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ORIGINAL ARTICLE

Smoking status is associated with mild cognitive impairment assessed with the mini-mental state examination in Japanese diabetic patients

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Abstract

Aims We assessed the association between smoking status and mild cognitive impairment (MCI) in Japanese diabetic patients.

Methods This cross-sectional study included 323 diabetic patients, aged 40–79 years, who were referred to an outpatient diabetic clinic between January and July 2013 at Shiga University of Medical Science Hospital (Otsu, Japan). Cognitive function was assessed using the mini-mental state examination (MMSE), and patients were classified into two categories: normal cognitive function (MMSE score ≥27) and MCI (MMSE score 22–26). Logistic regression analysis was used to estimate the multivariable-adjusted odds ratios (ORs) and 95 % confidence intervals (CIs) for MCI in current smokers and ex-smokers compared with never-smokers.

Results Of the 323 patients, 55 (17.0 %), 134 (41.5 %), and 134 (41.5 %) were current smokers, ex-smokers, and never-smokers, respectively. Of these, 68 (21.0 %) patients had MCI. After adjusting for age, sex, systolic blood pressure, body mass index, high-density lipoprotein cholesterol, estimated glomerular filtration rate, hemoglobin A1c, insulin therapy, sulfonylurea, history of coronary heart disease, exercise habit, drinking status, and education, the OR for MCI was 3.62 (95 % CI 1.26–10.40) in current smokers compared with never-smokers. In addition, the multivariable-adjusted ORs for MCI were 3.02 (95 % CI 0.64–14.32) in current smokers <30.0 pack-years and 4.90 (95 % CI 1.32–18.16) in current smokers ≥30.0 pack-years, compared with never-smokers (p for trend = 0.017).

Conclusions Current smoking, especially current smoking for which cumulative lifetime exposure was high, was associated with MCI, as assessed using the MMSE in Japanese diabetic patients.

Keywords Smoking · Mild cognitive impairment · Mini-mental state examination · Diabetes

Introduction

Vascular complications such as microvascular disease (e.g., retinopathy, nephropathy, and neuropathy) and macrovascular disease (e.g., coronary heart disease and stroke) are major problems in diabetic patients. In recent years, dementia has also attracted attention as a serious complication of diabetes [1–4]. A recent systematic review reported that the risk of dementia and mild cognitive impairment (MCI) was higher among diabetic patients than in the general population [5]. In that study, diabetic patients had a 2.5-fold higher risk for vascular dementia (VaD), a 1.5-fold higher risk for Alzheimer's disease, and a 1.2-fold higher risk for MCI [5]. Progression to dementia reduces quality of life, and imposes a burden on both the patients themselves and the family members supporting them [1]. It is also thought that cognitive impairment makes diabetes self-management difficult, though self-management is very important for diabetic patients. Furthermore, it is thought

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that a decrease in self-management ability leads to poor glycemic control and other serious complications. Therefore, it is important to prevent cognitive impairment among diabetic patients, and early intervention is essential.

MCI is an intermediate stage between normal cognitive function and dementia [6]. MCI patients have a significantly higher risk of dementia. It has been reported that 10–15, 60.5, and 100 % of MCI patients will develop full dementia within 1, 5, and 9.5 years, respectively, after being diagnosed with MCI [7]. Therefore, it is important that we pay attention to MCI in order to facilitate early intervention, and the identification of modifiable risk factors of MCI among diabetic patients is necessary to prevent MCI.

The association between smoking and cognitive impairment has been widely discussed in recent years. Early research reported that nicotine improves short-term cognitive performance and inhibits amyloid formation [8, 9]. More recently, this evidence has been questioned and claims made that the known negative effect of smoking on cardiovascular disease means that it is likely to be a risk factor for VaD [10]. A recent large cohort study reported that community residents who were smoking more than two packs a day had a 2.7-fold higher risk for VaD and a 2.1-fold higher risk for total dementia compared with never-smokers [11]. Similarly, in Japanese community residents, a dose–response relationship was noted between the years of cigarette smoking and the risk of total dementia [12]. However, the association between smoking and cognitive impairment is still controversial, and little attention has been paid to this among diabetic patients. The present study therefore aimed to assess the association between smoking status and MCI in Japanese diabetic patients.

