

Rosiglitazone and Cognitive Stability in Older Individuals With Type 2 Diabetes and Mild Cognitive Impairment

ANGELA M. ABBATECOLA, MD, PHD¹
 FABRIZIA LATTANZIO, MD, PHD¹
 ANNA M. MOLINARI, MD²
 MICHELE CIOFFI, MD²
 LUIGI MANSI, MD³

PIERFRANCESCO RAMBALDI, MD³
 LUIGI DICIOCCIO, MD⁴
 FEDERICO CACCIAPUOTI, MD⁵
 RAFFAELE CANONICO, MD⁵
 GIUSEPPE PAOLISSO, MD⁵

OBJECTIVE— Studies have suggested that insulin resistance plays a role in cognitive impairment in individuals with type 2 diabetes. We aimed to determine whether an improvement in insulin resistance could explain cognitive performance variations over 36 weeks in older individuals with mild cognitive impairment (MCI) and type 2 diabetes.

RESEARCH DESIGN AND METHODS— A total of 97 older individuals (mean \pm SD age 76 ± 6 years) who had recently (<2 months) started an antidiabetes treatment of metformin (500 mg twice a day) ($n = 30$) or metformin (500 mg/day)+rosiglitazone (4 mg/day) ($n = 32$) or diet ($n = 35$) volunteered. The neuropsychological test battery consisted of the Mini-Mental State Examination (MMSE), Rey Verbal Auditory Learning Test (RAVLT) total recall, and Trail Making Tests (TMT-A and TMT-B) performed at baseline and every 12 weeks for 36 weeks along with clinical testing.

RESULTS— At baseline, no significant differences were found between groups in clinical or neuropsychological parameters. Mean \pm SD values in the entire population were as follows: A1C $7.5 \pm 0.5\%$, fasting plasma glucose (FPG) 8.6 ± 1.3 mmol/l, fasting plasma insulin (FPI) 148 ± 74 pmol/l, MMSE 24.9 ± 2.4 , TMT-A 61.6 ± 42.0 , TMT-B 162.8 ± 78.7 , the difference between TMT-B and TMT-A [DIFFBA] 101.2 ± 58.1 , and RAVLT 24.3 ± 2.1 . At follow-up, ANOVA models tested changes in metabolic control parameters (FPI, FPG, and A1C). Such parameters improved in the metformin and metformin/rosiglitazone groups ($P_{\text{trend}} < 0.05$ in both groups). ANCOVA repeated models showed that results for the metformin/rosiglitazone group remained stable for all neuropsychological tests, and results for the diet group remained stable for the MMSE and TMT-A and declined for the TMT-B ($P_{\text{trend}} = 0.024$), executive efficiency (DIFFBA) ($P_{\text{trend}} = 0.026$), and RAVLT memory test ($P_{\text{trend}} = 0.011$). Results for the metformin group remained stable for the MMSE and TMTs but declined for the RAVLT ($P_{\text{trend}} = 0.011$). With use of linear mixed-effects models, the interaction term, FPI \times time, correlated with cognitive stability on the RAVLT in the metformin/rosiglitazone group ($\beta = -1.899$; $P = 0.009$).

CONCLUSIONS— Rosiglitazone may protect against cognitive decline in older individuals with type 2 diabetes and MCI.

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Older individuals with type 2 diabetes have a significantly higher risk of cognitive decline, especially mild cognitive impairment (MCI) and dementia (1–3). The mechanisms explaining the association between type 2 diabetes and cognitive decline are still under investigation. It has been shown that individuals

