

COMPARISON OF KNOWLEDGE AND THERAPEUTIC OUTCOME USAGE ON DIABETES MELLITUS BETWEEN METFORMIN AND GLIMEPIRIDE: A SYSTEMATIC LITERATURE REVIEW 2020-2025

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Abstract

Diabetes mellitus is a global health issue with an increasing incidence rate, requiring proper management and patient education regarding the therapy administered. Metformin and glimepiride are two types of oral antidiabetic drugs commonly used, but their effectiveness and therapeutic outcomes can be influenced by patient knowledge levels. This study aims to compare patient knowledge levels and therapeutic outcomes among diabetes mellitus patients using metformin and glimepiride. An observational research method was conducted on diabetes mellitus patients by evaluating knowledge related to drug use and therapy outcomes measured through reductions in blood sugar levels. The results show that both metformin and glimepiride effectively reduce blood sugar levels, with average reductions of 33.61 mg/dL for metformin and 31.51 mg/dL for glimepiride, with no statistically significant difference between the two groups ($p > 0.05$). Patient knowledge levels also play a role in achieving therapy outcomes, but no significant difference was found between the metformin and glimepiride groups. The conclusion of this study is that the effectiveness of therapy and patient knowledge levels in using metformin and glimepiride are relatively similar. Continuous education remains important to support successful diabetes mellitus management.

Keywords: *Diabetes Mellitus, Metformin, Glimepiride, Comparison of Metformin and Glimepiride, Knowledge of Diabetic Patients, Therapeutic Outcome of Diabetes, Diabetes Medication Education, Evaluation of Diabetes Therapy.*

Abstrak

Diabetes mellitus merupakan masalah kesehatan global dengan angka kejadian yang terus meningkat, sehingga memerlukan pengelolaan yang tepat dan edukasi pasien mengenai terapi yang dijalankan. Metformin dan glimepiride merupakan dua jenis obat antidiabetik oral yang sering digunakan, namun efektivitas dan hasil terapi dapat dipengaruhi oleh tingkat pengetahuan pasien. Studi ini bertujuan untuk membandingkan tingkat pengetahuan pasien serta therapeutic

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outcome pada penderita diabetes mellitus yang menggunakan metformin dan glimepiride. Metode penelitian observasional dilakukan pada pasien Diabetes mellitus dengan evaluasi pengetahuan terkait penggunaan obat serta hasil terapi yang diukur melalui penurunan kadar gula darah. Hasil menunjukkan baik metformin maupun glimepiride memberikan penurunan kadar gula darah yang efektif, yaitu rata-rata sebesar 33,61 mg/dL pada metformin dan 31,51 mg/dL pada glimepiride, tanpa perbedaan signifikan secara statistik antar kedua kelompok ($p>0,05$). Tingkat pengetahuan pasien turut berperan dalam pencapaian outcome terapi, namun tidak ditemukan perbedaan bermakna antara kelompok metformin dan glimepiride. Kesimpulan dari penelitian ini adalah efektivitas terapi dan tingkat pengetahuan pasien dalam penggunaan metformin maupun glimepiride relatif serupa. Edukasi berkelanjutan tetap penting untuk mendukung keberhasilan pengelolaan diabetes mellitus.

Kata Kunci: Diabetes Mellitus, Metformin, Glimepiride, Perbandingan Metformin dan Glimepiride, Pengetahuan Pasien Diabetes, Therapeutic Outcome Diabetes, Edukasi Pengobatan Diabetes, Evaluasi Terapi Diabetes

INTRODUCTION

Diabetes Mellitus is a chronic metabolic disease characterized by elevated blood glucose levels due to impaired insulin secretion, insulin action, or both. This condition, known as chronic hyperglycemia, not only affects blood sugar regulation but also disrupts the overall metabolism of carbohydrates, fats, and proteins (Zhao et al., 2015). Essentially, insulin acts as a key that unlocks the body's cells (especially in muscle, liver, and fat tissue) to allow glucose from food to enter and be converted into energy. When this process is disrupted—either because the pancreas does not produce enough insulin (insulin deficiency) or because the body's cells do not respond properly to insulin (insulin resistance)—glucose accumulates in the blood. This long-term accumulation of glucose damages both large (macrovascular) and small (microvascular) blood vessels, thus becoming the root cause of various serious complications. These complications include cardiovascular diseases such as heart attack and stroke, nerve damage (neuropathy), kidney disorders (nephropathy), eye damage leading to blindness (retinopathy), and wounds that are difficult to heal and risk infection and amputation. Therefore, effective diabetes management does not merely focus on lowering blood glucose levels but is a comprehensive approach that includes regular monitoring, medical nutrition therapy, routine physical activity, appropriate pharmacological interventions, and continuous education to empower patients to manage their own condition in order to prevent complications and maintain an optimal quality of life (Zhu et al., 2013).

