Improving Metabolic Control Leads to Better Working Memory in Adults With Type 2 Diabetes

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OBJECTIVE — The goals of this study were to determine whether improvements in metabolic control can ameliorate the cognitive dysfunction associated with type 2 diabetes and evaluate the possibility that such improvements are mediated by changes in circulating insulin or insulin resistance.

RESEARCH DESIGN AND METHODS — This randomized double-blind trial enrolled 145 subjects at 18 centers in the U.S. Older adults with type 2 diabetes receiving metformin monotherapy received add-on therapy with either rosiglitazone, a thiazolidinedione insulin sensitizer, or glyburide. Cognitive function was assessed at baseline and week 24 using the Digit Symbol Substitution Test, the Rey Auditory Verbal Learning Test, and the Cambridge Neuropsychological Test Automated Battery.

RESULTS — Pretreatment fasting plasma glucose (FPG) in both groups was similar, and after 24 weeks both treatment groups showed similar significant reductions in FPG (2.1–2.3 mmol/l). Working memory improved with both rosiglitazone ($P < 0.001$) and glyburide ($P = 0.017$). Improvement (25–31% reduction in errors) was most evident on the Paired Associates Learning Test and was significantly correlated ($r = 0.30$) with improved glycemic control as measured by FPG.

CONCLUSIONS — Similar and statistically significant cognitive improvement was observed with both rosiglitazone and glyburide therapy, and the magnitude of this effect was correlated with the degree to which FPG improved. These results suggest that a cognitive benefit is achievable with pharmacological interventions targeting glycemic control.

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Older adults with type 2 diabetes have an increased risk of cognitive dysfunction. Memory and mental processing speed are the cognitive domains most often compromised, whereas other cognitive skills (e.g., attention, problem-solving, and general intelligence) tend to be unaffected (1–3). Whether cognitive deterioration is a direct consequence of chronically elevated blood glucose levels or whether it reflects diabetes-associated hyperinsulinemia has not yet been determined, but increasing evidence suggests that elevated insulin levels may be associated with adverse effects on cognition (4–6) and an increased risk of Alzheimer's dementia (7).

If chronically elevated glucose and/or insulin levels are linked to poorer cognitive performance, one might predict that efforts to improve glycemic control or reduce hyperinsulinemia would ameliorate cognitive function or attenuate its decline. Results from three small studies provide only limited support for that possibility. Gradman et al. (8) treated 23 diabetic adults with glipizide for up to 7 months and found both a reduction in fasting plasma glucose (FPG) levels and marked improvement on a verbal learning test; other cognitive skills were unaffected. By comparison, no changes in either FPG or cognition were seen in an untreated group of 13 nondiabetic control subjects. Circumscribed improvements in cognition have also been reported in 16 diabetic adults over a 7-month period (9) and in two groups of 20 type 2 diabetes patients receiving either intensified inpatient treatment or "standard" treatment (10). None of these studies measured insulin, and so it is impossible to determine whether cognitive changes were associated with treatment-induced changes in insulin parameters.

Both the Diabetes Control and Complications Trial (11) and the U.K. Prospective Diabetes Study (12) demonstrated that improved metabolic control can prevent or reduce the severity of vascular complications. We initiated the following clinical trial to determine whether improving glycemic control would similarly ameliorate cognitive complications. One major goal was to evaluate the possibility that improvements in cognition are mediated by changes in circulating insulin or in insulin resistance. To that end, we compared the cognitive effects of treatment with two different classes of antidiabetes medications. Rosiglitazone is a thiazolidinedione insulin sensitizer that reduces glucose levels by increasing hepatic and peripheral tissue sensitivity to insulin (13), whereas, glyburide, a sulfonylurea, reduces glucose levels by enhancing insulin secretion from pancreatic β-cells (14). Little is known about the effects of glyburide on the brain, but recent reports suggest that glitazones may affect brain physiology (15,16). If improved cognition is largely a consequence of changes in insulin sensitivity or chronic hyperinsulinemia, those treated with rosiglitazone might be expected to perform significantly better than those treated with glyburide, regardless of changes in FPG.

RESEARCH DESIGN AND METHODS

— One hundred forty-five adults with type 2 diabetes were recruited

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Abbreviations: CANTAB, Cambridge Neuropsychological Test Automated Battery; FPG, fasting plasma glucose; HOMA, homeostasis model assessment; PAL, Paired Associates Learning.

