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A Comparative Assessment Of Safety, Efficacy, And Cost-Effectiveness Of Glipizide-Metformin And Glimepiride-Metformin Combination Therapy In Type-2 Diabetes Mellitus

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is a common metabolic syndrome that needs effective long-term glycemic controls. There is wide usage of fixed-dose combinations (FDCs) of metformin with sulfonylureas. Glipizide metformin and glimepiride metformin are among them and these combinations are not effectively compared in terms of clinical and economic outcomes.

Objectives: To compare the safety, efficacy and cost-effectiveness of glipizide metformin and glimepiride metformin fixed dose combination therapy in treating patients with T2DM.

Methods: A prospective comparative study was done over a period of 6 months in a tertiary care hospital in Chennai on 200 T2DM patients. The patients were randomly grouped into Group A (glimepiride 2 mg + metformin 500 mg) and Group B (glipizide 5 mg + metformin 500 mg) and the efficacy was measured by the changes of fasting blood sugar (FBS), postprandial blood sugar (PPBS), random blood sugar (RBS) and HbA1c. The safety was evaluated with the Naranjo causality scale, whereas cost-effectiveness was determined as the cost per cent reduction in glycemic parameters.

Results: Group A showed better glycemic control showing decreases in FBS (36.1%), PPBS (40.2%), RBS (30.1%), and HbA1c (16.8%) than Group B. The adverse drug reactions experienced in both groups were mild and similar. The overall therapy cost was a little higher in Group A but the cost per 1% glycemic reduction was more conducive pointing out to the better cost-effectiveness of the group.

Conclusion: The glimepiride metformin combination therapy is more effective and cost-effective with an equal safety margin and should therefore be the choice of therapy in the long-term management of T2DM.

Key Words: *Type 2 Diabetes Mellitus, Glimepiride, Glipizide, Metformin, Combination Therapy, Cost-Effectiveness, Glycaemic Control, Safety, Efficacy*

1. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by high blood sugar levels due to insufficient insulin production or the body's inability to use insulin effectively. Insulin is a hormone that regulates blood glucose levels and allows glucose to enter cells to produce energy. Diabetes mellitus is diagnosed when the blood glucose levels get too high, and this is seen among 10% of the world population. [1,2]

It was recorded on Egyptian papyrus more than 3500 years ago. Historical Indian writings referred to it as "honey urine," the ancient Chinese named it "wasting-thirst," and in the present day, it is known as "diabetes mellitus" (a condition associated with elevated blood sugar). Diabetes mellitus is a progressive, chronic metabolic disorder characterized by sustained hyperglycemia due to insulin secretion, action, or both. The burden of diabetes in the world has risen significantly over the past decades, and it is now among the topmost challenges in public health across the globe. The latest IDF Diabetes Atlas

update (2024) indicates that 589 million adults aged 2079 years (approximately 1 in every 9 adults worldwide) were living with diabetes, a significant increase since previous years before the pandemic. [3] Another report published in The Lancet in 2023 showed that in 2021, 828 million adults aged 18 years and above were diabetic, representing a 6.1% global prevalence of diabetes. [4] Nearly a quarter of a billion people, or 43 percent of all diabetics, have not been diagnosed yet. In 2024, the disease caused around 3.4 million deaths, that is, one death occurred every nine

