Dipeptidyl Peptidase-4 Inhibitors Have Protective Effect on Cognitive Impairment in Aged Diabetic Patients With Mild Cognitive Impairment

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Background. Older adults with type 2 diabetes have an increased risk for mild and severe cognitive impairment probably as consequence of chronic hyperglycemia or fasting plasma glucose levels. Variability in glucose level and recurrent hypoglycemic episodes are also associated with cognitive impairment. Dipeptidyl peptidase-4 inhibitor (DPP-4I) therapy affects glycemic variability. The purpose of this study was to evaluate the effect of DPP-4I therapy on changes in cognitive function in older patients with type 2 diabetes complicated by mild cognitive impairment.

Methods. This retrospective longitudinal study used data from a database of 240 older patients with type 2 diabetes, “drug naïve,” affected by mild cognitive impairment, subsequently treated for 2 years with antidiabetic drugs (DPP-4I group: DPP-4I + metformin, n = 120; SU group: sulfonylurea + metformin, n = 120) and reassessed in our ambulatory by comprehensive clinical, cognitive, instrumental examinations, and continuous subcutaneous glucose monitoring.

Results. At baseline, larger mean amplitude of glycemic excursion values correlated with poorer Mini-Mental State Examination and composite cognitive function scores. We found that higher body mass index, higher 2-hour postprandial glucose, and greater mean amplitude of glycemic excursion values measured at baseline were significant independent predictors of cognitive worsening. In addition, reduction in mean amplitude of glycemic excursions and the use of DPP-4I therapy predicted improvement in cognitive functions.

Conclusions. In older patients with type 2 diabetes affected by mild cognitive impairment, DPP-4I administration improves glucose control and protects against worsening in cognitive functioning.

Key Words: Older patients with type 2 diabetes—DPP-4 inhibitor treatment—Mild cognitive impairment.

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OLDER adults with type 2 diabetes have an increased risk for mild and severe cognitive dysfunction (1–4). Mechanisms underlying the impact of diabetes on the brain are currently unknown, but a multifactorial role seems very likely (5–7). Evidences suggest that worsening in cognitive functioning is a direct consequence of chronic hyperglycemia (8,9), as measured by glycated hemoglobin or fasting plasma glucose (FPG) levels (10). Indeed, chronic hyperglycemia is a major cause of oxidative stress in humans, propounding negative vascular effects in accelerating atherosclerosis (11–13). Recently, blood glucose fluctuations have been found more detrimental for the development of atherosclerosis than the sustained hyperglycemia (14) having a more specific triggering effect on oxidative stress. Indeed, glycemic variability (14) and recurrent hypoglycemic episodes (15,16) may be additional factors to be considered. Considering that the brain depends on the continuous glucose supply as principal energy source and acute plasma glucose changes alters regional cerebral blood flow, glucose swings may also affect cognitive function (17,18). Few studies evaluated the relationship between each class of oral hypoglycemic agents and cognitive performance. Gradman and colleagues (19) treated 23 diabetic adults with glipizide for up to 7 months and found both a reduction in FPG levels and an improvement on a verbal learning test. Short-term treatment by rosiglitazone was associated with an improvement in delayed memory and selective attention tests in older individuals with normal glucose tolerance and mild cognitive impairment (MCI) or early Alzheimer’s disease (AD) (20). In older adults with type 2 diabetes affected by MCI, an improvement in metabolic control parameters and in cognitive performance in patients using metformin plus rosiglitazone versus metformin was observed (21). Incretin therapy has not been evaluated in this regard. Several studies assessed the role of glucagon-like peptide-1 (GLP-1) on central nervous system function.
Such studies suggested that GLP-1 influences brain metabolism, stimulates neuritic growth in central nervous system neurons, and exerts neuroprotective actions against oxidative stress and cell death (22,23). Furthermore, GLP-1 was found to cross the blood–brain barrier and may effectively reduce brain AβPP-Aβ burden in AD (24–26). Several studies showed that the dipeptidyl peptidase-4 inhibitor (DPP-4I) therapy significantly reduces glucose excursions using continuous glucose monitoring (27–29). Recently, our study group (30) demonstrated that augmentation of GLP-1 by DPP-4 inhibitors enhances glucose-induced insulin secretion and decreases glucagon secretion over a daily period, as well as reduces HbA1c and glycemic fluctuations over a daily period.

