Association of Plasma DPP4 Activity With Mild Cognitive Impairment in Elderly Patients With Type 2 Diabetes: Results From the GDMD Study in China

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OBJECTIVE

Hyperglycemia, inflammation, and oxidative stress are thought to be involved in the pathogenesis of cognitive decline. Dipeptidyl peptidase-4 (DPP4) is a newly identified adipokine related to these risk factors. Hence, we aimed to investigate the association between plasma DPP4 activities and mild cognitive impairment (MCI) in elderly patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

We evaluated plasma DPP4 activity, inflammatory markers, and oxidative stress parameters in a cross-sectional sample of 1,160 patients with type 2 diabetes aged 60 years or older in China. MCI was diagnosed based on criteria established by the National Institute on Aging-Alzheimer’s Association workgroups.

RESULTS

Patients in the highest quartile of DPP4 activity had higher HbA1c, interleukin 6 (IL-6), CRP, nitrotyrosine, 8-iso-PGF2a, and lower Montreal Cognitive Assessment (MoCA) scores compared with subjects in the lowest quartile (P < 0.001). In the highest DPP4 quartile, MCI risk was higher (odds ratio 3.49; 95% CI 1.97–4.57) than in the lowest quartile after adjustment for potential confounders. The risk for MCI increased more with higher levels of DPP4 activity, IL-6, CRP, nitrotyrosine, and 8-iso-PGF2a (P < 0.05), but not with higher levels of HbA1c.

CONCLUSIONS

This study shows that increased DPP4 activities are independently associated with MCI in elderly patients with type 2 diabetes. The mechanisms might be partly explained by the effect of DPP4 on inflammation and oxidative stress. These observations raise further interest in DPP4 activity for its potential effect on these MCI-related risk factors as a biological marker or even a possible therapeutic target for MCI.

Type 2 diabetes is associated with an increased risk of accelerated age-related cognitive impairment and a higher incidence of dementia (1). Dementia is generally preceded by an intermediate stage, termed mild cognitive impairment (MCI), in which patients have cognitive complaints and objective disturbances on cognitive tests but in which their daily functioning is largely preserved (2). Although not all...
people with MCI will develop dementia (2), prospective population-based studies link type 2 diabetes to an increased risk of MCI (3,4). The presence of MCI might reduce the threshold at which a dementia process becomes symptomatic (5). Identifying potentially modifiable risk factors and therapeutic targets for MCI in elderly patients with type 2 diabetes is therefore of great importance for future diabetes health care initiatives and the reduction of cognitive morbidity, because once cognitive impairment becomes more advanced, interventions targeted at dementia pathogenesis are unlikely to delay further cognitive decline (5).

The cause of MCI in patients with type 2 diabetes is unknown but is most likely multifactorial. Chronic hyperglycemia is implicated, perhaps by promoting the development of cerebral microvascular disease (6). Inflammation and oxidative stress also appear to be involved in the pathogenesis of cognitive decline (5,7). These two factors form a vicious cycle that accelerates brain injury and cognitive impairment. Patients with type 2 diabetes with higher levels of blood glucose, inflammation, and oxidative stress might be more vulnerable to MCI.

Dipeptidyl peptidase-4 (DPP4) is a serine exopeptidase belonging to the S9B protein family that cleaves X-proline dipeptides from the N-terminus of polypeptides, such as chemokines, neuropeptides, and peptide hormones. DPP4 is a widely expressed multifunctional enzyme that exists as a membrane-anchored cell-surface protein or in a soluble form in the plasma (8). Our previous data suggested that increased plasma DPP4 activities were found in type 2 diabetes and promoted the development of hyperglycemia, inflammation, and oxidative stress (9,10). More interestingly, animal studies have proved that DPP4 inhibitors, such as sitagliptin or linagliptin, ameliorated cognitive impairment through suppressing inflammatory reaction or oxidative stress in different models of mice (11,12). Consequently, it is reasonable to speculate that DPP4 activity may be favorably correlated with MCI in elderly patients with type 2 diabetes.

