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Effectiveness of Combination Oral Antidiabetic Drugs and Their Impact on Clinical Outcomes in Type 2 Diabetes Mellitus Patients Using Systematic Literature Review and Meta-Analysis Method

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Oral Antidiabetic Combination, Effectiveness, Metformin Plus Sitagliptin, Metformin Plus Glimepiride, GDP, GDPP.

ABSTRACT
Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by elevated blood sugar levels due to reduced insulin secretion or progressive dysfunction of pancreatic β-cells, necessitating the use of combination antidiabetic drugs to optimize treatment. This study aims to evaluate the difference in the effectiveness of combination therapies (Metformin plus Sitagliptin vs. Metformin plus Glimepiride) on clinical outcomes in T2DM patients using a systematic literature review and meta-analysis. The research design is quantitative, following a systematic review methodology. A total of 475 articles were initially screened according to inclusion and exclusion criteria, with 5 articles ultimately selected for meta-analysis using a random-effects model. In this systematic review, the results showed that the Metformin plus Sitagliptin group demonstrated better reductions in HbA1c, while the Metformin plus Glimepiride group was more effective in controlling fasting blood sugar (GDP) and postprandial glucose (GDPP). Additionally, the Metformin plus Sitagliptin group was associated with more significant reductions in body weight and BMI. These findings provide insight into treatment decisions for managing T2DM, suggesting that specific combination therapies may be more effective for particular clinical outcomes. Defining acronyms such as GDP and GDPP within the abstract ensures clarity for readers unfamiliar with these terms.

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INTRODUCTION

Diabetes mellitus is a chronic and multifaceted disease that demands continuous medical intervention to maintain glycemic control. It is a leading cause of cardiovascular complications, which, if not addressed, significantly increases the risk of hypertension and myocardial infarction (Varela-Fernández et al., 2020). Given the rising prevalence of diabetes mellitus, selecting effective treatment regimens is critical. According to Basic Health Research (Riskesdas) data, the prevalence of diabetes mellitus in Indonesia rose from 5.7% in 2007 to 6.9% in 2013 and further increased to 8.5% in 2018 (Sudikno et al., 2015). The Ministry of Health's Information 2018 report indicates that the prevalence of diabetes among individuals aged ≥15 years varied regionally, with the lowest prevalence of 0.9% in NTT Province and the highest at 3.4% in DKI Jakarta.

The selection of Metformin combined with Sitagliptin and Glimepiride as the two primary therapies for comparison is grounded in the existing literature that supports the effectiveness of these combinations in achieving glycemic control (Bianchi et al., 2017). Metformin, as a first-line therapy, is well-established for its efficacy in lowering blood glucose levels and improving insulin sensitivity.

Sitagliptin, a DPP-4 inhibitor, complements this effect by enhancing incretin hormone activity, thus improving postprandial glycemic control. Glimepiride, a sulfonylurea, stimulates insulin secretion and has been widely used to manage blood sugar levels in diabetic patients. The rationale for comparing these combinations lies in their complementary mechanisms and the potential to optimize long-term outcomes for diabetic patients, a concept supported by recent clinical trials and therapeutic guidelines (Blahova et al., 2021). This study aims to further explore the comparative effectiveness of these combinations, given the rising burden of diabetes and its associated complications.

According to the results of the Lestari W, P (2020) Research on the Overview of the Effectiveness of the Use of Single and Combination Antidiabetic Drugs at the Fatmawati Central General Hospital (RSUP) in 2012, which shows that single antidiabetic drugs are more widely used than combination drugs. The single drug that is often used is metformin and Gliquidone as monotherapy, and the combination drugs used are glikuidone and gludepathic.

Then, on the pattern of use of oral antihyperglycemic drugs, the results were obtained that the combination of oral antihyperglycemic drugs (OHO) used at Pekanbaru Hospital in 2014 was a combination of metformin drugs – with oral drugs of the sulfonylurea group and a combination of metformin drugs with DPP-IV inhibitors, the combination of these two drugs equally lowered HbA1c, Post Prandial Glucose (PPG), and Fasting Post Glucose. This result is the same as the study of Subodh Kumar et all (2015) on the Safety and Efficacy of Glimepiride vs Sitagliptin in Combination with Metformin in Type II Diabetes Mellitus, namely: Glimepiride and sitagliptin are well tolerated when added to Metformin (Kumar et al., 2015).