Thus, our study aimed at investigating the effect of DPP-4I therapy on cognitive function in aged type 2 diabetics patients complicated by MCI and to evaluate whether asymptomatic hypoglycemic episodes affect changes in cognitive function.

PATIENTS AND METHODS

Study Population

This retrospective longitudinal study used data from a database of older patients with type 2 diabetes, admitted to outpatient Geriatric Centre of the Second University of Naples, who underwent comprehensive clinical, cognitive, and instrumental examinations and continuous subcutaneous glucose monitoring (CSGM). Of “drug naive” type 2 diabetics patients affected by MCI (n = 283), only data from subjects subsequently treated (by general practitioner or diabetes center or outpatient) with DPP-4I or sulfonylurea (SU) therapy, between January 1, 2008 and July 30, 2010, were analyzed (Figure 1).

Exclusion criteria included: treatment with insulin or any other oral antidiabetic or steroids or nonsteroidal anti-inflammatory drugs; recent acute illness and concomitant chronic disease, including kidney, liver, cardiovascular disease, severe uncontrolled hypertension (blood pressure ≥ 200/100 mmHg), hypercholesterolemia and hypertriglyceridemia, and cancer; presences of significant carotid plaques on a carotid ultrasound examination and cerebrovascular diseases or white matter lesions or significant signs of cortical or subcortical atrophy with an magnetic resonance imaging scan; diagnosis of dementia based on DSM-IV criteria; and required changes in diabetic therapy. According to the exclusion criteria, a total of 43 patients were excluded.

The final cohorts of 240 older patients with type 2 diabetes affected by MCI, treated with either metformin and DPP-4I (n = 120) and metformin with sulfonylureas (n = 120), were reassessed after 2 years, in our ambulatory, by comprehensive clinical, cognitive, instrumental examinations, and CSGM (Figure 1).

According to antidiabetic oral therapy, patients were divided into two groups: DPP-4I (vildagliptin 50 mg two times a day or sitagliptin 100 mg/day or saxagliptin 5 mg/day) in add on with metformin 1700 mg/day (DPP-4I group; n = 120) and SU (glimepiride 2 mg/day or glyburide 15 mg/day or glipizide 10 mg/day) in add on with metformin 1700 mg/day (SU group; n = 120).

All subjects gave their informed consent before participating in the study, approved by the Ethics Committee of our Institution.

Assessment of Glycemic Instability

A minimum of 48-hour period of continuous blood glucose monitoring was performed using CSGM (GlucoDay, A. Menarini Diagnostics, Florence, Italy). The sensor was
inserted on Day 1 and removed on Day 3 at midmorning. The device was calibrated using five capillary glucose readings per day. Data obtained in second and third day were considered valid for each patient, in order to avoid bias to both insertion and removal of the sensor. They consist of glucose readings every 5 min, providing about 550 readings in a 48-hour period. The mathematical formulae to assess glucose variability were taken from their original publications for inclusion in a computer program, Easy GV (available free for non-commercial use at www.easygv.co.uk) (31). The meal taken on the CSGM was standardized: breakfast contained 421 kcal (58% carbohydrate, 15% protein, and 27% fat), lunch contained 689 kcal (56% carbohydrate, 18% protein, and 26% fat), and dinner contained 490 kcal (51% carbohydrate, 24% protein, and 25% fat). In both groups, glycemic index of the meal was the same.

**Glycemic Evaluations**

FPG level and postprandial glucose (PPG) level, at baseline and after 2 years of therapy, were determined by mean of the fasting values (before breakfast) and by mean of 2-hour PPG levels (2hPPG), respectively, both recognized during CSGM.

**Calculation of Glycemic Indices**

The indices calculated for the intraday and interday glucose variability evaluation were as follows: Mean amplitude of glycemic excursions (MAGE) used for assessing glucose fluctuations during 48 hours (32). We used glucose profiles obtained from CSGM for MAGE calculation by measuring the arithmetic mean of differences between consecutive peaks and nadirs; measurement in the peak to nadir or nadir to peak direction was determined by the first qualifying excursion. This parameter was designed to quantify major swings of glycemia and to exclude minor ones. Only increases of more than 1 SD of the mean glycemic values were taken into account; continuous overall net glycemic action defined as the standard deviation of differences between current observation and previous 4-hour observation (33). The mean glucose concentration values defined as sum of the differences between successive glucose value divided by the total time measured in hours and standard deviation around the derived mean glucose concentration values obtained from 48-hour time points were used for evaluating the potential asymtomatic hypoglycemic episodes (standard deviation for asymptomatic hypoglycemia) (15).

