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Analysis of correlation between the mild cognitive impairment (MCI) and level of adiponectin in elderly patients with type 2 diabetes mellitus (T2DM)

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Abstract. – OBJECTIVE: To investigate the correlation between the mild cognitive impairment (MCI) and serum level of adiponectin in elderly patients with Type II diabetes mellitus (T2DM), so as to provide evidence for early diagnosis of MCI and effective evaluation of the impairment of cognitive functions, thereby preventing the impairment of cognitive function as early as possible.

PATIENTS AND METHODS: Clinical data were collected from 260 T2DM patients (≥ 60 years old) in Endocrine Department and 120 healthy subjects (≥ 60 years old) who underwent physical examination in our hospital between June 2015 and June 2017. According to the evaluation results of MCI, these T2DM patients were further divided into the T2DM + MCI group (n = 138) and the T2DM + NMCI group (n = 122). General data, including gender, age, disease history and body mass index (BMI), and the laboratory indexes, including serum adiponectin, fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c) and blood fat, were collected for statistical analysis in T2DM + MCI group, T2DM + NMCI group and healthy control group.

RESULTS: Comparisons among T2DM + MCI group, T2DM + NMCI group and healthy control group, showed that the serum level of adiponectin in T2DM + MCI group was significantly lower than those in remaining two groups ($p < 0.01$). Spearman correlation analysis revealed that score of Montreal Cognitive Assessment (MoCA) was positively correlated with the serum level of adiponectin ($r = 0.446$, $p < 0.01$). Multivariate linear regression analysis indicated that education (standard $\beta = 0.325$, $p = 0.003$), age (standard $\beta = -0.236$, $p = 0.016$), disease course of hypertension (standard $\beta = -0.242$, $p = 0.006$), disease course of diabetes mellitus (standard $\beta = -0.377$, $p < 0.001$) and the level of adiponectin were correlated with the cognitive impairment. The results of itemized assessment in MoCA scale showed that in T2DM + MCI group, the scores in visuospatial and executive abilities, attention, language and orientation were significantly lower than those in other two groups ($p < 0.01$). As for the delayed recall, the score in T2DM + MCI group was significantly lower than those in other two groups ($p < 0.01$), while the score in T2DM + NMCI group was lower than that in the healthy control group ($p < 0.01$); in terms of the naming ability and abstraction, no statistically significant differences were identified among three groups ($p > 0.05$).

CONCLUSIONS: Age, poor education, disease course of hypertension, disease course of diabetes mellitus and a low level of adiponectin in serum are the risk factors in MCI of T2DM patients. Besides, the level of adiponectin in serum of T2DM patients is correlated with the development of MCI; elderly T2DM patients are afflicted by cognitive impairment, mainly in visuospatial and executive abilities, attention, language, delayed recall and orientation.

Key Words:
Adiponectin, MCI, Risk factor, T2DM, Elderly.

Introduction

Diabetes mellitus is one of the most severe problems in public health in the 21st century all over the world. In China, Type 2 diabetes mellitus (T2DM) dominates in all diabetes mellitus patients with a portion of over 90%[1,2]. In recent years, a large-scale epidemic survey has indicated that with an increase in the prevalence rate of diabetes mellitus, an elevation has also been identified in the population of elderly diabetes mellitus patients; in addition, with an increase in age, prevalence rate of diabetes mellitus is also augmented. Thus, research on the development, prophylaxis and treatment of T2DM is of great realistic significance[3-5].

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Meanwhile, human beings are confronted with dementia as one of the major problems in global public health at present and in the future, in which Alzheimer's disease (AD), accounting for 50% in dementia cases, is mainly manifested by declines in memory and cognitive function, as well as the variations in personality, which result in severe impact on the social interaction, vocational development and living function of patients[6]. Mild cognitive impairment (MCI), a transition stage between the normal aging and mild dementia, can not only be evolved into dementia, but also persist for a long term, or even be reversed to the normal status in some cases[7-10]. Exploring the influencing factors of MCI and its development mechanism is of great significance for early diagnosis and intervention, as well as the prophylaxis and treatment of the progression in MCI.

