

Comparative Effectiveness of Antidiabetic Therapies on Clinical Outcomes in Type 2 Diabetes Mellitus Outpatients

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ORIGINAL ARTICLES

Submitted: 2 June 2025

Accepted: 1 July 2025

Keywords:

Antidiabetic drug, Effectiveness, Type 2 diabetes mellitus

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ABSTRACT

This study aims to determine the differences in the efficacy of oral antidiabetics, insulin, and combination therapy in outpatients with type 2 diabetes mellitus (T2DM). This study used observational analysis with retrospective data collection. A total of 303 outpatients with T2DM were included in this study. The research instrument used was secondary from medical record data and examination results of Fasting Plasma Glucose (FPG) and 2-hour plasma glucose (2-h PG) values when the patient first visited and the fourth month after the first visit. The patients' therapy is regarded as effective if the FPG test results range from 80-130 mg/dL and the 2-h PG test value is <180 mg/dL in the fourth month. In patients aged >60 years, it is said to be effective if the results of the FPG examination are around ≤ 180 mg/dL and the 2-h PG examination value is ≤ 200 mg/dL. Data were analyzed using Kruskal-Wallis analysis. Oral antidiabetics metformin and glimepiride had differences in observed effectiveness ($p=0.000$) < 0.05 for FPG and 2-h PG examinations in outpatients with type 2 diabetes mellitus. The type of oral antidiabetic glimepiride had differences in observed effectiveness ($p=0.002$) < 0.05 in the FPG examination and ($p=0.006$) < 0.05 in the 2-h PG examination. The oral antidiabetic drug groups metformin and glimepiride had differences in observed therapeutic effectiveness in outpatients with T2DM, while the insulin group and the combination group did not have differences in therapeutic effectiveness in T2DM patients.

Key Messages:

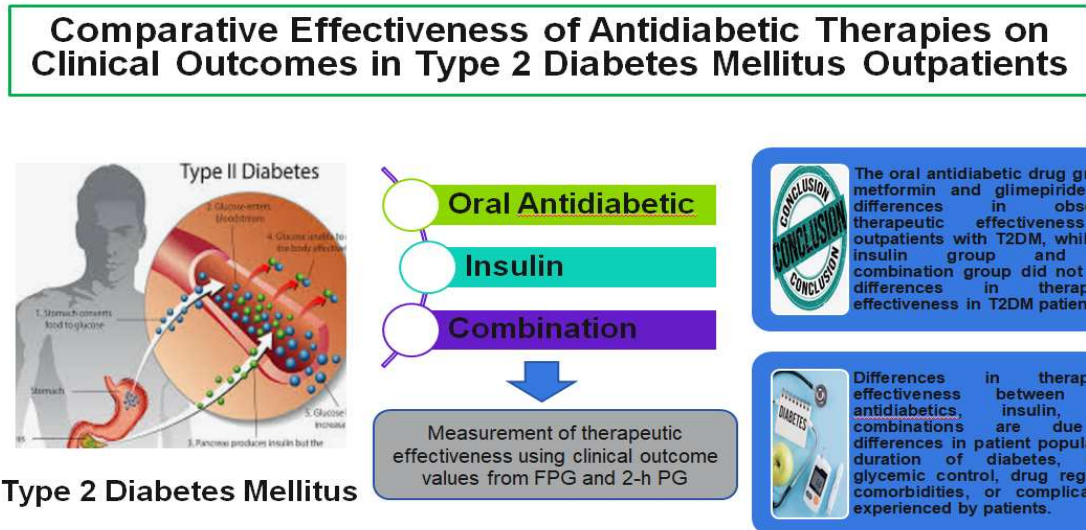
- Comparing the effectiveness of several types of antidiabetic therapy, namely the oral antidiabetic group, insulin group, combination group.
- Differences in therapeutic effectiveness between oral antidiabetics, insulin, and combinations are due to differences in patient population, duration of diabetes, initial glycemic control, drug regimen, comorbidities, or complications experienced by patients.