DPP4 inhibitors have already been widely used as a novel and effective anti-diabetic drug in clinical practice; however, to our knowledge, no study has evaluated the association between plasma DPP4 activity and MCI in elderly patients with type 2 diabetes or considered the possibility of identifying DPP4 activity as a biological marker or even a possible therapeutic target for MCI in type 2 diabetes in addition to its role as a target for antidiabetic drugs. Therefore, the aim of our study was to examine the association of plasma DPP4 activities and MCI in a cross-sectional population study of 1,160 elderly patients with type 2 diabetes in China. Next, we focused on the mechanisms and clinical implications for such an association by investigating the relationship between DPP4 activities and the above-mentioned pathogenic factors for MCI.

**RESEARCH DESIGN AND METHODS**

**Subjects**

This study used a cross-sectional design with the baseline participants in the Guangxi Diabetes and Metabolic Disorders (GDMD) Study, which is a cohort study designed to focus on the etiology, pathophysiology, complications, and comorbidities of type 2 diabetes and metabolic syndrome. The study enrolled for analysis 1,160 patients with type 2 diabetes aged 60 years or older (mean ± SD, 65.9 ± 4.3), who had undergone routine health examinations at the Medical Examination Center of the Affiliated Hospital of Guilin Medical University between 2013 and 2015. Inclusion criteria were previously diagnosed patients with type 2 diabetes aged 60 years or older, long-term residence (≥5 years) in China’s Guangxi province, and ability to give informed consent. The exclusion criteria were:

1. presence of diabetes ketosis or other acute diabetic complications in the most recent 3 months;
2. presence of any of the following diseases, including acute inflammatory diseases, autoimmune disease, malignancy, hypothyroidism, hypertensive crisis, dementia, heart, respiratory, liver, and kidney failure;
3. history of a central nervous system disease that could cause dementia;
4. history of auditory/visual disorders, psychological disturbances, and severe hypoglycemia;
5. use of possible or known drugs affecting cognitive function or DPP4 activity for more than 3 months or at any time within 12 months before the enrollment;
6. drug or alcohol abuse or dependence; and
7. patients with incomplete data.

The study was approved by the Drugs/Medical Apparatus & Instruments Ethics Committee at Affiliated Hospital of Guilin Medical University, and all participants gave written informed consent.

**Data Collection**

On the survey date, all enrolled patients underwent routine medical history inquiries, physical examinations, and laboratory measurements. Clinical research coordinators used a standard questionnaire to collect information on demographic characteristics, lifestyle risk factors, education level, annual income, diabetes therapy, diabetes duration, diabetic complications, MCI, self-reported medical history, and medications. Patients were instructed to maintain their usual physical activity and diet for at least 3 days before the survey. After an overnight fast of ≥10 h, venous blood samples were collected to measure blood lipids, HbA1c, interleukin 6 (IL-6), CRP, nitrotyrosine, 8-iso-PGF2a, and DPP4 activity. Blood samples were stored at −80°C, and all parameters were measured within 6 months of sample collection.

**Clinical and Laboratory Measurements**

Measurements of body weight, height, and BMI were described previously (13). Blood lipids, HbA1c, IL-6, CRP, nitrotyrosine, and 8-iso-PGF2a were measured as previously described (9,10).

Plasma DPP4 activity was determined as the rate of cleavage of 7-amino-4-methylcoumarin (AMC) from the synthetic substrate H-glycyl-prolyl-AMC (H-Gly-Pro-AMC; BioVision, Milpitas, CA). Briefly, prepare duplicate test samples (one for background control) up to 50 μL/well, adjust to 50 μL volume into a 96-well plate using DPP4 Assay Buffer (5 μL of plasma were mixed with 45 μL of assay buffer). Add 10 μL DPP4 Assay Buffer to one sample replicate and 10 μL DPP4 inhibitor (sitagliptin) to another sample as the sample background control. Mix well and incubate for 10 min at 37°C. Add 40 μL Reaction Mix (38 μL DPP4 Assay Buffer and 2 μL DPP4 Substrate H-Gly-Pro-AMC) into each well for each sample. Mix well and incubate for 30 min at 37°C. Liberation of AMC was monitored at excitation 360 nm
and emission 460 nm before and after incubation. DPP4 activity is expressed as the amount of cleaved AMC (nmol/min/mL or unit/L). One unit is defined as the amount of DPP4 that hydrolyzes the DPP4 substrate to yield AMC at 1.0 μmol/min at 37°C. DPP4 activity was measured in the absence or the presence of sitagliptin, a specific DPP4 inhibitor, to test the specificity of the enzymatic assay. In our samples, sitagliptin inhibited the assayed DPP4 activity by >95%. All samples were analyzed in duplicate in random order and blinded to the clinical status of the participants.

