

Research Article

Relationship between Cognitive Impairment and Serum Amyloid β -Protein, Adiponectin as well as CRP Levels in Type II Diabetes

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Abstract

Objective: The purpose of this study was to explore the plausible mechanism of type 2 diabetes patients' cognitive impairment by analyzing the levels of serum amyloid β -protein (A β 1-42), adiponectin and CRP.

Methods: We chose 84 patients diagnosed with type 2 diabetes and 60 healthy people as subjects. Clinical data were collected by Self-made questionnaires. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scales was used to access the cognitive functions. The serum A β 1-42 and adiponectin levels were individually determined with ELISA. C-reactive protein was detected by Siemens BNP II specific protein analyzer.

Results: Immediate memory, visual span, speech function, attention and delay memory scores of RBANS scale and standard scores in the case group were significantly lower than the control group. A β 1-42 levels in the case group were significantly higher than the control group. Age of patients was significantly negative related to RBANS scale subtest scores and standard scores in the case group. Years of schooling was significantly positive correlated to immediate memory, visual span, attention, delay memory scores and standard scores, while negative correlated with

speech function; after adjusting ages and years of schooling, A β 1-42 levels of patients in the case group were significantly negative, correlated with immediate memory, attention, delay memory scores and standard scores ($p < 0.05$). Adiponectin levels of patients in the case group were positive correlated with RBANS scale subtest scores and standard scores ($p < 0.05$).

Conclusions: Type 2 diabetes patients suffer from cognitive impairment and the mechanism may be associated with increased serum A β 1-42, and decreased adiponectin and inflammation reaction. Detection of serum A β 1-42 and adiponectin could be used as an indicator for the degree of cognitive impairment in Type 2 diabetes patients.

Keywords: A β 1-42; Diabetes; Cognition; Function; Damage

1. Introduction

Diabetes mellitus (DM) remains a global epidemic, with an estimated 400 million people affected by diabetes worldwide [1]. With the increase of people's living standards and living pressure, diabetes has become a major threat to young people. There are two major types of DM, including insulin-dependent diabetes (type 1 DM [T1DM]) and insulin-independent diabetes (type 2 DM [T2DM]). Approximately, 90% of people with diabetes have T2DM. The main damage of diabetics is long-term poor glycemic control, which leads to complications, including kidney disease, hypertension, infection, diabetic foot, etc. [2]. Furthermore, diabetes patients are often associated with cognitive impairment, decreased learning and memory ability, reduced understanding and judging ability, and even dementia [3]. The dementia risk for type 2 diabetes patients is about 1.5 to 2.0 times higher than the normal population. DM possesses a bidirectional relationship with major depressive disorder (MDD) [4]. MDD has significant effects on the course and outcome of diabetes [5]. Some studies revealed MDD has a specific association with T2DM [6]. Likewise, elevated depressive symptoms have been associated with a higher risk of developing T2DM [7]. However, connection of these two conditions is poorly characterized. Diabetes is closely associated with cognitive impairment and the mechanism is complicated. A series of pathological changes resulted from glycometabolic disorder or insulin resistance can cause hippocampus and other memory, study-related tissues and organs damaging, then causing cognitive impairment. This study provided the evidence-based medicine for related mechanism and early cognitive impairment screening by analyzing the connection between type 2 diabetes patients cognition and serum amyloid β -protein-42 (A β 1-42) levels.

2. Materials and Methods

2.1 Sample source

84 patients diagnosed with type 2 diabetes in the Department of Endocrinology, Xiangyang Central Hospital from January to December 2014 were selected as the case group, including 50 males and 34 females (aged from 25 to 75 years old). The selected patients were tested twice for fasting blood glucose (GLU), which conforms to 2013 China type 2 diabetes guidelines diagnostic criteria. The healthy subjects in medical examination center were chosen as the

control group, including 40 males and 20 females, aged from 28 to 72 years old. The control group had no history of diabetes and family history of diabetes after investigation, and their blood glucose was between 3.9 and 6.1 mmol/L.