Materials and methods

Study participants

This cross-sectional study included diabetic patients who were referred to an outpatient diabetic clinic between January and July 2013 at Shiga University of Medical Science Hospital (Otsu, Japan) [13, 14]. The exclusion criteria were those with dementia or those with gestational diabetes. Of 416 patients aged 40–79 years, 398 (95.7 %) patients agreed to participate in the survey. Of these patients, we excluded three who could not complete the mini-mental state examination (MMSE) because of injury or fracture of their dominant arm. Additionally, we excluded 38 with stroke and 34 with missing data. A total of 323 patients were included in the analysis.

Procedures

Smoking status was obtained using a self-administered questionnaire that was partially supported and reconfirmed by a personal interview with nurses. Smoking status was categorized as current smoker, ex-smoker, or never-smoker. Current smokers were asked to report the average number of cigarettes they smoked per day and the number of years that they had smoked. A pack-year was defined as smoking 20 cigarettes/day for 1 year. Current smokers were categorized by the number of pack-years into two subgroups: <30.0 and ≥ 30.0. Ex-smokers were categorized by the number of years since quitting into the following subgroups: ≥ 20, 10–19, and ≤ 9. The self-administered questionnaire also included demographic characteristics, medical history, and health-related habits. Drinking status was categorized as never-, ex-, or current drinker. Exercise habit was categorized as ≥ 2 times/week (≥ 30 min each) or <2 times/week. Information on glycemic control, complications, and treatment was collected through a review of the patient's medical records. The hemoglobin A1c (HbA1c) level, estimated glomerular filtration rate (eGFR), and high-density lipoprotein (HDL) cholesterol levels were collected by reviewing the patient's most recent medical records. HbA1c (%) was estimated as a National Glycohemoglobin Standardization Program equivalent value (%) and calculated using the formula HbA1c (%) = 1.02 × HbA1c (Japan Diabetes Society %) + 0.25 % [15].

The patients were weighed while wearing light clothing, and height was measured without wearing shoes. Body mass index (BMI) was calculated as the weight (kg) divided by the height squared (m^2). Blood pressure was measured twice for each patient using an automatic sphygmomanometer with the patients in a sitting position after resting for at least 5 min, and the mean value for each patient was recorded.

Definition of MCI

Cognitive function was assessed using the MMSE [16]. The MMSE is a measure of global cognitive function consisting of 11 (mainly multi-part) questions addressing orientation (time and place), immediate and delayed recall of three object names, understanding of simple commands, naming, simple arithmetic or spelling, and constructional praxis. MMSE was administered and scored by trained nurses. MMSE scores range from 0 to 30, with higher values indicating better cognitive function. In the study, patients were classified into two categories: normal cognitive function (MMSE score ≥ 27) and MCI (MMSE score 22–26) [17, 18].

Statistical analysis

Differences in characteristics between current smokers, ex-smokers, and never-smokers were determined by analysis of covariance (ANCOVA) for age with adjustments for sex, an ANCOVA for continuous data with adjustments for age and sex, and a χ^2 test for dichotomous and categorical data.

Logistic regression analysis was used to estimate the multivariable-adjusted odds ratios (ORs) and 95 % confidence intervals (CIs) for MCI in current smokers and ex-smokers compared with never-smokers. Age and sex were included in model 1; age, sex, systolic blood pressure, BMI, HDL cholesterol, eGFR, HbA1c, insulin therapy (yes or no), sulfonylurea (yes or no), history of coronary heart disease (yes or no), exercise habit ($\geq$2 times/week or <2 times/week), drinking status (never-, ex-, or current drinker), and education were included in model 2. In addition, patients were stratified into two age groups: 40–64 years and 65–79 years. We also conducted logistic regression analysis.

