

Effect of DPP-4 inhibitor on elderly patients with T2DM combined with MCI

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Abstract. The aim of this study was to investigate the effect of dipeptidyl peptidase-4 (DPP-4) inhibitor on blood sugar level and cognitive ability in elderly patients with type 2 diabetes mellitus (T2DM) combined with post-stroke mild cognitive impairment (MCI). Thirty patients received DPP-4 inhibitor (study group), while another thirty received sulfonylurea (control group). Six months after treatment, markers regarding blood sugar were improved in both groups (all $P < 0.05$) without intergroup differences (all $P > 0.05$); scores regarding cognitive ability improved in the study group (both $P < 0.05$) and were higher versus the control group (both $P < 0.01$); the study group had higher A β 1-42/A β 1-40 value versus the pretreatment value ($P < 0.001$), which differed from the control group ($P < 0.05$); tumor necrosis factor- α and interleukin-6 concentrations decreased in both groups, while the study group had greater reductions; C-reactive protein value decreased after treatment in the study group (all $P < 0.05$). Using DPP-4 inhibitor in elderly patients with T2DM combined with post-stroke

MCI can lower blood sugar and improve cognitive ability. The mechanism may be associated with the improvement of A β gathering and reduction in inflammatory response.

Introduction

Incidence of type 2 diabetes mellitus (T2DM) has been rising each year due to trends in population aging. It has been estimated that by 2040, there will be 615 million people suffering from T2DM (1). Meanwhile, morbidity of cognitive impairment (CI) increases as patients age. Some studies have documented that the incidence rate of CI is 5-10% in patients over 65 years old and 20-50% in patients over 85 years, with a higher prevalence in women than in men (2). Stroke is believed to be the second biggest factor in inducing CI (3). There have been studies revealing that T2DM is one of the common risk factors in causing stroke and CI. Thus patients with T2DM are more likely to have cognitive dysfunction after a stroke (4-6).

Regarding the pathogenesis, it has been reported that T2DM and CI share common lesion characteristics including A β gathering, decreased ability in regulating protein phosphorylation, and participation of chronic inflammatory factors; moreover, insulin resistance and damage to insulin signal transmission are also common pathological bases in the occurrence of both diseases (7,8). Glucagon-like peptide-1 (GLP-1) is an endogenous incretin. It can promote the release of insulin from islet cell and keep the glucose content at a relatively stable level in the body (9). Some recent studies have demonstrated that GLP-1 can not only affect pancreatic islet function but also display neurotransmitter-like and neuron growth factor-like properties (10). GLP-1 agents, such as liraglutide and exenatide, have been demonstrated to be able to mitigate neurodegeneration in Alzheimer's disease (AD) and decrease memory and learning disabilities when used in the rat model of AD (11,12). However, some studies have found that GLP-1 gets readily hydrolyzed by dipeptidyl peptidase-4 (DPP-4) in the body, causing loss of activity and function. DPP-4 inhibitors including sitagliptin, vildagliptin, and linagliptin reduce sugar level mainly through inhibiting GLP-1 hydrolysis (13). Currently, studies regarding the improvement of cognitive ability by DPP-4 were primarily carried out among patients with AD, whereas studies performed in patients with T2DM combined with post-stroke mild cognitive impairment

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Abbreviations: DPP-4, dipeptidyl peptidase-4; T2DM, type 2 diabetes mellitus; MCI, mild cognitive impairment; CI, cognitive impairment; GLP-1, glucagon-like peptide-1; AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; FBG, fasting blood glucose; 2hPG, 2-hour postprandial blood glucose; HbA1c, hemoglobin A1c; CRP, C-reactive protein; TNF, tumor necrosis factor; IL, interleukin; MoCA, Montreal Cognitive Assessment

Key words: cognitive impairment, blood sugar, efficacy

(MCI) were few (14,15). Therefore, in the present study, we used DPP-4 inhibitor in treating elderly patients with T2DM combined with post-stroke MCI and investigated its effect on patients' blood sugar level and cognitive ability.

