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Effect of Diabetes Mellitus on Daily Functioning and Cognition of Alzheimer's Disease Patients Evaluated by DASC-21

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Keywords
Alzheimer · Dementia · DASC-21 · Diabetes mellitus · Elderly

Abstract
Introduction: Diabetes mellitus (DM) is a risk factor for Alzheimer's disease (AD). It has also been pointed out that AD associated with DM may have unique characteristics. However, the characteristics of impairment in daily functioning when associated with DM have not been sufficiently investigated. ***Methods:*** In the present study, we compared the characteristics of 261 patients with AD diagnosed in the outpatient memory clinic of a university hospital, divided into diabetic and nondiabetic groups. The MMSE was used to assess cognitive function, and the Dementia Assessment Sheet for Community-based Integrated Care System 21-items (DASC-21) was used as an observational method to assess cognitive function and activities of daily livings. The two groups were compared. Furthermore, simple and multiple regression analysis was carried out in order to find the independent association of age, sex, education, DM, and HbA1c with the DASC-21 and each individual item of the DASC-21. ***Results:*** Diabetic subjects were as follows: MMSE 18.8 ± 4.0, DASC-21 46.0 ± 13.2, and HbA1c 7.07 ± 1.24%, respectively. On the other hand, nondiabetic subjects were as follows: MMSE 19.0 ± 4.5 and DASC-21 42.1 ± 12.2, respectively. In the diabetic group, total score of DASC-21 was higher (DM vs. nondiabetes mellitus [NDM]: 46.0 ± 13.2 vs. 42.1 ± 12.2; $p < 0.05$) and solving issues and common sense on the DASC-21 were higher than in the nondiabetic group (NDM) (DM vs. NDM: 8.58 ± 2.71 vs. 7.76 ± 2.66; $p < 0.05$). Multiple regression analysis showed that the presence of DM was the significant determinant of solving issues and common sense on the DASC-21 ($p < 0.05$). ***Conclusions:*** In AD patients, DM may be associated with impairment of solving issues and common sense.

Introduction

Many studies have shown that diabetes mellitus (DM) is a risk factor for the development of dementia [1, 2]. DM has been reported to be a risk factor not only for vascular dementia but also for Alzheimer's disease (AD) [1]. DM has also been reported to accelerate the progression of dementia after onset, with cognitive function declining twice as fast over a 5-year period [3].

However, it has been reported that among dementia patients with a diagnosis of AD, those with diabetes have different disease characteristics than those without DM. Sakurai et al. [4] reported that patients with AD who had

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DM showed a decline in the MMSE items that assessed attention and calculation ability by subtracting 7 consecutively when compared to the nondiabetic group. In a study using the Hasegawa Scale, they also reported that diabetic patients showed a decline in the word fluency test compared to nondiabetic patients [5]. Hanyu et al. [6] have shown that in AD with diabetes, not only the characteristics of cognitive decline but also the results of neuroimaging tests are different. They went on to study the disease and proposed a group of patients diagnosed with diabetic dementia, characterized by a longer duration of diabetes, older age, higher HbA1c, higher frequency of insulin treatment, and lower frequency of ApoE4 [7]. In diabetic dementia, they report that the ability to recall words is relatively maintained, the rate of cognitive decline is slow, and in addition, SPECT does not show the parietotemporal lobe decline that is the characteristic of AD [7]. From these studies, it is possible that diabetes may promote the pathogenesis of AD or dementia with diabetes is included in a different disease category, but much remains unknown.

DM has also been reported to cause impairment in daily functioning in association with cognitive decline [8–10]. Although dementia itself causes functional decline, it is necessary to examine how the coexistence of diabetes modifies functional impairment in daily life. In this study, whether there is a difference in impairment in daily functioning between patients with and without DM who were diagnosed with AD is examined. In addition to measuring cognitive function using the MMSE, cognitive function and impairment in daily functioning were examined using the Dementia Assessment Sheet for Community-based Integrated Care System 21-items (DASC-21), an observational assessment instrument that was developed to provide a quick assessment of the presence or absence of dementia in the community and has shown sufficient reliability and validity [11]. It is available in multiple languages: English, Spanish, French, Chinese, and Japanese [12]. The DASC-21 was also developed for use in the Initial-phase Intensive Support Team for Dementia, which conducts outreach to suspected dementia patients in the community and has been widely used in this field [13]. The DASC-21 as well as its shortened version, DASC-8, is also used to screen diabetic patients for cognitive and functional decline and to determine treatment goals according to their condition [14, 15]. In this study, the differences in AD patients with and without DM were examined, the clarification of which is expected to be useful for understanding the comorbid condition and managing patients.

