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Original Article

Comparison between the effects of sitagliptin and liraglutide on blood glucose and cognitive function of patients with both type 2 diabetes mellitus and post-stroke mild cognitive impairment

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Abstract: Objective: This study aimed to compare the effects of sitagliptin and liraglutide on blood glucose and cognitive function of patients with both type 2 diabetes mellitus (T2DM) and post-stroke mild cognitive impairment. Methods: A total of 60 such patients were enrolled and divided into two groups using the random number table method. The observation group was treated with sitagliptin (n=30), while the control group was treated with liraglutide (n=30). After 6 months of treatment, the patients' fasting blood glucose (FBG), 2-hour postprandial blood glucose (2hPG), and glycosylated hemoglobin (HbA1c) were evaluated, and their cognitive function was scored using the mini-mental state examination (MMSE) and the Montreal cognitive assessment (MoCA). In addition, the following indexes of the patients were determined and comparatively studied: Plasma Aβ1-40 and Aβ1-42, serum C-reactive protein (CRP), serum tumor necrosis factor-α (TNF-α), and serum interleukin-6 (IL-6). Results: After treatment, both groups showed significantly improved FBG, 2hPG, and HbA1c levels (all P<0.05), but there was no difference in those indexes between them (all P>0.05). After treatment, the observation group performed much better in terms of MMSE and MoCA (both P<0.05), and got significantly better results than the control group (P<0.01). After 6 months of treatment, the observation group showed significantly improved Aβ1-42/Aβ1-40 ratio (P<0.001), and there were significant differences between the two groups in the ratio after treatment (P<0.05). In addition, after treatment, both groups showed significantly lower concentrations of CRP, TNF-α, and IL-6 (all P<0.05), and the observation group showed higher concentrations than the control group (all P<0.05). Conclusion: Sitagliptin is more effective than liraglutide in improving the cognitive function of patients with both T2DM and post-stroke mild cognitive impairment, and its mechanism may be related to the amelioration of Aβ aggregation and alleviation of inflammatory response in vivo.

Keywords: Sitagliptin, liraglutide, type 2 diabetes mellitus, cognitive impairment, comparative study

Introduction

Nowadays, with the increasing of aging population, the incidence of type 2 diabetes mellitus (T2DM) is also rising year by year. Some studies believe that there will be 615 million people suffering from T2DM by 2040 [1]. The incidence of cognitive impairment in patients also increases as they grow older. A study found that the incidence of cognitive impairment was 5-10% in patients over 65 years old, and 20-50% in patients over 85 years old, and the incidence in female patients was higher than that in male patients [2]. Stroke is the second risk factor for cognitive impairment [3]. Some studies found that T2DM was one of the common risk factors leading to stroke and cognitive impairment, so patients with T2DM were more prone to suffer from cognitive impairment following stroke [4-6]. In terms of pathogenesis, some studies have shown that T2DM patients and patients with cognitive impairment have common pathological features, including Aβ aggregation, decreased protein phosphoryla-

tion regulation ability, and participation of chronic inflammatory factors, and insulin resistance and damage of insulin signals in transmission process are the common pathological basis of the two diseases [7, 8]. Glucagon-like peptide-1 (GLP-1) is an endogenous incretin, which can promote islet cells to release insulin so that glucose in vivo is in a relatively stable state [9]. Recent studies have found that GLP-1 not only affects islet function, but also has neurotransmitter-like effect and nerve-like growth factor effect [10]. Studies in recent years have also found that GLP-1 preparations such as liraglutide and exenatide can alleviate neurodegeneration in the Alzheimer's disease (AD), and can relieve memory and learning disorders in AD rat models [11, 12]. Dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin, vildagliptin, and linagliptin can reduce the blood glucose by suppressing the hydrolysis of GLP-1, and thus improves the cognitive function [13]. At present, the research on the role of DPP-4 inhibitors in cognitive improvement mainly focuses on AD patients [14, 15], and the advantages and disadvantages of GLP-1 and DDP-4 inhibitors on cognitive improvement remain unclear. This study mainly analyzed the effects of DPP-4 inhibitors and GLP-1 on blood glucose and cognitive function of patients with both T2DM and mild cognitive impairment (MCI) following stroke based on the treatment of them with the two drugs.