with type 2 diabetes who do not maintain optimal glycemic control (i.e., occurrences of hyperglycemic fluctuations) are more likely to start manifesting deficits in memory and mental processing speed functions (4). Interestingly, a decline in hyperglycemic levels has been associated with an improvement in cognitive function in older individuals with type 2 diabetes (4). Plasma glucose fluctuations are also considered to be responsible for a rise in reactive oxygen species (5), and a pro-oxidative effect of postprandial hyperglycemia may actively contribute to inappropriate regulation of vascular tone, leading to cognitive deficits (6). Alterations in the insulin signaling pathway have also been suggested as possible contributors to cognitive dysfunction, especially memory (7). Insulin receptors are selectively found in the hippocampus, and insulin modulates levels of important neurotransmitters involved in activating cognitive functions (7–9). Insulin resistance has been shown to be an independent determinant of lower cognitive performance in older individuals (10). Furthermore, impaired insulin response during midlife is associated with an increase risk of Alzheimer disease up to 35 years later (11). These findings strongly suggest that abnormal insulin action has deleterious effects on cognition.

A decline in insulin resistance may be beneficial to cognition in older individuals with normal glucose tolerance (NGT) and MCI or Alzheimer disease (12). In particular, short-term treatment with rosiglitazone was associated with an improvement in delayed memory and selective attention tests in older individuals with NGT and MCI or early Alzheimer disease (12). However, whether a rosiglitazone-mediated decline in insulin resistance could be advantageous for cognitive function in older individuals with both type 2 diabetes and MCI is unknown. Considering that such individuals have an extremely high risk of cognitive decline, an improvement in insulin resistance may have a protective impact. To test this hypothesis, we performed neuropsychological tests at timely intervals in a group of

From the ¹Italian National Research Center on Aging, Ancona, Italy; the ²Department of General Pathology, Second University of Naples, Naples, Italy; the ³Nuclear Medicine Division, Second University of Naples, Naples, Italy; the ⁴Department of Geriatric Medicine, "Santa Scolastica" Hospital, Cassino, Italy; and the ⁵Department of Geriatric Medicine and Metabolic Diseases, Second University of Naples, Naples, Italy.

Corresponding author: Giuseppe Paolisso, giuseppe.paolisso@unina2.it.

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The Second University of Naples retained access to all study data, and the sponsor did not participate in the study.

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older individuals with type 2 diabetes in poor metabolic control and MCI who had recently started an add-on antidiabetes agent, either metformin or rosiglitazone, to metformin monotherapy that was inadequate for control. We also included individuals who had recently begun a personalized diet program and had not previously used oral antidiabetes agents.

RESEARCH DESIGN AND METHODS

Ninety-seven older individuals (mean \pm SD age 76 ± 6 years) were selected from a group of ~ 200 individuals with type 2 diabetes in poor metabolic control and MCI. We included individuals who had recently (< 2 months) began a personalized diet program or had added to their metformin-based treatment of 500 mg/day an additional dose of 500 mg/day metformin or an additional dose of 500 mg metformin plus 4 mg/day rosiglitazone (Fig. 1). Physicians from our university outpatient offices were asked to refer older individuals with such conditions to our division for further selection. At the screening examination, participants underwent instrumental and clinical examinations to exclude the presence of severe macro- and microangiopathy (13), coronary heart disease, heart failure, severe hypertension (13), cancer, chronic obstructive pulmonary disease, upper limb paresis or paralysis, severe depression (14), and/or dementia. Neuropsychological testing was performed in those individuals with memory impairment at the screening visit to test for MCI (Fig. 1). The diagnosis of MCI was achieved according to published criteria (15) as follows: memory complaint referred by the subject and/or a family member; cognitive impairment in ≥ 1 domains (executive function, memory, language, or visuospatial); normal functional activities; and not having dementia. Our study sample consisted of 97 older individuals with type 2 diabetes and MCI undergoing antidiabetes treatment as follows: metformin (500 mg twice a day) (MF group) ($n = 30$); metformin (500 mg/day)+rosiglitazone (4 mg/day) (MF/Rosi group) ($n = 32$); and personalized diet (D group) ($n = 35$). Data collection started in February 2006 and was completed in October 2008. All subjects gave their informed consent before participating in the study, which was approved by the ethics committee of our institution.

