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The Effect of Insulin Administration on Medication Adherence in Type 2 Diabetes Mellitus Patients with Neurological Complications

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Abstract
Background*: Medication adherence is essential to achieving controlled blood sugar in diabetic patients. Insulin generally provides better glycemic control but is considered painful and requires special techniques. Insulin administration in patients with neurological complications requires particular consideration because these complications can cause physical and cognitive barriers.* ***Objective****: This study analyses the effect of insulin administration on medication adherence in diabetic patients with neurological complications and the influence of various confounding variables (baseline characteristics, medical and medication history).* ***Methods:*** *This observational study was conducted with a cross-sectional design at a government hospital in East Jakarta from September 2021 to January 2022. The sample was type 2 diabetes mellitus patients with neurological complications who received antidiabetics for at least six months. The neurological complications include central nervous disorders (such as stroke) and peripheral nervous disorders (such as neuropathy). The independent variable was insulin administration, while the dependent variable was adherence, measured using subjective methods [Adherence to Refills and Medications Scale (ARMS)] and objective methods (Medication Refill Adherence (MRA) and HbA1c].* ***Results****: Of 175 respondents, based on the three methods (MRA, ARMS, HbA1c), 13 respondents (7.4%) were adherent, namely one respondent (1.8%) in the insulin group and 12 respondents (10.1%) in the non-insulin group. Insulin administration affects adherence to antidiabetics by 0.123 times (95% CI: 0.015 - 1.024), or patients who use insulin have 87.7% lower adherence controlled by antidiabetic changes and the total number of medicines used.* ***Conclusion****: Insulin administration significantly affects medication adherence in diabetes mellitus patients with neurological complications.*

Keywords*: diabetes mellitus, insulin, adherence, neurological complications*

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INTRODUCTION

Diabetes mellitus is among the ten leading causes of death globally, with a 70% increase since 2000. Around 2.3 million women and 1.9 million men aged 20 – 79 are estimated to die from diabetes and its complications in 2019 (WHO, 2020). Indonesia had the seventh-highest number of people with diabetes in the world in 2019; the number of people with diabetes is around 10.7 million (International Diabetes Federation, 2019).

Pharmacological therapy in patients with type 2 diabetes mellitus consists of oral antidiabetic and injection antidiabetic (insulin) or a combination. Insulin is given if the target blood glucose level has not been achieved with two types of oral antidiabetics (Perkeni, 2021).

Medication adherence is essential in the effective management of diabetes mellitus. Adherence to antidiabetic use is associated with improved control of blood sugar levels (Doggrell & Warot, 2014). Uncontrolled blood sugar levels increase the risk of recurrent stroke by 1.45 times compared to patients with controlled sugar levels (Shou *et al*., 2015). Insulin generally provides better glycemic control, improving quality of life and reducing diabetic complications. On the other hand, it causes discomfort, pain, and aggravation and limits the patient's daily activities, affecting adherence and ultimately the success of therapy. In particular, the administration of drugs with special techniques, such as insulin, requires special consideration in patients with neurological complications because these complications can cause the patient to have physical and cognitive barriers and limitations due to disorders of the central and/or peripheral nerves. This may be will affect medication adherence. Complications are secondary diseases or conditions that develop during the primary disease or condition (Complication Definition & Meaning - Merriam-Webster, 2022). In patients with diabetes mellitus, neurological complications can include central nervous disorders (such as stroke) and peripheral nerve disorders (such as neuropathy) (Ireland *et al*., 2010).

Various studies in Indonesia have previously been undertaken to examine medication adherence with oral antidiabetics without considering the patient's comorbidities and generally use one or two measuring instruments (Salistyaningsih *et al*., 2011; Alfian, 2015; Adikusuma & Qiyaam, 2017; Nanda *et al*., 2018; Bulu *et al*., 2019). The purpose of this study was to analyse the effect of insulin administration on medication adherence in diabetes mellitus patients with neurological complications by using subjective methods [Adherence to Refills and Medications Scale (ARMS)] and objective methods [Medication Refill Adherence (MRA) and HbA1c measurement], as well as the effect of a various confounding variable on medication adherence.