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GRAPHICAL ABSTRACT



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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex chronic disease that requires multifactorial treatment therapies and care behaviors to prevent and delay complications and maintain patients' quality of life (1). Continuous glucose monitoring (CGM) is increasingly used in the treatment of type 2 diabetes mellitus, but its effects on glycemic control remain unclear. This study aimed to provide a comprehensive overview of the effects of CGM on glycemic control in adults with type 2 diabetes mellitus. T2DM is a metabolic disorder that occurs in the body due to decreased insulin activity or secretion. Pathological changes that occur in the patient's body as the disease progresses can trigger complications such as nephropathy, retinopathy, and cardiovascular complications (2). T2DM is one of the main risk factors for death in cardiovascular disease (3).

Based on global study data, the number of people with DM has been increasing over the years. In 2021, 541 million people and 319 million adults had Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG), and are expected to increase to 730 million and 441 million adults by 2025 (4). The results of Riskesdas data in 2013 showed an increase in the incidence of DM from (6.9%) in 2013, increasing to (8.5%) in 2018 from a total population of 250 million. Many factors can increase the prevalence of DM such as the habit of having an unhealthy diet, obesity and lack of physical activity greatly contribute to the increasing prevalence of DM disease (5).

The provision of therapy in T2DM patients aims to control the patient's blood glucose levels to stay within the expected limits. Drug therapy is usually given if blood glucose levels cannot be controlled or if nondrug therapy is not successful (4). T2DM therapy can involve oral antidiabetic drugs, insulin, or a combination of Tiazolidindion (TZD), alpha-glucosidase inhibitors, DPP-4 (Dipeptidyl peptidase-4) inhibitors, SGLT2 (Sodium Glucose Cotransporter 2) inhibitors and insulin (6).

The effectiveness of drug therapy in T2DM patients varies between individuals. It depends on the patient's blood glucose control factors, the risk of hypoglycemia, the patient's condition, and the impact on the quality of life of T2DM patients. Research conducted by Jamaluddin in 2022 showed that oral drugs are more effective than insulin or combination therapies (insulin and oral) as seen in the change from initial to final blood glucose levels. A Single therapy refers to treatment with only one drug. The use of treatment in T2DM patients can be considered effective because oral antidiabetics, particularly biguanides such as metformin, are the first-line treatment for T2DM patients (7).

A comparative assessment of oral antidiabetic therapy, insulin, and combination therapy is warranted to delineate their respective impacts on clinical outcomes, thereby understanding how each approach affects outcomes such as glycemic control and the incidence of hypoglycemia. Based on this, this

study aims to see the effectiveness of oral, insulin, and combination therapy antidiabetics on the clinical outcomes of T2DM outpatients. The difference between this study and the research conducted by Jamaluddin in 2022 is that the researcher only used one type of antidiabetic drug measured in each group and the measurement of clinical outcomes using only the parameters of FPG values before and after therapy, while in this study using more than one type of drug in each group and measuring the clinical outcomes of patients using the parameters of FPG and 2-h PG value before and after therapy.

METHODS

Research Design

This study was conducted retrospective cohort. The samples in the study were T2DM outpatients selected by purposive sampling. Data collected in the form of secondary data, namely medical record data of outpatients with T2DM including patient identity, type of therapy, and antidiabetic drugs used by patients, as well as plasma glucose examination data, namely FPG and 2-h PG values the first time the patient visits and the following four months. The patients' therapy is regarded as effective if the FPG test results range from 80-130 mg/dL and the 2-h PG test value is <180 mg/dL in the fourth month. In patients aged >60 years, it is said to be effective if the results of the FPG examination are around ≤ 180 mg/dL and the 2-h PG examination value is ≤ 200 mg/dL. This study was conducted in the outpatient pharmacy unit of a hospital located in Central Sulawesi, Indonesia. This location was chosen based on the process of determining therapy, which is greatly influenced by the decision of internal doctors who has the authority as a prescription writer and the main clinical decision maker in the management of type 2 DM patients and the hospital as a secondary referral facility becomes a reference point for primary level service facilities.

Population and Sample

The population used was all patients with type 2 DM in the outpatient department at one of the hospitals in Central Sulawesi. The sample used in this study was outpatient type 2 DM patients with blood glucose results exceeding 200 mg/dL. Inclusion criteria in this study were patients aged 26-75 years and receiving oral antidiabetic therapy, insulin, or a combination. Exclusion criteria in this study were patients receiving a combination of two oral antidiabetic drugs, such as metformin with glibenclamide or metformin with glimepiride. The sampling technique used was purposive sampling. This sampling technique was chosen to ensure the fulfillment of relevant inclusion criteria. This technique has the potential to cause selection bias because the sample was not taken randomly. It can affect the representativeness of the sample to the overall population of patients with diabetes mellitus.