Materials and methods

Patient characteristics. The present study was approved by the Ethics Committee of Heilongjiang Provincial Hospital, (Harbin, China) and informed consent was obtained from all individuals included in this study. Sixty patients treated in the department of neurology in Heilongjiang Provincial Hospital between January 2017 and June 2018 for T2DM combined with post-stroke CI were selected and randomized into a study group (treated with DPP-4 inhibitor) and a control group (treated with sulfonylurea) of 30 patients each. All patients were aged above 65 years.

Inclusion criteria were as follows: i) Patients who met the diagnostic criteria for T2DM (16); ii) patients who met the diagnostic criteria for post-stroke CI after assessment of cognitive ability and the condition was stabilized after treatment (17); iii) patients who met the following four criteria for MCI: a) patients with a score of ≥ 24 points in Mini-Mental State Examination (MMSE, 19 items, total score of 30 points); b) patients with a score of < 26 points in Montreal Cognitive Assessment (MoCA) if they had over 12 years of education (one point was added to the MoCA score if patients did not have over 12 years of education); c) patients were reported by themselves or their family members to have hypomnesia; d) activity of daily living score < 26 points (18); iv) patients had diabetes before stroke occurrence, and the antidiabetic drugs patients received were sulfonylurea and metformin instead of DPP-4 inhibitor.

Exclusion criteria were: i) Patients who were allergic to DPP inhibitor; ii) patients who had histories of craniocerebral trauma, epilepsy, and cerebrovascular disease; iii) patients who would not cooperate with cognitive testing; iv) patients who were taking glucocorticoid which would affect blood sugar level; v) patients who had cardiopulmonary insufficiency; vi) patients who had malignant tumors; vii) patients who had mental illness which would affect cognition.

Methods. According to a random number table, patients in the study were assigned to either a study group or a control group of 30 patients each. In the study group, patients received oral administration of 100 mg sitagliptin (Merck Sharp & Dohme, Ltd., registration number for imported medicine: H20090834), a DPP-4 inhibitor, one time per day and one pill each time; meanwhile, patients in the control group received sulfonylurea. If the blood sugar level was not lowered effectively, regular insulin would be administered temporarily to control the sugar content. Efficacy was evaluated at six months after treatment.

Outcome measures. Main outcome measures were: i) fasting blood glucose (FBG), 2-hour postprandial blood glucose (2hPG), and hemoglobin A1c (HbA1c) values before and six months after treatment; FBG and 2hPG were measured using Accu-Chek Performa blood glucose meter (Roche), while HbA1c was measured using DCA 2000 analyzer (Bayer); ii) MMSE and MoCA scores before and six months after treatment for cognitive evaluation.

Secondary outcome measures included C-reactive protein (CRP), tumor necrosis factor (TNF)- α , interleukin (IL)-6, and A β 1-40 and A β 1-42 values. Two tubes of venous blood (5 ml each) were collected from each patient at 8'clock in the morning before and six months after treatment. The blood samples were placed in sterile EDTA tubes and kept in a fridge at 4°C for 15 min. Afterward, samples were centrifuged at 1,500 x g at 4°C for 30 min to separate serum from plasma. The plasma was incubated with phosphate buffered saline containing 40 μ l protease inhibitor at -80°C. Levels of CRP, TNF- α , and IL-6 in serum were measured using immunoturbidimetry, while values of A β 1-40 and A β 1-42 in plasma were measured using ELISA.

Statistical analysis. SPSS 17.0 software was applied for statistical analysis. Continuous variables are expressed as mean \pm SD. t-test was performed if there were normal distribution and homogeneity of variance; comparison between two groups was conducted by independent-samples t-test; before versus after comparison within the group was performed by paired t-test; quartile was presented, and Wilcoxon rank-sum test was conducted if there were no normal distribution and homogeneity of variance. Pearson's Chi-squared test was performed for count data. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. There were no intergroup differences in sex, age, education background, body mass index, and comorbidities so that the results were comparable (all $P > 0.05$, Table I).