MATERIALS AND METHODS

This observational study used a cross-sectional design and was conducted at a government hospital in East Jakarta from September 2021 to January 2022. The sampling technique used was the consecutive sampling method. The inclusion criteria were typed 2 diabetes mellitus patients with neurological complications who had received at least six months of antidiabetes with a payment system by Badan Penyelenggara Jaminan Sosial (BPJS)/Indonesian Universal Covered Health Insurance and willingness to be respondents in this study.

Neurological complications are divided into central and peripheral nerve disorders. Central nervous disorders were divided into patients with and without stroke, while peripheral nervous disorders were divided into patients with and without. Both of these conditions are determined based on the doctor's diagnosis in the medical records.

Patients who redeemed antidiabetics outside the hospital where the study was conducted, whose medical record data were incomplete, and who did not fully answer the ARMS questionnaire were excluded from this study.

Using the Lemeshow formula (Lachenbruch *et al*., 1991) and previous research data (Osborn & Gonzalez, 2016), 95% confidence interval, and 70% test power, the minimum number of samples required is 53 samples for each group.

Data were collected in two ways, interviews with outpatients who had received medication for at least six months based on data obtained from the patient's medical records. Secondary data were medical history, medicine, and HbA1c from medical records.

Measurement of adherence with the subjective method was carried out using the Indonesian version of the Adherence to Refills and Medications Scale (ARMS) questionnaire, in which validity and reliability were determined. This questionnaire contains twelve questions: eight items from the drug use subscale to assess the patient's adherence to using prescribed drugs as directed, and four items from the prescription refill subscale to assess the patient's adherence to refilling his prescription. The ARMS questionnaire has been

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translated and validated in several countries, such as Iran, Korea, China, Spain, and Poland (Jin *et al*., 2016; Kim *et al*., 2016; González-Bueno *et al*., 2017; *Barati et al*., 2018; Lomper et al., 2018; Park *et al*., 2018 Chen *et al*., 2020; Kripalani *et al*., 2009; Zairina *et al*., 2022).

Measurement of adherence with the objective method was carried out based on changes in HbA1c values in the last two HbA1c examinations with a minimum distance of three months and using the percentage of Medication Refill Adherence (MRA) with the formula:

$$\mathrm{MRA} = \frac{\text{Number of prescribed treatment days for each refills}}{\text{Number of days between the refills}} \times 100 \quad (1)$$

Respondents are considered to be adherent if they met the criteria for adherence in all tests (overall), namely having an ARMS score of 12 (Kripalani *et al*., 2009), an MRA percentage of 80 - 120% (Kindmalm *et al*., 2007), and a decrease in the HbA1c value in the last two measurements 0.2% (Sherwani *et al*., 2016). Data were analysed using SPSS 26, namely descriptive analysis, different proportion analysis, and logistic regression analysis using the backward method.

This study also analysed the effect of various confounding variables derived from the patient's characteristics (age, gender, education, occupation, and body mass index) as well as the patient's medical and medication history (duration of diabetes diagnosed, antidiabetic changes, number of antidiabetic drugs, number of comorbidities, diagnosis of central and peripheral nervous disorders, total number of medications, herbal consumption, allergies, prescription iterations, and family/caregiver assistance). Diagnosis of central and peripheral nervous disorders data was obtained from the patient's medical record. Central nervous disorders were categorised into respondents with a history of ischemic or hemorrhagic stroke (stroke category) and did not have a history of stroke (non-stroke category). Non-stroke respondents include patients diagnosed with Parkinson's, dementia, depression, and others. We divided it into stroke and non-stroke because more than 80% of respondents had a stroke history. Peripheral nerve disorders were divided into patients with peripheral nerve disorders and those without. Diagnosis of peripheral nerve disorders includes neuropathy and peripheral pain.

