Acute Hyperglycemia Alters Mood State and Impairs Cognitive Performance in People With Type 2 Diabetes

ANDREW J. SOMMERFIELD, MRCP (UK)[1]
IAN J. DEARY, PHD[2]
BRIAN M. FRIER, MD[1]

OBJECTIVE — To examine the effects of acute hyperglycemia on cognitive function and mood in people with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Twenty subjects with type 2 diabetes, median age 61.5 years (range 53.1–72.0), known duration of diabetes 5.9 years (range 2.8–11.2), BMI 29.8 kg/m^2 (range 22.0–34.6), and HbA_{1c} 7.5% (range 6.7–8.4) were studied. Treatment modalities varied from antidiabetic medications to insulin. A hyperinsulinemic glucose clamp was used to maintain arterialized blood glucose at either 4.5 (euglycemia) or 16.5 mmol/l (hyperglycemia) on two occasions in a randomized and counterbalanced fashion. Tests of information processing, immediate and delayed memory, working memory, and attention were administered, along with a mood questionnaire, during each experimental condition.

RESULTS — Speed of information processing, working memory, and some aspects of attention were impaired during acute hyperglycemia. Subjects were significantly more dysphoric during hyperglycemia, with reduced energetic arousal and increased sadness and anxiety.

CONCLUSIONS — During acute hyperglycemia, cognitive function was impaired and mood state deteriorated in a group of people with type 2 diabetes. These findings are of practical importance because intermittent or chronic hyperglycemia is common in people with type 2 diabetes and may interfere with many daily activities through adverse effects on cognitive function and mood.

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Diabetes is associated with rapid fluctuations in blood glucose. Hyperglycemia is a frequent consequence of the relative or absolute insulin deficiency that is intrinsic to diabetes, and hypoglycemia is a common side effect of treatment with insulin and some antidiabetic medications (1). Because the brain is dependent on a continuous supply of glucose as its principal source of energy, changes in blood glucose concentration rapidly affect cerebral function. The adverse effects of acute hypoglycemia on cognitive function and on mood are recognized (2,3). However, less is known about the effects of acute hyperglycemia on cerebral function. Anecdotal descriptions by patients with diabetes suggest that when blood glucose is elevated, changes in mood (such as increased irritability and feelings of diminished well-being) occur and rapid thinking is more difficult.

Published data on the effects of acute hyperglycemia on cognitive function are contradictory. Two studies (4,5) have demonstrated impaired language skills and reduced IQ during hyperglycemia compared with euglycemia. Other studies have shown no effect of acute hyperglycemia on cognitive function (6–8) or mood (9). However, in the study by Gschwend et al. (6), only two tests were used to assess cognitive function, and in the studies by Draelos et al. (8) and Weinger et al. (9) the study cohorts had chronically poor metabolic control, which may have allowed cerebral adaptation to occur in response to prevailing high blood glucose concentrations. A further study by Sindrup et al. (10) showed that short-term hyperglycemia (blood glucose concentration 17.1 mmol/l) with physiological hyperinsulinemia was associated with increased sensory nerve conduction velocity and decreased motor latency in nondiabetic subjects.

Earlier studies have been confined to people with type 1 diabetes. Evidence is accumulating that people with type 2 diabetes are at risk of developing cognitive impairment (11,12). This is probably a consequence of synergistic interaction between metabolic derangements associated with diabetes and the structural and functional changes that occur within the central nervous system as part of the normal aging process. People with type 2 diabetes may be susceptible to cognitive dysfunction during short-term changes in blood glucose concentration. The present study examined the effects of acute hyperglycemia on a range of important cognitive function and key mood states in a group of people with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Twenty adults (12 men) with type 2 diabetes were studied, following recruitment from the diabetes outpatient clinic at the Royal Infirmary of Edinburgh. Baseline characteristics included median age 61.5 years (range 53.1–72.0), BMI 29.8 kg/m^2 (range 22.0–34.6), known duration of diabetes of 5.9 years (range 2.8–11.2), and HbA_{1c} 7.5% (range 6.7–8.4). HbA_{1c}, recorded in the month before the study, was measured by high-performance liquid chromatography (Variant II Hemoglobin

From the [1]Department of Diabetes, Royal Infirmary of Edinburgh, Edinburgh, U.K.; and the [2]Department of Psychology, University of Edinburgh, Edinburgh, U.K.

