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Effect of metformin on changes in cognitive function in patients with diabetes

당뇨병 환자에서 메트폴민 치료가 인지기능 변화에 미치는 영향 평가

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김 이 경

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The Department of Molecular Genomics,
Seoul National University
College of Medicine
Lee Kyung Kim

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by
Lee Kyung Kim

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Approved by Thesis Committee:

Professor _____Chairman
Professor _____Vice chairman
Professor _____

ABSTRACT

Introduction: Diabetes mellitus (DM) is a chronic disease that has high morbidity and mortality related to cardiovascular complications and microvascular disease, especially in the elderly. In addition, DM is known to increase the risk of Alzheimer's dementia by two to three times. Therefore it is important to inhibit its development and progression during the management of DM. However, there is a concern that metformin which is widely used as the first line antidiabetic medication is associated with a decrease in cognitive function. The aim of the present study is to investigate the associations between metformin use and cognitive impairment in patients with diabetes.

Methods: As an observational study, over 5457 patients registered with the Department of Mental Health of Boramae Medical center (BMC) and the Dementia Project from 2011 could be evaluated. We reviewed the medical records of patients and compared baseline characteristics according to DM and non-DM, and divided the DM groups into metformin user and nonuser groups then compared their cognitive function using mainly the Mini-Mental state Examination-KC (MMSE-KC), the Korean version of the Consortium to Establish a Registry for Alzheimer's Diseases Assessment (CERAD-K), activities of daily living (ADL) skills and Short form of the Geriatric Depression Scale (SGDS). Subjects performed the tests at baseline and at one- or two- year follow-up periods.

Results: Among the 2208 individuals who participated in this study, 608 had diabetes mellitus, and 34.7% (n=211) of the DM group used metformin at baseline. The mean age of metformin users was 73.8 years, and 38% were male. Patients with metformin were younger (73.8±7.5 vs. 75.5±7.9 years, p-value 0.01), had higher HbA1c levels, lower HDL – C levels, lower LDL – C levels, and lower AST levels, all showing statistical significance. There were no significant differences in cognitive dysfunction as assessed by MMSE-KC, CERAD, and ADL between metformin users and nonusers after adjusting for age, sex, education-year, HbA1c levels, and LDL levels. In an analysis of each component on the CERAD test, the working memory test revealed that metformin users required significantly more time to perform a certain task compared to nonusers. There was no significant association between metformin use and the progression of cognitive impairment.

Conclusions: Taken together, in this study, metformin treatment was not significantly associated with a higher risk of cognitive impairment in older adults with diabetes, after adjusting for age, gender, education duration, other variables and glycemic and metabolic controls. A well controlled study on a larger-scale is necessary in order to explain the effects and determine the association between metformin use and cognitive dysfunction more clearly.

Keywords: Diabetes, Metformin, Cognitive impairment, Alzheimer's disease, MMSE, CERAD

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INTRODUCTION

Diabetes as a risk factor for cognitive dysfunction

The prevalence of type 2 diabetes mellitus (T2DM) has been rising in many counties in the world [1]. Many studies have established the T2DM is a risk factor for cognitive dysfunction and dementia in elderly. Rotterdam study with 6,370 participants reported T2DM increased all dementia (RR; 1.9, 95% Confidence interval (CI) 1.3-2.8) and Alzheimer's disease (AD) (RR; 1.9, CI 1.2-3.1) [2]. In a population-based study conducted in Honolulu, Hawaii, with 2,574 Japanese-American males (diabetes: 900), T2DM was shown to increase the occurrence of all forms of dementia (RR: 1.5, 95% CI: 1.01–2.2), AD (RR: 1.8, 95% CI: 1.1–2.9), including vascular dementia (VD) (RR: 2.3, 95% CI: 1.1–5.0) [3]. In a study which systematically reviewed and summarized prospective observational studies, people with diabetes had a greater rate of decline in cognitive function and a greater risk of cognitive decline compared to people without diabetes [4].

Possible mechanisms about T2DM related cognitive dysfunction

The precise mechanisms underlying T2DM-related cognitive dysfunction or the development of dementia remain to be elucidated. However many hypothetical mechanisms have been proposed. Causative roles for hyperglycemia, hypoglycemia, vascular disease, inflammation, insulin resistance and amyloid deposition have been proposed with regard to cognitive dysfunction [5, 6]. Basic and animal experiments have indicated

that a hyperglycemic environment induces the proliferation of adult neural progenitors, but is damaging to their survival. The impaired neurogenesis found in T2DM subjects may underlie associated cognitive impairment and brain atrophy [7 , 8]. Diabetes is also associated with changes in both the blood-brain barrier (BBB) and transport functions of the cerebral micro vessels [9]. Dysfunction in the BBB may be associated with cognitive impairment and the incidence of dementia. Hyperglycemia, a major pathological characteristic of diabetes exerts a negative influence on cognition and causes structural changes in the hippocampus [10]. High glucose levels may have toxic effects on neurons in the brain through osmotic insults and oxidative stress [6]. Recurrent hypoglycemic attacks are one of the causes of cognitive impairment in the elderly. One longitudinal cohort study demonstrated that the attributable risk of dementia when compared to individuals with and without a history of hypoglycemia was 2.39% per year [11]. This may contribute to the decline of cognitive dysfunction. Patients with diabetes have a 2- to 6-fold increased risk in thrombotic stroke [12], and vascular disease has long been hypothesized to cause abnormalities in cognition in such patients. Also, the dysfunction of cerebral autoregulation with increasing age along with structural and functional alterations in cerebral blood vessels due to diabetes mellitus impairs the functioning of neurovascular units. These changes may induce functional deficits in neurons and increase neuronal degeneration and the susceptibility to hypoxia and ischemia, thus exasperating cognitive dysfunction [13]. Inflammation plays a role in the pathogenesis of insulin resistance (IR) and T2DM [14]. It has also

been suggested that inflammation is associated with the pathogenesis of AD [15]. Chronic low-grade inflammation may be a contributor to the disease process of AD. Proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) are known to be involved in the pathogenesis of both T2DM and AD [16]. As listed above, various characteristics of T2DM may be associated with cognitive dysfunction through the acceleration of AD pathology, ischemia or other mechanisms not yet found.

Importance of appropriate glucose control to prevent of decline of cognitive dysfunction; the impact of metformin

Appropriate glucose control and a decline in insulin resistance may improve cognition in older individuals with DM [17, 18, 19]. As a result, the role of anti-diabetic treatments to reduce or prevent cognitive decline is important. Metformin (MTF) is used as a first-line treatment for T2DM and reduces hyperglycemia and hyperinsulinemia by decreasing insulin resistance. It works by increasing glucose uptake in the muscle while reducing liver gluconeogenesis, as mediated by AMP-kinase [20]. However, metformin can lead to vitamin B_{12} deficiency because metformin inhibits the uptake of vitamin B_{12} from the distal ileum through competition with the receptors that absorb vitamin B_{12}. The rate of vitamin B_{12} deficiency among patients who are taking metformin can be as high as 30% [21]. Vitamin B_{12} is an essential vitamin for brain function; deficiency in this vitamin can lead to cognitive impairment in the elderly.

Controversies about the effects of metformin on the cognitive function; clinical study

Recently, an Australian clinical study which included AD and cognitively intact patients, with 126 participants with diabetes in all, reported that reduced cognitive performance was associated with metformin use after adjusting for age, sex, level of education, a history of hypertension, and serum vitamin B_{12} [22]. Also a case control study from the United Kingdom, found that long-term users of metformin were at greater risk of developing AD [23]. On the other hand, a population-based longitudinal study conducted in Singapore on aging in with diabetes reported that the long term use of metformin was significantly associated with the lowest risk of cognitive impairrment [24]. Another Taiwanese study of subjects aged 50 years or older found that the use of metformin significantly decreased the risk of dementia, after adjusting for cerebrovascular disease compared to those who took no medication (HR 0.76, 95% CI0.58-0.98) [25].