seconds, hence a significant cause of avoidable deaths. [3] In addition to the health consequences, the financial cost to the global economy is immense, as diabetes health spending will top USD 1 trillion in 2024. [3] It was believed that a Greek physician had first used the term "diabetes" in 300 BC. It came from the Greek word "to siphon," which refers to the signs of frequent urination and persistent thirst. [5] Throughout the 2000 years, doctors began to understand better diabetes to diagnose and treat it. Various treatment approaches, such as the cat cure, potato therapy, milk diet, etc., were developed even in the late 19th century. Still, they all ultimately resulted in the early death of many people. [6] A significant step in determining the function of the pancreas in blood glucose regulation was taken in 1889, when Oskar Minkowski and Joseph von Mering excised the pancreas from dogs and saw the development of diabetic symptoms and death shortly thereafter. [7] Paul Langerhans initially described the varieties of pancreatic cells and their functions. [8] The term "insulin" was only suggested as a name for the substance secreted by the islets of Langerhans in the early 1900s. Following a series of pancreatic secretion experiments, Frederick Banting and Charles Best administered an isolated secretion to diabetic dogs. The following notable decrease in blood glucose levels signalled the discovery of insulin as a treatment for diabetes, and with the assistance of John Macleod and James Collip, additional research was conducted to extract and purify insulin from adult cow pancreas. [9] Then, when Leonard Anthony became the first diabetic patient to receive insulin, history was created. [10] The dip and read urine test, which was created in the 1940s, was improved upon later on to provide more accuracy with just one drop of blood. Results of a trial on the efficacy of the medication metformin in lowering blood sugar levels were released in 1975. Originally released in France under the brand name Glucophage, it is now the first-line medication for preventing type 2 diabetes. [11] The United States' Minnesota performed the first pancreatic transplant in 1966 to treat type 1 diabetes. [12] The development of the first glucose meter in 1971, which used a blood glucose test to measure blood sugar levels, was another testing advance. [13] The insulin pump was invented by Dean Kamen in 1976 and is a portable device that gives insulin to diabetic people. The first human-based insulin, Humulin, was synthesized by Genentech in 1978, but it took an additional four years for it to reach the market before their animal tissue hoarding was stopped. [14] In actuality, the following ten years saw insulin analogs' production and clinical approval. Not only have we greatly advanced our knowledge of diabetes over the past 100 years or more, but we have also created state-of-the-art technology that will enable better diagnosis and treatment. As an "artificial pancreas," the Medtronic MiniMed was just approved as the first closed-loop clinical device in 2016. [15] Nevertheless, research continues in search of a cure for diabetes, with work such as islet cell transplantation. [16]

THE PROBLEM OF POST-COVID DIABETES AND ITS CONSEQUENCES:

Besides this increasing baseline prevalence, recent data elucidate an alarming rise in new-onset diabetes after COVID-19 infection, especially in corticosteroid use, systemic inflammation, and direct viral effects on the pancreatic beta cells. Even in the absence of steroid exposure, incidence of new-onset type 2 diabetes was reported in 1.1 percent of COVID-19 patients with mild infection and 4.1 percent of patients with moderate-to-severe disease in a large cohort study including 600,055 COVID-19 patients; [17] In an extensive meta-analysis of 4.4 million subjects, there were more than 60 000 new cases of diabetes, with a crude incidence rate of 1.37% 0.84% of type 2 diabetes and 0.017% of type 1 diabetes Diabetes [18] was also much more prevalent among COVID-19 survivors admitted to the hospital, as high as 16.7 percent, compared with 12 percent in influenza cohorts.[19] The pooled incidence (95% CI: 210%) of new-onset diabetes or hyperglycemia during the post-COVID period was estimated by another global review at 5% incidence. [20] Together with the findings, there is a risk that COVID-19 can catalyze the diabetes pandemic and highlight the necessity of long-term metabolic follow-up as a part of post-infection care.

FUNCTIONS OF INSULIN:

Insulin is a chemical messenger hormone that regulates blood sugar levels, which is produced by the pancreas. [21]

Initially body breaks down the food into glucose (the body’s main source of energy). Glucose enters the bloodstream and signals the pancreas to release insulin. Insulin helps glucose in the body’s blood enter into muscles, fat, and liver cells to use it for energy or store it for later use. [17] When glucose enters the cells and the levels in the bloodstream decrease, it signals the pancreas to stop producing insulin. [22

There are two types of diabetes mellitus:

Type1 diabetes mellitus

Type2 diabetes mellitus

TYPE 1 DIABETES MELLITUS:

Type 1 diabetes mellitus is a chronic autoimmune disease also known as insulin-dependent diabetes. In this condition body does not produce enough insulin. [23] In this autoimmune disease, the body itself destroys the cells in the pancreas that make insulin; this process goes on for months or years before any symptoms appear. [24] This condition can be developed at any age, but most commonly it is diagnosed between the ages of 4 to 6 and in early puberty (10 to 14 years). [25] In type 1 diabetes, the immune system attacks the beta cells in the pancreas and damages the cells that produce insulin. The cause of type 1 diabetes is not completely understood, but it is believed as a combination of both genetic and environmental factors.

Symptoms: excessive thirst, excessive hunger, unexplained weight loss, blurred vision, slow healing of cuts and sores, fatigue, frequent urination

TYPE 2 DIABETES MELLITUS:

Type 2 diabetes mellitus is a chronic condition developed due to high blood sugar levels. In this condition, either the pancreas doesn't produce enough insulin or the body doesn't use insulin effectively. [26] The main cause of type 2 diabetes is insulin resistance. Type 2 diabetes is also known as adult-onset diabetes. [26] Extremely high blood sugar levels also can lead to a serious complication called hyperosmolar syndrome (life life-threatening form of dehydration). [27]

Symptoms: increased thirst, frequent urination, excessive hunger, fatigue, slow healing, blurred vision, dry skin, unexplained weight loss.