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

from 18 centers in the U.S. Adults were eligible if they were receiving oral metformin combination therapy and had HbA_{1c} (A1C) ≤8%, BMI ≥27 kg/m^2, no evidence of dementia (score ≥27 on the Mini Mental State Examination [17]), and no evidence of current depression as determined by the Mini International Neuropsychiatric Interview (MINI) (18). Individuals with a history of hyperlipidemia or hypertension were required to have well-controlled diabetes after treatment for at least 8 weeks before randomization. Renal disease, alcoholism, stroke, unstable angina, a transient ischemic attack, congestive heart failure or any New York Heart Association class 3/4 coronary insufficiency, hepatic disease, lactic acidosis, a severe head injury, epilepsy, or other neurological disorder was exclusionary, as was treatment with psychotropic medications. Because several cognitive measures were available only in English, all subjects were required to be fluent in English.

Randomized controlled trial

During an 8-week screening period, patients received the same dose of metformin, but their second antidiabetes agent was discontinued. If, after 6 weeks of washout, FPG was >15 mmol/l, patients were excluded from further participation. After screening of 210 adults, eligible subjects were randomly assigned to receive 24 weeks of blinded add-on therapy with either rosiglitazone or glyburide. During the first 8 weeks of treatment, study medication was given as 4 mg rosiglitazone once daily or 2.5 mg glyburide once daily, with glyburide increased to 2.5 mg twice daily after 4 weeks of treatment. To titrate patients to equal glycemic control, FPG was assessed at weeks 8 and 16, and the dose was adjusted if FPG ≥7.8 mmol/l. Rosiglitazone could be increased to 8 mg once daily or 4 mg twice daily; glyburide could be increased to 5 mg twice daily or up to a maximal dose of 7.5 mg twice daily. No changes were made to the background dose of metformin during blinded treatment.

For random assignment to treatment, we used a computer-generated allocation sequence. Subjects were stratified to treatment group by age (≤60 or >60 years) and by premorbid intelligence, as measured by the North American Adult Reading Test, (i.e., score of ≤105 or >105) (19). This study was conducted in accordance with the Declaration of Helsinki and guidelines on good clinical practice. The institutional review board of each participating center approved the study protocol and the informed consent document. Written informed consent was obtained before the performance of any study procedures.

Outcome measures

Cognitive tests. The primary outcome was change in cognitive function after 24 weeks of treatment with rosiglitazone or glyburide. Cognitive tests were administered at week 0 and again at week 24 by staff blinded to subjects' treatment assignment. Testing occurred in the afternoon after lunch, provided that postprandial glucose was >5.6 and <16.7 mmol/l. Seven cognitive tests were performed: the Digit Symbol Substitution Test (20), the Rey Auditory Verbal Learning Test (21), and five tests selected from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (22,23). Two preassessment CANTAB tests were administered during screening to familiarize subjects with procedures. Those tests differed somewhat from the CANTAB tests administered in this study and were not scored. The CANTAB Paired Associates Learning (PAL) Test evaluated how efficiently subjects learned the locations of various geometric patterns presented on a computer screen. The difficulty level increased over multiple series (from six locations with three patterns up to eight locations with eight patterns). The CANTAB Pattern Recognition Memory measured subjects' ability to retain geometric designs by presenting 12 visual patterns followed by a forced-choice recognition test. The CANTAB Spatial Working Memory Test assessed how well subjects were able to keep track of the location of a token that was "hidden" in one of several boxes on the screen. CANTAB Reaction Time assessed how quickly subjects could respond when one of five circles illuminated on the screen. CANTAB Rapid Visual Information Processing measured sustained attention, freedom from distractibility, and psychomotor speed. Subjects saw single-digit numbers flash serially on the computer screen; their task was to press a paddle every time one of several specific sequences appeared. The Digit Symbol Substitution Test (20) measured psychomotor speed and required subjects to substitute numbers for symbols according to a preestablished code. The Rey Auditory Verbal Learning Test (21) assessed learning ability by presenting 15 words to subjects and asking them to recall the list; 5 such study-test trials were provided and the total recalled comprised the Rey Total Learning Score. The Rey Forgetting Score was the difference between the number recalled on trial 5 and the number recalled after a 20-min delay.

Parallel versions of all tests except the Digit Symbol Substitution Test, the CANTAB Spatial Working Memory Test, and CANTAB Rapid Visual Information Processing (which do not have parallel versions) were given at week 24.