RESULTS AND DISCUSSION

Characteristics of respondents

Table 1 shows the 175 respondent characteristics, consisting of 56 respondents who used insulin (insulin group) and 119 respondents who did not use insulin (non-insulin group). Patients taking insulin can take insulin alone or in combination with oral antidiabetics.

Table 1. Characteristics of respondents

Characteristics		Insulin n (%)[a]	Non-Insulin n (%)[a]	Total [b]	p-value (inter-group)
Age group	1 (35 - 44 years)	3 (5.4)	5 (4.2)	8 (4.6)	0.951 [c]
	2 (45 - 54 years)	10 (17.9)	23 (19.3)	33 (18.9)	
	3 (55 - 64 years)	25 (44.6)	47 (39.5)	72 (41.1)	
	4 (65 - 74 years)	14 (25.0)	33 (27.7)	47 (26.9)	
	5 (75+)	4 (7.1)	11 (9.2)	15 (8.6)	
Gender	Man	30 (53.6)	74 (62.2)	104 (59.4)	0.179 [c]
	Woman	26 (46.4)	45 (37.8)	71 (40.6)	
Education	Did not finish elementary school/did not go to school	1 (1.8)	2 (1.7)	3 (1.7)	0.478 [c]
	Elementary	4 (7.1)	9 (7.6)	13 (7.4)	
	Junior High School	4 (7.1)	8 (6.7)	12 (6.9)	
	Senior High School	14 (25.0)	46 (38.7)	60 (34.3)	
	College	33 (58.9)	54 (45.4)	87 (49.7)	
Work	Retired/not working	22 (39.3)	52 (43.7)	74 (42.3)	0.801 [c]
	PNS/TNI/POLRI	7 (12.5)	8 (6.7)	15 (8.6)	
	Self-employed/ trader	2 (3.6)	7 (5.9)	9 (5.1)	
	Private employees	5 (8.9)	9 (7.6)	14 (8.0)	
	Housewife	18 (32.1)	37 (31.1)	55 (31.4)	
	Other	2 (3.6)	6 (5.0)	8 (4.6)	
Body mass index (Kg/m^2)		25.77 ± 4.49	25.57 ± 4.15	25.64 ± 4.25	0.775 [d]

Information: [a] Value is expressed in n (%), the percentage in one category; [b] Values are expressed in n (%), percentage of all respondents; [c] Chi-squared test, [d] unpaired T-test because body mass index data is normal.

Table 1 shows that the respondents in this study consisted of respondents aged 55 - 64 years (41.1%), followed by 65 - 74 years (26.9%), 45 - 54 years (18.9%), over 75 years (8.6%), and 35 - 44 years old (4.6%). Male respondents were 59.4%, while female respondents were 40.6%. Most respondents were undergraduate (49.7%) and high school (34.3%). As many as 42.3% of respondents are not working or retired, and 31.4% are homemakers. Only eight respondents (4.6%) showed drug allergy but were not antidiabetic. Most respondents were overweight, whit a body mass index of 25.64 ± 4.25 Kg/m^2.

Respondent's medical and medication history

The respondent's medical and medication history is summarised in Table 2. Of the 175 respondents, 71 respondents (40.6%) had received antidiabetes for 6 - 12 months, 55 respondents (31.4%) for 12-24 months, and 49 respondents (28%) for more than 24 months. A small proportion of respondents (37.1%, n = 65) experienced changes in antidiabetics, which is the replacement or addition of antidiabetics. Sixty-five respondents (37.1%) got three antidiabetics, 59 respondents (33.7%) got two antidiabetics, and the rest received a single antidiabetic or a combination of four antidiabetics. The antidiabetic can be insulin and/or oral antidiabetic. Respondents who got four antidiabetics commonly received insulin; only one received four oral antidiabetics, which consisted of metformin, vildagliptin, gliclazide, and pioglitazone. Most respondents had stroke prevously (86.95%, n = 152). This rate is in line with the meta-analysis of 102 prospective studies involving 698782 people showed that diabetes increased the risk of ischemic stroke by 2.27 times and hemorrhagic stroke by 1.56 times. (Sarwar *et al*., 2010; Bloomgarden & Chilton, 2021). A total of 56 respondents (32.0%) were diagnosed with peripheral nerve disorders. A small proportion of respondents (20.0%, n = 35) received more than ten medicines, categorised as major polypharmacy (Kim *et al*., 2014).