Controversial results about the effects of metformin on the cognitive function; experimental data

Several animal studies and clinical researches suggest possible negative effects of metformin on cognitive dysfunction. Kacee et al. reported that the activation of AMPK pathways, a common target of metformin, results in gender-divergent cognitive effects in a murine model of the disease, which show that the activation of AMPK increased memory dysfunction in males but was protective in females [26]. In recent in vitro study, metformin was found

to increase the biogenesis of Aβ protein [27], which is evidence that metformin may promote the development of AD. Another animal study also suggested that metformin may attenuate tau phosphorylation and contribute to the progression of AD [28].

On the other hand, an experimental study with endothelial cells (ECs) suggested that metformin can exert a direct vascular anti-inflammatory effect by inhibiting NF-κB [29] by blocking the PI3-kinase/Akt pathway. Anti-inflammatory mechanisms of metformin can explain in part the apparent clinical reduction of macrovascular complications such as cardiovascular events after taking metformin. This may also be related a lower risk of cognitive impairment.

Oxidative damage plays an important role in the pathogenesis of diabetic neuropathy and neurodegenerative diseases. El-Mir et al. found a direct neuroprotective effect of metformin, using an etoposide-induced cell death model. They found that metformin also improved oxygen-glucose deprivation-induced neuronal injury [30] and proposed that metformin, beyond its antihyperglycemic role, can also function as a new therapeutic tool for diabetes-associated neurodegenerative disorders.

In other in vitro studies, metformin modified important steps in the biogenesis of neuritic plaque and neurofibrillary tangles or improved impaired neuronal insulin signaling [31], raising speculations about the potential to reduce the risk of developing AD. However, all of these observations involved the cortical neurons of mice, and the results may not be applicable to humans.

AIM OF STUDY

As metformin is the most widely used medication even in elderly diabetic patients, it is very important whether it would be harmful in cognitive function. The aim of the present study was to investigate the effect of metformin on cognitive impairment in patients with diabetes.

METHODS

Study design and Study population

We conducted a retrospective cohort study using longitudinal follow-up data from a database of dementia managed by Dongjak-gu and Boramae Medical Center (BMC).

The study subjects were identified from a database managed by the BMC-Dongjak-gu dementia center. They were among those, who took at least one MMSE-KC (Mini-mental state examination-KC) test during the baseline year (1 January, 2011 to 30 January, 2014). At baseline, more than 5,000 participant cases were identified. Among them, we excluded individuals who did not appear at the mental health department or at other department of BMC regularly. Therefore we could not obtain additional medical information. Finally, a total of 2208 subjects (mean age 77.1±6.7 years, male to female ratio = 780:1428) were enrolled. 718 subjects took one-year follow-up cognitive impairment test, including the MMSE-KC, and 317 participants were invited to return for a two-year-follow-up test for the purpose of evaluating their cognitive function. Among them 254 persons undertook both one and two-year-follow-up tests. In DM the group, all of them took the MMSE at baseline, 174 subjects took one-year follow-up MMSE and other cognitive tests, 75 took two-year follow-up test and only 59 subjects took cognitive function tests every year. (Figure 1)

Subjects were evaluated and categorized into diabetes and non-diabetes groups according to the following conditions 1) HbA1c≥6.5% at baseline or 2)

fasting plasma glucose≥126mg/dL or 3) subjects with history of a prescription diabetes medication (oral anti-diabetics; metformin, sulfonylurea, α-glucosidase inhibitor, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, or insulin). Finally, 608 subjects were classified as having diabetes mellitus.

This study was approved by the Institutional Review Board of Boramae Medical Center.

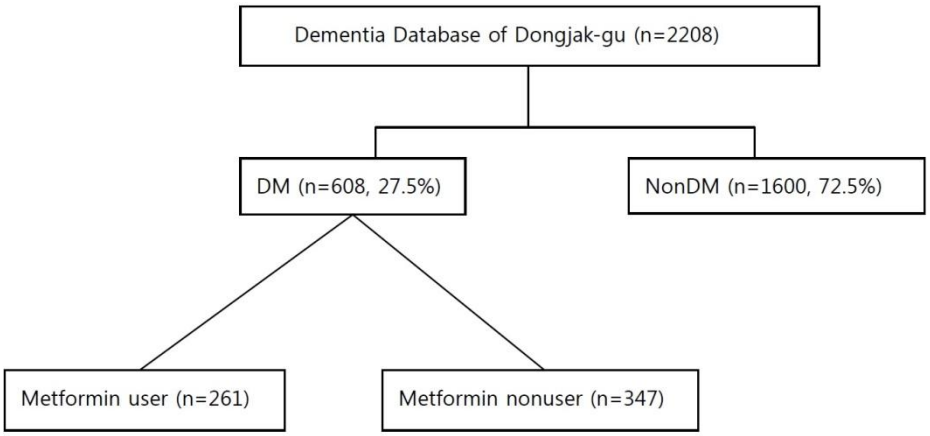


Figure 1. Subjects recruitment, inclusion and classification

Measurements of biochemical parameters

Fasting plasma glucose and HbA1c were measured to evaluate the status of diabetes at baseline and upon one- year and two-year follow-up periods. Other risk factors that may be confounders with regard to the relationship between metformin use and cognitive impairment were identified. Vitamin B_{12} levels, folate levels, and TSH levels were measured. Additional lipid profiles (total cholesterol, low-density lipoprotein-cholesterol (LDL-C) levels, high-density lipoprotein cholesterol (HDL-C) levels, triglyceride (TG) levels), and C -

reactive protein (CRP), insulin, serum creatinine, AST levels, and ALT levels, were all measured at baseline and during each follow-up.

Metformin use

During the baseline assessments, anti-diabetic medications taken in the past year were ascertained from self-reports and medical records reviews. All drug information, including the drug name, and duration of use, was recorded.

Evaluation of cognitive function

For evaluation of cognitive impairment Mini-Mental State Examination – KC (MMSE-KC), Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K), the Korean version of Barthel Activities of Daily living (ADL) index, Lawton ADL index, short form of geriatric depression scale (SGDS) were administered at baseline year, one-year and two-year follow up.

The Mini-Mental state Examination-KC (MMSE-KC), which has been validated for use in elderly Korean populations, was administered to measure the level of global cognitive function. It scores from 0 to 30 where higher scores indicate better cognition and scores of <25 cognitive impairment. It can be administered in 5 to 10 minutes. The Korean version of MMSE is composed of orientation (10 points), short-term memory registration and recall (6 points), attention (5 points), naming (2 points), following verbal commands (4 points), judgment (2 points), and copying a double pentagon (1

point) [supplements 1]. The MMSE-KC is assessed every year

To diagnose MCI, dementia, and other psychiatric disorders, the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease Assessment Packet (CERAD-K) is used by neuropsychiatrists. It contains the following elements: verbal fluency, the Boston naming test, word list memory (registration), visuo-constructional praxis, word list recall, word list recognition, recall of constructional praxis and trail making test A & B (working memory).

In addition, to evaluate skills related to activities of daily living (ADL), the Korean version of Barthel ALD index, which mainly measures physical ADL skills, and the Korean version of the Lawton ALD index for instrumental ADL were also administrated.[supplements 2]. Mood was assessed using the Short form of the Geriatric Depression Scale (SGDS).

Statistical analysis

Student's *t* tests and Mann-Whitney U-tests were used for continuous variables for comparison of characteristics between groups. Also χ^2 tests were used for a comparison of demographic and metabolic parameters between the baseline DM and non-DM groups and between metformin users and nonusers at baseline and follow-up.

An analysis of covariance (ANCOVA) was used to evaluate cognitive impairment as assessed by the MMSE-KC after adjustment for age, sex and level of education. A repeated measures ANOVA was used to analyze a trend of cognitive impairment as assessed by MMSE and each component of

CERAD battery during follow-up periods. Multivariate logistic regression tests were conducted to evaluate the odds ratio of metformin use to progression of cognitive impairment.

All statistical analyses were performed with SPSS software (version 18.0; SPSS, Chicago, IL). Data with a p value <0.05 were considered significant.

