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Association Between Antidiabetic Pattern with Medication Adherence in Type 2 Diabetes Patients at Buleleng Hospital

(*Hubungan Antara Pola Penggunaan Antidiabetik dengan Kepatuhan Pengobatan Pada Pasien Diabetes Melitus Tipe 2 Di Salah Satu Rumah Sakit Swasta Buleleng Bali*)

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ABSTRACT

Background: Type 2 diabetes mellitus (DM) is a chronic disease which requires long-term therapy. Medication adherence plays an important role for therapeutic success in patients with T2DM. Antidiabetic usage pattern might involve with some problems related to medication adherence. **Objectives:** The aim of this study was to analyze the association between antidiabetic usage pattern with medication adherence. **Methods:** This observational study was conducted cross-sectionally involving 90 participants of T2DM outpatient at Private Hospital in Buleleng Bali during July-September 2020. Patients were included if aged ≥18 years, received the same antidiabetic for three months before the study, signed informed consent, and provided with complete medical record data. Patients were excluded if appeared to be unwell, pregnant or breastfeeding. Demographic data and antidiabetic usage patterns were collected retrospectively based on the patient's medical records. Probabilistic Medication Adherence Scale (ProMAS) questionnaire was used to assess medication adherence. Data were analyzed with Kruskal-Wallis test. **Results:** The results showed that 55.6% patients were male, aged 46-65 years (61.1%), education predominantly by elementary school (37.8%), had suffered from DM for 5-10 years (46.7%), with comorbidities (50%), and without complications (77.8%). The antidiabetic usage pattern was dominated by a combination of two antidiabetics (53.3%). Most patients (42.2%) showed moderate-high medication adherence. There was no statistically significant association between antidiabetic usage pattern and medication adherence (p=0.275). **Conclusions:** A higher rate of medication adherence was found in patients taking combination of two antidiabetics compared to combination of three or four antidiabetics.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder characterized by increased blood glucose levels due to insulin resistance (Punthakee et al., 2018). Globally, the number of people with type 2 DM have reached more than 200 million and to be increasing year by year. In 2018, Indonesia was ranked at seventh out of the ten countries with the highest number of T2DM patients including 14.4 million sufferers as an increase of 1.6% from 2013 to 2018 (IDF, 2019). Bali is one of the provinces in Indonesia which was ranked fifth in terms of type 2 DM with 60,423 cases. Buleleng Regency accounted for 7,322 cases and was ranked as the third among any other regencies (Dinas Kesehatan Provinsi Bali, 2019; Kemenkes RI, 2019).

Type 2 DM is an incurable disease, but it can be controlled through long-life antidiabetic therapy to manage blood glucose levels and prevent the disease worsening or risk of complications (Fatimah, 2015). Therapy is adjusted to the patient's clinical condition based on therapeutic algorithm in the form of antidiabetic usage pattern such as single or combination therapy (ADA, 2019; Rasdianah et al., 2016). Although therapeutic guidelines are available, >50% of type 2 DM patients may be presented with uncontrolled blood glucose levels (Fiagbe et al., 2017; Kamuhabwa & Charles, 2014). Factors affecting blood glucose control include socioeconomic, physical activity, diet, knowledge, and medication adherence (Nanda et al., 2018).

World Health Organization (WHO) claimed that one of the factors contributing as the main problem in controlling blood glucose in DM patients was medication adherence (WHO, 2017). The study showed that the difference in patients' antidiabetic usage patterns including both monotherapy and combination therapy were related to medication adherence (Gordon et al., 2018; Pantuzza et al., 2017). Several studies have reported that >50% of patients receiving a combination of two antidiabetics showed more high non-adherence than those receiving monotherapy (Pantuzza et al., 2017; Rosyid, 2017). Another study explained that patients who received the combination therapy showed low adherence with an average fasting blood glucose level >180 mg/dL (Gamayanti et al., 2018).

