0.98), and 6.35 ± 1.92 versus 5.98 ± 0.92 ($P$ = 0.42), respectively.

**CONCLUSIONS** — Insulin detemir mixed with aspart had equivalent effects on blood glucose versus giving them as separate injections in children with type 1 diabetes.

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One of the barriers to good glycemic control in children with type 1 diabetes is multiple daily insulin injections (1,2). Mixing rapid-acting and slow-acting insulins in the same syringe would decrease the number of injections and may improve adherence (3,4). Although there are concerns that mixing the insulins would change the glucose excursion (5), mixing rapid-acting insulin (aspart or lispro) with slow-acting insulin glargine in the same syringe immediately before use did not change the glucose excursion and rates of hypoglycemia (3,4). We hypothesized that slow-acting insulin detemir mixed with aspart would have equivalent effects on blood glucose versus giving them as separate injections in children with type 1 diabetes.

## RESEARCH DESIGN AND METHODS

— The protocol was approved by the institutional review board of the Baylor College of Medicine. The study was designed to detect a 20% difference in mean area under the curve (AUC) for blood glucose values in the 72-h study period. We assumed the $r >$ 0.7 between repeated measures and that the SD for our excursion measure AUC was ~30%. With these specifications and assuming a 45% drop-out rate, we required 20 subjects to achieve the final necessary sample size of 11 subjects. Eighteen pediatric subjects with type 1 diabetes (11 males and 7 females) were recruited for this 20-day, randomized, crossover, and open-labeled study. These subjects were aged 14.75 ± 2.69 years and had A1C of 7.7 ± 0.7%. The first four subjects were aged 16 years and older as required by the U.S. Food and Drug Administration. The subjects were randomly assigned to either Study A (mixed insulins) or Study B (separate insulins) for the first 10 days. They were then crossed over for the last 10 days. Each subject underwent 72 h of continuous glucose monitoring (CGM) using CGMS iPro (Medtronics, Minneapolis, MN) on the last 72 h of Study A and Study B. Data of 48 h from midnight of the 1st day to midnight of the 3rd day of the 72-h CGM were used for analysis to ensure the same starting and ending times of monitoring for all subjects. The relative frequency of mild hypoglycemic episodes was calculated as the number of glucose values between 40 and 60 mg/dl divided by the total number of glucose values generated during the chosen 48 h of CGM. Sustained glucose values over time were calculated as AUC, index of blood glucose control as M-value, and glucose excursion as mean amplitude of glucose excursion (MAGE). The 48-h M-value for each treatment of each subject was calculated using the formula $M = M^{BS} + M^{W}$, where $M^{W}$ = (maximum blood glucose − minimum glucose)/20; $M^{BS}$ = the mean of MBSBS; MBSBS = individual M-value for each blood glucose value during the 48-h period and was calculated as (absolute value of [10 × log(blood glucose value/120)])[3] as being done for 24-h data by Schlichtkrull et al. (6). The 48-h MAGE for each treatment of each subject was calculated by modifying the method proposed by Service et al. (7) for CGM data as follows: summation of absolute value of [blood glucose − 48-h mean blood glucose] > 1 SD/$n$, where $n$ = number of absolute value of [blood glucose − 48-h mean blood glucose] being greater than 1 SD. The 48-h AUC, M-value, or MAGE were compared between Study A and Study B by paired $t$ test. Significance was chosen to be $P$ = 0.05. Data were expressed as means ± SD. The Wilcoxon signed rank test was used to compare the incidence of hypoglycemia in the two treatment groups. GraphPad Prism