Sugar blood content before and after treatment in the two groups. No intergroup differences were found in FBG, 2hPG, and HbA1c in the two groups before and after treatment (all $P > 0.05$). Compared with the pretreatment values, these markers improved significantly six months after treatment (all $P < 0.05$) (Table II).

Cognitive ability before and after treatment in the two groups. No intergroup differences were found in MMSE and MoCA scores in the two groups before treatment (both $P > 0.05$). However, at six months after treatment, the MMSE and MoCA scores in the study group improved significantly compared with the pretreatment scores (both $P < 0.05$). In the control group, the MMSE score was lower than that before the treatment ($P < 0.05$). Differences were observed between the two groups regarding these scores after treatment (both $P < 0.01$). (Table III and Fig. 1).

A β 1-42, A β 1-40, and A β 1-42/A β 1-40 levels in plasma before and after treatment in the two groups. There were no intergroup differences in A β 1-42, A β 1-40, and A β 1-42/A β 1-40 levels before treatment (all $P > 0.05$). However, at six months after treatment, the value of A β 1-42/A β 1-40 improved significantly in the study group ($P < 0.001$), whereas the levels of the other two markers were similar to those before treatment (both $P > 0.05$). A β 1-42/A β 1-40 value differed between the two groups after treatment ($P < 0.05$) (Table IV and Fig. 2).

Table I. Patient characteristics and baseline data.

Characteristics	Study group (n=30)	Control group (n=30)	χ^2/t value	P-value
Sex (male:female)	17:13	14:16	0.601	0.438
Age (years)	68.5±7.1	67.4±5.9	0.692	0.492
Education (year)	12.5±3.8	11.9±4.0	0.627	0.533
Body mass index (kg/m ²)	25.71±3.76	25.59±4.28	0.110	0.913
Diabetes duration	8.17±3.05	8.97±2.65	0.534	0.128
Stroke type			0.268	0.605
Ischemic stroke	15	17		
Hemorrhagic stroke	15	13		
Comorbidity				
Hyperlipemia			0.067	0.759
Yes	17	16		
No	13	14		
Hypertension			0.635	0.426
Yes	20	17		
No	10	13		
Coronary heart disease			0.287	0.592
Yes	10	12		
No	20	18		
Obesity			0.635	0.426
Yes	10	13		
No	20	17		
Hyperhomocysteinemia			0.373	0.542
Yes	22	24		
No	8	6		
Hyperuricemia			0.693	0.405
Yes	19	22		
No	11	8		

Table II. Sugar blood content before and after treatment in the two groups.

Sugar blood content	Study group	Control group	t value	P-value	Study group	Control group	t value	P-value
	Before treatment	Before treatment			After treatment	After treatment		
FBG (mmol/l)	9.51±1.24	9.29±1.32	0.666	0.508	7.19±1.81 ^a	7.17±1.77 ^a	0.050	0.960
2hPG (mmol/l)	16.89±3.77	16.70±4.69	0.170	0.866	10.47±3.80 ^a	10.56±2.59 ^a	0.103	0.918
HbA1c (%)	8.56±1.25	8.86±3.17	0.471	0.640	6.97±1.25 ^a	7.35±2.48 ^a	0.749	0.457

FBG, fasting blood glucose; 2hPG, 2-hour postprandial blood glucose; HbA1c, hemoglobin A1c. ^aP<0.05 vs. before treatment.

CRP, TNF- α , and IL-6 levels before and after treatment in the two groups. There were no intergroup differences in CRP, TNF- α , and IL-6 before treatment (all P>0.05). However, at six months after treatment, the levels of these markers improved greatly in the study group (all P<0.05). The control group had improved levels of TNF- α and IL-6 after treatment (both P<0.05). Intergroup differences were observed in the three markers after treatment, and the reductions in the study group were greater (all P<0.05) (Table V and Fig. 3).