**Identification of Symptomatic and Asymptomatic Hypoglycemic Events Measured During the 2 Years of Therapy and During CSGM**

Hypoglycemia was defined as an event with or without symptoms consistent with hypoglycemia, associated with plasma glucose concentration of less than 70 mg/dL (34). In our study, because the CSGM sensor reading remain 20% lower than venous plasma glucose concentration (35), hypoglycemia was defined as an interstitial glucose concentration of less than 56 mg/dL (15), which may be considered a compromise between the limitations of the continuous glucose monitoring system and the definition of hypoglycemia given by the American Diabetes Association (34). In addition, every time participants awoke during the night and experienced symptoms of hypoglycemia, glycemic level self-monitoring was performed and documented in the patients’ diary or derived from glucose profiles that diabetic patients usually transcribe daily.

**Assessment of Cognitive Functions**

MCI was diagnosed according to Petersen’s classification: (a) memory complaint, preferably corroborated by an informant; (b) cognitive impairment in more than or equal to one domain (executive function, memory, language, or visuospatial); (c) normal general cognitive function; (d) intact activities of daily living; and (e) no diagnosis of dementia (36). This diagnosis has been done from colleagues working in other hospitals and then confirmed by us or by us directly. The diagnosis of MCI was done before the prescription of hypoglycemic drugs.

Global cognitive function was assessed with Mini-Mental State Examination (MMSE) corrected for educational levels. A diagnosis of MCI was made if the MMSE score was 25–27, after adjusted for age and education. Such range identify a possible cognitive impairment different from a cutoff of less than 24 that define dementia (37,38). In several studies, a cutoff value of more than or equal to 24 or a score more than or equal to 26 and more than or equal to 23 were also used (39).

Activity functions were assessed with the instrumental activities of daily living and the basic activities of daily living, whereas depressive symptoms were assessed with the Geriatric Depression Scale (GDS short version) (40,41).

The aspects of executive, attention, and visuospatial function were assessed with Trail Making Test (TMT A and B) and Wechsler Adult Scale–Revised Digit Span, respectively. The TMT is a measure of attention, speed, and mental flexibility. It also tests spatial organization, visual pursuits, recall, and recognition (40). Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment. The Wechsler Adult Scale–Revised Digit Span is a measure of mental tracking as well as of brief storage and mental manipulation (40). The Digit Span requires the participant listen to increasingly longer lists of digits presented for immediate recall in the exact order presented (DSP–Forward) and in the reverse order (DSP–Backward). The two parts of Digit Span—Digits Forward and Digits Backward—were administered separately. Verbal Fluency
Test was used to evaluate semantic memory and requires participants to generate as many words as possible in 1 minute for a given letter (F, A, S) excluding nouns and variations of the same word (40). Both scores were given by the amount of words number to complete the test. The measures chosen for cognitive assessment correspond to those suggested in a proposal for standardizing cognitive assessment in diabetes, selected because of their reliability and their potential to detect cognitive deterioration (41).

**Statistical Analysis**

Statistical analyses were performed with the use of SPSS software (version 19). All data are presented as mean ± SD. A value of $p$ less than .05 was considered significant. Sample size calculation was estimated on an IBM PC computer by GPOWER software. Because the resulting sample size, estimated according to a global effect size of 25% with type I error of 0.05 and a power of 95%, was 210 patients, the number of required patients was set at 210. Continuous variables were compared by the Student $t$ test for independent variable. Correlation analyses were performed using Pearson or Spearman correlation coefficients, as appropriate. A cluster analysis was created by using the squared sum of $z$ scores, in order to obtain an overall value of attention and executive function test. A $z$ score indicates the position of an individual value of a variable in the total distribution of the variable in the population and is calculated as follows: (individual value – mean value)/$SD$. The analysis transforms the individual test scores to $z$ scores.

To create such a cluster analysis, given that the scores have different trends, we created a composite cognitive score of executive functions (Composite cognitive function score A), calculated as sum of the $z$ scores of TMT A, TMT B, and difference (DIFF) B-A, and a composite cognitive score of attention functions (Composite cognitive function score B), calculated as sum of the $z$ scores of DSP–Forward, DSP–Backward, and Verbal Fluency, respectively. Increase in Composite cognitive function score A indicates a cognitive worsening, whereas increase in Composite cognitive function score B indicates a cognitive improvement.