With the rapid development in society and economy, amelioration in living conditions of people and aging tendency in China, T2DM and cognitive impairment have also witnessed increases in prevalence rates. Moreover, the cognitive impairment caused by diabetes mellitus has also gained more and more attention of people[6,11]. In this work, enzyme-linked immunosorbent assay method was applied to measure the level of adiponectin in serum, and the MoCA scale was also adopted for evaluating the cognitive function of patients. Through comparisons of the adiponectin levels among T2DM + NMCI group, T2DM + MCI group and health control group, we aimed to investigate the correlation between the adiponectin level in serum and MCI in T2DM patients, and improve the early diagnostic and treatment method for decline in cognitive functions in T2DM patients, thereby contributing to preventing and delaying the development of dementia.

Patients and Methods

Patients

In this study, a total of 380 T2DM patients who were admitted to Suzhou Wujiang District First People's Hospital and healthy subjects who underwent physical examination in the physical examination center between June 2015 and June 2017 were enrolled. There were 212 males and 168 females aged between (60-91) years with an average of (78.78±9.54) years. In the health control group, there were 120 subjects aged between (60-93) years with an average of (72.62±10.15) years. Inclusion criteria of MCI group: patients who complained about the decline in memory, with a score fewer than 26 points in evaluation of MoCA scale, or a score of 0.5 points in clinical dementia rating (CDR). Furthermore, patients in the MCI group were divided into the T2DM + MCI group (n = 138) and the T2DM + NMCI group (n = 122) according to the diagnosis of MCI. Signed written informed consent was obtained from all participants before the study. This study was approved by the Ethics Committee of Suzhou Wujiang District First People's Hospital.

Methods

Collection of general data: through inquiry with all subjects, the general data, including name, gender, birth date, occupation, education, history of smoking or alcohol intake, as well as the history of hypertension, diabetes mellitus, coronary heart disease, cerebral stroke, and the current medication (like anticoagulant drug, antiplatelet drug, hypoglycemic drugs, hypotensive drug or fat-modulating drug), were obtained. General biochemical indexes, including fasting plasma glucose (FPG), 2 h postprandial glucose (2hPG), HemoglobinA1c (HbA1c) and blood fat [including total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C)], were measured in this study. With a Hitachi 7600-020 Automatic Biochemical Analyzer, the levels of TC, TG, LDL-C and HDL-C were determined using the enzymatic cycling assay; as for the levels of FPG and 2hPG, they were measured using the oxidase method; the level of HbA1c was detected via the chromatography method using the Variant II HbA1c Analyzer (Bio-Rad, Hercules, CA, USA). Measurement of adiponectin level in serum: enzyme-linked immunosorbent assay method was utilized to determine the level of adiponectin in serum of all subjects with the kit provided by R&D (Minneapolis, MN, USA), and all protocols and steps were performed in strict accordance with the instructions.

Neuropsychological research: all staffs designated for assessment underwent strict professional training courses, and according to the unified diagnostic criteria, assessment was carried out with MoCA scale and standardized terms including the following items: visuospatial and executive abilities, attention and concentration, calculation, memory, language, abstraction ability and orientation ability. As for MoCA scale, the total score was set as 30 points, and patients with a score not fewer than 26 points were considered

normal. To reduce the effect of education years on the results of measurement, 1 point was added for subjects with education year ≤ 12 years.

Statistical Analysis

All statistics were performed using Statistical Product and Service Solutions (SPSS) 20.0 software (IBM, Armonk, NY, USA). *t*-test was performed for the comparison of mean value, and x^2 test was used to detect the difference between groups. Comparison between groups was done using One-way ANOVA test followed by Least Significant Difference (LSD). Multi-group comparisons of non-normal distribution data were analyzed by rank sum test. Spearman correlation test was used to analyze the correlation between the level of adiponectin and MoCA score. Multivariate logistic regression analysis was used to analyze the risk factors of MCI. $p < 0.05$ suggested that the difference had statistical significance.

