MMAS-8 SCORE ASSESSMENT OF THERAPY ADHERENCE TO GLYCEMIC CONTROL OF PATIENTS WITH TYPE 2 DIABETES MELLITUS, TANJUNG PURWOKERTO, JAVA, INDONESIA (OCTOBER 2018)

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Abstract. Diabetes mellitus (DM) type 2, a metabolic disease caused by insulin resistance, remains a global health problem. Glycated hemoglobin (HbA1c) level is used to evaluate diabetes therapy, and a variety of factors influence HbA1c level, one of which is therapy adherence. A cross-sectional study of type 2 diabetes mellitus (DM2) patients (n = 92) at the Primary Health Facility, Tanjung Purwokerto, Indonesia was conducted to evaluate HbA1c levels and therapy adherence using an Indonesian language 8-item Morisky Medication Adherence Scale (MMAS-8) questionnaire. No single socio-demographic characteristic, (certain) co-morbidity or vitamins/iron supplementation was significantly associated with either of the two parameters. Correlations were observed between treatment adherence and age (r = 0.221, p-value = 0.034), and between therapy adherence and HbA1c levels (r = -0.221, p-value = 0.035). Construction of a receiver operating characteristic curve demonstrated that MMAS-8 score was not a reliable predictor of therapy adherence (area under curve = 0.58, 95% confidence interval (CI): 0.46-0.70), using HbA1c level <7% as the reference standard. In conclusion, reliance on MMAS system as the sole predictor of therapy adherence in DM2 patients should be considered with caution.

Keywords: diabetes therapy adherence, HbA1c level, MMAS-8 questionnaire, type 2 diabetes mellitus

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INTRODUCTION

Diabetes mellitus type 2 (DM2) is a metabolic disease caused by insulin resistance and by pancreatic beta cells' failure to produce sufficient insulin (Indonesian Society of Endocrinology, 2015). Diabetes is a global health problem, with increasing prevalence especially in developing and low-income countries (WHO, 2020). According to the Indonesian Basic Health Research (2019), prevalence of DM2 in Indonesia in 2019 is 1.5% and mortality from DM ranks sixth in the world (WHO, 2016a).

This disease significantly affects human resource quality and impacts health cost (WHO, 2016b). Thus, it is necessary not only to treat but also evaluate the treatment methods for their appropriateness and efficacy. One way to assess and evaluate DM therapy success is to measure blood HbA1c level, a marker of chronic glycemia describing average blood glucose level during the 2-3 months (The Indonesian Association of Endocrinologists, 2015; WHO, 2016b).

Because diabetes is associated with comorbidities and lifestyle, Sherwani *et al* (2016) recommend keeping HbA1c level <7%. Wulandari *et al* (2020) at Sanglah General Hospital, Denpasar, Bali, Indonesia, noted only 36% of DM2 patients are able of maintaining HbA1c below this recommended level. Controlling glycemic level is also a problem in other Asian countries. For instance, in Malaysia, 24% of DM2 subjects managed to maintain HbA1c level ≤7% (Hussein *et al*, 2015); and in Thailand, 35.7% have HbA1c level <7% (Reutrakul and Deerochanawong, 2016); but in China, 47.7% reach HbA1c level <7% (<53 mM) (Ma, 2018). Therapy adherence is one of the factors that influence HbA1c levels, but studies on the relationship between DM2 therapeutic adherence and HbA1c levels have produced inconsistent results. A review by Krapek *et al* (2004) reported patients who strictly adhere to DM2 therapy have lower levels of HbA1c. However, Jafarian-Amirkhizi *et al* (2018) in Iran noted no significant relationship between HbA1c levels and DM2 therapy adherence.

A Morisky Medication Adherence Scale (MMAS), a 4- (MMAS-4) or 8-item (MMAS-8) questionnaire, has been devised to determine non-adherence to a variety of medication (https://morisky.org/). In Indonesia, MMAS-8 in the Indonesian language was developed to assess DM2 therapy adherence (Rosyida *et al*, 2015). In Korea, MMAS-8 for DM2 therapy adherence has a sensitivity of 74.1% and a specificity of 38.3% (Lee *et al*, 2013), while MMAS-8 in Malay and Arabic language shows sensitivity and specificity of 77.61% and 45.37% and of 63.9% and 82.3% respectively (Al-Qazaz *et al*, 2010; Ashur *et al*, 2015).