Materials and methods

Clinical data

This study has been approved by the Ethics Committee of Linyi People's Hospital. A total of 60 patients with T2DM accompanied by cognitive impairment within 6 months after stroke admitted to the department of neurology of Linyi People's Hospital from January 2017 to June 2018 were selected and divided into an observation group and a control group using the random number table method. The observation group was treated with sitagliptin (n=30), while the control group was treated with liraglutide (n=30). All the patients included in this study were older than 65 years, and each of them signed an informed consent form.

Inclusion criteria

(1) Patients meeting the T2DM diagnosis criteria [16]; (2) Patients meeting the diagnosis criteria of post-stroke cognitive impairment [17]; (3) Patients meeting the diagnosis criteria of MCI [18]. The diagnosis covered four items: 1) The mini-mental state examination (MMSE) was employed to assess the mental state of the patients. MMSE consisted of 19 items, with a total score of 30 points, and the score of each included patient should be larger than or equal to 24 points; 2) The Montreal cognitive assessment (MoCA) was employed to assess the patients' cognitive function. The MoCA score of each included patient should be less than 26 points and his/her education time should be longer than 12 years. If the education time of the patient was shorter than or equal to 12 years, his/her finial score should be the obtained score plus one point; 3) The patients complained about their own memory deterioration or their family members complained about the patients' memory deterioration; 4) The activity of daily living (ADL) was adopted to assess their living ability, and the score should be lower than 26 points [19]. A patient meeting the requirements of the four items meantime could be diagnosed with MCI; (4) Patients getting a score between 0 and 42 points after being assessed using the National Institutes of Health Stroke Scale (NIHSS) [20]. A high NIHSS score indicates a severe neurological deficit. (5) Patients meeting the following requirements: they had diabetes before suffering from stroke, and had taken sulfonylureas, metformin or insulin for blood glucose reduction, but they had not received DPP-4 inhibitors or GLP-1. Meantime, they showed a stable condition after suffering from stroke and being treated, and they met the diagnosis of post-stroke cognitive impairment based on detection.

Exclusion criteria

(1) Patients allergic to sitagliptin or liraglutide; (2) Patients with a history of craniocerebral trauma, epilepsy, or cerebrovascular disease; (3) Patients unable to cooperate for the cognitive function evaluation; (4) Patients under the influence of glucocorticoid on blood glucose; (5) Patients comorbid with severe hypertension, coronary heart disease, or hyperlipidemia; (6) Patients comorbid with a malignant tumor; (7) Patients with a mental disease that affects cognition.

Methods

The enrolled patients were divided into two groups using the random number table meth-

Table 1. Comparison of general data and baseline data between the two groups

Projects	Observation group (n=30)	Control group (n=30)	X^2/t	P
Gender (Male:Female)	17:13	14:16	0.601	0.438
Age (years)	67.2±7.1	66.1±5.9	0.692	0.492
Education level (years)	12.7±3.8	12.1±4.0	0.627	0.533
BMI (kg/m^2)	25.82±3.76	25.70±4.28	0.110	0.913
Course of diabetes (years)	8.19±3.05	8.99±2.65	0.534	0.128
Stroke types				
Ischemic stroke	15	17	0.268	0.605
Hemorrhagic stroke	15	13		
NIHSS	19.92±5.43	20.7±5.52	0.917	0.363
ADL	21.42±3.13	22.15±3.17	0.471	0.640

od. Thirty of them were treated with DPP-4 inhibitor, sitagliptin (Merck & Co Inc, drug import registration number: H20090834) as an observation group. They took 100 mg of sitagliptin orally once a day, one tablet each time. The rest 30 patients were treated with liraglutide (Novo Nordisk A/S, drug import registration number: J20160004) through subcutaneous injection at an initial amount of 0.6 mg/d, and an amount of 1.2 mg/d after one week. The efficacy of the two drugs was evaluated after 6 months of treatment.