Discussion

Some clinical studies have displayed that elderly patients with T2DM are more likely to have CI, and the occurrence is often unnoticeable. The condition may be mild cognitive dysfunction in the beginning but turns to dementia as it progresses.

Pathogenesis of the disease may be associated with various factors, including A β gathering, chronic inflammation, and age, making CI more easily developed in elderly patients with

Table III. Score of cognitive ability before and after treatment in the two groups.

Scores	Study group	Control group	t value	P-value	Study group	Control group	t value	P-value
	Before treatment	Before treatment			After treatment	After treatment		
MMSE	25.42±1.22	25.37±1.16	0.108	0.914	26.83±0.91 ^a	22.70±1.80 ^a	11.201	<0.001
MoCA	22.50±1.94	22.20±2.35	0.538	0.592	23.73±2.03 ^a	22.23±2.18	2.759	0.008

MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment. ^aP<0.05 vs. before treatment within the same group.

Table IV. A β 1-42, A β 1-40, and A β 1-42/A β 1-40 levels in plasma before and after treatment in the two groups.

Markers	Study group	Control group	t value	P-value	Study group	Control group	t value	P-value
	Before treatment	Before treatment			After treatment	After treatment		
A β 1-42 (ng/l)	18.37±5.08	17.73±4.64	0.504	0.616	19.03±3.17	19.40±5.05	0.337	0.737
A β 1-40 (ng/l)	46.50±11.19	43.80±9.98	0.987	0.328	41.03±9.18	44.97±10.83	1.517	0.135
A β 1-42/A β 1-40	0.39±0.04	0.40±0.02	1.445	0.154	0.47±0.03 ^a	0.43±0.04	4.649	<0.001

^aP<0.05 vs. before treatment within the same group.

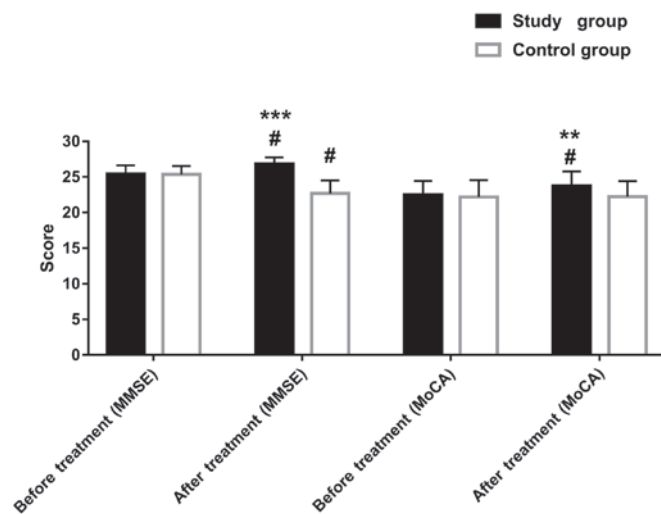


Figure 1. Score of cognitive ability before and after treatment in the two groups. MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment. ^{**}P<0.01, ^{***}P<0.001 vs. the control group; [#]P<0.05 vs. before treatment.

T2DM; moreover, the occurrence of CI is closely correlated with glucose variability (19). Some researchers have reported that CI is more likely to occur in T2DM patients with long-term insulin resistance and hyperinsulinemia, and T2DM is regarded as a risk factor of CI. Furthermore, patients with T2DM and CI often have brain insulin resistance (20). Studies on stroke have indicated that in patients who had a stroke, the injury to neurovascular unit due to cerebra hypoxia-ischemia can impair cognitive ability (21,22). Other studies have exhibited that DPP-4 inhibitor not only has better blood sugar lowering effect versus other hypoglycemic agents but also attenuates CI induced by AD (23-26). In the present study,