Instrumentation or Tools

The main instrument used in this study was patient medical record data before and after the examination, including patient sociodemographic (gender, age), patient clinical data (disease diagnosis, drugs and types of antidiabetic combinations, and therapy outcomes of FPG and 2-h PG values). Additional tools and instruments included: 1) Microsoft Excel is used to process data from medical records, such as age, gender, type of antidiabetic therapy, and therapy outcomes, in the form of Fasting Plasma Glucose (FPG) and 2-hour Postprandial Glucose (2-h PG) values. This data is then compiled and converted into an information format ready for further analysis. 2) The SPSS (Statistical Package for the Social Sciences) application is used as a tool to analyze research data statistically, especially data on the type of antidiabetic therapy group and therapy outcomes in the form of FPG and 2-h PG values.

Data Collection Procedures

This study's data collection was conducted in two stages: collecting patient data through medical records and testing the collected data using statistical analysis.

1. Patient data collection: Patient data were obtained from medical records, which included sociodemographic data (gender and age) and clinical data (disease diagnosis, drugs and types of antidiabetic combinations, and therapy outcomes in the form of FPG and 2-h PG values) taken in the first month of the patient's visit and the following four months.

2. Statistical data testing: Testing was conducted to determine differences in the types of antidiabetic therapy on therapy outcomes in the form of FPG and 2-h PG values used in patients with type 2 diabetes mellitus. Initial analysis was performed manually using Microsoft Excel, then the data was entered into the SPSS application for further statistical analysis.

Data Analysis

Data analysis was carried out descriptively and statistically, descriptive data analysis using data obtained from patient medical records. Data were presented in tables, including gender, age, type of antidiabetic therapy, and the effectiveness of plasma glucose reduction. Statistical data analysis was performed to see if there was a difference in the effectiveness of oral antidiabetic therapy, insulin, and combination on the first FPG and 2-h PG values and the fourth month after the first visit. Data were analyzed using the Statistical Package for the Social Sciences (SPSS). A normality test was performed using the Kolmogorov-Smirnov test to assess data distribution. The Kolmogorov-Smirnov test indicates a normal distribution if the Sig value is >0.05 , allowing the data to proceed to a parametric test using one-way ANOVA. If the data is not normal, the Sig value is <0.05 , so it can use a non-parametric test, namely Kruskal-Wallis. The Kolmogorov-Smirnov test helps determine whether a statistical analysis that relies on the assumption of a normal distribution can be used.

CODE OF HEALTH ETHICS

This study received ethical clearance from the Health Research Ethics Committee of the Faculty of Medicine, with approval number 9046/UN28.1.30/KL/2023, issued on November 06, 2023. All participants gave informed consent before participating in this study. The confidentiality of all participants was strictly maintained throughout the research process.

RESULTS

Respondent Characteristics

As shown in Table 1. The results showed that 303 T2DM outpatients became respondents in this study. Characteristics of respondents in the form of gender, age, and use of antidiabetics. In most cases, respondents were aged between 26 and 65 years (75%), and females dominated by gender (61%), and the oral antidiabetic group was the most widely used type of antidiabetic group (67%).