In a study conducted in India, patients who took Metformin-sitagliptin showed better control of lipid profiles when compared to patients who used the Metformin-Glimepiride combination, but the group that showed better glycemic control was patients who received the metformin/glimepiride combination (M. Sharma et al., 2016).

The research of Srikartika and Valentina Meta et al. (2016), which analyzed factors affecting drug adherence in patients with Type II Diabetes Mellitus (T2DM), revealed that only 39.60% of patients adhered to therapy, with gender playing a role in compliance. Male patients were more likely to adhere to treatment than female patients. Similarly, a study examining the relationship between adherence and therapy success in T2DM patients found that those receiving oral antihyperglycemic combination therapy (AHO) had low adherence rates, which subsequently increased morbidity and mortality risks. This highlights a significant issue, as many T2DM patients require multiple medications, underscoring the need for an optimal Fixed-Dose Combination (FDC) formulation to improve therapeutic outcomes.

Given the complexity of managing T2DM, particularly in low-resource settings or developing countries where treatment access and adherence are often compromised, this study's exploration of effective combination therapies is timely and crucial. The identification of a more effective combination—whether oral metformin plus glimepiride or metformin plus sitagliptin—addresses a critical gap in diabetes treatment protocols. The study's findings could significantly influence clinical practice, guiding physicians in selecting appropriate combination therapies for T2DM patients. This has the potential to improve patient outcomes and optimize resource use, particularly in regions where healthcare systems are strained.

Furthermore, the research holds implications for healthcare policy and management guidelines, as it provides evidence-based insights into combination therapy efficacy. These findings could support the development of more targeted treatment protocols, reducing the burden of non-adherence and enhancing patient management in both primary care and specialist settings. By contributing new knowledge on the comparative effectiveness of combination therapies, this study fills an existing gap in the literature, offering practical solutions to improve diabetes care on a global scale.

METHOD

The method used follows a Systematic Literature Review (SLR) approach based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study includes Randomized Controlled Trials (RCTs) published between 2010 and January 2020, which were selected to ensure the inclusion of recent and relevant findings within the last decade. The time frame was chosen to capture advancements in diabetes treatments and the availability of newer medications. Keywords used in the search include "Type 2 Diabetes Mellitus," "Sitagliptin," "Glimepiride," and "uncontrolled diabetes with metformin." The databases searched include Medline, Pubmed, Elsevier, and the Cochrane Library (CDSR). The focus on these databases ensures a comprehensive and diverse collection of studies from various regions. Data analysis was performed using RevMan 5.3 to address the research questions and assess the suitability of studies for inclusion. The PICOS (Population, Intervention, Comparison, Outcome, and Study Design) framework was applied, focusing on patients with Type 2 Diabetes Mellitus (T2DM) over 18 years old who are not well-controlled on metformin monotherapy, with criteria such as HbA1c > 6.5%, Fasting Plasma Glucose > 7 mmol/L, or Postprandial Glucose > 10 mmol/L.

This revised justification provides clearer reasoning for the inclusion/exclusion criteria regarding the publication years and geographical scope. The chosen years ensure the studies reflect modern medical practices, while the databases help ensure a wide range of geographical locations are represented.

