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Evaluation of Antidiabetic Drug Use in Type 2 Diabetes Mellitus Patients with Chronic Kidney Disease at Dr. M. Djamil Hospital Padang

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Abstract:- Type 2 diabetes mellitus is a disease caused by disturbances in the metabolism of carbohydrates, proteins, and fats, characterized by hyperglycemia. This disease is one of the risk factors for chronic kidney disease, which can affect life expectancy. This study aims to determine the pattern of antidiabetic drug use and the rationality of drug use, as well as its relationship with the patient's discharge condition. This retrospective study collected medical record data of type 2 diabetes mellitus patients with chronic kidney disease in 2018. The study found that 61 patients met the inclusion criteria. Based on sociodemographic characteristics, the majority of patients were female (68.9%), aged 46-55 years (36.1%), had completed high school education (47.5%), and were housewives (57.4%). The pattern of antidiabetic drug use in type 2 diabetes mellitus patients with chronic kidney disease was as follows: 13.11% of patients used novorapid, 11.47% used lantus, 11.47% used gliclazide, 1.63% used glimepiride, 37.7% used a combination of novorapid with levemir, 3.27% used a combination of novorapid with lantus, 3.27% used a combination of novorapid with gliclazide, 6.55% used a combination of lantus with apidra, 1.63% used a combination of levemir with gliclazide, and 9.83% used intravenous critical insulin drip. The rationality of drug use was 100% appropriate indication, 95.08% appropriate drug selection, 100% appropriate patient, 100% appropriate dose, 100% appropriate frequency, and 100% appropriate administration route. The chi-square test and Kruskal-Wallis test showed a p-value >0.05, indicating no significant relationship between sociodemographic characteristics and patient discharge condition, as well as no significant relationship between the rationality of antidiabetic drug use and patient discharge condition.

Keywords:- *Chronic Kidney Disease, Antidiabetic Drug, Rational, CKD, Type 2 Diabetes Mellitus.*

I. INTRODUCTION

Diabetes mellitus is a group of diseases that results from disturbances in carbohydrate metabolism, caused by reduced insulin secretion, decreased insulin activity, or a combination of both factors. It is characterized by increased blood sugar levels or hyperglycemia (1). Type 2 diabetes mellitus is the most commonly encountered type, caused by disruptions in the β cell receptor of the pancreas. Its prevalence continues to rise annually, accounting for almost 90% of cases. In the United States, the incidence rate reaches 9.6% in patients aged 20 years and above (2).

The prevalence of diabetes mellitus in the world had already hit 425 million people in 2017, with 98 million cases occurring in individuals aged between 65-79 years and 327 million cases in individuals aged between 20-64 years. The International Diabetes Federation predicts that the number of people with diabetes mellitus will escalate to 629 million by 2045. Indonesia is ranked as the 7th country with the highest prevalence of diabetes mellitus globally. A research called Basic Health Research (Riskesdas) in 2018 showed that the prevalence of diabetes mellitus in Indonesia increased by 1.6% from 2013 to 2018, with blood tests conducted on patients aged 15 years and above. According to the health profile of Padang city, diabetes mellitus was recorded as one of the most common diseases in 2016, with a total of 22,523 cases. In 2017, the number of people with type 2 diabetes mellitus or NIDDM (Non-Insulin Dependent Diabetes Mellitus) in Padang city was 13,795, which still ranks among the top 10 diseases experienced by the local community. (5)

To effectively manage diabetes mellitus, immediate action should be taken due to the potential complications it presents such as heart disease, neuropathy, retinopathy, stroke, and kidney failure (6). The management of this condition involves both non-pharmacological and pharmacological therapies. Non-pharmacological therapies include regular exercise, physical activity, education, and dietary management. On the other hand, pharmacological therapies involve the use of drugs such as insulin or oral antidiabetic medications (7). Oral antidiabetic medications for type 2 diabetes mellitus treatment include the sulfonylurea, biguanide, meglitinide, thiazolidinedione, alpha-glucosidase inhibitor, DPP-4 enzyme inhibitor, and SGLT-2 inhibitor groups (8). Effective therapy for diabetes mellitus involves achieving normal blood sugar levels, reducing symptoms of complications such as retinopathy, neuropathy, and nephropathy, as well as lowering the risk of cardiovascular disease (9).