Table 1. Characteristics of Respondent Outpatients with Type 2 Diabetes Mellitus

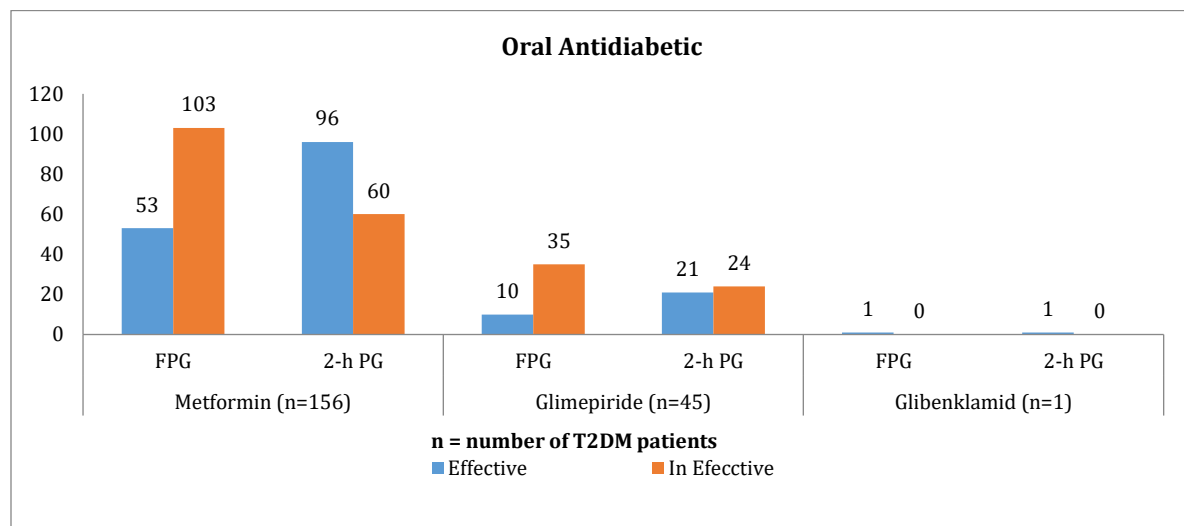
Characteristic	(n=303)	%
Gender		
Male	118	39%
Female	185	61%
Age		
26-65 years	227	75%
>65 years old	76	25%
Antidiabetic drug group		
Oral	202	67%
Insulin	53	17%
Combination	48	16%

Table 2 shows the use of antidiabetic and non-antidiabetic drugs by outpatients with type 2 diabetes mellitus (T2DM) during their hospital visits. Metformin was the most frequently used oral antidiabetic drug, taken by 156 patients. The most frequently used insulin was Novorapid, used by 39 patients. The most common combination of antidiabetic therapy was metformin and Levemir, used by 25 patients. The most frequently used non-antidiabetic drug among patients with T2DM was amlodipine, taken by 75 patients.

Table 2. Use of Antidiabetic and Non-Antidiabetic Drugs in Patients with T2DM

Type of Drug Therapy	n
Oral antidiabetic :	
Metformin	156
Glimepiride	45
Glibenklamid	1
Insulin:	
Levemir	10
Novorapid	39
Ryzodeg	4
Kombinasi:	
Metformin + Glimepiride + Levemir	4
Metformin + Levemir	25
Metformin + Levemir + Novorapid	10
Metformin + Novorapid	9
Total	303
Non-antidiabetic :	
Candesartan	26
Amlodipine	75
Omeprazol	10
Mecobalamin	9
Gabapentin	3
Asam mefenamat	3
Cetirizine	5
Mebendazol	15
Neurobion	4
Atorvastatin	3
Allupurinol	2
Total	155

From the results of the study shown in Figures 1, 2, and 3, the effectiveness of antidiabetic drug therapy is based on FPG and PG 2-hour values in T2DM outpatients at their first visit to the hospital and after four months of subsequent visits. In each antidiabetic group, it can be observed that more T2DM outpatients had ineffective therapy results. The oral antidiabetic metformin group showed effective results in the FPG examination for 53 patients and in the 2-hour PG examination for 60 patients out of a total of 156 patients. In the insulin therapy and combination therapy groups, almost all patients showed ineffective results.