RESULT AND DISCUSSION

Meta Results – Effect Size Analysis

Changes in HbA1c levels are illustrated in Fig. 1. Across all five studies (11–15) included in the meta-analysis conducted using Revman software; the results showed no statistically significant difference in the reduction of HbA1c between the two combination groups (P > 0.05). Specifically, the meta-analysis of the Metformin plus Sitagliptin group showed a weighted mean difference (WMD) of 0.03% (95% CI: -0.12 to 0.18, P = 0.72), indicating a minimal effect size. Although this reduction was not statistically significant, it is important to consider the potential clinical implications. A change of 0.03% in HbA1c may not reach significance, but even small reductions in HbA1c can contribute to better glycemic control in the long term, especially in high-risk populations. This aligns with findings from Anjoom et al., who also reported that the combination of Metformin and Sitagliptin showed efficacy in reducing HbA1c, although the effect was modest. Similarly, Manuj Sharma et al. observed that while the combination of sitagliptin (100 mg), glimepiride (1-2 mg), and metformin (1000 mg) resulted in a reduction in HbA1c by the 30th week, the changes were not statistically significant (P > 0.05). These findings suggest that while the effect sizes observed may be small, they could still inform treatment decisions, especially for patients who may benefit from a combination therapy that supports gradual and sustained glycemic control. Fig. 2 illustrates the meta-analysis results on fasting blood sugar levels (FBS) from the same five studies (11–15).

The result showed that the group (Metfomin plus Glimepiride) was better at reducing GDP levels in patients with insignificant (p>0.05), and the combination (Metfomin plus Glimepiride) showed a reduction of 4.13% (WMD= 4.13, 95% CI -4.45 to 12.71, p=0.35). This result is the same as the study conducted by Manuj, Sharma et all (8,15), namely, the group (Metformin plus glimepiride) was better at reducing GDP levels than (Metformin plus sitagliptin in the Preeti Singh et all (23) study At the 24-week study with a dose of Metformin 500 mg + glimepiride 10 mg and Metformin 500 mg + sitagliptin 100 mg, the results at the 12th-week group (Metformin Plus glimepiride) were better in lowering GDP levels, although the dose given in the study was too high when compared to the dose of this study.

In Fig. 3, the results of the meta-analysis from three journals (11–13) on blood sugar levels 2 hours after meals (GDP) demonstrate that the combination of Metformin and Glimepiride was more effective in reducing postprandial blood sugar levels compared to the combination of Metformin and Sitagliptin, showing a significant decrease of 9.73% ($p<0.05$) (WMD= 9.73, 95% CI 6.72 to 12.73, P=<0.0001). Similarly, Figs. 4 and 5 illustrate the impact of these drug combinations on weight and BMI. While Metformin plus Sitagliptin contributed to weight loss, Metformin plus Glimepiride was associated with weight gain (13–15), with a mean decrease of -2.26 kg (95% CI -4.00 to -0.52, P=0.01). However, the change in BMI was not statistically significant in either group, with a decrease in the Metformin plus Sitagliptin group of -0.28 kg ($p>0.05$) (WMD: -0.28, 95% CI -0.85 to 0.29, P=0.33).

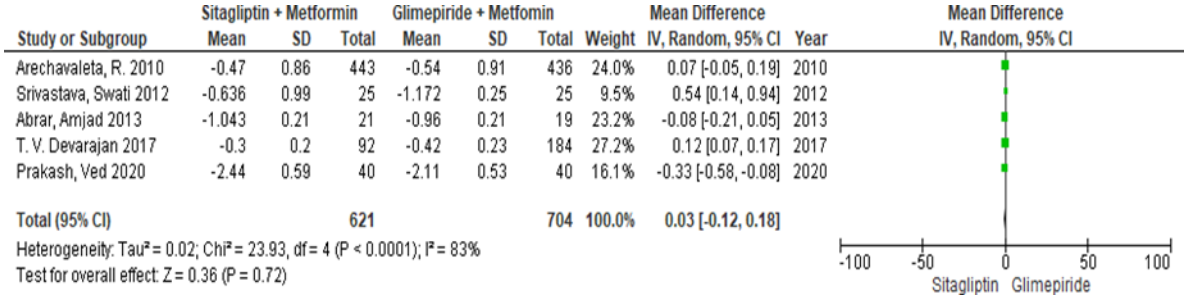

Figure 1. Comparison of HbA1c% change from baseline, between metformin + sitagliptin vs Metformin + Glimepiride (SD= standard deviation; CI= confidence interval; df= degrees of freedom.)