Multivariate regression analysis was performed to identify the effect of different metabolic variable on MMSE and composite cognitive function scores. In particular, the model was performed for evaluating the effects of FPG and PPG, Hba1c, $SD$, MAGE level changes, and antidiabetic therapy on MMSE and Composite cognitive function scores A and B.

Logistic regression analysis was performed to determine at baseline the risk of developing poor cognitive performance (MMSE < 25) and to test over time whether the variation (A) in metabolic parameters, glycemic variables levels, and antidiabetic therapy could predict cognitive improvement (MMSE ≥ 27). All clinically plausible variables with $p$ less than .05 in the respective bivariate analyses were considered for the models.

**Results**

**Baseline**

Clinical and metabolic characteristics and cognitive functions, both according to antidiabetic therapy, are reported in Table 1 and in Figure 2, respectively. At baseline, no significant differences in clinical, biochemical parameters, and neuropsychological test scores between two groups were found. Participants were mainly females (M/F = 94/146), old (72.8 ± 4.4 years), overweight (body mass index [BMI] = 27.4 ± 2.8 kg/m²), with poor metabolic control (FPG = 153 ± 14 mg/dL; 2hPPG = 172 ± 37 mg/dL; Hba1c = 8.1 ± 0.5%; MAGE = 72.8 ± 6.1 mg/dL; $SD$ for asymptomatic hypoglycemia = 37.6 ± 2.4), and cognitive scores revealing a MCI (MMSE = 26.1 ± 1.1; TMT A = 87 ± 26 seconds; TMT B = 202 ± 56 seconds; DIFF B-A = 115 ± 33 seconds; DSP–Forward = 5.5 ± 1.0; DSP–Backward = 4.7 ± 0.7; Verbal Fluency = 31.9 ± 3.5; Composite cognitive function score A = 0.01 ± 2.85; Composite cognitive function score B = 0.09 ± 2.12).

All participants were well functioning (basic activities of daily living = 5.7 ± 0.2 and instrumental activities of daily living = 6.7 ± 0.9) and were not depressed (GDS score = 3.6 ± 2.4).

At baseline, 2hPPG levels significantly correlated with a poor MMSE score ($r = −.166$, $p < .001$) and poor Composite cognitive function score A ($r = .242$, $p < .001$); higher Hba1c levels correlated with a poorer Composite cognitive function score A ($r = .413$, $p < .02$); and higher MAGE value correlated with a poorer MMSE ($r = −.156$, $p < .05$), Composite cognitive function score A ($r = .172$, $p < .008$), and Composite cognitive function score B ($r = −.122$, $p < .01$); similar results were found using continuous overall net glycemic action, mean glucose concentration, and standard deviation for asymptomatic hypoglycemia value (data not shown).

**Follow-up**

After 2 years of therapy, all baseline variables related to cognition were significantly improved after DPP-4I therapy but not after SU therapy (Figure 2), despite both groups displayed a similar improvement in metabolic control (Table 1). In addition, only in the DPP-4I group, decrease in standard deviation for asymptomatic hypoglycemia was observed (Table 1). No significant difference in cognitive parameters among patients taking different DPP-4I was found (data not shown). Correlation analysis showed that change in Hba1c value significantly correlated with change in MMSE score ($r = −.455$, $p < .001$), in Composite cognitive function score A ($r = .530$, $p < .001$) and B ($r = −.472$, $p < .001$). This relationship persisted after adjustment for the main anthropometric (BMI and waist–hip ratio) and metabolic (FPG, 2hPPG, and Hba1c) parameters, for systolic blood pressure and diastolic blood pressure ($r = −.225$, $r = −.242$).
Interestingly, correlation analyses showed that change in MAGE value significantly correlated with changes in MMSE score ($r = -0.438, p < .001$), in Composite cognitive function score A ($r = 0.562, p < .001$) and B ($r = -0.585, p < .001$) (Figure 3). This relationship persisted after adjustment for the main anthropometric (BMI and waist–hip ratio) and metabolic (FPG, 2hPPG, and HbA1c) parameters, for systolic blood pressure and diastolic blood pressure ($r = -0.144, p < .02$; $r = 0.242, p < .001$; $r = -0.222, p < .001$, respectively) values. In addition, there was a significant correlation between change in MMSE value and change in standard deviation for asymptomatic hypoglycemia ($r = -0.552, p < .001$).

