Cognitive impairment in elderly patients with type 2 diabetes mellitus: prevalence and related clinical factors

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Abstract

Aim Diabetes mellitus is reported to be a risk factor for dementia. We evaluated the cognitive function in elderly diabetic patients and estimated the prevalence of patients with cognitive impairment and looked for any related clinical factors.

Subjects and methods Using 281 elderly (65 years of age or older) Japanese patients with type 2 diabetes mellitus who were free of clinically evident cognitive impairment, we evaluated their cognitive function with the Mini Mental State Examination (MMSE).

Results The MMSE score of all the participants was 27.3 ± 2.4 with 31.3% of them being in the abnormal range (tentatively defined normal range as having an MMSE score of 27–30). Multiple regression analysis disclosed that fasting serum non-esterified fatty acid (NEFA), estimated glomerular filtration ratio (eGFR) and insulin treatment were significantly related factors for the MMSE score, in addition to age and schooling history, which are extremely strong factors.

Conclusions We revealed that approximately one-third of elderly type 2 diabetic patients who were free of clinically evident cognitive impairment had impaired cognitive function, demonstrating that the MMSE score was significantly correlated with fasting NEFA level, renal function, insulin treatment, age and schooling history.

Keywords Cognitive impairment · Elderly patient · Type 2 diabetes mellitus · Mini Mental State Examination · Non-esterified fatty acid

Introduction

Japanese society is rapidly aging, and elderly people (65 years of age or older) now account for one-quarter of the population. The percentage of elderly patients requiring medical care for diabetes has also been increasing. As diabetes mellitus is reported to be a risk factor for dementia [1, 2], it is important to comprehend the cognitive function in elderly diabetic patients for medical care especially in regards to certain situations, such as self-management education. We thus evaluated the cognitive function in elderly diabetic patients and estimated the prevalence of patients with cognitive impairment and looked for any related clinical factors.

Materials and methods

We studied 281 elderly (65 years of age or older, age: 73.4 ± 6.1 years old) Japanese patients with type 2 diabetes mellitus (male: 144 patients) who had visited the outpatient clinic of the Diabetic Center, Fuchu Hospital, at regular intervals. All of them were free of clinically evident cognitive impairment. Their duration of diabetes (years after diagnosis), body mass index (BMI) and HbA1c (average of four recent measurements obtained every 3 months) were 17.4 ± 10.0 years, 23.5 ± 3.5 kg/m² and $7.6 \pm 1.2\%$, respectively. Sixty seven percent of the patients were being treated with oral hypoglycemic agents, 27.3% with insulin, 5.3% with no anti-diabetic agents and

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0.4 (one patients) with glucagon like peptide-1 analog. Patients with complications of depression or cerebral infarction were excluded. Cognitive function was evaluated by the Mini Mental State Examination (MMSE) [3, 4] at postprandial state, and a score of 27–30 was defined as normal range, 24–26 as mild cognitive impairment (MCI) range and under 24 as dementia range. Blood sampling for measuring serum non-esterified fatty acid (NEFA) and other lipids was performed at fasting state in the morning (between 8:15 and 9:00 a.m. after an overnight fast for about 12–15 h). The estimated glomerular filtration ratio (eGFR) was calculated using the serum creatinine concentration. Hypertension was defined as patients treated by anti-hypertensive drugs. Coronary heart disease (CHD) was defined as a history of myocardial infarction, angina pectoris or coronary arterial bypass grafting. The present study was approved by the institutional review board of Fuchu Hospital. Informed consent based on the Helsinki Declaration, as revised in 2000, was obtained in writing from all participants at the MMSE test. Data are shown as mean $\pm$ SD. Statistical analysis was performed using Excel Statistics 2015, version 1.0 (Social Survey Research Information Co., Ltd., Tokyo, Japan), and a P value < 0.05 was considered significant.