**Figure 1. Effectiveness of Oral Antidiabetic**

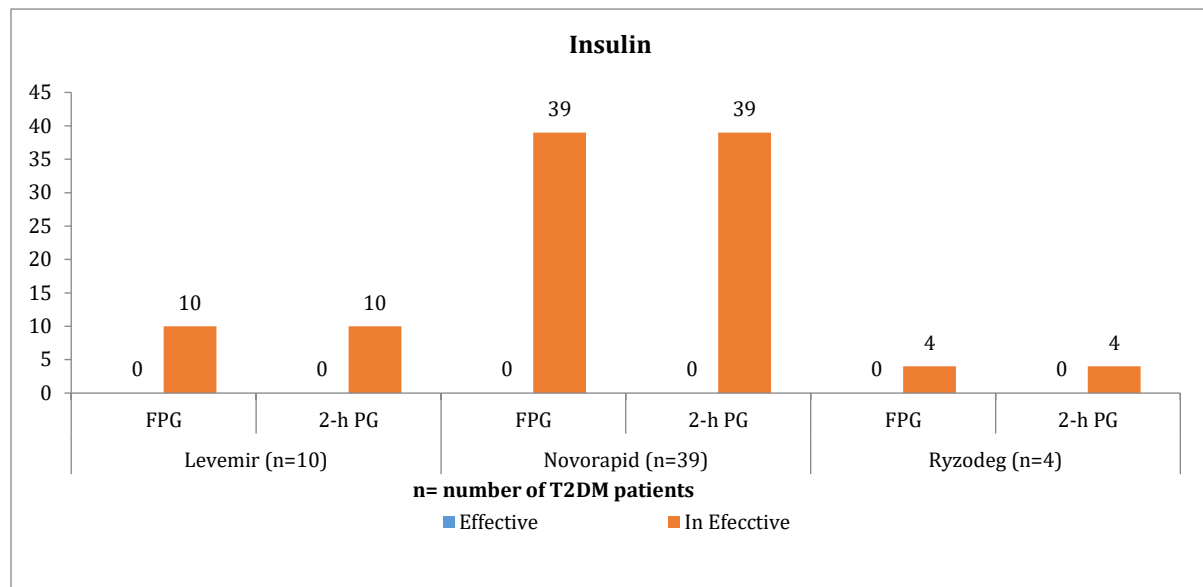


Figure 2. Effectiveness of Insulin

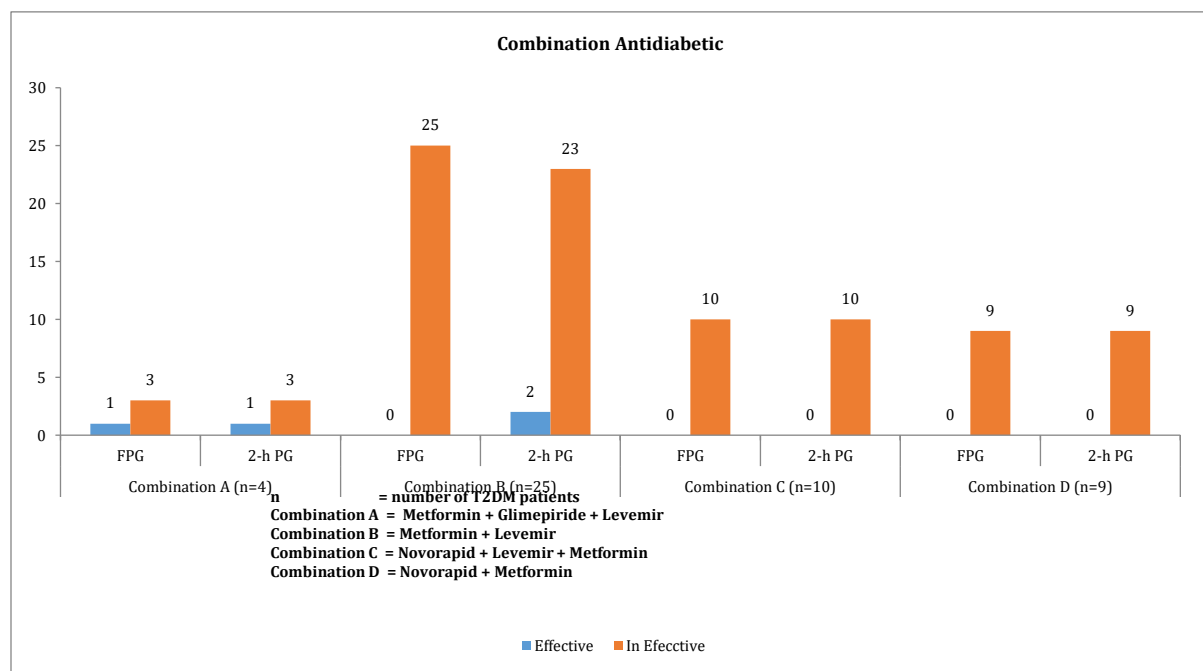


Figure 3. Effectiveness of Combination Antidiabetic

In this study, statistical data analysis was performed to assess the differences between oral antidiabetics, insulin, and combination therapies on the clinical outcomes of T2DM patients, specifically the FPG and 2-hour PG values. Before conducting the statistical analysis, a normality test was performed to determine whether the data were normally distributed. This test helps to decide whether statistical methods that assume normal distribution can be applied.