According to Oktrian's (2016) study, the use of antidiabetic drugs at Dr. M. Djamil Padang Hospital has become more accurate and rational, although 2.82% of the 72 patients studied were found to have inaccuracies. Alishia's research (2018) discovered drug use inaccuracies of 5.41% and dosing regimen inaccuracies of 4.35%. In another study conducted by Nurul in a hospital in Denpasar, 3 out of 72 samples studied had inaccuracies in drug selection. Similarly, Nova et al. (in Semarang) found a case of dose inaccuracy of 3.5%. Dedy et al.'s research in Padang revealed patient inaccuracies of 4.41% and dosing regimen inaccuracies of 59.18%. The irrational use of drugs has an impact on the clinical outcomes of patients. Furthermore, the use of inappropriate drugs is one of the significant risk factors for the occurrence of complications in this disease (10-14).

The kidneys play a crucial role in the excretion of antidiabetic drugs, including both oral medications and insulin. If the kidneys are overworked, the glomerular filtration rate may decrease, leading to complications such as chronic kidney disease. Due to the high prevalence of type 2 diabetes mellitus and its associated complications, it is important to manage this disease effectively through both pharmacological and non-pharmacological means. According to Ministry of Health Regulation No. 72 of 2016, one of the services provided by clinical pharmacists in hospitals is to assess the use of medications in patients. This assessment is aimed at gaining an understanding of medication usage patterns and identifying areas for improvement. The appropriateness of therapy is influenced by various factors, including the diagnostic process, selection of therapy, administration of therapy, and therapy evaluation. Conducting drug use evaluations is a structured process for ensuring that medications used are suitable, safe, and efficient, and it is performed on an ongoing basis as part of quality assurance efforts. (15)

Diabetes mellitus is a chronic disease that must be managed because it can lead to various complications and even death. Therefore, an evaluation is needed regarding the use of antidiabetic drugs in patients with type 2 diabetes mellitus and chronic kidney disease.

II. RESEARCH METHOD

A. Research Design and Data Collection

The method used in this study was descriptive analytic with a cross-sectional approach. Data collection was conducted retrospectively. The sampling technique used was purposive sampling. This study was conducted from September 2019 to January 2020 in the medical records installation of Dr. M. Djamil Padang Teaching Hospital. The inclusion criteria in this study were patients diagnosed with type 2 diabetes mellitus with chronic kidney disease in the internal medicine ward of Dr. M. Djamil Padang Teaching Hospital during the period of January-December 2018 who received antidiabetic therapy. Data collected included patient identity (medical record number, patient name, gender, age, occupation, highest education level), diagnosis, CKD stage, discharge condition, and therapy data (drug name, dose, route of administration, and frequency).

B. Data Analysis

The data were analyzed descriptively to determine the sociodemographic and clinical characteristics of patients towards their discharge condition and the rationality of antidiabetic drug use. Data were analyzed using chi-square and Kruskall Wallis tests with a 95% confidence interval (α=5%) using the SPSS program, then presented in tabular form. Conclusion was drawn based on the analysis results compared to the literature.

C. Ethical Approval

This study obtained ethical approval from the Health Research Ethics Committee Dr. M. Djamil Padang Hospital, West Sumatra, Indonesia (No. 344/KEPK/2019).

III. RESULTS AND DISCUSSION

There were 61 patients who met the inclusion criteria. The sociodemographic and clinical characteristics of the patients can be seen in table 1.

Table 1 The sociodemographic and clinical characteristics of the patients (n=61)

Demographic and clinical characteristics	Frequency (%)
Gender	
Male	19 (31.1)
Female	42 (68.9)
Age (year)	
26-35	3 (4.9)
36-45	12 (19.7)
46-55	22 (36.1)
56-65	18 (29.5)
>65	6 (9.8)
Education	
Elementary School	16 (26.2)
Junior High School	10 (16.4)
Senior High School	29 (47.5)
University	6 (9.8)
Employment	
Civil servant	1 (1.6)
Enterpriser	13 (21.3)
housewife	35 (57.4)
Other	8 (13.1)
No-working	4 (6.6)
Stage of CKD	
Stage III	1 (1.6)
Stage IV	5 (8.2)
Stage V	55 (90.2)
The patient's discharge condition	
Improve	46 (75.4)
Die	13 (21.3)
Not yet cured	2 (3.3)