Additionally, we classified patients into never-smokers and subgroups (<30.0 pack-years and $\geq$30.0 pack-years) of current smokers. Logistic regression analysis was used to estimate the multivariable-adjusted ORs and 95 % CIs for MCI. The group of never-smokers was used as the reference group. Moreover, we classified patients into never-smokers and subgroups ($\geq$20, 10–19, and $\leq$9 years since quitting) of ex-smokers. Logistic regression analysis was used to estimate the multivariable-adjusted ORs and 95 % CIs for MCI. The group of never-smokers was used as the reference group.

All data were analyzed using SPSS statistical software version 21.0 J (IBM SPSS Japan Inc., Tokyo, Japan). All reported *p*-values are two-tailed; values of <0.05 were considered statistically significant.

Results

The mean age of the 323 (207 men and 116 women) patients was 64.8 years. Among them, 55 (17.0 %), 134 (41.5 %), and 134 (41.5 %) were current smokers, ex-smokers, and never-smokers, respectively. Table 1 shows

Table 1 Characteristics of 323 Japanese diabetic patients according to smoking status

	Never-smokers	Ex-smokers	Current smokers	*p* value
n	134	134	55	
Age (years)	65.3 (63.2–67.3)	66.0 (64.1–67.8)	60.9 (58.2–63.6)	0.005
Men %	26.9	92.5	85.5	<0.001
Education $\geq$12 years (%)	87.3	83.6	81.8	0.551
Drinking status (%)				<0.001
Never-drinkers	76.1	32.8	36.4	
Ex-drinkers	5.2	14.9	25.5	
Current drinkers	18.7	52.2	38.2	
Exercise habit $\geq$2 times/week (%)	56.7	62.7	41.8	0.031
Diabetes duration (years)	18.2 (16.3–20.2)	16.1 (14.2–18.0)	14.3 (11.7–16.9)	0.089
Type 2 diabetes (%)	91.0	90.3	98.2	0.171
Treated with insulin therapy (%)	37.3	34.6	29.1	0.558
Use of sulfonylurea (%)	32.1	41.0	49.1	0.071
Diabetic retinopathy (%)	16.4	19.4	14.5	0.853
History of coronary heart disease (%)	17.2	24.6	21.8	0.332
Antihypertensive medicine (%)	58.2	56.7	50.9	0.651
Systolic blood pressure (mmHg)	137.3 (133.3–141.3)	135.6 (131.8–139.3)	129.6 (124.2–135.1)	0.084
Diastolic blood pressure (mmHg)	75.9 (73.7–78.0)	74.4 (72.4–76.4)	70.0 (67.1–72.9)	0.007
Body mass index (kg/m^2)	24.8 (24.0–25.6)	24.5 (23.7–25.2)	24.6 (23.5–25.7)	0.866
HDL cholesterol (mg/dl)	54.6 (51.5–57.6)	53.5 (50.6–56.3)	52.7 (48.6–56.8)	0.793
eGFR (ml/min/1.73 m^2)	71.6 (67.7–75.4)	71.1 (67.5–74.7)	79.0 (73.8–84.3)	0.028
HbA1c (%)	7.3 (7.1–7.5)	7.4 (7.2–7.6)	7.5 (7.2–7.8)	0.479

Dichotomous and categorical data were analyzed with the χ^2 test and are shown as %

Age was analyzed using analysis of covariance with adjustments for sex, and is shown as the mean (95 % confidence interval)

Normally distributed continuous data were analyzed using analysis of covariance with adjustments for age and sex, and are shown as the mean (95 % confidence interval)

HDL high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c

Table 2 Multivariable-adjusted ORs for MCI assessed using the mini-mental state examination according to smoking status