Address correspondence and reprint requests to Professor Brian M. Frier, Department of Diabetes, Royal Infirmary of Edinburgh, Edinburgh EH16 4ES, Scotland, U.K. E-mail: brian.frier@luht.scot.nhs.co.uk.

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

Testing System; BioRad Diagnostics Group, Hercules, CA) with a local nondiabetic reference range of 4.3–6.5%. Three of the subjects required insulin to treat their diabetes, five were taking a single antidiabetic drug, nine were taking a combination of antidiabetic drugs, and three were taking an antidiabetic drug and once-daily isophane (NPH) insulin. None of the participants had a history of any other chronic disease, previous head injury, seizure, blackouts, alcohol or drug abuse, or psychiatric illness. Subjects were screened for diabetes complications and were excluded if they had evidence of microvascular disease, with the exception of background retinopathy. The presence of retinopathy was ascertained using direct ophthalmoscopy, peripheral neuropathy by clinical examination, and nephropathy was presumed by the presence of established microalbuminuria. Ethical permission for the study was approved by the local medical research ethics committee. All subjects gave written informed consent for participation in the study.

Each subject participated in two laboratory sessions that were separated by at least 2 weeks. A modified hyperinsulinemic glucose clamp (13) was used to maintain blood glucose at a predetermined level. In each study condition, the arterialized blood glucose concentration was initially stabilized at 4.5 mmol/l for a period of 30 min. In the euglycemia condition, the blood glucose concentration was thereafter maintained at 4.5 mmol/l throughout the study. In the hyperglycemia condition, blood glucose was raised to 16.5 mmol/l over a period of 20 min. The blood glucose concentration was maintained at the predetermined target level for a further 10 min before commencing cognitive testing and was kept at this level for a further 80 min while the tests were administered. The subjects were not informed which arm of the study was being undertaken on each occasion, and the two sessions were performed in a randomized and counterbalanced fashion.

Cognitive function tests

Validated tests of information processing, tests of memory, and tests of attention were administered during each study condition.

Test of information processing

Trail Making B. This test, which was run on a handheld computer (14,15), assesses complex visual scanning and has a motor component.

Digit Symbol test. This is a test of coding performed at speed (16).

Reaction Time test. This is a test of psychomotor speed and information processing (17). SDs of the Simple and Four-Choice Reaction Times were also calculated, providing a measure of intra-individual variability, and the coefficient of variation was calculated.

Tests of memory. The memory and learning tests that were used in this study were chosen because they have previously been shown (18) to be sensitive to metabolic disturbances such as hypoglycemia.

Verbal memory tests. 1) Auditory Verbal Learning Test, immediate and delayed. This is a test of immediate memory capacity, retrieval efficiency, and learning. The delayed component measures longer-term retention (19). *2*) Logical Memory Test, immediate and delayed. The Logical Memory test (20), a test of verbal learning, measures immediate and delayed recall following auditory presentation.

Visual memory tests. 1) Visual Reproduction, immediate and delayed. This test measures immediate and delayed recall following nonverbal visual presentation (20). *2*) Benton Visual Retention Test. This is a test of immediate visual recall (21).

Working memory tests. 1) Digit Span Forwards and Backwards. In this test, a series of lists of numbers is presented verbally to the subject, and the lists progressively increase in length (20). *2*) Letter/Number Sequencing. A series of lists of numbers mixed with letters is presented verbally (20).

Tests of attention. The Test of Everyday Attention battery (22) was used to measure attention and includes tests of visual selective, auditory selective, divided, and sustained attention and of attention switching.

Parallel versions of the tests are available for the Auditory Verbal Learning Test, Logical Memory, the Benton Visual Retention Test, and the Test of Everyday Attention battery, and in the present study these were used to minimize a learning effect between the two study conditions. Throughout the study, the battery of tests was carried out in a fixed order.

Mood questionnaire

The University of Wales Institute of Science and Technology (UWIST) mood adjective checklist was used to document changes in mood experienced by the subjects during the two studies (23). There are three main mood states: energetic arousal (feeling lively/active versus tired/sluggish), tense arousal (feeling anxious/nervous versus relaxed/calm), and hedonic tone (feeling happy versus sad).