The data normality test in this study used the SPSS application. Data normality testing using the Kolmogorov-Smirnov test. In the Kolmogorov-Smirnov test, it is said to be normal if the Sig value is > 0.05 and if the Sig value < 0.05 indicates that the data is not normally distributed. The test results can be seen in table 4. The results of the normality test obtained the results of $0.000 < 0.05$, so it can be concluded that the results of the data on the examination of FPG values and 2-h PG values of T2DM patients who were intervened before and after were not normally distributed so that the test requirements were continued

using non-parametric type testing, namely Kruskal-Wallis testing. The Kruskal-Wallis statistical test was used to assess differences in the type of antidiabetic therapy on patient clinical outcomes.

Table 3. Differences Test of Antidiabetic Drug Therapy Group

Types of Antidiabetics	n	p-Value
Metformin :		
FPG	156	0.000
2-h PG	156	0.000
Glimepiride :		
FPG	45	0.002
2-h PG	45	0.006
Glibenklamid :		
FPG	1	0.317
2-h PG	1	0.317
Levemir :		
FPG	10	0.440
2-h PG	10	0.173
Novorapid :		
FPG	39	0.042
2-h PG	39	0.221
Ryzodeg :		
FPG	4	0.386
2-h PG	4	0.772
Metformin + Glimepiride + Levemir:		
FPG	4	0.439
2-h PG	4	0.439
Metformin + Levemir :		
FPG	25	0.190
2-h PG	25	0.264
Metformin + Levemir + Novorapid :		
FPG	10	0.450
2-h PG	10	0.272
Metformin + Novorapid		
FPG	9	0.757
2-h PG	9	0.353

Based on table 3. the results of the Kruskal-Wallis test of the antidiabetic group on the FPG and 2-h PG values at the initial examination and the 4th month, it is known that only the use of oral antidiabetics metformin and glimepiride had differences in observed effectiveness ($p=0.000$) < 0.05 for FPG and 2-h PG examinations in outpatients with type 2 diabetes mellitus. The type of oral antidiabetic glimepiride had differences in observed effectiveness ($p=0.002$) < 0.05 in the FPG examination and ($p=0.006$) < 0.05 in the 2-h PG examination. The oral antidiabetic group, glibenclamide, the insulin group, and the combination group did not have differences in therapeutic effectiveness in reducing FPG and 2-h PG values in outpatients with T2DM.

DISCUSSION

Table 1 shows that, the gender group with the highest percentage is females, accounting for 185 respondents (61%). Females have a higher prevalence of T2DM compared to males (8). Factors influencing the higher prevalence of T2DM in females are sex hormones, obesity thresholds in females, and insulin resistance in males (9). Males tend to have greater insulin resistance, visceral fat mass, and higher blood glucose values than females. However, waist circumference, a key marker of obesity, may serve as a better predictor of insulin resistance and the development of T2DM and CVD in females than in males (10).

In the age group, the highest percentage was in the age of 26-65 with 227 patients (75%). Age and genetic factors can be risk factors for T2DM. However, risk factors can be prevented by doing physical

activity and avoiding obesity and smoking (11). Leukocyte telomere length (TL) is associated with risk in T2DM. The correlation between telomere length and age in patients with T2DM is influenced by other factors such as hypertension, gender, obesity, smoking habits, and stress levels (12). Blood glucose levels are associated with increasing age due to reduced glucose tolerance and are associated with decreased peripheral cell sensitivity to insulin, which can affect blood glucose levels (13).

The largest group of oral antidiabetic drugs was 202 patients (67%). T2DM treatment algorithm starts with healthy lifestyle modification and oral monotherapy. In this study, many patients did not have DM complications and at the first visit, many patients had GDP values <200 mg/dL, so in their therapy patients received oral monotherapy. However, the selection of therapy for T2DM patients does not only depend on blood glucose values, individualized considerations, and a patient-focused approach. Many factors are considered in the choice of therapy for DM patients, one of which is the effect of drugs on cardiovascular and renal comorbidities and the effectiveness of reducing blood glucose (6).