Table 2. Medical and medication history of respondents

Characteristics		**Insulin n (%)**[a]	**Non-Insulin n (%)**[a]	**Total**[b]	**p-value (inter-group)**[c]
Duration of diagnosed diabetes	< 12 months	27 (48.2)	44 (37.0)	71 (40.6)	0.315
	12 - 24 months	14 (25.0)	41 (34.5)	55 (31.4)	
	> 24 months	15 (26.8)	34 (28.6)	49 (28.0)	
Antidiabetic changes in the last six months	Yes	30 (53.6)	35 (29.4)	65 (37.1)	0.002
	Not	26 (46.4)	84 (70.6)	110 (62.9)	
Number of antidiabetics (insulin and/or antidiabetic oral)	Single drug	0 (0.0)	33 (27.7)	33 (18.9)	< 0.001
	Combination of 2 drugs	9 (16.1)	50 (42.0)	59 (33.7)	
	Combination of 3 drugs	30 (53.6)	35 (29.4)	65 (37.1)	
	Combination of 4 drugs	17 (30.4)	1 (0.8)	18 (10.3)	
Number of comorbidities	≤ 3	25 (44.6)	52 (43.7)	77 (44.0)	0.517
	>3	31 (55.4)	67 (56.3)	98 (56.0)	
Central nervous system disorders	Stroke	53 (94.6)	99 (83.2)	152 (86.9)	0.027
	Non-stroke	3 (5.4)	20 (16.8)	23 (13.1)	
Peripheral nerve disorders	Yes	20 (35.7)	36 (30.3)	56 (32.0)	0.290
	Not	36 (64.3)	83 (69.7)	119 (68.0)	
Total amount of medicine	≤10	37 (66.1)	103 (86.6)	140 (80.0)	0.002
	>10	19 (33.9)	169 (13.4)	35(20.0)	
Consumption of herbs in the last six months	Yes	17 (30.4)	29 (24.4)	46 (26.3)	0.254
	Not	39 (69.6)	90 (75.6)	129 (73.7)	
Allergy	Yes	3 (5.4)	5 (4.2)	8 (4.6)	0.500
	Not	53 (94.6)	114 (95.8)	167 (95.4)	
Recipe iteration	Yes	34 (60.7)	95 (79.8)	129 (73.7)	0.007
	Not	22 (39.3)	24 (20.2)	46 (26.3)	
Family/ Caregiver support	Yes	41 (73.2)	69 (58.0)	110 (62.9)	0.037
	Not	15 (26.8)	50 (42.0)	65 (37.1)	

Description: [a] Value is expressed in n(%), percentage in one category; [b] Values are expressed in n(%), percentage of all respondents; [c] Chi-square test.

Medication adherence

Adherence to Refills and Medications Scale (ARMS)

The Indonesian version of the ARMS questionnaire in this study has obtained permission from the owner (Kripalani *et al*., 2009). Validity and reliability tests were carried out on the first 30 respondents and obtained valid results; each question on the questionnaire showed r results (correlated item-total correlation) greater than the r table (α = 0.05, df 28 (n-2)), and reliable, means having Cronbach's Alpha above 0.6, which is 0.829. The reliability test result of the ARMS questionnaire is close to Cronbach's value in the reliability test of the questionnaire translation conducted by previous researchers, which is 0.865 (Zairina *et al*., 2018). The ARMS score of the insulin group respondents was 12 - 24, while the respondents in the non-insulin group were 12 - 30. Based on the ARMS score, respondents were declared adherent if they had a score of 12 (Kripalani *et al*., 2009); as many as 43 respondents (24.6%) were adherent, consisting of 10 respondents (17.9%) in the insulin group and 33 respondents (27.7%) in the non-insulin group.