2.2 Exclusion criteria of two groups

The following is exclusion criteria: (1) association with acute complication of diabetes; (2) congenital mental retardation, multiple occurrences of cerebral stroke or insane person, epilepsy; (3) anti-depression drugs or immunosuppressants users; (4) severe liver and kidney dysfunction; (5) 2 years with alcohol dependence or drug abuse and dependence; (6) history of malignancy, infected patients; (7) refused to be in the group or did not fit the Scale testers.

2.3 Clinical data collection

Data in these two groups were collected, including gender, age, years of education, body mass index (BMI), recording fasting glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), glycosylated hemoglobin (HbA1C).

2.4 The repeatable battery for the assessment of neuropsychological status (RBANS) scale

Trained physician used RBANS scale to evaluate the cognitive function of patients. Patients completed subtest in 30-40 min, including immediate memory (memory studying, story retelling), visual span (graphic copying, positioning line), speech functions (pattern naming, semantic fluency), attention (digit span, coding test), delay memory (vocabulary memory, vocabulary recognition, story recall, graphic recall), etc. Scale scores were converted based on different ages of subjects, and then converted to standard scores.

2.5 Self-rating depression scale (SDS)

Trained physician performed the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) tests. The SDS and SAS were set up by Zung in 1971. A total of 20 items and four-grade score were used, wherein forward scoring and reverse scoring occupied half, respectively. The questionnaires were simple and easy to evaluate the depression and anxiety degree of patients. ≥ 50 percentage of patients were complicated with depression or anxiety, <50 percentage of patients were not complicated with depression or anxiety.

2.6 Serum A β 1-42, adiponectin and C-reactive protein (CRP) level assay

5 ml of fasting blood from two groups of patients were collected and centrifuged for 10 min. The serum was collected and stored at -80°C . The serum A β 1-42 and adiponectin levels were individually determined by ELISA (Jingmei bio-company). C-reactive protein was detected by Siemens BNP II specific protein analyzer.

2.7 Statistical methods

SPSS 20.0 software was used for statistical analysis, normal distributed measurement data was expressed as $(x \pm s)$, t test was conducted for comparison between groups; non-normal distributed measurement data was expressed as M

(P25, P75), non-parametric test was used for comparison between groups; count data analysis used χ^2 test. $P < 0.05$ was considered as statistical difference.

3. Results

3.1 Comparison of clinical data in two groups

Gender, age, years of education and TC, LDL-C levels of the two groups were compared and there is no significant difference. The levels of BMI, GLU and HbA_{1c} in the case group were significantly higher than control group ($p < 0.05$) (Table 1).

Group	Num	Age	Years of schooling	TC (mmol/L)	LDL-C (mmol/L)	BMI (kg/m ²)	GLU (mmol/L)	HbA _{1c} (%)
Case group	49	52.0 ± 13.2	11.2 ± 5.3	4.8 ± 0.9	3.5 ± 0.8	25.4 ± 2.6	5.1 ± 0.9	43.8 ± 12.1
Control Group	42	51.1 ± 11.8	10.7 ± 4.7	4.7 ± 1.1	3.4 ± 1.0	22.6 ± 4.1	8.2 ± 2.2	41.7 ± 10.6
T value	-	0.41	0.27	0.48	-0.37	4.67	8.48	12.14
P value	-	0.81	0.72	0.55	0.65	0.02	0.01	0.01

Table 1: Comparison of clinical data (x ± s).

3.2 The comparison of RBANS scale score and serum Aβ₁₋₄₂ levels in two groups

Immediate memory, visual span, speech function, attention and delay memory scores of RBANS scale and standard scores in the case group were lower than the control group, the difference was statistically significant ($p < 0.05$) (Table 1). Aβ₁₋₄₂ levels in the case group were higher than the control group, the difference was statistically significant ($p < 0.05$) (Table 2).

