Effects of Blood Glucose Rate of Changes on Perceived Mood and Cognitive Symptoms in Insulin-Treated Type 2 Diabetes

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Studies indicate that diabetes affects mood, cognitive function, and motor performance (1–5). As cognitive dysfunction and depressive mood symptoms have been reported with hyperglycemia (5–7), we hypothesized that the impact of insulin on blood glucose parameters would affect mood and cognitive symptoms. Consistent with our past post hoc findings (7), we specifically hypothesized that rapid pre- to postmeal blood glucose rate of change (BGRATE) correlates with negative mood and cognitive postmeal symptoms but not with energy or positive mood. We report the results of correlation analyses of BGRATE with symptoms from a pilot investigation designed to evaluate whether improvements in glycemic control seen with basal plus prandial insulin analog regimens compared with basal insulin analog in patients with type 2 diabetes (8–10) would lead to measurable mood and cognitive differences.

RESEARCH DESIGN AND METHODS

— A single-center, open-label, crossover, randomized, controlled clinical trial enrolled 60 adults with type 2 diabetes, A1C 7–10%, and prestudy use of metformin (with or without oral antihyperglycemic medications or once daily insulin). Pregnant or breast-feeding women and patients with a previous diagnosis of depression or treated with centrally acting medications (e.g., antidepressants or anxiolytics) were excluded.

Patients were randomly assigned to treatment with Humalog Mix 75/25 (insulin lispro mixture [75% lispro protamine suspension/25% lispro injection], Eli Lilly), twice daily subcutaneous injection (before breakfast and before dinner) for 12 weeks, followed by Lantus (insulin glargine; Sanofi-Aventis Pharmaceuticals), once daily subcutaneous injection (bedtime) for 12 weeks or the reverse sequence. Patients discontinued all prestudy diabetes therapy except metformin, which was continued along with the study insulins. Insulin was individually adjusted to target preprandial blood glucose levels <6.7 mmol/l (121 mg/dl) and 2-h postprandial blood glucose levels <8.0 mmol/l (144 mg/dl) after the morning and evening meals without increasing hypoglycemia. Hypoglycemia was defined as any time a patient experienced a sign or symptom associated with hypoglycemia or had a blood glucose level <3.5 mmol/l (<63 mg/dl).

The Beck Depression Inventory II (BDI-II) was administered at baseline and at the end of each crossover treatment (11). During the last 4 weeks of the two 12-week treatment periods, before breakfast and dinner and 1 h later, patients entered their blood glucose measurements and rated 13 perceived mood and cognitive symptoms (symptoms listed in Table 1) on a 0 ("Not at all") to 6 ("Extremely") scale using a handheld computer (Handspring Visor). This method is similar to those described in a previous study (7). The before and after breakfast and dinner blood glucose levels entered into the handheld computer were used to calculate BGRATE at breakfast and at dinner. BGRATE is a metric of speed of blood glucose (BG) change in milligrams per minute, i.e., $(BG^{time2} - BG^{time1})/(\text{Time } 2 - \text{Time } 1)$, for measurements of average blood glucose changes over a defined period of time (12). Symptom ratings after meals were clustered into Depressive, Anxious, Cognitive, and Energetic scores and then were correlated with respective mealtime BGRATE values. A *t* test was used for within-treatment comparison, and Koch's model was used for between-treatment comparisons. Pearson correlation analysis was performed to evaluate the correlation between BGRATE at breakfast and dinner with mood and cognitive symptoms after a meal.

RESULTS

— Of 60 patients screened, 45 were randomly assigned (mean ± SD age 52.6 ± 11.9 years, BMI 35.08 ± 8.4 kg/m^2, and duration of diabetes 11.9 ± 7.5 years). There were 33 completers (lispro mixture/glargine, $n = 17$; glargine/lispro mixture group, $n = 16$).

Postdinner blood glucose levels (millimoles per liter) were lower with lispro mixture treatment than with glargine (Table 1), but no significant between-treatment differences were noted in breakfast or dinner BGRATE (range 2.2 ± 0.7–3.1 ± 1.3 mmol/l). This finding was consistent with trends noted in patients' self-monitored blood glucose levels, which showed lower prelunch, 2-h postdinner, and bedtime levels with the lispro mixture than with glargine treatment (data on file). There were no severe hypoglycemic episodes, and no differences were noted in hypoglycemia incidence at the end point.

Consistent with our hypothesis, postmeal negative mood (depressive and anxious) and cognitive symptoms significantly

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Abbreviations: BDI-II, Beck Depression Inventory II; BGRATE, blood glucose rate of change.

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

Table 1—*Blood glucose parameters (combined periods by treatment) and correlation of symptoms with BGRATE*

	Lispro mixture	Glargine	Treatment comparison *P* value*
Blood glucose (mmol/l)			
n	28	28	
Before breakfast	8.5 ± 1.5	7.8 ± 2.0	0.056
After breakfast	11.0 ± 1.9	10.9 ± 2.1	0.642
Before dinner	9.8 ± 2.5	10.7 ± 3.0	0.076
After dinner	11.0 ± 2.3	12.3 ± 2.9	0.001
Correlation coefficients of symptom clusters† and BGRATE (rise from pre- to postmeal blood glucose)			
Depressive (sad/blue, not care/ apathetic, and slowed down/sleepy)	0.45§; 0.56§	0.39‡; 0.53§	
Anxious (restless/jittery, nervous/anxious, and irritable/frustrated)	0.43‡; 0.49§	0.41‡; 0.51§	
Cognitive (difficulty concentrating, slowed thinking/foggy, uncoordinated, and difficulty speaking)	0.48§; 0.55§	0.47§; 0.54§	
Energetic (alert/crisp/awake, energetic/ lively, and enjoying myself)	0.11; −0.16	0.13; −0.6	

Data are means ± SD or average scores: breakfast; supper. *Using Koch Model. †Scores were recoded to present % of time symptoms occurred. ‡$P < 0.05$; §$P < 0.01$.

correlated with BGRATE (a reflection of the rapid increase in blood glucose levels from pre- to postmeal) at both breakfast and dinner for both the lispro mixture and glargine. Further, consistent with our hypothesis, positive mood (energetic) did not correlate with BGRATE (Table 1). BDI-II scores decreased with both therapies from baseline (8.2 ± 6.0) to the end point (lispro mixture 5.5 ± 3.8; glargine 6.8 ± 5.9), with a significant decrease only with lispro mixture treatment ($P = 0.018$) but no end point difference between treatments ($P = 0.115$).

CONCLUSIONS — This pilot study investigating the potential effects of specific insulin regimens for type 2 diabetes showed that negative mood and cognitive symptoms reported 1 h after breakfast and supper significantly correlated with a rapid rise in pre- to postmeal blood glucose levels in insulin-treated patients, confirming earlier post hoc observations (7). No significant differences were seen for mood or cognitive symptoms between insulin regimens. A significant baseline-to-end point improvement occurred in BDI-II score in lispro mixture–treated patients.

In light of epidemiological evidence indicating an association between chronic effects of dysglycemia and brain function (13), studies with larger and more diverse samples are warranted to further evaluate the effects of insulin on mood or cognition and the impact of different insulin treatments on diabetes-related mood and cognitive changes.

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