Observation indexes

Main observation indexes: (1) The fasting blood glucose (FBG), 2 hour postprandial blood glucose (2hPG), and glycosylated hemoglobin (HbA1c) of the patients were determined before treatment and at 6 months after treatment. FBG and 2hPG were determined using the German Roche portable blood glucose meter, and HbA1c was determined using the German Bayer DCA2000 detector. (2) The cognition of the patients was assessed using MMSE and MoCA before treatment and at 6 months after treatment.

Secondary observation indexes: Blood indexes (CRP, TNF-α, IL-6, Aβ1-40, and Aβ1-42) of the patients were determined as follows: two tubes of venous blood (5 mL for each tube) were sampled from each patient at 8 o'clock in the morning before treatment and at 6 months after treatment, respectively. The sampled blood was stored in ethylenediamine tetraacetic acid (EDTA) tubes in a refrigerator at 4°C for 15 min, and then the samples were separated by centrifugation at 3300 rpm to separate plasma and serum. The separated plasma was added with phosphate buffered solution (Guangzhou Dingguo Biotechnology Co., Ltd., China) containing 40 μL of protease inhibitor, and then stored in a refrigerator at -80°C. C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) in the serum were determined using the immune turbidimetry, and Aβ1-40 and Aβ1-42 in the plasma were determined using the enzyme-linked immunosorbent assay.

Statistical analysis

The data were analyzed using SPSS 17.0, in which continuous variables were expressed by the mean ± standard deviation ($\bar{x}$ ± SD), and data conforming normal distribution and homogeneity of variance were checked using the t test. Comparison between groups was carried out using the independent-samples T test, and inter-group comparison before and after treatment was carried out using the paired t test. Enumeration data were analyzed using the Pearson chi-square test and expressed by X^2. P<0.05 indicated a significant difference.

Results

General data

There was no significant difference in sex, age, education level, body mass index (BMI), NIHSS, and ADL between the two groups, which were comparable (P>0.05). See **Table 1**.

Blood glucose level of the two groups before and after treatment

Before treatment, there was no significant difference between the two groups in FBG, 2hPG, and HbA1c (all P>0.05). After 6 months of treatment, there was a significant improvement in FBG, 2hPG, and HbA1c in the two groups (all P<0.05), but there was no difference between them in those indexes after treatment (all P>0.05). See **Table 2**.

Cognition score of the two groups before and after treatment

Before treatment, there was no significant difference between the two groups in MMSE and

Table 2. Comparison of blood glucose level of the two groups before and after treatment

Projects	Observation group	Control group	t value	P
FBG (mmol/L)				
Before treatment	9.51±1.24	9.29±1.32	0.666	0.508
After treatment	7.19±1.81#	7.17±1.77#	0.050	0.960
2hPG (mmol/L)				
Before treatment	16.89±3.77	16.70±4.69	0.170	0.866
After treatment	10.47±3.80#	10.56±2.59#	0.103	0.918
HbA1c (%)				
Before treatment	8.56±3.25	8.86±3.17	0.471	0.640
After treatment	6.97±1.25#	7.35±2.48#	0.749	0.457

Note: # indicates compared between after treatment and before treatment the difference is statistically significant (P<0.05).

Table 3. Comparison of cognition score of the two groups before and after treatment

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

Note: # indicates compared between after treatment and before treatment, the difference is statistically significant (P<0.05).

MoCA scores (both P>0.05), while after 6 months of treatment, the observation group got significantly improved MMSE and MoCA scores (both P<0.05), and the control group got a significantly lowered MMSE score after treatment (P<0.05). In addition, there were significant differences between the two groups in MMSE and MoCA scores after treatment (both P<0.01). See **Table 3** and **Figure 1**.

Plasma Aβ1-40, Aβ1-42, and Aβ1-42/Aβ1-40 of the two groups before and after treatment

Before treatment, there was no significant difference between the two groups in Aβ1-42, Aβ1-42, and Aβ1-42/Aβ1-40 (all P>0.05), while after 6 months of treatment, the observation group showed a significant improvement only in Aβ1-42/Aβ1-40 (P<0.001), and showed no difference in other two indexes (both P>0.05). In addition, there were dramatic differences between the two groups in Aβ1-42/Aβ1-40 after treatment (P<0.001). See **Table 4** and **Figure 2**.

