

Original Article

Clinical Characteristics for the Relationship between Type-2 Diabetes Mellitus and Cognitive Impairment: A Cross-Sectional Study

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ABSTRACT: We explored the potential differences in cognitive status, lipid and glucose metabolism, ApoEε4 alleles and imaging between diabetic and non-diabetic subjects. 83 subjects with normal cognitive function and 114 mild cognitive impaired patients were divided into four groups by history of diabetes. General demographics was collected from all participants followed by MRI scan, biochemical examinations and a series of neuropsychological tests. Student's t test, multiple regressions and one-way ANOVA were applied to investigate the differences between groups. Comparing diabetic patients with non-diabetic subjects in the mild cognitive impaired group, we found several decreased items in recall of three words in MMSE ($p=0.020$), AVLT and SCWT ($p<0.050$). The multiple linear regression revealed that two-hour glucose level ($B=-0.255$, $p<0.001$) and fasting C-peptide ($B=-0.466$, $p=0.001$) had negative effects on the score of MMSE. In addition, diabetic patients treated with insulin and other diabetes medication performed better in part of the AVLT ($p<0.050$) compared to patients with insulin treatment or oral antidiabetic medication only. Patients with metformin medication had a better memory outcome compared to patients with sulphonylurea medication in the AVLT long delay free recall ($p=0.010$). These findings show that patients of mild cognitive impairment with diabetes mellitus have a worse outcome in attention, information processing speed and memory compared to non-diabetic patients. Higher two-hour glucose level and C-peptide level may be risk factors for severe cognitive impairment in type-2 diabetes mellitus patients. The results of this study also suggest that medication may have effects on cognitive function.

Key words: Type-2 diabetes mellitus, mild cognitive impairment, C-peptide, blood glucose

The incidence of type-2 diabetes mellitus (T2DM) in China has dramatically increased in the last decade. Besides the well-known connection between T2DM and peripheral nervous system disease, the diabetes-induced lesions in the central nervous system (CNS), such as cerebrovascular disease and cognitive dysfunction, are receiving increased attention. Several epidemiological studies have found that T2DM is an independent risk factor for both Alzheimer's disease (AD) and vascular dementia (VaD) [1, 2]. In addition, further research has shown that T2DM may also exercise influence on the prevalence of mild cognitive impairment (MCI), which is

considered a pre-clinical stage of dementia. In Luchsinger and colleagues' study [3], the results indicated that diabetes mellitus is related to a relatively higher risk for all causes of MCI (about 1.5 fold). In another recent meta-analysis report, diabetes was shown to have higher risk for any dementia and MCI (1.46 for AD, 2.48 for VaD and 1.21 for MCI) [4].

The present studies have confirmed that T2DM is a robust risk factor for cognitive dysfunction. However, the precise mechanisms remain to be elucidated [5]. A wide range of metabolic and vascular disturbances have been proposed to explain the underlying mechanisms of

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T2DM-related cognitive impairment including impaired neurogenesis and blood-brain barrier (BBB), hyperglycemia and hypoglycemia, inflammatory and oxidative stress, microvascular and macrovascular dysfunctions, a disturbance in the insulin signaling pathways and the altered metabolism of beta-amyloid and tau [6-8]. To date, there are no explicit treatments to help ameliorate cognitive decline in patients with DM, but an emerging awareness of brain protection in diabetic treatments and diabetes management have seen an increase. Some studies have reported a benefit of improved cognition by the effect of blood glucose control while others indicated the efficacy of lipid-lowering therapy [9, 10]. Our study aimed to analyze the differences in neuropsychology, glucose and lipid metabolism, ApoE ϵ 4 genotype between MCI patients and normal controls with and without T2DM and to explore the possible role of the relevant factors in the pathogenesis of cognitive dysfunction. We hope that the hypothetical mechanisms underlying T2DM-related cognitive impairment combined with clinical evidence will provide a better perspective of diabetic treatments.