Results

Comparisons of The General Clinical Data and Laboratory Indexes

Among T2DM + MCI group, T2DM + NMCI group and health control group, comparisons of the education years, body mass index (BMI), diastolic pressure, history of smoking, history of alcohol intake, TG, TC, HDL-C and LDL-C showed that the differences had no statistical significance ($p > 0.05$; Tables I-II), while those of the systolic pressure, age, disease of hypertension, HbA1C, FPG, MoCA score and level of adiponectin in serum suggested that the differences had statistical significance ($p < 0.05$; Tables I-II). In T2DM + MCI group, the systolic pressure, age, disease course of diabetes mellitus and the disease course of hypertension were significantly higher or longer than those in other two groups ($p < 0.05$; Tables I-II). In T2DM + MCI group, the level of adiponectin in serum was significantly lower than those in T2DM + NMCI group ($p < 0.01$; Table II) and health control group ($p < 0.01$; Table II). Comparisons of the systolic pressure, age, disease course of diabetes mellitus, disease course of hypertension, MoCA score and the level of adiponectin in serum between the T2DM + MCI group and T2DM + NMCI group showed that the differences had statistical significance ($p < 0.05$; Tables I-II), while those of the gender, insulin therapy, FPG and HbA1c revealed that the differences had no statistical significance ($p > 0.05$; Tables I-II).

Analysis of the Correlation Between MoCA Score and the Level of Adiponectin in Serum

Results of Spearman analysis of the correlation between MoCA score and the level of adiponectin in serum showed that there was a positive correlation between the MoCA score and level of adiponectin in serum ($r = 0.446$, $p < 0.01$).

Comparisons of the MoCA Scores Among Three Groups

As for visuospatial and executive function, it was found that the score in T2DM + MCI group was significantly lower than those in T2DM + MCI group and health control group ($p < 0.01$), but the difference between T2DM + MCI group and health control group showed no statistical significance ($p > 0.05$). Attention: score in T2DM + MCI group was significanly decreased when compared with other two groups ($p < 0.01$), but

Table I. Baseline characteristics of included subjects.

	T2DM + MCI group	T2DM + NMCI group	Health control group
Gender (Male/Female)	68/70	72/50	70/50
Age (y)	86.03 ± 7.98**##	78.79 ± 7.24	77.60 ± 8.02
Education years (y)	10.87 ± 4.78	12.35 ± 3.53	11.95 ± 3.79
Systolic pressure (mmHg)	145.38 ± 15.23**#	138.56 ± 14.64	132.48 ± 14.58
Diastolic pressure (mmHg)	86.40 ± 8.76	85.42 ± 7.46	83.26 ± 8.59
Body mass index (kg/m^2)	24.56 ± 3.18	25.94 ± 4.05	24.41 ± 3.28
Duration of diabetes mellitus (y)	34.05 ± 8.12##	27.07 ± 8.00	–
Duration of hypertension (y)	33.59 ± 11.07**##	21.88 ± 9.32*	11.07 ± 8.14
History of smoking (Yes/No)	21/117	17/105	24/96
History of alcohol intake (Yes/No)	12/126	20/102	20/100
Treatment of insulin (Yes/No)	120/18	93/29	–
MoCA Score	21.95 ± 1.47**##	27.28 ± 1.39	27.89 ± 1.40

Note: *$p < 0.05$, **$p < 0.01$ in comparison with control group; #$p < 0.05$, ##$p < 0.01$ in comparison with T2DM + NMCI group

Table II. Laboratory indexes of included subjects.

	T2DM + MCI group	T2DM + NMCI group	Health control group
FBG (mmol/L)	9.48 ± 3.24**	9.15 ± 2.95**	4.97 ± 0.46
HbA1c (%)	8.66 ± 1.63**	8.52 ± 1.84**	5.40 ± 0.39
TC (mmol/L)	4.62 ± 1.16	4.50 ± 0.98	4.46 ± 1.21
TG (mmol/L)	1.82 ± 1.02	1.86 ± 1.43	1.61 ± 0.95
HDL-C (mmol/L)	1.01 ± 0.29	1.06 ± 0.32	1.04 ± 0.30
LDL-C (mmol/L)	2.59 ± 0.67	2.48 ± 0.71	2.36 ± 0.94
Adiponectin (ug/L)	226.28 ± 94.76**##	332.16 ± 114.07	398.25 ± 126.08

