Jurnal eduHealt
Volume 15 , Number 01, 2024, DOI 10.54209/eduhealth.v15i01
ESSN 2808-4608 (Online)
https://ejournal.seaninstitute.or.id/index.php/healt

Profile of the combination of two oral anti-diabetes drugs in patients diabetes melitus at Citra Husada hospital Jember

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Article Info
Keywords:
Diabetes Mellitus,
Oral anti-diabetes Drugs,
Antidiabetic

ABSTRACT
Diabetes melitus (DM) is a group of diseases with characteristic hyperglycemia that occurs due to impaired insulin secretion, insulin action, or both. The International Diabetes Federation (IDF) notes that Indonesia has the country with the fifth most significant number of diabetics in the world, with 19.5 million Indonesians aged 20-79 years suffering from the disease. Therefore this study aims to determine the profile of the use of a combination of two classes of oral hypoglycemic drugs in type 2 DM patients at Citra Husada Hospital in 2022. This research is a descriptive study with retrospective data collection. The population in this study were all outpatients diagnosed with Type 2 DM at Citra Husada Hospital in 2022. Source of medical record data. The number of samples using a population of 100 patients in the outpatient installation at Citra Husada Hospital. This study used a total sampling technique which is a sampling technique that uses all members of the population. Data analysis used univariate analysis in the form of proportions. Research results show that 100 samples are included in the inclusion criteria. Results of the study Most of the patient characteristics were female (61%), age range 56-65 years (39%), and hypertension co-morbidities (33%). The results of a combination study of two classes of oral anti-diabetes drugs, namely the sulfonylurea group (glimepiride at a dose of 3 mg, the drug frequency is taken once a day every morning with the thiazolidinedione group (pioglitazone at a dose of 30 mg, the drug frequency is taken once a day during the day) (35%). The most common used of combinations of two classes of oral anti-diabetes drugs in patients Diabetes melitus at Citra Husada Hospital are sulfonylureas and thiazolidinediones.

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INTRODUCTION

Diabetes mellitus (DM) is a group of diseases characterized by hyperglycemia that occurs due to impaired insulin secretion, insulin action, or both (ADA, 2019). Common complaints of diabetes mellitus are polyuria, polyphagia, and polydipsia. Diabetes mellitus is a non-communicable disease, diabetes is the main cause of blindness, heart attacks, strokes, kidney failure and leg amputations, 80% of diabetes incidents can be prevented or

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postponed. With optimal treatment management, diabetes can be controlled, and patients with diabetes can live healthier lives and live longer (WHO, 2021). Apart from this, diabetes mellitus that is not well controlled can also cause complications. In the acute stage, diabetes mellitus complications occur due to metabolic disorders such as hypoglycemia and hyperglycemia, while in the advanced stage, these disorders occur due to microvascular and macrovascular damage. One of the factors that plays a role in the emergence of complications from diabetes mellitus is the use of inappropriate medication [2]

World Health Organization (WHO) stated that in 2014, 8.5% of adults aged 18 years and over had diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths and 48% of all diabetes deaths occurred before the age of 70. There are 463 million people aged 20-79 years in the world suffering from diabetes mellitus. Between 2000 and 2019, there was a 3% increase in age-standardized death rates from diabetes. In lower middle income countries, diabetes death rates increase by 13% (WHO, 2021). Indonesia will see an increase in the number of diabetes sufferers from 8.4 million in 2000 to around 21.3 million in 2030. In 2021, the International Diabetes Federation (IDF) noted that Indonesia is the country with the fifth largest number of diabetes sufferers in the world, there are 19.5 million Indonesians aged 20-79 years suffer from this disease. According to the Ministry of Health in 2020, East Java was ranked fifth with a prevalence of diabetes mellitus, namely 2.6. Meanwhile, based on doctors' diagnoses in 2020, there were 35,951 diabetes mellitus sufferers in Jember Regency. [3].