	Never-smokers	Ex-smokers	Current smokers
Total			
MCI (%) (case/*n*)	16.4 (22/134)	23.9 (32/134)	23.6 (13/55)
OR (95 % CI) for MCI			
Model 1	1.0	3.46 (1.44–8.33)	3.75 (1.41–9.96)
Model 2	1.0	3.55 (1.40–9.05)	3.62 (1.26–10.40)
40–64 years			
MCI (%) (case/*n*)	12.7 (7/55)	21.2 (11/52)	18.2 (6/33)
OR (95 % CI) for MCI			
Model 1	1.0	4.32 (0.96–19.45)	3.26 (0.72–14.76)
Model 2	1.0	4.24 (0.82–21.78)	3.92 (0.75–20.45)
65–79 years			
MCI (%) (case/*n*)	19.1 (15/79)	25.6 (21/82)	31.8 (7/22)
OR (95 % CI) for MCI			
Model 1	1.0	3.27 (1.07–10.02)	4.66 (1.22–17.81)
Model 2	1.0	3.03 (0.87–10.54)	3.99 (0.89–17.83)
Men			
MCI (%) (case/*n*)	11.1 (40/36)	21.8 (27/124)	19.1 (9/47)
OR (95 % CI) for MCI			
Model 3	1.0	2.16 (0.70–6.68)	2.10 (0.58–7.55)
Model 4	1.0	2.13 (0.65–7.02)	1.85 (0.46–7.51)

Logistic regression analysis was used to estimate the adjusted ORs and 95 % CIs

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, systolic blood pressure, body mass index, HDL cholesterol, eGFR, HbA1c, insulin therapy (yes or no), sulfonylurea (yes or no), history of coronary heart disease (yes or no), exercise habit (≥2 times/week or <2 times/week), drinking status (never-, ex-, or current drinker), and education

Model 3: adjusted for age

Model 4: adjusted for age, systolic blood pressure, body mass index, HDL cholesterol, eGFR, HbA1c, insulin therapy (yes or no), sulfonylurea (yes or no), history of coronary heart disease (yes or no), exercise habit (≥2 times/week or <2 times/week), drinking status (never-, ex-, or current drinker), and education

MCI mild cognitive impairment, *OR* odds ratio, *CI* confidence interval, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c

characteristics of the patients according to smoking status. Age, sex, drinking status, exercise habit, diastolic blood pressure, and eGFR differed significantly among the three groups. Current smokers were the youngest and had the lowest systolic and diastolic blood pressure among the three groups.

MMSE scores of the 323 patients with diabetes ranged from 22 to 30. Of those patients, 68 (21.0 %) had MCI (MMSE score 22–26). Table 2 presents the ORs for MCI according to smoking status. The proportions of the patients who had MCI according to the MMSE were 16.4 % of the never-smokers, 23.9 % of the ex-smokers, and 23.6 % of the current smokers. The adjusted ORs and 95 % CIs for MCI were 3.55 (1.40–9.05) in ex-smokers and 3.62 (1.26–10.40) in current smokers compared with never-smokers after adjusting for age, sex, systolic blood pressure, BMI, HDL cholesterol, eGFR, HbA1c, insulin therapy, sulfonylurea, history of coronary heart disease, exercise habit, drinking status (never-, ex-, or current drinkers), and education. Although the statistical power was lower because of the small sample size, the trends seen in the results did not change when the age-specific analysis was performed. Additionally, we observed similar trends when we only analyzed the 207 men. We did not analyze the 116 women because the sample sizes of current smokers and ex-smokers were small.

Table 3 shows ORs for MCI according to pack-years of cigarette smoking. The proportions of patients with MCI according to the MMSE were 15.4 % of current smokers whose cumulative lifetime exposure was <30.0 pack-years and 31.0 % of current smokers whose cumulative lifetime exposure was ≥30.0 pack-years. The adjusted ORs and 95 % CIs for MCI were 3.02 (0.64–14.32) in current smokers whose cumulative lifetime exposure was <30.0 pack-years and 4.90 (1.32–18.16) in current smokers whose cumulative lifetime exposure was ≥30.0 pack-years, compared with never-smokers after adjustment for confounding factors (p for trend = 0.017).