Adherence is defined as the patient's attitude in adhering to medication followed by diet and lifestyle changes recommended by health professionals (García-Pérez et al., 2013). On the opposite, non-adherence to antidiabetics may induce clinical consequences such as uncontrolled blood glucose levels which can lead to complications, morbidity, and mortality. Therefore, the authors are interested to analyze the association between antidiabetic usage pattern with medication adherence in T2DM outpatient at Private Hospital Buleleng Bali.

MATERIAL AND METHODS

Materials

Research materials in this study were patient's medical record and filling out a questionnaire medication adherence (The Probabilistic Medication Adherence Scale) **(**Kleppe et al., 2015). This study was approved by the ethics committee of the Stikes Bina Usada in Bali (No.011/EA/KEPK-BUB-2021) and hospital permit.

Methods

This observational study was carried out cross-sectionally at outpatient service of a Private Hospital in Buleleng Bali during July-September 2020. The population were 300 patients. Patients were purposively sampled based on inclusion and exclusion criteria. The inclusion criteria were, aged 18 years, received the same antidiabetic drug for at least 3 months, signed informed consent, filled out the given questionnaire, and provided with complete medical record data. Exclusion criteria were, appeared to be uncooperative, pregnant or breastfeeding. Based on the sample calculation by using the Slovin formula, 90 patients were needed in the study.

Data collection related to antidiabetic usage pattern was carried out retrospectively based on patient's medical record, while data related to medication adherence was obtained through the questionnaire responses. The Probabilistic Medication Adherence Scale (ProMAS) questionnaire which consists of 18 question items was applied in the questionnaire and validated through a validity test with results >85% (Kleppe et al., 2015). The level of adherence was categorized into low (score 0-4), medium-low (scores 5-9), medium-high (scores 10-14), and high (scores 15-18). The antidiabetic usage pattern was categorized into monotherapy, combination of two antidiabetic drugs, combination of three antidiabetic drugs, and combination of four antidiabetic drugs. Demographic data and antidiabetic usage pattern were analyzed descriptively. The association between antidiabetic usage pattern with medication adherence was analyzed by using the Kruskal Wallis test with Statistical Package for the Social Science (SPSS) version 26 software.

RESULTS AND DISCUSSION

Demographic characteristics

Table 1 presents demographic characteristics were dominated by male patients (55.6%) and aged 46-65 years (61.1%). Some previous study reported similar demographic data that type 2 DM patients were mostly male and aged >45 years (Nordström et al., 2016; Pahlawati & Nugroho, 2019; Pardede et al., 2017). The accumulation of visceral fat in the abdominal cavity is a trigger for high prevalence of DM in male because it can lead to insulin resistance (Nordström et al., 2016). Along with aging, the ability of pancreatic cells to produce insulin tends to decrease (Azizah, 2019).

Majority of patients have lived with DM for 5-10 years (46.7%) and have joined elementary school education (37.8%). Duration of disease is related to acute and chronic complications risk (Javanbakht et al., 2012; Pratama et al., 2019; Zoungas et al., 2014). Education is related to the patient's disease knowledge about the disease. The lower education level is attended, the less knowledge coverage of the disease is experienced. Both factors may predispose to poor glycemic control, complications, and disease progressivity (Felea et al., 2014; Pahlawati & Nugroho, 2019).

In this study, 13.3% of patients had macrovascular complications and comorbid hypertension (37.8%). Macrovascular complications experienced by the subjects included coronary artery disease, congestive heart failure, and stroke. The complications may worsen the quality of life and patient's disease (Restada, 2016). Several studies have found that hypertension accompanies >80% of type 2 DM patients (Akın & Bölük, 2020; Nowakowska et al., 2020; Rajpathak, 2015). The mentioned hypertension was reported to be caused by an increase in the expression of vascular adhesion molecules, oxidative stress, and a decrease in oxide level (Khangura et al., 2018).