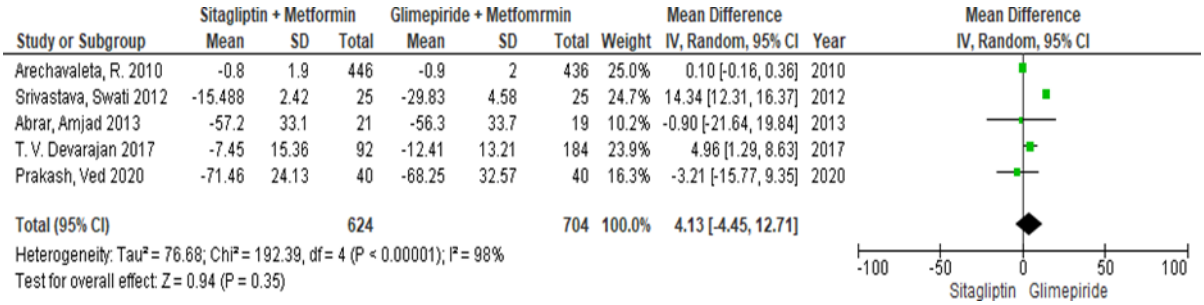

Figure 2. Comparison of GDP change from baseline, between metformin + sitagliptin vs Metformin + Glimepiride (SD= standard deviation; CI= confidence interval; df= degrees of freedom.)

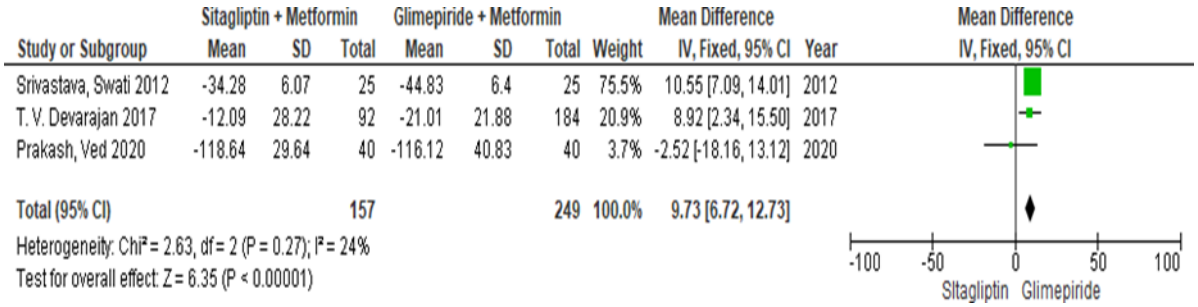

Figure 3. Comparison of GDPP change from baseline, between metformin + sitagliptin vs Metformin + Glimepiride (SD= standard deviation; CI= confidence interval; df= degrees of freedom.)

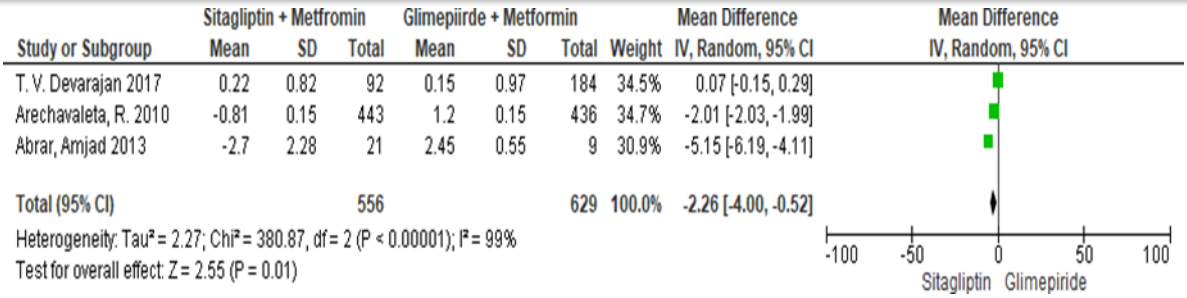

Figure 4. Comparison of weight change from baseline, between metformin + sitagliptin vs Metformin + Glimepiride (SD= standard deviation; CI= confidence interval; df= degrees of freedom.)