MATERIALS AND METHODS

Subject

All participants met the following criteria: 1) Male or female in the 50-95 age group 2) Have a certain level of education (at least 6 years), able to complete the neuropsychological tests 3) No history of neurologic or psychological illness 4) No abnormal results of thyroid hormones, vitamin B12, and folate. 5) No history of cardiovascular or cerebrovascular disease; Hachinski Ischemic Score \leq 4 6) No metal implants, able to complete the MR examinations and no evidence of cortical infarcts, hemorrhage, or structural brain disease other than atrophy, lacunes, or white matter lesions. The subjects were distributed into diabetic and non-diabetic groups using the WHO report for diagnosis and classification of diabetes mellitus in 1999 [11]. All the MCI patients were diagnosed following the Peterson clinical criteria proposed in 1999 [12].

According to the criteria mentioned above, a total of 83 non-cognitive impaired subjects were recruited in our study, 43 of which were with T2DM (22 males and 21 females) and the rest were normal controls without T2DM (23 males and 17 females). There was no significant difference in age ($p=0.063$) and most of the biochemical outcomes except for plasma glucose metabolism [fasting plasma glucose (FPG), two hour postprandial plasma glucose (2h-PG), and glycated hemoglobin (HbA_{1c})], which differed significantly between these two groups.

In the MCI group, 65 subjects had no history of T2DM

(33 males and 32 females) while another 49 participants had T2DM (24 males and 25 females). No significant difference was found in age ($p=0.091$). Plasma glucose metabolism also showed a different trend combined with a slight increase in triglycerides in MCI subjects without T2DM (Table 1).

The study was approved by the Research Ethics Committee of Rui Jin Hospital (affiliated to Shanghai Jiao Tong University School of Medicine, China). Written informed consent was also obtained from each participant.

Laboratory measures and genotyping

Plasma glucose concentrations (FPG, 2h-PG, and HbA_{1c}) and synchronous insulin [fasting insulin (FINS), and two hours insulin (2h-INS)] as well as fasting C-peptide (FCP), plasma lipid content [total cholesterol (TC), triglyceride (TG), high-density lipoproteins (HDL), and low-density lipoproteins (LDL)] were collected and analyzed by an automatic biochemical analyzer in one week after the clinical and neuropsychological assessment. Apolipoprotein ϵ 4 (*APOE ϵ 4*) genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism assays (PCR-RFLP) as described in our previous study [13].

Magnetic Resonance Imaging (MRI)

We measured the interuncal distance (IUD) and the intracranial width (ICW) at the suprasellar stern level from the axial MR scans acquired on 1.5 T GE Signa Horizon for all the subjects and then calculated the IUD/ICW according to previous reports [14, 15] (Figure 1).

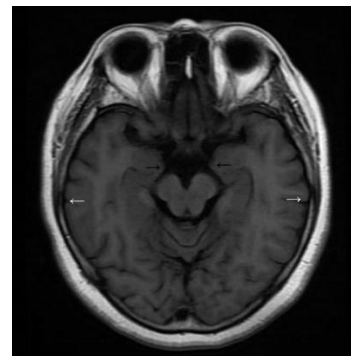


Figure 1. Brain MRI: measurement of the interuncal distance (IUD) and the intracranial width (ICW). IUD and ICW were acquired at the suprasellar stern level from the axial T1 images. The measurement of IUD is indicated by the black arrows and the ICW by the white arrows.

