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Cognitive Function in Type 2 Diabetes Mellitus Patients Taking Metformin and Metformin-Sulfonylurea

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Abstract

The most prescribed antidiabetic drugs in Indonesian primary health care are metformin or a combination of metformin and sulfonylurea. Studies on metformin have shown various impacts on cognitive decline in patients with type 2 diabetes mellitus, whereas sulfonylurea has been shown to reduce this impact. This study aimed to compare the impacts of metformin and metformin-sulfonylurea on cognitive function and determine what factors affected it. This cross-sectional study was conducted at Pasar Minggu Primary Health Care involving 142 type 2 diabetes mellitus patients taking metformin or metformin-sulfonylurea for >6 months and aged >36 years. Cognitive function was assessed using the validated Montreal Cognitive Assessment Indonesian version. The effects of metformin and metformin-sulfonylurea on cognitive decline showed no significant difference, even after controlling for covariates (aOR = 1.096; 95% CI = 0.523–2.297; p-value = 0.808). Multivariate analysis showed age (OR = 4.131; 95% CI = 1.271–13.428; p-value = 0.018) and education (OR = 2.746; 95% CI = 1.196–6.305; p-value = 0.017) affected cognitive function. Since a lower education and older age are likely to cause cognitive decline, health professionals are encouraged to work with public health experts to address these risk factors for cognitive function.

Keywords: cognitive decline, cognitive function, diabetes mellitus, metformin, metformin-sulfonylurea

Introduction

Indonesia has 10.7 million people with diabetes mellitus (2% of its population), ranking it seventh in the world.[1] Type 2 diabetes mellitus (T2DM) is a metabolic disease that can cause various complications. Patients with diabetes mellitus (DM) have a one-and-a-half-fold risk of decreased cognitive function compared to those without it.[2] Declines in cognitive function interfere with self-care management behaviors, such as adherence to medication, seeking proper care, glycemic control,[3] and managing the adverse effects of diabetes medications.[4-6]

Various antidiabetic drugs have been evaluated and investigated for their relationship with cognitive function. Metformin is the first line of antidiabetic therapy and is often used alone or in combination with sulfonylurea.[7] Studies that have examined the effects of metformin on cognitive function have yielded different results.[8,9] One study showed that metformin could have a protective effect on cognitive function.[9] Another study showed that metformin causes cognitive decline by creating amyloid plaques in the brain,[10] and B12 deficiency.[6] Another antidiabetic drug, sulfonylurea, was found to reduce the occurrence of cognitive decline in patients with DM.[4] However, another study among diabetic patients found that sulfonylureas increase the risk of hypoglycemia, which increases the risk of cognitive decline.[11] While, the combined use of metformin-sulfonylurea was able to reduced cognitive decline and dementia.[12] Further study should be conducted due to the limited evidence of the effects of the combination of metformin and sulfonylureas on cognitive function.

Although T2DM patients are at high risk for cognitive decline, cognitive function assessments are rarely performed. People with cognitive decline are at risk of having other advanced neurocognitive disorders that can increase the public health burden.[13] Therefore, cognitive assessments can help health care providers address this problem. In addition, considerations in choosing only metformin or a combination need to include comprehensive assessments to optimize therapy for T2DM patients. Aside from drug indications, the effects of medications on cognitive function are of paramount importance in

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therapy considerations.[8] Moreover, it is important to explore other factors that can exacerbate declines in cognitive function so that appropriate intervention steps can be taken. Therefore, this study aimed to compare the effects of metformin and a combination of metformin-sulfonylurea on cognitive function and investigated other factors affecting cognitive function.

Method

This cross-sectional study was conducted at Pasar Minggu Primary Health Care in South Jakarta, Indonesia. Data collection took place between October and December 2021. The T2DM patients of Pasar Minggu Primary Health Care could participate in the study if they met the inclusion criteria, were not disqualified by the exclusion criteria, were willing to be interviewed, and signed an informed consent form. A total of 142 T2DM patients were included in this study. The minimum sample size was calculated using the formula in Formula 1.[14] The minimum sample size was 49 participants per group with a P_1 value of 0.67 and a P_2 value of 0.35.[15]