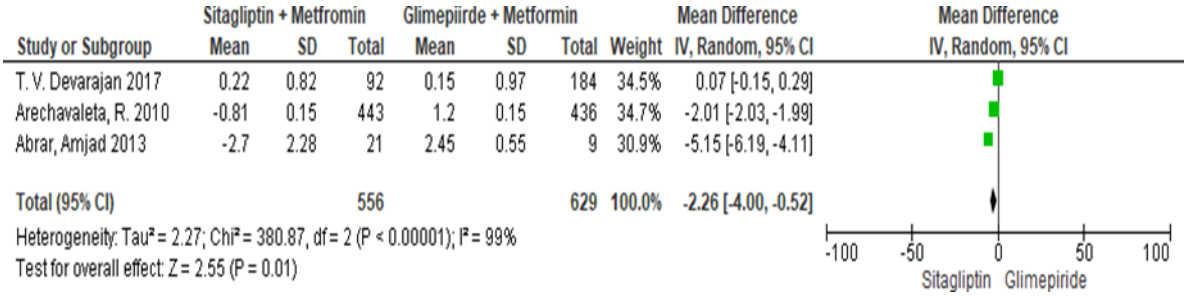

Figure 5. Comparison of BMI change from baseline, between metformin + sitagliptin vs Metformin + Glimepiride (SD= standard deviation; CI= confidence interval; df= degrees of freedom.)

Overview General characteristics of the research subject

Based on gender

Based on gender, the results of the meta-analysis show that the number of male patients is more than female; this result is the same as the research conducted by Rahmi Yosmar et al. (2018), which obtained the results that men are more likely to develop diabetes than women, as well as according to the International Diabetes Federation (IDF) in 2017, stating that 17.1 million more men with diabetes than patients woman. According to research conducted by Alexandra Kautzky et al. (2016), more fat accumulates around the waist and liver in men. While women have more subcutaneous fat that is safely stored in the thighs and hips. These results cause many men to develop diabetes with higher BMI values than women, and men tend to be more susceptible to obesity and other comorbid symptoms.

Based on age

Based on the results of the meta-analysis, the patient's age ranged from 49 to 59 years. This result is in line with the research of Komariah et al. (2020), which stated that increasing age is a risk factor for diabetes mellitus. This result is also in line with the International Diabetes Federation (IDF) statement that 20% of diabetics are over 60 years old (Ogurtsova et al., 2017). This result is also the same as the American Diabetes Association (ADA) (Association, 2014) stated that age over 45 years is one of the risk factors for the occurrence of type 2 diabetes.

Effectiveness of the use of combination oral antidiabetic drugs

From the literature and several treatment procedures for T2DM patients, it is informed that metformin is a first-line drug in the treatment of hyperglycemia in T2DM patients if the glycemic effect is not achieved with lifestyle modification (Gupta et al., 2015). Metformin is a biguanid group that has a mechanism of action, namely, stimulating glucose uptake by suppressing liver glucose production and reducing glucose absorption in the intestines and peripheral tissues by about 10-40% (Ratnasari & Bhargah, 2018) by not stimulating insulin secretion by the pancreatic gland (Ahmad & Chowdhury, 2019). This group of biguanids also improves insulin resistance, has a high initial response rate, is safe, does not increase body weight, and is beneficial to the lipid profile (Wijaya et al., 2015). Another

advantage of using metformin is that it can lower HbA1c by about 1–1.5%, has a relatively low price, minimizes hypoglycemic effects, and reduces the occurrence of cardiovascular complications by lowering LDL (Low-Density Lipoprotein) cholesterol levels (Amate et al., 2015). However, there is no consensus on the right drug to be combined with metformin if the patient's glycemic effect is not achieved.

There needs to be a lot of consideration of the patient's condition in giving combination drugs to T2DM patients, including side effects, weight gain, and the patient's glycemic effects and comorbidities. The Sulphonilurea group has been used frequently since 1950 and is one of the oral antidiabetic drugs that have the potential to reduce blood sugar levels in T2DM patients. Sulfonylureas are often combined with metformin because they have a good therapeutic effect and are relatively cheap and safe. Glimepiride is the third generation of the sulphonilurea group and is the most potent (Chan et al., 2015) because, at the lowest dose, it results in the greatest decrease in blood glucose and low cardiovascular risk. Unlike other sulfonylureas, glimepyride also improves the first-phase insulin response so that glimepyride improves early and late post-prandial hyperglycemia (Khairinnisa et al., 2020a). The results of a meta-analysis of randomized clinical trials (RCTs) showed that second- and third-generation sulphonilurea, including glimepiride, did not cause cardiovascular, myocardial infarction, or stroke. Glimepiride had a lower mortality rate than other sulphonilurea (Rados et al., 2016).

