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Evaluation of Anti-diabetic Drugs using ATC/DDD and DU90% Methods in Diabetes Mellitus Patients

(*Evaluasi Obat Antidiabetik menggunakan Metode ATC/DDD dan DU90% pada Pasien Diabetes Melitus*)

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ABSTRACT

Background: Diabetes Mellitus (DM), which results from insulin resistance, is closely linked to long-term damage to pancreatic beta cells, organ dysfunction, and organ failure, particularly in the eyes, kidneys, nerves, heart, and blood vessels. The development of the ATC/DDD system is necessary to increase global drug knowledge, ensure equitable drug availability, and promote responsible drug use. **Objectives:** This study aimed to identify data on patient characteristics and oral anti-diabetic drugs and insulin using the ATC/DDD and DU90% methods. **Material and Methods:** This study was a cross-sectional evaluation of oral anti-diabetic medications and insulin using the ATC/DDD method and DU90% at the Bala Keselamatan Bokor Turen Hospital from January to December 2022. The inclusion criteria were patients diagnosed with type 1 or type 2 diabetes mellitus, with or without comorbidities, who were treated with oral anti-diabetic medications and a combination of insulin and oral medications. In the present study, the incomplete medical record data served as the exclusion criteria. The sample for this investigation consisted of 238 patients selected using the complete sampling technique. **Results:** Most patients who used oral anti-diabetic medications and insulin were between the ages of 46 and 65 (71.34%), were female (73.2%), had standard body mass index (BMIs between 18.5 and 25), and had diagnoses of DM + HT (20.73%) and Type II DM (18.29%). Glulisin was the most used anti-diabetic drug, accounting for 589 DDD/100 days of hospitalization, and DU90% was 21.39%. **Conclusion:** Glulisin is the most frequently prescribed anti-diabetic medication at Bokor Turen Hospital.

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder. Risk factors, damage to insulin secretion, and sensitivity lead to increased blood glucose and changes in fat and protein metabolism (DiPiro, 2020). The lack of insulin function contributes to the development of microvascular, macrovascular, and neuropathy as a chronic consequence of DM (Almasdy *et al.*, 2015).

The *World Health Organization* (WHO) in 2023 states that in 2014, 8.5% of adults aged 18 years and over have diabetes. In 2019, diabetes was the direct cause of 1.5 million deaths, and 48% of all deaths from diabetes occurred before the age of 70. Furthermore, 460,000 deaths from kidney disease are caused by diabetes, and elevated blood glucose causes about 20% of deaths from cardiovascular disease (WHO, 2023). DM is more common in low- and moderate-income countries and countries undergoing major economic and demographic transformations. DM is a significant global health problem and requires proper prevention and management measures. DM in Indonesia is currently a serious problem. Most DM sufferers are type 2 DM groups. Therefore, it is essential to evaluate the use of the drug as a basis for selection to ensure that the drug is used appropriately, safely, and efficiently (Pitasari, Andayani, and Wijayanti, 2022).

There is a need to develop ATC/DDD systems to acquire knowledge about drug use worldwide to achieve equitable drug availability and prudent drug use, especially in developing countries. The primary purpose of the ATC/DDD system is to facilitate research on drug use and improve the overall quality of drug use (Tahar *et al.*, 2020). A retrospective study using a *cross-sectional study*, which evaluated drug use patterns and costs associated with Type 2 DM in Saudi Arabia, showed that biguanide (metformin) was most widely prescribed as a monotherapy drug followed by a *fixed-dose combination*. The effectiveness of monotherapy drugs decreases with the duration of treatment; in these cases, combination drugs are prescribed. The most commonly prescribed combination drug is a biguanide with sulfonylurea/biguanide with thiazolidinedione, according to guidelines by the *American Diabetes Association* (ADA). The combination of sitagliptin and metformin is most widely preferred and widely prescribed in *fixed-dose combination therapy*, followed by vildagliptin and metformin (Ali *et al.*, 2022). Combination drugs are used when a single pill cannot achieve the desired blood glucose level in diabetic patients (Okoro, Nmeka, and Erah, 2018).

Evaluation of the use of anti-diabetic drugs with ATC/DDD and DU90% methods can provide insight into the dominant drug use patterns and the extent to which these drugs follow existing treatment recommendations and guidelines. Therefore, this study evaluated oral anti-diabetic drugs and insulin using ATC/DDD and DU90% in DM patients with and without comorbidities at the Bokor Turen Salvation Army Hospital, a hospital with type D accreditation. Previous research in the form of case

studies analyzing the problem of non-compliance of Diabetes Mellitus patients at Bokor Turen Hospital (Chrisnawati, 2020), so the researcher wants to continue the study on evaluating the use of oral drugs and insulin in the same hospital.