Measures of psychological distress

The Brief Symptom Inventory comprises 53 symptoms of somatic and psychological distress that subjects rated on a 5-point scale (24); it yields nine symptom scales and a Global Severity Index. The Mini-International Neuropsychiatric Interview (18) is a short, structured psychiatric interview that screens for diagnosable psychiatric disorders and classifies disorders according to the DSM-IV and ICD-10 nosology. Both measures were administered before randomization and repeated at week 24.

Laboratory measures

Laboratory assessments were performed by Quest Diagnostic Laboratories (Van Nuys, CA) on blood samples collected in the fasting state. FPG concentrations were measured by an Olympus analyzer using an enzymatic method based upon the catalytic action of hexokinase on glucose and ATP to yield glucose 6-phosphate (Olympus Clinical Instruments Division, Lake Success, NY), AIC levels were measured by high-performance liquid chromatography (Variant Method; Bio-Rad, Hercules, CA), and serum insulin was measured by a double-antibody radioimmunoassay (Linco Method; Linco, St. Charles, MO). Safety monitoring included physical examinations, assessment of vital signs, weight, adverse events, and laboratory tests. Severe hypoglycemia was defined as episodes requiring third-party assistance to effect recovery.

Statistical analysis

The intent-to-treat population consisted of all randomized subjects with at least one valid observation for an efficacy variable while receiving treatment. All analy-

ses used the last observation carried forward for imputing on-therapy missing values from other on-therapy values. Of the 145 patients initially randomized, three were withdrawn before the first on-therapy visit and did not have a valid on-therapy assessment and one withdrew before taking blinded medication, yielding an intent-to-treat population of 141. All randomized subjects were studied for assessment of safety and tolerability. A significance level of 0.05 was used for all between-group comparisons. No adjustments were made for multiple comparisons because of the exploratory nature of this study.

For continuous variables, ANCOVA was used with a model that included effects for treatment, clinical center, baseline measurement, estimated IQ strata, and age strata. Treatment by covariate interactions were also explored. Differences between treatment groups with respect to change between baseline and week 24 were estimated by the least-squares mean difference from the ANCOVA model. Homeostasis model assessment (HOMA) of insulin sensitivity (%S) was based on FPG and insulin values (25). The signed rank-sum test and the Wilcoxon rank-sum test were used to compare week 24 values to baseline values within and between treatment groups, respectively. Linear relationships between cognitive tests and glycemic parameters were investigated post hoc for each treatment group using Pearson's correlation coefficients.

Sequential factor analysis with varimax orthogonal rotation was used to categorize the eight cognitive test variables into a more manageable number of cognitive domains before unblinding. Only subjects with cognitive test results for both baseline and week 24 assessments were included in subsequent analyses. Summary scores for the resulting cognitive domains were computed by summing the *z*-scores for the tests that contributed to that domain.

RESULTS — The sample was predominantly Caucasian (79%), with a mean age of 60 years (range 43–75), a diabetes duration of 6.6 years (1–27), and an estimated IQ in the average range (mean 106). Table 1 shows both treatment groups at baseline to be matched on BMI, AIC, FPG, hypertension, hyperlipidemia, and prior severe hypoglycemia. The mean final daily dose for subjects treated with rosiglitazone was 6.1 mg; for those treated with glyburide it was 8.1 mg.

Table 1—*Patient demographics and baseline characteristics*

	Rosiglitazone	Glyburide
n	69	72
Age (years)	60.7 ± 1.0	59.6 ± 0.8
Female sex (%)	43	36
Caucasian (%)	80	79
BMI (kg/m^2)	33.8 ± 0.7	32.5 ± 0.06
FPG (mmol/l)	9.9 ± 0.4	9.7 ± 0.3
A1C (%)	7.6 ± 0.1	7.6 ± 0.1
Fasting insulin (pmol/l)*	142.6 ± 8.4	134.8 ± 9.5
C-peptide (nmol/l)*	1.14 ± 0.06	1.02 ± 0.06
Diabetes duration (years)	6.6 ± 0.6	6.6 ± 0.6
Hypertension (%)	62	69
Hyperlipidemia (%)	54	58
Severe hypoglycemia (%)	5	5
Estimated IQ	105.5 ± 1.1	106.6 ± 1.0

Data are means ± SE unless otherwise noted. *Rosiglitazone (n = 58); glyburide (n = 64).