Based on Table 2. in the oral antidiabetic group, the most commonly used type is metformin. However, in patients with poorly controlled T2DM, the main factor contributing to increased levels of hepatic glucose production (HGP) and FPG is an increase in hepatic glucose (gluconeogenesis) (14). Metformin is the recommended choice at the beginning of treatment for T2DM patients due to its high effect in lowering HbA1c and a lower risk of hypoglycemia if used as monotherapy and the low cost of therapy (15,1). In this study, the use of sulfonylurea-class drugs was not as much as the use of metformin. Sulfonylureas are recommended as second-line treatment after metformin due to the hypoglycemic risk associated with their use, weight gain, and decreased glycemic tolerance (16).

All patients who used Novorapid insulin therapy in this study had FPG and 2-h PG values ≥ 250 mg/dL. Two patients had comorbidities such as pulmonary TB, and ten patients had complications such as diabetic neuropathy. Insulin Novorapid is a type of rapid-acting insulin analog that has a faster onset of about 5-15 minutes and a shorter duration of action of about 4-6 hours (17). The advantage of using insulin therapy is that it can reduce blood glucose by adjusting the therapeutic dose so that the glycemic target can be achieved (18).

The combination group using the most therapy was the metformin + Levemir group of 25 patients. In this group, 15 patients had comorbidities or complications of DM, such as stage 1 and stage 2 hypertension, diabetic neuropathy complications, and hypertension with diabetic neuropathy. Combination therapy between insulin and oral antidiabetics resulted in better glycemic control and reduced insulin requirements resulting in much lower doses of insulin use in T2DM patients (19). Combination therapy can increase the number of T2DM patients who achieve glycaemic targets compared to the use of metformin as monotherapy (20). In patients with certain clinical reasons and if the patient's target blood glucose goal has not been achieved, a combination of two oral antidiabetics and insulin can be considered (6).

In the non-antidiabetic drug group, the highest drug use was amlodipine. The state of hypertension in T2DM patients who experience hyperglycemia is due to intravascular fluid resistance, which results in an increase in body fluid volume accompanied by damage to the vascular system and increased peripheral arterial resistance (21). There is a significant relationship between insulin concentration and blood pressure. That amylin can increase the concentration of active rennin which is responsible for the activation of the Renin-Angiotensin-Aldosterone System (RAAS). This may contribute to the development of hypertension in patients with insulin resistance (22).

Effectiveness of Antidiabetic Therapy

In this study, the patient's antidiabetic drug therapy was said to be effective, if the laboratory examination showed FPG values ranging from 80-130 mg/dL and 2-h PG examination values < 180 mg/dL in T2DM patients ≤ 60 years old. As for patients who are >60 years of age, it is said to be effective if the laboratory results on the FPG examination range ≤ 180 mg/dL and the 2-h PG examination value ≤ 200 mg/dL in the fourth month after the first examination. In Table 3. the effectiveness of reducing FPG and 2-h PG values in each antidiabetic group shows that more outpatient T2DM patients have ineffective results. Several factors can affect the results of FPG and 2-h PG examination of T2DM patients, For instance,

differences in patient populations, duration of diabetes, baseline glycemic control, or specific drug regimens within the broader categories could contribute and including intrinsic factors of DM patients and patient therapy factors or the use of drugs other than antidiabetic drugs.

In this study, some patients received additional therapies besides antidiabetic drugs, which were related to complications or comorbidities such as pulmonary tuberculosis, hypertension, and hypertriglyceridemia. However, this study did not include assessments of parameters such as hematocrit levels or blood pressure measurements. Several previous studies have shown that intrinsic factors, such as elevated hematocrit in patients with T2DM due to chronic lung disease, hypertriglyceridemia, shock, and dehydration, can produce falsely low readings in FPG and 2h-PG tests. T2DM patients are also more susceptible to pulmonary infections due to microangiopathic changes in the basement membranes of pulmonary blood vessels and the respiratory epithelium, as well as non-enzymatic glycosylation of tissue proteins (23). Hematocrit impairment will affect the performance of blood glucose measurement in daily routine, so the level of hematocrit impairment will affect the blood glucose measurement of T2DM patients causing insulin dosing errors (24). Drug therapy other than antidiabetics used by patients can affect the results of GDP and GD2PP examinations, among others, T2DM patients undergoing routine hemodialysis therapy can cause blood glucose test results to tend to be higher, due to the influence of uric acid and ions such as sodium. The use of medical therapy such as acetaminophen, L-dopa, tolazamide, and ascorbic acid can affect blood glucose test values, due to chemical reactions to electrodes (25).