All samples in this study were taken from T2DM patients treated at the outpatient polyclinic for noncommunicable diseases at Pasar Minggu Primary Health Care. The data collection process was carried out via a consecutive sampling method. The participants in this study were selected based on the inclusion criteria: T2DM patients who used metformin alone or a combination of metformin and sulfonylurea for at least six months and aged 36 years and over. Metformin was primarily indicated for patients with an HbA1c value of less than 7.5%, while metformin-sulfonylurea was mainly given to patients with an HbA1c value of more than 7.5% or if monotherapy for three months resulted in an HbA1c value of more than 7%.[16]

The participants in their late adulthood were selected to distinguish the study subjects from type 1 diabetes mellitus (T1DM) patients, who are generally younger. Patients were then disqualified based on the exclusion criteria: used insulin, could not read or write, had difficulty in communicating, had mental disorders, diagnosed with dementia, and had mild depression as measured using the Indonesian version of the Beck Depression Inventory-II (BDI-II) questionnaire to reduce confounding factors that could affect the study variables. A flowchart of the participants' selection is shown in Figure 1.

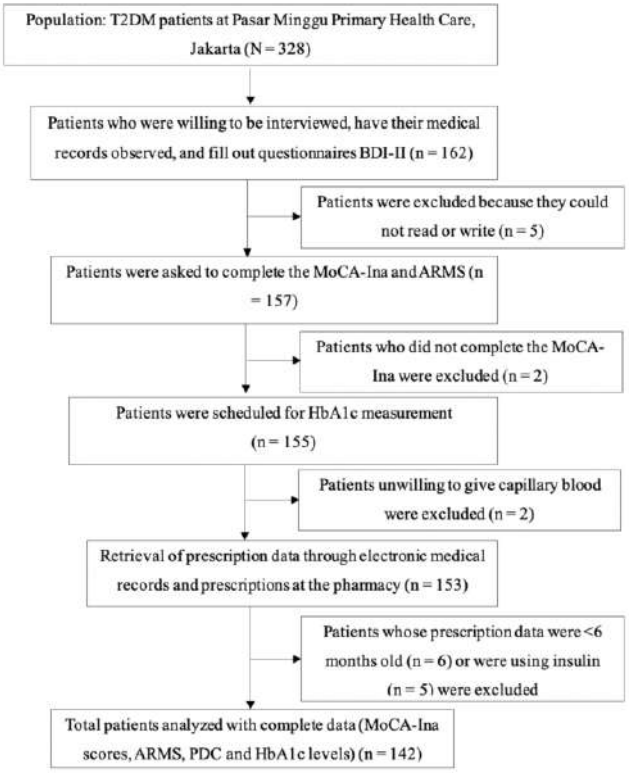
The outcome of this study was cognitive function. Cognitive function refers to problem-solving, learning, thinking, using stored information appropriately, remembering, and paying attention.[17] Cognitive function testing was carried out using the Montreal Cognitive Assessment Indonesian version (MoCA-Ina), which was previously validated.[18] Participants were considered to have not experienced a decline in cognitive function if they had a score ≥26.[19]

Patients who met the inclusion criteria were given the BDI-II questionnaire translated into the Indonesian language, which met validity and reliability tests. Patients with a BDI-II score above 17 were declared to have mild depression.[20] Based on the results of the BDI-II questionnaire, none of the patients in this study had mild depression. Patient demographic data were collected through

$$n = \frac{\left(z_{1-\alpha/2}\sqrt{2\bar{P}(1-\bar{P})} + z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right)^2}{(P_1-P_2)^2}$$

Notes:
$Z_{1-\alpha/2}$ = the normal standard deviation (SD) (5% for type 1 error [p-value<0.05] is 1.96)
$Z_{1-\beta}$ = the normal SD for 90% power (10% for type 2 error is 1.2816)
$P = (P_1+P_2)/2$
P_1 = the proportion of patients using metformin with cognitive decline
P_2 = the proportion of patients using metformin-sulfonylurea with cognitive decline

Formula 1. Sample Size



Notes: T2DM = Type 2 Diabetes Mellitus, MoCA-Ina = Montreal Cognitive Assessment Indonesian Version, ARMS = Adherence to Refills and Medications Scale

Figure 1. Flowchart of Participants' Selection

observation of medical records (the use of drug therapy, weight, height, duration of DM, and disease comorbidities) and interviews with a questionnaire (age, sex, education, and smoking record).

