

# Antidiabetic Regimen and Factors Associated with Glycemic Control in Patients with Type 2 Diabetes mellitus in Public Health Centers in Jakarta: A Cross-Sectional Study

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## ABSTRACT

The glycemic control of diabetes mellitus patients is affected by many factors, including its antidiabetic regimen. The purpose of this study was to describe the antidiabetic regimen used in patients with T2DM in the public health centers in Jakarta and to evaluate factors associated with glycemic control. A cross-sectional study was conducted in thirteen public health centers in Jakarta with HbA1C of  $\leq 7\%$  indicating good glycemic control and  $> 7\%$  poor glycemic control. Factors that were potentially associated with glycemic control were performed univariate analysis test. Association between antidiabetic regimen and glycemic control were done by Pearson chi-square test and Fisher exact test. Sulfonylureas and biguanides as a combination were the most frequent (63.5%) prescribed in patients, while metformin was the most widely used antidiabetic of all prescriptions (49,43%). Univariate analysis showed that age, duration of T2DM, route of administration, number of antidiabetics, and number of other daily regular drugs significantly ( $P < 0.05$ ) related to glycemic control. Sulfonylurea and biguanide as monotherapy appeared associated with good glycemic control. However, further analysis is still needed to confirm whether it was affected by the antidiabetic regimens as other factors might be involved.

Keywords: Type 2 Diabetes Mellitus; Antidiabetic regimen; Associated factors

## INTRODUCTION

Diabetes is a chronic disease caused by either the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces<sup>1</sup>. Type 2 diabetes mellitus (T2DM) is the most prevalent type of diabetes, with around 90% of all diabetes cases.<sup>2,3</sup>

Diabetes is a primary health issue that has reached a serious level. Now, nearly half a million people worldwide are having diabetes<sup>4</sup>. Indonesia is one of the 39 countries and territories of the International Diabetes Federation (IDF) Western Pacific region. The data from IDF showed the prevalence of diabetes in adults 6.2% from total more than 170 million adult population, where Jakarta appeared the highest prevalence of patients in Indonesia.<sup>5,6</sup>

An HbA1c level is a primary assessment for glycemic management, reflecting average blood glucose over approximately three months. Achieving an HbA1c target of 7% has been shown to reduce microvascular complications of both type 1 and 2 diabetes mellitus when early in the disease. HbA1c test

is widely used as a standard to describe glycemic control of diabetes patients. It has a strong predictive value of diabetes complications.<sup>2</sup>

Strategies therapy of diabetes Indonesia is based on HbA1C value. HbA1c less than 7.5% is usually treated with antidiabetic monotherapy, while a patient with HbA1c 7.5% or higher is treated with combination antidiabetics.<sup>7</sup> Metformin is the preferred first-line pharmacologic therapy for patients with type 2 diabetes mellitus. As long as it is not contraindicated, metformin should be continued while other agents, including insulin, should be concomitantly used with it.<sup>2</sup>

A study in diabetes patients with cardiovascular disease complications found sulfonylureas in combination and sulfonylurea monotherapy significantly ( $P < 0.05$ ) associated with good glycemic control, while combination biguanides and insulin therapy were found otherwise.<sup>8</sup> Another study in patients diabetes with renal complication showed a significant association of glycemic control with monotherapy of sulfonylureas ( $P < 0.001$ ), insulin therapy

( $P=0.005$ ), and the concurrent use of biguanides and insulin ( $P=0.038$ ).<sup>9</sup>

There are many factors associated with glycemic control. A study in Saudi Arabia found vitamin D deficiency, age, hypertension, dyslipidemia, asthma, and anxiety significantly ( $P<0.05$ ) related to the glycemic control of T2DM.<sup>10</sup> Other studies found the occupation, route of antidiabetic administration, and medication adherence associated with glycemic control.<sup>11</sup> Meanwhile, a study in the Chinese elderly showed the duration of diabetes, antidiabetic medication, and exercise-related to the control glycemic.<sup>12</sup>

In Indonesia, many kinds of antidiabetic regimens prescribe to the patients, but not all to patients in public health care centers. Certain regimens can be prescribed to the patients in public health care centers. Besides, no study specifically addresses glycemic control of the regimen prescribed to the patients in Indonesia. Therefore, this study aimed to describe the profile of antidiabetic regimens prescribed in public health care centers in Indonesia, especially Jakarta, and evaluate factors associated with glycemic control.