GLIPIZIDE-METFORMIN:

The glipizide and metformin combination is used to treat high blood sugar levels. Glipizide stimulates the release of insulin from the pancreas, directing the body to store blood sugar. Metformin has three different actions: it slows the absorption of sugar in the small intestine; it also stops from conversion of stored sugar into blood sugar, and it helps the body to use natural insulin more efficiently. [28,29]

Common side effects: headache, diarrhoea, hypoglycaemia.

GLIMEPIRIDE-METFORMIN:

Glimepiride and metformin combination medication is used to manage type 2 diabetes; Glimepiride belongs to a class of drugs called sulfonylureas that work by stimulating the pancreas to release more insulin helps to lower glucose levels. Metformin belongs to a class of drugs called biguanides. It works by reducing glucose production in the liver and improving the body's sensitivity to insulin. [30,31]

Common side effects: nausea, upper respiratory tract infection, dizziness.

2. MATERIALS AND METHODS:

This prospective comparative study was conducted to evaluate the safety, efficacy, and cost-effectiveness of glipizide–metformin and glimepiride–metformin fixed-dose combinations in the management of type 2 diabetes mellitus. The study was carried out at a tertiary care hospital in Chennai to determine the optimal therapeutic approach based on clinical and economic outcomes. This study was conducted for six months. This study included patients diagnosed with type 2 diabetes mellitus patients selected irrespective of sex. A total of 200 cases of type 2 diabetes mellitus patients were included in this study. The age limit should be < 18 years.

Age, sex, height, weight, and other associated diseases were noted. BMI was calculated, and instruction was given to patients to monitor their blood glucose level, HbA1C, and lipid profile at the initial visit to the hospital. Patients were informed to check their glucose levels regularly at an interval of 2 months. Primary parameters used for this study were fasting plasma glucose, postprandial glucose, HbA1C, and BMI. Secondary parameters used were serum cholesterol, serum creatinine, serum urea, and serum uric acid level. The required information was collected in a patient data collection form by the "Chart review method," which is well-suited to assess the results. In this study, we received patient case records and patient demography, admitting diagnosis, past medical and medication history, physician medication order, and other valuable findings. A sample of 200 patients was chosen, differentiated equally into two treatment groups; one group with 100 patients was given with Metformin500mg/Glimepiride, and the remaining 100 patients with Metformin 500mg/ Glipizide 5mg. During the 6 months of our period, we collected patients' blood sugar level data. Here we denoted the Group (A) as Metfomin500mg/ Glimepiride 2mg and Group (B) as Metformin500mg/ Glipizide 5mg. The entire collected and documented patient's data was analysed, and the efficacy was assessed by using blood sugar level data.

Statistical analysis:

The mean percentage reduction of glucose level (RBS, FBS, and PBS) obtained for Group A and Group B was compared. The group that showed the greatest percentage reduction in RBS, FBS, and PBS levels was noted, and the drug given to that group is supposed to be more efficient than the other.

3. RESULTS:

A total of 200 patients were recruited for our study. The study population was divided into 2 groups, i.e., Group A and Group B. The first 100 patients were included in Group (A) and were given Glimepiride 2mg/ Metformin 500mg. The remaining 100 patients were included in Group B and were given Glipizide/ Metformin 500mg.

GENDER WISE DISTRIBUTION:

On comparing both the groups of subjects given different drugs, Group A, which was provided with Glimepiride with Metformin, involved 51 male subjects and 49 female subjects, and Group B, which was provided with Glipizide with Metformin, included 46 male and 54 female subjects.

Group	Drug Combination	Male (n)	Female (n)	Total (n)
Group A	Glimepiride + Metformin (2 mg/500 mg)	51	49	100
Group B	Glipizide + Metformin (5 mg/500 mg)	46	54	100

Table 1: Gender-wise Distribution of Patients in Group A and Group B Receiving Different Combination Therapies

This is a table showing gender-wise distribution of participants of the study in 2 treatment groups. In Group A (Glimepiride + Metformin), there were 51 males and 49 females, whereas, in Group B (Glipizide + Metformin), there were 46 males and 54 females, and 100 subjects in each group.