Adherence was assessed by combining two measurement tools, the Indonesian version of the Adherence to Refills and Medications Scale (ARMS) and the proportion of days covered (PDC).[21,22] The participants were interviewed using the ARMS questionnaire. The PDC data were based on patients' visits over the last six months through the e-Puskesmas (an electronic system of patients' visits to primary health care).[22,23] Patients were considered adherent if their ARMS score was less than 12 and their PDC value was ≥80%. All the questionnaires (the Indonesian versions of ARMS, BDI-II, and the MoCA) had been through a translation and back-translation process were then tested for validity and reliability.[18,20,21] Peripheral blood samples were taken to measure HbA1c levels using the Abbott Afinion™ instrument. Hypertension and dyslipidemia were documented based on doctors' written statements in medical records, which means that the criteria for hypertension and dyslipidemia were not determine. Patients were considered smokers if they were current smokers at the time of the interview.

A comparison of the effects of metformin only and metformin-sulfonylurea on cognitive function was conducted. Univariate analysis was performed to describe patient's characteristics. To compare the impacts of the therapies on cognitive function, a Chi-square test was performed, where a p-value of <0.05 was considered significant. Variables with a p-value of <0.25 in the bivariate test or that theoretically had a significant effect on the function were included in the logistic regression. Logistic regression was used to control for confounding variables, and the last model was chosen based on the smallest precision value among all the models. To further identify the variables affecting cognitive function, predictive logistic regression using the backward elimination method was conducted. The variables were selected for the same reason as in the first logistic regression (control for variables). Variables with p-value<0.05 in the last model were considered factors affecting cognitive function. The data are expressed in proportions (n, %) for categorical variables and mean±SD or median (min-max) for numerical variables. The data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 28.0 ((IBM SPSS Statistics Grad Pack 28.0 for Windows or Mac; IBM Corp., Armonk, New York, USA).

Results

The participants in this study consisted of 142 T2DM patients at Pasar Minggu Primary Health Care. Females outnumbered males in each group, with 54 females (76.05%) in the metformin group and 55 males (77.47%) in the metformin-sulfonylurea group. There was a significant difference between the groups in terms of education (p-value = 0.044), as patients with more than 12 years of education were more dominant in the metformin group. Significant differences between groups were also seen in patients' HbA1c levels (p-value = 0.005), ARMS scores (p-value = 0.018), levels of adherence (p-value = 0.075), and vitamin B12 supplementation (p-value = 0.022). The mean age was 59.27 years (SD = 9.2) in the metformin group and 57.90 years (SD = 7.5) in the metformin-sulfonylurea group. There were no significant differences between the groups in age (p-value = 0.335), sex (p-value = 1.000), duration of diabetes (p-value = 0.063), PDC score (p-value = 0.707), body mass index (BMI) (p-value = 0.491), duration of drug consumption (p-value = 1.000), hypertension (p-value = 1.000), dyslipidemia (p-value = 0.595), or smoking (p-value = 1.000). The characteristics of the participants are shown in Table 1.

The participants who experienced a decline in cognitive function significantly outnumbered those who did not (66.90%; 95/142). The proportion of patients aged less than 65 years with normal cognitive function was significantly higher than that of patients aged older than 65 years (p-value = 0.022). Significantly different results were also found in terms of compliance (p-value = 0.024). Although a decline in cognitive function was predominantly observed among females, 71 (74.7%) patients, the difference between the sexes was insignificant. Differences in HbA1c levels were also insignificant despite participants with HbA1c levels of ≥7 being more likely to experience a decline in cognitive function. Education, duration of DM, ARMS score, PDC score, duration of drug consumption, vitamin B12 supplementation, BMI, hypertension, dyslipidemia, and smoking did not significantly increase the odds of cognitive decline (Table 2).

The metformin-sulfonylurea group had more participants who experienced cognitive decline than the metformin group. In the metformin group, the proportion of patients with decreased cognitive function was 63.4%, while that of patients with normal cognitive function was 36.6%. In the metformin-sulfonylurea group, 70.4% of the patients experienced decreased cognitive function. However, there was no significant difference between the two groups (OR = 1.376; 95% CI = 0.682–2.776; p-value = 0.373) (Table 3). To control confounding variables, a multivariate analysis was performed using logistic regression. Bivariate analysis was conducted to select variables that had p-value<0.25, which were age, education, adherence based on the ARMS questionnaire, and comorbid hypertension (Table 2). Sex, HbA1c, B12