Each participant underwent an in-person interview to assess general health

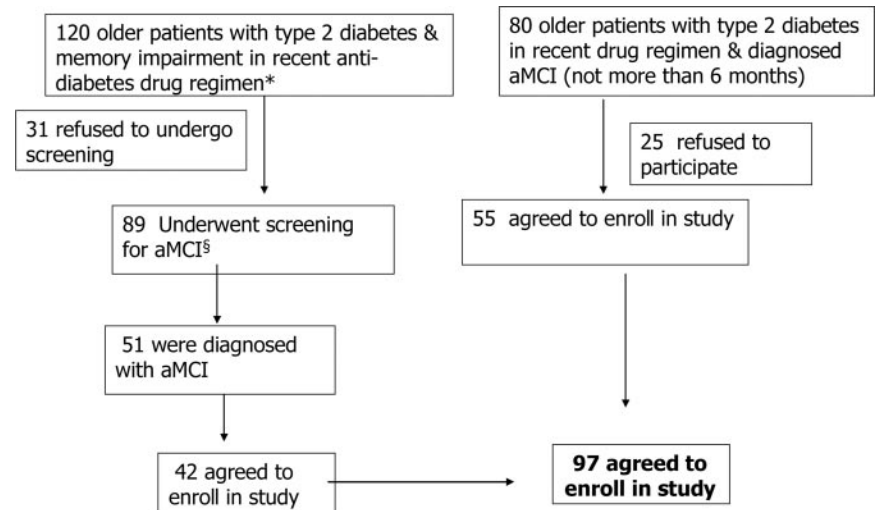


Figure 1—Patient recruitment flow diagram. *Oral antidiabetes drug initiated within the last 2 months. §According to data of Petersen (2004) (15). aMCI, amnesic MCI.

and function 3 weeks before beginning the protocol. The study protocol consisted of timely follow-up visits ($n = 4$) every 12 weeks for 36 weeks, which included a complete physical examination (including information on adherence to their oral antidiabetes or diet program), laboratory assessments, neuropsychological testing, and an electrocardiogram. At baseline and at the last follow-up visit, an echocardiogram and a cardiac stress test with a heart scan were performed.

Baseline blood pressure was recorded with a standard mercury sphygmomanometer on three occasions separated by intervals of 2 min and the average of the last two measures was used in the analysis. BMI was calculated as weight in kilograms divided by the square of height in meters. Habitual physical activity was assessed using a modified version of the European Prospective Investigation into Cancer and Nutrition (EPIC) physical activity questionnaire (16) and represented the physical activity covariate in statistical models.

Laboratory analysis

Fasting plasma insulin (FPI) was determined by a commercial double-antibody, solid-phase radioimmunoassay (intra-assay coefficient of variation $3.1 \pm 0.3\%$; cross-reactivity vs. proinsulin = 0.9% ; Sorin Biomedica, Milan Italy). Serum glucose (fasting plasma glucose [FPG]), A1C, serum lipid, and serum lipoprotein were quantified from fresh samples drawn after participants had been fasting for at least 12 h. Stable A1C levels were determined in triplicate on ion-exchange microcol-

umns at constant 18°C . Commercial enzymatic tests were used for serum total and HDL cholesterol and triglyceride determinations (Roche Diagnostics, Mannheim, Germany). Serum LDL cholesterol was calculated by the Friedewald formula.

Neuropsychological assessment

The Mini Mental State Examination (MMSE), Rey Auditory-Verbal Learning Test (RAVLT), Trail Making Test A (TMT-A), and Trail Making Test B (TMT-B) were used. All cognitive evaluations were made by physicians who were unaware of the study design.