Table 1A. Comparison of demographic information between control and mild cognitive impairment groups

| | Total number | Male (female) | Age (yrs) | Education (yrs) | APOE ε4 (+) carriers (%) |
|------------|--------------|---------------|-------------|-----------------|--------------------------|
| NC | | | | | |
| Non-DM | 40 | 23(17) | 64.45 ±8.98 | 12.69 ±3.39 | 25.0 |
| DM | 43 | 22(21) | 68.42 ±9.10 | 12.77 ±3.10 | 18.6 |
| <i>p</i> | | 0.563 | 0.063 | 0.925 | 0.434 |
| MCI | | | | | |
| Non-DM | 65 | 33(32) | 66.12 ±9.36 | 12.81 ±2.88 | 31.4 |
| DM | 49 | 24(25) | 68.68 ±8.23 | 11.78 ±3.76 | 24.5 |
| <i>p</i> | | 0.850 | 0.091 | 0.963 | 0.537 |

NC = non-cognitive impairment subjects; Non-DM = non type-2 diabetes mellitus subjects; DM = type-2 diabetes mellitus subjects; MCI = mild cognitive impairment subjects

Table 1B. Comparison of glucose metabolism between control and mild cognitive impairment groups

| | FPG mmol/L | 2h-PG mmol/L | FINS µl U/ml | 2h-INS µl U/ml | HbA _{1c} % | FCP ng/ml |
|------------|---------------|-----------------|-----------------|-------------------|------------------------|--------------|
| NC | | | | | | |
| Non-DM | 5.16 ±0.89 | 7.68 ±3.73 | 7.02 ±2.94 | 55.03 ±24.24 | 5.97 ±0.33 | 1.87 ±0.23 |
| DM | 6.63 ±1.23 | 10.55 ±3.27 | 11.85 ±19.42 | 51.41 ±35.39 | 7.02 ±1.71 | 2.24 ±1.35 |
| <i>p</i> | <0.001 | 0.006 | 0.509 | 0.485 | 0.002 | 0.175 |
| MCI | | | | | | |
| Non-DM | 5.07 ±0.60 | 7.22 ±1.26 | 9.27 ±5.97 | 80.43 ±69.19 | 5.6 ±0.82 | 3.07 ±1.13 |
| DM | 7.10 ±2.10 | 12.25 ±5.83 | 11.50 ±8.15 | 79.43 ±95.28 | 7.44 ±1.55 | 2.53 ±1.78 |
| <i>p</i> | <0.001 | <0.001 | 0.555 | 0.817 | <0.001 | 0.491 |

NC = non-cognitive impairment subjects; Non-DM = non type-2 diabetes mellitus subjects; DM = type-2 diabetes mellitus subjects; MCI = mild cognitive impairment subjects; FPG = fasting plasma glucose; 2h-PG = two hours postprandial plasma glucose; FINS = fasting insulin; 2h-INS = two hours insulin; HbA_{1c} = glycated hemoglobin; FCP = fasting C-peptide

Table 1C. Comparison of lipid metabolism between control and mild cognitive impairment groups

| | TC mmol/L | TG mmol/L | HDL mmol/L | LDL mmol/L |
|------------|--------------|--------------|---------------|---------------|
| NC | | | | |
| Non-DM | 4.49 ±0.97 | 1.31 ±0.69 | 1.32 ±0.27 | 2.80 ±0.83 |
| DM | 4.89 ±0.96 | 1.84 ±1.42 | 1.39 ±0.55 | 2.97 ±0.74 |
| <i>p</i> | 0.142 | 0.070 | 0.758 | 0.498 |
| MCI | | | | |
| Non-DM | 5.00 ±0.97 | 1.87 ±1.17 | 1.25 ±0.33 | 2.98 ±0.82 |
| DM | 4.96 ±0.98 | 1.43 ±0.77 | 1.31 ±0.34 | 3.19 ±0.73 |
| <i>p</i> | 0.741 | 0.042 | 0.649 | 0.186 |

NC = non-cognitive impairment subjects; Non-DM = non type-2 diabetes mellitus subjects; DM = type-2 diabetes mellitus subjects; MCI = mild cognitive impairment subjects; TC = total cholesterol; TG = triglyceride; HDL = high-density lipoprotein; LDL = low-density lipoprotein