## **METHODS**

### ***Study design and setting***

This was a cross-sectional study conducted in thirteen public health centers in Jakarta, Indonesia, from January to May 2020. This study was approved by the Faculty of Medicine's ethics committee of the University of Indonesia with Number: KET-81/UN2.F1/ETIK/PPM.00.02/2020.

### ***Study population and procedures***

This study population was T2DM patients at public health centers in Jakarta, taking at least one antidiabetic for at least three months. We included all the patients who attended a monthly gathering of the Chronic Disease Management Program (PROLANIS) on the day of the study conducted with criteria where a minimum age of 18 years, with or without comorbidities. The T2DM patients

who were pregnant and patients on dietary control alone were excluded from this study.

Potential subjects were screened by the trained research assistants and health workers in each public health center for enrolment eligibility into this study. Patients who met the requirements were asked to become a study subject by signing a participation agreement or informed consent and given information in advance. A structured questionnaire was given to obtain other factors potentially associated to the control glycemic such as socio-demographic (age, gender, education, and occupation) and clinical characteristics (duration of T2DM, other chronic diseases, number of antidiabetics, and other regular daily drugs) with double checking their medical records. Afterward, the trained health workers responsible in each public health center performed the HbA1c test on the patients.

### ***Statistical analysis***

All the collected data were statistically analyzed. A univariate analysis was performed to get the frequency of each characteristic. Glycemic control was based on the results of HbA1c examination with a controlled blood glucose (HbA1C) level  $>7\%$  indicated as poor glycemic control and vice versa.<sup>7,13</sup> Association between categorical variables was examined using the Pearson chi-square test with continuity correction. The Fisher exact test was used where the expected cell count was more than 20% or less than 5. A  $P$ -value of 0.05 was considered statistically significant.

## **RESULTS AND DISCUSSION**

### ***Characteristics***

A total of 323 patients from thirteen public health centers in Jakarta fulfilled the inclusion criteria from January to May 2020. As shown in **Kesalahan! Sumber referensi tidak ditemukan.I**, the study population slightly more (57.6%) geriatric patients with age more than or equal to 60 years old, and female-dominated with 69%. The patients, mostly (69.7%), had a moderate education level and were unemployed (82.7%).

Table I. Demographic and Clinical Characteristic of the patients

Characteristic	Total Patients (n, %)	HbA1c level (n, %)		P-value
		≤ 7%	> 7%	
<b>Age (y)</b>				
Geriatric (≥ 60)	186 (57.6)	86 (26.6)	100 (31.0)	0.002 <sup>a*</sup>
Non-geriatric (< 60)	137 (42.4)	39 (12.4)	98 (30.3)	
<b>Gender</b>				
Male	98 (30.3)	45 (13.9)	53 (16.4)	0.102 <sup>a</sup>
Female	225 (69.7)	80 (24.8)	145 (44.9)	
<b>Level of education</b>				
Basic	72 (22.3)	26 (8.0)	46 (14.2)	0.102 <sup>a</sup>
Moderate	199(61.6)	72 (22.3)	127 (39.3)	
High	52 (16.1)	27 (8.4)	25 (7.7)	
<b>Occupation status</b>				
Employed	56 (17.3)	25 (7.7)	31 (9.6)	0.393 <sup>a</sup>
Unemployed	267 (82.7)	100 (31.0)	167 (51.7)	
<b>Duration (y)</b>				
≤ 5	178 (55.1)	79 (24.5)	99 (30.7)	0.027 <sup>a*</sup>
>5	145 (44.9)	46(14.2)	99 (30.7)	
<b>Other chronic diseases</b>				
Non or 1	270 (83.6)	107 (33.1)	162 (50.5)	0.535 <sup>a</sup>
Two and above	53 (16.4)	18 (5.6)	35 (10.8)	
<b>Type of antidiabetic</b>				
Injection	5 (1.5)	-	5 (1.5)	0.014 <sup>a*</sup>
Oral	310 (96.0)	125 (38.7)	185 (57.3)	
Oral and Injection	8 (2.5)	-	8 (2.5)	
<b>Number of antidiabetics</b>				
1	65 (20.1)	45 (13.9)	20 (6.2)	0.001 <sup>a*</sup>
2	228 (70.6)	75 (23.2)	153 (47.4)	
3	30 (9.3)	5 (1.5)	25 (7.7)	
<b>Other daily regular drugs</b>				
< 2	234 (72.4)	101 (31.3)	133 (41.2)	0.011 <sup>a*</sup>
≥ 2	89 (27.6)	24 (7.4)	65 (20.1)	