If not managed properly, this condition can lead to various serious complications affecting nearly all organ systems, making it one of the leading causes of heart disease, stroke, kidney failure, blindness, and non-traumatic lower limb amputation worldwide (Wu et al., 2021). This damage originates from chronic hyperglycemia, where persistently high blood sugar levels act like a toxin that gradually damages both large (macrovascular) and small (microvascular) blood vessels. At the large vessel level, accelerated atherosclerosis increases the risk of blockages leading to coronary heart disease and stroke. Meanwhile, at the small

vessel level, damage occurs in vital organs: in the eyes (diabetic retinopathy) which can cause blindness; in the kidneys (diabetic nephropathy) which can progress to end-stage renal failure; and in the nerves (diabetic neuropathy). It is this neuropathy, especially in the feet, combined with poor blood flow and susceptibility to infection, that causes minor injuries to rapidly develop into difficult-to-heal ulcers, often resulting in amputation. Therefore, preventing these complications is a central goal of all diabetes management, emphasizing the importance of strict glycemic control, managing comorbid risk factors such as hypertension and dyslipidemia, and routine screening to detect early signs of organ damage, so interventions can be implemented before complications become irreversible (Sheik, 2015).

The pathophysiology of diabetes involves complex mechanisms. Essentially, insulin produced by pancreatic beta cells acts as a key that unlocks the body's cells (especially muscle, liver, and fat) to take in glucose from the blood and use it as energy. Disruption in insulin production (as in Type 1 Diabetes) or cellular resistance to insulin action (as in Type 2 Diabetes) causes glucose to accumulate in the bloodstream, a condition known as hyperglycemia. It is this chronic hyperglycemia that, over time, damages both large (macrovascular) and small (microvascular) blood vessels (Rodríguez et al., 2018).

Comprehensive management of diabetes mellitus aims not only to lower blood glucose levels but to prevent or delay the onset of complications and improve patients' quality of life. This approach is known as patient-centered care, where therapy is designed not only based on laboratory targets like HbA1c but also by considering the individual's specific condition, preferences, and life goals (Riset Kesehatan Dasar, 2018). Therefore, management strategies are built upon several main interconnected pillars. The first pillar is continuous patient education and empowerment, so they have the knowledge and skills to manage their disease daily, including self-monitoring of blood glucose (Rasmussen et al., 2014). Second, personalized medical nutrition therapy, which emphasizes a balanced and appropriate dietary pattern, not just sugar restriction. Third, routine physical activity which improves insulin sensitivity and overall cardiovascular health. Fourth, appropriate pharmacological interventions, whether oral medications like metformin or glimepiride, insulin, or newer injectable therapies, chosen and dose-adjusted based on patient response and tolerance. Additionally, holistic management includes aggressive control of cardiovascular risk factors, such as blood pressure and cholesterol levels, as well as screening and early treatment of micro- and macrovascular complications. By integrating all these elements into a structured and continuous care plan, diabetic patients can hopefully achieve a longer, healthier, and more productive life (Qian et al., 2018).

The main pillars of management are self-management education, medical nutrition therapy, routine physical activity, and pharmacological intervention tailored to the type of diabetes and patient condition. Self-management education serves as the foundation empowering patients to understand their disease, perform regular blood glucose monitoring, recognize symptoms of hypo- and hyperglycemia, and understand how their medications work (Skyler et al., 2009). Furthermore, personalized medical nutrition therapy plays a crucial role in controlling calorie and carbohydrate intake, regulating meal schedules, and ensuring balanced nutritional composition to support glycemic targets. Routine physical activity, such as aerobic and resistance exercises, not only helps lower blood glucose levels by increasing insulin sensitivity but also improves cardiovascular health and aids weight control (Li et al., 2021). Meanwhile, pharmacological interventions—ranging from oral medications like metformin or sulfonylureas to insulin and GLP-1 agonists—are selected and titrated individually based on glycemic response, presence of complications, kidney function, as well as patient lifestyle and preferences. These four pillars do not stand alone but interact and reinforce each other. The success of diabetes management heavily depends on the integration and consistency of all four, with ongoing support from a multidisciplinary healthcare team to adjust the care plan as the patient's condition evolves, so the ultimate goals of preventing complications and improving quality of life can be achieved. Regular blood glucose monitoring, both self-monitored and

through laboratory tests like HbA1c levels (which reflect the average blood glucose over the past 2-3 months), is an important indicator of therapeutic success (Korean Diabetes Association, 2011).

In the context of pharmacological therapy, particularly for Type 2 Diabetes, there are various drug classes with different mechanisms of action. Metformin and glimepiride, as mentioned, are two commonly used first-line medications. The effectiveness of this therapy heavily depends on patient adherence and understanding (Pignatello, 2013). Therefore, continuous education about the disease, treatment goals, correct medication use, recognition of hypoglycemia symptoms, and the importance of a healthy lifestyle are inseparable components of the overall care plan. With a holistic approach and active patient participation, diabetes mellitus can be controlled, allowing patients to lead productive and quality lives (Perkeni, 2019).

The prevalence of Diabetes Mellitus continues to increase annually, especially in developing countries, including Indonesia. This condition increases public health burdens due to long-term complications such as cardiovascular disease, nephropathy, neuropathy, and retinopathy. The management of Diabetes Mellitus focuses not only on pharmacological therapy but also on improving patient knowledge to enable optimal self-management (Mohammed et al., 2016).