AGE WISE DISTRIBUTION:

In the age wise distribution of Group(A) most of the patients belonged to the age group of 51-60 years (38%) followed by age group of 41-50 years (28%) and (22%) of subjects in the age group of 61-70 years and (12%) of subjects in the age group of 30-40 years.

Similarly, in the age wise distribution of Group (B),39% of the people belonged to the age group of 41-50 years and 26% of people belonged to 41-50 years and 24% of the subjects belonged to the age group of 61-70 years and 11% of subjects belonged to 30-40 years of age

Table 2: Age-Wise Distribution of Patients in Group A and Group B Receiving Combination Therapy

Age Group (Years)	Group A(Glimepiride + Metformin)	Group B(Glipizide + Metformin)
30–40	12%	11%
41–50	28%	39%
51–60	38%	26%
61–70	22%	24%
Total	100%	100%

This table illustrates how many participants in Group A and Group B there were in terms of age. Group A had the majority aged 51 60 years (38%), whereas Group B had most patients aged 41 50 years (39%), indicating difference in age demographics among treatment groups.

SAFETY RESULTS:

In this study, drug safety was assessed by assessing the ADRs which are produced by the antidiabetic medication during the study period, and the causality assessment was carried out the Naranjo's causality assessment scale. We did not observe any significant difference in ADR occurrence between the two groups

Table 3: Adverse Drug Reactions and Causality Assessment (Naranjo's Scale) in Group A and Group B

S.NO	TREATMENT GROUP	REACTION OBSERVED	CAUSALITY ASSESSMENT	NUMBER OF PATIENTS	TOTAL

			(Naranjo's scale)		
1	Group (A)	Weight grain	Probable	1	8
		Dizzy	Possible	1	
		Excess urination	Probable	2	
		Muscle pain	Possible	1	
		Loss of appetite	Possible	1	
		Head ache	Possible	2	
2	Group (B)	Loss of appetite	Possible	2	9
		Head ache	Possible	2	
		Feeling Weak	Possible	1	
		Hives	Possible	1	
		Muscle pain	Possible	1	
		Excess urination	Probable	2	

This table presents the adverse drug reactions (ADRs) observed in each of the two treatment groups as determined by the Naranjo scale. Group A included 8 mild ADRs and Group B included 9, with all the reactions defined as possible or probable, which demonstrates similar safety profiles.

EFFICACY RESULTS:

The mean percentage of reduction achieved in Group (A) from first follow-up to final follow-up (90 days after initial hospital visit) was 36.1 (FBS), 40.2 16.8 (HbA1c). (PBS), 30.1 (RBS).

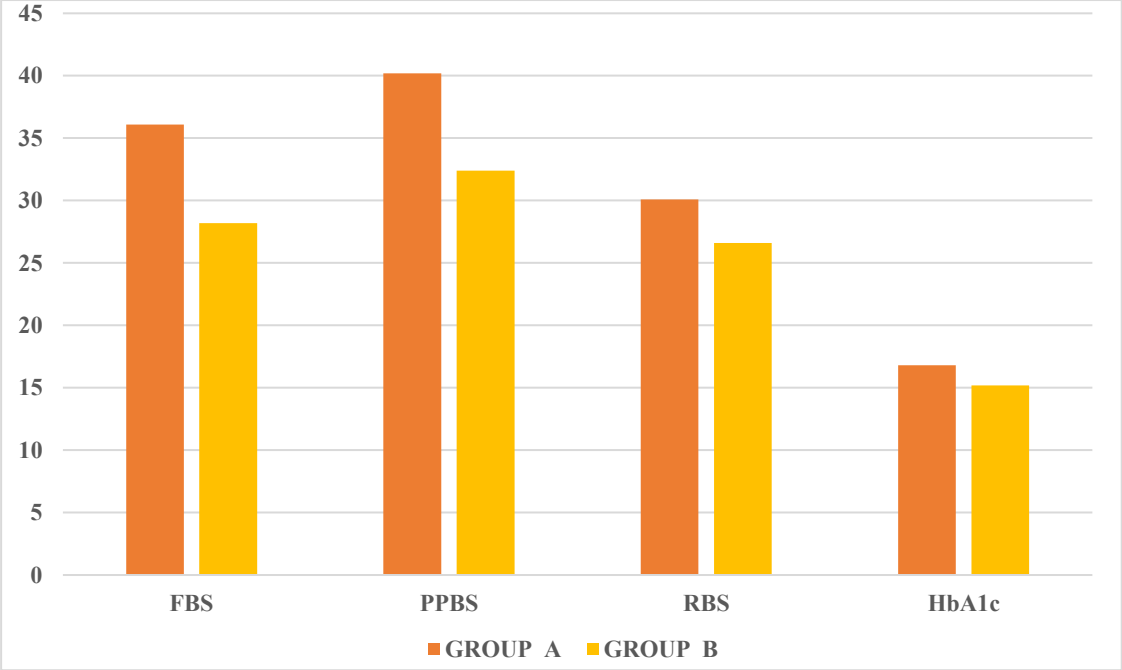
The mean percentage of reduction achieved in Group (B) from first follow-up to final follow-up (90 days after initial hospital visit) was 28.2 (FBS), 32.4 15.2 (HbA1c). (PBS), 26.6 (RBS).