Statistical analysis

The results were analyzed independently for each test. A general linear model (repeated-measures ANOVA) was used with order of session (euglycemia-hyperglycemia or hyperglycemia-euglycemia) as a fixed effect, and condition (euglycemia or hyperglycemia) as a within-subjects factor. The above models were repeated with the following variables added singly and separately: sex as a fixed effect and with age, glucose infusion rate, HbA_{1c}, and the three mood states as covariates. The order effect was retained in the models when reported in the results. A P value <0.05 was considered to be significant. The P values reported in the tables for the core model (including only condition and order) were generated from analyses without including sex and the covariates. The P value reported in the tables for the additional fixed effect of sex and the covariates refers to analyses in which these were added singly to the core model. Effect size was calculated using Eta^2. An Eta^2 score of 0.25–0.5 indicates a moderate effect size. Power was calculated using nQuery, which gives δ^2-based power for univariate repeated-measures ANOVA. α was set at 0.05 ($n = 20$). Between-level correlation was set at zero, which offers a conservative power estimate because correlations are generally modest and positive. The power to detect an effect size of 0.25 = 85% and to detect an effect size of 0.50 = 98%. All analyses were performed using SPSS version 11.0 for Windows.

RESULTS — A stable blood glucose plateau was achieved during each study condition. The mean (±SD) arterialized blood glucose concentration during the euglycemia condition was 4.5 ± 0.2 mmol/l and during the hyperglycemia condition was 16.7 ± 0.6 mmol/l. Statistical analysis revealed that no significant order effects had occurred for any of the outcome variables of this study. The significant effects of acute hyperglycemia on cognitive function remained significant in all analyses after controlling for sex, age, HbA_{1c}, and glucose infusion rate.

Table 1—*Results of tests of information processing during euglycemia and hyperglycemia in 20 adults with type 2 diabetes*

Subtest	Euglycemia	Hyperglycemia	*P*	*F*	Eta^2	Age	Sex	GIR	HbA_{1c}	TA	EA	HT
Digit Symbol Substitution test	70.2 ± 8.4	66.8 ± 7.8	0.03	5.64	0.24	0.38	0.26	0.65	0.71	0.64	0.57	0.96
Trail Making B test	40.9 ± 7.8	43.9 ± 8.0	0.04	4.77	0.23	0.74	0.77	0.34	0.32	0.38	0.39	0.39
Simple Reaction Time test												
Mean	359.9 ± 84.6	373.7 ± 72.3	0.10	2.99	0.14	0.81	0.43	0.76	0.33	0.41	0.28	0.08
SD	73.3 ± 11.2	77.5 ± 17.6	0.10	0.47	0.15	0.96	0.18	0.98	0.81	0.50	0.45	0.68
Coefficient of variation	21.09 ± 6.86	21.82 ± 6.01	0.38	0.82	0.01	0.92	0.19	0.82	0.65	0.31	0.09	0.16
Four-Choice Reaction Time test												
Mean	710.0 ± 116.7	775.7 ± 122.9	<0.0001	23.05	0.56	0.55	0.12	0.48	0.92	0.46	0.76	0.74
SD	133.1 ± 23.6	139.5 ± 41.2	0.09	0.68	0.18	0.09	0.48	0.60	0.70	0.67	0.34	0.26
Coefficient of variation	18.73 ± 2.77	18.22 ± 4.02	0.64	0.23	0.01	0.06	0.76	0.61	0.68	0.80	0.41	0.95
Number of errors	0.5 ± 0.1	0.4 ± 0.1	0.43	0.54	0.09	0.54	0.65	0.36	0.62	0.51	0.22	0.31

Data are means ±SD. The effects of age, sex, glucose infusion rate (GIR), HbA_{1c}, and mood as covariates are also shown (all *P* values). EA, energetic arousal; HT, hedonic tone;TA, tense arousal.

Tests of information processing

The results of these tests are summarized in Table 1. During acute hyperglycemia, performance was significantly impaired in the Trail Making B, Digit Symbol, and Four-Choice Reaction Time tests. Performance in the Simple Reaction Time test was not significantly impaired during hyperglycemia. The coefficient of variation for the Simple and Four-Choice Reaction Time tests was not significantly different between the euglycemia and hyperglycemia conditions.

Tests of memory

The results of the memory function tests are summarized in Table 2. Acute hyperglycemia had no significant effect on tests of immediate or delayed memory. Performance in two tests of working memory (Digit Span Backwards, Letter/Number Sequencing) was impaired during acute hyperglycemia.

Tests of attention

The results of the tests of attention are summarized in Table 3.