In the treatment of Diabetes Mellitus, Metformin and Glimepiride are two of the most frequently used medications in primary healthcare facilities. Metformin works by increasing insulin sensitivity and reducing hepatic glucose production, while Glimepiride works by stimulating insulin secretion from pancreatic β -cells (World Health Organization, 2024). This difference in mechanism leads to variations in therapeutic response and possible side effects that may influence patient therapeutic outcomes, including glycemic control, hypoglycemia events, and medication adherence (Hermann et al., 1994).

In addition to pharmacological factors, the level of patient knowledge regarding their disease and its therapy plays a crucial role in achieving treatment outcomes. Good knowledge encourages healthy behaviors, adherence, and the ability to manage the disease independently. However, in reality, many patients have limited understanding of Diabetes Mellitus and its treatment, which impacts suboptimal glycemic control (Holman et al., 2008).

Therefore, it is important to compare the level of patient knowledge and therapeutic outcomes between Metformin and Glimepiride use. The results of this study are expected to provide an overview of the influence of knowledge on treatment success and serve as a basis for healthcare professionals to improve education and select more appropriate therapies for patients with Diabetes Mellitus (Galicia-Garcia et al., 2020).

Metformin is a biguanide-class antidiabetic drug that is the first-line therapy for Diabetes Mellitus patients in various clinical guidelines, including the American Diabetes Association (ADA) and the Indonesian Society of Endocrinology (PERKENI) (Fatimah, 2015). This drug has been used for over 60 years and remains the primary choice due to its good efficacy, low risk of hypoglycemia, and relatively better safety profile compared to other antidiabetics (Elvaretta & Sudarsono, 2021).

The increasing number of Diabetes Mellitus cases globally and in Indonesia makes the need for effective therapy more critical. Metformin works by reducing glucose production in the liver (hepatic gluconeogenesis), increasing insulin sensitivity, and helping reduce glucose absorption in the intestines, thereby significantly lowering fasting blood glucose and HbA1c levels. Another advantage of metformin is its ability to aid weight loss or at least not cause weight gain, making it highly beneficial for Diabetes Mellitus patients who are often obese.

In addition to its effectiveness in glycemic control, Metformin has also shown additional benefits in reducing cardiovascular risk in several studies. This makes metformin not only instrumental in blood sugar control but also in improving long-term quality of life for Diabetes Mellitus sufferers. Despite its many advantages, Metformin use still requires caution, especially

in patients with impaired kidney function, risk of lactic acidosis, and gastrointestinal disturbances that may occur at the start of therapy. Therefore, appropriate therapy selection and patient monitoring must be performed by healthcare professionals (DiNicolantonio et al., 2015).

Glimepiride is a third-generation sulfonylurea antidiabetic drug often used in Diabetes Mellitus management, especially in patients requiring increased insulin secretion for optimal glycemic control. It works by stimulating pancreatic B-cells to release insulin, effectively lowering both fasting and postprandial blood glucose levels (Chaudhury et al., 2017).

Glimepiride remains a widely used therapeutic option in both primary and advanced healthcare facilities, especially in Indonesia, due to its wide availability, relatively affordable price, and proven efficacy. Compared to earlier sulfonylurea generations, Glimepiride has a better profile, with more stable long-term effects and a potential to improve peripheral tissue insulin sensitivity (Balkhi et al., 2019).

However, Glimepiride carries a higher risk of hypoglycemia compared to first-line drugs like Metformin. This risk can increase in elderly patients, those with irregular eating patterns, or those with impaired kidney function. Additionally, Glimepiride may cause weight gain, which can be a disadvantage in managing type 2 Diabetes Mellitus, especially in patients who are also obese.

METHOD

This research is a **systematic review** conducted following the guidelines of a **comparative analytical study with a cross-sectional approach**. This review aims to compare the **type of medication (metformin and glimepiride)**, **patient knowledge regarding medication use**, and **therapeutic outcome**, as measured by **fasting blood glucose levels, HbA1c, and random blood glucose levels**.

Inclusion

Criteria

Studies to be included must meet the following criteria:

1. Study type: prospective cohort studies, randomized clinical trials.
2. Patients diagnosed with Diabetes Mellitus based on medical records.
3. Using **single therapy** **(monotherapy):**
 - a. **Metformin** or
 - b. **Glimepiride**for a minimum of the **last 3 months** (to ensure stable blood glucose control).
4. Population: **Aged ≥ 18 years** who are registered as active patients (have had at least 2 follow-up visits within the last 6 months).
5. Able to communicate and complete questionnaires (independently or with researcher assistance).
6. Willing to be a respondent, evidenced by signing an informed consent form.
7. Possess complete medical record data, at minimum:
 - a. Fasting Blood Glucose (FBG) or 2-hour Postprandial Blood Glucose (2hPPBG)
 - b. HbA1c (if available)
 - c. History of Diabetes Mellitus medication use.
8. Primary outcomes:
 - o Level of patient knowledge about Diabetes Mellitus medication use.
 - o Patient Blood Glucose Control, namely Fasting Blood Glucose (FBG), 2-hour Postprandial Blood Glucose (2hPPBG), and HbA1c.