According to the sociodemographic characteristics of the patients, the majority of individuals suffering from type 2 diabetes with CKD are females, comprising 68.9% of the population. Research by Hongdiyanto suggests that the prevalence of type 2 diabetes is typically higher in women than in men, which may be attributed to the higher likelihood

of women having an increased body mass index (BMI). Additionally, the distribution of body fat is more easily accumulated in women due to factors such as premenstrual syndrome and postmenopause (16). After conducting bivariate analysis using a chi-square test, a p-value of 0.842 was obtained, indicating that the patient's gender is not significantly associated with their discharge condition.

According to the age range of the patients, the group between 46-55 years old is the most affected by type 2 diabetes. This finding is consistent with the research carried out by Oktrian (2017) where the highest frequency of patients with type 2 diabetes occurs in the age group above 45 years, around 70.43%. This suggests that individuals over the age of 45 are highly vulnerable to type 2 diabetes. This susceptibility is not only due to a decrease in body function and hormones but also to the low glucose diet control, which can lead to the depletion of pancreatic beta cells responsible for regulating insulin hormone secretion (10). Based on bivariate analysis, the obtained p-value is 0.948 ($p>0.05$), indicating that the patient's age range is not significantly related to the patient's discharge condition.

According to the study, the highest percentage of patients, which is 47.5%, had completed high school as their last education level. These findings are consistent with I Made Mertha's research in Denpasar in 2015, where high school graduates accounted for the highest percentage of individuals suffering from type 2 diabetes, at 40%. A person's educational level can influence their behavior in receiving information, including information about the disease and how to control risk factors that may lead to type 2 diabetes (17). The bivariate analysis revealed a p-value of 0.719 (>0.05), indicating that there is no significant relationship between a person's level of education and their discharge condition.

The majority of patients who suffer from type 2 diabetes are housewives, with a prevalence of 57.4% based on their employment status. According to Riskesdas in 2007, the highest prevalence of type 2 diabetes was observed among housewives. Grant's study in Adelaide, Australia suggested that individuals who are unemployed have a higher likelihood of developing type 2 diabetes (24). The bivariate analysis indicated a p-value of 0.493 ($p>0.05$), which implies that there is no significant association between employment status and the patient's discharge condition.

Furthermore, the study revealed that the most commonly found complication in patients with type 2 diabetes was CKD stage V, which accounted for 90.2%. This finding is consistent with Biff F. Palmer's research in the United States, where 44% of the studied sample suffered from type 2 diabetes with chronic kidney disease or CKD stage V. Type 2 diabetes is considered a risk factor for chronic kidney disease and cardiovascular disease (18). The bivariate analysis showed a p-value of 0.705 ($p>0.05$), indicating that there is no significant association between CKD stage and the patient's discharge condition.

The majority of type 2 diabetes patients with CKD who were discharged from the internal medicine ward of RSUP Dr. M. Djamil Padang showed improvement, with 46 patients (75.4%) experiencing this positive outcome. This suggests that the treatment of type 2 diabetes with CKD in this ward has been carried out to the fullest extent, even though it has not yet achieved a 100% success rate. These findings are consistent with those of Oktrian's study, which found that more patients were discharged with improved conditions than those who left in a deceased state (10).

Table 2. Drug usage pattern in Type 2 Diabetes Mellitus Patients with Chronic Kidney Disease (n=61)

Class of Drugs	**Frequency (%)**
Rapid acting insulin	8 (13.11)
Long acting insulin	7 (11.47)
Oral antidiabetic drug	8 (13.1)
Rapid acting insulin+ long acting insulin	29 (47.52)
Rapid acting insulin+ Oral antidiabetic drug	2 (3.27)
long acting insulin+ Oral antidiabetic drug iv Insulin	1 (1.63) 6 (9.83)

The data on medication usage suggests that type 2 diabetes patients with CKD tend to use insulin as their antidiabetic treatment. This finding is in line with Oktrian's study (2017) that shows hospitals mainly use insulin for managing high blood sugar levels in diabetic patients. Oral antidiabetic drugs such as biguanides and alpha-glucosidase inhibitors should be avoided for type 2 diabetes patients with kidney impairment, specifically with a glomerular filtration rate of less than 30 mL/minute/1.73. Therefore, insulin is the primary modality for managing such cases (8), (10). The most frequently used type of insulin is a combination of rapid-acting insulin and long-acting insulin. This is due to the fact that this combination can better lower blood sugar levels, fulfill basal and prandial insulin needs, and control blood glucose fluctuations, hypoglycemia, and weight gain in patients (19).