Serum CRP, TNF-α, and IL-6 of the two groups before and after treatment

Before treatment, there was no significant difference between the two groups in CRP, TNF-α, and IL-6 (all P>0.05), while after 6 months of treatment, the observation group showed a significant improvement in CRP, TNF-α, and IL-6 (all P<0.05), and the control group showed a significant improvement in TNF-α, and IL-6 after treatment (both P<0.05). In addition, after treatment, there were significant differences between them in CRP, TNF-α, and IL-6, and the observation group showed a more dramatic decrease than the control group (all P<0.001). See **Table 5** and **Figure 3**.

Discussion

Clinical studies have revealed that T2DM patients are more likely to suffer from cognitive impairment, and their cognitive impairment is insidious at the beginning, and only manifested as a mild disease, but it can develop into dementia with the aggravation of it. Its pathogenesis is related to many factors such as Aβ aggregation and deposition, long-term inflammation, and age dependence, so elderly T2DM patients are more likely to have cognitive impairment. One study revealed that cognitive impairment was strongly linked to blood glucose fluctuation [21], and one other study found that T2DM patients under insulin resistance and hyperinsulinemia for a long term were prone to having cognitive impairment [22]. In addition, the study also concluded that T2DM was a risk factor of cognitive impairment, and T2DM patients with cognitive impairment were usually accompanied by insulin resistance in the brain [22]. Studies on stroke revealed that stroke patients suffered from cognitive impairment due to the damage to neurovascular units caused by cerebral ischemia and hypoxia [23, 24]. Therefore, patients with both T2DM and stroke are more likely to suffer from cognitive impairment due to the

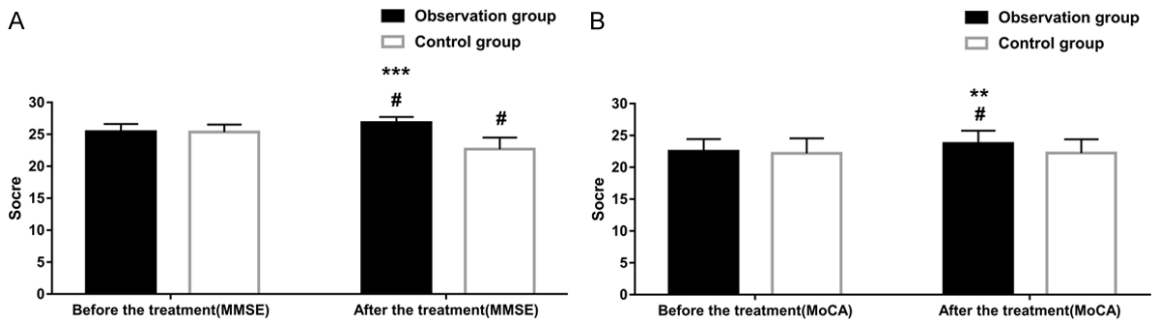

Figure 1. Cognition score of the two groups before and after treatment. Note: A: MMSE comparison before and after treatment. B: MoCA comparison before and after treatment. * indicates compared to control group, **P<0.01; ***P<0.001; # indicates compared to pre-treatment P<0.05.

Table 4. Comparison of plasma Aβ1-40, Aβ1-42, and Aβ1-42/Aβ1-40 of the two groups before and after treatment

Projects	Observation group	Control group	t value	P
Aβ1-42 (ng/L)				
Before treatment	18.37±5.08	17.73±4.64	0.504	0.616
After treatment	19.03±3.17	19.40±5.05	0.337	0.737
Aβ1-40 (ng/L)				
Before treatment	46.50±11.19	43.80±9.98	0.987	0.328
After treatment	41.03±9.18	44.97±10.83	1.517	0.135
Aβ1-42/Aβ1-40				
Before treatment	0.39±0.04	0.40±0.02	1.445	0.154
After treatment	0.47±0.03###	0.43±0.04	4.649	<0.001

Note: Compared between after treatment and before treatment, the difference is statistically significant, ###P<0.05.