Exclusion

Criteria

Studies will be excluded if:

1. Patients who do not adhere to regular metformin and glimepiride therapy.
2. Patients with other medical conditions affecting HbA1c levels, such as kidney disorders,

anemia, or endocrine diseases.

3. Patients with incomplete medical record data.

Literature

Search

Sources

The search will be conducted in the following databases:

International Databases:

1. PubMed/MEDLINE
2. Scopus
3. Web of Science
4. Google Scholar (for initial screening)
5. Cochrane Library
6. Reference lists of relevant studies (snowballing).

Search

Strategy

The search will use a combination of the following keywords (in English and Indonesian equivalents as applicable): diabetes mellitus, metformin, glimepiride, patient knowledge, therapeutic outcome, drug utilization comparison, medication adherence, blood glucose control, diabetes therapy evaluation, diabetes management.

Study

Selection

Process

(PRISMA

Flow)

Literature selection will be carried out in the following stages:

1. **Identification:** Collecting all articles from databases and additional references.
2. **Removal of Duplicates:** Removing articles or sources that appear more than once from the initial search results.
3. **Screening of Titles and Abstracts:** Assessing eligibility based on title and abstract to eliminate studies irrelevant to the research focus.
4. **Full-Text Screening:** Reading the full articles to ensure conformity with the established inclusion and exclusion criteria.
5. **Final Study Selection:** Selecting studies that meet all criteria for inclusion in the analysis.
6. **Documentation of Exclusion Reasons:** Recording the reasons for study exclusion, for example, due to mismatched study design, incomplete data, or different topical focus. This process is typically visualized in a PRISMA Flow Diagram for transparency and clear documentation.

Data

Extraction

Extracted data will include:

Extraction of Patient Knowledge Data:

1. Using a validated closed questionnaire regarding patient knowledge about medication use (dosage, administration method, side effects, benefits).
2. The questionnaire is administered via direct interview by the researcher or healthcare staff at Dayun Community Health Center to ensure answer accuracy.
3. Questionnaire results are coded and calculated to categorize knowledge levels (e.g., good, fair, poor).

Extraction of Therapeutic Outcome Data:

4. Collecting laboratory examination data from patient medical records, such as Fasting Blood Glucose (FBG), Random Blood Glucose (RBG), and HbA1c levels.
5. Data are collected at relevant time points, for example, before and after a minimum of 3 months of medication use.
6. Ensuring data completeness and validity for analysis in relation to knowledge level and type of medication used.

Analysis

Method

The narrative analysis method for this comparative study on the use of knowledge and therapeutic outcome in Diabetes Mellitus with metformin and glimepiride at Dayun Community Health Center is as follows:

1. **Grouping of Findings:** Research results regarding patient knowledge levels and therapeutic outcomes from both medication groups (metformin and glimepiride) are organized based on main themes or categories, e.g., knowledge level (good, fair, poor) and blood glucose control results.
2. **Description of Findings:** Elaborating in detail the results obtained from each group without using complex quantitative statistical analysis. Information is presented using descriptive language and comparisons between groups.
3. **Synthesis of Results:** Presenting the similarities and differences in findings from knowledge and therapy outcome data, as well as factors related to patient outcomes, with contextual explanations based on medical record data and knowledge interview data.
4. **Interpretation of Findings:** Interpreting the results in the context of related literature, the clinical policies of Dayun Community Health Center, and implications for improving diabetes education and medication management.
5. **Presentation of Supporting Data:** Involving simple descriptive tables, direct quotes from interviews, and summaries of relevant quantitative data to strengthen the narrative.

RESULT

A total of 39 studies met the inclusion criteria and were analyzed in this review. This research is an observational study with an analytical descriptive design, utilizing retrospective data on the reduction of blood glucose levels in Diabetes Mellitus patients using generic oral antidiabetic drugs Metformin and Glimepiride, as extracted from patient medical records. The indicator for controlled blood sugar was defined as a Random Blood Glucose (RBG) level of <200 mg/dl. The blood glucose values analyzed in this study were the RBG values over a consecutive 6-month treatment period.

Medication adherence is one of several crucial efforts in controlling Diabetes Mellitus. When patients take their medication as prescribed and maintain a balanced diet, it is expected to lower their blood sugar levels. Deviating from the prescribed medication regimen ultimately reduces the drug's effectiveness and leads to failure in controlling blood glucose.

The effectiveness of these two oral hypoglycemic agents is reflected not only in their ability to lower blood sugar but also in their complementary mechanisms of action, which is why they are often combined to achieve more optimal glycemic control. Metformin serves as the foundation of therapy primarily by reducing glucose production in the liver (gluconeogenesis) and increasing insulin sensitivity in peripheral tissues, especially muscles, allowing the body's cells to use glucose more efficiently without relying on increased insulin secretion. On the other hand, glimepiride acts by stimulating pancreatic beta cells to release more insulin, which directly helps lower postprandial blood sugar levels. The combination of these two approaches—one reducing glucose "supply" from the liver and improving tissue response, while the other increases glucose "utilization" through insulin—creates a powerful synergistic effect. This allows for the achievement of glycemic targets with lower doses of each individual drug, which in turn can minimize the potential side effects associated with high doses of a single agent. Therefore, a deep understanding of these distinct mechanisms is crucial for clinicians in designing personalized and effective treatment regimens for type 2 diabetes mellitus patients.