Results

Mean MMSE score of all the subjects was 27.3 ± 2.4 , near the lower limit of normal range, and approximately one-third of the patients were in the abnormal range, MCI range: 26.0%, dementia range: 5.3%. Prevalence of patients with MCI range increased in those over 70 years old and those with a dementia range of over 80 years old (Table 1). Stratified analysis of clinical parameters among the patient groups of cognitive range classified by the MMSE score is shown in Table 2. Ten parameters had statistical significance among cognitive ranges by multiple comparison test or chi-square test except BMI, fasting

serum level of LDL cholesterol, HDL cholesterol and triglycerides, prevalence of CHD and retinopathy, and alcohol consumption (Table 2). Among the ten parameters, NEFA was picked up and is shown as a scatter plot with the MMSE score in Fig. 1. Although statistical significance was not obtained from this univariate analysis, a trend for positive correlation between these parameters was seen. In order to elucidate the independent variables for the MMSE score, multiple regression analysis was performed using 228 patients whose above ten parameters were lined up (Table 3). The fasting NEFA level, eGFR and insulin treatment were determined to be a significantly correlated variable for the MMSE score, in addition to age and schooling history, which were extremely strong factors. In order to clarify the effects of insulin treatment on the cognitive function in elderly diabetic patients, clinical factors including the MMSE score were compared between patients with and without insulin treatment (Table 4). As expectedly, the MMSE score of the insulin-treated patients was significantly lower than that of the insulin-untreated patients when adjusted by age, schooling history, NEFA and eGFR. Insulin-treated patients had longer duration and higher HbA1c than those without insulin. Prevalence of one or more experiences of severe hypoglycemia (visit to the emergency outpatients unit because of conscious disturbance) was significantly higher in the insulin-treated group than in the untreated group.

Discussion

There is a small number of reports concerning morbidity of cognitive impairment in elderly type 2 diabetic patients who have no clinically evident cognitive impairment [5–7]. Our finding (approximately one-third of the patients had cognitive impairment) was almost consistent with the previous reports although classification of the cognitive impairment range was slightly different. These findings

Table 1 Distribution of cognitive function range classified by MMSE score in the patient groups divided by 5-year age intervals

Age (years old)	N	MMSE score	Prevalence of cognitive function range (%)		
			Normal	MCI	Dementia
65–69	89	28.2 ± 1.8	85.4	13.5	1.1
70–74	85	27.4 ± 1.9	68.2	31.8	0
75–79	54	27.1 ± 2.0	66.7	27.8	5.5
≥ 80	53	25.6 ± 3.3	43.4	35.8	20.8

Normal range: MMSE score from 27 to 30

MCI (mild cognitive impairment) range: MMSE score from 24 to 26

Dementia range: MMSE score equal to or below 23

MMSE Mini Mental State Examination

Table 2 Stratified analysis of clinical parameters among patient groups of cognitive function range classified by MMSE score

Parameters	Cognitive function range			P value
	Dementia	MCI	Normal	
	(N = 15) ^a	(N = 73) ^a	(N = 193) ^a	
Gender (male) ^a	40.0%	41.1%*	56.0%*	*<0.05
Age (years old) ^a	81.3 ± 5.7*,\$	75.0 ± 5.6*,\$	72.2 ± 5.7*,\$	*,\$*<0.001
S-history (years) ^a	9.3 ± 1.9*	10.4 ± 2.1 [#]	11.4 ± 2.5*,\$	*,\$*<0.05
BMI (kg/m ²) ^a	22.4 ± 4.1	23.7 ± 3.6	23.6 ± 3.5	
Duration (years) ^a	27.0 ± 11.7*,\$	17.3 ± 9.8*	16.7 ± 9.6 [#]	*,\$*<0.001
HbA1c (%) ^a	8.18 ± 1.34*,\$	7.49 ± 1.03*	7.55 ± 1.17 [#]	*,\$*<0.05
T-Chol (mg/dl)	169.3 ± 47.5*	189.7 ± 37.4	192 ± 31.3*	*<0.05
	(N = 12)	(N = 67)	(N = 168)	
LDL (mg/dl)	106.7 ± 25.7	113.7 ± 34.2	115.4 ± 27.3	
	(N = 11)	(N = 67)	(N = 177)	
HDL (mg/dl)	54.1 ± 17.1	56.7 ± 14.0	59.4 ± 17.8	
	(N = 12)	(N = 67)	(N = 169)	
TG (mg/dl)	125.9 ± 46.8	133.4 ± 68.8	124.3 ± 75.0	
	(N = 12)	(N = 67)	(N = 169)	
NEFA (μEq/l)	391.1 ± 262.4*,\$	615.3 ± 241.5*	622.0 ± 271.2 [#]	*,\$*<0.05
	(N = 9)	(N = 61)	(N = 158)	
eGFR (ml/min/1.73 ²)	55.1 ± 20.1*	61.4 ± 16.3 [#]	67.5 ± 19.4*,\$	*,\$*<0.05
	(N = 15)	(N = 71)	(N = 171)	
CHD ^a	6.7%	11.0%	10.9%	
P-Retinopathy	33.3%	23.9%	18.4%	
	(N = 12)	(N = 66)	(N = 169)	
Hypertension ^a	80.0%	71.2%*	56.0%*	*<0.05
Alcohol (g/day)	5.8 ± 12.8	5.8 ± 11.3	8.3 ± 16.9	
	(N = 11)	(N = 61)	(N = 171)	
Insulin treatment ^a	53.3%*	27.4%	21.2%*	*<0.05