MCI was diagnosed based on criteria established by the National Institute on Aging-Alzheimer’s Association (NIA-AA) workgroups (14). The criteria included 1) concern regarding a change in cognition (self/informant/clinician report), 2) objective evidence of impairment in one or more cognitive domains, which in this study were assessed by Montreal Cognitive Assessment (MoCA), 3) preservation of independence in functional abilities, measured by basic and instrumental activities of daily living (ADL questionnaires), and 4) not demented (based on the DSM-V criteria). The MoCA tests eight cognitive domains, visual–spatial ability, attention, executive function, immediate memory, delayed memory, language, abstraction, calculation, and orientation—for a maximum total score of 30. The normal MoCA score is ≥26, with 1 point added if the subject has fewer than 12 years of formal education (15). The final diagnosis of MCI was confirmed by a multidisciplinary team comprising neurologists, psychiatrists, and neuropsychologists.

Statistical Analysis
Statistical analyses were performed using the SPSS 16.0 software (SPSS Inc., Chicago, IL) and SAS 9.3 software. Normally distributed data are expressed as means ± SD, and variables (triglycerides [TG], IL-6, CRP) with a skewed distribution are reported as median (interquartile range) and log transformed to approximate normality before analysis. Categorical variables are represented by frequency and percentage. Clinical and biochemical characteristics were compared by an ANCOVA, χ², or t test. Associations between continuous variables were tested by the Pearson correlation analysis and partial correlation analyses. Multivariate logistic regression models were used to estimate the odds ratios (ORs) for MCI, elevated HbA1c, IL-6, CRP, nitrotyrosine, and 8-iso-PGF2a. Owing to a lack of current global guidelines regarding the normal reference range of IL-6, CRP, nitrotyrosine, and 8-iso-PGF2a in type 2 diabetes, the upper quartiles of IL-6, CRP, nitrotyrosine, and 8-iso-PGF2a were defined as elevated. Relative importance analysis (16) was used to explore the relative weights of DPP4 activity and potential confounders in the logistic regression models for MCI.

RESULTS
Clinical and Laboratory Characteristics
Table 1 summarizes the demographic characteristics and laboratory data of patients according to DPP4 activity quartiles. Overall, mean age was 65.9 years, BMI was 24.5 kg/m², diabetes duration was 11.1 years, HbA1c level was 7.6%, and DPP4 activity was 30.7 nmol/min/mL. Patients with higher DPP4 activities tended to be relatively old (P < 0.001), with high levels of BMI, TG, LDL-cholesterol (C), HbA1c, IL-6, CRP, nitrotyrosine, and 8-iso-PGF2a (all P < 0.05), longer diabetes duration (P = 0.003), and lower HDL-C and MoCA score (P < 0.001). They also had more diabetic nephropathy (P < 0.001), required more insulin (P < 0.001) and nonsteroidal anti-inflammatory drug (NSAID) use (P = 0.001), and exercised less (P = 0.028). The distribution of sex, current smoking, habitual alcohol consumption, education level, annual income, statin use, diabetic retinopathy, cardiovascular disease, systolic blood pressure (SBP), diastolic blood pressure (DBP), and total cholesterol did not differ according to DPP4 quartiles. Supplementary Table 1 reports characteristics of the 1,160 elderly patients with type 2 diabetes by MCI. Patients with MCI had higher IL-6, CRP, nitrotyrosine, 8-iso-PGF2a, DPP4 activity, and lower MoCA scores than those without MCI.

Association Between DPP4 Activity and MCI
Among the 1,160 elderly patients with type 2 diabetes included in this study, 351 (30.3%) had MCI. The prevalence of MCI according to DPP4 quartiles was 15.8%, 21.0%, 38.1%, and 46.2%, respectively.