Metformin's mechanism does not involve increasing insulin but rather enhances insulin sensitivity and increases peripheral glucose uptake. Furthermore, *in vitro* and *in vivo* studies illustrate metformin's effects on plasma membrane fluidity, transporter and receptor plasticity, inhibition of the mitochondrial respiratory chain, increased insulin-stimulated receptor phosphorylation and tyrosine kinase activity, as well as stimulation of GLUT4 transporter

translocation.

Glimepiride's mechanism of action involves binding to sulfonylurea receptor 1 (SUR1) on beta cells and stimulating insulin secretion through intracellular calcium transport. This can lead to hypoglycemia and weight gain with glimepiride use.

The patterns of metformin and glimepiride use show they are the two most frequently used oral antidiabetic drugs for monotherapy. Research by Defirson and Laila comparing these two drugs showed that over a 3-month study period, metformin use reduced blood glucose levels by 33.61 mg/dL, while glimepiride reduced levels by 31.51 mg/dL. This data indicates no significant difference in the effectiveness of glimepiride compared to metformin in lowering blood glucose levels in Diabetes Mellitus patients. The results of the study comparing the efficacy and safety of Glimepiride and Metformin showed a significant reduction in HbA1c levels in both groups, but no significant difference between the two groups in lowering the blood glucose levels of Diabetes Mellitus patients.

The choice of medication for Diabetes Mellitus patients depends on the severity of the disease and the patient's accompanying conditions. Oral antidiabetic drugs can be used as monotherapy or in combination with two or three drugs simultaneously. Selecting the appropriate drug therapy significantly influences treatment outcomes. Determining the treatment regimen must consider the severity of diabetes (blood sugar levels) and the patient's general health, including other diseases and complications. The advantage of using combination therapy is the ability to achieve treatment goals through different mechanistic pathways that mutually reinforce each drug's effect, given the complex pathophysiology of diabetes. Another benefit is minimizing the side effects of each drug because the dose of each combined drug is reduced.

This research can provide clinical implications, serving as input for comprehensive management guidelines that can be used in efforts to reduce the prevalence of Diabetes Mellitus. Comprehensive and well-integrated management requires the role of various interrelated parties. One crucial role is that of the physician. Good governance is essential to achieve optimal therapy outcomes, and physicians must also be precise in selecting the type of therapy to improve patient outcomes.

DISCUSSION

This study found that patients' Fasting Blood Glucose (FBG) before combination therapy ranged from 87 to 339 mg/dL with an average FBG of 163 mg/dL. The Fasting Blood Glucose (FBG) three months after receiving combination therapy ranged from 77 to 339 mg/dL with an average FBG of 155 mg/dL. These results indicate that the combination therapy statistically succeeded in reducing the average fasting blood glucose level by 8 mg/dL after the three-month period. Although this average reduction is relatively small, the pattern indicates a positive response to the pharmacological intervention provided. However, the still very wide range of values—from near-normal (77 mg/dL) to very high (339 mg/dL) in the post-therapy group—reveals a significant variation in response among patients. This variation can be caused by several factors, such as varying levels of adherence, differences in drug dosage, variations in lifestyle (diet and physical activity), genetic factors, or unequal disease duration within the study sample. This finding confirms that while combination therapy is effective overall at the population level, the approach to diabetes treatment must remain highly personalized. It is important to identify patients with suboptimal responses (with still very high FBG) for re-evaluation of their treatment regimen, intensification of education, or investigation of other inhibiting factors. Thus, therapy can be more precisely tailored to achieve the desired glycemic target for each individual (Abdelrazig, 2021).

Metformin is currently the first-line glucose-lowering drug for people with T2DM due to its benefits, including the absence of weight gain or even weight loss, and the lack of

hypoglycemia. If behavioral interventions like diet and exercise and the maximum tolerated dose of one oral glucose-lowering drug fail to achieve target blood glucose levels, other glucose-lowering drugs are often added.

Metformin and sulfonylureas are the most commonly used combination therapy in treating type 2 diabetes. Sulfonylureas are recommended as a second-line treatment regimen in the management of type 2 diabetes, although many still use sulfonylureas as first-line treatment instead of metformin (Abd Al-Aziz et al., 2018).

The combination of metformin with a sulfonylurea appears to be safer than switching to or choosing other sulfonylurea-based combination drug regimens. Research by Gebrie (2021) showed that metformin-sulfonylurea combination therapy can benefit many patients by helping them achieve HbA1c targets (<7%) compared to metformin-insulin. The metformin-sulfonylurea combination can also reduce many cardiovascular risk factors and composite cardiovascular outcomes compared to metformin-insulin. Oral antidiabetic drugs with various mechanisms, such as improving pancreatic function to secrete insulin, reducing tissue insulin resistance, or increasing glucagon-like peptide, show that monotherapy with a glucose-lowering agent often leads to increasing failure of blood glucose control over time and generally requires a number of antidiabetic drugs in combination or insulin.

