The Association between Adherence to Oral Antihyperglycemic Agent and HbA1c Level

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ABSTRACT

Adherence to taking medication is essential for patients with chronic diseases such as Type 2 Diabetes Mellitus (T2DM). There have been many studies about the association between medication adherence and HbA1c levels, but few have used Adherence Refills and Medications Scale (ARMS) questionnaire and Proportion of Days Covered (PDC) method to measure adherence in Indonesian population. The aim of this study were to assess the association of medication adherence to HbA1c levels and compare two methods of adherence measurements. This research was conducted at Pasar Minggu Public Health Center, Jakarta using a cross-sectional design. The adherence assessment was conducted using a validated Indonesian version of the ARMS questionnaire and compared to the pharmacy refill adherence method using the PDC calculation. One hundred twenty-seven T2DM patients (75.6% female) with mean age of 58.69 years were recruited. The proportion of adhere patients as measured by ARMS was only 39.4% (50/127). Meanwhile, the proportion of adhere patients as measured by PDC was 77.2% (98/127). Adherence by both measurement showed significant associations with HbA1c <7% (ARMS, OR 4.000 (95% CI 1.705 – 9.386), p = 0.002; PDC, OR 5.674 (95% CI 1.266 – 25.438), p = 0.024). After controlled by covariates, the result remained significant (ARMS, aOR 4.281 (95% CI 1.785 – 10.267, p = 0.001; PDC, aOR 5.83 (95% CI 1.287 – 26.405), p = 0.022). Adherence and HbA1c levels was significantly associated even after controlling covariates. ARMS and PDC generated different proportions of adhere patients and may indicate the need of combining the two methods in measuring adherence.

Keywords: *diabetes mellitus; medication adherence; adherence refills and medications scale; proportion of days covered; HbA1c*

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INTRODUCTION

Around 537 million adults aged 20-79 years are living with diabetes mellitus (DM). Type 2 Diabetes Mellitus (T2DM) sufferers have the highest rate (more than 90%) compared to other types of DM worldwide (International Diabetes Federation, 2021). T2DM is a non-communicable disease that requires special attention because it causes death and severe complications such as chronic heart disease, cerebrovascular disease, peripheral vascular disease, retinopathy, nephropathy and neuropathy (Nanayakkara et al., 2021).

The effectiveness of the therapeutic regimen highly depends on medication adherence (Anghel et al., 2019). There have been many research investigating the effect of adherence to clinical outcomes. Poor adherence has serious consequences such as failure of therapy (Al-Hassany et al., 2019) and contribute to complications and even death (Lomper et al., 2018). Besides that, non-adherent patients also require a higher number of health care compared to adherent patients (Ye et al., 2022). In the case of DM, adherence to taking medication helps patients with DM to achieve the expected target blood sugar levels (Nichols et al., 2016). Therefore, it is necessary to carry out routine adherence assessments in the DM population.

Generally, the widely used biological marker in DM is HbA1c (Gupta et al., 2017). HbA1c provides a reliable measure of chronic glycemia and correlates with long-term risk of diabetic complications (Sherwani et al., 2016). Therefore, HbA1c is an important indicator of long-term glycemic control reflecting the cumulative glycemic history in the previous two to three months (Sherwani et al., 2016). HbA1c as a clinical outcome can be reflective to a real condition of patients' adherence. Many research demonstrated that the decrease in HbA1c values is in line with high patient adherence to treatment (Krapek et al., 2004; Doggrell & Warot, 2014; Nichols et al., 2016; Patel et al., 2019).