MATERIAL AND METHODS

Research Methods

The study design used *a cross-sectional study* with retrospective data collection through patient medical records. Quantitative evaluation of the use of anti-diabetic drugs using ATC / DDD and DU 90% techniques. This research has gone through the health research ethics committee with no E.5.a/145/KEPKUMM/V/2023.

Population and Sample

This population consists of patients hospitalized with a diagnosis of DM and without comorbidities at the Bokor Turen Salvation Army Hospital. The study sample included patients hospitalized with a diagnosis of DM and without comorbidities from January to December 2022 and who met the inclusion and exclusion criteria. Inclusion criteria include patients aged ≥ 17 years with a diagnosis of DM and without comorbidities. Exclusion criteria were patients whose medical record data was incomplete.

Sampling Techniques

The sampling technique was total sampling, where the number of samples was equal to a population of 164 patients and met the criteria for inclusion and exclusion of the study.

Data Analysis

The calculation in evaluating the use of ATC / DDD method anti-diabetic drugs in the hospitalization of the Bokor Turen Salvation Army Hospital uses the formula:

$$\frac{\text{DDD}}{100}\text{bed} - \text{days} = \frac{\text{total antibiotics (gram)}}{\text{DDD WHO (gram)}}\text{x}\,\frac{100}{\text{LOS}}$$

DU 90% is used to identify the amount of drug used as much as 90% of the total use of prescribed medicines and compare it with the amount of residual drug use (RI, 2017). The efficiency of drug use must be observed if the amount of drug use in 10% is more. The DU value of 90% is known after calculating DDD / 100 days of hospitalization per year.

RESULTS

Demographic Characteristics of Diabetes Mellitus Patients

The demographic characteristics of Diabetes Mellitus patients at the Bokor Turen Salvation Army Hospital from January to December 2022 were 238. This study's sample size was 164 patients in age, gender, BMI, diagnosis, comorbidities, drug names, administration intervals, and duration of

administration. Judging from the most significant number, in the age characteristics of 117 patients aged 46-65, as many as 120 were female, and as many as 88 patients had a regular Body Mass Index (BMI) of 18.5-25 (Table 1).

Table 1. Data on the Characteristics of Diabetes Mellitus Patients

Characteristic of Patient	Parameter	n (%)
Age	17-45	12 (7,32)
	46-65	117 (71,34)
	66-95	35 (21,34)
Mean ± SD	58,78 ± 2,52	
Gender	Female	120 (73,2)
	Male	44 (26,8)
BMI	Underweight <18,5	6 (3,66)
	Healthy weight 18,5-25	88 (53,66)
	Overweight >25	70 (42,68)
Mean ± SD	24,63 ± 1,08	

The description of DM and or without comorbidities at the Bokor Turen Salvation Army Hospital showed that the most patients with a diagnosis of DM and Hypertension (HT) were 34 patients (20.73%), followed by patients with a diagnosis of Type 2 DM as many as 28 patients (18.29%). At the same time, DM patients with other comorbidities have fewer than ten patients (Table 2).

Table 2. Description of Patients with Diabetes Mellitus and or Without Comorbidities

Diagnosis with comorbidities	n (%)
DM (HT)	34 (20,73)
DM Type 2	28 (18,29)
DM (HT, CAD)	6 (3,66)
DM (anemia)	5 (3,05)
DM (CAD)	5 (3,05)
DM (CKD)	5 (3,05)
DM (CVA)	5 (3,05)
DM (COPD)	5 (3,05)
DM (CVA, HT)	4 (2,44)
DM (anemia, thalassemia)	3 (1,83)
DM (dyspepsia)	3 (1,83)
DM (GERD, HT)	3 (1,83)
DM (HT, anemia)	3 (1,83)
DM (asthma)	2 (1,22)
DM (DKD)	2 (1,22)
DM (DKD, HT)	2 (1,22)
DM (HT, CKD)	2 (1,22)
DM (HT, HF)	2 (1,22)
DM (HT, Vertigo)	2 (1,22)
DM (STEMI)	2 (1,22)
DM (Vertigo)	2 (1,22)
DM (GERD)	1 (0,61)
DM (Anemia, PAD)	1 (0,61)
DM (AKI)	1 (0,61)
DM (Anemia, CKD)	1 (0,61)
DM (Anemia, Dyspepsia)	1 (0,61)
DM (Angina, Thalassemia)	1 (0,61)