Diabetes mellitus can be treated through 2 therapies, namely non-pharmacological therapy and pharmacological therapy. Non-pharmacological therapy is carried out with a healthy lifestyle by adjusting diet and exercising regularly. Meanwhile, pharmacological therapy uses antidiabetic drugs. Oral antidiabetic therapy that can be given to diabetes mellitus sufferers includes sulfonylureas, biguanides, thiazolidinediones, maglitinides, α-glucosidase inhibitors [4]. The aim of giving antidiabetic drugs to diabetes mellitus patients is to control blood sugar levels, so that the condition of diabetes sufferers can remain stable and prevent complications (Balkhi & Algahtani, 2019). The use of antidiabetic drugs is divided into 4 types, namely, single oral therapy, oral combination, triple combination, and combination injection (ADA, 2019). Single therapy is given first to patients diagnosed with diabetes mellitus, and if blood sugar levels remain uncontrolled with single therapy, then therapy can be increased to a combination of two drugs, namely the drug given in the first line combined with another class of antidiabetic drug with a different mechanism of action. different, or if the patient's HbA1C from the start is > 9% then they can immediately be given a combination of 2 other drugsl (Balkhi & Algahtani, 2019).

A preliminary study was carried out at Citra Hospital found that the population of patients experiencing diabetes mellitus for the period 2022 is 16%, the classes of antidiabetic drugs that are often used are sulfonylureas, biguanides, thiazolidinediones and gluconeogenesis inhibitors.

Based on the above background, it is necessary to carry out research regarding the profile of the use of a combination of two oral anti-diabetes drugs in diabetes mellitus

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patients at Citra Husada Hospital so that it can help in providing appropriate and effective therapy for patients so as to improve patient therapy outcomes.

METHOD

This research is a non-experimental research with retrospective data collection method and descriptive research design. The data source used is the patient's medical record data. The sample in this study was all type 2 diabetes mellitus patients who used combination of two oral anti-diabetes drugs in patients Diabetes melitus at Citra Husada Hospital Jember with a total of 100 patients. The sampling technique used the total sampling technique.

RESULTS AND DISCUSSION

This research was conducted at Citra Husada Hospital Jember. Therefore this study aims to determine the profile of the use of a combination of two classes of oral hypoglycemic drugs in type 2 DM patients at Citra Husada Hospital in 2022. This research is a descriptive study with retrospective data collection.The population in this study were all outpatients diagnosed with Type 2 DM at Citra Husada Hospital in 2022. Source of medical record data. The number of samples using a population of 100 patients in the outpatient installation at Citra Husada Hospital. This study used a total sampling technique which is a sampling technique that uses all members of the population. Data analysis used univariate analysis in the form of proportions. Research results show that 100 samples are included in the inclusion criteria. Patient characteristics based on age and sex can be seen in the table below :

Table 1. Results of Identification of Data Characteristics Based on Age of Diabetes Mellitus Patients at Citra Husada Hospital in 2022

No	Age Range (Years)	(n)	Persentage (%)
1	18-25	1	1
2	26-35	3	3
3	36-45	10	10
4	46-55	22	22
5	56-65	39	39
6	>65	25	25
	Total	100	100

Source: Secondary data (medical records)

The majority of diabetes mellitus sufferers are in the 56-65 year age group at 39% with a frequency of 39 sufferers. According to Amin & Juniati (2017), the age classification is teenagers aged 18-25 years, early adults aged 26-35 years, late adults aged 36-45 years, early elderly aged 46-55 years, late elderly aged 56 -65 years, and seniors >65 years. The age limit uses the theory of aging which occurs slowly and is divided into several stages. The transition stage occurs at the age of 35-45 years and is the stage where symptoms of aging begin to occur which already show signs of decreased physiological

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function in the body which can manifest in various diseases. Symptoms and signs of aging that occur in the transition stage become more obvious, this stage is called the clinical stage which occurs at the age of 45 years and over which includes a decline in all body system functions, including the immune system, metabolism, endocrine, sexual and reproductive, cardiovascular, gastrointestinal. , muscles and nerves. Degenerative diseases are starting to be diagnosed, activities and quality of life are reduced due to physical and psychological disabilities which are very disturbed [8]. As we get older, the function or ability of parts of the body's organs begins to decrease, including the work of pancreatic beta cells in obtaining insulin, causing blood sugar levels to rise. Age over 40 years is the age at risk of contracting diabetes mellitus because of glucose intolerance and the aging process which results in a reduction in pancreatic beta cells producing insulin. Diabetes mellitus mostly affects people over 45 years of age and begins to increase over the age of 65 years.