Visual selective attention. The mean number (±SD) of map symbols circled in 1 min was significantly fewer during hyperglycemia. The number of symbols circled in 2 min was also lower during hyperglycemia, but the difference did not achieve statistical significance. In the telephone search task, no difference was demonstrated between euglycemia and hyperglycemia in the number of symbols located. The mean (±SD) time taken to complete the task during euglycemia was significantly faster than that during hyperglycemia.

Auditory selective attention. The auditory elevator test with reversal was significantly affected by hyperglycemia. However, performance in the elevator with distraction test was not impaired.

Sustained attention. Sustained attention was not affected by hyperglycemia.

Attention switching. In the visual elevator task, no difference was observed in the raw score between the two study conditions. However, a significantly longer time was required to complete each switch of the visual elevator task during hyperglycemia.

Divided attention. In the task that involved search of a telephone directory while counting, no significant difference was observed in the number of symbols that were located during either study condition. The time taken to complete the task was longer during hyperglycemia com-

Table 2—*Results of tests of memory during euglycemia and hyperglycemia in 20 adults with type 2 diabetes*

Subtest	Euglycemia	Hyperglycemia	*P*	*F*	Eta^2	Age	Sex	GIR	HbA_{1c}	TA	EA	HT
Immediate memory												
Immediate Logical Memory	27.2 ± 4.3	26.1 ± 4.1	0.16	2.13	0.11	0.93	0.16	0.67	0.41	0.52	0.47	0.88
Immediate AVLT	35.0 ± 5.7	32.4 ± 4.9	0.09	3.33	0.16	0.78	0.12	0.43	0.56	0.46	0.46	0.38
Benton Visual Retention Test	6.2 ± 1.2	5.9 ± 0.9	0.30	1.16	0.06	0.82	0.88	0.31	0.32	0.21	0.63	0.18
Visual Reproduction	76.9 ± 7.6	77.9 ± 7.5	0.51	0.44	0.02	0.64	0.95	0.79	0.39	0.30	0.12	0.66
Working memory												
Digit Span Forwards	9.6 ± 1.3	9.2 ± 1.6	0.33	0.99	0.05	0.53	0.18	0.53	0.41	0.48	0.54	0.61
Digit Span Backwards	8.6 ± 1.5	7.9 ± 1.3	0.01	5.01	0.30	0.13	0.09	0.49	0.36	0.61	0.55	0.89
Letter/Number Sequencing	10.4 ± 1.9	9.4 ± 1.6	0.02	6.94	0.25	0.24	0.10	0.60	0.38	0.17	0.31	0.87
Delayed memory												
Delayed Logical Memory	13.2 ± 2.1	12.3 ± 2.2	0.09	3.16	0.15	0.54	0.18	0.78	0.51	0.85	0.68	0.72
Delayed AVLT	8.2 ± 2.2	7.8 ± 1.9	0.26	6.23	0.07	0.25	0.46	0.94	0.26	0.62	0.40	0.06
Delayed Visual Reproduction	14.1 ± 9.2	10.8 ± 8.2	0.08	3.58	0.17	0.41	0.31	0.36	0.76	0.59	0.31	0.70

Data are means ± SD. The effects of age, sex, glucose infusion rate (GIR), HbA_{1c}, and mood as covariates are also shown (all *P* values). AVLT, Auditory Verbal Learning Test; EA, energetic arousal; HT, hedonic tone; TA, tense arousal.

Table 3—*Results of tests of attention during euglycemia and hyperglycemia in 20 adults with type 2 diabetes*