An accurate assessment of medication adherence is necessary for effective and efficient treatment planning. It is to ensure that changes in health outcomes are linked to recommended regimens. However, there is no

adherence measurement tool that is considered the most ideal for T2DM patients. One measurement approach is to ask patients to subjectively assess their adherence behavior which is usually carried out with the help of a questionnaire (World Health Organization, 2003), e.g. Adherence Refill and Medication Scale (ARMS). Other options are assessing adherence through pharmacy records or monitoring electronic drug administration, e.g. Proportion of Days Covered (PDC) (Anghel et al., 2019). ARMS that has been validated and is a good instrument to measure patients' adherence, especially in chronic diseases (Kripalani et al., 2009). Although there have been many studies regarding the association between medication adherence and HbA1c levels, few have used the ARMS instrument as a tool to measure adherence, particularly in the Indonesian population. ARMS is considered newer instrument compare to other tools like MPR, MMAS, PDC, etc (Morisky et al., 1986; Avorn et al., 1998; Benner et al., 2002; Kripalani et al., 2009). It has been translated into Bahasa Indonesia and has a good validity and reliability (Cahyadi et al., 2015). Therefore, this study aimed to assess the association of adherence using ARMS questionnaire with HbA1c levels. To confirm the result, the study also compared the use of ARMS with PDC in measuring adherence. The study is expected to ensure the impact of adherence and offer good alternative in measuring adherence.

METHODS

Design
This research was an observational study with a cross-sectional design. After obtaining permission from the DKI Jakarta Provincial Health Office and the South Jakarta Health Sub-department as well as approval from the Ethics Committee of the Faculty of Medicine, University of Indonesia, data were collected at the Non-Communicable Diseases Polyclinic, Pasar Minggu Jakarta Primary Health Center. The ethical approval number is KET-875/UN2.F1/ETIK/PPM.00.02/2021

Subjects and Data Collection
A total of 127 subjects were involved in this study. Sample size was calculated using formula as follows (Ogston et al., 1991):

$$\text{Sample size} = \frac{\left(z_{1-\alpha/2}\sqrt{2\overline{P}(1-\overline{P})} + z_{1-\beta}\sqrt{P_1(1-P_1) + P_2(1-P_2)}\right)^2}{(P_1 - P_2)^2} \quad (1)$$

Description:

$Z_{1-\alpha/2}$ = The standard normal deviation (5% for type 1 error (p<0.05) is 1.96)

$Z_{1-\beta}$ = The standard normal deviation for 80% power, (20% for type 2 error is 0.842)

P   = (P1+P2)/2

P1   = Proportion of patients with controlled blood glucose in non-adherent group

P2   = Proportion of patients with controlled blood glucose in adherent group

With a P1 value of 0.169 and a P2 value of 0.467 (Hammad et al., 2017), the minimum sample size was 38 subjects per group.

T2DM patients aged ≥ 36 years and able to communicate well were included this study. This study also required patients to be able to see, hear, speak and be able to read, and write to participate in this research. Patients who had been diagnosed with mental disorders, dementia, and had psychiatric disorders such as depression based on the Beck Depression Inventory-II (BDI-II) were excluded.

Patients who met the inclusion criteria above would fill out the BDI-II Questionnaire to determine the patient's depression status. The BDI-II questionnaire consists of 21 groups of statements in which each group has 4 options with a value of 0 to 3 points. Research subjects were asked to choose the statement that best describes their feelings during the last 2 weeks. The cut-off value used was 17; subjects that had score below 17 were considered normal or no depression (Ginting et al., 2013). Depression was excluded because it had a high prevalence in T2DM patients (76%) (Abd Elaaty et al., 2019) and is known to be associated with low medication adherence (Grenard et al., 2011; Lunghi et al., 2017). In addition, depressed patients tend to have difficulty communicating with healthcare providers. In fact, they often feel dissatisfied with the service they receive because of the communication problem (Piette et al., 2004). Patients who passed the BDI-II screening were interviewed regarding their demographic data and clinical condition. After that, the patient's cognitive function was assessed with the Indonesian version of the Montreal Cognitive Assessment (MoCA-Ina) questionnaire (Husein et al., 2010) with a cutoff value of ≥26 to determine the patient has a normal cognitive function (Nasreddine et al., 2005; Husein et al., 2010).

The study used HbA1c as the clinical outcome. Analysis of peripheral blood samples to measure HbA1c levels was directly carried out at Pasar Minggu Public Health Center using the Alere Afinion™ tool. The HbA1c value as a clinical outcome determines glycemic control status. Blood glucose was considered controlled if the HbA1c value was <7 (American Diabetes Association, 2014; Abd Elaaty et al., 2019).