Table 1D. Comparison of MR scan between control and mild cognitive impairment groups

| | IUD cm | ICW cm | IUD/ICW |
|---------------|-----------|------------|-----------|
| NC | | | |
| Non-DM | 2.43±0.27 | 12.80±0.63 | 0.19±0.02 |
| DM | 2.57±0.36 | 12.71±0.58 | 0.20±0.03 |
| p | 0.131 | 0.567 | 0.068 |
| MCI | | | |
| Non-DM | 2.51±0.41 | 12.71±0.72 | 0.20±0.31 |
| DM | 2.50±0.33 | 12.65±0.60 | 0.20±0.03 |
| p | 0.880 | 0.667 | 0.895 |

NC = non-cognitive impairment subjects;
 Non-DM = non type-2 diabetes mellitus subjects;
 DM = type-2 diabetes mellitus subjects;
 MCI = mild cognitive impairment subjects;
 IUD = interuncal distance;
 ICW = intracranial width

Clinical and neuropsychological assessment

Clinical and neuropsychological assessments included the Mini-Mental State Examination (MMSE), Auditory Verbal Learning Test (AVLT), Clinical Dementia Rating (CDR), and Stroop Color Words Test (SCWT). We used

the Chinese version of the MMSE in our study with cutoff points according to the educational level: 17/18 for illiterates, 20/21 for those with primary school education, and 24/25 for subjects with middle school or higher education [16]. According to the previous study, the AVLT immediate recall (a full score of 36) and long delayed free recall (20 minutes after with a full score of 12) were measured to assess the memory of subjects [17]. In this study, we added another two other components into the evaluation: the AVLT 5-minute recall (a full score of 12) and long delay cued recall. The CDR is a five-point scale with six independent domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) [18]. Normally, CDR-0 connotes no cognitive impairment, CDR-0.5: very mild dementia, CDR-1: mild, CDR-2: moderate, and CDR-3: severe. The SCWT contains three parts in which SCWT-A and SCWT-B measure attention and processing speed while SCWT-C mainly focuses on executive function [19]. In addition, other neuropsychological test including Activity of Daily Living (ADL), Neuropsychiatric Inventory (NPI), Hamilton Depression Rating Scale (HAMD), and Hachinski Ischemic Score (HIS) were also used to evaluate subjects' status. Demographic information such as age, sex, past history of diabetes mellitus, and current medication were collected at the same time.

Table 2. Comparison of cognitive function between MCI patients without diabetes and MCI patients with diabetes

| | MCI (non-diabetic) n=65 | MCI (diabetic) n=49 | p |
|--|-------------------------------|---------------------------|--------|
| Recall in MMSE (3 words) | 2.04 ± 0.84 | 1.57 ± 1.08 | 0.020* |
| MMSE total score | 27.12 ± 2.35 | 25.84 ± 3.58 | 0.099 |
| AVLT immediate recall (36 words) | 13.05 ± 5.08 | 10.89 ± 3.87 | 0.066 |
| AVLT 5-minute recall (5 min/12 words) | 3.55 ± 2.83 | 2.41 ± 2.01 | 0.031* |
| AVLT long delay free recall (20 min/12 words) | 3.03 ± 2.79 | 1.93 ± 1.89 | 0.049* |
| AVLT long delay cued recall | 0.55 ± 1.31 | 0.74 ± 1.22 | 0.379 |
| SCWT-A performance time (s) | 30.86 ± 10.77 | 36.26 ± 13.86 | 0.035* |
| SCWT-A correct number (50) | 49.13 ± 3.07 | 48.17 ± 7.77 | 0.750 |
| SCWT-B performance time (s) | 45.56 ± 13.38 | 51.50 ± 21.16 | 0.253 |
| SCWT-B correct number (50) | 48.54 ± 2.93 | 44.73 ± 10.98 | 0.046* |
| SCWT-C performance time (s) | 91.47 ± 36.3 | 100.88 ± 58.82 | 0.688 |
| SCWT-C correct number (50) | 44.72 ± 8.02 | 43.18 ± 9.56 | 0.457 |