4. TABLE 4: COMPARISON OF PERCENTAGE REDUCTION IN BLOOD GLUCOSE LEVEL BETWEEN GROUP (A) AND GROUP (B) AFTER FINAL FOLLOW-UP

SL NO	NUMBER OF GROUPS	FBS	PPBS	RBS	HbA1c
1	GROUP A	36.1	40.2	30.1	16.8
2	GROUP B	28.2	32.4	26.6	15.2

This table corresponds to the effectiveness of the two treatment groups in terms of the percentage change in fasting blood sugar (FBS), postprandial blood sugar (PPBS), random blood sugar (RBS), and HbA1c. All the parameters exhibited more reductions in Group A than in Group B.

Figure 1: Comparison of Percentage reduction in blood Glucose level between Group (A) and Group (B) after final follow-up.



COST-ANALYSIS RESULTS:

The total cost of Glimepiride therapy for 90 days was 279. We used Isryl-M tablets containing 2mg Glimepiride and 500mg Metformin for our study. The price of 1 pack of Isryl M containing 1 tablet unit was 15.50.

The total cost of Glipizide therapy was 275.76 rupees. We used Glynase-MF tablets containing 5mg Glipizide and 500mg Metformin for our study. The price of 1 pack of Glynase MF containing 10 tablets was 15.32.

The cost for getting a 1% reduction in FBS for Group (A) is 14.38 Rupees, 4.63 Rupees less than Group (B).

The cost for getting a 1% reduction in PBS for Group (A) is 9.238 Rupees, 2.2 rupees less than Group (B).

The cost for getting a 1% reduction in RBS for Group (A) is 10.03 Rupees, 5.63 Rupees less than Group (B).

Table 4: Cost-Effectiveness Analysis of Glycemic Parameter Reduction in Group A

SL NO		BASELINE PARAMETER	EAN PERCENTAGE (%) REDUCTION	COST FOR GETTING 1%REDUCTION IN RUPEES
1	279	FBS	36.1	7.72 RUPEES
2		PPBS	40.2	6.94 RUPEES
3		RBS	30.1	9.26 RUPEES
4		HbA1c	16.8	16.60 RUPEES