Table 3. Evaluation of Antidiabetic Drug Use (n=61)

Type of evaluation	**Frequency (%)**
appropriate indication	61 (100)
appropriate patient	61 (100)
appropriate drug selection	58 (95.08)
appropriate dose	61 (100)
appropriate frequency	61 (100)
appropriate administration route	61 (100)

The accuracy of indication in type 2 diabetes patients with CKD in the internal disease ward of RSUP Dr. M. Djamil Padang in 2018 was 100% accurate indication. An antidiabetic drug is said to have an accurate indication if the patient is given a drug that is appropriate for the doctor's diagnosis to treat the disease they are suffering from. Antidiabetic drugs are given to patients diagnosed with type 2 diabetes with classic symptoms/complaints and high blood sugar levels. The results of this accuracy of indication are in line with Nurul's (2016) and Dedy's (2015) research, which showed an accuracy of indication of 100%. This is because

the inclusion criteria were type 2 diabetes patients who were hospitalized with uncontrolled blood sugar levels (13), (14). The Kruskal-Wallis test showed a p-value of 1.000 (p>0.05), indicating no significant relationship between accuracy of indication and patient discharge condition.

The precision of medication refers to medication that is given to patients that is appropriate for their condition or drug of choice. The precision of drug selection in this study was found to be 95.08%. Two cases were identified in patients with codes P7 and P21, in which the prescribed antidiabetic medications were Novorapid and Gliclazide. However, this combination was deemed inappropriate because, according to the American Diabetes Association in 2015, the use of oral antidiabetic drugs such as sulfonylureas, DPP IV inhibitors, and GLP-1 agonists should be avoided or discontinued during insulin therapy. Combining sulfonylureas (such as Gliclazide) with insulin is not recommended because they work by increasing insulin hormone secretion, which can result in hypoglycemia. This was confirmed in this study with patient code P7, whose final blood sugar level was only 67 mg/dL, and the target fasting blood sugar level had not been achieved (9), (20).

The third case was found in a patient with code P10 who was prescribed a combination of Levemir and Gliclazide antidiabetic drugs. Similar to the previous cases, the use of this combination of antidiabetic drugs is not recommended by ADA. This study is in line with Mogensen's research (2014) where the combination of insulin with sulfonylurea drugs can cause hypoglycemia and also increase the risk of stroke and cardiovascular disease (20), (21). The Kruskal-Wallis test yielded a p-value of 0.603 (p>0.05), indicating no significant relationship between the accuracy of drug selection and the patient's discharge condition. The medication accuracy for patients with type 2 diabetes mellitus and CKD in the internal medicine ward of Dr. M. Djamil Padang Hospital in 2018 was reported to be 100%. The researchers attributed the appropriateness of the antidiabetic drugs given to the fact that they were not contraindicated with the patients' physiological and pathological conditions. The Kruskal Wallis test yielded a p-value of 1.000 (p>0.05), indicating no significant relationship between medication accuracy and patients' discharge conditions. However, Dedy's study reported a medication inaccuracy rate of 4.41%. In this particular case, several patients had common complaints of nausea, bloating, and itching with fasting blood sugar levels of 115 mg/dL and 2-hour postprandial blood sugar levels of 130 mg/dL. These patients were prescribed metformin, which could significantly affect their digestive tract and worsen their condition (14).

The precision of administering medication at the correct frequency is 100%. The Kruskal Wallis test revealed a p-value of 1.000 (p>0.05), indicating that there is no significant correlation between the precision of medication frequency and patients' discharge status. The precision of medication frequency was assessed using patient medical records. Fast-acting insulin such as Novorapid and Apidra is administered three to four times daily, whereas long-acting insulin such as Lantus and Levemir is given once per day in the evening. Oral antidiabetic medications like gliclazide are prescribed 1-3 times per day, and glimepiride only requires once-a-day dosing (9). Medication frequency is typically aligned with established intervals and guidelines. However, administering medication too frequently, such as four times a day, may reduce medication adherence and, consequently, impact the patient's discharge status (22).