The independent association of MMSE and composite cognitive function scores with changes in glucose parameters were evaluated by multivariate analysis. A model including $\Delta$ FPG, $\Delta$ postprandial glycemia, $\Delta$ HbA1c, $\Delta$ SD for asymptomatic hypoglycemia, $\Delta$ MAGE, and anti-diabetic therapy, as independent variables, explained 20%, 29%, and 32% of MMSE, Composite cognitive function scores A, and B variability, respectively. In such analyses, only the change in postprandial glycemia and in MAGE were independently associated with MMSE ($\beta = 0.199, p < .002; \beta = -0.294, p < .008$), Composite cognitive function score A ($\beta = -0.219, p < .001; \beta = 0.30, p < .004$), and Composite cognitive function score B ($\beta = -0.207, p < .01; \beta = -0.601, p < .001$).

### Table 1. Clinical and Metabolic Characteristics of 240 Older Patients With Type 2 Diabetes at Baseline and After 2 Years of Treatment According To Antidiabetic Therapy

<table>
<thead>
<tr>
<th>Variables</th>
<th>DPP-4I Group</th>
<th>SU Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n = 120$ Baseline</td>
<td>$p^*$ 2 Years of Therapy</td>
</tr>
<tr>
<td>Age (y)</td>
<td>73.1 ± 4.2</td>
<td>75.4 ± 4.1</td>
</tr>
<tr>
<td>Male/females sex</td>
<td>49/71</td>
<td>49/71</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.1 ± 3</td>
<td>26 ± 3.2</td>
</tr>
<tr>
<td>WHR</td>
<td>0.91 ± 0.07</td>
<td>0.89 ± 0.07</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130 ± 6</td>
<td>123 ± 5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85 ± 5</td>
<td>80 ± 3</td>
</tr>
<tr>
<td>Metabolic profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>152 ± 13</td>
<td>109 ± 12</td>
</tr>
<tr>
<td>2hPPG (mg/dL)</td>
<td>173 ± 35</td>
<td>142 ± 9</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.9 ± 0.5</td>
<td>7.2 ± 0.4</td>
</tr>
<tr>
<td>MAGE (mg/dL)</td>
<td>73.5 ± 6.3</td>
<td>47.4 ± 11.4</td>
</tr>
<tr>
<td>SD for asymptomatic hypoglycemia</td>
<td>37.3 ± 2.8</td>
<td>18.3 ± 3.1</td>
</tr>
</tbody>
</table>

Notes: Data are means ± SD. BMI = body mass index; DPP-4I = dipeptidyl peptidase-4 inhibitor; FPG = fasting plasma glucose; MAGE = mean amplitude of glycemic excursions; PPG = postprandial; SD for asymptomatic hypoglycemia = standard deviation for asymptomatic hypoglycemia; SU = sulfonylurea; WHR = waist–hip ratio.

*p*DPP-4I group after 2 years of therapy vs baseline.
†SU group after 2 years of therapy vs baseline.
‡DPP-4I group vs SU group after 2 years of therapy.
Figure 3. Relationship between change in mean amplitude of glycemic excursions (MAGE) and change in MMSE, Composite cognitive function scores A and B. MMSE, Mini-Mental State Examination.
Logistic regression model was used to investigate predictors of worsening in cognitive functioning (MMSE < 25) at baseline (Table 2, baseline). We found that baseline BMI, 2hPPG, and MAGE values (odds ratio: 1.11, p < .003; odds ratio: 1.01, p < .01; odds ratio: 1.37, p < .008, respectively) were significant independent predictors of cognitive worsening (Table 2, baseline).

Similarly, testing the predictive values of glucometabolic parameters (waist–hip ratio, BMI, FPG, 2hPPG, HbA1c, standard deviation for asymptomatic hypoglycemia, MAGE) variation and antidiabetic therapy on cognitive improvement (MMSE > 27) over 2 years of therapy (Table 2, after 2 years of therapy), reduction in MAGE as well as introduction of DPP-4I therapy were predictors of MMSE improvement (Table 2, after 2 years of therapy).