Table 1. Demographic characteristics

Demographic characteristics		**N (%)**
Gender	Female	40 (44,4)
	Male	50 (55,6)
Age (years)	18-45	9 (10%)
	46-65	55 (61,1)
	>65	26 (28,9)
Level of Education	No education	6 (6,7)
	Elementary school	34 (37,8)
	Junior high school	13 (14,4)
	Senior high school	17 (18,9)
	Undergraduate or postgraduate	20 (22,2)
Duration of disease	<5 years	41 (45,5)
	5-10 years	42 (46,7)

	>10 years	7 (7,78)
Complications	Without complication	70 (77,8)
	Macrovascular	
	Coronary Artery Disease	8 (8,9)
	Congestive Heart Failure	2 (2,2)
	Stroke	2 (2,2)
	Microvascular	
	Diabetic Nephropathy	1 (1,1)
	Chronic Kidney Failure	6 (6,7)
	Diabetic Neuropathy	1 (1,1)
	With comorbidities	
	Hypertension	34 (37,8)
	Osteoarthritis	5 (5,6)
Comorbidities	Gout	3 (3,3)
	Benign Prostatic Hyperplasia	1 (1,1)
	Dyslipidemia	1 (1,1)
	Epilepsy	1 (1,1)
	Without comorbidities	45 (50)

Antidiabetic usage pattern

In table 2, mostly patients have taken combination of two oral antidiabetics and insulin (53.3%). There are several studies conducted in Germany and Indonesia showing similar results to this study, that the use of combination of two antidiabetics in outpatients was more frequent than monotherapy, combination of three, and combination of four antidiabetic drugs (Engler et al., 2020; Hapsari, 2014; Sappo et al., 2017).

Table 2. Antidiabetic usage pattern

Antidiabetic usage pattern	N (%)
Monotherapy	
Oral antidiabetic drug	
Metformin	3 (3,3%)
Glimepiride	1 (1,1%)
Insulin	
Insulin glulisine	6 (6,7)
Insulin aspart	4 (4,4)
Insulin lispro protamine/insulin lispro	6 (6,7)
Total monotherapy	20 (22,2)
Combination of two antidiabetic drugs	
Combination of oral antidiabetic drugs	
1. Biguanides and sulfonylurea	
Metformin and glimepirid	6 (6,7)
Metformin and gliclazide	1 (1,1)
Combination of oral antidiabetic drug and insulin	
1. Biguanide and rapid acting insulin	
Metformin and insulin glulisine	7 (7,8)
Metformin and insulin aspart	4 (4,4)
2. Sulfonylurea and rapid acting insulin	
Glimepirid and insulin aspart	2 (2,2)
Glimepirid and insulin glulisine	1 (1,1)
3. Biguanide and premixed insulin	
Metformin and insulin aspart protamine/insulin aspart	1 (1,1)
4. Alpha glucosidase inhibitor and premixed insulin	
Acarbose and insulin aspart protamine/insulin aspart	1 (1,1)
5. Thiazolidinediones and premixed insulin	
Pioglitazone and insulin lispro protamine/insulin lispro	1 (1,1)
Combination of insulin	
1. Rapid acting insulin and long acting insulin	
Insulin glulisine and insulin glargine	6 (6,7)
Insulin glulisine and insulin detemir	1 (1,1)
Insulin aspart and insulin glargine	9 (10)
Insulin aspart and insulin detemir	1 (1,1)
2. Long acting insulin and premixed insulin	
Insulin glargine and insulin lispro protamine/insulin lispro	7 (7,8)
Total combination of two antidiabetics	48 (53,3)
Combination of three antidiabetic drugs	
Combination of oral antidiabetic drugs	
1. Biguanide, sulfonylurea, and thiazolidinediones	
Metformin, gliclazide, and pioglitazone	2 (2,2)
Metformin, glimepirid, and pioglitazone	9 (10)
Combination of oral antidiabetic drugs and insulin	
1. Biguanide, sulfonylurea, and rapid acting insulin	
Metformin, glimepiride, and insulin aspart	1 (1,1)
Metformin, glimepiride, and insulin glulisine	2 (2,2)
2. Biguanide, thiazolidinediones, and rapid acting insulin	
Metformin, pioglitazone, and insulin glulisine	1 (1,1)
3. Biguanide, rapid acting insulin, and long acting insulin	
Metformin, insulin aspart, and insulin glargine	2 (2,2)
4. Thiazolidinediones, alpha glucosidase inhibitor, and premixed insulin	
Pioglitazone, acarbose, and insulin lispro protamine/insulin lispro	1 (1,1)
Total combination of three antidiabetic drugs	18 (20)
Combination of four antidiabetic drugs	
Combination of oral antidiabetic drugs	