The effectiveness of therapy using oral antidiabetic drugs, insulin, and their combination in this study showed different results compared to previous research conducted by Jamaluddin in 2022. That study explained differences in the effectiveness of insulin, oral antidiabetic drugs, and combination therapies in patients with T2DM (7). In addition, there was no difference in the effectiveness of the single antidiabetic drug glibenclamide, compared with the combination of glibenclamide and metformin in T2DM patients on FPG measurements in T2DM patients (26). This is because differences in patient population, duration of diabetes, baseline glycemic control, and specific drug regimens within the broader category may contribute to differences in outcomes. The difference in the effectiveness of therapy in the metformin oral antidiabetic drug group in this study is due to T2DM patients who are effective in drug use therapy are diabetes mellitus patients who do not have comorbidities and complications, while patients who have complications such as diabetic neuropathy tend to be ineffective in their therapy.

In this study, no differences were observed in the reduction of fasting plasma glucose (FPG) and 2-hour postprandial glucose (2h-PG) levels between patients treated with insulin therapy and those receiving combination therapy. This finding may be influenced by the presence of complications or comorbidities in a subset of patients within the insulin group, such as pulmonary tuberculosis, hypertension, and hypertriglyceridemia, which could affect glycemic control outcomes. Furthermore, the lack of statistical significance may also be attributed to the relatively small sample sizes and the heterogeneity of patient characteristics in both the insulin and combination therapy groups. These factors potentially limited the ability to detect meaningful differences. T2DM patients who have comorbid asthma, hypertension, and DM complications will affect glycaemic control. In addition, clinical factors such as duration of T2DM, FGD, estimated glomerular filtration rate (eGFR), cholesterol, and low-density lipoprotein (LDL) levels (27). Patients who used oral antidiabetic therapy plus insulin had almost twice the likelihood of poor glycaemic control than those who only used oral antidiabetic drugs (28). Treatment of T2DM patients using pharmacological drug therapy cannot achieve optimal blood glucose target goals if not balanced with behavioral alteration. Behavior affects the risk of failure of T2DM control by 4.156 times greater (29). In addition, pharmacists have an important role in improving patient compliance with drug use through communication, information, and education to improve patient quality of life (30).

Implications in Type 2 Diabetes Mellitus Therapy

The findings of this study are expected to contribute to a better understanding of the effectiveness of antidiabetic drug therapy in patients with type 2 diabetes mellitus (T2DM). This study found that the oral antidiabetic agents metformin and glimepiride demonstrated more consistent results in reducing fasting plasma glucose (FPG) and 2-hour postprandial glucose (2h-PG) levels compared to glibenclamide.

These results support the use of metformin and glimepiride as potential first-line therapies for T2DM patients without severe complications. In contrast, no differences were observed between the insulin and combination therapy groups in reducing FPG and 2h-PG levels. Therefore, physicians are encouraged to consider additional clinical factors. Such as the presence of comorbidities, patient tolerance, and the need for individualized and holistic approaches when making therapeutic decisions for patients requiring insulin or combination regimens.

Limitations

This study has several limitations that need to be considered. First, the retrospective study design may limit the ability to directly control for variables. Second, there are potential unmeasured confounding factors, such as comorbidities and patient adherence to treatment, which may affect the outcome of therapy. Third, this study relies heavily on the accuracy and completeness of data from medical records, which may contain recording bias. Fourth, the study population was from one hospital, so the results may not be generalizable to the wider population. Finally, the relatively short follow-up period of four months may limit understanding of the long-term effectiveness of therapy.

CONCLUSION

The oral antidiabetic drug groups, metformin, and glimepiride, demonstrated differences in therapeutic effectiveness among outpatients with T2DM. In contrast, no significant differences in therapeutic effectiveness were observed between the insulin group and the combination therapy group. These variations in effectiveness among therapeutic groups may be attributed to the complex nature of T2DM, which requires a multifactorial and individualized treatment approach tailored to each patient's clinical condition.

FUNDING

This research did not obtain external funding.

ACKNOWLEDGMENTS

The authors would like to express their sincere gratitude to colleagues and students who assisted in data collection and resources.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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