Medication Refill Adherence (MRA)

The percentage of MRA is 20.73-114.86%. Respondents are declared adherent if the MRA is 80-120% (Kindmalm *et al*., 2007). Based on the MRA percentage, there were 87 respondents (49.7%) who were adherent, namely 25 respondents (44.6%) in the insulin group and 62 respondents (52.1%) in the non-insulin group.

Glycosylated hemoglobin (HbA1c)

Adherence based on HbA1c was determined based on changes in HbA1c values in the last two examinations, taken from medical record data. Respondents were declared adherent if they showed a 0.2% decrease in HbA1c value because it reduced mortality by 10% (Sherwani *et al*., 2016). Based on the reduction in HbA1c, there were 63 respondents (36%) who were adherent, namely 26 respondents (46.4%) in the insulin group and 37 respondents (31.1%) in the non-insulin group.

The medication adherence results using each of these measuring instruments and the combination of the three measuring instruments are summarised in Table 3.

The effect of insulin administration and confounding variables was analysed using the backward method in multivariate logistic regression. Before multivariate analysis, bivariate analysis was performed for each confounding variable (Table 4).

Confounding variables that had a p-value less than 0.25 were included in the multivariate logistic regression analysis, which included body mass index, changes in antidiabetic in the last six months, number of comorbidities, diagnosis of peripheral nerve disorders, the total number of medicines consumed by respondents, and consumption of herbs. In addition, age and gender were also included in the multivariate analysis. The effect of insulin administration and the confounding variables were analysed by logistic regression analysis using the backward method. The logistic regression analysis showed that the variables that needed to be controlled in determining the effect of insulin administration on medication adherence were antidiabetic changes in the last six months and the total number of medications used by patients (Table 5).

Table 3. Medication adherence

Characteristics		Insulin n (%)[a]	Non-Insulin n(%)[a]	Total n (%)[b]	p-value (inter-group)[c]
ARMS	Adherent	10 (17.9)	33 (27.7)	43 (24.6)	0.109
	Non-adherent	46 (82.1)	86 (72.3)	132 (75.4)	
MRA	Adherent	25 (44.6)	62 (52.1)	87 (49.7)	0.224
	Non-adherent	31 (55.4)	57 (47.9)	88 (50.3)	
HbA1c	Adherent	26 (46.4)	37 (31.1)	63 (36.0)	0.036
	Non-adherent	30 (53.6)	82 (68.9)	112 (64.0)	
Overall	Adherent	1 (1.8)	12 (10.1)	13 (7.4)	0.042
	Non-adherent	55 (98.2)	107 (89.9)	162 (92.6)	

Information: [a] Value is expressed in n(%), a percentage in one category; [b] Values are expressed in n(%), percentage of all respondents; [c] Chi-square test; Overall, adherence is measured using the three measurement methods, the patient is declared adherent if the results of the three methods show adherence.

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Table 4. Differences in respondent adherence based on characteristics, medical history, and medication history