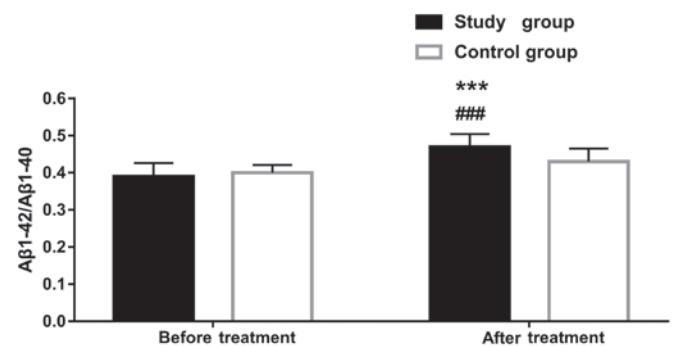


Figure 2. A β 1-42/A β 1-40 level in plasma before and after treatment in the two groups. ^{***}P<0.001 vs. the control group; ^{###}P<0.001 vs. before treatment.

we compared the efficacy of DPP-4 inhibitor sitagliptin with that of sulfonylurea in the treatment and observed that the two agents performed similarly in lowering blood sugar content. However, in terms of improving cognitive ability, the study group given DPP-4 inhibitor exhibited better MMSE and MoCA scores than the control group, which aligns with the studies above.

It has been demonstrated that A β gathering, decreased ability in regulating protein phosphorylation, and the participation of chronic inflammatory factors are common lesion characteristics in both T2DM and CI (27). Regarding the mechanism of improving cognitive ability, we studied the A β gathering and chronic inflammatory factors. Some researchers have reported increased A β expressions in cerebral cortex and hippocampus of mice with diabetes, whereas using DPP-4 inhibitor decreases A β expression levels in these two areas (27). Another study has documented a reduction in A β expression in the cerebrospinal fluid of AD patients (28).

Table V. CRP, TNF- α , and IL-6 levels before and after treatment in the two groups.

Factors	Study group Before treatment	Control group Before treatment	t value	P-value	Study group After treatment	Control group After treatment	t value	P-value
CRP (mg/l)	6.64 \pm 1.81	6.90 \pm 1.84	0.917	0.363	4.80 \pm 1.52 ^a	7.57 \pm 1.48	7.153	<0.001
TNF- α (μ g/ml)	124.51 \pm 18.22	123.80 \pm 17.87	0.154	0.878	85.01 \pm 15.90 ^a	102.66 \pm 16.12 ^a	4.269	<0.001
IL-6 (μ g/ml)	351.37 \pm 37.86	351.00 \pm 37.32	0.038	0.969	273.27 \pm 25.64 ^a	318.34 \pm 29.73 ^a	6.287	<0.001

CRP, C-reactive protein; TNF- α , tumor necrosis factor- α ; IL-6 - interleukin-6. ^aP<0.05 vs. before treatment within the same group.