Multivariate logistic regression analysis demonstrated that the ORs for MCI were higher with increasing DPP4 quartiles. The OR was 4.38 (95% CI 2.90–6.61) for MCI after adjustments for age, sex, BMI, current smoking, habitual alcohol consumption, leisure-time physical activity, education level, annual income, diabetes therapy, statin use, NSAID use, duration of diabetes, diabetic nephropathy, cardiovascular disease, SBP, TG, and HDL-C. Interestingly, further adjustment for IL-6 and nitrotyrosine reduced the magnitude of the OR for MCI to 3.49 (95% CI 1.97–4.57, P < 0.001), but this association was not attenuated by additional adjustment for HbA1c (Table 2). Relative importance analysis showed that raw relative weight and rescaled relative weight of DPP4 activity were 0.054 and 65.3% in logistic regression for MCI, respectively (Supplementary Table 4).
The risk of MCI was more pronounced among participants with rising DPP4 activities and higher levels of IL-6 (Fig. 1A), CRP (Fig. 1B), nitrotyrosine (Fig. 1C), and 8-iso-PGF2α (Fig. 1D); however, this increasing trend of MCI risk was not observed in higher levels of HbA1c (Fig. 2). Even in the lowest quartiles of IL-6, CRP, nitrotyrosine, and 8-iso-PGF2α, the risks for MCI were 2.45- to 4.89-fold higher in the highest DPP4 quartile than in the lowest quartile (Fig. 1).

**CONCLUSIONS**

Several key findings emerged from this cross-sectional study assessing the relationship between DPP4 activity and MCI. Study results demonstrated that 1) increased plasma DPP4 activities were negatively associated with MoCA score and positively associated with MCI in elderly patients with type 2 diabetes; 2) such association was paralleled by an increase in inflammation and oxidative stress in peripheral circulation; and 3) higher levels of HbA1c were not associated with an increased risk of MCI.

Systemic inflammation has been suggested to play an important pathogenic role in the late severe stages of cognitive decline, and inflammatory markers, such as IL-6 and CRP, were only found to be elevated in dementia, but not in MCI (17,18). However, the results of our study were inconsistent with this research. We
found that patients with type 2 diabetes with MCI had higher levels of IL-6 and CRP than those without MCI. Previous studies of groups with type 2 diabetes also lent support to our findings (19,20). We believe this divergence might result from variability in assay procedures for inflammatory cytokines and diagnosis of MCI to some extent. More importantly, most studies supporting that systemic inflammation may be a later event in the pathophysiological cascade of cognitive decline did not specifically exclude low-grade chronic inflammatory diseases such as type 2 diabetes, cardiovascular disease, or stroke, which may have contributed to overlap between the MCI and control groups. We consequently speculate that the elevation in peripheral inflammatory markers could occur at a very early stage, well before the deterioration of cognitive decline in type 2 diabetes. The proinflammatory effects of DPP4 and its mechanisms have been well established by previous research (21,22).

In this study, we also found an association between systemic inflammation and DPP4 activity in type 2 diabetes: IL-6 and CRP levels were positively related to DPP4 activities and increased across DPP4 quartiles; moreover, the risk of MCI became more pronounced among patients with rising DPP4 activity and higher levels of IL-6 and CRP. Taken together, it may therefore be hypothesized that DPP4 might promote the development of MCI partly through its proinflammatory function.

Aside from systemic inflammation, oxidative stress has also been shown to lead to cognitive impairment. Even at the stage of MCI, damage inflicted by oxidative stress to key proteins leads to deficiencies in systems important to the brain, such as neurotransmitter release, cell signaling, energy metabolism, and the proteasome, which might lead to the progression and pathogenesis of cognitive decline (7). In addition, oxidative parameters in the circulation were also higher in patients from MCI groups than in the control group (23,24). In line with these findings, the levels of nitrotyrosine and 8-iso-PGF2a in this study showed a similar trend and were higher in elderly patients with type 2 diabetes with MCI than in those without MCI. MCI risk increased across nitrotyrosine and 8-iso-PGF2a quartiles. DPP4 increases reactive oxygen species generation in endothelial cells in a dose-dependent manner (25). Consistently, our data also supported a positive relationship among nitrotyrosine, 8-iso-PGF2a, and DPP4 activity. The ORs for elevated oxidative stress were higher with increasing DPP4 activity quartiles. More importantly, the risk of MCI increased across DPP4 quartiles, and this trend becomes more pronounced among subjects with both higher levels of oxidative stress parameters and DPP4 activity. Because solid evidence has proved the pathogenetic role of DPP4 in oxidative stress, we speculate that DPP4-induced oxidative stress might, at least in part, promote MCI development as well.