The addition of glimepiride to metformin therapy has been studied in a study involving 370 patients divided into a metformin group, a glimepiride group, and a group (metformin plus glimepiride). Studies show that the combination of Metformin and glimepiride is more effective in controlling blood glucose compared to the use of both drugs as monotherapy. Combination therapy was also significantly more effective in lowering HbA1c (Khairinnisa et al., 2020b). In subsequent studies, the combination of glimepiride and metformin was shown to be effective and safe for T2DM patients who failed oral monotherapy with antidiabetes (S. Sharma et al., 2018).

Then the latest group of drugs that are often used in treatment management is the DPP IV inhibitor class, which has a working mechanism to increase the levels and action of Glucagon Like Peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Polypeptide (GIP), as well as increase insulin secretion and suppress glucagon secretion from pancreatic alpha cells. GLP-1 works to stimulate insulin release and inhibit glucagon release so that blood sugar levels are maintained (Sihotang et al., 2018). DPP IV inhibitors are widely reported to lower blood glucose without any hypoglycemic risk if added with metformin (Kristin, 2016). Sitagliptin is a DPP IV inhibitor class drug with good tolerance to changes in HbA1c, protects cardiovascular, lowers blood pressure without increasing weight, and improves the quality of life of patients with diabetes mellitus. Sitagliptin also did not increase the risk of cardiovascular, myocardial infarction, ischemic stroke, or heart failure when compared to metformin (Shin & Kim, 2016). The combination of sitagliptin and metformin is excellent at lowering hyperglycemia and not gaining weight (Sani et al., 2022a).

The results of the meta-analysis conducted in this study showed that the addition of sitagliptin therapy to the regimen of patients with T2DM who are currently undergoing metformin monotherapy may result in a decrease in HbA1c values; this result is also similar to the addition of sulfonylurea plus metformin therapy. Both lower HbA1c. but Sitagliptin is better at lowering HbA1c levels by about 0.04%. In this result, we can see that there is a relationship between these two drug combinations in terms of HbA1c clinical outcome value but not significant (Devarajan et al., 2017). From the results of the meta-analysis conducted on GDP and GDPP values, there was a change in the decrease in GDP values of around 4.13%, and GDPP of around 9.13% occurred in the Metformin + Glimepiride combination drug group compared to the Metformin + Sitagliptin combination group. Then, the results of the meta-analysis conducted on BMI and Weight values showed that (Metformin Plus sitagliptin) resulted in a greater weight loss, which was about 2.3 kg compared to the combination of drugs

(Metformin Plus Glimepiride), which tended to increase weight. Sitagliptin also works to increase endogenous GLP 1 so that it can delay gastric emptying, as well as increase satiety and weight (Lundby-Christensen et al., 2016).

Effect of Fixed Dose Combined on Clinical Outcomes

From previous research, it is known that the level of compliance of people with DM is inversely proportional to the number of drugs that must be taken; the less the amount of medication that must be taken, the better the level of compliance. This fact is in line with the concept of fixed-dose combination (FDC), which is combining drugs with ≥ 2 active components in fixed proportions into a single dosage form (Vijayakumar et al., 2017). One of the reasons for using the FDC formula in T2DM therapy is to strengthen the therapeutic efficacy of the drug. Currently, a number of FDCs are available to treat T2DM, including Janumet (sitagliptin 100 mg + Metformin 500 mg) and Amaryl M (glimepiride 100 mg/ Metformin 500 mg). (10.50 km)

Efficacy and safety of FDC and Glimepiride combination – Metformin

A randomized, double-blind study conducted by González-Ortiz compared the effectiveness of the use of Glimepiride and metformin FDC compared to glibenclamide and metformin FDC in 152 T2DM patients. The glimepiride group showed fewer hypoglycemic effects when compared to the glibenclamide group.