1. Biguanide, sulfonylurea, thiazolidinediones, and alpha glucosidase inhibitor	
Metformin, glimepirid, pioglitazon, and acarbose	4 (4,4)

The use of combination of two antidiabetic drugs, both oral and insulin, aims to achieve blood glucose levels in accordance with the criteria for controlling type 2 DM therapy, preventing disease worsening, complications, morbidity, and mortality. In the treatment of type 2 DM, the administration of antidiabetic drugs is adjusted to clinical conditions and individual patient's needs (Wexler et al., 2021). Based on guidelines from the ADA (2019) and Indonesian Endocrinologist's Association PERKENI (2019), therapy is started by giving an oral antidiabetic metformin (if not contraindicated). Then, if the target of blood glucose level is not achieved for three months, the therapy is increased to using combination of two antidiabetics. However, if the two antidiabetics are not able to help, either combination of three antidiabetics or intensive therapy with insulin is given.

In this study, the combination of insulin aspart and insulin glargine was the most frequent used drug in combination of two antidiabetics (10%). A study conducted in Denpasar also showed that the combination of insulin aspart with insulin glargine was the most often used in patients with type 2 DM (Kartika et al., 2013). The use of insulin combinations has some advantages including reducing basal hepatic glucose expenditure by 50%, increasing peripheral glucose uptake by 20%, and increasing insulin sensitivity (Benedetti & Orsini-Federici, 2010). The combination of insulin aspart with insulin glargine is included in the basal bolus regimen. The basal bolus regimen is the regimen that most closely resembles physiologic insulin secretion. Insulin aspart is bolus insulin which serves to meet the body's need for insulin at the time after meal. Insulin glargine is basal insulin that serves to supply insulin needs during sleep, fasting, and before meals (Gamayanti et al., 2018; Lukito, 2020).

Medication adherence

Based on the questionnaire responses scoring described in table 3, the results presented that there was 1 question item (item number 2) out of the 18 question items which received the largest percentage of incorrect answers at 51.11%. It means, there were still many patients who were taking drugs later then the proper time. In the study of Nanda et al., (2018), patients were often late in taking medication due to forgetfulness, busy activities, traveling, bored or lazy, and fatigue. The results obtained based on the category of adherence level in table 4 indicated that the majority of patients had a moderate-high level of adherence (42.22%). Similarly, previous studies found that >40% of type 2 DM patients had moderate-high adherence rates (Attyia et al., 2013; Pratama et al., 2019; Romadhon et al., 2020). Treatment adherence plays an important role in glycemic control, risk of complications, and patient's quality of life (Mokolomban et al., 2018; Rana et al., 2019). Factors that correlate to high medication

adherence are such as individual factors and the health care system (García-Pérez et al., 2013; Kirkman et al., 2015).