Cognitive function range: normal, MMSE score from 27 to 30; MCI (mild cognitive impairment), MMSE score from 24 to 26; dementia, MMSE score equal to or below 23

MMSE Mini Mental State Examination, S-history schooling history, BMI body mass index, T-Chol total cholesterol, LDL low-density lipoprotein cholesterol, HDL high-density lipoprotein cholesterol, TG triglyceride, NEFA non-esterified fatty acid, eGFR estimated glomerular filtration ratio, CHD coronary heart disease, P-Retinopathy pre- or proliferative diabetic retinopathy, Alcohol alcohol consumption

*, #, \$ Significant difference between two cognitive function ranges

^a Parameters in which patients' numbers of cognitive function range are: dementia (N = 15), MCI (N = 73) and normal (N = 193)

have important implications for medical care of elderly diabetic patients, especially in cases when detailed explanations are required for the patients such as self-monitoring of blood glucose or insulin self-injection.

A depressive state [8] is an important factor affecting the MMSE score in addition to schooling history. In the present study, patients diagnosed as having depression were excluded. Among 88 patients with an MMSE score less than 27, 45 were assessed for depressive state by the geriatric depression scale (GDS)-15 [9]. The average scale of GDS-15 was 3.8 ± 2.2 , and no one had a scale of more

than 10, which indicates depression. These findings suggest that depressive state did not largely affect the present results.

Abnormality of blood glucose [10] (hyperglycemia, hypoglycemia and fluctuation of blood glucose [11]), insulin resistance [12, 13] and risk factors for atherosclerosis [14–16] such as hypertension, dyslipidemia, metabolic syndrome and renal dysfunction [17–19] were already reported to be associated with cognitive impairment in diabetic patients. In the present study, renal function (eGFR) was extracted as a significantly related factor,

consistent with the previous reports. As renal dysfunction is thought to be a risk factor for atherosclerosis, although the patients who had been diagnosed as having cerebral

infarction were excluded in the present study, impaired renal function might affect the cognitive function through atherosclerotic changes in the cerebral arteries.

Severe hypoglycemia in aged patients was reported to be a trigger of cognitive impairment in elderly diabetic patients [20, 21]. In the present study, HbA1c was not an independent variable, but insulin treatment was an independent factor for the MMSE score (Table 3), and the MMSE score in the insulin-treated patients was significantly lower than that in the untreated patients (Table 4). This may be due to the higher prevalence of severe hypoglycemia in the insulin-treated group (Table 4), and this result was also consistent with the previous findings [20, 21].

This is the first report to our knowledge in which the fasting serum NEFA level is associated with cognitive impairment in elderly type 2 diabetic patients.