The MMSE was assessed for global cognitive function (17) and covers many cognitive skills with scores ranging from 0 to 30. The Trail Making Test is a visuo-motor speeded task that consists of two parts: TMT-A and TMT-B. TMT-A, a visual scanning test, requires one to draw a line connecting consecutive numbers from 1 to 25. TMT-B adds cognitive flexibility to TMT-A and requires one to draw a line connecting numbers and letters in alternating sequence (17). The score is given by the amount of time in seconds to complete the task (17). Although time to completion scores are typically used to examine aspects of attention and executive function (17), the difference between the two scores, TMT-B minus TMT-A (DIFFBA), provides a measure of cognitive efficiency (18). The RAVLT was used to measure immediate memory span (11). The sum of the five presentations of the immediate recall of a 15-word list was used in analyses. Depression was evalu-

ated using the Geriatric Depression Scale (14).

Echocardiographic assessment

All participants underwent two-dimensional echocardiography at baseline and at the 36th week of follow-up using echocardiographs with M-mode, two-dimensional, and pulsed, continuous-wave with color-flow Doppler capabilities.

Cardiac stress test with heart scan

Scintigraphic acquisition was made at rest and during exercise. Stress consisted of supine dynamic exercise on a bicycle ergometer, beginning with 25 W at 60 rpm and increasing by 25-W steps over 2 min until reaching the 75-W load. This work was maintained for 4 min for the stress scintigraphic scan. During exercise, electrocardiogram standard recordings were taken every 2 min. For radionuclide angiography, erythrocytes were labeled "in vivo" with 25 mCi of ^{99m}Tc-pertechnetate. The studies were performed with a small field of view gamma camera (Basi-CAM; Siemens, Erlangen, Germany) equipped with a low-energy, general purpose, parallel hole collimator. Energy discrimination was provided by a 20% window centered over the 140-keV photopeak of ^{99m}Tc. Angioscintigraphic parameters were evaluated at rest and at 75 W.

Statistical analyses

Statistical analyses were performed using SPSS (version 15.0; SPSS, Chicago, IL). All data are presented as means \pm SD. To approximate normal distributions, log-transformed values for plasma triglyceride and insulin were used in statistical analyses and back-transformed for data presentation. ANOVA was used to evaluate the differences in clinical and metabolic characteristics according to the antidiabetes group. FPG, FPI, and A1C were evaluated over time using ANOVA within and between groups. Partial correlations investigated the relationship between two variables independently of covariates. A repeated-measures ANCOVA was created to determine the change in cognitive performance within each group over time after adjustment for cofounders such as age, sex, years of education, BMI, diabetes duration, systolic blood pressure physical activity, depression, A1C, FPG, and triglycerides. Partial correlations were performed at baseline in the whole study group among cognitive