Table 2. Results of Identification of Data Characteristics Based on Gender of Diabetes Mellitus Patients at Citra Husada Hospital in 2022

No	Gender	(n)	Persentage (%)
1	Male	39	39%
2	Female	61	61%
	Total	100	100

Source: Secondary data (medical records)

The majority of Diabetes Mellitus sufferers are mostly women, namely 61 people with a percentage of 61%, while a small number are men, namely 39 people with a percentage of 31%. Gender is an analytical concept used to identify differences between men and women from a non-biological perspective, namely from social, cultural and physiological aspects [9]. Women have a higher body fat composition compared to men, so women get fat more easily which is associated with the risk of obesity and diabetes [10]. According to Imelda (2019) the amount of fat in men is 15-20% of body weight while in women it is 20-25% of body weight. So the increase in fat levels in women is higher than in men, so the risk of diabetes mellitus in women is 3-7 times higher than in men, namely 2-3 times.

Women are more at risk of diabetes because physically women have a greater chance of increasing body mass index and women have higher cholesterol than men and there are also differences in carrying out all daily activities and lifestyle which greatly influence the incidence of diabetes mellitus. . The hormones estrogen and progesterone have the ability to increase the insulin response in the blood. When menopause occurs, the insulin response decreases due to low estrogen and progesterone hormones. Another influencing factor is women's body weight, which is often not ideal, so this can reduce insulin response sensitivity.

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Table 3. Results of Identification of Data Characteristics Based on Comorbidities of Diabetes Mellitus Patients at Citra Husada Hospital in 2022

No	Concomitant Diseases	(n)	Persentage (%)
1.	Hipertensi	19	19
2.	Katarak	3	3
3.	Neuropati Diabetes	6	6
4.	Neuropati Diabetes dan Arthritis	10	9
5.	Neuropati Diabetes dan Hipertensi	6	4
6.	Neuropati Diabetes, Arthritis dan Gagal Ginjal	1	1
7.	Alergi	1	2
8.	Jantung Iskemik, Penyakit Paru Obstruktif kronis	1	1
9.	Katarak dan Hipertensi	1	1
10.	Komplikasi penyakit arteri perifer	2	2
11.	Tukak Saluran Pencernaan	5	5
12.	Arthritis	1	1
13.	Komplikasi neurologis, neuropati diabetes dan stroke	1	1
14.	Jantung Iskemik kronis dan Asma	1	1
15.	Jantung Iskemik	1	1
16.	Gagal Jantung	1	1
17.	Neuropati diabatees, arthritis, peptic ulcer kronis, hiperlipidemia	1	1
18.	Hiperplasia prostat	2	2
19.	TBC	2	2
20.	Dermatitis	1	1
21.	Sirosis hati, hepatitis virus kronis C	1	1
22.	Tanpa penyakit penyerta	21	21
	Total	100	100

Source: Secondary data (medical records)

Comorbidities in diabetes mellitus patients at Citra Husada Hospital are the majority of diabetes mellitus with hypertension in 33 patients amounting to 33%. Insulin plays a role in increasing glucose uptake in many cells and in this way also regulates carbohydrate metabolism, so that if insulin resistance occurs by cells, glucose levels in the blood can also be disturbed. According to PERKENI, diabetes that is not well controlled will cause acute and chronic complications. Hypertension occurs due to atherosclerosis and large blood vessels, especially arteries due to atheroma plaque deposits and neuropathy due to damage and dysfunction in nerve structures due to increased polyol pathways, decreased myoinositol formation, decreased Na/K ATPase, thus causing damage to nerve structures, segmental demyelination, or axonal atrophy [12].