Table 1. Characteristics of the patients

Demographic parameters	
Age, years	81.4±5.7
Sex	M108/F153
MMSE	19.0±4.3
HDS-R	16.5±5.2
DASC-21	43.2±12.6
CDR	1.22±0.85
Education, years	11.0±2.6
HbA1c, %	6.12±0.98
DASC-21	
Memory	6.47±1.88
Orientation	5.70±2.10
Solving issues/common sense	7.99±2.69
IADL outside	8.04±3.07
IADL inside	7.11±2.85
Physical ADL (1)	4.26±2.20
Physical ADL (2)	3.60±1.40
MMSE	
Temporal orientation	2.46±1.54
Spatial orientation	3.33±1.30
Registration	2.94±0.30
Serial 7S	1.88±1.54
Recall	0.53±0.82
Naming	1.96±0.24
Repetition	0.75±0.43
Follow a 3-stage command	2.73±0.63
Read and obey	0.97±0.18
Writing	0.67±0.47
Copy drawing	0.71±0.45

Materials and Methods

Participants

This study was carried out from August 2018 to July 2021. The outpatient clinic of the Department of Geriatrics and Cognitive Disorders at Fujita Health University Hospital received 855 first visits during the study period. Of them, a total of 261 participants with AD evaluated by the DASC-21 were enrolled and were separated into two groups according to the presence of type 2 diabetes (DM), that is, 73 diabetics and 188 nondiabetic (nondiabetes mellitus [NDM]) participants.

Procedure

In the outpatient clinic, assessment of dementia subjects involved a careful interview for the medical history, a physical examination, blood tests, Hasegawa Dementia Scale-Revised (HDS-R) [16], Mini-Mental State Examination (MMSE) [17], DASC-21, the Clinical Dementia Rating (CDR) [18, 19], other psychological tests, brain imaging test, and information on their regular medicine. The DASC-21 is a list of 21 questions about impairments of cognitive functions and functioning in daily life that are commonly observed in people with dementia [11]. Furthermore, the 21 questions were classified into 7 subcategories. Each question was assessed by a 4-point Likert scale (from 1 to 4). Subjects with a

Table 2. Characteristics of patients between diabetic and nondiabetic

Parameters	DM 73	NDM 188	*p* value
Age, years	82.2±5.5	81.2±5.7	0.20
Sex	M34/F39	M73/F115	0.18
MMSE	18.8±4.0	19.0±4.5	0.77
HDS-R	15.9±5.1	16.8±5.2	0.21
DASC-21	46.0±13.2	42.1±12.2	0.026*
CDR	1.32±0.75	1.18±0.88	0.25
Education, years	11.3±2.5	10.9±2.7	0.38
HbA1c, %	7.07±1.24	5.71±0.39	0.00*
DASC-21			
Memory	6.73±1.89	6.38±1.87	0.18
Orientation	6.10±2.24	5.55±2.03	0.059
Solving issues/common sense	8.58±2.71	7.76±2.66	0.028*
IADL outside	8.36±3.09	7.91±3.06	0.30
IADL inside	7.64±2.86	6.91±2.83	0.061
Physical ADL (1)	4.68±2.35	4.10±2.12	0.054
Physical ADL (2)	3.88±1.61	3.51±1.31	0.055
MMSE			
Temporal orientation	2.33±1.50	2.51±1.55	0.41
Spatial orientation	3.23±1.23	3.37±1.33	0.42
Registration	2.96±0.20	2.93±0.34	0.59
Serial 7S	1.97±1.60	1.85±1.52	0.55
Recall	0.58±0.85	0.52±0.82	0.81
Naming	1.99±0.12	1.95±0.27	0.23
Repetition	0.70±0.46	0.78±0.42	0.19
Follow a 3-stage command	2.73±0.67	2.72±0.61	0.85
Read and obey	0.97±0.16	0.96±0.19	0.69
Writing	0.68±0.47	0.67±0.47	0.82
Copy drawing	0.70±0.46	0.72±0.45	0.76

DM, diabetes mellitus; NDM, nondiabetes mellitus. * $p < 0.05$.