The accuracy of medication route is 100%. Based on the Kruskal Wallis test, the obtained p-value was 1.000 (p>0.05), which means there is no significant relationship between medication route accuracy and patients' discharge conditions. The administration of both fast-acting and long-acting insulin is given subcutaneously because the absorption is usually slow and constant, resulting in a long-lasting effect. Meanwhile, gliclazide and glimepiride are given orally. For critical intravenous drip, it is given intravenously. This medication route is carried out in critical conditions or during pre-operation. The purpose is to ensure that the medication is not absorbed and has a faster effect compared to subcutaneous administration (14), (22).

The accuracy of drug dosage is 100%. From the Kruskall Wallis test, the p-value obtained was 1.000 (p>0.05), which means there was no significant relationship between drug dosage accuracy and patients' discharge conditions. To determine the accuracy of insulin dosage in type 2 diabetes mellitus patients with CKD, it is calculated based on the total daily insulin (TDI). To determine TDI, the patient's weight is needed, where TDI is given at a rate of 0.5-1 unit/kg BW. Of the total daily insulin, 60% is rapid-acting insulin given three times a day (insulin prandial) and 40% is long-acting insulin given once a day at night before bed. According to NKF KDOQI in 2012, the use of insulin in type 2 diabetes mellitus patients with CKD, whether in stage 3, 4, or 5, does not require dosage adjustment as insulin use is based on patient response. For dosage adjustment of sulfonylurea drugs in diabetes mellitus patients with CKD, the glimepiride dose usually starts at 1 mg once a day, and the use of glibenclamide should be avoided in diabetes mellitus patients with kidney disease. For other second-generation sulfonylurea drugs such as glipizide, gliclazide, and gliquidone, no dosage adjustment is necessary (8) (23). In contrast to Dedy's study at a hospital in Padang City, there was a 59.18% inaccuracy of dosage regimen in patients. Novorapid (rapid-acting insulin) is injected 15 minutes before or immediately after a meal to help control metabolism and transport glucose from the blood into cells so that the patient's blood sugar level can be eached. However, in Dedy's study, some patients were not injected with insulin because they had eaten before. Type 2 diabetes mellitus patients should still be given The precision of drug dosing is perfect at 100%. The Kruskall Wallis test shows a p-value of 1.000 (p>0.05), indicating that there is no significant correlation between the accuracy of drug dosing and patients' discharge conditions. In type 2 diabetes mellitus patients with CKD, the accuracy of insulin dosing is calculated based on the total daily insulin (TDI), which requires the patient's weight, with a TDI dose of 0.5-1 unit/kg BW. Rapid-acting insulin accounts for 60% of the TDI and is administered three times daily (insulin prandial), while long-acting insulin makes up 40% and is given once a day at night before bed. According to NKF KDOQI in 2012, there is no need to adjust insulin doses for type 2 diabetes mellitus patients with CKD,

regardless of whether they are in stage 3, 4, or 5, as insulin use is based on the patient's response. To adjust the dosage of sulfonylurea drugs in diabetes mellitus patients with CKD, the glimepiride dose typically begins at 1 mg once a day, and glibenclamide should be avoided in diabetes mellitus patients with kidney disease. No dosage adjustment is necessary for other second-generation sulfonylurea drugs such as glipizide, gliclazide, and gliquidone (8) (23). In contrast to Dedy's study at a hospital in Padang City, 59.18% of patients had an inaccurate dosing regimen. Novorapid (rapid-acting insulin) is administered 15 minutes before or immediately after a meal to help regulate metabolism and glucose transport from the blood into cells, leading to the attainment of normal blood sugar levels. However, some patients were not given insulin in Dedy's study because they had already eaten. Type 2 diabetes mellitus patients should still be given insulin to maintain blood sugar levels close to normal levels (14).

CONCLUSION

The rational use of drugs is 100% accurate in terms of indication, patient, dosage, frequency, and route of administration, and 95.08% accurate in terms of drug selection. There was no significant relationship between the accuracy of drug use and the patient's discharge condition.

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