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Table 4. Results of Identification of a Combination of Two Oral Antidiabetic Drugs in Diabetes Mellitus Patients at Citra Husada Hospital

	Administration of Group 2 Drug Combinations	Medicine name	(n)	Persentage (%)	Total Persentage (%)
1	Sulfonilurea + Inhibitor DPP-4	Glimepirid+Vildagliptin	3	3	
		Gliclazide + Sitagliptin	1	1	
		Glimepirid+ Sitagliptin	1	1	
		Total	5	5	
2	Sulfonilurea + Biguanid	Glimepirid+Metformin	29	29	
		Gliclazide+ Metformin	5	5	
		Total	34	34	
3	Sulfonilurea + Tiazolidinedion	Glimepirid+Pioglitazon	50	50	
		Gliclazide + Pioglitazon	6	6	
		Jumlah	56	56	
4	Tiazolidinedion + Inhibitor DPP-4	Pioglitazon + Vildagliptin	1	1	
		Total	1	1	
5	Biguanid + Inhibitor DPP-4	Metformin+ Vildagliptin	1	1	
		Total	1	1	
6	Sulfonilurea+ penghambat alfa glukosidase	Glimepirid+Acarbose	1	1	
		Total	1	1	
7	Sulfonilurea +Sulfonilurea	Glimepirid+ Gliclazide	1	1	
		Jumlah	1	1	
8	Thiazolidindione+ penghambat alfa glukosidase	Pioglitazon +Acarbose	1	1	
		Total	1	1	100

Source: Medical Record Secondary Data

The 2 types of combination treatment that are often used in diabetes mellitus patients at Citra Husada Hospital are sulfonylureas and thiazolidinediones in 56 patients amounting to 56% and followed by a combination of 2 classes of sulfonylurea and biguanide drugs in 34 patients amounting to 34%. Combination therapy is by giving a combination of two or three groups of oral antidiabetics (ADO) if with single ADO the target blood glucose level has not been achieved. Therapy with combination ADO (separately or a fixed combination in the form of a single tablet), two types of drugs from groups that have different mechanisms of action must be selected [13].

Apart from choosing the type of antidiabetic, choosing the correct antidiabetic dose is also one of the factors that influences the success of therapy. Choosing the right dose can

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reduce the risk of hypoglycemia, which is one of the side effects of antidiabetics. In addition to using it correctly, choosing the antidiabetic dose can reduce the risk of side effects.

The main action of sulfonylureas is to increase insulin production from the pancreas. The mechanism of sulfonylurea drugs is to stimulate the release of stored insulin, reduce the insulin secretion threshold, and increase insulin secretion as a result of glucose stimulation [13], while the main action of thiazolidinediones drugs is to reduce insulin resistance by increasing glucose uptake and metabolism in muscle and tissue. adipose. This study is in line with research by Hanefeld, (2017) that the addition of pioglitazone to existing sulfonylurea therapy resulted in a 1.2% reduction in HbA1c after 1 year in 319 patients. This research is also in line with Maclsaac's (2018) research results which suggest that the addition of thiazolidinediones to the combination of metformin or sulfonylurea reduces HbA1c levels by 0.6-1.8% for 6-36 months.

This research is also in line with research by Mas Ulfa & Arfiana in 2020 which stated that the combination of glimepiride with pioglitazone is effective in reducing blood glucose levels because the two OADs have mutually supportive working mechanisms, namely they can stimulate insulin release. Apart from reducing blood glucose levels, pioglitazone can also normalize the lipid profile in diabetes mellitus patients by reducing triglycerides, free fatty acid and lipid peroxide and can improve low lipoprotein density. Glimepiride is a second generation Sulfonyl Urea (SU) with a working mechanism of activating β-pancreatic cells. After Glimepiride binds to the specific SU receptor, it will close ATP-sensitive potassium channels as a result of which insulin will be released from β-pancreatic cells. Research conducted at the UK Prospective Diabetes Study (UKPDS) on diabetes mellitus patients who received Sulfonyl Urea therapy including Glimepiride can reduce macrovascular complications in diabetes mellitus sufferers by 15%, the incidence of Acute Myocardial Infarction (AMI) decreased by 16%. The use of Glimepiride is highly recommended for diabetes mellitus patients on a fat diet. Glimepiride can reduce Fasting Plasma Glucose (FPG) and HBA1c.