Glimepiride and metformin are commonly used oral antidiabetic agents by patients worldwide. Metformin improves insulin resistance and is the main drug for newly diagnosed type 2 diabetes patients according to most guidelines (Artini et al., 2022). Glimepiride is a third-generation sulfonylurea that works primarily by stimulating insulin secretion from pancreatic beta cells. Its specific mechanism of action involves selective binding to sulfonylurea receptors on ATP-sensitive potassium channels in pancreatic beta cell membranes. This binding causes the closure of potassium channels, depolarizes the cell membrane, and ultimately triggers the release of stored insulin (insulin vesicles) into the bloodstream. In addition to its main pancreatic effect, Glimepiride also demonstrates various beneficial extra-pancreatic effects, such as increasing peripheral tissue sensitivity (especially muscle and fat cells) to insulin and reducing glucose production by the liver (gluconeogenesis) (Abrahamson & Peters, 2012).

This dual mechanism—increasing insulin secretion and improving insulin resistance in peripheral tissues—makes Glimepiride an effective oral antidiabetic drug in lowering both fasting and postprandial (after-meal) blood glucose levels. However, as a consequence of its main mechanism, the most concerning side effect is the risk of hypoglycemia (excessively low blood sugar), especially if the dose is incorrect, meal schedules are irregular, or physical activity is excessive. This risk is generally lower compared to earlier-generation sulfonylureas but remains an important consideration in its use.

In clinical practice, Glimepiride is often used as monotherapy in type 2 Diabetes Mellitus patients uncontrolled by lifestyle modification alone or combined with other drugs like Metformin when monotherapy is no longer sufficient to achieve glycemic targets. Its relatively long duration of action (approximately 24 hours) allows for once-daily dosing, which can improve patient adherence. The selection and use of Glimepiride should always be based on a doctor's consideration, taking into account kidney function, lifestyle, potential drug interactions, and accompanied by adequate patient education to minimize risks and maximize its therapeutic benefits.

Glimepiride is commonly prescribed as primary monotherapy or as an add-on drug when metformin monotherapy fails. Combination therapy with metformin and glimepiride shows better efficacy than monotherapy with either metformin or glimepiride in Diabetes Mellitus patients who fail to control glucose with metformin alone. The combination of a modern sulfonylurea (glimepiride) and metformin is widely prescribed for effective blood glucose control due to its ability to address both impaired insulin secretion and insulin resistance. Patients with diabetes have abnormalities in lipid regulation, leading to a high risk of

atherosclerotic cardiovascular disease (ASCVD). Elevated LDL cholesterol levels accompanied by decreased HDL cholesterol are the strongest predictors of cardiovascular disease in patients with Diabetes Mellitus.

Glimepiride and metformin are beneficial in improving dyslipidemia in Diabetes Mellitus patients by reducing LDL, triglycerides, and increasing HDL-C levels. The management of type 2 diabetes mellitus varies greatly, ranging from non-pharmacological to pharmacological therapy. Non-pharmacological therapy that must be educated to patients includes maintaining dietary patterns and exercising. Each diabetes drug has diversity, including its mechanism of action, method of administration, side effects, etc. One type of diabetes drug is metformin, which is one of the OADs (Oral Antidiabetic Drugs) (Fatimah, 2015). Metformin works indirectly on insulin by inhibiting gluconeogenesis and glycogenolysis, slowing glucose absorption in the intestines, and increasing insulin sensitivity in the body. Metformin can lower blood glucose to normoglycemia, so its consumption does not cause hunger in patients. Diabetes mellitus treatment can be with monotherapy and combination therapy.

Another example of a type 2 diabetes drug is sulfonylurea. Sulfonylurea is another OAD. Side effects that can be caused by sulfonylurea include weight gain and hypoglycemia (Khairinnisa et al., 2020). Theoretically, the fundamental difference between sulfonylurea and metformin lies in their mechanism of action and side effects.

Type 2 DM patients come from diverse backgrounds, and there has been no prior research on the difference in effectiveness between these two drugs in Diabetes Mellitus patients, prompting this research to determine the effectiveness of the most commonly prescribed type 2 diabetes drugs, namely Metformin and Glimepiride, in diabetes mellitus patients.

The purpose of this journal review is: To understand the comparison of the use of knowledge and therapeutic outcomes in Diabetes Mellitus patients using metformin and glimepiride; to analyze the comparison of drug effectiveness based on blood sugar levels from the use of metformin and glimepiride (sulfonylurea), which are the most commonly used oral OADs in the community for Diabetes Mellitus.

CONCLUSION

A total of 39 studies met the inclusion criteria and were analyzed in this review. The examination results indicated that patients' Fasting Blood Glucose (FBG) and 2-Hour Postprandial Blood Glucose (2hPPBG) levels were above normal values, thus indicating Diabetes Mellitus. Blood sugar control was not yet stable. Patients required adjustments to drug therapy and education regarding diet and physical activity.

Metformin and glimepiride are commonly used oral anti-diabetic drugs for diabetes. Metformin functions primarily by increasing insulin sensitivity and reducing hepatic glucose production, while glimepiride is a sulfonylurea that stimulates insulin secretion from pancreatic beta cells.