Confounding Variables		Adherent n (%)[a]	Non-adherent n (%)[a]	Total n (%)[b]	p-value (inter-group)[c]
Age	35 - 44 years old	0 (0.0)	8 (100.0)	8 (4.6)	0.419
	45 - 54 years old	2 (6.1)	31 (93.9)	33 (18.9)	
	55 - 64 years old	5 (6.9)	67 (93.1)	72 (41.1)	
	65 - 74 years old	6 (12.8)	41 (87.2)	47 (26.9)	
	75+	0 (0.0)	15 (100.0)	15 (8.6)	
Gender	Man	8 (7.7)	96 (92.3)	104 (59.4)	0.559
	Woman	5 (7.0)	66 (93.0)	71 (40.6)	
Education	Did not finish elementary school/did not go to school	1 (33.3)	2 (66.7)	3 (1.7)	0.406
	Elementary	1 (7.7)	12 (92.3)	13 (7.4)	
	Junior High School	0 (0.0)	12 (100.0)	12 (6.9)	
	Senior High School	5 (8.3)	55 (91.7)	60 (34.3)	
	College	6 (6.9)	81 (93.1)	87 (49.7)	
Work	Retired/ Doesn't work	6 (8.1)	68 (91.9)	74 (42.3)	0.817
	PNS/TNI/ POLRI	1 (6.7)	14 (93.3)	15 (8.6)	
	Self-employed/ trader	1 (11.1)	8 (88.9)	9 (5.1)	
	Private employees	0 (0.0)	14 (100.0)	14 (8.0)	
	Housewives	5 (9.1)	50 (90.9)	55 (31.4)	
	Other	0 (0.0)	8 (100.0)	8 (4.6)	
Body mass index	Normal	5 (14.7)	29 (85.3)	34 (19.4)	**0.081** *
	Abnormal	8 (5.7)	133 (94.3)	141 (80.6)	
Duration of diagnosed diabetes	< 12 months	7 (9.9)	64 (90.1)	71 (40.6)	0.594
	12-24 months	3 (5.5)	52 (94.5)	55 (31.4)	
	> 24 months	3 (6.1)	46 (93.9)	49 (28.0)	
Antidiabetic changes in the last six months	Yes	8 (12.3)	57 (87.7)	65 (37.1)	**0.058***
	Not	5 (4.5)	105 (95.5)	110 (62.9)	
Number of antidiabetics	Single drug	4 (12.1)	29 (87.9)	33 (18.9)	0.415
	Combination of 2 drugs	2 (3.4)	57 (96.6)	59 (33.7)	
	Combination of 3 drugs	6 (9.2)	59 (90.8)	65 (37.1)	
	Combination of 4 drugs	1 (5.6)	17 (94.4)	18 (10.3)	
Number of comorbidities	≤3	4 (5.2)	73 (94.8)	77 (44.0)	**0.242** *
	>3	9 (9.2)	89 (90.8)	98 (56.0)	
Central nervous system disorders	stroke	11 (7.2)	141 (92.8)	152 (86.9)	0.532
	Non-stroke	2 (8.7)	21 (91.3)	23 (13.1)	
Peripheral nerve disorders	Yes	6 (10.7)	50 (89.3)	56 (32.0)	**0.201** *
	Not	7 (5.9)	112 (94.1)	119 (68.0)	
Total amount of medicine	≤10	12 (8.6)	128 (91.4)	140 (80.0)	**0.223***
	>10	1 (2.9)	34 (97.1)	35 (20.0)	
Recipe iteration	Yes	10 (7.8)	119 (92.2)	129 (73.7)	0.540
	Not	3 (6.5)	43 (93.5)	46 (26.3)	
Consumption of herbs	Yes	5 (10.9)	41 (89.1)	46 (26.3)	**0.233** *
	Not	8 (6.2)	121 (93.8)	129 (73.7)	
Family/ caregiver support	Yes	8 (7.3)	102 (92.7)	110 (62.9)	0.569
	Not	5 (7.7)	60 (92.3)	65 (37.1)	

Information: [a] Value is expressed in n(%), percentage in one category; [b] Values are expressed in n(%), percentage of all respondents. * p-value < 0.25, the variable was included in the multivariate logistic regression analysis.

Table 5. Effect of insulin administration and confounding variables on medication adherence