Table 1. Participants' Characteristics

Variable	Category	Drug Consumption		n	p-value
		Metformin	Metformin-sulfonylurea		
		(n = 71)	(n = 71)		
Age, year	Mean±SD	59.27±9.2	57.90±7.5	-	0.335
Age, n (%)	6–65 years old	52 (73.2)	57 (80.3)	109	0.427
	>65 years old	19 (26.8)	14 (19.7)	33	
Sex, n (%)	Male	17 (23.94)	16 (22.53)	33	1.000
	Female	54 (76.05)	55 (77.47)	109	
Education, n (%)	>12 years	43 (60.6)	30 (42.3)	73	0.044
	≤12 years	28 (39.4)	41 (57.7)	69	
HbA1c, %	Mean±SD	7.64±1.4	8.85±1.8	-	<0.001
HbA1c level, n (%)	HbA1c<7	24 (33.8)	9 (12.7)	33	0.005
	HbA1c≥7	47 (66.2)	62 (87.3)	109	
Duration of DM, n (%)	≤5 years	46 (64.8)	34 (47.9)	80	0.063
	>5 years	25 (35.2)	37 (52.1)	62	
ARMS	≤12	38 (53.5)	23 (32.4)	61	0.018
	>12	33 (46.5)	48 (67.6)	81	
Proportion of days covered (PDC)	≥80%	50 (70.4)	53 (74.6)	103	0.707
	<80%	21 (29.6)	18 (25.4)	39	
Adherence, n (%)	Adherent	29 (40.8)	18 (25.4)	47	0.075
	Non-adherent	42 (59.2)	53 (74.6)	95	
Duration of drug consumption, n (%)	<12 months	2 (2.8)	3 (4.2)	5	1.000
	≥12 months	69 (97.2)	68 (95.8)	137	
Vitamin B12 supplementation	Yes	59 (83.1)	46 (64.8)	105	0.022
	No	12 (16.9)	25 (35.2)	37	
BMI, kg/m^2	Mean±SD	26.50±4.7	26.80±4.5	-	0.690
BMI in category, n (%)	Skinny–normal (≤25)	30 (42.3)	25 (35.2)	55	0.491
	Overweight–obese (>25)	41 (57.7)	46 (64.8)	87	
Hypertension	No	28 (39.4)	29 (40.8)	57	1.000
	Yes	43 (60.6)	42 (59.2)	85	
Dyslipidemia	No	26 (36.6)	22 (31.0)	48	0.595
	Yes	45 (63.4)	49 (69.0)	94	
Smoker	No	68 (95.8)	67 (94.4)	135	1.000
	Yes	3 (4.2)	4 (5.6)	7	

Notes: SD = Standard Deviation, HbA1c = Hemoglobin A1C, DM = Diabetes Mellitus, ARMS = Adherence to Refills and Medications Scale, BMI = Body Mass Index

supplementation, and BMI were still included in the multivariate analysis because they substantially affected cognitive function. The effect of cognitive function remained insignificant after controlling for confounding variables (Table 4).

Table 5 shows the last model of multivariate analysis using the predictive model. It shows that age (OR = 4.131; 95% CI = 1.271–13.428; p-value = 0.018) and education (OR = 2.746; 95% CI = 1.196–6.305; p-value = 0.017) affected cognitive function.

Discussion

Metformin is an antidiabetic drug widely used alone or in combination with sulfonylurea.[7,11] Both regimens can affect cognitive function, either positively or negatively.[8,11] In this study, the participants were predominantly females because they suffered from T2DM at a higher rate than males. Interestingly, males were 35.2% more at risk of experiencing cognitive decline than females, which is in line with the previous study.[1] However, a study found that women tend to experience more cognitive decline than men.[24] Therefore, more study is needed on sex and cognitive decline.[25]

Participants who suffered from T2DM for less than five years used metformin more (64.8%) than participants who suffered from T2DM for more than five years (35.2%). Participants with a T2DM duration of more than five years used metformin-sulfonylurea (52.1%) more than metformin only (47.9%). This condition was caused by uncontrolled blood sugar levels in more participants, so that the treatment target was not reached. The antidiabetic medicines of those patients were combined with therapy, following the guidelines which recommended metformin as the first line of antidiabetic therapy. If a patient's HbA1c value is more than 7.5% or monotherapy for three months results in an HbA1c value of more than 7%, then metformin-sulfonylurea will be prescribed with a different mechanism.[16]

This study's findings indicated no significant difference between metformin only and metformin-sulfonyl-