Note: *$p < 0.05$, **$p < 0.01$ in comparison with control group; #$p < 0.05$, ##$p < 0.01$ in comparison with T2DM + NMCI group.

there remained no statistically significant difference in comparison between other two groups ($p > 0.05$). In terms of the language, the score in T2DM + MCI group was significantly lower than those in other two groups ($p < 0.01$), and the differences in comparison between T2DM + NMCI group and health control group showed no statistically significant difference ($p > 0.05$). In comparison of the delayed recall, the score in T2DM + MCI group was remarkably declined when compared with other two groups, while the score in T2DM + NMCI group was significantly lower than that in the health control group ($p < 0.01$). For orientation, the score in T2DM + MCI group was significantly lower than those in other two groups ($p < 0.01$), while the difference between other two groups showed no statistical significance ($p > 0.05$). Comparisons of the naming ability and abstraction ability among three groups showed that the differences had no statistical significance ($p > 0.05$; Table III).

Identifying the Factors Affecting Cognitive Functions Through Multivariate Linear Regression Analysis

Furthermore, multivariate linear regression analysis was carried out with MoCA score as the dependent variable, and level of adiponectin in serum and other risk factors as the independent variables, and the results (Table IV) showed that education years (standard $\beta = 0.325$, $p = 0.003$), age (standard $\beta = -0.236$, $p = 0.016$), disease course of hypertension (standard $\beta = -0.242$, $p = 0.006$), disease course of diabetes mellitus (standard $\beta = -0.377$, $p < 0.001$) and adiponectin level in serum (standard $\beta = 0.201$, $p = 0.042$) were correlated with the cognitive impairment. MoCA score was negatively correlated with the age, disease course of diabetes mellitus and disease course of hypertension, and positively correlated with the education years and adiponectin level in serum.

Discussion

Prevalence rate of dementia is continuously increasing all over the world, especially in the elderly population[6-11]. Thus, the discovery of the influencing factors of MCI and pathogenesis, early diagnosis and intervention, are critical to prophylaxis and treatment of disease in progression, and improvement in life quality. Adiponectin, a kind of hormonal protein secreted by adipocytes, is correlated with multiple diseases, including

Table III. Comparison of MoCA scores among groups (score).

Ability	T2DM + MCI group	T2DM + NMCI group	Health control group
Visuospatial and executive	3.68 ± 0.79**##	4.64 ± 0.38	4.56 ± 0.62
Name	2.90 ± 0.27	2.97 ± 0.17	2.96 ± 0.19
Attention	4.21 ± 0.93**##	5.47 ± 0.76	5.82 ± 0.58
Language	2.05 ± 0.51**##	2.69 ± 0.49	2.70 ± 0.46
Abstract	1.75 ± 0.46	1.84 ± 0.33	1.89 ± 0.37
Delayed recall	1.88 ± 1.04**##	3.59 ± 0.85**	4.03 ± 0.74
Orientation	5.34 ± 0.62**##	5.83 ± 0.35	5.81 ± 0.44
Sum	21.95 ± 1.47**##	27.28 ± 1.39	27.89 ± 1.40

Note: *$p < 0.05$, **$p < 0.01$ in comparison with control group; #$p < 0.05$, ##$p < 0.01$ in comparison with T2DM + NMCI group.

Table IV. Multivariate Logistic regression analysis of risk factors related to MCI.

	Non-standard regression coefficient		Standard coefficient β	t	p
	B	SE			
Constant	29.147	1.829	–	17.296	0.000
Education years	0.158	0.049	0.325	4.017	0.003
Age	-0.076	0.415	-0.236	-2.128	0.016
Duration of diabetes mellitus	-0.149	0.033	-0.377	-4.904	0.000
Duration of hypertension	-0.066	0.027	-0.242	-2.815	0.006
Adiponectin	0.004	0.002	0.201	2.163	0.042

Note: $p < 0.05$ suggested statistical significance.