Treatment-induced changes in glycemic variables

After 24 weeks of treatment, both groups showed similar, statistically significant ($P < 0.0001$) reductions in FPG. For subjects receiving metformin and rosiglitazone, FPG declined ~21%, from 9.88 ± 0.37 to 7.77 ± 0.24 mmol/l ([95% CI −2.73 to −1.52]; $P < 0.0001$); for those receiving metformin and glyburide, FPG declined ~24%, from 9.66 ± 0.31 to 7.33 ± 0.21 ([−2.88 to −1.73]; $P < 0.0001$). The magnitude of decline was comparable in the two treatment groups. Similar proportions of subjects treated with rosiglitazone (59%) and glyburide (61%) achieved the glycemic titration target of FPG <7.77 mmol/l.

Consistent with its mechanism of action as an insulin sensitizer, significant reductions ($P < 0.05$) from baseline in both fasting insulin (−17.81 ± 8.1 pmol/l [95% CI −34.11 to −1.52]) and C-peptide (−0.12 ± 0.05 nmol/l [−0.22 to −0.02]) were seen only in participants treated with rosiglitazone for 24 weeks. Significant increases ($P < 0.05$) from baseline were observed for both insulin (22.87 ± 9.9 pmol/l [3.11–42.63]) and C-peptide (0.10 ± 0.05 nmol/l [0.01–0.20]) in those treated with glyburide. HOMA %S improved (median change 8.6% [5.2–12.4]; $P < 0.0001$) for rosiglitazone, but not for glyburide (1.0% [−2.2 to 4.9]); between-group differences were statistically significant ($P < 0.01$).

Treatment-induced changes within cognitive domains

Sequential factor analysis generated three factors. Factor 1 was designated "Working Memory" (27.5% of variance) and comprised the CANTAB PAL Test, CANTAB Rapid Visual Information Processing, CANTAB Spatial Working Memory Test, and Digit Symbol Substitution Test. Factor 2, "Learning Ability" (17.4% of variance), included the Rey Total Learning Score and CANTAB Pattern Recognition Memory. Factor 3, "Cognitive Efficiency" (14.3% of variance), included the Rey Forgetting Score and CANTAB Reaction Time.

Significant improvement on Working Memory measures was noted from baseline to week 24 in both the rosiglitazone (−0.7 ± 1.6 [95% CI −1.0 to −0.1]; $P < 0.001$) and the glyburide treatment groups (−0.6 ± 1.9 [−1.0 to −0.1]; $P < 0.02$), as indexed by a reduction in errors, but there was no difference between rosiglitazone and glyburide in terms of their effects on Working Memory ([−0.4 to 0.4]; $P > 0.40$). No significant changes at week 24 were noted either on measures of Learning Ability (0.1 ± 1.5 [−0.3 to 0.4]; 0.1 ± 1.7 [−0.2 to 0.6]) for groups treated with rosiglitazone or glyburide, respectively, or on measures of Cognitive Efficiency (−0.1 ± 1.7 [−0.5 to 0.3]; 0.0 ± 1.5 [−0.3 to 0.4]).

Treatment-induced effects on individual cognitive and mood tasks

Within the Working Memory domain, performance after treatment changed significantly on only one of the four tests

Table 2—*Cognitive test scores: baseline and change from baseline*

Cognitive test	Rosiglitazone	Glyburide	Treatment difference (95% CI)*
n	66	70	
PAL†			
Baseline‡	33.1 ± 2.3	28.8 ± 2.1	
Change from baseline	−10.2 ± 1.8	−7.1 ± 1.8	0.36 (−2.3 to 6.2)
P value	<0.0001	<0.001	
Pattern Recognition Memory: delayed§		66	70
Baseline	9.7 ± 0.2	9.8 ± 0.2	
Change from baseline	−0.2 ± 0.3	−0.0 ± 0.3	0.20 (−0.4 to 0.8)
P value	0.548	>0.999	
Spatial Working Memory§		66	70
Baseline	37.2 ± 2.0	32.9 ± 2.3	
Change from baseline	1.0 ± 1.9	0.6 ± 1.9	0.27 (−7.3 to 2.1)
P value	0.606	0.764	
Rapid Visual Information Processing‖		66	70
Baseline	524.7 ± 14.8	503.2 ± 11.7	
Change from baseline	−15.4 ± 12.2	−3.7 ± 11.6	0.85 (−28.9 to 24.1)
P value	0.211	0.750	
Reaction Time‖		66	70
Baseline	397.7 ± 8.3	409.5 ± 7.4	
Change from baseline	13.0 ± 8.7	3.7 ± 6.1	0.95 (−20.1 to 18.7)
P value	0.138	0.540	
Digit Symbol Substitution Test§		67	70
Baseline	43.4 ± 1.3	43.0 ± 1.5	
Change from baseline	0.3 ± 0.9	1.7 ± 0.9	0.13 (−0.5 to 3.9)
P value	0.768	0.078	
Rey Auditory Verbal Learning Test: immediate§		67	69
Baseline	47.7 ± 1.0	49.6 ± 1.0	
Change from baseline	1.4 ± 0.8	1.6 ± 1.0	0.80 (−2.0 to 2.6)
P value	0.094	0.104	
Rey Auditory Verbal Learning Test: delayed¶		67	69
Baseline	1.9 ± 0.3	2.0 ± 0.3	
Change from baseline	0.1 ± 0.4	0.2 ± 0.3	0.78 (−0.6 to 0.8)
P value	0.708	0.565	