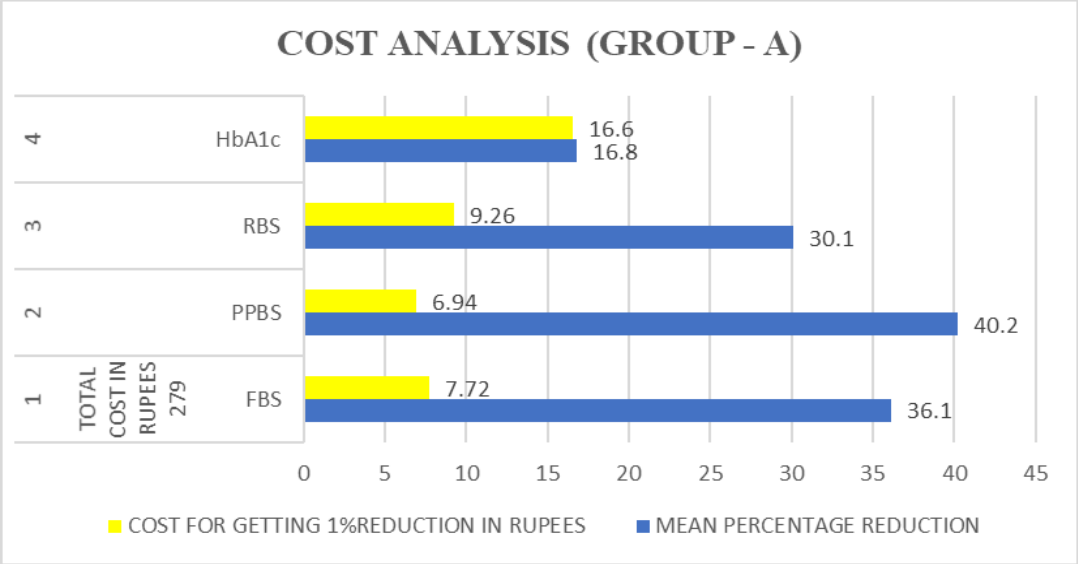


Figure 2: Cost-Effectiveness of Glycaemic Parameter Reduction in Group A: Comparative Analysis of Cost per 1% Reduction and Mean Percentage Reduction

5. DISCUSSION:

This current study assessed and compared the efficacy, safety, and cost-effectiveness of two fixed-dose combination drugs, Glimepiride with Metformin and Glipizide with Metformin, in patients having Type 2 Diabetes Mellitus (T2DM). We have found that the Glimepiride + Metformin combination showed better glycemic control as it showed a higher percentage decrease in FBS, PPBS, RBS, and HbA1c levels than the Glipizide + Metformin group. These findings correspond with the previous findings indicating that glimepiride might provide superior glycemic control across the second-generation sulfonylureas in the combination with metformin. [32]

Regarding efficacy, the current study revealed a percentage of HbA1c reduction of 16.8 in the Glimepiride group and 15.2 in the Glipizide group. The superiority of Glimepiride in regard of glycemic control and reduction of HbA1c levels compared to Glipizide was also evidenced in a randomized comparative study by Schernthaner et al. which suggested that this may be attributed to its longer action duration and glucose-dependent insulin-releasing properties. [33] In another trial, Marre et al. indicated similar results and confirmed the better glycemic efficacy of Glimepiride as a combination therapy. [34]

In our study, safety was similar in both groups, and the adverse drug reactions (ADRs) were mild (dizziness, weight gain, and headache). The result is consistent with the safety outcomes of a study by DeFronzo et al., in which both combinations had manageable side effect profiles devoid of any serious adverse events that prompted discontinuation. [35]

In a pharmacoeconomic view, the overall cost of Glimepiride treatment was a little more than that of Glipizide, but it had a lower cost per unit of glycemic improvement. This is similar to results obtained by Kaku et al., who stated that better glycemic control with Glimepiride may lead to long-term cost reduction due to less diabetes-related complications. [36]

Another critical role that has also been emphasized in the given study is the combination of patient teaching and lifestyle modifications, as the latter have a crucial part in the effective management of T2DM.

6. CONCLUSION:

The comparative analysis assessed the safety, efficacy, and cost-effectiveness of two fixed-dose combination drugs, including Glimepiride (2 mg) + Metformin (500 mg) and Glipizide (5 mg) + Metformin (500 mg) to treat patients with Type 2 Diabetes Mellitus (T2DM). In a 6-month follow-up study on 200 patients, the 2 combination therapies showed clinically significant reduction in glycemic control. Compared with the Glipizide-Metformin group, the Glimepiride-Metformin combination was linked with a numerically larger decrease in fasting blood sugar (36.1%), postprandial blood sugar (40.2%), random blood sugar (30.1%), and HbA1c (16.8%). Nevertheless, although these data show a certain tendency in favor of the Glimepiride combination both regarding glycemic parameters and cost-effectiveness per glycemic improvement unit, these findings must be viewed with caution and cannot be interpreted as a definitive proof of superiority. The two treatment groups had comparable profiles in regard to safety. Adverse drug reactions (ADRs) were not serious but rather described as “probable” or “possible” according to the Naranjo causality assessment scale. There were no serious ADRs or discontinuations due to therapy, which means that both regimens are tolerable and clinically safe to be used long-term with relevant monitoring.

According to the pharmacoeconomic point of view, the total cost of therapy in Glimepiride was slightly more, but the cost per one percent glycemic decrease was less as compare to Glipizide. This implies that the Glimepiride-Metformin treatment could present a better cost-effectiveness pattern within the chronic illness management.

Also, the availability of patient education leaflets with information on disease awareness and lifestyle change promotes a holistic management of T2DM, indicating the value of comprehensive management as well.

In conclusion, the two fixed-dose combinations have proven glycemic control, reasonable safety, and are cost-effective. The Glimepiride-Metformin combination tended to be more beneficial in certain outcomes and this needs to be investigated in larger and longer studies.

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