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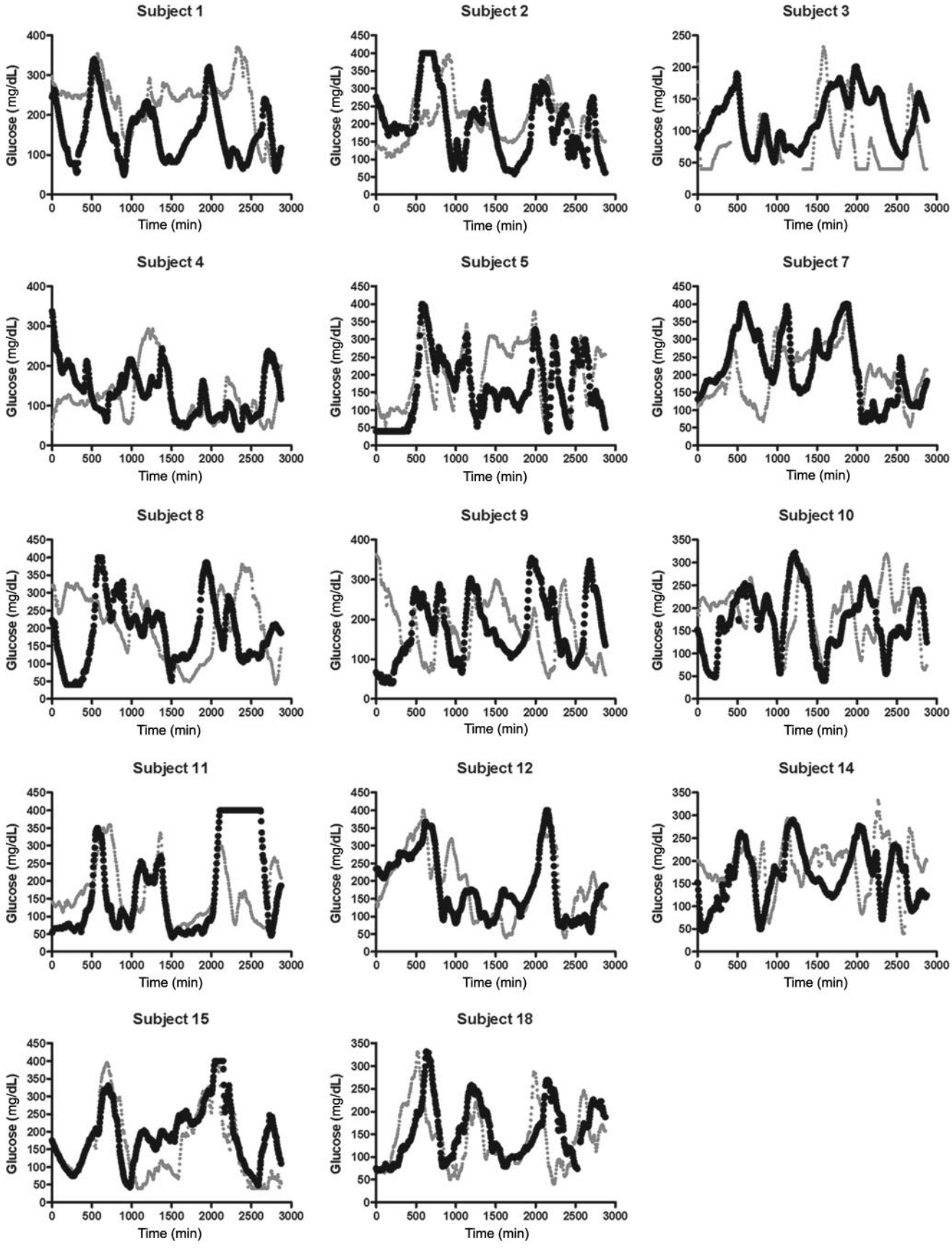


**Figure 1—***The 48-h CGM tracings for each subject taking detemir separately from aspart (gray lines) and detemir mixed with aspart (black lines).*

(GraphPad Software, La Jolla, CA) was used to analyze the data.

**RESULTS** — Fourteen subjects completed this 20-day, randomized, crossover, open-labeled study. One male subject dropped out because of a very active sports schedule and could not continue participation. Three subjects (two males and one female) had trouble with the CGM tracing and, therefore, were excluded from the final analysis. Figure 1 shows 48-h CGM tracing for 14 subjects. AUC was 457 ± 70 mmol/hour/l for Study A compared with 469 ± 112 mmol/hour/l for Study B ($P = 0.58$). The M-value was 39.67 ± 15.37 for Study A compared with 39.75 ± 9.69 for Study B ($P = 0.98$). MAGE was 6.35 ± 1.92 mmol/l for Study A compared with 5.98 ± 0.92 mmol/l for Study B ($P = 0.42$). Relative frequency of mild hypoglycemic episodes was 5.3 ± 5.2% for Study A versus 6.7 ± 11.1% for Study B ($P = 0.95$). There was no severe hypoglycemia in either group.

**CONCLUSIONS** — In this study, we present data showing that insulin detemir mixed with aspart given twice daily had equivalent effects on blood glucose when compared with giving detemir and aspart as separate injections twice daily in children with type 1 diabetes. There was no increase in hypoglycemia in either treatment. Further studies are needed to study the long-term consequences of mixing and the effect on glycemic control.

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