Table 1—Baseline clinical characteristics according to antidiabetes group

	All	D group	MF group	MF/Rosi group
<i>n</i>	97	35	30	32
Age (years)	76 \pm 6	77 \pm 6	75 \pm 6	76 \pm 6
Sex (male/female)	53/44	18/17	17/13	18/14
Diabetes (years)	5.7 \pm 3.3	5.2 \pm 3.3	5.6 \pm 2.9	6.1 \pm 3.7
BMI (kg/m ²)	27.7 \pm 3.5	28.3 \pm 3.9	27.3 \pm 3.4	27.4 \pm 3.0
Waist-to-hip ratio	0.89 \pm 0.8	0.90 \pm 0.8	0.89 \pm 0.8	0.91 \pm 0.8
FPG (mmol/l)	8.44 \pm 1.11	8.44 \pm 1.22	8.28 \pm 0.94	8.5 \pm 0.89
FPI (pmol/l)	148 \pm 74	150 \pm 75	149 \pm 73	147 \pm 13
A1C (%)	7.5 \pm 0.5	7.5 \pm 0.4	7.4 \pm 0.6	7.5 \pm 0.4
Cholesterol (mmol/l)	5.68 \pm 0.83	5.71 \pm 0.75	5.68 \pm 0.85	5.63 \pm 0.93
LDL (mmol/l)	3.46 \pm 0.85	3.49 \pm 0.80	3.51 \pm 0.85	3.39 \pm 0.93
HDL (mmol/l)	1.01 \pm 0.28	1.03 \pm 0.31	1.01 \pm 0.28	0.98 \pm 0.26
Triglycerides (mmol/l)	2.55 \pm 0.58	2.56 \pm 0.7	2.48 \pm 0.56	2.60 \pm 0.45
Systolic blood pressure (mmHg)	150 \pm 21	150 \pm 19	147 \pm 18	153 \pm 24
Diastolic blood pressure (mmHg)	85 \pm 7	85 \pm 7	85 \pm 7	84 \pm 7
Ejection fraction (%)	52.7 \pm 2.9	53.9 \pm 2.5	52.4 \pm 2.2	51.7 \pm 3.2
Physical activity*	2.8 \pm 1.0	2.8 \pm 1.0	2.7 \pm 1.1	2.8 \pm 1.0
MMSE	24.0 \pm 2.5	22.9 \pm 2.1	24.1 \pm 2.3	24.0 \pm 3.0
TMT-A (s)	67.6 \pm 42.6	72.2 \pm 46.5	61.5 \pm 30.6	67.8 \pm 48.1
TMT-B (s)	161.1 \pm 63.7	158.7 \pm 60.0	172.7 \pm 61.8	162.5 \pm 76.8
DIFFBA (s)	101.2 \pm 58.1	111.6 \pm 60.1	95.0 \pm 44.9	98.2 \pm 68.1
RAVLT	24.5 \pm 2.3	24.8 \pm 2.5	24.7 \pm 2.2	24.0 \pm 2.1

Data are means \pm SD. *According to EPIC questionnaire (see RESEARCH DESIGN AND METHODS).

test scores (MMSE, TMT-A, TMT-B, DIFFBA, and RAVLT) and FPI levels, while adjusting for age, years of formal education, diabetes duration, and treatment group. To test the association between the variation of FPI on neuropsychological testing, separate linear mixed-effects regression models were created with cognitive performance tests (MMSE, TMT-A, TMT-B, DIFFBA, and RAVLT) as dependent variables after adjustment for the above covariates including group, as fixed effects in the entire population. An interaction term of FPI \times time was also included to estimate the change of FPI and change in cognitive scores over time. The same statistical models were also performed in the M/Rosi group.

RESULTS

Baseline

There were no significant differences found among clinical, biochemical, and neuropsychological testing according to antidiabetes group. Participants were overweight (BMI 27.7 \pm 3.5 kg/m²) with poor control of the following metabolic parameters: FPG 8.6 \pm 1.3 mmol/l, FPI 145.6 \pm 17.8 pmol/l, and A1C, 7.5 \pm 0.5%. All subjects had good functional

status (activities of daily living 5.9 \pm 0.1 and instrumental activities of daily living 6.9 \pm 0.8) and were not depressed (Geriatric Depression Scale score 3.5 \pm 2.2). Baseline clinical characteristics according to antidiabetes group are reported in Table 1.

At baseline, partial correlations were performed between metabolic control parameters (FPI, FPG, and A1C) and neuropsychological test scores (MMSE, TMT-A, TMT-B, DIFFBA, and RAVLT) in all participants after controlling for age, years of education, diabetes duration (years), and antidiabetes group. We found that higher FPI levels independently correlated with worse RAVLT test scores ($r = -0.227$; $P = 0.029$) and higher A1C levels correlated with longer times of execution on the TMT-B and the DIFFBA ($r = 0.212$, $P = 0.42$; $r = 0.213$, $P = 0.43$, respectively). There were no significant correlations found between FPG and any neuropsychological test.

Follow-up

All participants ($n = 97$) completed the study protocol without any adverse effect. No participant experienced a cardiovascular event. Participants adhered to their antidiabetes program during the observation period.