Table 3. Respondent responses to ProMAS questionnaire

No	Questions	Yes (n (%))	No (n (%))
1	It has happened at least once that I forgot to take (one of) my medicines.	35 (38,89%)	55 (61,11%)
2	It happens occasionally that I take (one of) my medicines at a later moment than usual.	46 (51,11%)	44 (48,89%)
3	I have never (temporarily) stopped taking (one of my) medicines.	65 (72,22%)	23 (25,56%)
4	It has happened at least once that I did not take (one of) my medicines for a day.	33 (36,67%)	57 (63,33%)
5	I am positive that I have taken all the medication that I should have taken in the previous year.	60 (66,67%)	30 (33,33%)
6	I take my medicines exactly at the same time every day.	52 (57,78%)	38 (42,22%)
7	I have never changed my medicine use myself.	85 (94,44%)	5 (5,56%)
8	In the past month, I forgot to take my medicine at least once.	30 (33,33%)	60 (66,67%)
9	I faithfully follow my doctor's prescription concerning the moment of taking my medicines.	64 (71,11%)	26 (28,89%)
10	I sometimes take (one of) my medicines at a different moment than prescribed (e.g., with breakfast or in the evening).	29 (32,22%)	61 (67,78%)
11	In the past, I once stopped taking (one of) my medicines completely.	17 (18,89%)	73 (81,11%)
12	When I am away from home, I occasionally do not take (one of) my medicines.	36 (40%)	54 (60%)
13	I sometimes take less medicine than prescribed by my doctor.	8 (8,89%)	82 (91,11%)
14	It has happened (at least once) that I changed the dose of (one of) my medicines without discussing this with my doctor.	4 (4,44%)	86 (95,56%)
15	It has happened (at least) once that I was too late with filling a prescription at the pharmacy.	13 (14,44%)	77 (85,56%)
16	I take my medicines every day.	57 (63,33%)	33 (36,67%)
17	It has happened (at least once) that I did not start taking a medicine that was prescribed by my doctor.	10 (11,11%)	80 (88,89%)
18	I sometimes take more medicines than prescribed by my doctor.	11 (12,22%)	79 (87,78%)

Individual factors related to demographic characteristics patients include gender, age, education, duration of DM and complications. In this study, majority of patients were male (55.56%) aged 46-65 years (61.1%). The high medication adherence in men can be highly supported by family's role and self-motivation to be able to improve their quality of life (Almira et al., 2019). Meanwhile, the high level of adherence in the previously mentioned age range can be affected by patient's experience in obtaining health services at younger age. For example, when a patient receives treatment instructions by health professionals, the treatment process will become the patient's experience for the next treatment process (Hestiana, 2017).

The high level of medication adherence in this study was also related to the level of higher education (diploma, bachelor's, master's degree) possessed by 22.2% of patients and duration of patients having

type 2 DM for 5-10 years (46.7%). Higher education affects the extent of knowledge and understanding of patients about the medication. Therefore, patients will tend to be more obedient to the treatment. Meanwhile, the high adherence in during the disease progression was due to the high understanding of the patient on the treatment received according to the doctor's instructions or prescription, and the patient's understanding of the complications that might occur if they did not comply with the treatment (Rasdianah et al., 2016).

Table 4. Level of medication adherence

Level of medication adherence	N (%)
Low (0-4)	1 (1,1)
Moderate-low (5-9)	15 (16,7)
Moderate-high (10-14)	38 (42,2)
High (15-18)	36 (40)
Total	90 (100)

High adherence was also related to the number of patients who did not have any complication (77.78%). One study stated that the treatment received in patients who did not experience complications tended to be less complex than patients who experienced complications. Therefore, patients who did not experience any complication had higher medication adherence compared to patients who experienced complications (Almira et al., 2019). In addition to demographic characteristics, the health care system may have an effect on patient medication adherence. Health care system factors include interaction or communication between health care professionals and patients. Improving the quality of interaction between health professionals and patients may provide positive feedback to patients after obtaining information about the treatment they have received. In addition, the ability of doctors or health professionals to provide complete, accurate, and clear information will increase patients medication adherence (Bagonza et al., 2015; Datak & Febriani, 2020; Kardas et al., 2013).