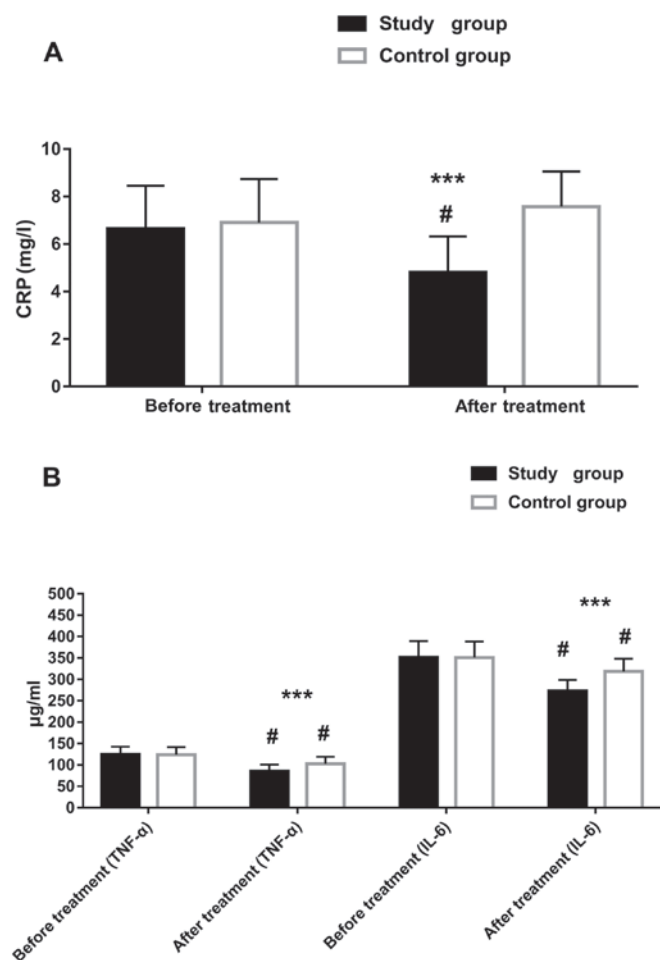


Figure 3. CRP, TNF- α , and IL-6 levels before and after treatment in the two groups. (A) CRP level before and after treatment, (B) TNF- α and IL-6 levels before and after treatment. CRP, C-reactive protein; TNF- α , tumor necrosis factor- α ; IL-6, interleukin-6. ***P<0.001 vs. the control group; #P<0.05 vs. before treatment.

However, it is not easy to perform a cerebrospinal fluid test during an early diagnosis of CI. Therefore, clinical studies were performed to find more easy-to-measure biomarkers in blood. Some studies on A β 1-40 and A β 1-42 have observed different expression changes including rising, no-change, and reduction in these two markers in plasma of patients with MCI (29-31). Moreover, the ratio of A β 1-42 to A β 1-40 has been found to decrease in patients with MCI, and the ratio reduces even much more in patients with AD (31). The

high blood sugar content in T2DM can induce an immunoinflammatory response. It has been revealed that levels of CRP, TNF- α , and IL-6 can all elevate in T2DM patients (32). Inflammatory factors also exist in patients with CI. Some studies have reported elevated levels of various inflammatory factors in CI patients, leading to neuroinflammation. Due to inflammatory response, microglia and astrocyte can be excessively activated and produce toxic substances that damage neurons, thereby causing neuron denaturalization and apoptosis (33). IL-6 is a type of inflammatory factor. Previous studies reported that IL-6 expression could begin to increase in plasma during the early stage of AD (34). However, another study reported no difference in IL-6 expression in serum between patients with MCI and normal people (35). CRP, a marker commonly used in clinic, is a protein synthesized in liver mediated by inflammatory factors such as IL-6 (36). In the present study, we compared the study group with the control group and found no intergroup differences in A β 1-40 and A β 1-42 in plasma before and after treatment in patients. After treatment, the study group had a significantly higher ratio of A β 1-42 to A β 1-40 than the control group. Moreover, no intergroup differences were observed in CRP, TNF- α , and IL-6 levels before treatment, whereas these values were much lower in the study group than in the control group after treatment. These results align with previous findings.

There were still some limitations in the study. The sample size was small, requiring a study with a larger sample size in the future. Also, the study period was relatively short, and the study was affected by several external factors including area of infarction or bleeding, the difference in the treatment plan for infarction and bleeding, and recovery duration. Therefore, a longer follow-up will be needed in future studies.

In conclusion, using DPP-4 inhibitor in treating elderly patients with T2DM combined with post-stroke MCI can decrease blood sugar level and improve cognitive ability. The mechanism may be associated with the improvement of A β gathering and reduction in the inflammatory response in the body.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JX recorded and compared sugar blood content and wrote the manuscript. CW and CP conceived and designed the study. CP and HX were responsible for the collection and analysis of the experimental data. LX and XC interpreted the data and drafted the manuscript. XW and NW were responsible for the comparison of CRP, TNF- α and IL-6, and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Heilongjiang Provincial Hospital (Harbin, China). Patients who participated in this research had complete clinical data. Signed written informed consents were obtained from the patients and/or guardians.

Patient consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no competing interests.

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