Diagnosis with comorbidities	n (%)
DM (CAD, COPD)	1 (0,61)
DM (CAD, CVA, HT)	1 (0,61)
DM (CAD, HT)	1 (0,61)
DM (CAD, STEMI)	1 (0,61)
DM (CAD, TB)	1 (0,61)
DM (CKD, HT, TB)	1 (0,61)
DM (CKD, STEMI)	1 (0,61)
DM (CKD, Thallasemia)	1 (0,61)
DM (COPD, Dyspepsia)	1 (0,61)
DM (COPD, HT)	1 (0,61)
DM (CVA, susp. COVID-19)	1 (0,61)
DM (Gastritis)	1 (0,61)
DM (GERD, HF)	1 (0,61)
DM (Hepatitis)	1 (0,61)
DM (HF)	1 (0,61)
DM (HF, CAD, COPD)	1 (0,61)
DM (HF, Hepatitis)	1 (0,61)
DM (HT, HF, dyspepsia)	1 (0,61)
DM (HT, CA infarct)	1 (0,61)
DM (HT, CAD, GERD)	1 (0,61)
DM (HT, CAD, Parkinson)	1 (0,61)
DM (HT, COPD, CVA)	1 (0,61)
DM (HT, COPD, Dyspepsia)	1 (0,61)
DM (HT, Dyspepsia)	1 (0,61)
DM (HT, HF, CAD)	1 (0,61)
DM (HT, STEMI)	1 (0,61)
DM (myalgia)	1 (0,61)
DM (PAD)	1 (0,61)
DM (PAD, Vertigo)	1 (0,61)
DM Type 1 (HT)	1 (0,61)

CAD= coronary artery disease, CKD= chronic kidney disease, CVA= Cerebrovascular Accident, GERD= Gastroesophageal Reflux Disease, DKD= Diabetic Kidney Disease, HF= Heart Failure, PAD= Peripheral Artery Disease, AKI= Acute Kidney Injury, COPD= Coronary Obstructive Pulmonary Disease, STEMI= ST-Elevation Myocardial Infarction

The DM treatment profile seen in the 12 months of 2022 shows that anti-diabetic drugs are the most used in insulin glulisine, with a dose strength of 100U/ml in as many as 71 patients. This was followed by insulin glulisine with a dose strength of 100U / ml for as many as 57 patients. The third highest use was insulin aspart 100U / ml, as many as 54 patients. Concerning the administration interval of most anti-diabetic drugs, they are given every 24 hours a day, with the duration of most drug administration being 4-6 days (Table 3).

Table 3. Profile of Anti-diabetic Drug Use in Year 2022

Characteristic of Patient	Parameter	n (%)
Type of drug	Acarbose 50 milligrams	5 (1,7)
	Insulin Glulisine 100 IU/ml	57 (19,5)
	Insulin Glargine 100 IU/ml	71 (24,2)
	Glibenclamide 5 milligrams	3 (1)
	Gliquidone 30 milligrams	18 (6,1)
	Glimepiride 2 milligrams	18 (6,1)
	Glimepiride 3 milligrams	18 (6,1)
	Glimepiride 4 milligrams	18 (6,1)
	Insulin Lispro 100 IU/ml	7 (2,4)
	Insulin Detemir 100 IU/ml	38 (13)
	Metformin 500 milligrams	20 (6,8)
	Insulin Aspart 100 IU/ml	54 (18,4)
	Pioglitazone 30 milligrams	1 (0,3)
	Insulin Degludec + insulin Aspart 100 IU/ml	1 (0,3)
Interval of administration	24 hours	157 (53,6)
	12 hours	21 (7,2)
	8 hours	114 (38,9)
	6 hours	1 (0,3)
Duration of administration	1-3 days	127 (43,3)
	4-6 days	166 (56,7)

Evaluation of the Use of Anti-diabetic Drugs with ATC/DDD and DU 90% Methods

The results of the evaluation of the use of anti-diabetic drugs using the ATC / DDD method showed that the use of antidiabetics that are often used is insulin glulisine with a dose strength of 100U / ml of 589.02 DDD / 100 days of hospitalization, which means that during 100 days of treatment in the hospital around 589 diabetic patients received insulin glulisine amounting to 40 IU every day. The total number of patients hospitalized and using anti-diabetic drugs from January to December 2022 was 568 days. The second most significant use of anti-diabetic medications was insulin aspart with a dose strength of 100U / ml of 519.72 DDD / 100 days of hospitalization, which means that during 100 days of hospitalization in the hospital, around 520 DM patients received insulin aspart of 40 IU (Table 4).