Table 2. Factors Increasing the Odds of Cognitive Function Decline

Variable	Category	Cognitive Function		p-value	OR (95% CI)
		Decline	Normal		
		(n = 95)	(n = 47)		
Age, year	Mean±SD	56.06±6.7	59.83±8.9	0.011	-
Age, n (%)	≤65 years old	67 (70.5)	42 (89.4)	0.022	Ref
	>65 years old	28 (29.5)	5 (10.6)		3.510(1.257–9.801)
Sex, n (%)	Male	24 (25.3)	9 (19.1)	0.548	Ref
	Female	71 (74.7)	38 (80.9)		0.701 (0.296–1.658)
Education, n (%)	>12 years	43 (45.3)	30 (63.8)	0.057	Ref
	≤12 years	52 (54.7)	17 (36.2)		2.134 (1.040–4.381)
HbA1c, %	Mean ± SD	8.3±0.9	8.2±0.1	0.896	-
HbA1c level, n (%)	HbA1c<7	24 (25.3)	9 (19.1)	0.548	Ref
	HbA1c≥7	71 (74.7)	38 (80.9)		0.701 (0.296–1.658)
Duration of DM, n (%)	≤5 years	50 (52.6)	30 (63.8)	0.277	Ref
	>5 years	45 (47.4)	17 (36.2)		1.588 (0.774–3.258)
ARMS	<12	35 (36.8)	26 (55.3)	0.062	Ref
	≥12	60 (63.2)	21 (55.3)		2.087 (1.025–4.249)
Proportion of days covered (PDC)	≥80%	70 (73.7)	33 (70.2)	0.813	Ref
	<80%	25 (26.3)	14 (29.8)		0.842 (0.388–1.826)
Adherence, n (%)	Adherent	25 (26.3)	22 (46.8)	0.024	Ref
	Non-adherent	70 (73.7)	25 (53.2)		2.464 (1.184–5.127)
Duration of drug consumption, n (%)	<12 months	2 (2.1)	3 (6.4)	0.414	Ref
	≥12 months	93 (97.9)	44 (93.6)		3.170 (0.511–19.661)
Vitamin B12 supplementation	Yes	67 (70.5)	38 (80.9)	0.264	Ref
	No	28 (29.5)	9 (19.1)		1.765 (0.754–4.128)
BMI, kg/m²	Mean±SD	27.27±4.3	26.34±4.7	0.254	-
BMI in category, n (%)	Skinny–normal (≤25)	38 (40.0)	17 (36.2)		Ref
	Overweight–obese (>25)	57 (60.0)	30 (63.8)	0.797	0.850 (0.413–1.751)
Hypertension	No	33 (34.7)	24 (51.1)		Ref
	Yes	62 (65.3)	23 (48.9)	0.092	1.960 (0.963–3.991)
Dyslipidemia	No	65 (68.4)	29 (61.7)		Ref
	Yes	45 (63.4)	49 (69.0)	0.543	1.345 (0.648–2.791)
Smoker	No	89 (93.7)	46 (97.9)		Ref
	Yes	6 (6.3)	1 (2.1)	0.501	3.101 (0.362–26.535)

Notes: OR = Odds Ratio, CI = Confidence Interval, SD = Standard Deviation, Ref = Reference, HbA1c = Hemoglobin A1C, DM = Diabetes Mellitus, ARMS = Adherence to Refills and Medications Scale, BMI = Body Mass Index

Table 3. Impacts of Metformin-Only and Metformin-sulfonylurea Use on Cognitive Function Decline

Variable	Category	Cognitive Function		p-value	OR (95% CI)
		Decline (<26)	Normal (≥26)		
Drug consumption	Metformin	45 (63.4)	26 (36.6)	0.373	Ref
	Metformin-sulfonylurea	50 (70.4)	21 (29.6)		1.376 (0.682–2.776)

Notes: OR = Odds Ratio, CI = Confidence Interval, Ref = Reference

urea on cognitive function (OR = 1.376; 95% CI = 0.682–2.776; p-value = 0.373). After controlling for education and adherence, there was still no significant difference (aOR = 1.214; 95% CI = 0.590–2.499; p-value = 0.598). These results were in line with several studies that found that these two therapies did not differ significantly regarding their impacts on cognitive function.[11,15] This condition can be caused by vitamin B12 supplementation; 59 patients (83.1%) and 46 patients (64.8%) consumed it in the metformin and metformin-sulfonylurea group, respectively. The use of long-term metformin has been shown to cause B12 deficiency.