A progressive improvement in A1C and FPG was observed in those using oral antidiabetes drugs, whereas those using a personalized diet showed a significant worsening of these parameters ($P_{\text{trend}} < 0.05$) (Fig. 2). Nevertheless, despite the evidence that A1C showed a similar decline in both groups using oral antidiabetes agents, FPI levels significantly improved in the MF/Rosi group only (Fig. 2).

Using separate ANOVA repeated models, we found that the interaction terms MMSE \times group, TMT-A \times group, TMT-B \times group, DIFFBA \times group, and RAVLT \times group were all statistically significant ($P = 0.018$, $P < 0.001$, $P < 0.001$, $P = 0.001$, and $P < 0.001$, respectively). The MMSE and the TMT-A did not significantly vary over time in any group. However, TMTB and DIFFBA significantly worsened in the D group ($P = 0.024$ and $P = 0.026$, respectively), whereas there were no significant variations over time in the MF or MF/Rosi groups (data not shown). The RAVLT memory score significantly declined over time in the D and MF groups ($P_{\text{trend}} = 0.011$ and $P_{\text{trend}} = 0.004$, respectively), whereas the MF/Rosi group did not show any significant variations over time ($P = 0.414$). In ANCOVA repeated models adjusted for age, sex, years of education, BMI, diabetes duration, systolic blood pressure, physical activity, depression, A1C, FPG, and triglycerides, we found that the following interaction terms, MMSE \times group, TMT-A \times group, TMT-B \times group, DIFFBA \times group, and RAVLT \times group were all statistically significant ($P = 0.017$, $P < 0.001$, $P = 0.004$, $P < 0.001$, and $P < 0.001$, respectively).

A further analysis was used to test whether the variation in FPI levels could predict cognitive performance over time. Considering that mean FPI levels in the entire study sample were significantly lower compared with baseline values (145.6 ± 17.8 vs. 140.3 ± 18.4 ; $P < 0.05$), we performed an initial regression model in the entire study population, adjusting for multiple confounders. We found that the interaction term, FPI \times time, independently predicted neuropsychological test score variations in the TMT-B and RAVLT only (Table 2). As reported previously, the MF/Rosi group also demonstrated a significant decline in FPI levels; therefore, the same analysis was performed in the MF/Rosi group in which FPI \times time independently pre-