Based on facts and theory, researchers assume that the thiazolidinediones group can be used with sulfonylureas or insulin and also metformin to reduce blood glucose levels. In this study, at Citra Husada Hospital, oral antidiabetic drugs were administered, namely sulfonylurea and thiazolidinediones, namely glimepiride and pioglitazone. The administration of antidiabetic drugs given is not in accordance with the first line use of a combination of antidiabetic drugs which should be given a combination of biguanides and sulfonylureas.

In this study, the dominant comorbidity of diabetes mellitus was hypertension. In this case, administration of sulfonylureas and pioglitazone is not appropriate, because they can increase the effect of antidiabetics and increase insulin sensitivity. The use of a combination of the drug glimepiride with the drug pioglitazone which is given simultaneously with hypertension drugs, for example telmisartan, can interact by increasing the effect of antidiabetic drugs, increasing insulin sensitivity, which can cause hypoglycemia in patients. (Abdelrazig, 2021). This class of drugs is given because the combination with metformin

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cannot be tolerated or is contraindicated, so the second choice is represented by thiazolidinediones (Derosa, 2017).

Thiazolidinediones are PPAR-γ agonists. This drug increases insulin sensitivity in muscle, liver and fat tissue indirectly. The prospective pioglitazone Clinical Trial In macrovascular Events (Proactive Study) study stated that pioglitazone reduces mortality from non-fatal myocardial infarction and stroke infarction in patients with type diabetes mellitus who are at high risk of macrovascular disease. The combination use of metformin and pioglitazone is associated with a reduction in total CVD events, the risk of ischemic stroke, and an increased risk of heart failure compared to the combination use of DPP4i and metformin (Bathari, 2020).

Sulfonylureas and thiazolidinediones exert their glucose-lowering effects through different mechanisms of action. Sulfonylureas stimulate insulin secretion, while thiazolidinediones are insulin sensitizers. Both agents offer excellent improvements in glycemic control when given as monotherapy or in combination (Sari, 2017). Thiazolidinediones protect the structural and functional integrity and functionality of b-cells and complement sulfonylureas by inducing and maintaining insulin elevation. This combination is particularly effective in the early stages of the disease when b-cell function is at its highest, allowing maximum benefit to be gained from the insulin secretory capabilities of the sulfonylureas and the b-cell protective effects of the thiazolidinediones [12].

Table 5. Results of Dosage Identification and Frequency of Combination of Two Oral Anti-Dabetes Drugs in Diabetes Mellitus Patients at Citra Husada Hospital in 2022

Administration of Group 2 Drug Combinations	Medicine name	Dosage (mg)	Frequency	(n)	Persentage (%)
Sulfonilurea + Inhibitor DPP-4	Glimepirid+ Vildagliptin	3 mg,50 mg	Pagi 1 tab, Siang 1 Tab	3	3
	Gliclazide + Sitagliptin	60 mg,30 mg	Pagi 1 tab, Siang 1 Tab	1	1
	Glimepirid+ Sitagliptin	4mg, 100mg	Pagi 1 tab, Siang 1 Tab	1	1
	Total			5	5
Sulfonilurea + Biguanid	Glimepirid+Metformin	2mg,500mg	Pagi 1 tab, Malam 1 Tab	8	8
	Glimepirid+Metformin	2mg, 850mg	Pagi 1	1	1