To examine the robustness of this relationship between DPP4 activity and MCI and to obtain information on potential mechanisms that could mediate the observed relationship, we performed a set of logistic regression models comparing risk of MCI between patients in the lowest DPP4 activity group and in highest DPP4 activity group. Interestingly, further adjustment for IL-6 and nitrotyrosine yielded only a reduction of the MCI risk across the DPP4 activity quartiles. Moreover, we further tested for interactions of DPP4 with the respective other variables in Fig. 1 by adding DPP4 activity (continuous variable), IL-6, CRP, nitrotyrosine, and 8-iso-PGF2a and their interactions into the logistic regression model. However, the results of interaction analysis were not statistically significant (data not shown). This may point to additive effects rather than synergistic effects between DPP4 activity and inflammation/oxidative stress, suggesting these markers as different mechanisms contributing to increased risk of MCI. In addition, increased DPP4 activity in the individuals with high MCI risk may not be merely a consequence of enhanced inflammation and oxidative stress, because even within the lowest IL-6, CRP, nitrotyrosine, and 8-iso-PGF2a quartiles, the risks for MCI were still 2.45- to 4.89-fold higher in the highest DPP4 quartile than in the lowest quartile. Considering the multiple pleiotropic effects of DPP4 activity, the mutual effects between DPP4 activities and other factors might also exert some influence on the development of MCI in type 2 diabetes.

Although chronic hyperglycemia is implicated in the pathogenesis of cognitive impairment, findings supporting the association between glycemic control and cognition decline are inconsistent (5). In one study, for example, Xu et al (26) found that uncontrolled diabetes was associated with increased dementia risk, whereas another study reported

| Table 2—Logistic regression analysis of the association of DPP4 activity and MCI |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Q1              | Q2              | Q3              | Q4              | P               | Q1              | Q2              | Q3              | Q4              | P               |
| DPP4 activity  |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| (nmol/mL/min)  |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| <23.3          |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| 23.3–30.6      |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| 30.7–38.3      |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| >38.3          |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| DPP4 (n%)      |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| 46 (15.8)      |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| 61 (21.0)      |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| 110 (38.1)     |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| 134 (46.2)     |                 |                 |                 |                 |                 |                 |                 |                 |                 |                 |
| Model 1        | 1.0             | 1.42 (0.93–2.17) | 0.105           | 3.27 (2.21–4.86) | <0.001          | 4.58 (3.10–6.76) | <0.001          | 4.38 (2.90–6.61) | <0.001          | 4.34 (2.87–6.57) | <0.001 |
| Model 2        | 1.0             | 1.27 (0.82–1.96) | 0.283           | 3.39 (2.24–5.11) | <0.001          | 4.38 (2.90–6.61) | <0.001          | 4.34 (2.87–6.57) | <0.001          | 4.34 (2.87–6.57) | <0.001 |
| Model 3        | 1.0             | 1.27 (0.82–1.97) | 0.281           | 3.38 (2.24–5.11) | <0.001          | 4.34 (2.87–6.57) | <0.001          | 4.34 (2.87–6.57) | <0.001          | 4.34 (2.87–6.57) | <0.001 |
| Model 4        | 1.0             | 1.27 (0.82–1.98) | 0.280           | 3.06 (2.01–4.65) | <0.001          | 3.75 (2.46–5.71) | <0.001          | 3.75 (2.46–5.71) | <0.001          | 3.75 (2.46–5.71) | <0.001 |
| Model 5        | 1.0             | 1.29 (0.83–2.01) | 0.253           | 3.01 (1.98–4.57) | <0.001          | 3.49 (1.97–4.57) | <0.001          | 3.49 (1.97–4.57) | <0.001          | 3.49 (1.97–4.57) | <0.001 |

Data for the models are shown as the OR (95% CI). Model 1: Crude model. Model 2: Model 1 + age + sex + BMI + current smoking + habitual alcohol consumption + leisure-time physical activity + education level + annual income + diabetes therapy + statin use + NSAID use + duration of diabetes + diabetic nephropathy + cardiovascular disease + SBP + TG + HDL-C. Model 3: Model 2 + HbA1c. Model 4: Model 2 + IL-6. Model 5: Model 4 + nitrotyrosine.
that HbA\textsubscript{1c} was not associated with dementia in type 2 diabetes (27). With regard to the relationship between slight diabetes-associated cognitive decrements and HbA\textsubscript{1c} in elderly patients with type 2 diabetes, the results also varied in different age groups (28,29). This study found a positive relationship between DPP4 activity and HbA\textsubscript{1c}, but we did not find an association between increased risk of MCI and higher levels of HbA\textsubscript{1c}. The OR for MCI according to DPP4 quartiles was not reduced after further adjustment of HbA\textsubscript{1c}. The reasons for this discrepancy could be summarized as follows: First, HbA\textsubscript{1c} reflecting glycemic control in the last 3 months might not be able to assess chronic hyperglycemia.

