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

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Daniel J. Cox PhD\textsuperscript{1}, Anthony McCall, MD, PhD\textsuperscript{1}, Boris Kovatchev PhD\textsuperscript{1}, Samiha Sarwat MS\textsuperscript{2}, Liza L. Ilag MD\textsuperscript{2}, Meng H. Tan MD\textsuperscript{2}.

\textsuperscript{1}University of Virginia Health Sciences Center, Charlottesville, Virginia, USA
\textsuperscript{2}Eli Lilly and Company, Indianapolis, Indiana, USA

Direct correspondence to Dr. Daniel J. Cox, Psychiatry and Neurobehavioral Sciences, University of Virginia Health Sciences Center, Charlottesville, Virginia, 22908
E-mail: djc4f@virginia.edu

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Running title: Insulin effects in perceived mood symptoms
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 insulin’s impact on blood glucose (BG) parameters would affect mood and cognitive symptoms. Consistent with our past post hoc findings (7), we specifically hypothesized that rapid pre- to post-meal BG rate of change (BGRATE) correlates with negative mood and cognitive post-meal symptoms but not with energy/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+prandial insulin analog regimens compared to 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 pre-study metformin use (±oral antihyperglycemic medications or once-daily insulin). Pregnant or breastfeeding women and patients previously diagnosed with depression or treated with centrally-acting medications (e.g. antidepressants, anxiolytics) were excluded.

Patients were randomly assigned to treatment with Humalog® Mix 75/25 (insulin lispro mixture [LM 75%, NPL/25% lispro], Eli Lilly and Company) twice-daily sc injection (pre-breakfast and pre-dinner) for 12 weeks, followed by Lantus® (insulin Glargine, Sanofi-Aventis Pharmaceuticals) once-daily sc injection (bedtime) for 12 weeks, or the reverse sequence. Patients discontinued all pre-study diabetes therapy except metformin, which was continued with study insulins. Insulin was individually adjusted to target pre-prandial BG <6.7 mM (121 mg/dL) and 2-hr postprandial BG levels <8.0 mM (144 mg/dL) after the morning and evening meals without increasing hypoglycemia. Hypoglycemia was defined as any time a patient experienced a sign/symptom associated with hypoglycemia or had a BG <3.5 mM (<63 mg/dl).

Beck Depression Inventory-II (BDI-II) was administered at baseline and the end of each cross-over treatment (11). During the last 4 weeks of the two 12-week treatment periods, at pre-breakfast and dinner and one-hour later, patients entered their BGs 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 is similar to methods described in a previous study (7). The pre- and post-breakfast and dinner BGs entered in the handheld computer were used to calculate BGRATE at breakfast and at dinner. BGRATE is a metric of speed of BG change in mg/minute, i.e. \( \frac{(BG_{time2} - BG_{time1})}{(Time2-Time1)} \), 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 then correlated with respective mealtime BGRATE. T-test was used for within-treatment comparison and Koch’s model for between treatment comparisons. Pearson correlation analysis was performed to evaluate the correlation between BGRATE at breakfast and dinner with mood and cognitive symptoms post-meal.
RESULTS

Of 60 patients screened, 45 were randomized (mean ± SD age 52.6 ± 11.9 years, BMI 35.08 ± 8.4 kg/m², and duration of diabetes 11.9 ± 7.5 years). There were 33 completers (LM/Glargine, n=17/ Glargine/LM group, n=16).

Post-dinner BG (mM) was lower with LM treatment compared to glargine (Table 1) but no significant between-treatment differences were noted in breakfast or dinner BGRATE (range: 2.2 ± 0.7 to 3.1 ± 1.3). This was consistent with trends noted in patients’ self-monitored BG which showed lower pre-lunch, 2-hr post-dinner, and bedtime BG with LM compared to glargine treatment (data on file). There were no severe hypoglycemic episodes and no differences were noted in hypoglycemia incidence at endpoint.

Consistent with our hypothesis, post-meal negative mood (depressive and anxious) and cognitive symptoms significantly correlated with BGRATE (a reflection of the rapid increase in BG from pre-to post-meal) at both breakfast and dinner for both LM and glargine. Further, consistent with our hypothesis, positive mood (energetic) did not correlate with BGRATE (Table 1). BDI-II scores decreased in both therapies from baseline (8.2 ± 6.0) to endpoint (LM: 5.5 ± 3.8, Glargine: 6.8 ± 5.9), with a significant decrease only with LM treatment (p=0.018), but no endpoint 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 one hour after initiating breakfast and supper significantly correlated with rapid rise in pre-to post-meal BG in insulin-treated patients, confirming earlier post hoc observations (7). No significant differences were seen on mood or cognitive symptoms between insulin regimens. A significant baseline-to-endpoint improvement occurred in BDI-II score in LM-treated patients.

In light of epidemiologic 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 insulin’s effects on mood or cognition and the impact of different insulin treatments in diabetes-related mood and cognitive changes.

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References


Table 1. Blood Glucose Parameters (Combined Periods by Treatment), and Correlation of Symptoms with BGRATE (14)

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>Lispro LM Mean ± SD</th>
<th>Glargine Mean ± SD</th>
<th>p-value †</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. BG (mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-breakfast</td>
<td>8.5 ± 1.5</td>
<td>7.8 ± 2.0</td>
<td>0.056</td>
</tr>
<tr>
<td>Post-breakfast</td>
<td>11.0 ± 1.9</td>
<td>10.9 ± 2.1</td>
<td>0.642</td>
</tr>
<tr>
<td>Pre-dinner</td>
<td>9.8 ± 2.5</td>
<td>10.7 ± 3.0</td>
<td>0.076</td>
</tr>
<tr>
<td>Post-dinner</td>
<td>11.0 ± 2.3</td>
<td>12.3 ± 2.9</td>
<td>0.001</td>
</tr>
<tr>
<td>B. Correlation of Symptom clusters + and BGRATE (rise from Pre- to Post-meal BG)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive</td>
<td>0.45 ; 0.56</td>
<td>0.39* ; 0.53</td>
<td></td>
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<tr>
<td>Average Score (Sad/blue, Not care/apathetic and Slowed down/Sleepy)</td>
<td></td>
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<tr>
<td>Anxious</td>
<td>0.43* ; 0.49</td>
<td>0.41* ; 0.51</td>
<td></td>
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<tr>
<td>Average Score (Restless/jittery, Nervous/anxious and Irritable/frustrated)</td>
<td></td>
<td></td>
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<tr>
<td>Cognitive</td>
<td>0.48 ; 0.55</td>
<td>0.47 ; 0.54</td>
<td></td>
</tr>
<tr>
<td>Average Score (Difficulty concentrating, Slowed thinking/Foggy, Uncoordinated and Difficulty speaking)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Energetic</td>
<td>0.11 ; -0.16</td>
<td>0.13 ; -0.06</td>
<td></td>
</tr>
<tr>
<td>Average Score (Alert/Crisp/Awake, Energetic/Lively and Enjoying myself)</td>
<td></td>
<td></td>
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</tbody>
</table>

† Scores were recoded to present % of time symptoms occurred.
†† Using Koch Model.
¶ Correlation Coefficient
* p<0.01; # p<0.05