In Indonesia, HbA1c test is relatively expensive and so not all patients can afford this test, except those who have medical insurance to cover the cost. Thus, it is necessary to determine whether determination of DM2 therapy adherence using the MMAS-8

questionnaire can accurately assess glycemic control. Here, MMAS-8 questionnaire was applied to a cohort of DM2 patients attending a regular visit at the Primary Health Facility, Tanjung Purwokerto, central Java, Indonesia to determine the association of MMAS-8 scores with HbA1c levels. The findings should assist in determining the usefulness of MMAS-8 in assessing adherence to DM2 therapy without recourse to measuring HbA1c level in this particular population.

MATERIALS AND METHODS

Study method and recruitment of participants

A cross-sectional study was designed to assess the association of DM2 therapeutic adherence using the MMAS-8 questionnaire with glycemic control based on HbA1c level. Participants were recruited among DM2 patients (approximately 300-350) attending monthly visits at the Primary Health Facility, Tanjung Purwokerto, central Java, Indonesia. DM2 patients (n = 92) diagnosed using a PERKENI Consensus criteria (Indonesian Society of Endocrinology, 2015) were interviewed during October 2018. All patients were prescribed oral antidiabetics, none requiring insulin therapy.

The study protocol was approved by Ethics Committee on Human Research, Faculty of Medicine, Jenderal Soedirman University (approval no. 1145/UN23.07.5.1/PN.1/2018). Prior written permission was obtained from each participating patient.

MMAS-8 questionnaire

An Indonesian language MMAS-8 questionnaire form, whose reliability and validity of assessing MD2 therapy adherence were previously established (Rosyida *et al*, 2015), consisted of eight questions, answers to which were recorded by a member of the research team. A positive answer received a score of 1 (one) and negative answer 0 (zero). MMAS-8 score classification is as follows: 8 = high adherence, 6-7 = moderate adherence, and ≤5 = low adherence (Rosyida *et al*, 2015). Demographic data of the participants were obtained at the same interview.

Laboratory procedures

HbA1c level was measured using a venous blood sample (3 ml) taken from antecubital vein at the Laboratory of Medico Labora Purwokerto, Indonesia employing (NycoCard Reader II) (Alere™, Oslo, Norway), with HbA1c level of <7% (mmol/mol) indicating adequate control of blood sugar level (Sherwani *et al*, 2016).

Statistical analysis

Data were analyzed by univariate and bivariate statistics using a Mann-Whitney and Kruskal-Wallis tests. Correlation between therapy adherence and HbA1c level was determined by a Spearman test. A p-value <0.05 is considered statistically significant. A receiver operating characteristic (ROC) curve was also constructed to determine the potential of MMAS-8 score in assessing therapy adherence (Dahlan, 2017).

RESULTS

Participants were patients with type 2 diabetes mellitus (n = 92) attending the Primary Health Facility Tanjung Purwokerto, 84 (91%) ≥50 years of age, 47 (51%) females, 71 (77%) having attended elementary or middle school, 45 (49%) with DM2 ≤4 years in duration, 65 (71%) having received treatment ≥3 years, 58 (63%) with no family history with DM2, 78 (85%) accepting their DM2 status, and almost all (83%) not ashamed to admit having this ailment (Table 1). Almost all patients (98%) did not consume alcohol, the majority (74%) participated in mild-moderate physical exercise, nearly all (97%) had no history of kidney disease, liver disease or gastrointestinal bleeding, and 4% were being prescribed H2 antagonists or trimethoprim. In addition to diabetes medication, 2 and 10% were taking iron and vitamin C and/or E supplementation respectively.

MMAS-8 scores revealed 59 (64%) patients with poor therapy adherence, reflected by 52 (56%) patients with HbA1c level ≥7%, but no single parameter evaluated is significantly correlated with therapy adherence or HbA1c level (Table 1). However, increasing age was positively associated therapy adherence (MMAS-8 score) (r = 0.221, p-value = 0.034), and elevated HbA1c level was associated with poor therapy adherence (r = -0.221, p-value = 0.035). A ROC curve revealed MMAS-8 score was moderately useful in assessing therapy adherence (area under curve = 0.58, 95% CI: 0.46-0.70, where 0.50 indicates uninformative classifier) (Fig 1).