Subtest	Euglycemia	Hyperglycemia	*P*	*F*	Eta^2	Age	Sex	GIR	HbA_{1c}	TA	EA	HT
Visual selective attention												
Map Search (1 min)	35.0 ± 6.7	32.2 ± 5.1	0.04	3.36	0.22	0.17	0.21	0.39	0.44	0.31	0.26	0.41
Map Search (2 min)	64.8 ± 7.4	62.5 ± 8.7	0.31	1.07	0.06	0.60	0.57	0.57	0.41	0.27	0.44	0.72
Telephone Search (raw score)	3.6 ± 0.7	3.7 ± 0.6	0.34	0.95	0.05	0.11	0.19	0.30	0.62	0.44	0.51	0.96
Telephone Search (total time)	58.7 ± 8.3	67.0 ± 13.1	0.04	2.91	0.27	0.43	0.24	0.56	0.71	0.61	0.16	0.76
Auditory selective attention												
Elevator Counting (with distraction)	8.8 ± 1.1	8.3 ± 1.3	0.12	2.71	0.13	0.56	0.50	0.83	0.47	0.32	0.28	0.06
Elevator Counting (with reversal)	5.3 ± 1.7	4.4 ± 1.4	0.01	7.44	0.29	0.12	0.08	0.49	0.50	0.38	0.24	0.17
Attention switching												
Visual Elevator (raw score)	8.9 ± 1.1	8.5 ± 0.9	0.17	2.01	0.10	0.69	0.85	0.08	0.90	0.19	0.87	0.59
Visual Elevator (switch time)	4.3 ± 1.0	4.7 ± 0.9	0.001	17.44	0.49	0.15	0.43	0.60	0.26	0.09	0.63	0.20
Divided attention												
Telephone Search (with counting total time)	62.3 ± 9.5	67.2 ± 17.1	0.10	2.71	0.12	0.56	0.25	0.78	0.53	0.42	0.21	0.60
Telephone Search (with counting time per target)	1.0 ± 0.6	1.2 ± 0.6	0.05	4.45	0.20	0.31	0.37	0.59	0.62	0.46	0.54	0.68
Sustained attention												
Elevator Counting	6.6 ± 0.68	6.7 ± 0.67	0.79	0.07	0.01	0.1	0.18	0.68	0.38	0.30	0.31	0.27
Lottery	9.6 ± 0.7	9.7 ± 0.6	0.63	0.24	0.01	0.48	0.18	0.93	0.67	0.27	0.82	0.26

Data are means ±SD. The effects of age, sex, glucose infusion rate (GIR), HbA_{1c}, and mood as covariates are also shown (all *P* values). EA, energetic arousal; HT, hedonic tone; TA, tense arousal.

pared with during euglycemia, but this difference was not significant. The time-per-target score, which is the ratio of the number of circled symbols divided by the time taken for the task, was significantly higher during acute hyperglycemia.

Mood

The results of the mood questionnaire are shown in Fig. 1. Hedonic Tone and Energetic Arousal scores were significantly lower during hyperglycemia (decreased happiness and alertness), whereas feelings of Tense Arousal were greater (increased agitation).

CONCLUSIONS

— The present study demonstrated that acute hyperglycemia in people with type 2 diabetes significantly impaired speed of information processing, working memory, and some aspects of attention. It also had a profound detrimental effect on key mood states.

It was apparent from the results of the present study that performance was impaired during acute hyperglycemia in tests that required a speedy response, suggesting that accuracy was preserved at the expense of speed. For example, in the Map Search, a test of visual selective attention, significantly fewer symbols were identified after 1 min during hyperglycemia when compared with euglycemia. However, in the overall 2-min score no significant difference was observed, which indicates that a "ceiling effect" is reached after 2 min. In the Telephone Search test and the Telephone Search While Counting test, no significant difference could be discerned in the total number of symbols located during either study condition, but the time taken to complete these tests was significantly longer during hyperglycemia. In the Visual Elevator task no significant difference in the raw score was observed during hyperglycemia compared with euglycemia, but the time taken to complete each switch was significantly greater during hyperglycemia.

The cognitive domains that were

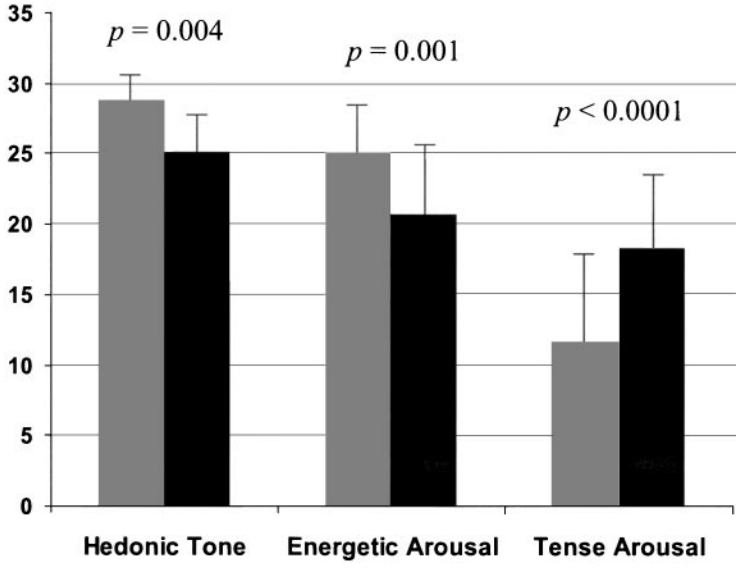

Figure 1—*Graph showing mean (±SD) scores of the UWIST mood adjective checklist during euglycemia (▨) and hyperglycemia (■).*