<sup>a</sup>Pearson chi-square test with continuity correction; \*statistically significant ( $P < 0.05$ )

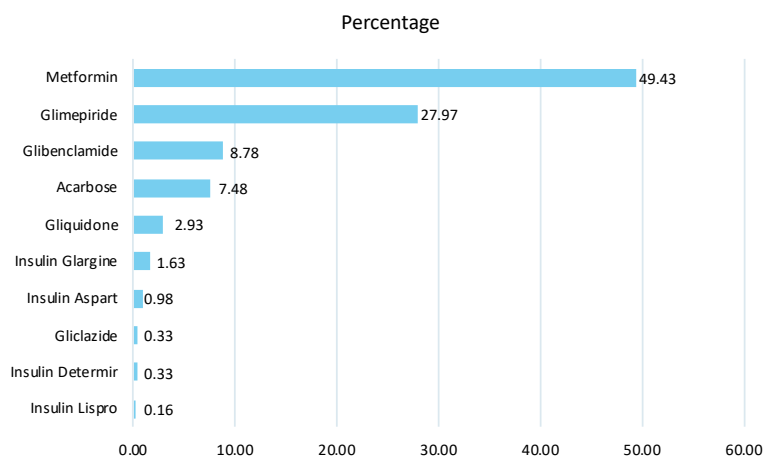
Clinical characteristics showed more frequency (55.1%) of patients with T2DM less than or equal to 5 years and mostly without or with one other chronic disease. The majority (96.5%) of the patients prescribed oral antidiabetic and most of them (70.6%) with the combination of two antidiabetics. As for other daily regular drugs used of the patients, 72.4% of the patients had less than two drugs other than antidiabetic.

This study showed age, duration of T2DM, type of antidiabetic, number of

antidiabetics, and other daily regular drugs significantly related to glycemic control.

#### **Antidiabetic regimens**

The result showed that biguanides as monotherapy was significantly ( $P=0.001$ ) associated with good glycemic control. All the prescribed drugs were under the national formulary of Indonesia. In this study, metformin was the only biguanides prescribed in patients of public health centers in Jakarta. Metformin was the most commonly used



**Figure 1. Antidiabetics pattern in T2DM patients**

antidiabetic agent in this study population (Figure 1). Metformin is an anti-diabetic which recommended as initial therapy in T2DM.<sup>2,7</sup> Some studies reported that metformin monotherapy lowered HbA1c by 1-1.12%.<sup>14,15</sup> Metformin works by increasing the sensitivity of insulin so that the insulin is used effectively. Metformin also decreases glucose production from the liver.<sup>16</sup>

The regimens of antidiabetic taken by the patients in public health centers in Jakarta showed in Table II. Out of 323 of the patients, it showed a combination of sulfonylureas and biguanides was the most frequent (63.5%) prescribed in patients. In this study, metformin was the only biguanide class taken by the patients. Meanwhile, glimepiride, glibenclamide, gliquidone, and gliclazide were the sulfonylureas class taken by the patients.

The other daily regular drugs taken by the patients were shown in Table II. In this study, selective calcium channel blockers were the most common concurrent drugs used by the patients.

#### **Association between antidiabetic regimen and glycemic control**

The association between antidiabetic regimens and glycemic control also showed in Table II. This study found sulfonylurea ( $P=0.003$ ) and biguanides ( $P=0.001$ ) as monotherapy was significantly associated

with good glycemic control. Whereas, the combination of both was significantly ( $P=0.010$ ) associated with poor glycemic control. In addition, the triple combination of  $\alpha$ -glucosidase inhibitors, sulfonylurea, and biguanides also showed a significant ( $P=0.041$ ) association with poor glycemic control.

Sulfonylureas monotherapy was also significantly ( $P=0.003$ ) associated with good glycemic control. In this study, metformin was the only biguanides prescribes in patients of public health centers in Jakarta. Glimepiride is the most commonly used sulfonylureas in the population of this study. The sulfonylureas mechanism of action involves a direct secretory effect on the pancreatic islet beta-cells. They act to enhance the sensitivity of the beta-cell pancreatic to glucose.<sup>17</sup> Sulfonylureas monotherapy reported lowered HbA1c by 1.51% more than placebo.<sup>18</sup>