DISCUSSION

In the study, over half of the study participating DM2 subjects failed to maintain HbA1c level <7% and a similar proportion obtained MMAS-8 scores in moderate to low therapy adherence status. No single patient's characteristics and psychological conditions is significantly associated with these observations, but increase in age is associated with better therapy adherence. ROC curve demonstrated a moderate ability of MMAS-8 score as diagnostic parameter of therapy adherence.

A majority of DM2 patients not only in central Java (this study) but in Banjarmasin (Hertanto and Mulyani, 2017) and Banda Aceh (Ramadhan and Marissa, 2015) are unable to maintain their HbA1c level below the required level. Mellergård *et al* (2020) in their study in Skåne University Hospital, Sweden, also reported no difference among HbA1c levels and socio-demographic factors, such as marital status, gender, age, education level, duration of diabetes, and type of drug prescribed. Conducting an observation in six study sites in USA, Krapek *et al* (2004) applied multivariate test and found good therapy adherence, as measured by MMAS scores, was associated with low HbA1c levels, while in Yogyakarta, Chaliks and Andayani (2012) demonstrated an inverse relationship between therapy adherence and HbA1c levels. In our study, MMAS-8 scores were negatively related with HbA1c levels (r = -0.221,

Table 1

Demographic profile, MMAS-8 score and HbA1C level of participants (n = 92) with type 2 diabetes mellitus (DM2) attending Primary Health Facility, Tanjung Purwokerto, central Java, Indonesia (October 2018)

Parameter	MMAS-8 score				HbA1c level			
	8[a] Number (%)	≤5[b] Number (%)	Median (Min -Max) of MMAS-8 score	p-value*	<7%[a] Number (%)	≥7%[b] Number (%)	Median (Min -Max) of HbA1c level	p-value*
Gender								
Male	15 (16)	30 (33)	5.0 (2-7)	0.483[c]	20 (22)	25 (27)	7.3 (5.4-12.1)	0.972[c]
Female	18 (20)	29 (31)	5.0 (0-8)		20 (22)	27 (29)	7.2 (5.1-14.0)	
Age								
<50 years old	2 (2)	6 (6)	4.0 (0-8)	0.531[c]	4 (4)	4 (4)	7.6 (6.1-11.6)	0.637[c]
≥50 years old	31 (34)	53 (58)	5.0 (0-8)		36 (39)	48 (52)	7.3 (5.1-14.0)	
Education level								
Elementary school	13 (14)	22 (24)	5.0 (2-7)	0.968[d]	14 (15)	21 (23)	7.3 (5.1-12.1)	0.665[d]
Middle school	14 (15)	22 (24)	5.0 (0-8)		16 (17)	20 (22)	7.6 (5.9-14.0)	
High school	6 (7)	15 (16)	5.0 (2-7)		10 (11)	11 (12)	7.1 (5.4-11.3)	
Family history of DM2								
Yes	12 (13)	22 (24)	5.0 (2-7)	0.850[c]	13 (14)	21 (23)	7.5 (5.6 -12.1)	0.156[c]
No	21 (23)	37 (40)	5.0 (0-8)		27 (29)	31 (34)	7.1 (5.1-14.0)	

Table 1 (cont)