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Administration of Group 2 Drug Combinations	Medicine name	Dosage (mg)	Frequency	(n)	Persentage (%)
	Glimepirid+Metformin	3mg, 500mg	Tab, Malam 1 Tab 2 kali sehari	8	8
	Glimepirid+Metformin	4mg, 500mg	Pagi 1 tab Malam 1 tab	23	23
	Glimepirid+Metformin	4mg, 850mg	Pagi 1 tab Malam 1 tab	2	2
	Gliclazide + Metformin	80mg,500 mg	Pagi 1 tab, Siang 1 tab	1	1
	Gliclazide +Metformin	60mg,500mg	Pagi 1tab, Siang 1 Tab	1	1
	Total			37	37
Sulfonilurea + Tiazolidine Dion	Glimepirid,+Pioglitazon	3mg, 30mg	Pagi 1 tab, siang 1 tab	35	35
	Glimepirid+ Pioglitazon	4mg, 30mg	Pagi 1 tab, siang 1 tab	15	15
	Pioglitazon+ Gliclazide	30mg,80mg	Pagi 1 tab, siang 1 tab	1	1
	Gliclazide + Pioglitazon	60mg,30mg	Pagi 1 tab, siang 1 tab	3	3
	Gliclazide + Pioglitazon	80mg,30mg	Pagi 1 Tab, malam 1 Tab	2	2
	Gliclazide +Pioglitazon	60mg,30mg	Pagi 1 tab, siang 1 tab	1	1
	Total			53	53

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Administration of Group 2 Drug Combinations	Medicine name	Dosage (mg)	Frequency	(n)	Persentage (%)
Tiazolidine dion + Inhibitor DPP-4	Pioglitazon + Vildagliptin	30mg, 50mg	Siang 1 Tab, Pagi 1 Tab, Malam 1 Tab	1	1
	Total			1	1
Biguanid + Inhibitor DPP-4	Metformin+ Vildagliptin	500mg,50mg	Pagi 1 tab, siang 1 tab	1	1
	Total			1	1
Sulfonilurea+ penghambat alfa glukosidase	Glimepirid+Acarbose	4mg,50mg	Pagi 1 tab Malam 1 tab	1	1
	Jumlah			1	1
Sulfonilurea + Sulfonilurea	Glimepirid+ Gliclazide	4mg, 60mg	Pagi 1 tab, siang 1 tab	1	1
	Jumlah			1	1
Thiazolidindion+ penghambat alfa glukosidase	Pioglitazon +Acarbose	30mg, 100 mg	Pagi 1 tab, siang 1 tab	1	1
	Jumlah			1	1
		Total			100

Source: Secondary data (medical records)

Dosage and frequency of the combination of two oral anti-diabetic drugs in diabetes mellitus patients at Citra Husada Hospital, mostly sulfonylurea and thiazolidinediones, namely the combination of glimepirid, a dose of 3 mg with a frequency of once a day, taken in the morning and pioglitazone, a dose of 30 mg, once a day, taken in the morning. during the day as many as 35 patients amounting to 35%. The glimepirid dosage is 1 mg, 2 mg, 3 mg, and 4 mg once a day, while the pioglitazone dosage is 15 mg, 30 mg, and 45 mg once a day (DiPiro et al, 2020). The administration of glimepirid is before meals and pioglitazone does not depend on meal times [18]. In the treatment of diabetes mellitus, administering drug doses as far as possible must take into account the condition of the function of the body's organs, for example the condition of the function of the kidneys which has decreased function so that when administering drug doses as therapy it will have an effect. The time interval for using a drug is very important in using a drug because it can affect the

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duration of the drug's effectiveness, namely the time difference between the time it starts working and the time it takes for the drug to fall back to the minimum concentration. Inappropriate drug use intervals can lead to inappropriate drug use frequency [19].

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CONCLUSION

The use of a combination of two oral antidiabetic drugs at Citra Husada Hospital, namely the sulfonylurea and thiazolidinediones with the drug names glimepiride and pioglitazone. Dosage and frequency of the combination of two oral anti-diabetic drugs at Citra Husada Hospital, namely glimepirid, dose of 3 mg, once a day every morning, with pioglitazone, dose of 30 mg, frequency once a day in the afternoon.

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