It was also discussed in a multicenter study that had been conducted in France to compare the effects of the combination of glimepiride and metformin with both drugs as monotherapy. Approximately 370 T2DM patients were randomly assigned metformin, glimepirid, or metformin+glimepirid. The combination of metformin + glimepyride was significantly more efficient in controlling HbA1c ($P<0.001$), fasting blood glucose ($P<0.001$), and post-prandial blood glucose ($P<0.001$). Studies show that the addition of glimepiride to metformin in patients with uncontrolled T2DM with metformin administration alone results in superior glycemic control compared to glimepiride or metformin as monotherapy (Chatterjee et al., 2017)

Then a study conducted by Thangavel Mahalingam Vijayakumar et al (2017) compared the efficacy of the use of the combination of Glimepiride 2mg + Metformin 100mg with a fixed combination of FDC (Glimepiride 2mg/metformin 500mg), obtained the result that the FDC combination group was better at reducing HbA1c levels, and GDP. Without increasing cardiovascular risk, the myocardium (Vijayakumar et al., 2017).

Effect of Fixed Dose Combined Use of Sitagliptin and Metformin on Clinical Outcomes

In a randomized, open-label study conducted by Migoya et al., compared the use of sitagliptin and metformin in the form of FDC with doses (sitagliptin 50mg, Metformin 500mg) with non-FDCs with doses (Sitagliptin 50 mg and metformin 1000mg) that were tried on 48 T2DM patients, and gave results that the use of FDC tablets significantly reduced HbA1c levels in T2DM patients (Cheekireddy et al., 2016).

Efficacy and safety of FDC Sitagliptin – Metformin

Research on Sitagliptin/metformin (Janumet) as an additional combination therapy for patients with type 2 diabetes mellitus. This research is a narrative review research that obtained the results. Metformin plus Sitagliptin combination therapy has a tolerable effect on patients with diabetes mellitus, and this combination provides self-compliance to T2DM patients. This combination is very effective in lowering HbA1c levels and losing weight and does not cause hypoglycemic effects (Sani et al., 2022b).

Research related to the use of Metformin plus Sitagliptin is still rarely found in Indonesia, and the results of this meta-analysis cannot be directly applied to T2DM patients in Indonesia because it may have different patient characteristics from each country. The results of this meta-analysis show that both drug combinations control HbA1c levels, but the combination of Metformin plus Sitagliptin is good at reducing HbA1c levels, as well as weight loss, while the Metformin plus Glimepiride group is

good at controlling GDP and GDPP levels compared to Metformin plus Sitagliptin, Metformin plus Glimepiride has more side effects compared to the combination of Metformin plus Sitagliptin, Side effects of the combination of Metformin plus Glimepiride can increase weight, while the combination of Metformin plus Sitagliptin does not increase weight. and safer in use as an anti-diabetic, the rarity of research related to citagliptin in Indonesia is likely due to the price of citagliptin, which is quite expensive compared to glimepiride. This literature study was created to examine the heterogeneity of the use of the combination Metfomin plus Sitagliptin with Metfomin plus Glimepiride.

CONCLUSION

The results of the meta-analysis indicated no significant difference between the two combination groups in terms of HbA1c clinical outcomes. However, the combination of Metformin plus Sitagliptin was more effective in reducing HbA1c levels in patients with type 2 diabetes mellitus compared to Metformin plus Glimepiride. When considering GDP (glycated protein) clinical outcomes, although there was no significant difference, the Metformin plus Glimepiride group showed greater effectiveness in reducing GDP levels. This combination was also superior in reducing GDPP (glycated protein postprandial) levels compared to Metformin plus Sitagliptin.

For healthcare professionals, these findings suggest tailoring treatment choices based on patient characteristics; for patients needing a stronger reduction in HbA1c, especially those with weight concerns, Metformin plus Sitagliptin may be a better choice due to its efficacy in reducing HbA1c and promoting weight loss or stability. For patients where GDP reduction is a priority, especially those with a lower risk of weight gain, Metformin plus Glimepiride might be preferable, as it significantly reduces GDP but may lead to weight gain.

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