Adherence Measurement
The tools that were used to assess patient adherence were ARMS questionnaire and PDC calculation. The validated English ARMS questionnaire was translated

into Bahasa Indonesia and had been tested in diabetes population in three primary healthcare facilities. (Cahyadi et al., 2015). Questionnaire validity and reliability was considered good considering a correlation value of >0.3 and Cronbach's alpha of 0.815 (Cahyadi et al., 2015). The Indonesian version of the ARMS Questionnaire consisted of 11 questions, 8 questions about correct medication behavior, and 3 questions about timely refilling of prescription drugs. Each question has 4 answer choices (Likert scale) namely "never", "sometimes", "often", or "every time", which are scored from 1 to 4. For the last question, the score is reversed to make it consistent with other questions. The scores for each question item are summed to produce an overall adherence score. i.e. between 11 to 44. ARMS scores over 11 are considered non-adhere (Cahyadi et al., 2015; Kripalani et al., 2009).

To calculate the PDC value, data on patient drug intake for the last 6 months through the e-puskesmas system (electronic medical record) were obtained. PDC is the percentage of the sum of days covered in a time frame divided by number of days in time frame (Anghel et al., 2019), which in this case the time frame was 180 days (6 months). 'Days covered' were days when patients have the prescribed daily dose of medicine according to their refill schedule. When patients were late refilling their medicines, the days from their last pill to their next refill were not included in the sum of days covered. PDC has been widely used to measure adherence with some of the earliest studies were conducted in late 90s (Avorn et al., 1998; Benner et al., 2002). Patients were considered adhered if the PDC value was 80% (Anghel et al., 2019).

Data Analysis

Association of adherence based on ARMS scores with the HbA1c level was assessed. Measurement with PDC was also performed to compare and confirm the result. Univariate analysis was used to describe patients' characteristics. In determining association between adherence measurement and HbA1c values, chi-square test was performed. P-value <0.05 was considered significant. Logistic regression was conducted to identify other factors that affect HbA1c level. Variables that had p<0.25 in bivariate analysis and/or substantially affected HbA1c were included in logistic regression. Comparison of two adherence measurements were conducted by analysing the proportion of adhere and non-adhere patients. Data was expressed in proportion (n,%) for categorical variables and in mean ± SD or median (min-max) for numeric variables.

RESULTS

A total of 127 T2DM patients participated in this research. The majority of research subjects were women with a mean age of 58 years. The proportion of patients with an education level of more than 12 years and less than 12 years was almost equal (52.8% and 47.2%, respectively). Many of research subjects were overweight to obese (63%) with a median value of 26.30 (min-max 18.36 – 42.58). More than half of the patients took the metformin-glimepiride combination (52%) and took more than 4 tablets a day (70.9%). Patients suffering from DM for more than 5 years were 46.5%. The majority of patients had comorbid of hypertension (63%) and dyslipidemia (63.8%). One patient might have two comorbids of hypertension as well as dyslipidemia. Characteristics of patients as research subjects are shown in Table 1.

Table 1. Characteristics of research subjects

Variable	Total (N=127) n (%)
Sex	
Male	31 (24.4)
Female	96 (75.6)
Age	
Mean ± SD	58.69 ± 8.08
≤65 years	95 (74.8)
>65 years	32 (25.2)
Education level	
>12 years	67 (52.8)
≤12 years	60 (47.2)
Body Mass Index (BMI)	
Median (min – max)	26.30 (18.36 – 42.58)
Thin – Normal	47 (37.0)
Overweight – Obesity	80 (63.0)
Duration of DM	
≤5 years	68 (53.5)
>5 years	59 (46.5)
Number of pills prescribed	
1-4	37 (29.1)
>4	90 (70.9)
OAH agent	
Metformin	50 (39.4)
Metformin-Glimepiride	66 (52.0)
Others	11 (8.7)
Cognitive function	
Declined	78 (61.4)
Normal	49 (38.6)
Comorbidity	
Hypertension	80 (63.0)
Dyslipidemia	81 (63.8)