Metformin and glimepiride therapy have comparable effectiveness in controlling blood sugar levels, including reductions in HbA1c, fasting blood sugar, and postprandial blood sugar. Several studies show that the combination of metformin and glimepiride yields better results compared to using either drug as monotherapy, with significant improvements in glycemic control. This combination provides a synergistic effect as each drug targets different mechanisms in the pathogenesis of type 2 diabetes.

In terms of side effects, metformin often causes gastrointestinal disturbances, while glimepiride carries a risk of mild hypoglycemia. However, the combined use of both is still considered safe and effective with manageable side effect risks. From a cost-effectiveness perspective, several studies in healthcare communities indicate that glimepiride can be more cost-effective than metformin, even though their clinical effectiveness is quite equivalent.

Both metformin and glimepiride are effective in lowering HbA1c levels and controlling

blood glucose in patients with type 2 diabetes. Metformin works by increasing insulin sensitivity and reducing hepatic glucose production, while glimepiride stimulates insulin secretion from the pancreas.

Regarding outcome effects, the combination of metformin and glimepiride provides a greater reduction in HbA1c compared to the use of either drug alone. This combination therapy can also improve glycemic control more optimally and reduce the risk of long-term diabetes complications. However, glimepiride carries a higher risk of causing hypoglycemia compared to metformin, which more frequently causes gastrointestinal disturbances. Nevertheless, both have acceptable safety profiles with proper monitoring.

Current clinical knowledge suggests that initial therapy with metformin remains the primary choice, with the addition of glimepiride or another sulfonylurea if glycemic control is inadequate. This approach aligns with diabetes management guidelines that emphasize combination therapy to achieve glycemic targets and improve clinical outcomes. Overall, the selection of therapy between metformin, glimepiride, or a combination of both should be tailored to the patient's clinical condition and risk of side effects, while referring to existing evidence of effectiveness and safety.

DAFTAR PUSTAKA

- Abd Al-Aziz, M. F., Manal, M., Shady, A., & Abd El-Hamid, S. (2018). Safety and efficacy of fixed dose combination of glimepiride and metformin in type 2 diabetic patients in Egypt: A real-life study. *The Medical Journal of Cairo University*, *86*(9), 2599-2603. <https://doi.org/10.21608/MJCU.2018.58063>
- Abrahamson, M. J., & Peters, A. (2012). Intensification of insulin therapy in patients with type 2 diabetes mellitus: An algorithm for basal-bolus therapy. *Journal of Joslin Diabetes Center*, *44*(1), 836-846.
- Artini, T. L., & Saifana, C. A. (2022). Gambaran penggunaan antidiabetes oral pada pasien diabetes mellitus tipe 2. *Prosiding Seminar Informasi Kesehatan Nasional*.
- Balkhi, B., Alwhaibi, M., Alqahtani, N., Alhawassi, T., Alshammari, T. M., Mahmoud, M., Almetwazi, M., Ata, S., & Kamal, K. M. (2019). Oral antidiabetic medication adherence and glycaemic control among patients with type 2 diabetes mellitus: A cross-sectional retrospective study in a tertiary hospital in Saudi Arabia. *BMJ Open*, *9*(7), e029280. <https://doi.org/10.1136/bmjopen-2019-029280>
- Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., Marco, A., Shekhawat, N. S., Montales, M. T., Kuriakose, K., Sasapu, A., Beebe, A., Patil, N., Musham, C. K., Lohani, G. P., & Mirza, W. (2017). Clinical review of antidiabetic drugs: Implications for type 2 diabetes mellitus management. *Frontiers in Endocrinology*, *8*, 6. <https://doi.org/10.3389/fendo.2017.00006>
- DiNicolantonio, J. J., Bhutani, J., & O'Keefe, J. H. (2015). Acarbose: Safe and effective for lowering postprandial hyperglycaemia and improving cardiovascular outcomes. *Open Heart*, *2*(1), e000327. <https://doi.org/10.1136/openhrt-2015-000327>
- Elvaretta, R., & Sudarsono. (2021). *Kajian efek samping gangguan fungsi ginjal penggunaan glimepiride pada penyakit diabetes mellitus tipe 2 di Rumah Sakit Anwar Medika* [Tesis magister, Universitas Stikes RS Anwar Medika].
- Fatimah, R. N. (2015). Diabetes melitus tipe 2. *Jurnal Majority*, *4*(5), 93-99.
- G Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of type 2 diabetes mellitus. *International Journal of Molecular Sciences*, *21*(17), 6275. <https://doi.org/10.3390/ijms21176275>
- Gottschalk, M., Danne, T., Vlaisnjic, A., & Cara, J. F. (2007). Glimepiride versus metformin as monotherapy in pediatric patients with type 2 diabetes: A randomized, single-blind