Analysis of association between antidiabetic usage pattern with medication adherence

The results of analysis in table 5 show $p>0.05$, which means there was no significant association between antidiabetic usage pattern with level of medication adherence. Several previous studies found similar results reporting that there was no association between antidiabetic usage pattern with medication adherence ($p>0.05$) (Aminde et al., 2019; Nandini et al., 2020; Thapar et al., 2020). Based on the results of this study, the highest level of medication adherence was found in patients who used a combination of two antidiabetic drugs (22.2%), while the lowest medication adherence was found in patients who used a combination of three antidiabetic drugs (1.1%). This is supported by previous research which found that the majority of type 2 DM patients receiving combination therapy with two antidiabetics showed higher adherence compared to those receiving monotherapy or combination of three and four antidiabetic drugs (Araya et al., 2020; Heissam et al., 2015; Makhmari et al., 2018; Pantuzza et al.,

2017). The high level of medication adherence can be explained by several things. A study claimed that the high adherence in using combination of two antidiabetics might be caused by the amount and frequency of taking the drug, or the low side effects. The less the number of drugs received, the higher the chances of patients adhering with their treatment. Besides, lower frequency of drug use (once a day) may increase medication adherence. The low side effects felt by patients when undergoing treatment can also improve patients' medication adherence. In type 2 DM patients, the frequent side effects, such as hypoglycemia, gastrointestinal disorder, and weight gain may cause a decrease in patient adherence to those who receive antidiabetic treatment (Edi, 2015; Khunti et al., 2019; Rathish et al., 2019).

Factors that affect the results of analysis in this study were related to the high number of patients taking combination of two antidiabetic drugs and demographic characteristics. In table 2, it shows that 53.3% of patients used combination of two antidiabetics, so it was possible that patients with this combination showed the highest adherence. Demographic characteristics including gender, age, duration of disease, education, and complications also affect medication adherence (Abebaw et al., 2016; Petrenchik & Loh, 2020). Although the results showed that there was no significant association, the results in table 4 illustrate the influence between antidiabetic usage pattern and medication adherence. The results showed a decrease in adherence along with the increase in the number of therapies. The highest adherence was presented by patients who used combination of two antidiabetics, followed by combination of three antidiabetic drugs, and combination of four antidiabetic drugs. These results are in accordance with the theory which states that the more therapy the patient consumes, the lower the medication adherence the patient does and vice versa (Gordon et al., 2018; Kassahun et al., 2016). The low adherence in patients who received combination of three or four antidiabetics might be caused by the patient's weariness in taking a lot of drugs. Furthermore, using a lot of drugs can also increase the patient's concern or fear of possible side effects. Hence, these reasons can affect the patient's medication adherence (Bagonza et al., 2015; Nanda et al., 2018; Pantuzza et al., 2017).

Table 5. Association between antidiabetic usage pattern and medication adherence

Antidiabetic usage pattern	Level of medication adherence					p value
	Low	Moderate-low	Moderate-high	High	Total	
Monotherapy	0	3 (3,3%)	7 (7,8%)	10 (11,1%)	20 (22,2%)	
Two combinations	0	8 (8,9%)	20 (22,2%)	20 (22,2%)	48 (53,3%)	
Three combinations	1 (1,1%)	4 (4,4%)	8 (8,9%)	5 (5,7%)	18 (20,1%)	0,275*
Four combinations	0	0	3 (3,3%)	1 (1,1%)	4 (4,4)	
Total	1 (1,1%)	15 (16,6%)	38 (42,3%)	36 (40%)	90 (100%)	

This study has several limitations including the minimal sample size and the method of measuring adherence in the form of self-reports which can lead to fairly high estimate of adherence. The method was also not able to picture the whole indicators of medication adherence, such as the process of how patients consumed the drugs, how frequently patients took the drugs, and how precise the dose or amount was taken. To overcome the limitations of this study, further research can increase the number of samples by changing the significance level and applying other medication adherence measurement methods such as the pill count method

CONCLUSION

Based on the results of this study involving type 2 DM patients at the outpatient service of a private hospital in Buleleng, there was no significant association between the antidiabetic usage pattern and medication adherence (p=0.275). However, the results tended to indicate an effect of antidiabetic usage pattern on medication adherence. Patients who received a combination of two antidiabetic drugs showed higher adherence than those who took the combination of three and four antidiabetic drugs.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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