Second, the association between HbA\textsubscript{1c} and cognitive decline in elderly patients with type 2 diabetes could simply be a manifestation of hyperglycemia-mediated increased propensity to diabetic vascular complications.

Third, our data indicated that patients with MCI had higher prevalence of diabetic nephropathy compared with those without MCI. Because chronic kidney disease is a well-known contributor to cognitive decline and a common cause of anemia beginning in stage 3 chronic kidney disease, resulting in shortened red cell survival or loss, it might lead to discordance between mean glucose levels and HbA\textsubscript{1c} levels, thereby falsely lowering HbA\textsubscript{1c} as a measure of mean glycemic levels.

Fourth, our study excluded individuals with a history of severe hypoglycemia, possibly narrowing the range of HbA\textsubscript{1c} values.

Finally, this divergence may result from the race, age, sample size, duration of diabetes, different assessments of cognitive decline, and heterogeneity of MCI.

Because this was a cross-sectional study, we cannot draw a causal conclusion that increased DPP4 activities promote the development of inflammation, oxidative stress, and MCI in type 2 diabetes. Although no direct evidence completed to date links MCI back to the regulation of DPP4 activity, the parallel increase in inflammation, oxidative stress, and DPP4 activity could be interpreted in an opposite way.

**Figure 1**—Adjusted ORs for MCI according to the quartiles of DPP4 activity and IL-6 (A), CRP (B), nitrotyrosine (C), and 8-iso-PGF\textsubscript{2a} (D). Adjusted for age, sex, BMI, current smoking, habitual alcohol consumption, leisure-time physical activity, education level, annual income, diabetes therapy, statin use, NSAID use, duration of diabetes, diabetic nephropathy, cardiovascular disease, SBP, TG, and HDL-C.
adversely affect the utility of HbA1c as an accurate measure of mean glycemic control.

Fourth, the study did not evaluate some other risk factors related to DPP4 activity, such as glucagon-like peptide 1 (30), which could also be associated with cognitive decline.

Finally, although MoCA is more sensitive than the Mini-Mental Status Exam (31) to detect MCI in diabetes, it is still a screening test, and specific cognitive domains, such as episodic memory, cannot be examined in relation to DPP4 activities.

In conclusion, we provide the first evidence that increased plasma DPP4 activities are associated with a high risk of MCI in elderly patients with type 2 diabetes. From a clinical perspective, we speculate that the underlying mechanisms may be partly explained by the effect of DPP4 on inflammation and oxidative stress but not on HbA1c. Moreover, if increased DPP4 activity is involved in the pathogenesis of MCI in type 2 diabetes, reduction in DPP4 activity might be a novel treatment. DPP4 inhibitors, which are widely used antidiabetic drugs in clinical practice, may also possess efficacy in the treatment of MCI. However, no randomized clinical trials have attempted to modify DPP4 activity in the treatment of MCI in elderly patients with type 2 diabetes. With the potential benefits of concurrent improvement of glycemic control and MCI, research on the efficacy of DPP4 inhibitors for treatment of MCI in type 2 diabetes is awaited. The possibility of identifying increased plasma DPP4 activity as a novel biological marker or even a suitable therapeutic target for the prevention and treatment of MCI in elderly type 2 diabetic patients may represent an avenue of future investigation in this field. However, owing to the nature of our cross-sectional study and the confounders, such as diabetic nephropathy that are likely to be present, our speculation remains to be clarified by further research.

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Author Contributions. T.Z. was responsible for study design and coordination, guided the statistical analysis, and revised the manuscript. T.Z., L.Q., and B.C. performed the statistical analysis and prepared the manuscript. X.H., Z.Z., Y.L., H.L., S.Q., G.L., and Q.L. performed data collection and reviewed the manuscript. All authors read and approved the final manuscript. T.Z. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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