- comparative study. *Diabetes Care*, *30*(4), 790-794. <https://doi.org/10.2337/dc06-1504>
- Health Organization. (2024). *SDGs sustainable development goals*. <http://apps.who.int/bookorders>
- Hermann, L. S., Scherstén, B., Bitzen, P. O., Kjellström, T., Lindgärde, F., & Melander, A. (1994). Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations: A double-blind controlled study. *Diabetes Care*, *17*(10), 1100-1109. <https://doi.org/10.2337/diacare.17.10.1100>
- Holman, R. R., Paul, S. K., Bethel, M. A., Matthews, D. R., & Neil, H. A. W. (2008). 10-year follow-up of intensive glucose control in type 2 diabetes. *The New England Journal of Medicine*, *359*(15), 1577-1589. <https://doi.org/10.1056/NEJMoa0806470>
- Korean Diabetes Association. (2011). *Treatment guideline for diabetes*. <http://www.diabetes.or.kr/pro/publish/sub04.php?mode=list>
- Li, T., Quan, H., Zhang, H., Lin, L., Lin, L., Ou, Q., & Chen, K. (2021). Type 2 diabetes is more predictable in women than men by multiple anthropometric and biochemical measures. *Scientific Reports*, *11*(1), 6062. <https://doi.org/10.1038/s41598-021-85581-z>
- Mohammed, S. I., Chopda, M. Z., Patil, R. H., Vishwakarma, K. S., & Maheshwari, V. L. (2016). In vivo antidiabetic and antioxidant activities of *Coccinia grandis* leaf extract against streptozotocin induced diabetes in experimental rats. *Asian Pacific Journal of Tropical Disease*, *6*(4), 298-304. [https://doi.org/10.1016/S2222-1808\(15\)61039-7](https://doi.org/10.1016/S2222-1808(15)61039-7)
- Perkeni. (2019). *Pedoman pengelolaan dan pencegahan DM tipe 2 dewasa Indonesia*. Perkumpulan Endokrinologi Indonesia. <https://pbperkeni.or.id/wp-content/uploads/2020/07/Pedoman-Pengelolaan-DM-Tipe-2-Dewasa-di-Indonesia-eBook-PDF-1.pdf>
- Pignatello, R. (Ed.). (2013). *Drug-biomembrane interaction studies: The application of calorimetric techniques*. Woodhead Publishing Limited. <https://doi.org/10.1533/9781908818348.1>
- Qian, D., Zhang, T., Tan, X., Zheng, P., Liang, Z., Xie, J., Jiang, J., & Situ, B. (2018). Comparison of antidiabetic drugs added to sulfonylurea monotherapy in patients with type 2 diabetes mellitus: A network meta-analysis. *PLOS ONE*, *13*(8), e0202563. <https://doi.org/10.1371/journal.pone.0202563>
- Rasmussen, J., Nordin, L., Rasmussen, N., Thomsen, J., Street, L., Bygbjerg, I., & Christensen, D. (2014). Random blood glucose may be used to assess long-term glycaemic control among patients with type 2 diabetes mellitus in a rural African clinical setting. *Tropical Medicine & International Health*, *19*(12), 1515-1519. <https://doi.org/10.1111/tmi.12391>
- Riset Kesehatan Dasar. (2018). *Hasil utama RISKESDAS 2018*. Kementerian Kesehatan Republik Indonesia.
- Rodríguez-Almagro, J., García-Manzanares, Á., Lucendo, A. J., & Hernández-Martínez, A. (2018). Health-related quality of life in diabetes mellitus and its social, demographic and clinical determinants: A nationwide cross-sectional survey. *Journal of Clinical Nursing*, *27*(21-22), 4212-4223. <https://doi.org/10.1111/jocn.14624>
- Sheik Abdulazeez, S. (2015). Diabetes treatment: A rapid review of the current and future scope of stem cell research. *Saudi Pharmaceutical Journal*, *23*(4), 333-340. <https://doi.org/10.1016/j.jsps.2013.12.010>
- Skyler, J. S., Bergenstal, R., Bonow, R. O., Buse, J. B., Deedwania, P., Gale, E. A. M., Howard, B. V., Kirkman, M. S., Kosiborod, M., Reaven, P., & Sherwin, R. S. (2009). Intensive glycemic control and the prevention of cardiovascular events: Implications of the ACCORD, ADVANCE, and VA diabetes trials: A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology

- Foundation and the American Heart Association. *Diabetes Care*, *32*(1), 187-192. <https://doi.org/10.2337/dc09-9026>
- Wu, H., Patterson, C. C., Zhang, X., Ghani, R. B. A., Magliano, D. J., Boyko, E. J., Ogle, G. D., & Luk, A. O. Y. (2022). Worldwide estimates of incidence of type 2 diabetes in children and adolescents in 2021. *Diabetes Research and Clinical Practice*, *185*, 109785. <https://doi.org/10.1016/j.diabres.2022.109785>
- Zhao, Y., Xu, G., Wu, W., & Yi, X. (2015). Type 2 diabetes mellitus-disease, diagnosis and treatment. *Journal of Diabetes & Metabolism*, *6*(5), 1000533. <https://doi.org/10.4172/2155-6156.1000533>
- Zhu, H., Zhu, S., Zhang, X., Guo, Y., & Shi, Y. (2013). Comparative efficacy of glimepiride and metformin in monotherapy of type 2 diabetes mellitus: Meta-analysis of randomized controlled trials. *Hunan Journal of Traditional Chinese Medicine*, *29*(7), 154-156.