DASC-21 score of 31 or more were categorized as having suspected cognitive impairment or dementia.

AD was defined according to the criteria of the National Institute on Aging-Alzheimer's Association workgroups [20]. Other dementia diagnoses were also given according to each standard set of criteria.

Only patients with AD were enrolled in the present study. We excluded cases of normal, mild cognitive impairment, serious head injury, major depression, other mental disorders, and other type of dementia. The diagnosis of DM was done based on a fasting plasma glucose level of ≥126 mg/dL, a random plasma glucose level of ≥200 mg/dL, or HbA1c level of ≥6.5% [21] or in cases where antidiabetic drugs were used.

Statistical Analysis

The data are expressed as mean ± standard deviation. A cross-sectional analysis of cognitive status was performed using Student's *t* test for continuous data and the χ^2 test for categorical data. Simple and multiple regression analysis were carried out in order to find the independent association of age, sex, education, DM, and HbA1c with the DASC-21 and each individual item of the DASC-21. *p* values <0.05 were considered statistically significant. The data analysis was carried out using SPSS version 28.0 for Windows.

Results

In total, 261 (DM: $n = 73$, NDM: $n = 188$) subjects were enrolled (Table 1). For all subjects, mean age was 81.4 ± 5.7 years, MMSE was 19.0 ± 4.3, and DASC-21 was 43.2 ± 12.6 (Table 1).

Data from diabetic subjects were as follows: mean age was 82.2 ± 5.5 years, MMSE was 18.8 ± 4.0, DASC-21 was 46.0 ± 13.2, and HbA1c was 7.07 ± 1.24%. On the other hand, data for nondiabetic subjects were as follows: mean age was 81.2 ± 5.7 years, MMSE 19.0 ± 4.5, and DASC-21 was 42.1 ± 12.2. In the diabetic group, total score on the DASC-21 was higher (DM vs. NDM: 46.0 ± 13.2 vs. 42.1 ± 12.2; $p < 0.05$) and solving issues and common sense on the DASC-21 were higher than in the nondiabetic group (DM vs. NDM: 8.58 ± 2.71 vs. 7.76 ± 2.66; $p < 0.05$) (Table 2).

In the details of diabetic therapy, 17 patients with diabetes were not treated with any drugs. Of the other 56 diabetes patients, 41 were prescribed dipeptidyl peptidase-4 inhibitors. On the other hand, the number of pa-

Table 3. Details of diabetic therapy

Drugs	*N*
No medication	17
Sulfonylurea	5
Glinide	11
DPP4 inhibitor	41
GLP-1 receptor agonist	6
Biganide	7
Thiazolidine	5
α-Glucosidase inhibitor	14
SGLT2 inhibitor	7
Insulin	6
Combination of therapy	
Oral 1 type	22
Oral 2 types	16
Oral ≥ 3 types	7
Insulin	3
Insulin and oral	1
Insulin and GLP-1	1
GLP-1	1
GLP-1 and oral	3
GLP-1, insulin, and oral	1

DPP4 inhibitor, dipeptidyl peptide 4 inhibitor; GLP-1 receptor agonist, glucagon-like peptide-1 agonist; SGLT2 inhibitor, sodium glucose cotransporter 2 inhibitor; Oral, oral hypoglycemia drug; GLP-1, GLP-1 receptor agonist.

tients using sulfonylurea drugs and insulin was small. Furthermore, 30% of diabetes patients used only one type of oral hypoglycemic drug (Table 3).

Simple regression analysis on total score of DASC-21 and solving issues and common sense on the DASC-21 suggested a correlation with the presence of DM ($p < 0.05$) (Table 4), whereas multiple regression analysis only showed that the presence of DM was the significant determinant of solving issues and common sense on the DASC-21 ($p < 0.05$) (Table 4). Simple and multiple regression analysis on total score of DASC-21 and each individual item of the DASC-21 were not correlated with HbA1c.

Discussion

In the present study, there was significant difference between the diabetic and nondiabetic groups in total score of DASC-21 and an individual item, solving issues and common sense on the DASC-21 among older people, although only the solving issues and common sense on the DASC-21 was significant in multiple regression analysis. On the other hand, total and individual item scores of MMSE showed no significant differences between the groups.