MMSE = Mini-Mental State Examination;
 AVLT = Auditory Verbal Learning Test;
 SCWT = Stroop Color Words Test;
 MCI = mild cognitive impairment subjects

Statistical analysis

All data analyses were performed using SPSS. Independent samples *t*-test was applied to test inter-group differences in continuous variables while Chi square test was used for categorical variables. To assess correlations between the MMSE performance and the clinical characteristics, stepwise multiple regression was used. In order to investigate the differences between treatments, one-way analysis of variance (ANOVA) was applied in the three groups (with insulin treatment only, with oral anti-diabetic medication only, and with a combination of insulin with other diabetes medication). A *p*-value of less than 0.05 was considered significant.

RESULTS

Comparison of cognitive function between subjects with and without diabetes

In the normal cognitive function group, there was no significant difference in MMSE, AVLT, and SCWT between diabetic and non-diabetic subjects. However, MCI patients with T2DM demonstrated a worse performance vs non-diabetic MCI patients in these tests: recall of three words in MMSE ($p=0.020$), AVLT 5-minute recall ($p=0.031$) and long delayed free recall ($p=0.049$), the correct number of SWCT-B ($p=0.046$) and performance time in SWCT-A (Table 2).

Comparison of laboratory measures, genotyping and MR examination between subjects with and without cognitive impairment

The plasma glucose and lipid concentrations, *APOE* $\epsilon 4$ genotyping as well as the brain MR examinations including IUD, ICW and IUD/ICW, showed no significant difference between normal cognitive function and MCI groups.

Stepwise multiple regression model of MMSE scores

Correlations between the MMSE score and diabetic duration, glucose and lipid metabolism were demonstrated in Table 3. The stepwise linear regression revealed that the better performance in MMSE was linked to lower 2h-PG (Coefficient = -0.255, $p<0.001$) and FCP (Coefficient = -0.466, $p=0.001$).

Comparison of cognitive function of T2DM patients with different treatments

We divided patients with T2DM into three groups: with insulin treatment only, with oral antidiabetic medication

only, and a combination of insulin with other diabetes medication. To evaluate the performance in neuropsychological test of the three groups, we applied the one-way ANOVA test. As shown in Table 4, the difference in AVLT long delay cued recall between groups was significant ($p =0.002$). Diabetic patients with a combination of insulin and other diabetes medication performed better in AVLT long delay cued recall ($p=0.001$) compared to patients with insulin treatment only, and superior performance in AVLT long delay cued recall ($p =0.001$), SCWT-B performance time ($p=0.049$) and correct number ($p=0.009$) vs patients with oral antidiabetic medication only. However, the outcome of patients with insulin treatment was only better than that of patients with oral antidiabetic medication in SCWT-B correct number ($p=0.018$).

We further compared the results of T2DM patients with metformin medication and with sulphonylurea. We found that patients with metformin medication had a better memory outcome compared to patients with sulphonylurea medication in AVLT long delayed free recall ($p =0.010$).

Table 3. Correlation between MMSE scores and clinical characteristics

| | Coefficient | <i>p</i> |
|-------------------|-------------|----------|
| Duration | 0.216 | 0.966 |
| FPG | -0.029 | 0.449 |
| 2h-PG | -0.255 | <0.001* |
| FINS | -0.090 | 0.993 |
| 2h-INS | -0.127 | 0.939 |
| HbA _{1c} | -0.264 | 0.257 |
| FCP | -0.466 | 0.001* |
| TC | -0.111 | 0.780 |
| TG | -0.006 | 0.971 |
| HDL | -0.068 | 0.854 |
| LDL | -0.103 | 0.469 |

FPG = fasting plasma glucose;

2h-PG = two hours postprandial plasma glucose;