The scatter plot with NEFA and MMSE scores is shown in the Fig. 1 for visualization of the relationship between these continuous variables. Unfortunately, statistical significance was not obtained from this univariate analysis

Fig. 1 Scatter plot with fasting serum NEFA level and MMSE score. *MMSE* Mini Mental State Examination

Table 3 Multiple regression analysis of clinical parameters for MMSE score in elderly patients with type 2 diabetes mellitus ($N = 228$)

Explanatory variable	Standard partial regression coefficient	<i>t</i> Value	<i>P</i>
Gender (0: male, 1: female)	−0.080	−1.290	0.198
Age (years old)	−0.239	−3.618	<0.001
Schooling history (years)	0.293	4.628	<0.001
Duration (years)	−0.042	−0.644	0.520
HbA1c (%)	0.103	1.570	0.118
Total cholesterol (mg/dl)	0.104	1.732	0.085
NEFA (μEq/l)	0.145	2.408	0.017
eGFR (ml/min/1.73 ²)	0.129	2.045	0.042
Hypertension (0: no, 1: yes)	−0.024	−0.391	0.696
Insulin treatment (0: no, 1: yes)	−0.160	−2.317	0.022

MMSE Mini Mental State Examination, *NEFA* non-esterified fatty acid, *eGFR* estimated glomerular filtration ratio

Table 4 Comparison of MMSE score and other clinical parameters between patients with and without insulin treatment

Clinical parameters	With insulin ($N = 69$)	Without insulin ($N = 212$)	<i>P</i>
Age (years old)	74.6 ± 6.5	73.0 ± 5.9	0.059
Schooling history (years)	10.8 ± 2.4	11.2 ± 2.4	0.304
Duration (years)	20.8 ± 11.5	16.3 ± 9.3	0.001
Body mass index (kg/m ²)	23.5 ± 3.9	23.5 ± 3.4	0.865
Severe hypoglycemia	12 (5.7%)	0 (0%)	<0.001
HbA1c (%)	8.5 ± 1.4	7.3 ± 0.9	<0.001
NEFA (μEq/l)	617.1 ± 331.8	609.8 ± 244.7	0.696
eGFR (ml/min/1.73 ²)	61.4 ± 21.2	66.6 ± 18.0	0.051
MMSE score	26.5 ± 3.2	27.5 ± 2.0	<0.001*

MMSE Mini Mental State Examination, *NEFA* non-esterified fatty acid, *eGFR* estimated glomerular filtration ratio

* Adjusted by age, schooling history, NEFA and eGFR

($N = 228$, $R = 0.085$, $P = 0.199$); multiple regression analysis disclosed the NEFA as one of the significant factors (Table 3) for the MMSE score. From the stratified analysis (Table 2), a significant difference of the NEFA level was also obtained among the three cognitive function ranges. From these results, the fasting serum NEFA level was thought to be an important isolated modulator for the MMSE score.

Population-based studies that investigated the relationship between fatty acid intake and cognitive function reported that saturated fat increased the risk of dementia [22], whereas unsaturated fat from fish oil was inversely related to incident dementia [22]. Altered composition of NEFA in the aged brain was also reported to be associated with cognitive performance in dogs [23] and in patients with Alzheimer's disease [24]. The composition of serum NEFA may be an important factor for cognitive function in elderly patients, although the fraction of serum NEFA was not measured in our study. In type 1 diabetic patients, it was reported that medium-chain triglyceride ingestion improved cognition induced by hypoglycemia [25]. The authors of this article considered that medium-chain triglyceride was thought to be a source of medium-chain fatty acids that were rapidly absorbed and oxidized in the liver, resulting in an excess of acetyl-CoA and, in turn, the rapid production of ketones, one of the limited energy sources for the brain. Their speculative theory supports our result that the serum NEFA level was associated with cognitive function (the higher the NEFA level is, the better the cognitive function). The subjects in our study were outpatients, and their blood glucose levels were relatively well controlled; none had tested positive for urine ketones. Although serum ketone bodies were not measured in our study, slightly increased ketones derived by the NEFA might be an energy source for brain cells resulting in a good score of MMSE. Taking this into account, further examination should be considered.

In conclusion, approximately one-third of elderly type 2 diabetic patients who were free of clinically evident cognitive impairment have impaired cognitive function, and their MMSE score correlates significantly with the fasting serum NEFA level, eGFR and insulin treatment, as do age and schooling history.

Compliances with ethical standards

Conflict of interest The authors declare no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standard of the responsible committee on human experimentation (institutional and national) and with Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

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