RESULTS

Baseline characteristics of study population by DM

Among the 2208 individuals, 608 (27.5% of the total) were in the DM group and 1600 were in the non-DM group. A comparison of baseline characteristics according to DM and non-DM group status is shown in the Table1. There were no significant differences in the mean age (74.9 year ± 7.8 vs. 74.6 years ± 9.0), male percentage (35% vs. 34.3%), education-years (7.15±5.2 vs. 6.70±5.3) between subjects in DM and non-DM groups. The mean MMSE scores between the two groups were compatible (17.02±7.22 in DM group vs. 17.52±7.36 in non DM group). Subjects in the DM group had higher scores on the Lawton IADL1 and IADL2 assessments, with statistical significance (IADL1; 8.9±5.4 vs. 8.1±5.7, p=0.005, IADL2; 12.7±8.7 vs. 11.6±9.0, p=0.021). SGDS, which reflects depression, was significantly higher in patients in the DM group (p=0.006). Vitamin B12 levels, glucose levels, HbA1c levels, serum creatinine levels and the prevalence of albuminuria were much higher in the DM group than in the non-DM group, with all results statistically significant. Total cholesterol levels, HDL-C levels and LDL-C levels were significantly lower in patients with DM. The prevalence rate of hypertension, and stroke were higher in the DM group than in the non-DM group. More statins were taken by subjects in the DM group compared to those in the non-DM group (43.9% vs. 16.3%, p<0.001).

Table 1. Baseline characteristics of study participants by DM

	DM (n=608)	nonDM (n=1600)	P-value
Age (year)	74.9±7.8	74.6±9.0	0.339
Sex (% of male)	38.0	34.3	0.111
HTN Hx (%)	37.7	23.9	<0.001
Stroke Hx (%)	4.8	2.7	0.022
Statin (%)	43.9	16.3	<0.001
Education (year)	7.15±5.2	6.70±5.3	0.069
Glucose (mg/dL)	143.6±63.2	106.0±23.8	<0.001
HbA1c (%)	7.3±1.7	5.7±0.5	<0.001
Insulin (uIU/mL)	10.5±11.4	12.0±22.0	0.571
Total cholesterol (mg/dL)	163.3±41.7	182.4±38.4	<0.001
HDL-C (mg/dL)	46.0±13.8	50.8±14.0	<0.001
LDL-C (mg/dL)	97.0±33.3	114.6±31.4	<0.001
Triglyceride (mg/dL)	127.9±67.8	115.8±57.2	0.001
AST (IU/L)	26.5±20.4	28.4±34.3	0.242
ALT (IU/L)	20.9±20.5	19.6±21.3	0.249
serum Creatinine (mg/dL)	1.12±0.95	0.89±0.50	<0.001
Vitamin B_{12}(ng/mL)	907.0±976.4	796.3±817.2	0.045
Folate (ng/mL)	9.0±11.4	8.1±17.6	0.386
TSH (uIU/mL)	2.39±2.6	2.51±4.7	0.628
Free T4 (ng/dL)	1.24±0.22	1.22±0.25	0.263
Albuminuria (%)	12.2	2.6	0.003
MMSE	17.0±7.2	17.5±7.4	0.150
CERAD	38.2±20.2	38.7±22.0	0.648
Barthel_ADL	13.8±7.6	13.8±8.1	0.989
Lawton_IADL1	8.9±5.4	8.1±5.7	0.005
Lawton_IADL2	12.7±8.7	11.6±9.0	0.021
SGDS	7.1±4.1	6.6±4.1	0.006

MMSE;mini mental status examination, CERAD;the Consortium to Establish a Registry for Alzheimer's Diseases Assessment Packet, ADL; activities of daily living, IADL; instrumental activities of daily living, HDL;high density lipoprotein, LDL; low density lipoprotein, SGDS; Short form of Geriatric Depression Scale, HTN; hypertension

Comparison of medical histories and biochemical parameters between metformin users and nonusers

Metformin users accounted for 34.7% (n=211) of the DM group at baseline. The mean age of metformin users was 73.8 years, and 38.4% were male. Patients treated with metformin were younger (73.8 years ± 7.5 vs. 75.5 years ± 7.9, p=0.01) than patients who did not take metformin. Metformin users had significantly higher HbA1c levels. Vitamin B_{12} levels and folate levels were not different (Vitamin B_{12}; 841.3±602.7 vs. 935.0±1097.0 and folate; 7.98±5.4 vs. 9.41±13.1) between the MTF user group and the MTF nonuser group (Table 2). Metformin users had lower HDL-C, LDL-C levels and AST levels compared to those who did not use metformin. Metformin users took more statins than MTF nonusers (70.6% vs. 29.7, p<0.001). Among metformin nonusers, only 28.2% received medication for DM, whereas almost all MTF users (97.2%) took other types of medications for DM (such as sulfonylurea, dipeptidyl peptidase 4 inhibitors, and thiazolidinedione).

Table 2. Baseline characteristics of study participants by Metformin use

	MTF (n=211)	nonMTF (n=397)	P-value
Age (year)	73.8±7.5	75.5±7.9	0.010
Sex(% of male)	38.4	37.8	0.930
Education (year)	7.5±5.2	7.0±5.2	0.253
Glucose (mg/dL)	150.0±68.3	140.0±60.0	0.095
HbA1c (%)	7.6±1.8	7.1±1.6	<0.001
Total cholesterol (mg/dL)	158.1±41.2	166.4±41.8	0.209
HDL-C (mg/dL)	44.6±12.9	46.6±14.2	<0.001
LDL-C (mg/dL)	88.4±31.5	100.5±33.5	0.003
Triglyceride (mg/dL)	132.2±67.0	125.4±68.3	0.305
AST(IU/L)	24.1±12.3	28.0±23.9	0.013
ALT(IU/L)	19.3±10.2	21.8±20.7	0.098
Creatinine (mg/dL)	1.01±0.5	1.18±1.13	0.015
VitB_{12} (ng/mL)	841.3±602.7	935.0±1097.0	0.561
Folate (ng/mL)	7.98±5.4	9.41±13.1	0.909
TSH (uIU/L)	2.22±2.11	2.48±2.86	0.359
Free T4 (ng/dL)	1.26±0.24	1.22±0.22	0.154
Albuminuria (%)	12	6.8	0.175
HTN Hx (%)	26.5	43.6	<0.001
Stroke Hx (%)	3.3	5.5	0.317
SU (%)	55.9	15.60	<0.001
TZD (%)	4.3	1.3	0.024
DPP4i (%)	28.0	4.3	<0.001
Statin (%)	70.6	29.7	<0.001

Statistical significance test for TG, VitB12, and folate were done by Mann-Whitney U-test, SU; sulfonylurea, TZD;thiazolidinedione, DPP4i;dipeptidyl peptidase 4 inhibitor, Statin; HMG-CoA reductase inhibitor

Cognitive impairment according to metformin use at baseline

The MMSE score of diabetic patients was 17.07±7.22. There were 25 (11.85%) and 60 (15.11%) individuals in the MTF user group and in the nonuser group, respectively, whose MMSE-K scores were under 1SD.

There were no significant differences in MMSE-K (17.28±7.30 vs. 16.88±7.18, p=0.521), CERAD (39.56±18.28 vs. 37.44±21.20, p=0.232), and ADL scores (13.89±7.37 vs. 13.74±7.79, p=0.603) between MTF users and nonusers (Table 3). After adjusting for age, sex, and education-years, there was no significant differences in MMSE scores, CERAD and ADL (Table 3, $P^{*)}$.

Age, HbA1c and LDL-C levels were different significantly between MTF users and nonusers; thus, we adjusted for HbA1c and LDL-C levels. After adjusting for HbA1c level, cognitive function as assessed by MMSE, CERAD was not significantly different between MTF users and nonusers (Table 3, $P^{\dagger}$).

Table 3. Comparison of cognitive function between metformin user and nonuser group at baseline.