In contrast to the combination of two antidiabetics, *i.e.* sulfonylureas and biguanides, they showed significant ( $P=0.010$ ) association with poor glycemic control. A combination of sulfonylureas with other oral antidiabetic reported a reduction of HbA1c by 1.62%.<sup>18</sup> On top of that, the combination of antidiabetic is recommended to treat patients with T2DM.<sup>7</sup> However, there is also another study such as a meta-analysis study which reported the increased relative risk (RR) of the composite endpoint of cardiovascular hospitalization or mortality using combination

Table IIa. Association between antidiabetic regimen and glycemic control

Antidiabetic Regimens	Total Patients (n, %)	HbA1c level (n, %)		P-value
		≤ 7%	>7%	
<b>α-glucosidase inhibitors</b>				
Yes	3 (0.9)	1 (33.3)	2 (66.7)	0.667 <sup>b</sup>
No	320 (99.1)	124 (38.8)	196 (61.3)	
<b>α-glucosidase inhibitors, Biguanides</b>				
Yes	11 (3.4)	4 (36.4)	7 (63.6)	0.569 <sup>b</sup>
No	312 (96.3)	121 (38.8)	191 (61.2)	
<b>α-glucosidase inhibitors, Insulin</b>				
Yes	1 (0.3)	-	1 (100)	0.613 <sup>b</sup>
No	322 (99.7)	125 (38.8)	197 (61.2)	
<b>α-glucosidase inhibitors, Sulfonylureas</b>				
Yes	3 (0.9)	2 (66.7)	1 (33.3)	0.333 <sup>b</sup>
No	320 (99.1)	123 (38.4)	197 (61.5)	
<b>α-glucosidase inhibitors, Sulfonylureas, Biguanides</b>				
Yes	27 (8.4)	5 (18.5)	22 (81.5)	0.041 <sup>a*</sup>
No	296 (91.6)	120 (40.5)	176 (59.5)	
<b>α-glucosidase inhibitors, Sulfonylureas, Insulin</b>				
Yes	1 (0.3)	-	1 (100)	0.613 <sup>b</sup>
No	322 (99.7)	125 (38.8)	197 (61.2)	
<b>Biguanides</b>				
Yes	55 (17.0)	39 (70.9)	16 (29.1)	0.001 <sup>a*</sup>
No	268 (83.0)	86 (32.1)	182 (67.9)	
<b>Biguanides, Insulin</b>				
Yes	1 (0.3)	-	1 (100)	0.613 <sup>b</sup>
No	322 (99.7)	125 (38.8)	197 (61.2)	
<b>Biguanides, Insulin (In 2 combination)</b>				
Yes	1 (0.3)	-	1 (100)	0.613 <sup>b</sup>
No	322 (99.7)	125 (38.8)	197 (61.2)	
<b>Insulin</b>				
Yes	2 (0.6)	-	2 (100)	0.375 <sup>b</sup>
No	321 (99.4)	125 (38.9)	196 (61.1)	
<b>Insulin (In 2 combination)</b>				
Yes	3 (0.9)	-	3 (100)	0.229 <sup>b</sup>
No	320 (99.1)	125 (39.1)	195 (60.9)	
<b>Sulfonylureas</b>				
Yes	6 (1.9)	6 (100)	-	0.003 <sup>b*</sup>
No	317 (98.1)	119 (37.5)	198 (62.5)	
<b>Sulfonylureas, Biguanides</b>				
Yes	205 (63.5)	68 (33.2)	137(66.8)	0.010 <sup>a*</sup>
No	118 (36.5)	57 (48.3)	61 (51.7)	
<b>Sulfonylureas, Biguanides, Insulin</b>				
Yes	3 (0.9)	-	3 (100)	0.229 <sup>b</sup>
No	320 (99.1)	125 (39.1)	195 (60.9)	

**Table IIb. Association between antidiabetic regimen and glycemic control**

Antidiabetic Regimens	Total Patients (n, %)	HbA1c level (n, %)		P-value
		≤ 7%	>7%	
<b>Sulfonylureas, Insulin</b>				
Yes	1 (0.3)	-	1(100)	0.613 <sup>b</sup>
No	322 (99.7)	125 (38.8)	197 (61.2)	

<sup>a</sup>Pearson chi-square test with continuity correction; <sup>b</sup>Fisher's Exact test; \*statistically significant ( $P < 0.05$ )

metformin and sulfonylurea.<sup>19</sup> In this study, a combination of biguanide and sulfonylurea was the most common (63.4%) regimen antidiabetic taken by the patients.