Similar data were found using Composite cognitive function scores A and B as dependent variables (data not shown).

Along 2 years of therapy, less than 6% of patients experienced at least one objectively confirmed hypoglycemic event. The frequency of hypoglycemic events was slightly but not statistically more elevated in the SU than DPP-4I groups.

**DISCUSSION**

Our results suggest that reduction in glucose fluctuations and DPP-4I treatment in aged type 2 diabetes patients

| Table 2. Predictors of Having MMSE Scores Low (<25) at Baseline (A) and High (>27) After 2 y of Therapy (B) (n = 240) |
|---|---|---|
| **Baseline** | OR* | 95% CI | p |
| Age | 1.05 | 0.97–1.21 | 0.12 |
| WHR | 0.90 | 0.03–1.69 | 0.82 |
| BMI | 1.11 | 1.03–1.21 | 0.003 |
| FPG | 1.02 | 0.98–1.05 | 0.62 |
| 2hPPG | 1.04 | 1.00–1.09 | 0.04 |
| HbA1c | 1.13 | 0.46–2.80 | 0.87 |
| SD for asymptomatic hypoglycemia | 1.22 | 0.95–1.57 | 0.20 |
| MAGE value | 1.37 | 1.11–1.69 | 0.008 |
| **After 2 y of therapy** | | | |
| Age | 0.97 | 0.09–1.07 | 0.37 |
| A WHR | 0.93 | 0.05–1.71 | 0.62 |
| A BMI | 1.03 | 0.73–1.44 | 0.86 |
| A FPG | 1.01 | 0.94–1.14 | 0.89 |
| A 2hPPG | 1.02 | 0.98–1.05 | 0.09 |
| A HbA1c | 2.08 | 0.62–6.09 | 0.23 |
| A SD for asymptomatic hypoglycemia | 1.02 | 0.85–1.21 | 0.86 |
| A MAGE value | 0.86 | 0.76–0.97 | 0.009 |
| Therapy | 0.88 | 0.45–0.99 | 0.03 |

**Notes:** BMI = body mass index; FPG = fasting plasma glucose; MAGE = mean amplitude of glycemic excursions; MMSE, Mini-Mental State Examination; PPG = postprandial glucose; SD for asymptomatic hypoglycemia = standard deviation for asymptomatic hypoglycemia; WHR = waist–hip ratio.

Bold values indicate results with statistical significance.

*All the ORs are adjusted for all tailed variables.

†DPP-4I therapy calculated as 1 and SU therapy calculated as 2.

affected by MCI are accompanied by corresponding improvements in cognitive functioning.

We observed significant improvements in global cognitive performances, mainly attentional and executive functions, which are frequently impaired in older patients with type 2 diabetes with MCI.

The risk of worsening cognitive status in older persons with diabetes mellitus is significantly higher than in those without diabetes mellitus and numerous investigations have been undertaken to determine the underlying mechanisms for such risk (1–18). The present study found that BMI, 2hPPG, and MAGE values were significant predictors of worsening of cognitive performances, suggesting the need for starting or improving drug therapy for a better glycemic metabolic control.

Diabetes represents a risk factor for worsening in cognition. So far, longitudinal and meta-analyses studies suggest that diabetes increases the risk for developing dementia (42) with a more than 50% increased risk of AD and doubled risk of vascular dementia. Poor glycemic control and uncontrolled glucose swings (17) may negatively affect cognitive function through a rise in oxidative stress, inducing an overproduction of superoxide producing subsequent nitrosative stress with generation of metabolic derivatives such as peroxynitrite and nitrotyrosine. The toxicity of these substances can lead to neuronal damages by direct neurotoxic effect and, furthermore, to a decline in cognitive performance.

Thus, control of fasting glucose and HbA1c without control of glycemic excursions over a daily period may be not sufficient to reduce oxidative stress and inflammation (11–13). Daily glucose fluctuations rather than chronic sustained hyperglycemia exhibited a more specific triggering effect on oxidative stress (14). In support of the link among glucose swing, oxidative stress and cognitive impairment is our recent study (17), demonstrating a significant relationship between acute glucose swings obtained by MAGE value and cognitive performance impairment.