	MTF	n	nonMTF	n	P	P*	P†
MMSE-KC	17.28±7.30	211	16.88±7.18	397	0.521	0.678	0.827
CERAD	39.56±18.28	190	37.44±21.20	326	0.232	0.129	0.092
Barthel_ADL	13.89±7.37	207	13.74±7.79	391	0.603	0.071	0.372
Lawton_IADL1	8.68±5.11	207	8.97±5.58	391	0.781	0.162	0.851
Lawton_IADL2	12.61±8.42	207	12.73±8.94	391	0.973	0.525	0.647
SGDS	7.14±3.93	207	7.13±4.17	391	0.792	0.514	0.865

P for unadjusted value. P* for age, sex and education year-adjusted results. P† for age, sex, education year and HbA1c-adjusted MMSE, CERAD, ADL, IADL.

Cognitive dysfunction assessment over the follow-up period

We processed the follow-up MMSE data through last observation carried forward (LOFC) imputation. Repeated measured ANOVA analysis used to analyze the trend of MMSE change. The decline of MMSE score during follow-up period both in MTF users and in nonusers was statistically significant ($p<0.001$). However, there was no difference in the slope of MMSE value change between MTF users and nonusers (Baseline; 17.28±7.30 vs.16.88±7.18, one-year follow-up; 16.99±7.37 vs. 16.82±7.07, two-year follow-up; 16.73±7.43 vs. 16.59±7.17) (Figure 2) .

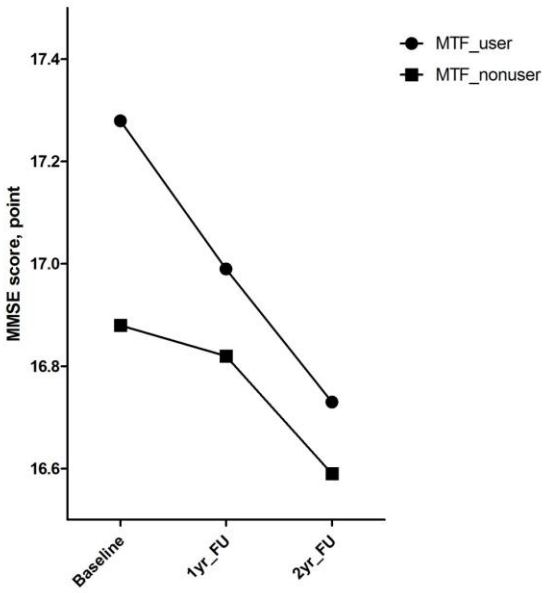


Figure 2. MMSE-K scores changes between metformin users and nonusers during follow-up periods.

The decline of MMSE score during follow-up period in each group was statistically significant ($p<0.001$). However, there was no difference in the slope of MMSE value change between MTF users and nonusers.

Because there was a significant difference in the total scores of CERAD battery after an adjustment for age between MTF users and nonusers at baseline (38.32 ± 1.41 vs. 38.21 ± 1.07, p=0.037) (Table 4), we analyzed changes of CERAD battery between MTF users and nonusers during the follow-up periods after adjusting for age by repeated measured ANOVA with processed follow-up data through LOFC imputation. In our study, the decline of CERAD score during follow-up periods in each group was statistically significant (p=0.024). However, there was no difference in the decreasing trend of CERAD battery value change between MTF users and nonusers (Baseline; 39.56 ± 18.28 vs. 37.44 ± 21.20, one-year follow-up; 38.94 ± 18.75 vs. 36.74 ± 21.81, two-year follow-up; 38.40 ± 19.09 vs. 36.02 ± 22.13) (Figure 3).

CERAD battery is consisted of four parts, such as assessment of language, memory, attention, and working memory, we analyzed each component of CERAD battery according to MTF use during the follow-up periods after adjusting for age and adjusting for age, sex and education years (Table 4). There were significant differences in Boston naming (7.39 ± 0.29 vs. 7.24 ± 0.22, p=0.027 after adjusting for age, p=0.014 after adjusting for age, sex, education-years), word registration (9.57 ± 0.40 vs. 9.57 ± 0.30, p=0.030 after adjusting for age), praxis (7.38 ± 0.25 vs. 7.00 ± 0.19, p=0.034, 0.009 after adjusting for age, sex, education-years) and trail making test B (working memory) (291.50 seconds ± 9.82 vs. 268.43 seconds ± 7.45, p=0.005) at baseline. We found statistically significant decline in verbal fluency score

(p=0.002), Boston naming score (p<0.001), word registration score (p=0.014), and praxis score (p=0.009) during follow-up periods in each group. However, there were no differences in the slope of each component between MTF users and nonusers, respectively. Train making test B revealed that MTF users required significantly more time than MTF nonusers did to perform task during follow-up periods (p=0.037) (Figure 4).

Table 4. Assessment of each component of CERAD battery over follow up period

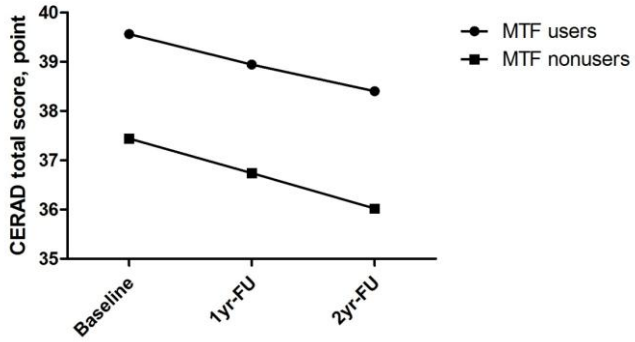
Baseline	MTF (n=183)	nonMTF (n=316)	P	P*
CEARD	38.32 ± 1.41	38.21 ± 1.07	0.037	0.129
Verbal fluency	7.67 ± 0.36	7.66 ± 0.27	0.174	0.140
Boston naming	7.39 ± 0.29	7.24 ± 0.22	0.027	0.014
Word registration	9.57 ± 0.40	9.57 ± 0.30	0.030	0.105
Word recall	1.86 ± 0.19	2.14 ± 0.14	0.402	0.239
Word recognition	4.86 ±0.25	4.70 ± 0.19	0.141	0.221
Constructive praxis	7.38 ± 0.25	7.00 ± 0.19	0.034	0.009
Recall of praxis	1.86 ± 0.19	2.14 ± 0.14	0.408	0.810
Trail making A (sec)	168.87 ± 9.64	158.06 ± 7.32	0.459	0.835
Trail making B (sec)	291.50 ± 9.82	268.43 ± 7.45	0.005	0.008

1-year-follw-up	MTF (n=72)	nonMTF (n=100)	P	P*
CEARD	34.38 ± 1.95	36.04 ± 1.65	0.610	0.264
Verbal fluency	6.21 ± 0.53	7.72 ± 0.45	0.724	0.737
Boston naming	6.86 ± 0.43	6.96 ± 0.36	0.960	0.805
Word registration	8.90 ± 0.57	9.26 ± 0.48	0.566	0.614
Word recall	1.12 ± 0.20	1.19 ± 0.17	0.046	0.030
Word recognition	3.86 ± 0.38	4.19 ± 0.32	0.039	0.035
Constructive praxis	7.43 ± 0.37	6.72 ± 0.31	0.730	0.843
Recall of praxis	1.27 ± 0.25	1.55 ± 0.21	0.886	0.468
Trail making A (sec)	185.12 ± 15.20	165.91 ± 12.84	0.861	0.604
Trail making B (sec)	315.62 ± 14.28	288.19 ± 12.07	<0.001	0.001

2-year-follw-up	MTF (n=31)	nonMTF (n=40)	P	P*
CEARD	33.42 ± 3.15	35.48 ± 2.77	0.643	0.774
Verbal fluency	5.99 ± 0.74	6.76 ± 0.66	0.048	0.058
Boston naming	6.40 ± 0.67	6.79 ± 0.59	0.045	0.142
Word registration	9.32 ± 0.95	8.85 ± 0.88	0.407	0.392
Word recall	1.29 ± 0.36	1.52 ± 0.32	0.819	0.730
Word recognition	3.35 ± 0.63	4.55 ± 0.55	0.847	0.627
Constructive praxis	7.06 ± 0.54	7.00 ± 0.48	0.809	0.494
Recall of praxis	1.086 ± 0.325	1.083 ± 0.286	0.666	0.506
Trail making A (sec)	218.50 ± 23.16	177.34 ± 20.38	0.312	0.287
Trail making B (sec)	337.10 ± 19.90	299.75 ± 17.51	0.012	0.012