Group	Num	Immediate memory	Visual span	Speech function	Attention	Delay memory	Standard scores
Case group	49	29.0 ± 10.2	32.2 ± 5.3	24.9 ± 4.6	40.5 ± 18.4	41.4 ± 9.6	32.9 ± 6.9
Control Group	42	38.0 ± 8.8	34.7 ± 3.7	32.7 ± 6.0	48.9 ± 12.3	45.6 ± 6.1	36.2 ± 5.9
Analysis of Variance F	-	0.9609	5.799	5.979	5.898	5.659	1.406
P value of variance	-	0.328	0.018	0.616	0.017	0.012	0.239
T value	-	-4.469	-2.607	-6.836	-2.067	-2.467	-2.482
P value	-	0	0.011	0	0.011	0.016	0.015

Group	Num	A β 1-42 (pg/ml)	A β 1-42 absorbance	Depression self-rating standard scores	Anxiety self-rating standard scores	adiponectin (ug/l)	CRP (mg/L)
Case group	49	499.8 \pm 566.1	0.26 \pm 0.39	44.6 \pm 7.1	40.4 \pm 8.1	310.5 \pm 132.2	2.2 \pm 1.2
Control Group	42	234.7 \pm 233.6	0.13 \pm 0.18	40.4 \pm 9.1	36.9 \pm 5.1	380.2 \pm 168.8	0.9 \pm 0.7
Analysis of Variance F	-	42.066	12.717	3.216	6.485	-	-
P value of variance	-	0	0.001	0.076	0.013	-	-
T value	-	2.994	2.045	2.492	2.514	2.625	3.252
P value	-	0.004	0.045	0.0015	0.014	0.012	0.021

Table 2: Comparison of two groups RBANS scale scores ($x \pm s$, unit: points).

3.3 Correlation efficient between age, years of education, serum A β 1-42, Adiponectin, CRP levels of case group and RBANS scale scoring

The ages of patients in the case group and RBANS scale subtest scores and standard scores were negatively correlated ($p < 0.05$). The years of schooling were positively related with immediate memory, visual span, attention and delay memory scores and standard scores, while negatively correlated with speech function ($p < 0.05$). After adjusting ages and years of schooling, A β 1-42 levels of patients in the case group were negatively correlated with immediate memory, attention, delay memory scores and standard scores ($p < 0.05$). The adiponectin levels of patients in the case group were positive correlated with RBANS scale subtest scores and standard scores ($p < 0.05$), as shown in Table 3.

Variable	Immediate memory	Visual span	Speech function	Attention	Delay memory	Standard scores
Age	-0.612	-0.434	-0.612	-0.495	-.0421	-0.701
Years of schooling	0.665	0.352	-0.456	0.446	0.406	0.688
A β 1-42*	-0.521	-0.122	-.0212	-0.255	-0.388	-0.692
Adiponectin	0.582	0.477	0.125	0.378	0.495	0.357
CRP	0.120	0.133	0.088	0.076	0.034	0.058

*Indicate that age and years of education were adjusted in the row

Table 3: Correlation efficient between age, years of education, serum A β 1-42, Adiponectin, CRP levels of case group and RBANS scale scoring (r).

4. Discussion

Cognition refers to human brain which accepts the outside world information, processes, converses to internal psychological activities, so as to obtain knowledge or application knowledge process, which contains memory, language, visual space, implementation, calculation, understanding, judging, etc. Cognitive impairment also known as cognitive decrease, cognitive deficits or cognitive disability, refers to the damage of above-mentioned cognitive functions, while the social occupation or daily life is unaffected, and it cannot be explained by known medical or psychiatric disorders. It is a clinical state between the normal aging and mild dementia. When there are two or more involvement in the above cognitive domain, and impacts on daily or social capacities of individuals, it can be diagnosed as dementia. Cognitive impairment is a type of mental disorder disease, cognitive deficits or disorder.