FINS = fasting insulin;

2h-INS = two hours insulin;

HbA_{1c} = glycated hemoglobin;

FCP = fasting C-peptide;

TC = total cholesterol;

TG = triglyceride;

HDL = high-density lipoprotein;

LDL = low-density lipoprotein

DISCUSSION

A wide range of cognitive domains was reported to be impaired in older patients with T2DM, which has a close relation with the pathological mechanisms. Insulin and its signaling pathways not only regulate glucose and energy

metabolism, but also modulate learning and memory [20]. As cognition-related structures such as the hippocampus and entorhinal cortex have a high density of insulin receptors and can produce insulin locally, an obstacle in any of the insulin signaling pathways can give rise to cognitive dysfunction most of which relates to memory, attention and executive functions [21, 22]. In addition, the evidence from neuroimaging also supports the view that T2DM impacts cognition. Using single photon emission computed tomography (SPECT) in elderly diabetic patients, it was reported that there is a reduction in cerebral perfusion of the fronto-temporal region, a region

that plays an important role in memory, judgment, attention, learning ability and other functions [23]. Furthermore, a resting-state functional MRI study confirmed altered amplitude of low-frequency fluctuations (ALFF) in many brain regions of T2DM patients, which reflected poor neurocognitive performances [24]. Our study also found that MCI patients with T2DM had worse performances in memory, attention, and information processing speed. These results correlated with the acknowledged pathological mechanisms and neuroimaging.

Table 4. Comparison of cognitive functions between insulin, oral anti-diabetic therapy and combined therapy groups

| | Insulin treatment only | Oral antidiabetic medication only | Combined treatment | ANOVA |
|--|------------------------|-----------------------------------|--------------------|-------------------------|
| Number | 12 | 59 | 9 | |
| AVLT immediate recall (36 words) | 14.70 ± 5.17 | 12.83 ± 5.03 | 16.75 ± 5.63 | F = 2.406 p = 0.097 |
| AVLT 5-minute recall (5 min/12 words) | 3.90 ± 3.28 | 3.78 ± 2.65 | 5.25 ± 2.86 | F = 1.000 p = 0.373 |
| AVLT long delay free recall (20 min/12 words) | 3.50 ± 3.03 | 3.33 ± 2.70 | 4.75 ± 3.28 | F = 0.905 p = 0.409 |
| AVLT long delay cued recall | 0.40 ± 0.70 | 1.17 ± 1.81 | 3.38 ± 2.26 | F = 6.971 *p = 0.002 |
| SCWT-A performance time (s) | 31.80 ± 12.56 | 32.20 ± 12.11 | 26.75 ± 7.07 | F = 0.729 p = 0.486 |
| SCWT-A correct number (50) | 50.00 ± 0.00 | 48.72 ± 6.80 | 49.75 ± 0.71 | F = 0.260 p = 0.772 |
| SCWT-B performance time (s) | 41.90 ± 11.13 | 47.96 ± 18.95 | 34.86 ± 6.75 | F = 2.286 p = 0.110 |
| SCWT-B correct number (50) | 49.70 ± 0.95 | 46.52 ± 7.73 | 49.88 ± 0.35 | F = 1.556 p = 0.219 |
| SCWT-C performance time (s) | 73.20 ± 20.36 | 92.83 ± 50.35 | 68.88 ± 21.50 | F = 1.547 p = 0.220 |
| SCWT-C correct number (50) | 46.10 ± 6.57 | 44.10 ± 8.95 | 47.00 ± 2.51 | F = 0.595 p = 0.555 |