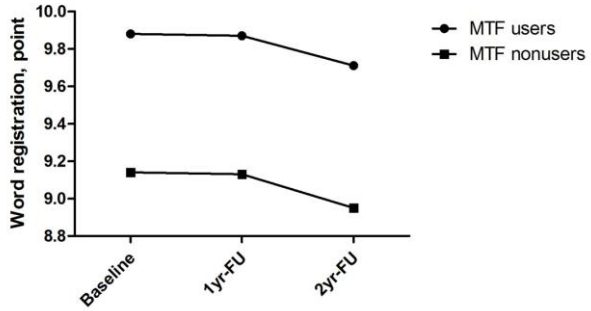
P for age-adjusted results, P* for age, sex, and education u-year adjusted results. All values are suggested mean ± (standard error).

Figure 3. CERAD battery score changes between metformin users and nonusers during follow-up periods.

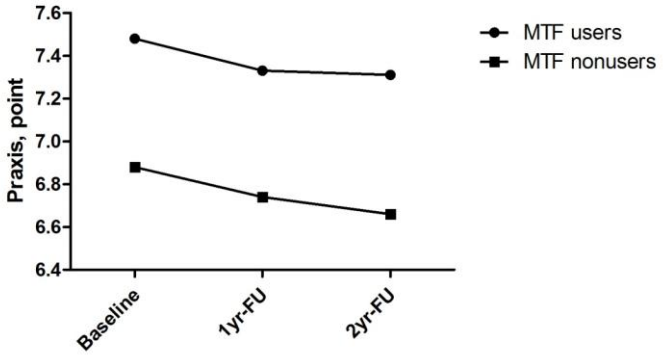


The decline of CERAD score during follow-up periods in each group was statistically significant (p=0.024). However, there was no difference in the slope of CERAD value change between MTF users and nonusers.

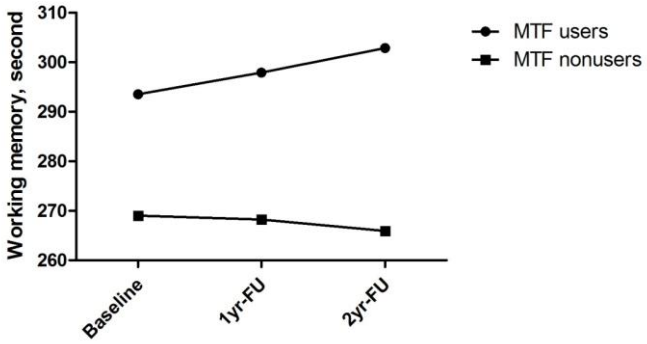
Figure 4. Each component of CERAD battery score changes between metformin users and nonusers during follow-up periods.



(A) Word registration assessment; the decline of scores during follow-up periods in each group was statistically significant (p=0.014). However, there was no difference in the slope of registration score change between MTF users and nonusers.



(B) Praxis assessment; the decline of praxis score during follow-up periods in each group was statistically significant (p=0.009). However, there was no difference in the slope of praxis score change between MTF users and nonusers.



(C) Working memory assessment (Trail making test B); there was no difference in working memory score during follow-up periods in each group. However, MTF users required more time to perform task than nonusers did (p=0.037).

Cognitive dysfunction assessment over the follow-up period between age-matched MTF users and MTF nonusers

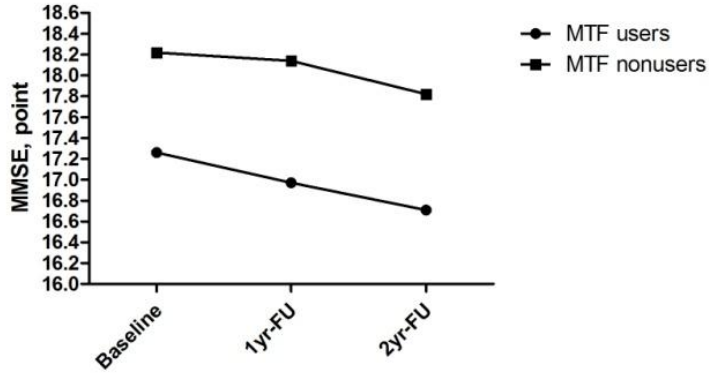
As there was a significant difference in ages between MTF users and nonusers, we created two groups matched for age. There were 210 persons in each group and there was no significant difference in age, education year at baseline. There was no specific trend changed in other parameters; higher HbA1c levels, lower HDL-C levels and LDL-C levels, lower serum creatinine levels in MTF users. Significant difference previousely observed in AST levels disappeared. However, with regard to history of hypertension and medication, statistically significant differences were not overcome. (Table 5). We found that patient treated with metformin got lower scores in MMSE ($P<0.001$), CERAD total score ($P=0.001$), verbal fluency test ($P=.0003$), and word registration score ($p=0.034$) during follow-up periods. This shows the opposite trend when compared to the previous total group analysis. But MTF users got higher scores in word recognition test ($p=0.018$). There were significant declines but no differences in the slope of each component between MTF users and nonusers, respectively (Figure 5). Significant difference previously observed in word recall, praxis, and working memory (trail making test B) between two groups disappeared.

Table 5. Baseline characteristics of study participants between age-matched MTF users and MTF nonusers

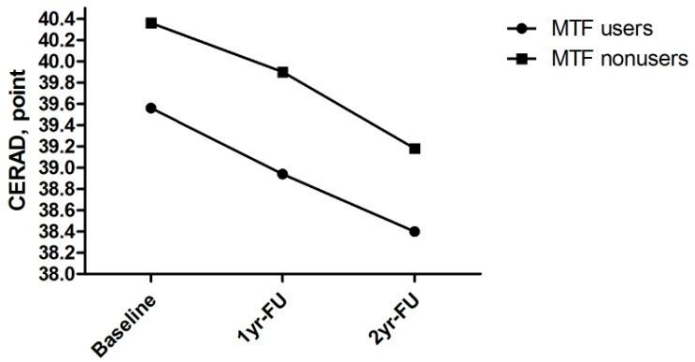
	MTF (n=210)	nonMTF (n=210)	P-value
Age (year)	73.7±7.3	73.8±7.2	0.872
Sex(% of male)	38.1	40.0	0.764
Education (year)	7.4±5.1	7.8±5.3	0.544
Glucose (mg/dL)	149.8±68.4	136.4±56.6	0.045
HbA1c (%)	7.6±1.8	7.0±1.4	<0.001
Total cholesterol (mg/dL)	158.2±41.3	169.1±41.3	0.011
HDL-C (mg/dL)	44.6±12.9	47.9±15.0	0.038
LDL-C (mg/dL)	88.4±31.5	101.2±33.7	0.004
Triglyceride (mg/dL)	132.4±67.1	128.2±66.9	0.572
AST(IU/L)	24.1±12.3	28.1±25.4	0.060
ALT(IU/L)	19.4±10.2	23.3±28.8	0.086
Creatinine (mg/dL)	1.00±0.5	1.20±1.13	0.032
VitB_{12} (ng/mL)	841.3±602.7	1053.4±1409.3	0.117
Folate (ng/mL)	7.98±5.4	9.30±14.3	0.370
TSH (uIU/L)	2.22±2.11	2.36±2.75	0.632
Free T4 (ng/dL)	1.26±0.24	1.21±0.24	0.073
Albuminuria (%)	12	10.0	0.789
HTN Hx (%)	26.7	48.1	<0.001
Stroke Hx (%)	3.3	4.8	0.622
SU (%)	56.2	15.2	<0.001
TZD (%)	4.3	1.0	0.062
DPP4i (%)	27.6	4.8	<0.001
Statin (%)	70.5	29.0	<0.001