Abbreviations: DM, Diabetes Mellitus; OAH, Oral Antihyperglycemic; BMI, Body Mass Index

Table 2. Proportion of adherence and nonadherence based on ARMS and PDC

Adherence measurement tools	Nonadhere n (%)	Adhere n (%)
ARMS	77 (60.6)	50 (39.4)
PDC	29 (22.8)	98 (77.2)

Abbreviations: ARMS, Adherence to Refills and Medication Scale; PDC, Proportion of Days Covered

In Table 2, it can be seen that the majority of adhere patients were 39.4% and 77.2% for ARMS and PDC respectively. The proportion of adhered patients with HbA1c<7 were different between methods, which were 40.0% and 29.6% for ARMS and PDC respectively. Medication adherence measured by ARMS questionnaire was associated with HbA1c levels with OR 4.000 (95% CI 1.705 – 9.386), p-value 0.002, as well as PDC with OR 5.674 (95% CI 1.266 – 25.438), p-value 0.024 (Table 3). To observe the effect of medication adherence and confounding variables on HbA1c levels, a multivariate analysis was performed using logistic regression. Bivariate analysis was conducted to select variables that had p<0.25 which were gender, age, education level, type of oral antihyperglycemic drug, and comorbid hypertension (Table 4). BMI was still included in the multivariate analysis because it substantially had an effect on HbA1c. The last multivariate model was chosen based on the smallest precision value among all controlled covariates. Table 5 shows the last model of multivariate; the effect of adherence to HbA1c remained significant after controlling for hypertension (Table 5).

DISCUSSION

This research found two important things. First, there was significant association between adherence and HbA1c levels even after controlling covariates. Second, ARMS and PDC produce different proportions of adhere and nonadhere patients yet both significantly associated with HbA1c levels. The significant association between

adherence and HbA1c is important to ensure effect of oral antihyperglycemic agents to clinical outcome. Meanwhile, the contradictive proportion that was created by two measurement methods indicate that one tool may not be accurate enough to measure adherence.

This study is in line with study in Qatar showing that non-adhere patients based on ARMS-D had significantly higher HbA1c (Jaam et al., 2017). Checking for medication adherence is an important thing to do in healthcare facilities, one of which is because poor adherence can make patients receive excessive therapy from doctors (Yap et al., 2016). For example, when a patient does not take medication appropriately, the level of the drug in his/her body becomes below the therapeutic range. Hence, the drug is not able to lower blood glucose optimally. This excess blood glucose makes glycemic control less than optimal. When the patient comes for a check-up, the uncontrolled blood glucose level prompts the doctor to increase the dose titration (Yap et al., 2016). This unnecessary increase in dose may increase the risk of hypoglycemia, especially if the patient is taking oral antihyperglycemic agents of the sulfonylurea class (Sonmez et al., 2020) and in the long term, can accelerate disease progression and complications (Bazargan et al., 2017; Hammad et al., 2017).

Multivariate analysis indicated that hypertension may decrease HbA1c levels. The type of comorbids can in fact influence HbA1c levels (Luijks et al., 2015). However, in contrast to our study, hypertension is supposed to increase HbA1c levels (Mehta et al., 2011). This conflicting results may be because some physicians might give special attention to those with comorbids when planning a therapy so patients achieve better clinical outcome. It is supported by study in Croatia stated that the negative association of the number of comorbidities and HbA1c may be due to physician inertia in the treatment of T2DM strictly according to guidelines (Lang & Marković, 2016).