B12 deficiency can affect the development and maintenance of the peripheral and central nervous systems. B12 deficiency also affects the blood-brain barrier and thus affects the small blood vessels in the brain. These conditions lead to cognitive decline.[26] B12 supplementation can help improve cognitive function.[27] However, not all T2DM patients took B12 supplements, which affected the results of this study. The ineffectiveness of treatment,

Table 4. Logistic Regression for Controlling Confounding Variables

Model	Confounding variable	Category	p-value	OR	95% CI
Crude	Drug consumption	Metformin	0.373	Ref	0.682–2.776
		Metformin-sulfonylurea		1.376	
Adjusted[a]	Drug consumption	Metformin	0.700	Ref	0.512–2.712
		Metformin-sulfonylurea		1.178	
	Age	≤65 years old	0.023	Ref	1.308–13.748
		>65 years old		4.240	
	Sex	Male	0.219	Ref	0.202–1.442
		Female		0.540	
	Education	>12 years	0.016	Ref	1.224–6.893
		≤12 years		2.904	
	BMI	Skinny–normal (≤25)	0.462	Ref	0.583–3.281
		Overweight–obese (>25)		1.383	
	HbA1c	HbA1c<7	0.320	Ref	0.222–1.635
		HbA1c≥7		0.603	
	ARMS	<12	0.682	Ref	0.395–5.912
		≥12		1.279	
	Adherence	Adherent	0.348	Ref	0.535–5.912
		Non-adherent		1.778	
	Hypertension	No	0.164	Ref	0.795–3.882
		Yes		1.757	
	B12 Supplementation	Yes	0.506	Ref	0.521–3.742
		No		1.397	
Adjusted[b]	Drug consumption	Metformin	0.808	Ref	0.523–2.297
		Metformin-sulfonylurea		1.096	
	Education	>12 years	0.098	Ref	0.890–3.949
		≤12 years		1.875	
	Adherence	Adherent	0.040	Ref	1.036–4.678
		Non-adherent		2.202	

Notes: OR = Odds Ratio, CI = Confidence Interval, HbA1c = Hemoglobin A1C, ARMS = Adherence to Refills and Medications Scale, BMI = Body Mass Index
[a]Adjusted for all variables that had p-value<0.25 in the bivariate analysis or that could theoretically affect cognitive function
[b]The most precise model.

Table 5. Effects of Variables on Decline in Cognitive Function

Variable	Category	p-value	OR	95% CI
Age	≤65 years old	0.018	Ref	1.271–13.428
	>65 years old		4.131	
Education	>12 years	0.017	Ref	1.196–6.305
	≤12 years		2.746	

Notes: OR = Odds Ratio, CI = Confidence Interval

which resulted in the treatment goals not being achieved, also affected the results. In this study, 67.6% of the metformin group and 87.6% of the metformin-sulfonylurea group had an HbA1c level ≥7. According to previous studies, high HbA1c levels result in cognitive function decline.[28,29]

The use of sulfonylureas has a high risk of causing hypoglycemia. Cognitive dysfunction in diabetes can be caused by repeated episodes of moderate to a severe hypoglycemia. During an episode of acute hypoglycemia, patients experience impaired global cognitive function and working memory, delayed verbal and visual memory, and impaired visual-spatial and visual-motor skills.[30] However, when combined with metformin, sulfonylureas reduce the occurrence of cognitive decline.[31] Sulfonylureas also have neuroprotective functions, modulating proinflammatory cytokine release and reducing neuronal loss and necrosis.[32] Although the use of sulfonylureas can cause hypoglycemia, which then triggers cognitive decline, supporting the higher proportion of patients with cognitive decline,[30] in the metformin-sulfonylurea group, its neuroprotective effects and the addition of metformin may have contributed to the insignificant difference between groups. Since data on which patients experienced hypoglycemia were unavailable, further study is needed to confirm this finding.

This study's results demonstrate that metformin only and metformin-sulfonylurea did not affect cognitive function. Therefore, to identify the factors that affect cognitive function, a predictive model was created, and a logistic regression was performed using the enter method. The result revealed that age and education affected cognitive function. Previous studies have found that education is a nonmedical protective factor against cognitive decline.[33,34] The lower the level of education, the higher the risk of cognitive decline. Individuals with higher le-

vels of education are not only at lower risk for cognitive distraction, but also show better cognitive performance than those with low education.[33]

Education is thought to play a role in increasing resistance to neurodegenerative processes. Experiences gained during education, such as continuous exposure to cognitive stimulation and opportunities to gain knowledge and skills, affect an individual's cognitive ability.[34] Furthermore, age is associated with physiological functional decline in various organ systems, including the psychomotor system and cognitive function in the brain. Changes in anatomy and physiology that inevitably occur during aging affect cognitive function.[35] The age difference between DM patients can also explain why some experience neurocognitive morbidity that is clinically significant while most are unaffected.