Statistical significance test for TG, VitB12, and folate were done by Mann-Whitney U-test, SU; sulfonylurea, TZD;thiazolidinedione, DPP4i;dipeptidyl peptidase 4 inhibitor, Statin; HMG-CoA reductase inhibitor

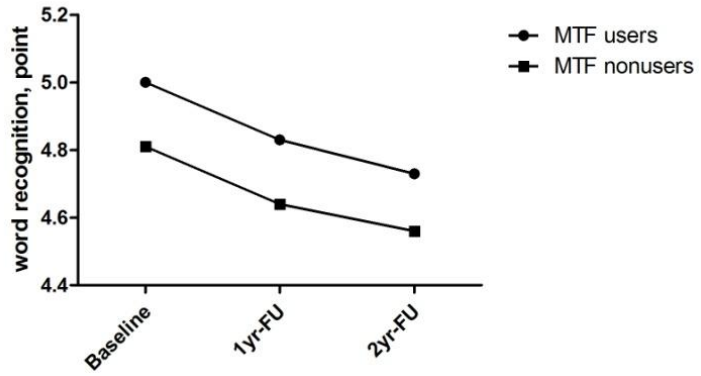
Figure 5. Cognitive function changes between age-matched metformin user group and nonuser group during follow-up periods.



(A) MTF users got lower MMSE scores. The decline of MMSE score during follow-up period in each group was statistically significant ($p<0.001$). However, there was no difference in the slope of MMSE value change between MTF users and nonusers.



(B) The score is found to be lower in the MTF user group. The decline of CERAD score during follow-up period in each group was statistically significant ($p=0.001$). However, there was also no difference in the slope of MMSE value change between MTF users and nonusers.



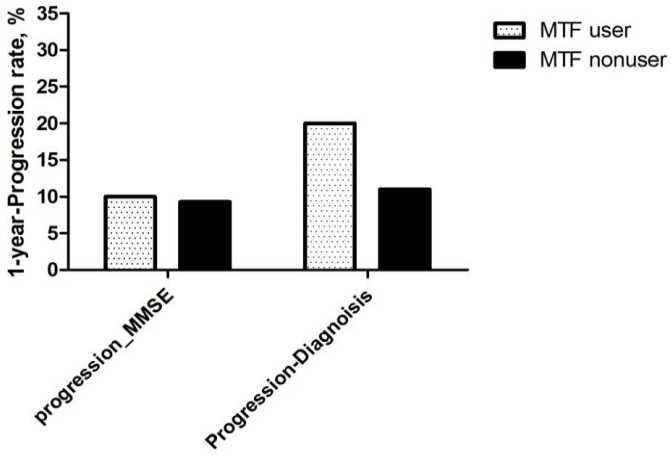
(C) Word recognition test; the decline of word recognition score during follow-up periods in each group was statistically significant (p=0.018). However, there was no difference in the slope of praxis score change between MTF users and nonusers.

Association of metformin use and progression of cognitive impairment

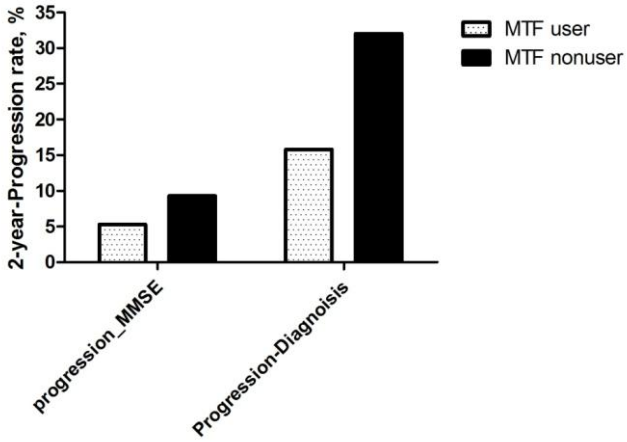
Cognitive performance was categorized into four strata by MMSE score; “most impaired’ (MMSE<18), “mildly impaired” (MMSE 18-23), “minimally impaired” (MMSE 24-27), and “not impaired” (MMSE 28-30). Cognitive performance was also evaluated by neuropsychiatrist and categorized into five strata by diagnosis; Normal, MCI, mild AD, moderate AD, and severe AD. Progression was defined when the categories worsened for a participant according to MMSE grade or diagnosis. Nonprogression refers to those whose diagnoses of cognitive function remained the same or improved during the follow-up. At baseline and during the two-year follow-up, there were no association between metformin use and progression (Figure 6).

Multivariate analyses of relationship between metformin use and cognitive impairment upon one- and two-year-follow-up controlling for the confounding effects of age, sex, education years, HbA1c, LDL cholesterol levels, and Vitamin B12 levels are shown Tables 5 and 6. Only age was positively related to cognitive impairment progression (OR = 1.051, 95% CI 1.007-1.096, p= 0.023) at one-year-follow-up after adjusting for age, sex, education-years and metformin use. Other variables were not significntly related to cognitive dysfunction.

Figure 6. Proportion of cognitive impairment progression as assessed by MMSE grade and diagnosis between metformin users and non-users at one-year and two-year follow-up.



A) Progression of cognitive dysfunction according to MTF use at one-year follow-up. There were 60 patients who were using metformin from baseline utill their one-year follow-up, and 635 who had never taken metformin. (progression defined by MMSE grade, MTF user; 6/60 (10%), p=0.817, progression by diagnosis, MTF user;12/60 (20%), p=0.285)



B) Progression of cognitive dysfunction according to MTF use at two- year follow-up. There were 19 patients who used meformin from baseline untill their two-year follow-up and 194 had never used metformin up to the point of two-year follow-up (for each definition of progression, the p-values were 1.000, and 0.194, respectively).

Table 6. Multivariate logistic regression models for variables associated with 1-year- progression

Risk factors	Model 1			Model 2			Model 3			Model 4		
	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*
Age	1.051	1.008-1.097	0.021	1.051	1.007-1.096	0.023	1.039	0.989-1.091	0.131	1.070	0.994-1.151	0.072
Sex	0.569	0.265-1.219	0.147	1.762	0.822-3.780	0.146	1.826	0.749-4.454	0.186	1.660	0.513-5.373	0.387
Education	1.000	0.609-1.815	0.989	1.001	0.936-1.070	0.982	1.001	0.926-1.082	0.984	1.019	0.915-1.135	0.731
Baseline MTF use				0.949	0.497-1.814	0.875	1.120	0.542-2.311	0.760	1.474	0.497-4.365	0.485
Baselin HbA1c							0.915	0.726-1.154	0.454	1.054	0.794-1.400	0.714
Baseline Vit. B12										1.000	1.000-1.001	0.426
Baseline LDL-C										1.004	0.991-1.018	0.533

The dependent variable was the 1-year-progression of cognitive dysfunction in all statistical models. Cognitive dysfunction risk factors at baseline evaluation entered as independent variables. Age, Sex, and education-year were included as independent variables in all statistical models. Baseline metformin use was included as independent variables in model 2. Baseline HbA1c was included as an independent variable in model 3 and LDL-C level, vitamin B12 level were included as an independent variables in model 4.

Table 7. Multivariate logistic regression models for variables associated with 2-year- progression

Risk factors	Model 1			Model 2			Model 3			Model 4		
	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*	OR	95%CI	*p*
Age	1.012	0.957-1.070	0.680	1.009	0.955-1.066	0.023	1.032	0.961-1.108	0.391	1.028	0.940-1.123	0.545
Sex	0.565	0.189-1.688	0.307	1.781	0.593-5.352	0.146	2.109	0.519-8.574	0.297	1.429	0.307-6.647	0.649
Education	0.934	0.849-1.028	0.163	0.936	0.850-1.031	0.982	0.941	0.836-1.058	0.308	0.907	0.783-1.052	0.197
Baseline MTF use				0.613	0.239-1.573	0.875	0.909	0.320-2.578	0.857	1.000	1.000-1.001	0.802
Baselin HbA1c							0.955	0.707-1.290	0.764	0.992	0.682-1.445	0.968
Baseline Vit. B12										0.993	0.975-1.012	0.486
Baseline LDL-C										1.399	0.366-5.350	0.624

The dependent variable was the 2-year-progression of cognitive dysfunction in all statistical models. Cognitive dysfunction risk factors at baseline evaluation entered as independent variables. Age, Sex, and education-year were included as independent variables in all statistical models. Baseline metformin use was included as independent variables in model 2. Baseline HbA1c was included as an independent variable in model 3 and LDL-C level, vitamin B12 level were included as an independent variables in model 4.