Diabetes cognitive impairment is characterized as acquired cognitive and behavior deficits. Type I diabetes and type 2 diabetes can cause cognitive deficits. Type I diabetes, mainly manifests as study memory, solving problems and psychomotor speed decreased slightly. In addition to declined studying and memory capacity, type II diabetes cognitive impairment also manifests as a moderate degree of language memory or complex information processing capacity decline, such as attention, performing ability, spatial processing capacity and memory decreasing but with few on motor reaction time and immediate memory affected. T2DM has been considered as an independent risk factor of mild cognitive impairment and the occurrence rate of type 2 diabetes mellitus complicated with mild cognitive impairment is 10.8%~17.5%. The mild cognitive impairment can progress into Alzheimer and vascular dementia. Studies have shown that the chance is twice more than non-diabetic patients at risk of T2DM converting to Alzheimer.

Cognitive impairment can be assessed and quantified by a specific cognitive function screening scale. RBANS scale is a tool developed by the Randolph screening for Alzheimer's disease and has good recognition effects on cognitive impairment caused by various reasons. Scoring patients in group by a physician from endocrinology department, scoring control group selected from the medical examination center by the same physician. β -amyloid precursor protein (APP) is hydrolyzed by α -, β - and γ -secretase enzyme to 2 major metabolites, $A\beta_{0-40}$ and $A\beta_{1-42}$. In normal situation, $A\beta_{0-40}$ is the main in the brain. $A\beta_{1-42}$ is generated by amyloid precursor protein hydrolysis in the presence of β secretase enzyme and can be produced by tissue cells from the whole body. Excess soluble monomeric $A\beta_{1-42}$ gradually aggregates to form a toxic fibrosis precipitate, which induces and participates in a series of pathological changes.

The results of this study showed that the RBANS scale subtest scores and standard scores of the case group are lower than the control group, suggesting that type 2 diabetic patients have cognitive impairment. Table 3 shows the serum $A\beta_{1-42}$ and RBANS Scale standard score are negatively correlated, suggesting that the elevated $A\beta_{1-42}$ level is associated with cognitive impairment. After adjustment for age and education years, partial correlation analysis showed that there is a correlation between $A\beta_{1-42}$ and RBANS Scale standard score. There is a positive correlation between years of education and immediate memory, visual span, attention, delayed memory scores and standard

scores, indicating a high level of education, strong learning ability, and improving themselves adapting to the environment. A β 1-42 level changing in type 2 diabetes patients influence their cognitive function, speculating possible mechanism: (1) A β and insulin compete for insulin-degrading enzyme (IDE) together and IDE is the key enzyme in the degradation process of A β . On one hand, A β and insulin compete for IDE together, and the prior option of IDE is insulin. So A β degradation decreases when insulin increases [8], resulting in relative increase of A β 1-42. Gathering of excess A β 1-42 further exacerbates insulin resistance and oxidative stress, resulting in a vicious cycle of A β 1-42 production and accumulation, leading to senile plaque and neurodegenerative disease; (2) Disorder transportation across the blood brain barrier of A β 1-42 leads to A β 1-42 deposition in the brain tissues, white matter and hippocampus formation damage, which resulting in central conduction system damage. Hypoglycemic state interferes with the brain's energy metabolism, resulting in selective neuronal necrosis and hippocampal atrophy, recurrent hypoglycemia may cause cumulative damage to the brain. That is the main reason for persistent cognitive impairment [9]; (3) a variety of inflammatory signaling pathway abnormality resulting in imbalance expression of inflammatory factors (TNF α , IL-1, IL-6), and over-activation of endogenous inflammatory response in the nervous system, further leading to various degenerative brain pathology changes, such as neuronal apoptosis, A β deposition and neurofibrillar tangles. This is one of the start factors of diabetes cognitive impairment progress [10-11]. TNF α is a proinflammatory cytokine with multiple performance produced by activated microglia, by releasing cytotoxicity substances and other inflammatory cytokines, causing elevated general levels of inflammatory cytokines and inducing more glial cells to produce free radical, causing damage to more neuron and death of a large number of glial cells. Less A β phagocytosis results in A β deposition in the brain. The excessive accumulation of A β 1-42 in the brain forms oligomers and adhere to neurons, specifically acting on the synapses and disturbing signal transmission between neurons, causing significant memory decline. Imaging can also observe that the bilateral hippocampal volume reduction and extensive brain atrophy exist in type 2 diabetes patients and associated with the cognitive decline degree.