Table 4. Analysis of the Use of Anti-diabetic Drugs using the ATC / DDD Method

No.	ATC code	Type of Drugs	DDD (WHO)	Length of Stay (LOS)	DDD/100 bed-days
1	A10AB06	Insulin Glulisine 100 IU/ml	40 IU	568 days	589,02
2	A10AB05	Insulin Aspart 100 IU/ml	40 IU		519,72
3	A10BB12	Glimepiride 2 milligrams	2 milligrams		474,28
		Glimepiride 3 milligrams			426,85
		Glimepiride 4 milligrams			221,38
4	A10AE04	Insulin Glargine 100 IU/ml	40 IU		426,85
5	A10AE05	Insulin Detemir 100 IU/ml	40 IU		221,38
6	A10BA02	Metformin 500 milligrams	2 grams		198,80
7	A10BB08	Gliquidone 30 milligrams	60 milligrams		129,22
8	A10AB04	Insulin Lispro 100 IU/ml	40 IU		85,20

No.	ATC code	Type of Drugs	DDD (WHO)	Length of Stay (LOS)	DDD/100 bed-days
9	A10BF01	Acarbose 50 milligrams	0,3 grams		43,55
10	A10BB01	Glibenclamide 5 milligrams	10 milligrams		31,24
11	A10BG03	Pioglitazone HCl 30 milligrams	30 milligrams		22,72
12	A10AD06	Insulin Degludec + insulin Aspart 100 IU/ml	40 IU		11,36

The 90% DU in this study was used to evaluate the use of anti-diabetic drugs in the top 90% of services in the population. There were 12 anti-diabetic assessed drugs in 90% DU, and showed that insulin glulisine, insulin aspart, glimepiride 2 milligrams, glimepiride 3 milligrams, glimepiride 4 milligrams, insulin glargine 100U/ml, insulin detemir 100U/ml, and metformin 500 milligrams were anti-diabetic drugs that accounted for 90% of the highest anti-diabetic drug use in the DM patient population at the Bokor Turen Salvation Army Hospital (Table 5).

Table 5. Profile of Anti-diabetic Drug Use with DU Method 90%

ATC code	Type of Drugs	DDD/100 bed-days	Percentage	Cumulative	DU 90% segment
A10AB06	Insulin Glulisine 100 IU/ml	589,02	21,39%	21,39%	DU90%
A10AB05	Insulin Aspart 100 IU/ml	519,72	18,88%	40,27%	
A10BB12	Glimepiride 2 milligrams Glimepiride 3 milligrams Glimepiride 4 milligrams	474,28	17,23%	57,49%	
A10AE04	Insulin Glargine 100 IU/ml	426,85	15,50%	73,00%	
A10AE05	Insulin Detemir 100 IU/ml	221,38	8,04%	81,04%	
A10BA02	Metformin 500 milligrams	198,80	7,22%	88,26%	
A10BB08	Gliquidone 30 milligrams	129,22	4,69%	92,95%	DU 10%
A10AB04	Insulin Lispro 100 IU/ml	85,20	3,09%	96,05%	
A10BF01	Acarbose 50 milligrams	43,55	1,58%	97,63%	
A10BB01	Glibenclamide 5 milligrams	31,24	1,13%	98,76%	
A10BG03	Pioglitazone 30 milligrams	22,72	0,83%	99,59%	
A10AD06	Insulin Degludec + Insulin Aspart 100 IU/ml	11,36	0,41%	100%	

DISCUSSION

Insulin glulisine (Apidra) in this study occurred in patients with Type 2 diabetes with comorbidities, such as hypertension, coronary artery disease (CAD), and chronic kidney disease (CKD). On average, DM patients who get insulin Apidra are given every 8 hours, and this drug is widely presented to 76% of female patients with an age range of 58-61 years. This insulin is widely recommended at the Bokor Turen Salvation Army Hospital because it can lower blood sugar levels quickly and has a more negligible risk of hypoglycemia. Following the 2021 PERKENI guidelines, insulin Apidra is a rapid-acting insulin generally used with food. Insulin Apidra is designed to rapidly decrease glucose levels in the blood after a meal or when blood glucose levels are high. Insulin Apidra is commonly combined

with basal insulins such as Lantus (insulin glargine) and Levemir (insulin detemir) (Soelistijo et al., 2021). A study examining the clinical effects of Type 2 DM patients with cardiovascular comorbidities where patients used insulin rapid-acting showed that it could have beneficial effects from insulin glulisine administration associated with death and stroke. Still, there was no difference in coronary heart disease (CHD) or cardiovascular disease (CVD) (Svensson et al., 2017).