The correlation between higher HbA1c levels and lower cognitive function in individuals with diabetes is already known in literature (43). In our study, MAGE excursions were strongly correlated with cognitive functioning, independently of the main markers of sustained chronic hyperglycemia (HbA1c and FPG) (17). Zhong and colleagues (44) get similar conclusions, although the association between MAGE and MMSE was weaker, possibly because the participants had flat glucose excursions and almost good glucose control. These results support the view that glucose variability should be considered a main target of treatment in older patients with type 2 diabetes in order to preserve cognitive functioning.

Here, we found that acute glucose fluctuations predicted changes in MMSE score and in Composite cognitive function scores A and B, independently of the main anthropometric (BMI and waist–hip ratio) and metabolic (FPG, 2hPPG,
and A1C) variables; interestingly enough, DPP-4I but not SU treatment predicted improvement in MMSE score and in Composite cognitive function scores A and B. A possible explanation for such effect of DPP-4I seem related to both glycemic excursions improvement and reduction in oxidative stress, effects absent along with sulfonylurea treatment. Such hypothesis is strengthened by our recent data showing daily vildagliptin administration to reduce HbA1c, glycemic fluctuations, oxidative stress, and markers of systemic inflammation in older patients with type 2 diabetes (45).

DPP-4I therapy improves mainly executive and attentive cognition, independently of the main markers of sustained chronic hyperglycemia (FPG, PPG, A1C) and glucose swing (MAGE). No significant difference in cognitive parameters among patients taking different DPP-4I (vildagliptin vs sitagliptin vs saxagliptin) was found. Indeed, sample sizes for DPP-4I subgroups is too small for performing an appropriate statistical analysis which cannot really help us to test the potential differences in MAGE between the two groups and impact on cognitive functions. Moreover, the main aim of our study was to verify the possible class effect on cognitive performance and not the effect of each drug. Notwithstanding, further studies will be helpful to address such a question.

Whether a possible direct role of DPP-4I or indirect (through a rise in GLP-1) per se impact on cognitive performance in older patients with type 2 diabetes occurs, it needs further investigations. In fact, reduction in plasma GLP-1 levels might be associated to a reduced neuroprotective action mainly on hippocampal regions (46), where AD-related degenerative neuropathology is particularly evident. The relationship between GLP-1 and brain is supported by the evidence that GLP-1 influences brain metabolism, stimulates neuritic growth in central nervous system neurons, and exerts neuroprotective actions against oxidative stress and cell death (22,23). Importantly, GLP-1 can cross the blood–brain barrier and may effectively reduce brain AβPP-Aβ burden in AD (24,25) and counteract β-amyloid toxicity in models of AD (47).

Finally, hypoglycemia might be a further factor to take into account for explaining the effect of DPP-4I on cognitive function (15,16). In DPP-4I group, we observed a significant reduction in standard deviation for asymptomatic hypoglycemia values and a significantly inverse relationship between change in MMSE value and change in standard deviation for asymptomatic hypoglycemia. Our findings demonstrate that the use of DPP-4I was associated with a reduced number of symptomatic or asymptomatic hypoglycemia as also widely reported for such class of drugs (48). Such effect had an opposite trend along with sulfonylurea administration. Thus, the protective effect of DPP-4I on hypoglycemia might be an additional protective effect on cognitive function.

Some limitations in this study need to be emphasized. First, this was a retrospective longitudinal analysis of patients considered to be eligible for the study. This could be a potential selection bias. Besides, our database is limited to the variables that were collected for clinical management, and some patients with MCI may have been excluded because of missing data. However, these were the data available, and our study demonstrates that a significant number of diabetic patients affected by MCI indeed benefit from DPP-4I therapy. However, the findings need to be confirmed in a larger study. Second, although along study duration, less than 6% of patients reported at least one objectively confirmed hypoglycemic event, effectively we were unable to investigate properly mild and or moderate hypoglycemic events during these 2 years. The number of mild/moderate hypoglycemic episodes might have been underreported in the patients’ diary and therefore, underestimated. However, no severe hypoglycemic event have been reported, neither by patients nor by family members, forcing the patients to reach hospital.

In conclusion, reduction in glucose fluctuation and DPP-4I administration in older patients with type 2 diabetes affected by MCI ameliorate glucose control (as either chronic sustained hyperglycemia or glycemic swings or number of hypoglycemia) and protect against worsening in cognitive functioning.

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Conflict of Interest
Paolisso Giuseppe is member of Novartis, Lilly, Takeda and Novo Nordisk Boards.

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