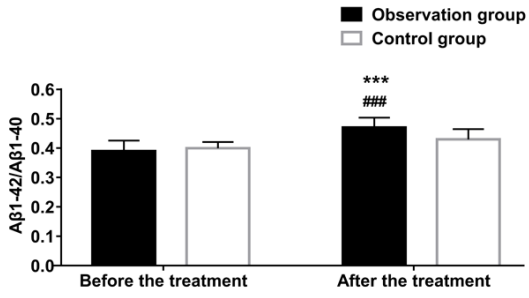

Figure 2. Comparison of plasma Aβ1-42/Aβ1-40 of the two groups before and after treatment. Note: * indicates compared to control group, ***P<0.001; # indicates compared to pre-treatment, P<0.05. ###P<0.001.

combined action of the two diseases. GLP-1 is an endogenous incretin, which can not only maintain glucose homeostasis, but also improve cognitive function [9, 10]. GLP-1 is prone to losing its function after being hydrolyzed by DPP-4 in vivo. Further studies have found that compared with other hypoglycemic drugs, DPP-4 inhibitors not only can better lower blood glucose [25-27], but also can alleviate cognitive impairment [28]. In this study, DPP-4 inhibitors, sitagliptin and sulfonylurea drugs, were used for treatment and compared. It turned out that there was no difference in hypoglycemic effect between the two drugs. However, the improvement of MMSE and MoCA scores in the observation group using a DPP-4 inhibitor for cognitive improvement was significantly better than that in the control group, which was consistent with the above research results.

Previous studies found that Aβ aggregation, decreased ability of regulating protein phosphorylation, and co-participation of chronic inflammatory factors are common pathological features of T2DM and cognitive impairment [7, 8]. In order to find out the mechanism of improving cognitive function, this study studied both Aβ aggregation and chronic inflammatory factors. Previous studies have detected increased Aβ expression in cerebral cortex and hippocampus of diabetic rats, and decreased Aβ expression in the two sites of them after being treated with DPP-4 inhibitors [29]. Another study found that the expression of Aβ in cerebrospinal fluid of AD patients was decreased [30]. However,

Table 5. Comparison of serum CRP, TNF-α, and IL-6 of the two groups before and after treatment

Projects	Observation group	Control group	t value	P
CRP (mg/L)				
Before treatment	6.64±1.81	6.90±1.84	0.917	0.363
After treatment	4.80±1.52#	7.57±1.48	7.153	<0.001
TNF-α (μg/mL)				
Before treatment	124.51±18.22	123.80±17.87	0.154	0.878
After treatment	85.01±15.90#	102.66±16.12#	4.269	<0.001
IL-6 (μg/mL)				
Before treatment	351.37±37.86	351.00±37.32	0.038	0.969
After treatment	273.27±25.64#	318.34±29.73#	6.287	<0.001

Note: # indicates compared between after treatment and before treatment, the difference is statistically significant (P<0.05).