Insulin aspart (novorapid) was given to patients with type 2 diabetes with comorbid HT accompanied by CAD, ST-Elevation Myocardial Infarction (STEMI), and Heart Failure (HF). The interval of insulin administration averaged every 8 hours per day and was used by 66% of female patients with an average of 58-61 years. Like insulin glulisine, insulin aspart can also quickly lower blood sugar levels and has a low risk of hypoglycemia. Insulin aspart is also rapid-acting, which provides therapeutic effectiveness after 15 minutes, with the peak of therapeutic efficacy occurring within 1-2 hours and can last up to 4-6 hours. In the case of the population in Japan, administering insulin aspart to type 2 DM patients can significantly reduce cardiovascular complications within 5 to 10 years, resulting in improved quality of life and lower costs compared to *human insulin* (Pollock et al., 2011).

The third most significant use of anti-diabetic drugs is glimepiride doses of 2 milligrams, 3 milligrams, and 4 milligrams. This drug is given to patients with type 2 diabetes with cardiovascular comorbidities and an interval of 24 hours per day and primarily female patients (83%) with an average age of 58 years. Regular glimepiride is combined with insulin or another oral medication such as metformin. Similarly, metformin was used in female patients (81%), with an average age of 58-61 years, a 12-hour drug administration interval and patients suffering from DM with cardiovascular comorbidities. Metformin is usually combined with glimperide or glibenclamide. In the case study of type 2 DM patients with CVD, the average patient suffering from DM was around 5.7 ± 4.8 years. CVD suffered by type 2 DM patients in the form of hypertension (68.5% of patients); dyslipidemia (47.9% of patients); CAD (25.4% of patients); Transient Ischemic Attack (TIA) in 3.6% of patients; peripheral artery disease (PAD) accounted for 4.8% of patients and heart failure in 2.9% of patients. Type 2 DM patients with various comorbidities receive the drug glimepiride/metformin Fixed Dose Combination (FDC) as a first-line therapy because glimepiride/metformin FDC is more effective than metformin alone for type 2 DM patients with comorbidities. As many as 68.2% of FDC patients achieved blood pressure within optimal limits. Most of the other patients experienced an increase in glycemic parameters and a change in body weight of about 18.4%. 59.2% of patients experienced weight loss (Ray et al., 2022). Glimepiride is a sulfonylurea class drug that has pharmacological effects to increase insulin production by pancreatic beta cells. The most common side effects are hypoglycemia and weight gain.

Insulin glargine was used in patients with type II DM with cardiovascular comorbidities. The dosage strength used was 100 IU/ml, with a 24-hour drug administration interval. Insulin glargine was mostly used by female patients (71%), and the average age was 58 years. According to a review article, the use of insulin glargine as a basal insulin analog lowers triglycerides causes less weight gain, causes less hypoglycemia when compared to intermediate-acting insulin and has a neutral effect on blood pressure (Joseph & Donner, 2015). According to The Outcome Reduction with Initial Glargine Intervention (ORIGIN trial), the results of the glargine trial showed no increase in cardiovascular risk (Gerstein et al., 2012).

The next anti-diabetic drug in the DU 90% is insulin detemir. In the market, this insulin was known as insulin Levemir (trade name). In this study, insulin detemir was mostly used by 69% of female patients with type II DM with cardiovascular comorbidities. The average age of the patients was 58 years, and the time interval of insulin administration was 24 hours. A systematic review study shows insulin detemir can improve glycaemic control with lower cardiovascular risk and no weight gain in patients with type II DM (Czech et al., 2015).

The limitation of this study is that data were taken only retrospectively from patients' medical record data, and no direct observations were made on DM patients. For Bala Keselamatan Bokor Turen Hospital to provide an overview of drug use patterns in patients with diabetes mellitus. The results of this study can later be used as a basis for determining the selection of anti-diabetic drugs for patients by applicable standards.

CONCLUSION

Based on the analysis of demographic data and treatment profiles of DM patients, DM patients are dominated by the age group of 46-65 years, with women who use anti-diabetic drugs more. Patients with comorbidities use more anti-diabetic medications than patients with non-comorbid DM. Evaluation of anti-diabetic drugs ATC / DDD method shows that insulin glulisine (Apidra) is most used in DM patients with and without comorbidities. Through the DU method, 90% of glulisine, aspart, glargine, glimepiride, detemir, and metformin drugs were most widely used in DM patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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