Model	Confounding Variables	Category	p-value	OR	95% Confidence Interval (Min-Max)
Crude	Antidiabetic	Insulin Non-Insulin	0.084	0.162	0.021 - 1.279
Multivariate	Antidiabetic	Insulin Non-Insulin	0.054	0.113	0.012 - 1.041
	Age	35 - 44 years old	0.628		
		45 - 54 years old	0.999	0.000	0.000
		55 - 64 years old	0.999	0.000	0.000
		65 - 74 years old	0.999	0.000	0.000
		75+	1.000	1.573	0.000
	Gender	Man Woman	0.783	0.821	0.202 - 3.335
	Body mass index	Normal Abnormal	0.045	4.345	1.031 - 18.311
	Antidiabetic changes	Yes Not	0.020	5.431	1.305 - 22.595
	Number of comorbidities	≤ 3 > 3	0.201	0.374	0.083 - 1.690
	Peripheral nerve disorders	Yes Not	0.305	2.104	0.508 - 8.719
	Total amount of medicine	≤ 10 > 10	0.208	5.008	0.408 - 61.445
	Consumption of herbs	Yes Not	0.075	3.739	0.877 - 15.942
Adjusted	Antidiabetic	Insulin Non-Insulin	0.053	0.123	0.015 - 1.024
	Antidiabetic changes	Yes Not	0.020	4.171	1.254 - 13.878
	Total amount of medicine	≤ 10 > 10	0.487	2.131	0.253 - 17.960

This study shows that respondents' characteristics (age, gender, education, occupation, and body mass index) did not impact medication adherence statistically significantly. The results shown on the variables of age and sex are following a study conducted by Sham *et al*. in Pakistan which showed that age and gender were not significantly associated with patient adherence (Shams *et al*., 2016). Regarding education, medication adherence appears to improve as the respondent's education level increases. This is in line with the review of articles and meta-analyses by Al Shaikh *et al*. (2016) that education improves patient adherence.

Bivariate analysis showed that respondents with a stroke history showed lower adherence than patients without a stroke history. The proportion of stroke respondents adherent was 7.2%, while the non-stroke respondents were 8.7%. This is in accordance with a study conducted by Bauler *et al.* (2014) which stated that adherence to medication after a stroke was influenced by various barriers and facilitators. On the other hand, respondents with peripheral nerve disorders show a higher proportion of adherence. This contrasts with previous studies showing that peripheral neuropathy was the most patient-reported complication affecting adherence (Zhang *et al*., 2021). Patients with more than three comorbidities showed a higher proportion of adherence. This result contradicts the research conducted by Saadat *et al*., which states that the more comorbidities, the lower the patient's adherence (Saadat *et al*., 2015). This is due to increased patient comorbidities followed by increased visits to different specialists, so patients' adherence is better (Capoccia *et al*., 2016). However, the effect of these three variables on medication adherence was not statistically significant. This is in line with research on the impact of comorbidities on adherence to antihypertensive use (Saadat *et al.*, 2015).

Respondents who experienced antidiabetic changes showed higher adherence than those who did not experience antidiabetic changes (12.3% vs 4.5%). The antidiabetic change in the adherent respondents was the addition of antidiabetics, which improved the patient's HbA1c.

Based on the results of measuring adherence using MRA, ARMS, and HbA1c values changes, there were 13 respondents (7.4%) who were adherent, namely one respondent (1.8%) in the insulin group and 12 respondents (10.1%) in the non-insulin group. Based on the results of multivariate analysis, insulin administration affected patient adherence in using the antidiabetics by 0.123 times (95% CI: 0.015 - 1.024) or patients who received insulin had 87.7% lower adherence than patients who did not receive insulin after being controlled by antidiabetic changes and amount of the total drug used by the patient at the time of data collection from the medical records.

Based on the three measuring instruments, only 13 out of 175 respondents were adherent. Therefore, further research is needed to analyses variables other than insulin administration that cause low medication adherence in diabetes mellitus patients with neurological complications.

The limitations of this study include the sample of only 175 respondents with patients using insulin only 56 respondents, the sampling location was only one hospital, and using the indirect adherence measurement method. In the MRA method, the patient is assumed to use the drug every day since the antidiabetic prescription was received until the next visit. Another limitation is that this study has not analysed other variables that may affect the HbA1c value.

CONCLUSION

The results showed that the adherence of diabetes mellitus patients was low, especially in patients who used insulin. The administration of insulin significantly affects patient adherence in diabetes mellitus patients with neurological complications, which is influenced by the confounding variable of antidiabetic changes and the total number of medicines used by the patients. The results of this study are expected to help hospital decision-makers and health care providers when initiating insulin administration and improve medication adherence in patients using insulin.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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