Another combination of three antidiabetics, *i.e.*  $\alpha$ -glucosidase inhibitors, sulfonylureas, and biguanides, showed significant ( $P=0.041$ ) association with poor glycemic control. A triple combination of antidiabetics is also included in guideline therapy of T2DM. The combination is usually given to the patients with HbA1c more than 9% which happened chronically.<sup>7</sup> Thus, the patients with such a high level of glucose might be experience glucotoxicity. This causes the inability of beta-cell pancreatic to maintain sufficient insulin secretion, and instead release less insulin though glucose levels increased.<sup>2</sup> Furthermore, a combination of triple oral antidiabetics in addition to metformin or sulfonylurea showed statistically and clinically more effective at reducing blood glucose than combination dual therapy with metformin and sulfonylurea.<sup>20</sup> As in this study, acarbose is the only  $\alpha$ -glucosidase inhibitor used by the patients.

Regarding the factors associated with glycemic control in this study, age appeared significantly related to glycemic control ( $P=0.002$ ). Geriatric showed more patients with good glycemic control than adult patients, while patients with poor glycemic control were also slightly more in geriatric patients. Some guidelines recommend higher HbA1c goals for elderly patients than younger adults. A study suggested that although lower HbA1c levels reduced mortality from some

observational studies, aggressive glucose-lowering benefits in older adults have not been seen in randomized trials.<sup>21</sup> However, evidence proposes that better glycemic control in older adults is evenly necessary for maintaining functional independence and cognition to prevent hypoglycemia in such populations.<sup>22</sup>

In this study, the duration of T2DM showed a significant association with the glycemic control of the patients. Poor glycemic control occurred in the same percentage in both patients with duration DM less than or more than five years, while good glycemic control happened more in patients with a duration of T2DM less than or equal to 5 years. A study found the worse the glycemic control, the longer a patient had diabetes. The study showed five to ten years duration and in patients with a history of diabetes for more than ten years compared patients with less than five years of illness (OR = 1.74; OR = 2.55, respectively).<sup>23</sup>

This study found the number of medications taken by the patient both antidiabetic and other daily regular drugs represented an association with the patients' glycemic control. This result was similar to a study that found the number of drugs significantly associated with glycemic control.<sup>23</sup> However, there is also another study that showed otherwise which found the poor glycemic control was not affected by a number of drugs.<sup>24</sup>

Most of the patients were taken oral antidiabetic, which showed more patients with poor control glycemic, while other types

of antidiabetic administration, *i.e.* injection and combination oral and injection antidiabetic only showed in patients with poor control glycemic. A study presented an increased risk for both inadequate and very poor glycemic controls in insulin use (either as monotherapy or combination with an oral antidiabetic).<sup>25</sup> Meanwhile, another study found, adding insulin on the combination of oral antidiabetics showed a more significant reduction in HbA1c.<sup>26</sup> Many factors cause poor glycemic control in patients who have taken an injection antidiabetic. A study showed improved insulin injection technique, higher patient satisfaction, and better glycemic control, resulting in the proper selection of pen and professional education.<sup>27</sup> Therefore, further study to investigate the cause of poor glycemic control in patients taking injection antidiabetic needed.

This study was conducted in thirteen public health centers representing most of the Indonesian population, therefore it can reflect the profile antidiabetic regimen used in public health centers in Indonesia. This study was conducted cross-sectionally where patient HbA1c test taken and other factors might be associated collected and recorded, which made the data more reliable.

Nevertheless, there are a lot of other factors associated with the glycemic control of T2DM patients. Moreover, this study only depicted descriptively the glycemic control of the patients, where some of the patients may be received monotherapy as they might have good glycemic control or otherwise. Therefore, whether the condition of glycemic control was affected by the antidiabetic regimen cannot be confirmed. In addition, other factors might be associated with glycemic control, not all collected and assessed due to limited tools and sources. The study also did not analyze the concurrent diseases that might be related to the choice of the antidiabetic regimen, which also affects control glycemic. The impact of each of the antidiabetic regimens in glycemic control could not describe; therefore, further analysis is still needed.

## CONCLUSION

Sulfonylurea and biguanide as monotherapy showed to be associated with good glycemic control, while combination dual antidiabetic and triple antidiabetic with sulfonylurea and biguanide showed related to poor glycemic control of the patients. However, whether the condition of glycemic control was affected by the antidiabetic regimen cannot be fully confirmed. Therefore, further analysis is still needed. In addition, this study also found that underlying factors such as age, duration of the disease, administration route, number of antidiabetics used, and concurrent drug used were statistically related to the patients' glycemic control.

## COMPETING INTEREST

None declared

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