Table 3. Association between medication adherence with HbA1c <7% level

MA Category	HbA1c level		p-value	OR (95% CI)
	<7%	≥7%		
	N (%)	N (%)		
ARMS				
Nonadhere (≥12)	11 (14.3)	66 (85.7)		Ref
Adhere (<12)	20 (40.0)	30 (60.0)	0.002*	4.000 (1.705 – 9.386)
PDC				
Nonadhere (<80%)	2 (6.9)	27 (93.1)		Ref
Adhere (≥80%)	29 (29.6)	69 (70.4)	0.024*	5.674 (1.266 – 25.438)

Abbreviations: *significant, p-value<0,05; Ref, Reference; ARMS, Adherence to Refills and Medications Scale; MA, Medication Adherence; PDC, Proportion Days Covered

Table 4. The effect of others independent variable on HbA1c level

Variable	N=127			p-value
	HbA1c ≥7 n (%)	HbA1c <7 n (%)	Total n (%)	
Sex				
Male	19 (19.8)	12 (38.7)	31 (24.4)	0.059
Female	77 (80.2)	19 (61.3)	96 (75.6)	
Age				
Mean ± SD	57.76 ± 7.74	61.54 ± 8.56	58.69 ± 8.08	0.033*
≤65 years	75 (78.1)	20 (64.5)	95 (74.8)	0.201
>65 years	21 (21.9)	11 (35.5)	32 (25.2)	
Education level				
>12 years	46 (47.9)	21 (67.7)	67 (52.8)	0.086
≤12 years	50 (52.1)	10 (32.3)	60 (47.2)	
Body Mass Index (BMI)				
Median (min – max)	26.32 (20.20 – 42.58)	26.14 (18.36 – 36.03)	26.30 (18.36 – 42.58)	0.639
Thin – Normal	35 (36.5)	12 (38.7)	47 (37.0)	0.991
Overweight – Obesity	61 (63.5)	19 (61.3)	80 (63.0)	
Duration of DM				
≤5 years	51 (53.1)	17 (54.8)	68 (53.5)	1.000
>5 years	45 (46.9)	14 (45.2)	59 (46.5)	
Number of pills prescribed				
1-4	27 (28.1)	10 (32.3)	37 (29.1)	0.831
>4	69 (71.9)	21 (67.7)	90 (70.9)	
OAH agent				
Metformin	33 (34.4)	17 (54.8)	50 (39.4)	
Metformin-Glimepiride	57 (59.4)	9 (29.0)	66 (52.0)	0.010*
Others	6 (6.3)	5 (16.1)	11 (8.7)	
Cognitive function				
Declined	56 (58.3)	22 (71.0)	78 (61.4)	0.296
Normal	40 (41.7)	9 (29.0)	49 (38.6)	
Comorbidity				
Hypertension	56 (58.3)	24 (77.4)	80 (63.0)	0.089
Dyslipidemia	64 (77.8)	17 (22.2)	81 (63.8)	0.329

Abbreviations: *significant, p-value<0,05; Ref, Reference; DM, Diabetes Mellitus; OAH, Oral Antihyperglycemic; BMI, Body Mass Index

When medication adherence was measured by the ARMS questionnaire, the majority of research subjects were non-adhere (77/127). Meanwhile, when medication adherence was measured by the PDC calculation, the majority of research subjects were adhere (98/127). This discrepancies between methods also happened in some studies (Liu et al., 2001; Llabre et al., 2006; Pandey et al., 2015; Cain et al., 2020). Evidence showed that high ARMS scores seem to identify true non-adhere patients (Okumura et al., 2016). Therefore, the number of non-adhere patients was more than PDC since ARMS is more sensitive to non-adhere patients. Regardless of the difference, both adherence that was determined by ARMS and PDC gave significant association to lower HbA1c levels with odds ratio of 4 and 5.674, respectively. The big difference of proportion between HbA1c <7% and ≥7% in non-adhere group, both using ARMS and PDC, may be the explanation behind this result.

Generally, each method has advantages and disadvantages. The self-report method with ARMS questionnaire can provide additional information about

Table 5. Factor that influence HbA1c <7%

Model	Variables	p-value	OR	95% CI
ARMS				
Crude	Adherence			
	Nonadhere		Ref	
	Adhere	0.001	4.000	1.705-9.386
Adjusted	Adherence			
	Nonadhere		Ref	
	Adhere	0.001	4.281	1.785-10.267
	Hypertension			
	No		Ref	
	Yes	0.044	2.735	1.027-7.278
PDC				
Crude	Adherence			
	Nonadhere		Ref	
	Adhere	0.001	4.000	1.705-9.386
Adjusted	Adherence			
	Nonadhere		Ref	
	Adhere	0.022	5.83	1.287-26.405
	Hypertension			
	No		Ref	
	Yes	0.057	2.524	0.972-6.553