Parameter	MMAS-8 score				HbA1c level			
	8[a] Number (%)	≤5[b] Number (%)	Median (Min -Max) of MMAS-8 score	*p*-value*	<7%[a] Number (%)	≥7%[b] Number (%)	Median (Min -Max) of HbA1c level	*p*-value*
Duration of DM2								
≤4 years	13 (14)	32 (35)	4.0 (0-8)	0.592[d]	20 (22)	25 (27)	7.3 (5.9-11.6)	0.489[d]
5-9 years	16 (17)	20 (22)	5.0 (0-7)		16 (17)	20 (22)	7.2 (5.1-14.0)	
≥10 years	4 (4)	7 (8)	5.0 (3-7)		4 (4)	7 (8)	8.1 (6.0-12.1)	
Duration of therapy								
<3 years	7 (8)	20 (22)	4.0 (0-7)	0.106[c]	12 (13)	15 (16)	7.1 (5.9-14.0)	0.921[c]
≥3 years	26 (28)	39 (42)	5.0 (2-8)		28 (31)	37 (40)	7.3 (5.1-12.7)	
Acceptance DM2 illness								
Yes	26 (28)	52 (56)	5.0 (0-8)	0.240[c]				
No	7 (8)	7 (8)	5.5 (2-7)					
Feeling ashamed to admit having DM2								
Yes	5 (5)	11 (12)	4.0 (2-7)	0.555[c]				
No	28 (30)	48 (52)	5.0 (0-8)					
Therapy adherence								
High - moderate					17 (19)	16 (17)	6.9 (5.6-12.7)	0.061[c]
Low					23 (25)	36 (39)	8.0 (5.1-14.0)	
Alcohol consumption								
Yes					1 (1)	1 (1)	7.3 (6.9-7.7)	0.925[c]
No					39 (42)	51 (56)	7.3 (5.1-14.0)	

Table 1 (cont)

Parameter	MMAS-8 score				HbA1c level			
	8[a] Number (%)	≤5[b] Number (%)	Median (Min -Max) of MMAS-8 score	*p*-value*	<7%[a] Number (%)	≥7%[b] Number (%)	Median (Min -Max) of HbA1c level	*p*-value*
Vitamins C and E consumption								
Yes					6 (7)	3 (3)	6.7 (5.9-9.0)	0.152[c]
No					34 (37)	49 (53)	7.5 (5.1-14.0)	
History of gastrointestinal bleeding, kidney disease, liver disease								
Yes					1 (1)	2 (2)	7.3 (6.5-7.7)	0.725[c]
No					39 (43)	50 (54)	7.3 (5.1-14.0)	
Physical activity								
Mild - moderate					29 (32)	39 (42)	7.3 (5.1-14.0)	0.735[c]
Heavy					11 (12)	13 (14)	7.2 (6.0-12.7)	
H2 antagonists and trimethoprim consumption								
Yes					3 (3)	1 (1)	6.7 (6.5-7.3)	0.329[c]
No					37 (40)	51 (56)	7.4 (5.1-14.0)	
Iron supplementation								
Yes					2 (2)	0 (0)	6.7 (6.5-6.9)	0.422[c]
No					38 (41)	52 (57)	7.3 (5.1-14.0)	
DM2 therapy adherence	33 (36)	59 (64)	5.0 (0-8)					
HbA1c level					40 (43)	52 (57)	7.3 (5.1-14.0)	