Cognitive decline has been shown to significantly increase morbidity and mortality and reduce the quality of life, increasing the public health burden.[36] People with cognitive decline are at risk of having other neurodegenerative diseases, such as Alzheimer's disease, which increases the cost burden per patient by as much as USD6,784.[37] A declines in cognitive function can interfere with self-care management behaviors, such as adherence to medication. As education and age can affect cognitive decline, people in the public health sector should be encouraged to pay more attention to nonmedical factors that affect cognitive decline. For populations with less than 12 years of education, special education sessions and health promotion can be implemented to develop knowledge, attitude, and behavior about the importance of good medication management.

Elderly patients need special attention from health professionals to manage their treatment. Collaboration between health professionals has been shown to improve the quality of patient care in the long term.[38] Programs in Indonesian primary health care, such as the Prolanis and Integrated Service Post for Older People/*Pos Pelayanan Terpadu Lansia* (Posyandu Lansia), can be a means for health providers to encourage the elderly with cognitive decline to visit primary health care facilities to monitor and treat their diseases and achieve optimal quality of life and prevent complications.[39,40] At any rate, health professionals are encouraged to work with public health experts to address the effect of medical and nonmedical factors on patient health status.

Strengths and Limitations

This study has some limitations, one of which is its cross-sectional design. A cross-sectional design cannot determine the causal factors of the study variables. Second, this study was only conducted at one primary helath care. Hence, selection bias might have affected the validity of the results, as the sample was not representative of the overall population in Indonesia. Moreover, the sample size was limited and predominantly comprised women, thus limiting statistical power.

However, the inclusion and exclusion criteria, including the minimum antidiabetic therapy duration, helped reduce the limitation. The MoCA-Ina instrument used to measure cognitive function also had high validity and reliability. The metformin and metformin-sulfonylurea groups, the most widely used therapies for T2DM in the primary health care, were examined. Therefore, the results could be useful for assessing the safety of antidiabetic therapies in the community. Given the limitations of the study and the widespread use of metformin and its combination with a sulfonylurea, further study is needed.

Conclusion

This study does not find a significant difference between the impacts of metformin only and the combination of metformin-sulfonylurea on cognitive function. Even though confounding variables are controlled for, the results are not statistically significant. The factors that most affect cognitive decline are education and age.

Abbreviations

T2DM: Type 2 Diabetes Mellitus; MoCA-Ina: Indonesian version of the Montreal Cognitive Assessment; BDI-II: Beck Depression Inventory-II; HbA1c: Hemoglobin A1C; PDC: Proportion of Days Covered, ARMS: Adherence to Refills and Medications Scale; BMI: Body Mass Index.

Ethics Approval and Consent to Participate

This study passed an ethical review conducted by the Health Research Ethics Committee in the Faculty of Medicine at Universitas Indonesia (KEPK FK UI; approval number KET-936/UN2.F1/ETIK/PPM.00.02/2021). Research approval was also given by the Special Capital Region of Jakarta Health Office and then forwarded to the South Jakarta Municipality Health Office and the Pasar Minggu Primary Health Care of South Jakarta.

Competing Interest

The authors declare that there are no significant competing financial, professional, or personal interests that might have affected the performance.

Availability of Data and Materials

The data were not made publicly available, as they contained information that could compromise the privacy of the research participants.

Authors' Contribution

RS contributed to conceptualization, data curation, funding acquisition, investigation, methodology, project administration, supervision, validation, writing, reviewing, and editing. AR contributed to conceptualization, data curation, formal analysis, methodology, supervision,

validation, investigation, writing, reviewing, and editing. All the authors discussed the final results and contributed to the final manuscript. NFS contributed to conceptualization, data curation, methodology, supervision, validation, investigation, writing, reviewing, and editing. PP contributed to conceptualization, methodology, supervision, validation, investigation, writing, reviewing, and editing. HWR contributed to data curation, formal analysis, supervision, writing, reviewing, and editing.

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