Data are *n* or means ± SD. *Based on ANCOVA model: change = age strata + North American Adult Reading Test strata + baseline + treatment + center. †Number of errors. ‡*P* value for treatment by baseline interaction = 0.6195. §Total correct. ‖Time (milliseconds). ¶Forgetting score (trial 5 − delayed recall).

comprising that domain. Subjects treated with rosiglitazone improved their performance on the CANTAB PAL Test by ~30%, making an average of 10.2 ± 1.8 fewer errors (95% CI −13.7 to −6.6; $P <$ 0.0001). Treatment with glyburide was similarly associated with an improvement of ~25%, with subjects making an average of 7.1 ± 1.8 fewer errors (−10.6 to −3.6; $P < 0.001$). For rosiglitazone, the effect size (*d*) (26) for change was −0.69 ± 0.02 (95% CI −1.04 to −0.34); for glyburide, $d = -0.48 \pm 0.02$ (−0.81 to −0.14). The difference between the two treatment groups was not statistically significant ($P > 0.30$). As illustrated in Table 2, no changes in performance over time were evident on any other cognitive test.

Treatment was not associated with onset of current depressive disorders as measured by the Mini International Neuropsychiatric Interview at week 24 for subjects treated with rosiglitazone (3%) or glyburide (1.4%). Similarly, rates of psychological distress, as measured by the Global Severity Index from the Brief Symptom Inventory, were comparable between the two treatment groups (24.6 vs. 23.6%) and did not change over time.

Associations among glucose, insulin, and working memory

Treatment-associated changes in FPG were associated with improvements in Working Memory performance regardless of drug used. There was a strong correlation between decline in FPG and reduction in PAL errors ($r = 0.30$; $P <$ 0.02) for both rosiglitazone and glyburide. In contrast, there was no significant correlation between PAL performance and changes in circulating insulin. For subjects treated with rosiglitazone, the correlation between change in HOMA %S and PAL errors was −0.15 ($P > 0.40$); for glyburide treatment, the correlation coefficient was 0.03 ($P > 0.70$).

CONCLUSIONS — Results from this randomized trial demonstrate that treatment-induced reductions in FPG levels are accompanied by corresponding improvements in cognition, which occur within 24 weeks of therapy initiation. The effect sizes observed were moderate, and further study will be required to determine their clinical relevance. As expected, treatment with rosiglitazone but not glyburide was associated with significant im-

provements in circulating insulin and insulin sensitivity. Contrary to our hypothesis, however, changes in insulin parameters had no impact on cognitive function, at least in this group of diabetic adults with better-than-average metabolic control.

Our study shows that working memory is uniquely sensitive to glycemic manipulations, with this effect being most evident on a single cognitive test: the CANTAB PAL Test. What is it about this task that renders it so sensitive to changes in FPG? Of all our tests, the CANTAB PAL Test is the most cognitively demanding insofar as it requires subjects to pay attention to (and discriminate among) different patterns and different locations as well as to use strategies to form associations between a specific pattern and a specific location and to hold as many as eight of these pattern/location associations in memory during a study-test trial. Optimal performance on this task relies on the integrity of a wide range of interconnected brain areas, including the prefrontal cortex, mesial temporal cortex (with hippocampus), parietal cortex, posterior cortical visual areas, and basal ganglia (27,28), whereas other CANTAB tests activate fewer brain areas (28).