AVLT = Auditory Verbal Learning Test;
SCWT = Stroop Color Words Test

Although there was no significant difference in glucose and lipid metabolism as well as brain imaging, the results of linear regression suggested that the level of FCP might influence cognitive function in patients with T2DM. C-peptide is a link of a-/b-chains of the insulin molecule. Neither liver enzymes nor external insulin will perturb the concentration of C-peptide in the blood. Thus, it has become a core intermediate product for the analysis of insulin release. However, recent studies revealed that C-peptide is not restricted to its use in the measurement of insulin as it also plays important roles in a variety of

physiological processes [25]. Through studying patients with type one diabetes mellitus (T1DM), C-peptide was found to be involved in inflammation, cognitive function, microcirculation and regulatory effects on various features such as neurotrophic factors, pain sensitivity and glomerular filtration [26]. Under physiological concentrations, C-peptide demonstrates its power in anti-inflammatory, immunomodulatory and neuroprotective effects. Damage may occur in patients with T1DM due to the absence of C-peptide whereas those with T2DM may be harmed because of an excess of C-peptide, causing

complications in cardiovascular and nervous systems [27, 28]. The finding in this study suggests that FCP is negatively correlated with the MMSE scores in patients with T2DM probably because of its underlying mechanism.

Meanwhile, the 2h-PG levels also showed a negative correlation with cognition function. Previously, a large-sample perspective study with a median follow-up of 6.8 years suggested that higher average glucose levels were related to an increased risk of dementia [29]. The mechanism of this phenomenon revealed that hyperglycemia might cause an increasing risk of microvascular disease and structural changes in the hippocampus [30]. Besides, Morby [31] pointed out that even among the elderly population with higher-blood glucose levels in the normal range, the frontal cortex could be impacted to result in impairment in working memory, executive function, information processing speed and language. Another research focusing on the relationship between MCI and diabetes suggested an association of MCI with diabetes mellitus in the aspects of onset, duration and severity [32]. Both clinical and mechanistic studies provided clear clues that a better control in blood glucose is essential for the prevention of patients with T2DM from developing cognitive impairment. Our study, again, confirmed this viewpoint.

Will the different choice of treatment affect the cognitive function in patients with T2DM? Some previous literature reported that insulin therapy might slow down the decline of cognition in patients with T2DM [33]. For our study, however, better outcomes of cued recall, attention and information processing speed were witnessed in the combination-therapy group compared to oral antidiabetic medication group while patients with insulin treatment performed better than those with oral antidiabetic medication only in one of the tests for attention and information processing speed. Beerli and colleagues [34] reported in a postmortem study that lower neuritic plaque density in the hippocampus, entorhinal cortex, and amygdala was found in patients receiving a combination of insulin and other diabetes medication. This may explain the phenomenon in our study. In addition, patients with metformin medication exhibited a better memory outcome compared to patients with sulphonylurea medication. Metformin is known as one of the first line treatment for T2DM. Metformin improves glucose metabolism mainly by suppressing hepatic glucose production and altering pathways of insulin signaling [35]. It has been confirmed that metformin could cross the blood-brain barrier (BBB) then directly pose anti-inflammatory and neuroprotective effects on CNS [36]. Animal models also demonstrated that metformin effectively improves peripheral insulin sensitivity in rats under insulin resistant condition. Metformin was also

shown to significantly decrease peripheral and brain oxidative stress levels and prevent brain mitochondrial dysfunction so that the learning behavior was improved in experimental rats [37].

In conclusion, our study found that for MCI patients, those with T2DM showed poor performance in cognitive functions, including attention, information processing speed and memory. Both 2h-PG and FCP had a negative correlation with cognitive function, indicating that cognitive function may deteriorate without a strict supervision of blood glucose and fasting C-peptide. In addition, patients treated with the combination therapy ended up with a better outcome in multiple cognitive domains compared to those treated with insulin only or oral antidiabetic medication only. Furthermore, in the oral antidiabetic medication group, patients with metformin medication had a better preservation of memory than those with sulphonylurea. Because of limited information from imaging in this study, we are looking forward to elaborate the difference in brain structure and function between patients with or without diabetes mellitus by functional magnetic resonance imaging (fMRI) in future.

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