DISCUSSION

Our data indicate that treatment with metformin is not significantly associated with a higher risk of cognitive impairment in elderly adults with diabetes after adjusting for age, gender, education duration, and other variables including glycemic control status, LDL-C levels and vitamin B_{12} levels.

It is well known that patients with diabetes are at an increased risk for AD. Various characteristics of T2DM may be associated with cognitive dysfunction through the acceleration of AD pathophysiology. Therefore, it is important for diabetes patients to control the diabetes appropriately to prevent deterioration of cognitive function.

Metformin is the most widely used medication for T2DM. However, there is continued controversy about the relationship between metformin use and a decline of cognitive function, as not all studies reported equivalent results.

The results of our study also suggest that effect of metformin on cognitive function is not so simple to say definitively positive or negative. There were differing results depending on which indicators were applied or which variables were adjusted to evaluate cognitive impairment.

It is important to clarify the relationship between metformin use and cognitive dysfunction, as there will be an increasing number of older adult with DM and cognitive impairment. Our work is consistent with several prior investigations, and it extends those findings in several ways. Some significant

differences exist between that trial and the present work. First, we could assess cognitive function longitudinally by accessing one- and two-year follow-up data. Therefore, we could evaluate the relationship between metformin use and the progression of cognitive dysfunction. Many previous studies utilized cross sectional study design with limitations with regard to progression. Second, we administered several tests in addition to the MMSE to evaluate cognitive function. Thus, we could offer fine diagnoses.

There was a significant age-difference in comparison between MTF users and nonusers at baseline. After adjusting for age by using statistical methods, there was significant difference in CERAD battery results. So we made age-matched MTF nonuser group in order to overcome age-difference. Age-matched nonusers showed higher scores in MMSE, CERAD battery, and word recognition test (Figure 5). It was somewhat opposite trend when compared with the previous analysis. Since there was no difference observed in slope of changes on cognitive function between MTF users and nonusers, it could explained by other difference of the metabolic characteristics of MTF users rather than taking metformin itself.

First of all, a geriatric dementia cohort study reported that the age of the elderly is the most relevant factor in cognitive impairment [32]. MTF users were younger than nonusers in total group analysis. Considering the result of the geriatric study, young age in MTF user group gave the possibility to show a relative good scores in cognitive function test, so that we could not find out the same results after creating age-matched group.

However, as can be shown in the table 5, baseline characteristics between

two age-matched groups had not changed significantly except age. Patients taking metformin still had higher HbA1c level, took more medications to control DM and had more histories of hypertension. It demonstrates that blood glucose control and hypertension can affect on the cognitive function more strongly. It also proves that there may be confounding variables other than age failed to control.

As an observational study unobserved confounding variables could be a threat to our analysis. Over 97% of MTF users took other types of medications for DM, whereas only 28% of MTF nonusers received medication at baseline, which suggests that MTF users had high-severity diseases and high levels of comorbidity, which may have influenced their cognitive functions. It is known that effect of DM on dementia becomes lower in advanced dementia. Therefore, if there were more subjects with high severity disease in MTF user groups, the relationship between MTF use and cognitive dysfunction might have been underestimated.

Some studies reported that compared to persons found to have no cognitive impairment, rate of cognitive decline during follow-up increased approximately twofold in MCI and fourfold in AD [33]. The initial status of cognitive function may influence the changes in cognitive deterioration. So we planned to divide study population into three groups according to initial cognitive function state; normal, MCI, and AD group and evaluate their changes on cognition. But there were few cases followed up to analyze. It could be one of limitations in this study.

The follow-up intervals were not long enough that they did not

sufficiently show subtle progression of cognitive impairment. Therefore, cases of progression may have been underestimated. Also even though we analyzed serial follow up data, there were only 44 cases which recorded both 1 year follow up and 2 year follow up test. That is not enough to find out statistically significant change.

Finally, nearly all of those in our population were registered in a dementia database and took medication for the regulation of AD. The effects of such medications on their cognitive function could not be adjusted.

In summary, the findings of this observational study indicate that there is no certain evidence whether the use of metformin increases the risk of developing AD. These results suggest that there is not sufficient evidence to hesitate to prescribe metformin as a first-line treatment for elderly subjects with cognitive dysfunction. However, some indicators which reflect cognition showed significant deterioration after adjusting for age, possible a confounder. A well controlled study on a large scale is necessary in order to confirm these effects.

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Supplement 1

간이 정신상태 검사 (MMSE-KC)

실시요령

■ 문항 중 *[이탤릭체]* 로 씌어진 부분은 검사의 시행 지침이다.

■ 문항 중 굵은 글씨로 씌어진 글은 피검자에게 읽어 주는 부분이다.

■ 문항 중 밑줄 친 부분은 질문의 정답이다.

■ 피검자의 응답을 '틀림', '맞음', '평가 안 됨'으로 평가하여 문항 오른쪽에 있는 '0', '1', '9'에 O 표를 한다.

■ 일부 문항의 채점은 뒤편에 제시한 기준을 참조한다.

■ 총점은 '9'로 평가된 항목을 제외한 나머지 점수의 합계이다.

*검사자는 **"지금부터 000 님의 기억력과 집중력을 알아보기 위해 몇 가지 질문을 드리겠습니다. 질문 중 몇 가지는 쉽지만 몇 가지는 어려울 수도 있습니다."**라는 말로 검사를 시작한다.*

질 문	틀림	맞음	평가 안됨
1. 올해는 몇 년도입니까?	0	1	9
2. 지금은 무슨 계절입니까?	0	1	9
3. 오늘은 며칠입니까?	0	1	9
4. 오늘은 무슨 요일입니까?	0	1	9
5. 지금은 몇 월입니까? *[피검자가 음력을 사용하면 음력으로 묻는다.]*	0	1	9
6. 우리가 있는 이곳은 무슨 도/ 특별시/ 광역시입니까?	0	1	9
7. 여기는 무슨 시/ 군/ 구입니까?	0	1	9
8. 여기는 무슨 읍/ 면/ 동입니까?	0	1	9
9. 우리는 지금 이 건물의 몇 층에 있습니까?	0	1	9
10. 이 장소의 이름은 무엇입니까?	0	1	9

11. 지금부터 제가 세 가지 물건의 이름을 말씀드리겠습니다. 끝까지 다 들으신 다음에 세 가지 물건의 이름을 모두 말씀해 보십시오. 그리고 몇 분 후에는 그 세 가지 물건의 이름들을 다시 물어 볼 것이니 들으신 물건의 이름들을 잘 기억하고 계십시오.

나무, 자동차, 모자

이제 000 님께서 방금 들으신 세 가지 물건 이름을 모두 말씀해 보세요.

[문항 11 은 첫 응답으로만 평가한다. 첫 응답에서 물건의 이름을 모두 말하지 못하는 경우는 문항 13 의 지연 회상을 정확하게 검사하기 위해 '물건 이름을 불러주고 기억하도록 하는 과정'을 3 회까지 반복할 수 있다.]

나 무	019
자동차	019
모 자	019

12. 지금부터 제가 000 님께 다섯 글자로 된 단어 하나를 말씀해 드릴 것이니 따라 해 보십시오.

'삼 천 리 강 산'

[피검자가 글자를 순서대로 바르게 말할 수 있도록 필요하다면 이 단어를 몇 차례 반복하여 말해 줄 수 있다.]