Working memory tests are known to activate structures in the parietal and temporal lobes and in the prefrontal cortex of humans (29) and to increase cerebral glucose utilization in multiple brain regions. For example, primates performing spatial working memory tasks manifest a large (33–43%) increase in local cerebral glucose utilization in the caudate nucleus (30)—a brain region that receives a rich network of efferents from the dorsolateral prefrontal cortex as well as from the parietal and temporal cortical regions. Increased cerebral glucose utilization has also been reported in the prefrontal (19%) and inferior parietal cortex (11–20%) (31), as well as in the hippocampus (18–24% increase) (32). Similar increases in hippocampal glucose utilization have also been inferred from studies measuring extracellular glucose levels in rats performing a cognitively demanding spatial maze (33). If a task such as the CANTAB PAL Test is dependent on multiple cortical structures that, when activated, require high levels of glucose for optimum performance, we would expect that any condition that affects brain glucose could have a measurable effect on test performance.

Variations in peripheral glucose levels are now thought to induce changes in the availability and metabolism of glucose in the brain, although there is not complete agreement over the details of these processes. Cerebral blood flow may decrease during chronic hyperglycemia in humans with type 2 diabetes (34), brain glucose metabolism may be reduced after chronic hyperglycemia (35), and the density of glucose transporters at the blood-brain barrier may be down- or upregulated in response to increases or decreases in peripheral glucose levels (36,37). If diabetic patients ordinarily experience chronically elevated blood glucose levels, and if this adversely affects the availability and/or utilization of glucose within the brain, then individuals with poorer metabolic control might have more difficulty performing cognitively demanding tasks, particularly those, like working memory tasks, which engage multiple cortical regions. It is plausible that improvements (i.e., reductions) in peripheral blood glucose levels may lead to a corresponding increase in brain glucose availability as well as relative improvements in performance on certain cognitive tasks (38). This possibility is congruent with recent animal research demonstrating that lowering blood glucose levels (i.e., inducing hypoglycemia) can subsequently facilitate performance during euglycemia on hippocampal-mediated spatial memory tasks (39). It is also consistent with our finding of a robust correlation between the magnitude of a treatment-induced change in plasma glucose and a reduction in number of errors on the CANTAB PAL Test.

According to our interpretation, improved performance should not occur on all cognitive measures but should be limited only to those that engage cortical systems that have particularly high glucose metabolism requirements (e.g., the hippocampus, basal ganglia, and prefrontal cortex). Our findings support that view, as do results from Gradman et al. (8) who found only the cognitively demanding selective reminding test to be affected by improvements in FPG. The learning skills of older adults with poorer glucoregulation (40) or with type 2 diabetes (3) may be particularly influenced by these glycemic variations (41) because of the known changes in the integrity of hippocampal and prefrontal brain regions associated with both normal aging (42,43) and with diabetes (44).

Insulin affects the central nervous system (45) and could potentially modulate a range of cognitive functions. Insulin receptors are widely distributed within the brain (46), particularly in the hippocampus, and insulin crosses the blood-brain barrier via a receptor-mediated active transport process (47). Animal studies have demonstrated that central insulin administration leads to improvements on spatial memory tasks (48) and can ameliorate the memory deficits associated with streptozotocin-induced diabetes (49). Research with nondiabetic humans has demonstrated that intranasally administered insulin may improve performance on measures of verbal memory (50). Nevertheless, despite increasing evidence of possible linkages between insulin and cognition (51), we found no evidence that treatment-induced differences in circulating insulin or insulin sensitivity were associated with a corresponding improvement in cognition.

Our study has a number of limitations. Because diabetic subjects were not compared with nondiabetic adults, we cannot determine the extent of cognitive impairment in our diabetic sample. Our finding of moderate improvements may be a consequence of having evaluated individuals with modest cognitive deficits who had few comorbid conditions and were in relatively good metabolic control at study entry. More substantial improvements in cognitive function might have been observed had we studied subjects with greater cognitive impairment. The absence of nondiabetic control subjects also precludes a determination of "practice effects" that could occur after repeated testing. Our use of alternate test forms for the memory tests (in which practice effects are most likely to occur) as well as our 24-week test/retest interval is liable to have reduced the likelihood that familiarity with the testing materials contributed to our pattern of results. The fact that only a subset of tests showed any improvement and the magnitude of that improvement was correlated with the treatment-associated reduction in FPG leads us to conclude that our results are not an artifact of repeated testing.

In summary, we found that treatment-induced improvements in FPG are associated with a corresponding improvement on a cognitively demanding test of working memory after only 24 weeks of therapy. The underlying mechanisms remain poorly understood, and further study is required to determine not only whether these benefits are maintained over an extended period of time but also whether adults with more severe cogni-

tive impairment would show greater improvement in performance with treatment.

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