The problem-solving (solving issues) is an operation that involves making probabilistic predictions about various options to first identify those viable options [22]. Problem-solving, as an executive function, is cognitively related to frontal lobe functions such as attention [23]. In the current study, no significant difference was found when assessed by MMSE, but it was shown as a decline in problem-solving when assessed by DASC-21. Therefore, we consider that the difference was not shown in cognitive function as in previous studies but was shown as a functional decline in DASC-21 [4–6].

In the relationship between blood glucose control and cognitive function, hyperglycemia was associated with slower performance on the psychomotor task, slower mental subtraction speed, and increased subtraction errors [24]. When poorly controlled diabetic patients with insulin or oral hypoglycemic drugs were treated, the scores of both the digit symbol test and the Benton test were partially improved. This suggested that glucose control is important for the maintenance of cognitive function and that cognitive impairment is partially reversible [25]. The present data showed the HbA1c of the diabetic group was relatively good. In other words, a steady blood glucose in diabetic patients does not strongly affect cognitive function. Various reasons were suspected. First, the Japanese yearly change in mean HbA1c of type 2 DM has decreased between 2005 and 2020 [26]. Second, there were few severe hypoglycemic episodes in these diabetic patients. Hypoglycemia is one risk factor for dementia. Among older patients with type 2 DM, a history of severe hypoglycemic episodes was associated with a greater risk of dementia [27]. Intensive blood-glucose control with sulfonylureas or insulin had a greater risk of hypoglycemic episodes than conventional control [28]. In the present data, the number of patients using sulfonylureas or insulin was small. Third, the Japanese clinical guideline for elderly DM patient care was first presented in 2016, recommending [29] that older adults with multiple coexisting chronic illnesses, cognitive impairment, or functional dependence should have less stringent glycemic goals [29]. The number of patients in the present study using sulfonylureas or insulin may also have been small in our study. Therefore, severe hypoglycemia attacks may also have been avoided. In relation to the existence of DM and ADL, HbA1c was not also correlated with ADL in the present data. One of the reasons we suspected was that blood glucose control of DM patients was fine in the present study. A Japanese study reported that there were no significant differences between diabetic and no diabetic patients in basic and instrumental ADL [30], although these subjects were younger than in the present study.

Table 4. Simple and multiple regression analyses

	Regression coefficient	*p* value	95% CI
a Simple regression analysis for the determinant of DASC-21			
Age	0.081	0.190	−0.90 to 0.452
Sex	−0.006	0.923	−3.28 to 2.972
Education	−0.003	0.960	−0.596 to 0.566
DM	0.137	0.026*	0.455–7.251
b Simple regression analysis for the determinant of problem-solving issue/common sense			
Age	0.051	0.413	−0.034 to 0.082
Sex	0.004	0.954	−0.648 to 0.687
Education	−0.001	0.987	−0.126 to 0.124
DM	0.136	0.028*	0.089–1.540
c Multiple regression analysis for the determinant of DASC-21			
Age	0.081	0.202	−0.096 to 0.451
Sex	−0.012	0.853	−3.612 to 2.989
Education	0.007	0.916	−0.591 to 0.658
DM	0.119	0.059	−0.122 to 6.733
d Multiple regression analysis for the determinant of solving issue/common sense			
Age	0.045	0.475	−0.037–0.080
Sex	−0.003	0.961	−0.728–0.693
Education	0.000	0.988	−0.134–0.135
DM	0.125	0.048*	0.008–1.484

DM, diabetes mellitus. * $p < 0.05$.

There were several limitations of the present study. First, it was carried out in only one outpatient memory clinic. Data from DM clinics or other outpatient clinics are needed. Second, the duration of DM and diabetic complications were not investigated in the present study.

Conclusion

We concluded that there was significant difference between the diabetic and nondiabetic groups in solving issues and common sense on the DASC-21 among older people. Furthermore, the clinical usefulness of the DASC-21 in older patients with multiple comorbidities was shown in the present study.

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Statement of Ethics

The present study was approved by the Institutional Review Board of Fujita Health University Hospital [HM19-047], and written informed consent was obtained from all of the participants. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H. Yoshino designed the study, collected the data, completed analysis, and wrote the paper. H. Takechi completed analysis and reviewed the paper.

Data Availability Statement

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

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