Table 3 Multivariable-adjusted ORs for MCI assessed using the mini-mental state examination according to pack-years of cigarette smoking

	Never-smokers	Current smokers		*p* for trend
		<30.0 pack-years	≥30.0 pack-years	
MCI (%) (case/*n*)	16.4 (22/134)	15.4 (4/26)	31.0 (9/29)	
OR (95 % CI) for MCI				
Model 1	1.0	2.50 (0.62–10.07)	4.58 (1.37–15.31)	0.013
Model 2	1.0	3.02 (0.64–14.32)	4.90 (1.32–18.16)	0.017

A pack-year was defined as smoking 20 cigarettes/day for 1 year

Logistic regression analysis was used to estimate the adjusted ORs and 95 % CIs

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, systolic blood pressure, body mass index, HDL cholesterol, eGFR, HbA1c, insulin therapy (yes or no), sulfonylurea (yes or no), history of coronary heart disease (yes or no), exercise habit (≥2 times/week or <2 times/week), drinking status (never-, ex-, or current drinker), and education

MCI mild cognitive impairment, *OR* odds ratio, *CI* confidence interval, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c

Table 4 Multivariable-adjusted ORs for MCI assessed using the mini-mental state examination according to years since quitting

	Never-smokers	Ex-smokers			*p* for trend
		≥20 years	10–19 years	≤9 years	
MCI (%) (case/*n*)	16.4 (22/134)	18.0 (9/50)	21.6 (8/37)	31.9 (15/47)	
OR (95 % CI) for MCI					
Model 1	1.0	1.85 (0.58–5.88)	2.28 (0.72–7.23)	4.28 (1.59–11.38)	0.003
Model 2	1.0	2.02 (0.58–6.90)	2.67 (0.77–9.30)	5.09 (1.67–15.52)	0.004

Logistic regression analysis was used to estimate the adjusted ORs and 95 % CIs

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, systolic blood pressure, body mass index, HDL cholesterol, eGFR, HbA1c, insulin therapy (yes or no), sulfonylurea (yes or no), history of coronary heart disease (yes or no), exercise habit (≥2 times/week or <2 times/week), drinking status (never-, ex-, or current drinker), and education

MCI mild cognitive impairment, *OR* odds ratio, *CI* confidence interval, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *HbA1c* hemoglobin A1c

ORs for MCI according to years since quitting are presented in Table 4. The proportions of the patients with MCI according to the MMSE who were ex-smokers and had quit ≥20, 10–19, and ≤9 years prior were 18.0, 21.6, and 31.9 %, respectively. The adjusted ORs and 95 % CIs for MCI in ex-smokers who had quit ≥20, 10–19, and ≤9 years prior were 2.02 (0.58–6.90), 2.67 (0.77–9.30), and 5.09 (1.67–15.52), respectively, compared with never-smokers after adjusting for confounding factors (p for trend = 0.004).

Discussion

The main finding of the present study was that current smokers had an elevated risk for MCI compared with never-smokers after adjusting for confounding factors. Additionally, we found that the risk for MCI increased in a dose-dependent manner with the number of pack-years of exposure (i.e., the long-term effect of cigarette smoking). Moreover, in the study, ex-smokers had a higher risk for MCI. However, the risk was attenuated in ex-smokers who had quit for ≥10 years.