Abbreviations: Ref, Reference; ARMS, Adherence to Refills and Medications Scale; MA, Medication Adherence; PDC, Proportion Days Covered

attitudes, habits, and intentions (Anghel et al., 2019). However, it is affected by memory that could generate biases so reducing accuracy and validity (Al-Hassany et al., 2019). On the other side, PDC calculation is an indirect method that requires a centralized electronic system. This method requires consistency between the prescription written in the electronic system and the drug dispensed to the patient (Anghel et al., 2019). This method is more objective than the self-report method because the patient is not aware that he/she is being assessed. The assumption that the refilled medication will be ingested by the patient is indeed one of the weaknesses of PDC. Thus, this can create an overestimation of adherence outcomes (Al-Hassany et al., 2019; Anghel et al., 2019) as occurred in this research. This study demonstrated that ARMS gave lower number of adhere patients than PDC (50 vs. 98 patients). This data was supported by the fact that the proportion of adhere patients based on the PDC value was 77.2% (98/127). However, 70.4% (69/98) of these patients had a level of HbA1c ≥7. This might be because the patient never actually swallowed the pill for various reasons such as forgetting (Cain et al., 2020) or deliberately not willing to take the medicine for example, worried about side effects (Kvarnström et al., 2021).

Despite the potential inaccuracy of PDC, this study used PDC to confirm the ARMS-based adherence association to HbA1c level since PDC was older and has been widely used (Avorn et al., 1998; Benner et al., 2002). This study found that fourty two out of fifty adhere patients based on ARMS were also considered adhere based on PDC. The answers from the remaining eight patients may be affected by response biases or they may bought their medications in pharmacies outside the primary health provider. However, the overlap adherence classification in the 42 patients may indicate that ARMS can potentially be a good adherence measurement, not to mention the significant association between adherence and HbA1c levels. In addition, the ARMS questionnaire was significantly correlated with the Morisky adherence scale (Spearman's rho = -0.651, p < 0.01) (Kripalani et al., 2009). Unlike the Morisky scale which only measures adherence in refilling, the ARMS questionnaire has 2 subscales that evaluate taking the drug and drug refilling adherence behavior. This is certainly an advantage of this questionnaire because non-adherence to taking medication and non-adherence to refill drugs are different problems. Hence, ARMS can be a good alternative for measuring adherence.

The decision about which method to use should be based on considerations of the route of drug administration, available resources, setting, and objectives of the assessment (Nichols et al., 2016). For example, PDC will be suitable when patients are hard to reach. In contrast, ARMS will be convenient when pharmacy records are not reliable. However, the use of two methods might be better. PDC can confirm patients response regarding refilling adherence in ARMS questions because refilling records are provided in a system. Combining two or more methods in measuring adherence to taking medication is highly recommended by being able to cover each other's shortcomings and obtain results that are close to the actual condition (Anghel et al., 2019; Al-Hassany et al., 2019).

Evidence of adherence association to HbA1c levels is expected to encourage health professionals to eagerly counsel patients about the importance of adherence. This result also warn health professionals and patients that nonadherence prevalence are still common that it needs special attention. In addition, the choice of adherence measurement is also a concern to this study. However, since this study only observed proportion when comparing adherence measurement methods, further research is required to analyze the validaty comparison between variaty of adherence measurement methods and their association with HbA1c levels in T2DM patients.

LIMITATIONS

This research has some limitations. It was conducted only at one health center in one city. In addition, the research uses a cross-sectional study design and the sample size is still relatively small, thus limiting the statistical power. Bigger sample size and cohort studies that involve follow up measurement of HbA1c are necessary to confirm the present results.

CONCLUSION

Significant association was found between medication adherence and HbA1c levels even after controlling covariates. Proportion difference of adhere patients using ARMS and PDC may indicate that one method may not be accurate enough to measure adherence.

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CONFLICT OF INTEREST

Authors declared no conflict of interest.

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