most adversely affected by hyperglycemia in people with type 2 diabetes were information processing speed and working memory. Performance in three of the four processing speed tests was significantly impaired during hyperglycemia. In the memory domain, the only two tests affected were of working memory; acute hyperglycemia did not have a significant detrimental effect on tests of immediate and delayed memory. This suggestion is supported by the "attention" results, which also demonstrated a reduction in speed of information processing (rather than accuracy), and this was particularly apparent in tests of attention that made demands on working memory, e.g., visual elevator switch time, which requires storage and manipulation of information.

In addition to the specific cognitive demands of the tasks affected by hyperglycemia, impairment of performance in these tests may reflect their relative complexity. Davis et al. (5) demonstrated that in children with type 1 diabetes cognitive function was impaired during acute hyperglycemia but that this was limited to complex tests of cognitive ability. In the present study, performance in relatively simple tests of information processing (Simple Reaction Time), memory (tests of immediate and delayed verbal and visual memory, Digit Span Forwards), and attention (Lottery and Elevator Counting) was not affected by acute hyperglycemia. However, during acute hyperglycemia a significant decrement in performance was observed in comparatively more difficult tasks, such as the Four-Choice Reaction Time test, Digit Span Backwards, Letter/Number Sequencing, and Elevator Counting with Reversal.

Mood was also adversely affected by acute hyperglycemia. The changes in mood included increased feelings of agitation and anxiety (increased tense arousal), increased feelings of tiredness and lethargy (decreased energetic arousal), and decreased feelings of happiness (decreased hedonic tone). Further analysis of the cognitive function test results with mood as a covariate demonstrated that the impairment in cognitive function occurred independently of changes in mood state.

The results of the present study indicate that acute hyperglycemia has a significantly adverse effect on various aspects of cognitive function and mood. However, with the exception of the Four-Choice Reaction Time test, the Eta^2 values for the tests of cognitive function were modest. The study had 80% power to detect an effect size of $\delta^2 = 0.21$. Therefore, we were not able to detect small effect sizes. However, at that level, they might not be of great practical significance. The number of subjects included in the study is large by comparison with most glucose clamp studies. Apart from giving more confidence in the results, this was also done because of the relatively large numbers of cognitive outcomes, which were included because they have been found to be sensitive to the effects of hypoglycemia. These obviously carry the possibility of type I errors, and it will be useful to carry out a further study using a larger sample to try and replicate these findings. Nevertheless, it was important for this first, systematic study of the cognitive effects of hyperglycemia to include the main domains of cognitive function. The effects of acute hypoglycemia on cognitive function have been observed to return to normal within 90 min of the restoration of euglycemia (24,25). It is not known whether the effect of hyperglycemia on cognitive function or mood is sustained or protracted, and this will require further investigation.

Some indirect evidence suggests that hyperglycemia may have adverse affects on cerebral function. For example, acute hyperglycemia has been shown (26) to enhance cerebral damage resulting from ischemic stroke. There is also accumulating evidence to suggest that chronic hyperglycemia, as indicated by surrogate markers such as the presence of peripheral neuropathy or retinopathy, is involved in the pathogenesis of the cognitive impairment associated with diabetes (27–29).

The findings of the present study are in concordance with anecdotal reports from people with type 2 diabetes and are supported by the results of two recent studies. Cox et al. (30) have demonstrated changes in mood and impairment in cognitive function during acute hyperglycemia in people with type 1 and type 2 diabetes, and a study (31) in Canada has shown impairment of cognitive function in people with type 2 diabetes following oral ingestion of 50 g of carbohydrate. Taken together, these findings are of practical importance to people with type 2 diabetes in whom exposure to moderate and intermittent hyperglycemia is common. Working memory and processing speed are fundamental aspects of cognition in everyday life. The deleterious effects of hyperglycemia on cognitive function and mood states may significantly interfere with many activities of daily living and may influence therapeutic strategies aimed at treating postprandial hyperglycemia.

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