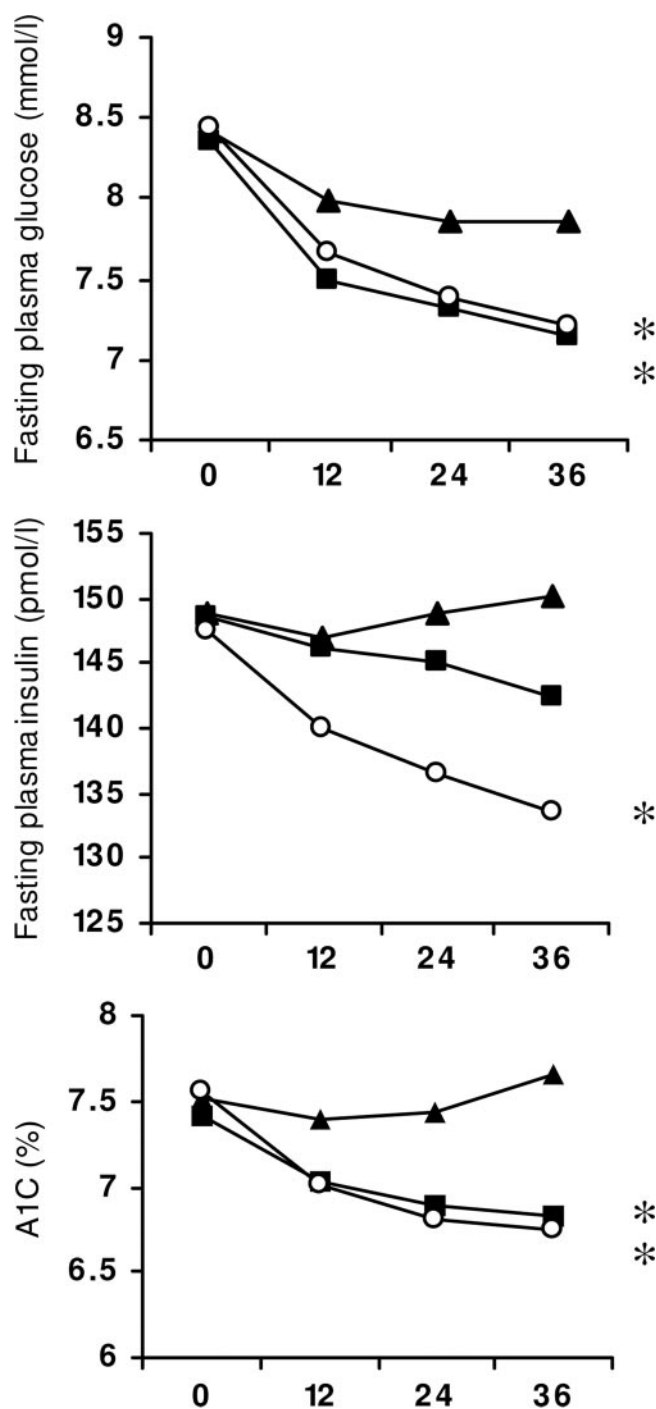


Figure 2—Changes in A1C, cardiovascular PPG, and FPG over time according to antidiabetic treatment. ▲, D group; ○, MF/Rosi group; ■, MF. * $P_{\text{trend}} < 0.05$ within the group over time. PPG = postprandial glucose, FPG = fasting plasma glucose.

dicted variations in the RAVLT test only (Table 2).

CONCLUSIONS— In older individuals with type 2 diabetes and MCI, we observed an improvement in metabolic control parameters (A1C, FPG, and FPI) in those using oral antidiabetes agents metformin or metformin+rosiglitazone

compared with those using a well-controlled personalized diet over 36 weeks. We also found that a well-controlled diet was associated with a significant decline in cognitive performance on executive functioning and memory tests, whereas monotherapy with metformin was associated with a decline in memory performance. The MMSE and

Table 2—Predictors of longitudinal cognitive performance variation over 36 weeks of follow-up

	TMT-B		RAVLT	
	β	P value	β	P value
All participants (n = 97)				
Time	-61.4730	0.134	5.9875	<0.001
Age (years)	3.5150	0.004	-0.0988	0.012
Group	-25.5932	0.002	0.5240	0.048
FPI	38.2203	0.129	-0.3998	0.715
Time \times FPI	18.0139	0.024	-2.2636	<0.001
MF/Rosi group (n = 32)				
Time	-70.6536	0.189	0.7851	0.699
Age (years)	1.2301	0.574	-0.0315	0.645
FPI	49.0536	0.069	-0.4850	0.510
Time \times FPI	15.8370	0.064	-1.899	0.009

Each model was adjusted for the following covariates: sex, formal education, diabetes duration (years), depression, FPG, systolic blood pressure, BMI, triglycerides, and A1C.

TMT-A were not sensitive to small changes in over time, and this may be explained by the fact that such neuropsychological tests do not show significant variations over a short observational period compared with tests measuring cognitive flexibility, cognitive efficiency, and memory (18). We found that the use of metformin + rosiglitazone was associated with stable cognitive performance on all neuropsychological tests over time. Our findings suggest that an improvement in circulating insulin levels may have a protective role against cognitive decline and also suggest that additional use of insulin sensitizers, like rosiglitazone, in older individuals with type 2 diabetes at a significantly higher risk of cognitive decline may be beneficial. Improvement in metabolic and glycemic control has been shown to be associated with a better cognitive performance status only in older individuals with type 2 diabetes and good cognitive status (4,19). Furthermore, reductions in hyperglycemic fasting glucose levels were accompanied by corresponding improvements in cognition, whereas significant improvements in FPI levels were not during a 24-week trial (4). Indeed, our findings add further clarification to the literature by demonstrating that improvements in FPG were not associated with changes in cognitive performance, whereas the improvement in FPI levels predicted cognitive change in older individuals with type 2 diabetes and MCI. In particular, the MF/Rosi group demonstrated a significant decline in FPI, which in turn, predicted changes in performance on memory, the leading deficit of amnesic MCI. The metabolic and hemo-