잘 하셨습니다. 이번에는 이 단어를 맨 뒤 글자부터 거꾸로 말해 보십시오.

☐☐☐☐☐

[피검자의 답을 위의 네모 칸에 기록한다. 점수는 뒤편에 제시한 기준에 따라 계산하여 우측 네모 칸에 기록한다.]

☐점

13. 조금 전에 제가 기억하라고 말씀드렸던 세 가지 물건의 이름이 무엇 인지를 말씀하여 주십시오, 019

나 무	019
자동차	019
모 자	

14. *[열쇠를 보여주며]* 이것을 무엇이라고 합니까? 019

[도장을 보여주며] 이것을 무엇이라고 합니까? 019

[실제 열쇠와 도장을 보여준다.] 019

15. 제가 하는 말을 끝까지 듣고 따라 해 보십시오. 한 번만 말씀드릴 것이니 잘 듣고 따라 하십시오. 019

간 장 공 장 공 장 장

[한 번만 말해주고 반복하지 않는다.]

16. 지금부터 제가 말씀드리는 대로 해 보십시오. 한 번만 말씀드릴 것이니 잘 들으시고 그대로 해 보십시오.
제가 종이를 한 장 드릴 것입니다. 그러면 그 종이를 오른손으로 받아, 반으로 접은 다음, 무릎 위에 올려 놓으십시오.
[지시를 끝낸 후에 종이를 건네준다. 지시를 반복하거나 옆에서 도와주면 안 된다.]

오른손으로 받는다.	0 1 9
반으로 접는다.	0 1 9
무릎 위에 놓는다.	0 1 9

17. *[별지의 오각형 그림을 가리키며]* 여기에 오각형이 겹쳐져 있는 그림이 있습니다. 이 그림을 아래 빈 곳에 그대로 그려보세요. 0 1 9

18. 옷은 왜 빨아서 입습니까? 0 1 9

19. 다른 사람의 주민등록증을 주웠을 때 어떻게 하면 쉽게 주인에게 돌 려 줄 수 있습니까? 0 1 9

총 점	( )/ 30

Supplement 2

한국어판 바텔 ADL Index

평가자 이름 _____

대변 조절
0=전혀 조절하지 못한다(혹은 관장이 필요하다).
1=가끔 조절에 실패한다(주 1회).
2=대변 조절에 문제가 없다.

소변 조절
0=전혀 조절하지 못하거나 카테터(도뇨관)를 끼고 있으면서 스스로 관리하지 못한다.
1=가끔 조절에 실패한다(하루에 1회 미만).
2=소변 조절에 문제 없다(7일 이상).

얼굴 단장하기
0=다른 사람의 도움이 필요하다.
1=세수, 머리감기, 양치질, 면도를 혼자서 한다

화장실 사용
0=혼자서 사용할 수 없다.
1=도움이 필요하지만 어느 정도는 혼자 사용
(필요한 용품준비는 도움을 받아도 상관없다). 할 수 있다.
2= 다른 사람 도움 없이 사용한다.

식사하기
0=혼자서는 식사가 불가능하다.
1=일부는 도움이 필요하다.
2=음식이 앞에 있으면 혼자서 식사 할 수 있다

옷입기
0=혼자서는 못 입는다.
1=절반 정도는 혼자서 입을 수 있다.
2=혼자서 입는다(단추잠그기, 지퍼올리기, 끈묶기 포함).

[최종]옮겨가기(침상과 의자 사이)
0=불가능함. 앉아서 균형을 잡을 수 없다.
1=상당한 도움(한두 사람의 신체적인 도움)이 있으면 앉을 수 있다
2=약간의 도움(말로 하는 혹은 신체적인 도움)이 있으면 옮겨갈 수 있다.
3=스스로 할 수 있다.

이동
0=이동할 수 없다.
1=휠체어로 혼자서 다닐 수 있다(코너 도는 것
포함).
2=한 사람 도움(말로 하는 혹은 신체적)으로
보행이 가능하다.
3=혼자서 이동할 수 있다(지팡이는 사용해도무방하다).

계단 오르내리기
0=불가능하다.
1=말로 하는 혹은 신체적인 도움이 필요하다. (승강기 이용 포함)
2=혼자서 계단을 오르내릴 수 있다.

목욕
0=다른 사람 도움이 필요하다.
1=샤워 혹은 목욕을 혼자서 할 수 있다.

국문 초록

서론: 당뇨병은 고령에서 유병율이 높은 대표적 만성 질환으로 여러 가지 미세혈관 합병증과 심혈관질환으로 인한 이환율과 사망률이 높은 질병이다. 또한 알츠하이머성 치매의 위험을 2-3 배 높이는 것으로 알려져 있어 이의 발생과 진행을 억제하는 것 또한 당뇨병 환자 치료에서 매우 중요한 부분이라 할 수 있다. 그런데 당뇨병의 일차치료제로 권장되는 메트폴민이 인지 기능의 저하와 관련되어 있다는 우려가 있다. 메트폴민 복용 시 비타민 B12 의 결핍이 발생할 수 있는 것으로 알려져 있는데 이는 뇌신경 기능에 필수적인 비타민으로 이의 부족은 노인에서 인지기능 저하를 가져올 수 있다. 실제 여러 연구들에서 보고된 바에 의하면 메트폴민의 복용과 인지기능 장애에 대해서는 논란이 있다. 이에 본 연구에서는 동작구 보건소와 공동으로 진행된 치매환자 등록 사업의 데이터베이스를 이용하여 메트폴민의 복용이 인지기능 저하와 관련되어 있는지를 알아보고자 한다.

방법: 2011 년 이후 보라매병원 정신건강의학과 치매환자 등록사업 대상자로 등록된 2000 여명의 환자 중 최소 2 번 이상 인지 기능 평가를 받았고, 보라매 병원에서 당뇨병으로 치료받는 환자를 대상으로 후향적으로 의무기록을 검토하여 당뇨군과 비당뇨군으로, 당뇨

군은 메트폴민 복용군과 비복용군으로 나누어 MMSE, CERAD score 를 중심으로 인지기능 장애 정도를 비교하고, 인지기능과 관련되었다고 알려진 생화학적 인자들에 대한 검사를 시행하여 분석하고 1 회 이상의 인지기능 추적 검사 자료를 검토하여 실제 복용군에서 인지기능 저하가 있는지를 평가한다.

결과: 2208 명의 연구대상자중 당뇨군은 608 명이었으며 이중 34.7%인 211 명이 연구 시작 시기부터 메트폴민을 복용하고 있었다. 이들은 메트폴민을 복용하지 않는 군에 비하여 유의하게 나이가 적었으며 (73.8±7.5 vs. 75.5±7.9 years, p-value 0.01), 당화혈색소는 높았다. 나이와 성별, 교육연령, 당화혈색소를 보정한 후 MMSE, CERAD 및 ADL 로 인지기능 저하를 평가하였을 때 메트폴민 복용군과 비복용군 사이의 통계적 유의성은 관찰 할 수 없었다. CERAD 평가의 한 항목인 길만들기 검사 B 항목에서는 메트폴민 복약군에서 시간이 경과함에 따라 같은 검사를 수행하는데 유의하게 더 많은 시간이 소요 됨을 확인 할 수 있었다. MMSE score 및 진단명으로 평가하였을 때 인지 기능 저하의 진행과 메트폴민의 복용사이의 유의한 상관관계는 관찰되지 않았다.

결론: 결론적으로 1 년 혹은 2 년의 인지기능을 추적한 결과 메트폴민 복용이 인지기능 악화와 직접적으로 관련되었다는 증거는 찾을 수 없었다. 더 정확한 관련성을 알기 위해서는 좀더 대규모의 섬세

한 연구가 필요하겠으며, 당뇨병의 1 차 약제로 노년층의 인지기능 악화를 두려워하여 메트폴민을 투약하지 않는 것은 근거가 불충분하다.

주요어 : 당뇨, 메트폴민, 인지기능 장애, MMSE, 알츠하이머병,
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