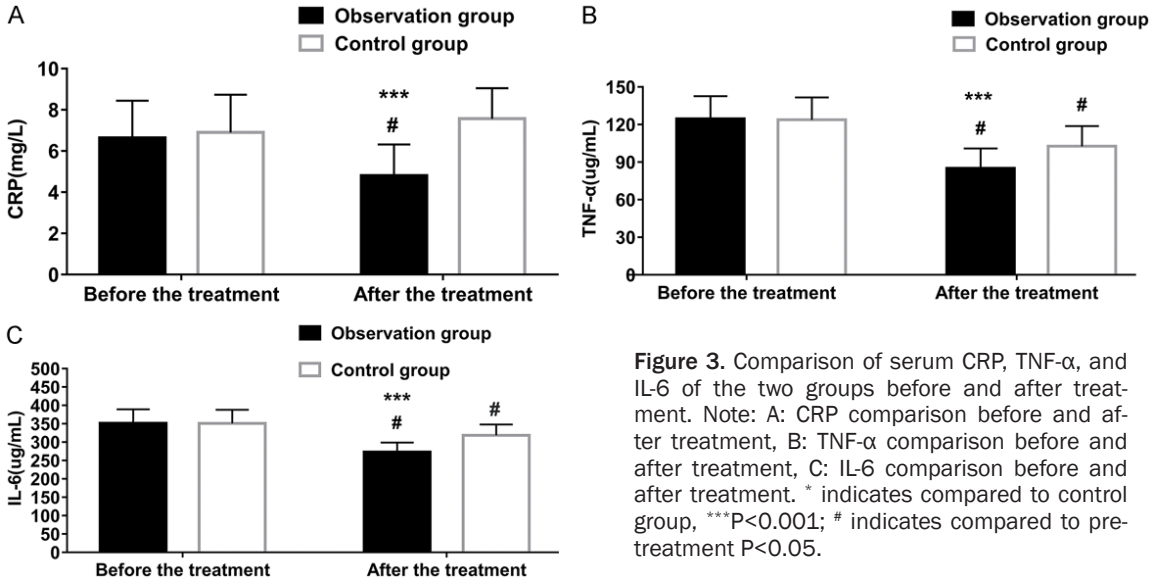

Figure 3. Comparison of serum CRP, TNF-α, and IL-6 of the two groups before and after treatment. Note: A: CRP comparison before and after treatment, B: TNF-α comparison before and after treatment, C: IL-6 comparison before and after treatment. * indicates compared to control group, ***P<0.001; # indicates compared to pre-treatment P<0.05.

cerebrospinal fluid is not easy to detect in the early diagnosis and screening of cognitive impairment patients. In order to find more convenient biomarkers, blood-related indicators were studied clinically. Previous studies on plasma Aβ1-40 and Aβ1-42 revealed that patients with MCI may show different expression states of plasma Aβ1-40 and Aβ1-42, including increased, unchanged and decreased expression of them [31-33]. A study on the Aβ1-42/Aβ1-40 ratio revealed that the ratio was decreased in patients with MCI, and it was decreased more significantly in AD patients [33]. T2DM brings immuno-inflammatory response through the stimulation of hyperglycemia. A study revealed that CRP, TNF-α, and IL-6 in T2DM patients were increased [34]. Patients with cognitive impairment also have inflammatory cytokines. A study found that various inflammatory cytokines in patients with cognitive impairment were increased, resulting in neuroinflammation, under which microglia and astrocytes were excessively activated, and may produce toxic substances that damage neurons, eventually causing degeneration and apoptosis of neurons [35]. IL-6 is one of inflammatory cytokines. A previous study concluded that the expression of plasma IL-6 had begun to increase in patients with early AD [36], but one other study pointed out that there was no difference in the expression of serum IL-6 between patients with MCI and normal people [37]. CRP, a protein synthesized in the liver under the mediation of inflammatory cytokines such as IL-6, is commonly used as a clinical detection index [38]. In this study, comparison between the observation group and the control group revealed that there were no significant differ-

ences between them in plasma Aβ1-40 and Aβ1-42 before treatment, and the observation group showed a significantly higher Aβ1-42/Aβ1-40 than the control group after treatment, which was consistent with the above research results. Furthermore, there were also no significant differences between them in CRP, TNF-α, and IL-6 before treatment, while the observation group showed significantly lower expression of them than the control group after treatment, which was also consistent with the above research results.

The deficiencies and prospects of this study are as follows: the sample size of this study is small, and it needs to be further expanded for research. Moreover, this study spends a relative short observation time, and is affected by many external factors, such as infarct size or hemorrhage area, difference between treatment schemes for infarction and hemorrhage, and recovery time of diseases. Therefore, it is required to prolong the follow-up for research.

To sum up, DPP-4 inhibitors can reduce blood glucose and improve cognitive function for patients with both T2DM and post-stroke MCI, and its mechanism may be related to the amelioration of Aβ aggregation and alleviation of inflammatory response in vivo.

Disclosure of conflict of interest

None.

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