dynamic profile of diabetes, including comorbidities such as hypertension, hyperinsulinemia, and obesity, modulates vascular health and neuronal activity through multiple overlapping mechanisms. Thus, there is a strong interaction between vascular and neurodegenerative aspects involved in cognitive impairment in aging. The impact of chronic hyperglycemia on cognition has been shown to reduce brain glucose metabolism (20) and lead to endothelial damage in concert with altered insulin signaling (21). However, besides the well-known effects of chronic hyperglycemia on cognitive impairment either by direct neuronal damage mediated by advanced glycosylation end products or by micro- and macrovascular endothelial damage, another important mechanism that has been suggested is linked to the association between peripheral hyperinsulinemia and reduced brain β -amyloid clearance by altered cerebral insulin degrading enzyme activity (21).

There is also growing interest in preventing and treating Alzheimer disease during a preclinical state, such as MCI (transitional state between normal cognition and Alzheimer disease). Watson et al. (12) demonstrated that the insulin sensitizer, rosiglitazone, was useful in older individuals with NGT and MCI or early Alzheimer disease for measures of delayed memory and selective attention after 6 months of treatment. Furthermore, these authors also reported that plasma β -amyloid levels remained stable for the rosiglitazone-treated subjects, whereas such levels declined in the placebo group. This finding was explained by the fact that

there is a progressive decline in plasma Ab42 as Alzheimer disease progresses, indicating increased brain sequestration of β -amyloid. Unfortunately, our study protocol did not include the measurement of circulating β -amyloid levels, which have been shown to undergo significant changes during treatment with rosiglitazone. Future investigations should include parameters testing the concentrations of circulating β -amyloid in older individuals with diabetes and MCI. The most important limitation of our study is the observational design, which only allows for speculation. Indeed, we were able to identify a specific group of older individuals at a significantly high risk for dementia, by limiting our testing to those with MCI and recent antidiabetes treatment. The literature is lacking data on cognitive performance variations over time in older individuals with type 2 diabetes and MCI and to the best of our knowledge only one recent Japanese study showed that a drug in the same class, pioglitazone, improved cognition using the Alzheimer disease assessment scale and the Wechsler logical memory learning test in individuals with type 2 diabetes and Alzheimer disease or MCI (22). However, this was an open-controlled trial and the risk of biases cannot be ruled out. Pioglitazone has also been shown to reduce the risk of stroke, thus suggesting a protective role on the cerebral vascular bed (23). Our findings support consideration of the use of glitazones in older individuals with type 2 diabetes and MCI for future double-blind clinical trials. Furthermore, one may hypothesize that an improvement in insulin sensitivity seems to have a more important role on cognitive performance in older individuals with type 2 diabetes and MCI than in those with NGT and MCI. Another important limitation was the fact that we did not compare subjects with diabetes and MCI with those with NGT and MCI. However, recent randomized trials testing the use of rosiglitazone in individuals with NGT and Alzheimer disease or MCI were terminated because of a lack of effect (24–25), thus underlining the fact that insulin sensitivity alone may not be crucial for cognition in individuals with NGT.

In summary, this present study provides encouraging evidence that insulin sensitizers, such as rosiglitazone, not only may be important for reaching metabolic control in type 2 diabetes but may also protect against cognitive decline. Large

clinical trials testing the use of thiazolidinediones will determine whether mechanisms related to improved insulin resistance play a protective role against the evolution of dementia in older individuals with diabetes and MCI.

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No potential conflicts of interest relevant to this article were reported.

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