*Significant at $p < 0.05$

[a]Good; [b]Poor; [c]Mann-Whitney test; [d]Kruskal-Wallis test

Max: maximun; Min: minimum

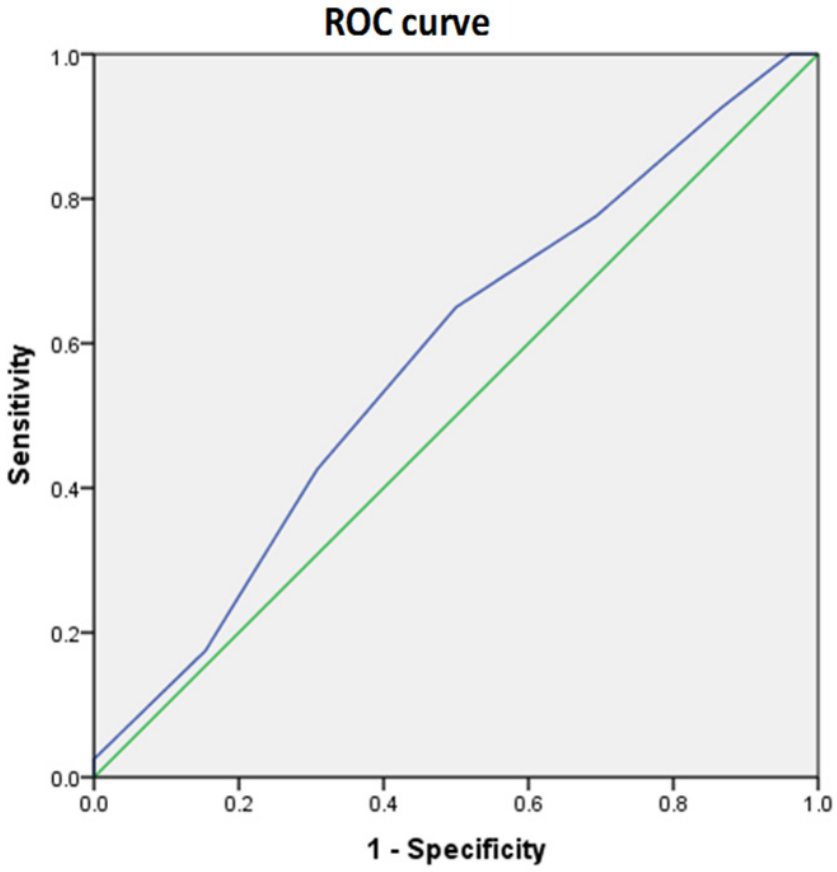

Fig 1 - Receiver operating characteristic (ROC) curve of MMAS-8 score diagnostic ability to predict glycemic control of type 2 diabetes mellitus patients receiving diabetes therapy

Patients (n = 92) were recruited at monthly medical examination at Primary Health Facility, Tanjung Purwokerto, central Java, Indonesia (October 2018). Therapy adherence was based on blood HbA1c level <7% at time of visit.

p-value = 0.035). These results provide an early warning that low adherence is associated with elevated HbA1c levels and become the basis for doctors to give more serious and assertive attention when treating DM patients with low levels of adherence.

In an earlier study in South Kalimantan, Srikartika *et al* (2016) noted education level, type of work, income level, type of medication, duration of DM2, and (certain) comorbidities do not affect therapy adherence, although female participants

are less compliant due to more frequent lapses in taking medication. However, identification of factors impacting therapy adherence, such as age, information access, perception of disease seriousness, duration of illness, variety of drugs, drug side effects, psychological factors, and financial status, is challenging and results vary depending on geographical location of study population and life style (García-Pérez *et al*, 2013).

In general, psychological status of DM2 patients in our study was good. Inonu *et al* (2018) reported 75% of DM2 patients in Bandarlampung accepted their medical condition and Agustina and Widayati (2009) found 50% of their study population in Yogyakarta are open to revealing their DM2 condition. Handindyastiti and Insiyah (2017) divided factors affecting self-acceptance into two types: internal (sincerity, confidence and acceptance of one's strengths and weaknesses) and external (environment and social support).

Contrary to our observations, Bonita *et al* (2017) found a relationship between physical activity and low HbA1c levels. It is worth noting the majority patients in our study were retired civil servants or military personnel who lived in urban areas and did not participate in strenuous physical exercise. Umpierre *et al* (2011) recommend combining physical exercise (aerobic and endurance training) and dietary management to reduce HbA1c level.

Kidney disease, alcohol consumption and iron supplementation can increase HbA1c level, while liver disease, bleeding, and vitamins C and E supplementation reduce HbA1c levels (Unnikrishnan *et al*, 2012). On the other hand, H2 antagonists cause depletion of vitamin B12, thereby increasing HbA1c levels (Zdilla, 2015; Unnikrishnan *et al*, 2012). However, only a very low proportion of participants in our study fell into these categories.

With increasing age, HbA1c levels are higher as control of glycemic levels as a result of increase in insulin resistance (of as yet unknown etiology) (Dubowitz *et al*, 2014). The decrease in HbA1c with age in the present study is a promising sign that senior patients realize the need of strict adherence to diabetes medication to maintain a sound quality of life.

A major weakness of the present study was the small size, which precludes generalization of the findings to the general population. A larger cohort involving multi centers will be required to confirm or negate the results. The possible existence of recall bias should also be taken into consideration (Lee *et al*, 2013), which can readily be corrected through examination of medical records and/or other documented sources.

In conclusion, the study disappointingly reveals MMAS-8 score was not a reliable predictor of adherence to diabetes medication compared to measurement of blood HbA1c level in type 2 diabetes mellitus

subjects. Thus, reliance only on the MMAS procedure as a screening tool at the primary health level of therapy adherence for control of type 2 diabetes in Indonesia should be accepted with caution.

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CONFLICTS OF INTEREST DISCLOSURE

The authors declare no conflicts of interest.

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