Adipose tissue is an active endocrine organ. Adiponectin is one of adipokines from adipose tissue, which exerts biological effects mainly by combining with its acceptors Adipo R1 and Adipo R2. These two acceptors are expressed in skeletal muscle, liver, pituitary and brain endothelial cells [12]. Adiponectin is associated with variety of diseases including diabetes, obesity, abnormal lipid metabolism, hypertension and other cardiovascular disease, i.e. neurodegenerative diseases. Adiponectin function as endocrine hormones and can improve insulin sensitivity, improve insulin resistance, anti-intimal hyperplasia, improve lipid metabolism, anti-hyperglycemia, anti-inflammatory, anti-atherosclerosis. Insulin is a neurotrophic factor. A long time serious shortage of insulin can cause neuron degeneration. Craft and others find that daily intranasal insulin therapy can improve mild cognitive impairment which forgetfulness is the main symptom [13]. At the same time, these results show that the memory function is changed with the A β 1-42 level and the altered ratio of tau protein and A β 1-42. Table 2 shows T2DM serum adiponectin levels are significantly lower than the control group, but A42 levels are in contrast. Table 3 shows that adiponectin levels are positively correlated with RBANS scale subtest scores and standard scores [14], indicating that adiponectin and A β 1-42 are risk factors causing cognitive impairment. Adiponectin also adjusts mood state, anti-depression, enhances memory and improves cognitive function and other beneficial effects [15]. Related

studies show that adiponectin may improve blood-brain barrier function and brain energy supply, protect the cells, inhibit neuronal apoptosis by generating and accumulation of A β 1-42 and other mechanisms to get involved in improving cognitive impairment [16].

CRP is a typical acute phase protein synthesized in the liver. In patients with tissue injury or infection, there will be a sharp rise in the CRP levels in the body. CRP as a sensitive marker of inflammation has been involved in a variety of human development of inflammation. Studies have shown that the abnormal high CRP expression can be detected in senile plaques and neurofibrillary tangles of Alzheimer patients. The abnormal high expression levels of inflammatory cytokines in elderly patients with T2DM may be through the following mechanisms eventually leading to cognitive dysfunction: significantly higher levels of inflammatory factors may prompt the Tau protein phosphorylation and be associated with fibrous Ab deposition and undernourished neurite formation [17-18].

In short, Type 2 diabetes patients could lead to cognitive impairment, and the process of its occurrence is associated with A β 1-42 serum levels remaining higher for a long time, adiponectin reduction and elevated CRP levels induced by inflammation factors. Adiponectin can lead to cognitive impairment by A β 1-42 deposition occurrence and aggravation, resulting in learning, living ability decreasing, severe cases can be developed to dementia. Therefore, it is recommended that patients newly diagnosed with type 2 diabetes should be monitored regularly, and makes the necessary intervention to delay the occurrence of cognitive impairment to improve the quality of life of diabetes patients.

T2DM significantly impairs the cognitive function in elderly patients. The impact of DM metabolism on cognitive functions in elderly patients should be taken seriously. Starting from prevention to reduce the prevalence of Alzheimer and delay its course effectively. In conclusion, Type 2 diabetes patients suffer from cognitive impairment and the mechanism may be associated with increased serum A β 1-42, and decreased adiponectin and inflammation reaction. Detection of serum A β 1-42 and adiponectin could be used as an indicator for the degree of cognitive impairment in Type 2 diabetes patients.

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Disclosure of Conflict of Interest

None.

Author Contributions

Shanshan Li and Jiubo Fan conceived and designed the experiments; Haiju Liu and Ji Ma performed the experiments; Baoan Li analyzed the data.

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