The present study showed that current smoking—especially current smoking for which cumulative lifetime exposure was high—was associated with MCI, as assessed using the MMSE, in Japanese diabetic patients. These findings are in accordance with previous community-based cohort studies [11, 12]. Therefore, cigarette smoking might be associated with MCI in diabetic patients as well as in the general population. Smoking is an important risk factor for arteriosclerosis and vascular disease, and could influence cognitive function through them. However, in this study, after adjusting for many factors such as blood pressure, cholesterol, and history of coronary heart disease, the risk for MCI was not attenuated in current smokers. Smoking is also a significant source of oxidative stress [19], which influences cognitive function [20]. Therefore, oxidative stress may play a role in the association between smoking and cognitive function. In previous studies, insulin therapy

was associated with cognitive impairment, probably through hypoglycemia [21, 22]. In the present study, insulin therapy had no effect on MCI (data not shown). However, current smokers had an elevated risk for MCI compared with never-smokers, even after adjusting for insulin therapy. Although the mechanisms by which smoking affects cognitive function are unclear, cigarette smoking may be a modifiable risk factor for MCI among diabetic patients.

In the study, although ex-smokers had a higher risk for MCI, the risk was attenuated in long-term ex-smokers. A recent cohort study reported that long-term ex-smokers who had quit for ≥10 years did not show a greater cognitive decline than never-smokers, while ex-smokers who had quit relatively recently showed a greater decline in cognitive function than never-smokers [23]. Because residual effects of smoking on cognitive function may still be evident approximately a decade after smoking cessation, it is necessary to quit smoking as soon as possible to prevent MCI. In our study, among 55 current smokers, the mean age that they started to smoke was 20 years, and the mean age that they were diagnosed with diabetes was 46 years (data not shown). The mean age of the 55 current smokers was 60 years; they were still smoking many years after they had initially been diagnosed with diabetes. This group may have high nicotine dependence because of its members' long-term exposure. Therefore, early and active intervention for smoking cessation is important for current smokers with diabetes to prevent future MCI.

There are several limitations of the present study. First, the cross-sectional design cannot prove causality. Therefore, a prospective study is necessary. Second, the subjects were limited to the patients of one university hospital. Third, the sample size of current smokers was low. Hence, further investigation with a larger sample size is necessary to confirm these results. Fourth, MCI was evaluated using just one test (MMSE). MCI and dementia are diagnosed not only by MMSE but also by the impairment of patients' activities of daily living (ADL) or instrumental ADL (IADL). The American Academy of Neurology defines MCI using the following five criteria: (1) memory complaint, (2) objective memory impairment, (3) normal general cognitive function, (4) intact ADL, and (5) dementia is not present [24]. Hence, a further investigation to assess MCI using other criteria, including the ADL or IADL, is necessary to confirm our results. Fifth, we did not separately assess the association between smoking status and MCI in types 1 and 2 diabetes because the sample size of patients with type 1 diabetes was low. However, we observed similar results when we analyzed 297 patients with type 2 diabetes (see Tables S1–S3 in the Electronic supplementary material). Finally, we did not evaluate the number of pack-years in ex-smokers.

Despite these potential limitations, the present findings support the conclusion that cigarette smoking may be a modifiable risk factor for MCI among diabetic patients. Cognitive impairment is a major problem in diabetic patients, and it is important to prevent MCI among diabetic patients. We think that avoiding smoking is better than smoking cessation for preventing MCI, and also that it is important that medical workers intervene to facilitate smoking cessation as soon as possible.

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Compliance with ethical standards

Conflicts of interest Nao Sonoda, Akiko Morimoto, and Naomi Miyamatsu declare that they have no conflict of interest. Satoshi Ugi, Katsutaro Morino, Osamu Sekine, Ken-ichi Nemoto, and Hiroshi Maegawa received scholarship grants from Takeda Pharmaceutical Co., Ltd., Astellas Pharma Inc., Merck Sharp & Dohme Corp., Kowa Pharmaceutical Co., Ltd., AstraZeneca K.K., Teijin Pharma Ltd., Nippon Boehringer Ingelheim Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., and Ono Pharmaceutical Co., Ltd..

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Ethics Committee of Shiga University of Medical Science) and with the Helsinki Declaration of 1964 and later revisions. Informed consent was obtained from all patients included in the study.

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