T2DM, hyperlipidemia, obesity, cardiovascular diseases, and neurodegenerative diseases (including AD)[12-16]. The results of this study showed that the level of adiponectin in serum in the T2DM groups was significantly lower than that in the health control group, which, similar to the previous results, showed that adiponectin level in serum is closely correlated with T2DM. In studies on different races, it has been reported that hypoadiponectinemia is closely associated with the IR and hyperinsulinemia, and the decrease in adiponectin level can easily lead to development of T2DM, IR and obesity. Adiponectin can regulate not only the cerebral metabolism, sensitivity of insulin, memory and cognitive functions, but also the severe inflammatory responses caused by MCI and AD. Particularly in AD, adiponectin is conducive to regulation of glucose metabolism and mitochondrial dysfunction[13,14]. The results of this study showed that the level of adiponectin in serum of patients in T2DM + MCI group was significantly lower than those in T2DM + NMCI group and health control group, and MoCA score was positively correlated with the level of adiponectin in serum, indicating that adiponectin can affect the cognitive function, and is involved in improving the memory and cognitive function.

Previous studies[8-10] have shown that age, gender, education, marriage, BMI, smoking, alcohol intake, hypertension, disease course of diabetes mellitus, hyperlipidemia, obesity, stroke, life style, environmental factors, genetic factors and other correlated diseases are believed to be the risk factors leading to cognitive impairment. In this study, results showed that systolic pressure, age, disease courses of diabetes mellitus and hypertension were significantly higher and longer than those in the T2DM + NMCI group and health control group, indicating that multiple factors affect the cognitive function of T2DM patients. Since the risk factors in MCI of T2DM patients remain unclear, multivariate linear regression analysis was performed with MoCA score as the dependent variable, and the level of adiponectin in serum as well as other risk factors as the independent variables, and the results showed that MoCA score was negatively correlated with the age and disease courses of diabetes mellitus and hypertension, and positively correlated with the education years and level of adiponectin in serum. This suggested that poor education, high blood glucose and pressure as well as the adiponectin level in serum, are risk factors in MCI of T2DM patients, and MCI in T2DM may be induced by multiple factors. Studies[6,11] have shown that cognitive functions are affected by various factors, like disease course of diabetes mellitus, control of blood glucose, HbA1c level, insulin administration, hypoglycemia, microvascular complications and medication. In this work, it was found that the disease course of diabetes mellitus in patients of T2DM + MCI group was significantly longer than that in T2DM + NMCI group, and negatively correlated with MoCA score, similarly to the results in previous studies. Thus, disease course of diabetes mellitus is a major factor influencing the cognitive dysfunction. Mild or moderate cognitive impairment is always complicated in T2DM patients. According to the current researches, domains that are mostly affected by cognitive impairment in T2DM mainly include attention, calculation ability, visuospatial and executive abilities and delayed recall[6]. The results of this report showed that impairment in multiple domains also existed in the cognitive impairment in elderly T2DM patients, and major domains were severely affected included visuospatial and executive ability, attention, delayed recall, language and orientation.

As a cross-sectional study with the clinical data of case as subject, this paper was limited by a small size of sample; in order to enhance the

reliability and persuasion of this investigation, a large sample-size and multi-center study with extensive range is expected. In addition, the results of this study were inevitably affected by confounding factors, like living habits and environmental conditions. Thus, more reliable data and conclusions require a long-term follow-up and observation of patients.

In conclusion, the level of adiponectin in serum is correlated with the MCI in T2DM, which provides new ideas for reducing the prevalence rate of MCI in T2DM patients. Risk factors of MCI in T2DM patients include education years, age, disease courses of hypertension and diabetes mellitus and adiponectin. For diabetes mellitus patients complicated with MCI, adiponectin is expected to be a promising therapeutic target, which can provide the evidence for substitutive therapy of exogenous supplementation of adiponectin for cognitive decline in elderly T2DM patients.

Conclusions

We observed that in the T2DM patients with MCI, the adiponectin level in serum was decreased, positively correlated with the MoCA score, and closely correlated with the development of MCI. Decrease in the adiponectin level may affect the cognitive function of diabetes mellitus patients. Early diagnosis and treatment of cognitive dysfunction in diabetes mellitus may be a promising strategy for preventing, treatment or even delaying the development of dementia. For T2DM patients complicated with MCI, adiponectin is a potential therapeutic target in medication.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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